EXPERIMENTS
IN
ORGANIC CHEMISTRY

BY

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SECOND EDITION

D. C. HEATH AND COMPANY
BOSTON NEW YORK CHICAGO
ATLANTA SAN FRANCISCO DALLAS
LONDON

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PRINTED IN THE UNITED STATES OF AMERICA

PREFACE

A brief statement of the general policy adopted in the construction of this book perhaps will reveal most easily the points of departure from the manuals already available for use in laboratory courses of elementary organic chemistry. It has become the practice in this country to provide the beginning student with carefully standardized and detailed directions, in order that a good technique may be acquired with the greatest possible economy of time and materials, and to this policy I subscribe wholeheartedly. There is no novelty in the preference for preparations rather than experiments involving only test reactions, or in the opinion that the most stimulating and useful preparations are those which proceed smoothly and in good yield. It is hardly necessary in these days to state that every effort has been made to keep the cost of chemicals at a minimum, and a few preparations which have become old favorites have been abandoned regretfully for this reason. Careful attention has been given to the matter of utilizing the products accumulating from one experiment as starting materials for other preparations, for this plan is both economical and instructive.

Less orthodox is the view that some of the reactions of aliphatic chemistry can be illustrated perfectly well, and to considerable advantage, with the use of aromatic compounds. Some of the transformations characteristic of the aldehydes, acids, halides, and esters proceed particularly well when simple aromatic substances are employed as the starting materials, and the use of such substances permits greater diversity and often provides a welcome change from the succession of preparations involving only liquid reagents and liquid products. The early introduction of compounds containing the "mysterious" phenyl group does not appear to be at all confusing to the students or to detract from their interest, at a later period, in the chemistry of the benzene nucleus. It may be said in this connection that the Grignard reaction offers no great difficulties when introduced at a time corresponding to the elaboration in the lectures of some of the striking applications of the synthesis, and that it is a distinct event to the student.

In the belief that a truly helpful manual should attempt to answer, rather than to ask, some of the many questions which arise in connection with the experiments, the quizzing of the student on his preparation and reading has been left in the hands of the laboratory instructors, and an effort has been made to provide the student with useful reading matter. To this end prefaces introducing and explaining the experimental procedures have been included, and it is hoped that this may be of assistance in encouraging intelligent preparation in advance of the laboratory period. Another function of the introductions is to emphasize the value of test reactions in identification work and in the separation of mixtures. Experiments with carbonyl compounds and with amines develop further the theme of qualitative analysis and a special experiment placed at the end of Part I is devoted to the identification of unknowns. This provides a review and a practical application of nearly all the tests previously studied. Only a limited number of types are included, and the average student can identify about six unknowns in four afternoon periods. Over one hundred inexpensive chemicals have been used with success for the purpose and the list will be furnished gladly to interested teachers. It is most enlightening to use as unknowns some of the student's own preparations! One gram of material is usually more than adequate, and the outlay of test reagents is very modest.

Some provision for the particularly interested and gifted students has been made by the inclusion of special experiments and alternate preparations. Some of these are of more than the usual difficulty, some are too expensive or too hazardous for general class use, and some may be assigned for the purpose of supplying a chemical desired for use by the class. The "Martius Yellow" experiment properly belongs in the group of special preparations, and it may be used as the basis for an interesting form of competitive test. Other special experiments can be assigned in connection with the rather elaborate discussions of steam and vacuum distillation. In order to meet further requirements in this direction, and in order to make the book useful to students in advanced courses and to beginners in research, a number of notes, suggestions, and references have been incorporated in Part II of the manual in a somewhat condensed form.

Preliminary versions of nearly all the experiments of Part I have been used in course work at Bryn Mawr and Cambridge, and the reactions and comments of the students have been very helpful. The present directions are based both upon these experiences and upon a considerable amount of experimentation. Although a certain measure of novelty may be claimed for some of the experiments, the book as a whole is based upon the work of many distinguished predecessors, whose number is too great to permit individual acknowledgments.

A number of friends have contributed helpful suggestions, and I am glad to acknowledge the valuable counsel of Professor E. P. Kohler, the assistance of Dr. C. L. Bickel in the preparation of the chapter on semi-microanalysis, and the criticisms and suggestions kindly offered by Dr. G. H. Carlson, Dr. N. Weiner, Dr. G. F. Wright, and by several of the assistants in "Chemistry 2." The method of making rubber stamps is the contribution of Mr. A. M. Seligman. I am greatly indebted to Mary Fieser for valuable technical assistance, for the drawings from which the wax plates were constructed, and for a preliminary draft of the scheme of qualitative analysis.

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CAMBRIDGE, MASSACHUSETTS
April, 1935

PREFACE TO THE SECOND EDITION

In this edition the experiments designed for a first course in organic chemistry have been revised in certain details and extended by the inclusion of directions for the preparation of sulfanilamide, for the synthesis of vitamin K_1 and related compounds, and for the isolation of the principal acid constituent of rosin. The material of a more advanced character included in the second part of the book has been expanded considerably, and Parts I and II are now available in separate printings.

Part II constitutes a miscellany of notes on procedure and technique designed for the general guidance of advanced students. Although certain specific experiments are indicated, the general plan has been to provide a broad foundation of information and references on the basis of which illustrative experiments can be selected according to individual or local interests and with reference to the equipment and starting materials available.

Much of the new material of Part II is based upon the experiences, observations, and opinions of my collaborators in recent researches. I take pleasure in acknowledging particularly the invaluable assistance and advice of Dr. E. B. Hershberg, who kindly contributed the section on glass blowing and who is responsible for the design of the majority of the pieces of apparatus illustrated in the engravings. For other contributions and suggestions, I am indebted to Drs. J. Cason, H. J. Creech, Max Tishler, J. K. Wolfe, J. L. Wood, and R. B. Woodward, and to W. von E. Doering, R. C. Clapp, E. R. Coburn, W. H. Daudt, and H. Heymann. Mary Fieser again has contributed generously to the book by editing the manuscript, checking the references, reading the proof, and compiling the indexes.

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CAMBRIDGE, MASSACHUSETTS
February 10, 1941

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EXPERIMENTS IN
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SECOND EDITION

EXPERIMENTS IN ORGANIC CHEMISTRY

INTRODUCTION

Instruction in the laboratory methods of organic chemistry has a purpose beyond the obvious one of providing practical training essential to the prospective chemist. In affording an opportunity for the student to become acquainted with a number of representative organic compounds, to observe their special properties and characteristic behaviors, and to have some experience with the methods of handling them, such work forms a supplement to a lecture course which is essential to a full understanding and appreciation of the subject. With thought and study much information regarding the general theory of the carbon compounds can be gained in the organic laboratory, and there is in addition ample opportunity for acquiring manipulative skill and dexterity. Organic compounds present such an interesting array of properties and reactions, and the methods of manipulation are so ingenious, that work in the organic laboratory is usually found to be a stimulating experience. For those who become particularly interested and who develop suitable proficiency there is a wide field even in an elementary course for special experimentation.

The Nature of the Experiments. — Most of the laboratory operations of organic chemistry have to do with the preparation, the purification, or the characterization of compounds and there is some grouping of the experiments given below according to this classification. The first few sections deal largely with the common methods of purifying organic substances, and the preparations which follow require constant use of these methods in the separation of the reaction product from the by-products and tars almost invariably formed in the course of the reaction.

The samples prepared and purified are all to be tested for purity, and this is an important part of the characterization; they are also used in making practice tests of the reactions and properties characteristic of the types of which the substances are representatives. This matter of testing is given further emphasis in special chapters, and toward the end of the book the problem is presented of identifying certain substances by the application of the various tests studied.

Precautions. — Work in the organic laboratory is attended with certain special hazards, the chief of which is that from fire, for nearly all of the liquid chemicals and the solvents are highly inflammable substances, and the use of a free flame cannot be avoided in a great many of the common operations. Fortunately, however, methods have been developed for handling the inflammable materials with almost complete safety, and the realization of the danger should not be a source of alarm but rather a cause for the utmost caution. The warnings and precautions given in this book and further supplemented by such special laboratory rules as may be issued by the instructor must be followed explicitly. There is further danger of injury in the handling of acids, alkalies, metallic sodium, and bromine, and in working with such extremely poisonous substances as potassium cyanide; but the careful and thoughtful worker who heeds all advice and instructions given can perform experiments with such substances with equanimity.

In order to be prepared for an accident to yourself or to others, familiarize yourself with the safety devices and first-aid supplies of your laboratory, and read the instructions given on page 7.

In addition to recognizing the possibility of injury to the person it must be borne in mind that considerable care has to be exercised to avoid damage to the clothing and to the laboratory. Perhaps the chief source of difficulty is in the use of concentrated sulfuric acid, for the acid almost invariably drips when poured from a reagent bottle and its destructive action on wood, wool, cotton, and other materials is extremely rapid. Remember this and always pour the reagent over a sink when possible and always look for any drippings on the side of the bottle or elsewhere and wash immediately with plenty of water. Reagent bottles and flasks containing sulfuric acid must be put away in the desk in such a way that there is no possibility of their spilling. Solutions of alkalies are particularly destructive to wool and to the skin and they must be handled with the same care.

It is hardly necessary to point out that, quite apart from considerations of safety and protection, neat and careful manipulation is a mark of good technique. With a wet and a dry towel always handy, desks can be kept spotlessly clean. By washing vessels as soon as they have been used, or at least shortly afterwards. a supply of clean apparatus can be assured. Incidentally, tars and dirt are always most easily removed when they are fresh and while one still remembers the nature of the material and hence can judge of the best loosening agent. It is obvious that solid waste and papers must not be thrown into the sink. It is clear further that in handling noxious gases or vapors consideration for one's neighbors if not for one's self demands the use of a hood or of a suitable confining device.

Bending glass and boring corks. — The experiences gained in elementary courses should not be forgotten. A wash bottle should be constructed at the beginning of the course and used whenever an opportunity presents itself. Glass tubing can be cut cleanly by making a short but distinct file mark, placing the thumbs together on the side opposite the cut, and exerting a slight pressure. Bends are made most easily by heating the glass in the smoky flame of a burner provided with a wing top. The ends of glass tubes and stirring rods always should be fire polished.

There are several points to be remembered in selecting and boring a cork stopper. A cork used in contact with a hot liquid, as when it supports a thermometer in a distilling flask, becomes considerably softened and it may have to be pushed in further in order to make a tight fit. It is thus advisable to select a cork which originally fits only a short distance into the flask and which may even seem to be too large. Before being bored it is softened in a press or by wrapping it in paper and rolling it under the foot; this diminishes the chance of the cork splitting and it also reduces the size. A cork borer is selected which will give a hole slightly smaller than that desired, and it is held in the right hand and worked into the cork held in the left hand. The best way to bore a straight hole perpendicular to the face of the cork is to turn the cork in the left hand after each twist of the borer and to observe and correct the alignment after each cut. After the borer has been driven half way through the cork, it is withdrawn, the plug is pushed out, and the remainder of the hole is cut from the other side. This gives a clean hole on each side and all that is required to meet in the middle is careful centering and proper alignment. The hole is then smoothed and reamed to the desired size by the careful application of a round file, testing with the tube to be inserted so that a perfect fit is obtained. The tube is grasped close to the cork and carefully worked in by twisting. If it is held too far from the cork, or if one tries to force the tube into a hole which is too small, there is danger of receiving a severe cut from the breaking of the tube.

Rubber stoppers ordinarily are not used in contact with hot organic liquids or vapors because these substances dissolve in the rubber and cause it to swell. There are other uses for rubber stoppers, however, as in a filter flask, and the cutting of rubber requires a different technique. The stopper is painted with glycerol, which acts as a lubricant, and a particularly sharp cork borer is twisted in under only slight pressure but with a very vigorous circular motion. The proper cutting takes time and restraint, for too much pushing simply leads to a ragged hole of very small diameter. The insertion of a glass tube into a rubber stopper, and also into a rubber tube, is greatly facilitated by moistening the rubber with glycerol; water is not as satisfactory as this lubricant, but it is better than nothing. After some usage rubber often sticks tightly to glass and special care must be taken not to break the glass tube in removing it. A stopper frozen to a glass tube is easily loosened by moistening the small end of a spatula (page 27) with glycerol, inserting it between the rubber and the glass, and working it around the circumference of the tube; the other end is loosened in the same way.

Amounts of reagents are often of great importance and wherever an exact amount is specified this is to be weighed or measured as accurately as the apparatus available permits. Even when the quantity does not have to be exact it is important to keep within reasonable limits both to insure the success of the operation and to avoid needless waste. Where the directions call for the use, for example, of 3–5 cc. of a liquid the figures should be taken to indicate the upper and lower limits and one should aim to adhere to the specifications. A convenient approximate measure of 1 cc. is given by a 2 cm. column of liquid in an 11 × 75 mm. test tube. It is well at the start to measure all volumes accurately in order to gain experience sufficient for making reliable estimations. It is much more difficult to guess weights on account of the great differences in the density and the state of compactness of common materials. Thus the approximate volumes occupied by one gram each of crystalline iodoform (CHI_3), animal charcoal, and crystalline benzoic acid (C_6H_5COOH) are 1 cc., 7 cc., and 12 cc., respectively. Reliable estimates can only be made after practice weighings, and it is particularly important to do this in the case of animal charcoal. An 11 × 75 mm. test tube holds approximately 0.5 g. of charcoal when lightly packed.

Preparation for laboratory work. — In order to work efficiently it is quite essential to study the experiments in advance and to lay definite plans for the utilization of the time available. Certain operations, such as the heating of a reaction mixture, often require definite, stated periods of time and it is obviously necessary to arrange for this. It often happens that there are periods in an experiment during which the operator's full attention is not required, and the intelligent worker makes good use of these periods by working on other experiments, cleaning apparatus, obtaining supplies for future operations or otherwise busying himself.

It is an excellent plan to make some entries in the notebook in advance of the laboratory period. In case the experiment is in the nature of a preparation, this can include a suitable heading, a reference to the procedure which is to be followed, the equations involved, a diagram of the apparatus to be used and a summary of the quantities of reagents required. This will save much time in getting the experiment under way and the notebook will be in good shape for the recording of observations as they are made. Whatever further directions regarding the taking of notes may be issued by the instructor it is well to remember that only original notes recorded at the time of making the observations have any value in actual scientific practice.

IN CASE OF ACCIDENTS

FIRE

Burning Clothing: Prevent the person from running and thus fanning the flames. Wrap the person in a blanket or laboratory coat to smother the flames, or use a shower bath. Beat out small fires with a towel.

Burning Reagents: Turn out all flames from burners and remove everything which may ignite. Use a fire extinguisher or carbon tetrachloride, but not water. Smother a small fire in a vessel by covering it with asbestos paper or an asbestos-wire gauze.

Treatment of Burns: Do not use water but at once apply tannic acid solution or an ointment and then consult a doctor.

Tannic Acid Solution: Use a freshly prepared 5 per cent solution and sop it on freely. After about 24 hours this forms a dark, protective crust which begins to peel off when new skin has formed.

Ointments: "Butesin Picrate," "Unguentine," "Beebe" salve.

INJURIES FROM CHEMICALS

The immediate application of a suitable washing agent may prevent an otherwise severe injury. Speed is all important.

Acids on the Skin: Wash at once with a large volume of water, as by drenching the part affected under the tap. Then wash with sodium bicarbonate solution. In case of a severe acid burn, disinfect the wound, dry and apply an ointment as for an ordinary burn (not tannic acid).

Alkalies on the Skin: Wash thoroughly with a large volume of water, then wash with about 1 per cent acetic acid solution.

In case of a severe wound, apply a disinfectant, dry the skin and cover with an ointment as for a burn (not tannic acid).

Bromine on the Skin: Cover at once with plenty of glycerol (glycerine) and rub this into the skin in order to reach and react with the bromine which has penetrated into the pores. Dry and apply an ointment.

Organic Substances on the Skin: Wash freely with alcohol, then with soap and warm water.

Reagents in the Eye: Wash at once with water cupped in the hand, then use an eye cup and neutralize the reagent as follows: for acids use dilute sodium bicarbonate solution; for alkalies use boric acid solution.

CUTS

Disinfect and apply a bandage. Holding filter paper on a cut often serves to stop the flow of blood. Ethyl alcohol is a good disinfectant.

PART I

EXPERIMENT 1

DETECTION OF THE ELEMENTS

Carbon and Hydrogen. — Inorganic compounds, with few exceptions, do not burn as do organic substances, and they of course never blacken on heating from the formation of charcoal. Thus if a substance burns with a flame or chars on heating it is probably organic. Organic compounds containing the elements C, H, O, and also S, N, or halogen, usually can be burned completely by heating and there is left at most only a slight spot of carbon or of some impurity. Metal salts of organic acids may be regarded as having an inorganic part, e.g., the metal. Such a compound chars on being heated but it does not burn completely even on strong ignition. Instead it leaves an inorganic residue (which may contain enough unburned carbon to appear gray rather than white). This may consist of a carbonate (from a sodium or potassium salt), an oxide (from a calcium salt), a sulfate (from a salt containing sulfur), or a mixture of such substances. The conclusive proof that a compound is organic is furnished by the detection of carbon and hydrogen on heating the substance with copper oxide in the manner given below, when it undergoes combustion with the formation of carbon dioxide and water. There is no simple test for oxygen.

Experiment: Heat a very small amount of sugar, $C_{12}H_{22}O_{11}$, on a crucible cover, an asbestos gauze which has been well burned out, or a knife blade (*not* a silver spatula) until it chars and then burns. Test sodium benzene sulfonate, $C_6H_5SO_3Na$, in the same way and describe the results.

To detect carbon and hydrogen mix about 0.1 g. of sugar with about 1 g. of fine, ignited copper oxide in a test tube and fit the test tube with a stopper carrying a glass tube bent at an angle so that the escaping gases can be bubbled under the surface of calcium hydroxide solution contained in a second test tube. If, on heating the mixture and allowing some time for the air to be displaced, this solution becomes turbid[1] the sample contains carbon; the formation of droplets of water on the upper walls of the heated tube establishes the presence of hydrogen in the compound. Remove the delivery tube from the limewater before allowing the copper oxide to cool.

Halogen. — The most convenient test for halogen in an organic compound consists in burning a trace of the sample on a copper wire (Beilstein). A volatile copper halide is formed and imparts a characteristic green color to the flame. The standard tests used in inorganic qualitative analysis cannot be applied directly to most organic halogen compounds for the reactions are ionic in character and the compounds in question do not ionize (exception: amine salts). The tests, however, can be used if the organic halide is first decomposed by fusing it with either lime or sodium. The organic substance is thereby destroyed and the halogen is converted into a calcium or sodium halide, which is soluble in water and gives a precipitate with silver nitrate. The method of fusing with sodium is the same as that described below under the test for nitrogen; the filtered solution is made acidic with nitric acid and boiled for 5 minutes to expel any hydrogen cyanide, dilute silver nitrate solution is added, and a heavy precipitate indicates the presence of halogen.

Experiments: (1) *Beilstein Test.* — Heat the end of a copper wire to redness until the flame is no longer colored. Let the wire cool, plunge it into a small pile of the substance to be tested, and reheat the end with its adhering crystals. If the sample is a liquid, use one or two drops to moisten the wire and be sure that the copper is not hot enough to volatilize the sample before it reaches the flame. Try the test on *p*-bromoacetanilide (solid) and on carbon tetrachloride (a liquid).

[1] The precipitate of calcium carbonate sometimes dissolves on reaction with more carbon dioxide as the result of the formation of the soluble bicarbonate.

(2) *Calcium Oxide Fusion.* — Heat a small lump of pure lime contained in a test tube strongly in the Bunsen flame and while it is still very hot, quickly add two drops of carbon tetrachloride. Allow the tube to cool, wash the contents into a beaker with 10 cc. of distilled water, add dilute nitric acid until distinctly acidic, and boil. Test with litmus and add more acid if required. Filter the solution if cloudy and add 2–3 cc. of 5 per cent silver nitrate solution. A distinct precipitate should appear.

Nitrogen. — To obtain a compound of this element which is amenable to the standard (ionic) test reactions, the organic nitrogen compound is fused with metallic sodium.[1] This destroys the organic material and the metal unites with nitrogen and with some of the carbon which is always present to form sodium cyanide. The cyanide is extracted with water, ferrous sulfate is added to produce first ferrous cyanide, $Fe(CN)_2$, and then sodium ferrocyanide, $Na_4Fe(CN)_6$. The addition of ferric chloride, and the acidification of the solution, now causes the precipitation of Prussian blue, $Fe_4[Fe(CN)_6]_3$.

Experiment: (Use sulfanilic acid, $C_6H_7O_3NS$, and test for both N and S.) Support a small soft glass test tube (75 mm.) in a vertical position by pushing it through a square of asbestos paper and resting the latter on the open jaws of a clamp. Dry a piece of sodium[2] about the size of a small pea with a filter paper, place it in the tube, and heat with a flame until it melts and begins to vaporize. Before it cools appreciably drop in a small pinch of the sample and heat with the flame until the end of the tube is red hot (there may be a slight explosion).[3] While

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[1] An improved method of fusion with potassium carbonate and magnesium is described by Baker and Barkenbus, *Industrial and Engineering Chemistry, Analytical Edition*, **9**, 135 (1937).

[2] Handle sodium with great care. Keep it under kerosene until ready to use; do not take it up in the fingers; dry it quickly and just before use. Small scraps are best placed in the bottle for "Sodium Residues." Never destroy scraps with water; use alcohol. Use a *small* piece in this experiment and be careful in carrying out the fusion and in decomposing the product.

[3] In testing a liquid substance use 2–3 drops and be even more careful to have the sodium very hot (vaporized) at the time of adding the liquid; otherwise it may distil before reacting.

the tube is still hot, and with the asbestos still attached to serve as a guard, drop the tube with care into a small beaker containing 10–15 cc. of distilled water. The tube should crack and the sodium will then react violently with the water. Crush the glass and the charred material, boil for a few minutes, and filter. Save a part of the solution for the sulfur test below. (In case the sample is to be tested also for halogen proceed as described on page 11.)

To a portion of the solution add 5–6 drops of ferrous sulfate solution, 2 drops of ferric chloride solution, and 1–2 cc. of dilute sodium hydroxide solution. Make sure that it is alkaline by testing with litmus and then boil for a minute or two. Ferrous and ferric hydroxides precipitate and sodium ferrocyanide is formed. Now cool and acidify with dilute sulfuric acid. The brown precipitate dissolves, the ferric chloride reacts with the ferrocyanide to produce Prussian blue, which appears as a fine blue precipitate. If the amount of nitrogen in the sample is very small, or if in fusing much of the material volatilized before it reacted, no precipitate may be visible at first and one obtains only a greenish-blue solution. If this is shaken well and allowed to stand for a time, the precipitate may become perceptible, particularly if the solution is filtered and the paper examined carefully. In case of failure repeat the fusion, being careful to have the sodium hot enough so that its vapor begins to rise in the tube at the moment the sample is added.

Sulfur: (A) Sodium Fusion. — The fusion of a sulfur compound with sodium gives sodium sulfide. This may be detected by the violet or brown coloration produced by adding sodium nitroprusside, $Na_2Fe(CN)_5NO$ (equation not known definitely), or by the precipitation of lead sulfide from a solution of sodium plumbite. The latter test is the more sensitive.

Experiment: To a portion of the alkaline solution obtained from the sodium fusion of the sample (see under "Nitrogen") add a drop or two of sodium nitroprusside solution and see if there is a deep coloration. For the second test, prepare a solution of sodium plumbite by adding dilute sodium hydroxide solution to about 0.5 cc. of 0.1 *M* lead acetate solution until the initial precipitate just redissolves, and add a portion of the alkaline solution under investigation. A black precipitate or a colloidal brown suspension indicates the presence of sulfur. Freshly prepared sodium plumbite solution should be used.

(B) **The Carius Test.** — The principle involved here is to destroy the organic compound by oxidation with nitric acid, the sulfur being converted into sulfuric acid, which is easily identified. It is a convenient method in those cases where it is easily applicable, but many sulfur compounds are decomposed by nitric acid only when heated with this reagent in a sealed tube at 250-300°.

Experiment: Cover a small spatulaful of sulfanilic acid with 3 cc. of concentrated nitric acid in a large Pyrex test tube and warm the mixture carefully until the rather vigorous reaction begins and then heat more strongly. When no further reaction occurs on heating, pour in distilled water until the tube is about half-filled, and add 3 cc. of 5 per cent barium nitrate solution. A white precipitate of barium sulfate indicates the presence of sulfur.

EXPERIMENT 2

DISTILLATION

This operation is of great use in the organic laboratory for the purification of volatile compounds and in judging the purity of such substances. Traces of colored impurities which are either non-volatile or slightly volatile are easily eliminated in this way. It frequently happens in the preparation of an organic liquid that the product is accompanied by small amounts of materials some of which are more volatile, some less volatile than the substance itself. Hence in carrying out the distillation the first portion or fraction of the distillate is collected separately (" fore-run ") and discarded, and as the boiling point rises close to the true boiling point of the desired product the receiver is changed and the main fraction is collected until the liquid has nearly all distilled or until a further appreciable rise in the boiling point indicates that the less volatile " after-run " is beginning to come over.

A pure liquid boils very constantly at a definite point which is defined as the temperature at which the vapor pressure of the liquid is just equal to the atmospheric pressure. A change in the boiling point during the progress of a distillation is a definite indication that the liquid is not pure (or that it is a mixture of two or more components which may be individually " pure "). The converse proposition, however, is not always true, and it is not always safe to conclude from the constancy of a boiling point that the liquid is a pure individual. Thus if two miscible liquids of similar structural type boil at exactly the same temperature a mixture of the two will also boil at or very near that temperature. Furthermore, some liquids form constant-boiling mixtures, that is, mixtures which will distil completely without any change in the boiling point or in the composition of the distillate. An example of such an " azeotropic " mixture is the so-called 95 per cent alcohol (95.57 per cent alcohol, 4.43 per cent water, by weight), b.p. 78.15°; pure alcohol boils at 78.37°.

The boiling point of a liquid is of course dependent upon the external pressure, being raised or lowered as the pressure increases or decreases, though not in direct proportion. Since boiling points are usually recorded for the normal atmospheric pressure of 760 mm. of mercury, one should always note the barometric pressure close to the time of making a distillation and make at least a qualitative allowance for any wide deviation from the normal. Table I will give some idea of the magnitude of the effect of pressure.

TABLE I

VARIATION IN BOILING POINTS WITH PRESSURE

PRESSURE	B.P. WATER	B.P. BENZENE
780 mm.	100.73°	81.22°
770 mm.	100.37°	80.79°
760 mm.	100.00°	80.36°
750 mm.	99.63°	79.93°
740 mm.	99.26°	79.50°

To make an accurate determination of a boiling point one must be sure that the thermometer is accurate enough for the purpose (calibrate!); but even then there is one source of error which it may not be easy to avoid. If the boiling temperature is very high there may be a considerable column of mercury in the stem of the thermometer which is not as hot, and thus not expanded as much, as the main body of mercury in the bulb. The temperature recorded is thus too low. In the present experiment, however, the boiling points are so low that the error from this source is negligible. The error due to the exposed thread of mercury will be referred to in a later discussion (Experiment 4).

Experiment: (1) *Calibration of Thermometer.*—Test the 0° point with a well-stirred mixture of crushed ice and pure water. The boiling point of water, corrected according to Table I, will serve as a standard at 100°. Arrange the apparatus for distillation as shown in Fig. 1, using a 125-cc. distilling flask. All cork fittings should be perfectly tight, for the same apparatus is to be used later with inflammable liquids. The bulb of the thermometer should be slightly below the opening of the side tube, and in the center. Fill the flask about one-half full with distilled water, add a small piece of porous plate to prevent bumping, and distil as long as is necessary to establish with certainty the boiling point. The flask may be heated rather rapidly until boiling begins; the flame should then be decreased and adjusted so that the distillate drops at a regular rate (about one drop per second). Remember that it takes an appreciable time at the beginning for the vapor to heat thoroughly the upper part of the flask and the thermometer. It is a mistake to distil too slowly, for the thermometer may then momentarily cool from lack of sufficient contact with fresh vapor. On the other hand, the flame used should not be so large that it heats directly a part of the vapor rather than just the liquid. This superheating is particularly likely to occur at the end of a distillation when

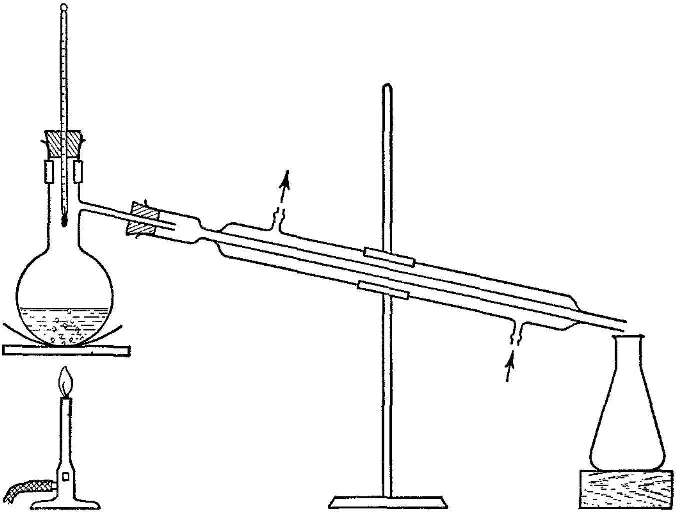


Fig. 1. — Distillation Apparatus

the volume of liquid becomes so small that heating of the vapor is inevitable.

When you have obtained a constant reading of the boiling point, remove the flame, let the flask cool somewhat, add through a long-stemmed funnel a solution of a small spatulaful of the dyestuff Orange II in a little water, and distil again for a few minutes. This will show how completely a non-volatile substance can be eliminated. It is also of interest to know that this solute raises the temperature of the boiling water slightly but that it does not alter the temperature of the condensed vapor (for none of it is present in the vapor phase).

The corrections noted at 0° and 100° should be applied to subsequent observations in these two temperature regions but do not necessarily indicate the performance of the thermometer at other temperatures.

(2) *Boiling Point of Pure Benzene and of a Mixture.* — For this purpose the flask should be washed with water and the whole apparatus must be dried *thoroughly*,[1] for water is not soluble in benzene and any moisture present will cloud the distillate. Pour 25 cc. of benzene into the flask, introduce a small chip of porous plate, make sure that all connections are tight, and distil as before, using a very small flame and continuing long enough to get several accurate readings and to note the constancy of the boiling point. Compare your result (corrected!) with the figures of Table I (to one decimal place).

Now remove the flame, and as a precaution extinguish it, let the flask cool somewhat and pour the contents into a dry measuring cylinder. The flask should be drained but not dried.

---

[1] To dry rapidly a flask or other piece of apparatus wipe any water from the outside with a towel, rinse the inside with a very small quantity of acetone from a "wash acetone" bottle and discard the wet solvent, rinse again with a liberal quantity of acetone and pour this back into the bottle. Drain, and lead to the bottom of the flask a stream of dry, compressed air. Acetone is also a good solvent with which to clean flasks; in this case, of course, the solvent is *not* returned to the bottle. Drying also can be accomplished by washing with alcohol to take out the water, followed by the more volatile ether; acetone, however, is more convenient for it is both miscible with water and easily volatile.

Pour back 15 cc. of benzene, add 15 cc. of toluene (b.p. 110.6°), and distil again after adding a fresh piece of plate to promote even boiling (the first piece, if still present, will be found to have lost its activity when the liquid cooled). Distil at a regular rate and collect the distillate in the measuring cylinder. Make some such record as the following and plot the results:

1st 5 cc. distilled at t^1 to t^2
2nd 5 cc. distilled at t^2 to t^3
3rd 5 cc. distilled at, etc.

EXPERIMENT 3

FRACTIONAL DISTILLATION

In both laboratory and technical operations the problem often arises of separating by distillation a mixture of two or more liquids all of which are present in appreciable amounts, rather than as traces. The separation of such a mixture into various fractions, some of which are rich in a particular component, often may be achieved by what is termed a fractional distil-

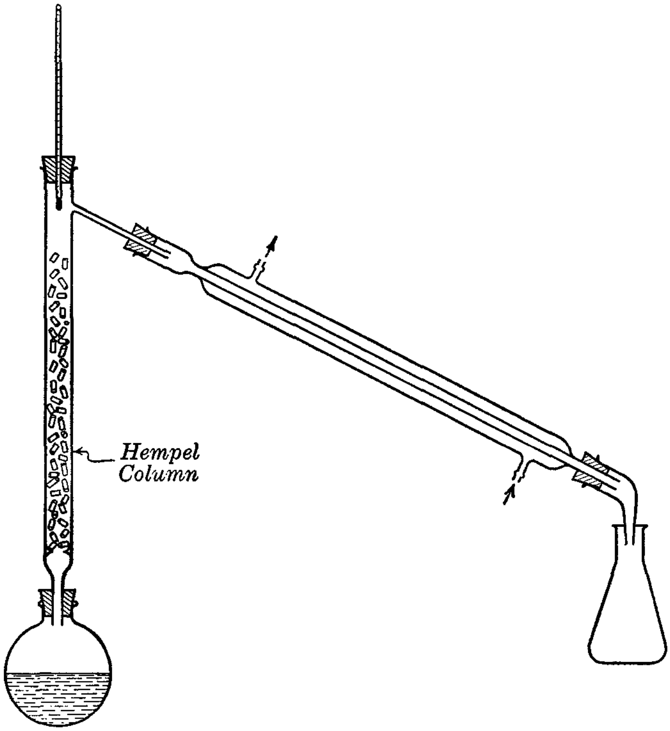


FIG. 2. — Distillation with a Fractionating Column

lation. The success of the process is dependent in the first place upon the difference in the boiling points of the components. It is an easy matter to separate ether (b.p. 35°) and nitrobenzene (b.p. 210°); but it will be obvious from the preceding experiment that the separation of benzene and toluene is a difficult matter (30° difference in b.p.). The more volatile benzene cannot distil without carrying along with it a considerable amount of toluene. If the mixture is separated into, say, four fractions of progressively increasing boiling point, the first fraction will be somewhat richer than the others in benzene, the fourth fraction will be richer in toluene. A further concentrating of the two components in the two end fractions can be achieved by fractionally distilling each of the four fractions and combining the more and less volatile parts with appropriate parts of other fractions.

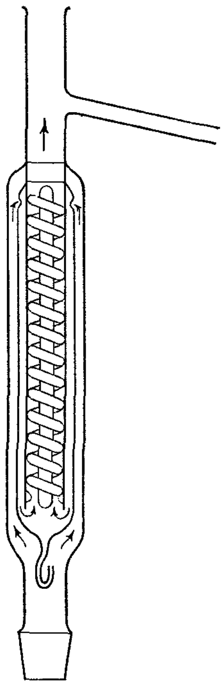


Fig. 3.--Widmer Fractionating Column

This process of course can be repeated many times with steadily improved results, but the separation of mixtures would be a very tedious and inefficient operation if it were not for a great improvement which can be made in the technique of the distillation itself. This consists in the use of a fractionating column, an example of which is illustrated in Fig. 2. There are a great many kinds of columns of varying degrees of efficiency, ranging from the simple Hempel column shown here, which is simply a glass tube packed with beads or short tubes, to extremely elaborate and intricate constructions designed for the highest efficiency. One of the most useful types is that designed by Widmer and shown in Fig. 3. The principle in each case is the same. The column provides a cooling space where a part of the vapor of the boiling mixture condenses and trickles down through the beads or other packing material. It is of course the less volatile component (e.g., toluene) which tends to condense first. Now the fresh vapor from the flask must force its way up through the descending condensate, and in doing so there is a heat interchange, because the vapor is hotter than the liquid. Some of the liquid vaporizes, and this of course is its more volatile part; the less volatile constituents of the vapor are condensed, dropping back into the flask. Similar partial condensation of the vapor (and partial volatilization of the condensate) occurs at several different levels of the column and it will be seen that the column effects what amounts to several separate distillations. The liquid which continually drops back into the flask from the column corresponds to a fraction which, in an ordinary distillation, would be collected from the condenser and put back in the flask by hand for a subsequent distillation.

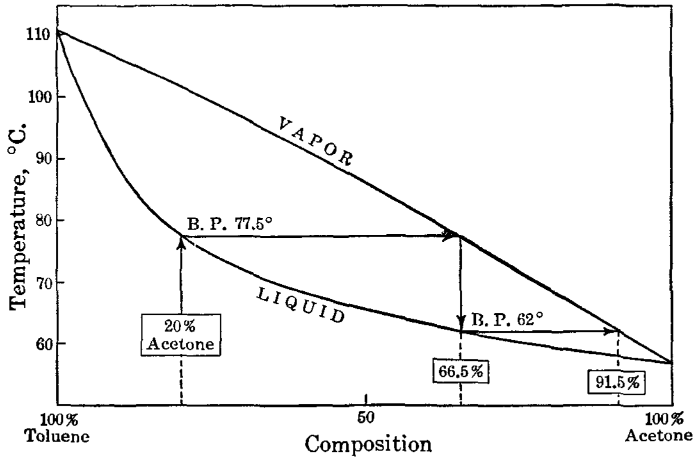


Fig. 4. — Distillation Curves

In order to appreciate fully the theory of fractional distillation it is necessary to consider distillation curves such as those given in Fig. 4 for mixtures of acetone and toluene. The composition is plotted on the abscissa: the concentration of toluene varies from 100 per cent at the left to zero per cent at the right of the chart, while that of the acetone increases from zero per cent at the left to 100 per cent at the extreme right. The mixture at the mid-point contains equal parts by weight of the two components. The lower curve marked " liquid " is drawn through the boiling points of liquid mixtures of various compositions; more strictly speaking, these " boiling points " are the temperatures at which the mixtures *begin* to boil. Thus pure (100 per cent) toluene boils at 110.6°, pure acetone boils at 56.5°, and the 50 : 50 mixture begins to boil at 65.5°. In the last case the boiling point increases along the liquid curve to the left as distillation progresses and the liquid remaining becomes richer in toluene and poorer in the more volatile acetone. It should be noted that this curve was determined experimentally and that it applies only to the particular pair of liquids under discussion. For other pairs the curves may be of different shape or character.

The upper vapor curve now requires explanation. It gives for each mixture of acetone and toluene the temperature at which the vapor *begins* to condense. If the 50 per cent liquid mixture is heated it starts to boil at 65.5°, but if it is completely vaporized and allowed to cool the first condensation of the vapor occurs at a temperature of 86°, corresponding to the intersection of the 50 per cent vertical with the vapor curve. The last of the vapor will of course condense when the temperature drops to 65.5°. It is only with pure toluene or pure acetone that the boiling point of the liquid is the same as the condensing temperature of the vapor and hence the curves come together only at the two ends of the chart. The vapor curve like the liquid curve is derived from experimental observations.

The course of a fractionation may now be followed with reference to the chart. Suppose that a solution of 20 parts of acetone and 80 parts of toluene is distilled, and suppose for the sake of simplicity that a large volume of the mixture is used and that only a very small proportion of the total is collected in the first fraction. The chart shows that this fraction will boil at 77.5°, and a parallel line constructed at this temperature intersects the vapor curve at a point corresponding to 66.5 per cent of acetone, that is, the vapor mixture at the temperature indicated contains 66.5 per cent of the more volatile constituent. When this first fraction is redistilled the initial boiling point is not that of the original mixture (77.5°) but corresponds rather to the intersection of the 66.5 per cent vertical with the liquid curve, namely 62°. The distillation of a small quantity of the fraction boiling at 62° gives 91.5 per cent acetone. It is evident that repeated fractionations will result in a distillate still richer in acetone, and that the toluene tends to concentrate in the higher-boiling residues. The picture given here is of course ideal, and in actual practice one would distil the 20 per cent mixture not just until a few drops of condensate had collected at 77.5° but until the boiling point had risen to some appreciably higher temperature, say 85°. A larger distillate would be obtained and it would be somewhat less rich in acetone than pictured above. The reasoning, however, is the same in either case. In theory it is of advantage to make a large number of small-volume fractionations, and this is precisely what is accomplished by the use of a suitable column.

In laboratory practice it is found expedient both to use a column and to redistil the fractions. The following experiment is designed to illustrate the technique of fractional distillation and to demonstrate the value of even a very simple type of column. You are instructed below to carry out a separation with the use of a column; in order to save your time, the results obtained by a reliable worker operating *without* a column are given in Table II for purposes of comparison.

Experiment: Arrange the apparatus for fractional distillation as shown in the diagram (Fig. 2), using a 200-cc. round-bottomed flask attached securely to the column (a distillation tube packed with sections of glass tubing). The thermometer bulb should again be just below the side tube of the column. To prevent undue evaporation, attach an adapter to the end of the condenser in the manner shown. The flask should rest on an asbestos-centered wire gauze, and if the column is properly supported no clamp is needed on the flask itself. Measure

TABLE II

Fractionation without a Column

Mixture: 60 cc. Carbon Tetrachloride, 60 cc. Toluene					
Fraction	Temp. Interval	Volume of Fraction in cc.			
		1st Dist'n.	2nd Dist'n.	3rd Dist'n.	4th Dist'n.
I	To 82°	0	8.5	19.3	28.5
II	82– 93°	45.0	44.3	30.5	21.0
III	93–104°	44.5	31.2	23.8	15.3
IV	104–111°	26.7	29.0	34.5	39.3
Residue.......	....	1.8	1.5	2.2	2.0
Losses........	....	2.0	3.5	4.2	4.2

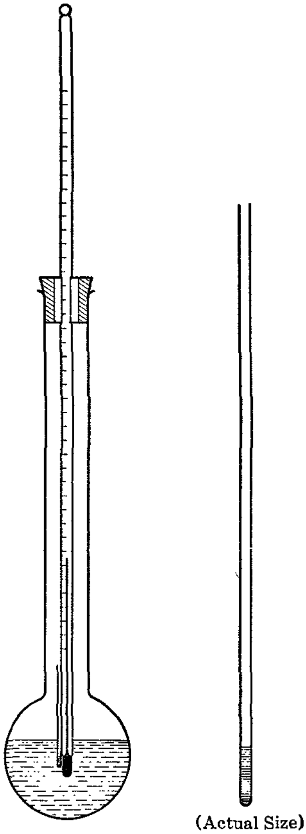
into the flask 120 cc. of the prepared mixture of equal volumes of carbon tetrachloride (b.p. 77°, sp. gr. 1.58) and toluene (b.p. 110.6°, sp. gr. 0.866). Add a chip of porous plate and distil carefully at a regular rate, and in such a manner that there is a steady flow of condensate dropping back from the condenser. Collect the portion which distils up to 82° in a 50-cc. or 125-cc. Erlenmeyer flask labelled " I, to 82°." When this temperature is reached change the receiving flask and collect the next portion in another clean flask marked " II, 82–93°." When the boiling point reaches 93° change to a third flask, " III, 93–104°," and finally use a fourth flask, " IV, 104–111° " for the fraction boiling in the range indicated. Allow the apparatus to cool somewhat, so that the vapor in the flask and the column condenses. Pour this condensate into a flask marked " V, Residue," and drain the distilling flask well. This completes the first distillation; the volumes of the various fractions are to be measured and recorded in a table similar to Table II.

In beginning the second distillation pour the liquid in flask I into the round-bottomed flask, distil and collect the portion boiling up to 82° in flask I. When the boiling point reaches 82° remove the flame, allow the flask to cool slightly and pour into it the contents of II. Again distil, collecting the part boiling up to 82° in I and that boiling at 82–93° in **II**. Remove the flame, cool slightly, and add to the distilling flask the contents of III. Distil again, collecting the fractions in the appropriate receiving flasks. Proceed in the same way with the material in flask IV. After this second distillation is completed, allow the column to drain and pour the residue into flask V. Again measure the volumes and record the results.

The carbon tetrachloride should now be fairly well concentrated in fraction I, the toluene in fraction IV (and in the residue). If the volumes of the two middle fractions are very large, indicating a poor separation, carry out a third distillation. Compare your results with those given in Table **II**.

EXPERIMENT 4

DETERMINATION OF MELTING POINTS



(Actual Size)

FIG. 5. — Melting Point Apparatus and Capillary Tube

This is a very common and important operation for it affords a means of judging the purity of crystalline organic substances and of identifying them. As carried out by the organic chemist the determination is very simple and rapid, and requires but a minute quantity of the sample. It is inferior only in accuracy to the method used in physical chemistry for determining the freezing point of a liquid (the temperature at which the solid and liquid phases are in equilibrium). The method will be best understood by considering the apparatus which is to be used (Fig. 5). A very small amount of the sample is packed into the sealed end of a capillary tube which is then attached to a thermometer centered in a heating bath. The flask is heated slowly and regularly and one can observe easily the temperature at which the sample melts. In the type of vessel shown the convection currents rise around the outer walls of the bulb and then descend and converge at the center. The mechanical stirring required in other types of apparatus is unnecessary.

It may be noted that this melting point bath is only one of a great host of contrivances designed for the same purpose. There are other types relying on the convection principle for the steady uniform heating of the thermometer bulb and the small tube containing the sample. There are baths which can be stirred by hand, baths with a rotary stirrer propelled by an air blast, by suction, or by electricity, and baths with an up-and-down stirrer actuated by a discarded windshield wiper. The bulb flask shown in the drawing has many advantages other than its simplicity and low cost, and it is recommended both for beginners and for research workers. When the thermometer bulb is properly centered and when the heating is done carefully entirely reliable results may be obtained. A more elaborate form is shown on page 326, and the beginning student will do well to adopt one feature of this set-up, namely, the test tube suspended on a wire to receive used capillaries.

Another piece of equipment required in this and in all other work involving the manipulation of solid organic substances is a good spatula. Porcelain and horn spatulas are almost useless in the organic laboratory. For the experiments described in this manual a small spatula made of sterling silver or of nickel and having the design shown in Fig. 6 will be found most useful. Whether silver alloy or nickel is used, the spatula should never be heated in a flame for this will ruin it. It is bad practice to use a spatula as a stirring rod. The metal can be kept spotlessly clean by polishing it with steel wool, and when the spatula is properly cared for it will last almost indefinitely.

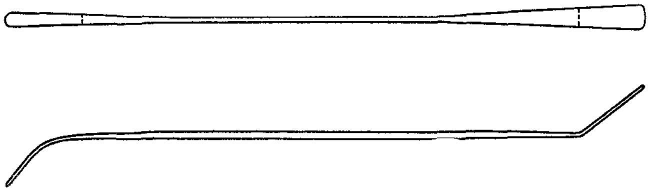


FIG. 6. — Silver Spatula (top and side view) Made from No. 8 Coin Silver Wire, Length 18 cm.

Theory. — A completely pure substance melts very sharply, that is, there is not more than 0.5° difference between the point at which a breaking down of the crystalline structure is first observed and the temperature at which the sample becomes completely liquid. With a less pure sample there may be a considerable temperature range over which melting occurs. It is obvious, then, that the sharpness of the melting point furnishes a criterion of the purity of the material tested, also that one should always report the melting point range, if there is one, rather than the point of initial or final melting, or an average.

An impure substance not only shows an unsharp melting point but it melts, or at least begins to melt, at a temperature lower than the melting point of the pure material. This affords a second criterion of purity. The " impure " sample may, of course, be a mixture of two compounds each of which was individually pure before the mixing, but even so the mixture will show a low (and an unsharp) melting point as compared with one or the other of the pure components. If substance A has mixed with it a little of substance B, the mixture will melt below the melting point of A; if B is contaminated with a little of A, the melting point of the sample will be below that of pure B. If A and B melt at exactly the same temperature then all possible mixtures of A and B will melt at temperatures below the common melting point. Just as salt lowers the freezing point of water, so A depresses the melting point of B, and B that of A.

These facts form the basis of the important operation known as the " mixed melting point " determination, which may be explained by an example. Suppose that a substance, C, is being studied with the object of identifying it, and that it is found to melt at 116–117°. A study of the literature shows that the known compounds D, E, and F all melt at or very near this same temperature and the properties of the unknown compound C are such that it appears possible that it is identical with any one of the three known compounds. On determining the melting points of the mixtures CD, CE, and CF (mixed melting point determinations) it is found that C depresses the melting points of D and E but not that of F. Therefore C and F are samples of the same compound, and the unknown is identified.

There is one source of error in melting point determinations which is not easily avoided but for which a correction can be made. This arises from the fact that unless a special type of apparatus or a special thermometer (short) is used there may be unequal heating of the mercury in the stem of the thermometer. At high temperatures the upper part of the mercury thread is much cooler than the mercury in the bulb of the thermometer; it is not expanded as much as the bulk of the mercury, hence the reading is lower than the true temperature. The error introduced is not appreciable at 100°, but it may amount to 3–5° at 200°, 6–10° at 250°. This error due to the column of mercury exposed above the heating bath may be eliminated roughly by applying a stem correction calculated according to the formula:

$$\text{Stem Correction (in degrees)} = 0.000154\ (t-t')N$$

where the fraction represents the difference in the coefficients of expansion of glass and of mercury, t is the temperature read, t' is the average temperature of the exposed column of mercury (determined, approximately, by reading the temperature of a second thermometer whose bulb is placed midway between the bath and the point on the first thermometer corresponding to t), and N represents the length, measured in degrees, of the thread exposed between the top of the heating liquid and the point t. The correction is subject to the obvious inaccuracy of determining the quantity t'.

Experiment: The long-necked, round-bottomed melting point flask is supported by means of a clamp at the very top of the neck on an asbestos-centered wire gauze at a height convenient for heating. A calibrated thermometer is fitted through a cork in the manner shown in the drawing, a section of the cork being cut away so that the thermometer scale may be visible. The bulb of the thermometer should be adjusted carefully to the exact center of the outer flask. If possible choose a thermometer with a very short bulb. The bulb of the flask is three-quarters filled with concentrated sulfuric acid. This serves as a convenient heating liquid for temperatures up to 280°.[1] If the acid darkens after long use or from contamination, add a small crystal of sodium nitrate or a drop of concentrated nitric acid; the bath will clear after the next good heating.

The capillary melting point tubes are best made by drawing out 12 mm. tubing, and the student should strive by practice to acquire some skill in the at first difficult feat of producing 10–15 good tubes in a single drawing. The large tube is rotated in the hottest part of the Bunsen flame until it is very soft and begins to sag. It should not be drawn at all during the heating. Remove it from the flame, hesitate for a second or two, and then draw it out steadily but not too rapidly. To cut the long tube into sections bring a sharp file which rests on your forefinger underneath the tube, rest your thumb over the place to be cut, and gently draw in the file so as to produce a slight scratch. On applying gentle pressure with the thumb the tube will now break clean.[2] The tube is sealed by touching the end to the very edge of a small flame. The proper size of the tube is indicated in the sketch, Fig. 5. A number of these tubes will be required in the course of the year.

The capillary tube is filled by crushing a very small pile of crystals on a filter paper or a piece of clay plate with the silver spatula and pushing the powder with the open end of the tube against the spatula. The sample may be shaken down to the bottom by gentle stroking with a file, or it may be tamped down by dropping it through a long vertical tube onto a hard surface. The column of solid should be not more than 2–3 mm. in length and it should be tightly packed. If the sample is in the form of a compact cake it is often convenient to fill the capillary by cutting out a tiny cylinder with the open end of the tube and then shaking it down.

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[1] This is true only for the particular type of apparatus recommended; when using for the heating bath an open beaker or a vessel not provided with a long neck the acid fumes so badly that a practical limit is reached at about 200°.

[2] The tubes can be cut nicely with the sharp edge of a broken clay plate or with a razor blade.

The melting point tube is held to the thermometer simply by capillary attraction. To attach it the thermometer is partially withdrawn and held in an oblique position with the bulb resting on the back lip of the flask. This steadies it and prevents spilling of acid; never withdraw it completely. The capillary is touched to the drop on the thermometer and this liquid is painted onto the side of the thermometer. The capillary will now stick nicely to this wetted spot and can be slid into the proper position, that is, with the substance just opposite the center of the thermometer bulb. The best way of inserting the thermometer without knocking off the capillary is to keep it always parallel to and touching the back wall of the flask. Make sure that the bulb is submerged and properly centered and that the column of substance is in the proper position.

In heating the bath it is admissible to apply a rather strong flame until the temperature rises to about 20° of the melting point. If the approximate melting temperature is not known, make first a rapid, approximate determination and then a more slow and careful one. In order to obtain good results it is essential that the heating during the last 15–20° rise be both slow and regular (2° per minute). Observe carefully both the sample and the temperature and record the temperatures of initial and of final melting. The flask (Pyrex!) may be detached and cooled for a second determination as follows: with an air blast, if the temperature is above 100°; under the tap, if it is no hotter than 100°.

The melting point apparatus will be used throughout the year. After completing the following experiments, remove the thermometer, save the cork, stopper the flask containing the acid with a cork (loosely, until it is cold), and put it away in an upright position (best in a beaker). Be very careful to see that the acid cannot spill or leak, for it will destroy any wood with which it comes in contact. To discard the acid after each period of use would be wasteful.

(1) Determine the melting point of either urea (m.p. 133°)

or cinnamic acid (m.p. 133°) and see how well you can check the figures given (1–2° is satisfactory).

(2) Determine the melting point of either unknown X, unknown Y, or unknown Z (they all melt close to 130°).

(3) By carrying out mixed melting point determinations see if the unknown selected is identical with either urea or cinnamic acid.

(4) Construct a rough chart showing the melting points of mixtures of urea and cinnamic acid of approximately the following compositions:

Urea	Cinnamic Acid	M.P. (Mid-point of Range)
100%	0%	133°
80%	20%	Prepare these mixtures and determine each m.p.
50%	50%	
20%	80%	
0%	100%	133°

Each of the three mixtures should be prepared by making small piles of the two substances of sizes estimated to be in the right ratio, and then mixing them very thoroughly with a spatula. In constructing the chart, plot temperatures on the ordinate and, on the abscissa, plot the percentage of urea from left to right (0–100 per cent) and of cinnamic acid in the reverse direction.

EXPERIMENT 5

CRYSTALLIZATION

Theory. — The best and the most useful method of effecting the thorough purification of organic compounds is by the process of crystallization, except in those cases where the physical properties are such as to render the method inapplicable. Briefly described, the process consists in dissolving the substance to be purified in some suitable solvent at the boiling point, filtering the hot solution to remove particles of dust, paper or other insoluble material, and allowing the hot solution to cool and the crystallization of the dissolved material to take place. In the ideal case nearly all of the substance being purified will separate in a nicely crystalline condition and the soluble impurities will all remain in solution in the "mother liquor." It is obvious that a good solvent for the purpose is one in which the substance dissolves readily at the boiling point, but in which it is only sparingly soluble in the cold.

In addition to the two kinds of impurities mentioned, the substance often contains a trace of some extraneous coloring matter (usually resinous) which goes into solution but which, instead of remaining entirely in the mother liquor, is partly adsorbed by the crystals. The method used to remove such material is very simple: before filtering the hot solution to remove insoluble impurities, a small amount of finely divided animal charcoal (" bone black ") is added. Since the charcoal has a much greater adsorptive power, the coloring matter is largely removed in the filtration, along with the insoluble charcoal. Even though the solution is not completely clarified by such treatment it is often found that the foreign coloring matter which fails to adhere to the charcoal will not contaminate the crystals but will remain in the mother liquor.

The great beauty of purification by crystallization lies in the fact that the aggregation of molecules to form a crystalline structure represents a process which is far more delicate and selective than the forcing of molecules to pass from the liquid to the gaseous state by the application of heat. While it is impossible to separate by distillation two liquids having the same boiling point, it is frequently found that a solid compound can be separated by crystallization from a second compound of the same solubility, or even from one which is somewhat less soluble. The explanation of this extraordinary fact is to be found in the phenomenon of supersaturation. It is well known that a hot solution, if clean and undisturbed, may cool several degrees below the temperature at which the solution becomes saturated without the separation of any crystals. That a solution is supersaturated can be shown by inoculating it with a tiny crystal of the solute to serve as "seed," or by rubbing the liquid against the walls of the vessel with a stirring rod; crystallization usually begins at once.

If a solution of two compounds of about the same degree of solubility is allowed to cool slowly and without movement, both substances, if present in about equal amount, may remain in supersaturated solution. If a crystal of one component, A, is carefully introduced, further crystals of A may deposit, while B stays in solution in a supersaturated condition. In a second case suppose that B is present in only very small amounts and that the solution is saturated with respect to A at a temperature not much below the boiling point. When such a solution cools it usually happens that A crystallizes well without any seeding, while B remains in the mother liquor (which will now be saturated with respect to A, supersaturated with respect to B). It will be obvious that this is of great advantage when one is endeavoring to purify compound A; also, that the whole process might be spoiled by cooling the solution too rapidly, by stirring it, or even by jarring the solution, for this might well be sufficient to relieve the condition of supersaturation and cause B to crystallize along with A. It is thus well to make a practice of allowing crystallizations to occur spontaneously and without disturbance. The chemist following this procedure has the incidental satisfaction of observing some very beautiful phenomena.

Solvents. — The most useful solvents are listed in the first column of Table III; the properties given should be noted carefully and remembered. Some of the liquids differ greatly in their solvent power for various organic compounds. It is useful to know that alcohol usually dissolves the same type of compound as glacial acetic acid, but to a less extent; that petroleum ether is similar to ligroin, but has less solvent action; that ether is usually found to be similar in solvent action to benzene. It is also true that different types of solvents (e.g., ligroin and water) usually are greatly different in their solvent action. Thus a substance which dissolves easily in ligroin is almost invariably insoluble in water. These facts serve to illustrate the most fundamental generalization concerning the solubilities of substances in various solvents: *similia similibus solvuntur.*

TABLE III

SOLVENTS	B.P.	F.P.	SOLVENT-PAIRS
* Glacial acetic acid	118°	17°	Glacial acetic acid — water
Water	100°	0°	
* Alcohol	78°		Alcohol — water
* Benzene	80°	5°	Benzene — ligroin
* Ligroin	60–90°		
* Petroleum ether	30–65°		Ether — petroleum ether
* Ether	35°		

* *Inflammable*

It is often of great convenience to use a mixture of two solvents, a " solvent-pair." The two solvents must, of course, be mutually miscible. Benzene forms a homogeneous solution with ligroin but it does not mix with water and it is miscible with alcohol only in certain limited proportions. Suitable solvent-pairs are indicated in Table III. The advantage to be gained from the use of these mixtures arises from the fact that the substance to be crystallized is invariably much more soluble in one member of the pair than in the other. Thus the substance may be so soluble in alcohol that it will dissolve but will not crystallize, while in water it is practically insoluble. Neither solvent by itself would be of any value, but by using a suitable mixture of the two one may have available a solvent having just the right dissolving power to permit satisfactory crystallization. The way to prepare such a mixture is to dissolve the substance in alcohol and add water at the boiling point drop by drop. Each drop produces a cloudiness which at first quickly clears. When the solution just fails to clear on shaking, a few drops of alcohol are added to effect this result and the solution is now saturated at the boiling point and should be in just the right condition for crystallization.

Selection of Solvent. — The best way of selecting a solvent for the crystallization of a given compound is to carry out simple solubility tests with a few of the common solvents. If the substance dissolves easily in a cold solvent this medium obviously would be unsuitable by itself, but it may be useful to observe before discarding the solution if a second solvent with which the first forms a " pair " will cause the solid to precipitate. If the substance fails to dissolve in a cold solvent, the latter should then be heated to boiling. If dissolution now occurs one should cool the solution under the tap and if necessary rub the walls with a stirring rod to be sure that it will separate on cooling. By reheating and allowing the test solution to cool slowly, one can see if well-formed crystals are obtainable.

In making such tests it is economical of both time and materials to use small test tubes (11 × 75 mm.). A convenient stand may be made by boring holes in a small block of wood. A very small pinch of the sample and about a quarter-inch column of solvent are all that are required. The solid particles should be broken by crushing them against the walls with a rounded stirring rod. For adding the small amounts of liquids required it is convenient to use a dropping tube. This is just a section of glass tubing about 23 cm. long and drawn down to a delivery tip at one end; three or four of them should be kept on hand for different solvents and reagents. Always add water from a wash bottle.

Preparing the Solution. — The best type of vessel for a crystallization is the Erlenmeyer flask. It is superior to a beaker in the following respects: it is more easily handled and more convenient for filtration, it decreases evaporation and hence fire risk, and it prevents the formation of a crust. The substance to be purified is placed in the flask, covered with what is judged an insufficient quantity of an appropriate solvent, and the flask is heated with constant shaking on the steam bath. Never use a flame except when the solvent is not inflammable. After good boiling and after breaking any lumps with a flattened stirring rod,[1] further small portions of solvent are added to bring the material into solution. To minimize the crystallization of the hot solution during filtration a further quantity of solvent is added so that the solution is no longer saturated. A piece of porous plate is introduced, a stemless funnel is rested in the opening of the flask, and the solution is boiled so that the vapor warms the funnel. After fitting in a filter paper and moistening it with solvent, the funnel is transferred to a receiving flask (Erlenmeyer) and the hot solution is filtered. A little fresh solvent, poured into the first flask and warmed, is used to wash the paper. In a successful operation very little material crystallizes on the paper; any such solid must be scraped back into the first flask, redissolved and refiltered. The stemless funnel is prescribed both because crystals almost invariably plug the stem of an ordinary funnel and because the use of a filter stand is avoided. The filtered solution, which usually deposits some crystals even during the filtration, is reheated to bring all of the material into solution. It is a good plan to boil the solution (after adding a piece of porous plate) with the funnel in place until the refluxing liquid washes the tip of the funnel and the paper clean of adhering solid. The solution is now set aside to cool undisturbed.

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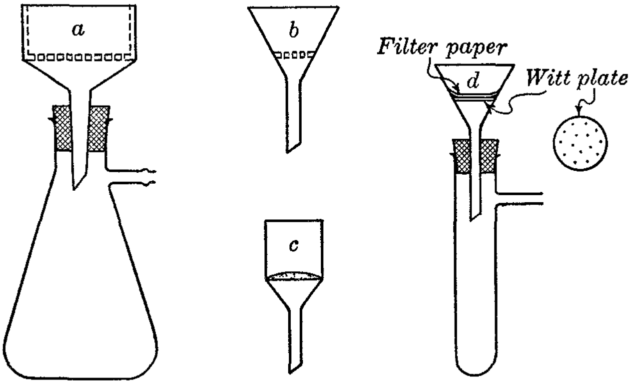
[1] This is made by heating the tip of a section of glass rod to redness and pressing it onto a piece of asbestos board.

Collecting the Crystals. — Four different assemblies for filtering with the suction of the water-pump are illustrated in Fig. 7. In using the Büchner or the Hirsch funnel a filter paper should be selected or cut so that it covers the plate completely but does not fold up against the sides. The paper for the Witt plate should be cut slightly larger than the plate. In any case after turning on the suction the paper should be moistened with some of the solvent used in the crystallization and pressed down until it is firmly held in place by the suction. In collecting the crystals it is often convenient to pour some of the mother liquor from the filter flask back into the Erlenmeyer flask to wash out adhering crystals. The crystalline material is then pressed down well with a spatula or with a flat bottle stopper and washed with enough fresh solvent to remove completely the adhering mother liquor which, on drying, would contaminate the crystals. The suction should be released before the washing and applied again after the crystals have been drenched.



a. Büchner Funnel
b. Hirsch Funnel
c. Sintered Glass Funnel
d. Ordinary Funnel

FIG. 7. — Apparatus for Filtering by Suction

After the product is well drained the funnel is removed, inverted over a large filter paper, and the crystalline cake is either blown out (with the hand protecting the lips) or scraped onto the paper and spread out to dry. A sample large enough for a melting point determination can be dried in a few minutes by pressing it on successive dry parts of a filter paper or clay plate.

Experiments: (1) *Test the solubilities of the following compounds:*

Resorcinol, $C_6H_4(OH)_2$, a dihydroxy compound
Anthracene, $C_{14}H_{10}$, an aromatic hydrocarbon
Benzoic acid, C_6H_5COOH, an acid, contains the hydroxyl group
Sodium naphthionate, $(C_{10}H_8N)SO_3Na$, an organic compound having an inorganic group (compare it with sodium sulfate)

in each of these solvents:

Water, a hydroxy compound which ionizes
Benzene, C_6H_6, an aromatic hydrocarbon
Ligroin, a mixture of aliphatic hydrocarbons

until you are convinced of the general truth of the rule that "like dissolves like." From these and further solubility tests, suggest a good solvent or solvent-pair with which to purify each of the first three compounds.

(2) *Decolorization of a Solution.* — Crude phthalic acid, $C_6H_4(COOH)_2$, is to be crystallized, with the aid of animal charcoal,[1] until a colorless sample is obtained. Dissolve 2 g. of the crude material in slightly more than the minimum quantity of water in a 50-cc. Erlenmeyer flask, add a small spatulaful of animal charcoal, boil for a few minutes, and filter the hot solution.

(3) *Purification, and Testing for Purity.* — Take the melting point of a crude sample of *p*-nitroaniline. Crystallize 5 g. of the material until you believe it to be pure. Give your evidence for this belief. Record the weight of pure product and turn it in to the assistant.

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[1] The special decolorizing carbons known as Norit and Darco are particularly effective.

EXPERIMENT 6

EXTRACTION

The use of a solvent for the extraction of an organic substance from a mixture containing other materials not soluble in the solvent is a process which requires little comment. The importance of this simple operation can be appreciated from the fact that it affords a means of isolating the colored pigments and the perfumes from the flowers, of extracting the chlorophyll present in green plants, and of obtaining a great many valuable drugs, essences, flavors and dyes from natural sources. The most generally useful solvent is ether, partly because of its great solvent power, partly because, being very volatile (b.p. 35°), it can be removed easily from the substance extracted at a temperature so low that little decomposition of even a highly sensitive product is likely to occur. Since the structure of ether, $CH_3CH_2OCH_2CH_3$, represents a combination of an oxygen-containing compound with a considerable portion which is hydrocarbon in character, ether is a good solvent for compounds of both the types mentioned, and this covers a considerable range of organic types.

Even when the substance to be extracted is only slightly soluble, there is a way of performing a satisfactory separation without the use of the large amount of solvent which might be thought necessary. The principle of the Soxhlet extractor, illustrated in Fig. 8, is to use the same solvent over and over again in a continuous and automatic operation. The solid to be extracted is placed in the thimble made of filter paper; ether vapor rises in the tube on the right, ether solution is returned to the flask after filtering through the thimble.

A second process of importance is the extraction from water of a dissolved organic substance by shaking the solution with ether, or with some other immiscible solvent, and then separating the two layers in the funnel designed for the purpose. This is useful both because the substance is more easily recovered from the ether extract than from the original water solution on account of the greater volatility of ether, and because the substance is usually more soluble in ether than in water and thus can be collected in a smaller volume of solvent. Since organic compounds usually dissolve better in ether than in water, while the reverse is true of inorganic salts, it will be seen that the organic material tends to go into the ether layer while the inorganic substances will remain in the water. Extraction with ether is thus a very widely used method of separating a product from a reaction mixture, for this almost always contains inorganic salts.

Shaken with a mixture of two immiscible solvents such as ether and water, a substance distributes itself between the two layers in the ratio of its solubilities in these two solvents (when these solubilities are finite quantities). If it is more soluble in ether than in water, and if equal volumes of the two liquids are used, then more of it will be found in the upper layer of ether than in the water. Even though the volumes used are not the same, it is always true that the *concentration* of this substance will be greater in the ether layer than in the water layer. The underlying principle is that the "distribution ratio" for the partition of a substance (X) between two solvents is a constant, invariant quantity which may be expressed, for the common case of the water-ether pair as follows:

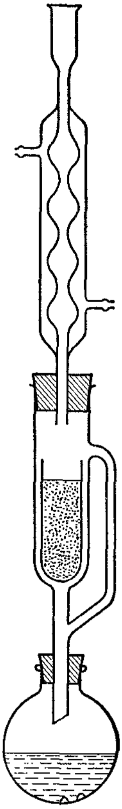


FIG. 8. — Modified Soxhlet Extraction Apparatus

$$\text{Distribution Ratio, } K = \frac{\text{Concentration of } X \text{ in the ether layer}}{\text{Concentration of } X \text{ in the water layer}}$$
$$= \frac{\text{Solubility of } X \text{ in ether}}{\text{Solubility of } X \text{ in water}}$$

Applied to the extraction of a substance such as acetic acid which is miscible with both water and ether in all proportions (infinitely soluble), the only difference is that the ratio, K, cannot be found from the ratio of solubilities, but must be determined by experiment (by shaking a known quantity of the acid with equal volumes of the two solvents and determining the concentration in the aqueous layer by titration with standard alkali). It still remains true that the ratio of the concentrations in the two solvents is always the same for a given temperature, regardless of the relative volumes used and the amount of material being distributed.

This distribution law is of great importance in attacking certain special problems such as, for example, the theory of narcosis, and the separation of the degradation products of the proteins. In such work it is necessary to take account of the fact that the above equation applies rigidly only to the ideal case in which the two solvents are completely insoluble in each other and that this situation is seldom met in actual process. Thus water dissolves 5.3 per cent of its weight of ether, ether dissolves 1.4 per cent of its weight of water. In accurate work it is necessary to correct for these deviations from the ideal condition.

For the purposes of ordinary organic laboratory work it is sufficient to know the principle of the process of extraction and to appreciate one important consequence of the theoretical formulation. This is that in extracting a substance from a water solution with ether it is more efficient to make several extractions with small volumes of ether than to use the same total volume of ether in a single extraction. The former method actually extracts more material than the latter. This can be seen most clearly by solving the following problem.

Problem: A certain reaction yielded 300 cc. of an aqueous solution containing 30 g. of malonylnitrile, $CH_2(CN)_2$, from which it is desired to isolate the nitrile by ether extraction. The solubility of malonylnitrile in ether and in water is 20.0 g. per 100 cc. and 13.3 g. per 100 cc., respectively. What weight of the malonylnitrile could be recovered by extraction with (a) three 100-cc. portions of ether; (b) one 300-cc. portion of ether. Suggestions: For each extraction let x equal the weight extracted into the ether layer. In the first case, (a), the concentration of the ether layer can be expressed as $x/100$; that in the water layer is $(30 - x)/300$. The ratio of these quantities is equal to K, or 20/13.3.

Experiment: Separation of a Mixture. — Like other compounds of carbon, the organic acids are for the most part soluble in ether. Their metal salts, however, are partly inorganic and they are no more soluble in this solvent than are the completely inorganic salts. Like the latter compounds, the sodium salts of the organic acids are almost invariably soluble in water, even though the acids from which they are derived are water-insoluble substances. The separation of an organic acid from other organic products which are not acidic is easily accomplished by dissolving the mixture in ether and shaking the solution with an aqueous solution of sodium hydroxide, sodium carbonate or sodium bicarbonate. The acid forms a salt which is extracted to the water layer, the other organic material remains dissolved in the ether.

The mixture to be separated contains equal parts of the following two compounds: benzoic acid, C_6H_5COOH, m.p. 121°; triphenylcarbinol, $(C_6H_5)_3COH$, m.p. 162°. In a 100-cc. separatory funnel, the stopcock of which has been properly greased, place 4 g. of the prepared mixture and dissolve it in 40 cc. of ether. Add 30 cc. of 10 per cent sodium bicarbonate solution, stopper the funnel tightly with a cork or rubber stopper, and shake cautiously, occasionally releasing the pressure produced both by the carbon dioxide liberated by reaction of the acid with the carbonate and by the volatilization of the ether from the heat of the hands. In shaking a separatory funnel the vessel should be clasped in such a way that both the stopper and the stopcock are held in place. The pressure is released not by removing the stopper, but by inverting the funnel and carefully turning the stopcock. As the evolution of carbon dioxide becomes less pronounced shake more vigorously, and when there is little further reaction let the layers separate, loosen the stopper, and carefully draw off the aqueous solution (lower layer) into a 125-cc. Erlenmeyer flask. A further small volume of this solution usually drains from the walls, particularly if the funnel is given a rotary twist, and this should be collected. Extract again with a 30 cc. portion of sodium bicarbonate solution and combine this extract with the first one.

Pour the ethereal solution into a dry 125-cc. Erlenmeyer flask from the mouth of the funnel (it would be contaminated with water if run out of the stem), and rinse the funnel with a little ether. Add 2–3 g. of anhydrous sodium sulfate and set the solution aside to dry while working up the other product.

The aqueous solution of sodium benzoate contains also a certain amount of dissolved ether which carries along with it some triphenylcarbinol. Heat the solution on the steam bath for a few minutes until most of the ether has been driven off. Now cool the solution well and filter it by gravity from any material which separates and which is to be discarded, and acidify the solution with dilute hydrochloric acid. It is well to carry out this operation in a beaker and to add the acid slowly and with stirring, for there is considerable foaming due to the liberation of carbon dioxide from the excess carbonate. Collect the solid which precipitates, wash it with water, dry and weigh it.

The ethereal solution is now filtered into a second Erlenmeyer flask, using a little ether to rinse the flask and to wash the material on the filter paper. To distil the ether add a chip of porous plate (very necessary when boiling ether), place the flask on the steam bath, and connect it by means of a bent glass tube to a condenser arranged for downward distillation. Use for the receiver a filter flask connected by means of an adapter. This gives a closed system except for the side arm of the receiving flask. To prevent ether vapor from escaping here and catching fire, a rubber tube is attached and arranged to conduct the vapor to the floor. Distil the ether completely and scrape out the solid residue and let it dry. Record the weight.

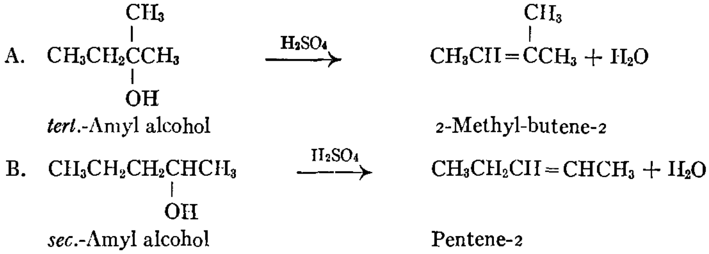
Determine now the melting point, first of the original mixture and then of each of the products of the extraction, and from the results and from the weights you will be able to judge of the success of your separation. After completing the remaining part of the experiment, place the two samples in the containers provided.

Consider now for comparison the possibility of separating the original mixture by fractional crystallization. Make solubility tests with the two samples isolated above as well as with a fresh portion of the original mixture, and see if by crystallization you can isolate either one or the other component, or possibly both of them in a pure condition (use 4 g.). If you find the proper solvent it should not be difficult to obtain one of the substances in a reasonably pure condition; but you will probably be unable to isolate more than one component in the time available. Compare the advantages and disadvantages of the two methods of separation.

EXPERIMENT 7

THE AMYLENES (2-Methyl-Butene-2 and Pentene-2)

Amylene is a general name for the five isomeric ethylenic hydrocarbons of the formula C_5H_{10}. Two of them are readily available through the dehydration of appropriate amyl alcohols as follows:



$$\text{A.}\quad CH_3CH_2\overset{CH_3}{\underset{OH}{C}}CH_3 \xrightarrow{H_2SO_4} CH_3CH{=}\overset{CH_3}{C}CH_3 + H_2O$$

tert.-Amyl alcohol — 2-Methyl-butene-2

$$\text{B.}\quad CH_3CH_2CH_2\underset{OH}{C}HCH_3 \xrightarrow{H_2SO_4} CH_3CH_2CH{=}CHCH_3 + H_2O$$

sec.-Amyl alcohol — Pentene-2

In each case the dehydration theoretically can proceed in two ways; but it is found that the chief reaction products are, as indicated in the equations, those in which the double bond is adjacent to the end of the chain, rather than at the end itself. The other possible isomers are formed, but in relatively small amounts. It invariably is found that a tertiary alcohol is more easily dehydrated than a secondary alcohol, while a primary alcohol reacts the least easily of all. Thus a stronger solution of sulfuric acid is required to bring about reaction B than is required for reaction A (see directions). The use of 95 per cent sulfuric acid ("concentrated") is avoided because this has a tendency to cause a polymerization (gum formation) of these unsaturated hydrocarbons. Carry out either preparation A or B.

A. 2-Methyl-butene-2.[1] — Pour 36 cc. of water into a 200-cc. round-bottomed flask and cautiously add with shaking 18 cc. of

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[1] Norris and Joubert, *Journal of the American Chemical Society*, **49**, 873 (1927); Norris, "Organic Syntheses," Coll. Vol. I, 421 (1932).

concentrated sulfuric acid. This "1 : 2 acid" is now cooled under the tap and 30 g. (36 cc.) of *tert.*-amyl alcohol is added slowly. The mixture is shaken thoroughly and the flask is connected by means of a bent glass tubing to a 45 cm. Liebig condenser, fitted with an adapter, and heated on the steam bath. A 125-cc. Erlenmeyer flask packed in an ice bath serves as the receiving flask; to lessen the evaporation the space between the adapter and the mouth of the flask may be plugged loosely with cotton. All connections must be tight and a rapid stream of water should be run through the condenser, for the amylene is very volatile (and also inflammable).

For the most efficient heating it is a good plan to use the largest ring which will hold the flask, to insert a match stick between the ring and the flask to allow steam to rise around the upper walls of the container, and to wrap the flask with a towel to confine the steam. Turn on the steam until there is just a slight escape; an excess does no good and it is wasteful. The flask is heated until the distillation of the hydrocarbon has practically ceased (1–2 hr.). To remove traces of sulfurous acid from the product the distillate is transferred to a separatory funnel and about 10 cc. of 10 per cent sodium hydroxide solution is added. Note that this aqueous solution sinks to the bottom. Stopper the funnel and shake it well, occasionally releasing the pressure, after inverting the funnel, by turning the stopcock. Now separate and discard the water layer and pour the hydrocarbon layer through the mouth of the funnel into a clean, dry flask. To dry the product add about 2 g. of anhydrous calcium chloride, insert a stopper loosely in the flask, and allow it to stand for about one-half hour, best with occasional shaking.

Decant the dried hydrocarbon into a distilling flask of suitable size, attach a thermometer and a clean, dry condenser, and distil from a water bath, taking the same precautions as before to avoid evaporation losses. Collect in a weighed bottle the portion boiling at 37–43°. Pure 2-methyl-butene-2 boils at 38.4°; the yield reported in the literature is 84 per cent of the theoretical amount; the average student yield is about 50 per cent.

B (Alternate). Pentene-2. — Proceed as directed in A but with the following changes: use 30 g. (36 cc.) of *sec.*-amyl alcohol, and a mixture of 36 cc. of water and 36 cc. of concentrated sulfuric acid (i.e., " 1 : 1 acid "). The pure hydrocarbon boils at 36.4°; the yields reported are from 65–80 per cent. Collect the fraction boiling at 35–41°.

Test Reaction: Hydration. — In a test tube shake with good cooling a mixture of 1 cc. of the amylene (either A or B) with an equal volume of cold 68 per cent sulfuric acid until it is completely dissolved. Then add an equal volume of water, cool, and if a layer of the alcohol does not separate at once add a small amount of sodium chloride to decrease its solubility. Note the odor. Each hydrocarbon is reconverted into the alcohol from which it was prepared. Write the reactions.

QUESTIONS

1. From what other amyl alcohols could each of the above amylenes be obtained by dehydration?

2. If perfectly pure pentene-2 is desired, which amyl alcohol would you suggest as the best starting material?

3. Which of the following alcohols would be expected to undergo dehydration "very easily," "easily," or not at all: $CH_3CH_2CH_2OH$, $(CH_3)_2CHOH$, $(CH_3)_3CCH_2OH$?

EXPERIMENT 8

REACTIONS OF THE SATURATED AND UNSATURATED HYDROCARBONS

The following test reactions of the three main types of aliphatic hydrocarbons not only serve to illustrate the chemistry of the compounds concerned but also furnish useful methods of determining the particular category to which other substances of the general group belong. In addition to studying the reactions and equations involved, one should gain some experience in using the reactions for test purposes. At the end of the experiment these tests are to be applied for the characterization of a few materials about which you probably are not yet informed.

Saturated Hydrocarbons. — For the following tests use a sample of purified ligroin, b.p. 90–100°.[1] This consists of a mixture of a great many paraffin hydrocarbons in which, judging from the boiling point range, heptanes probably predominate. Be sure that the test tubes used are dry except in those cases in which one reagent is an aqueous solution.

(1) **Action of Bromine Water.** — Pour about 1 cc. of the ligroin into each of two test tubes, add about 3 cc. of bromine water, shake the tubes well and keep one of them in the desk and out of the light. Expose the other tube to the bright sunlight (or hold it close to a light bulb for a longer period of time) and observe the results. As soon as a change is noted, compare the appearance of the material which has been kept in the dark. Note that any hydrogen bromide is absorbed in the water.

(2) **Bromine in a Non-aqueous Solvent.** — To about 1 cc. of the purified ligroin add 4–5 drops of a solution of bromine in carbon tetrachloride and expose the solution to the sunlight. Breathe across the mouth of the tube to detect HBr, also test the vapor with moist litmus paper.

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[1] The material supplied should be purified by the method described on page 364.

(3) **Action of Potassium Permanganate.** — Add 2–3 drops of a mixture of equal parts of 1 per cent potassium permanganate solution and dilute sulfuric acid to 1 cc. of ligroin and shake well for a minute or two. If the reagent is consumed, add further portions.

(4) **Action of Sulfuric Acid.** — Add 1 cc. of ligroin to about 2 cc. of concentrated sulfuric acid. Is there any apparent reaction? Any warming? Which is the heavier liquid?

Ethylenic Hydrocarbons. — Use your sample of amylene in making these tests. Compare the results with those obtained above and summarize the observations in the form of a table. Note that in tests (1) and (2) it is unnecessary to expose the mixture to the sunlight. The tests to be applied may be summarized as follows (judge the volumes approximately):

(1) Add 1 cc. of amylene to 3 cc. of bromine water, shake.

(2) To 1 cc. of amylene add 4–5 drops of the solution of bromine in carbon tetrachloride. (Note the absence of hydrogen bromide.)

(3) Test 1 cc. of amylene for unsaturation to acid permanganate as above.

(4) To 3 cc. of concentrated sulfuric acid add carefully 1 cc. of amylene.

Acetylenic Hydrocarbons. — The acetylene required may be taken from the supply bottle which is kept filled by means of a Prest-O-Lite tank, or it may be prepared in the following simple generator: a few lumps of calcium carbide are placed in a small distilling flask which is fitted with a small dropping funnel containing water, and to the side arm of which a piece of rubber tubing is attached. On dropping water slowly into the calcium carbide a stream of acetylene issues from the delivery tube (after displacement of the air). Some mixtures of acetylene with air are explosive; keep the generator away from all flames.

(1) **Action of Bromine.** — Bubble the gas through about 10 cc. of bromine water. Note the odor of the product formed.

(2) **Action of Potassium Permanganate.** — Bubble the gas through a mixture of 2–3 drops of 1 per cent potassium permanganate solution and 5 cc. of dilute sulfuric acid.

(3) **Special Test: Acetylides.** — Prepare the inorganic reagents as follows:

A. Ammoniacal silver nitrate solution: To 5 cc. of 5 per cent silver nitrate solution add ammonium hydroxide by drops until the first precipitate dissolves.

B. Ammoniacal cuprous chloride solution: To a solution of 2 g. of copper sulfate crystals and 1 g. of sodium chloride in 10–15 cc. of hot water add a solution of 1 g. of sodium bisulfite in 5 cc. of water and 5 cc. of 10 per cent sodium hydroxide solution. Shake, cool, pour off the clear solution and wash the white solid with water by decantation. Dissolve the cuprous chloride in a little ammonium hydroxide solution and dilute with water to a volume of about 10 cc.

Now bubble acetylene gas through each of these solutions and note the character of the precipitated metal acetylide. The precipitates if dried become highly explosive, and they must be destroyed completely by the following treatment: Let the precipitate settle, wash it once with water by decantation, add a mixture of equal volumes of concentrated nitric acid and water (2–3 cc. of each) and warm gently until the solid is completely decomposed.

Testing for Unsaturation. — Using any of the above tests (other than the special ones) which seem particularly reliable, see if you can distinguish which of the following substances are saturated, and which are unsaturated (or contain some unsaturated material):

Pinene, the principal constituent of turpentine oil
Paraffin oil, a purified petroleum product
Gasoline from the "cracking" process
Cyclohexane
Rubber (A convenient sample for testing is the viscous solution of rubber in benzene which is marketed as an adhesive ("Grippit"). Squeeze a drop of this onto a stirring rod and dissolve it in more benzene. In making the tests with permanganate or with bromine in carbon tetrachloride, use only a drop of the former in dilute sulfuric acid, and just enough of the latter to produce a coloration.)

EXPERIMENT 9

n-BUTYL BROMIDE

Alkyl bromides can be prepared by heating the alcohol with constant-boiling hydrobromic acid (47 per cent HBr), but there are two ways of avoiding the use of this rather costly reagent, and one or the other of these methods is usually employed where possible. The first method is to use a mixture of the alcohol in question, aqueous sodium bromide solution, and sulfuric acid. The acid reacts with the salt in an equilibrium reaction to produce hydrogen bromide which, in turn, converts the alcohol into the alkyl bromide. In the second method the hydrogen bromide required is produced by bubbling sulfur dioxide into a mixture of bromine and water. The sulfurous acid reduces the bromine and is itself oxidized to sulfuric acid. The alcohol is now added and the reaction proceeds as before. It will be seen that in each method sulfuric acid is present in the reaction mixture, either before or after the formation of the hydrogen bromide. This imposes certain limitations on the two methods: the dehydrating action of sulfuric acid may result in the conversion of a part of the alcohol into an unsaturated hydrocarbon, and of a further quantity into the ether. These side-reactions obviously decrease the yield. Secondary and particularly tertiary alcohols are so easily dehydrated (see Experiment 7) that the methods under discussion are never used for the preparation of the corresponding bromides; the HBr-method in these cases gives far better results.

The use of the two methods described is limited largely to the preparation of primary alkyl bromides. Here the bromine-sulfur dioxide method almost invariably gives good results. The sodium bromide-sulfuric acid method is somewhat more convenient, but its use is limited to the lower members of the series. An alcohol of high molecular weight does not dissolve well enough in the mixture on account of the presence in the water of the inorganic salts (NaBr, $NaHSO_4$). It is, however, well suited to the present preparation, for *n*-butyl alcohol is fairly soluble in water.

Before carrying out a preparation of this kind it is well to look up the physical properties of the reagents and of the product which is being prepared. This information may be of great service in regulating the temperatures and in the course of the separation and purification of the product. At the same time it is convenient to analyze the details of the directions and note the molar proportion of the different reagents. To illustrate these points an analysis of the present preparation is given in the two tables which follow. In all subsequent preparations you are to construct in advance similar tables.

PREPARATION: *n*-Butyl bromide

REAGENTS	MOL. WEIGHT	AMOUNT	MOLES		SP. GR.	B.P.
			ACTUAL	THEORET.		
NaBr.	103	65 g.	0 63	0 50	. . .	. . . .
H_2SO_4	98	92 g.	94	.50	1 84	. . .
C_4H_9OH	74	37 g.	.50	.50	0 810	117°

PRODUCT: $CH_3CH_2CH_2CH_2Br$

MOL. WEIGHT	WEIGHT		% YIELD	SP. GR.	B.P.	
	THEORET.	ACTUAL			GIVEN	FOUND
137	68.5 g.			1.3	101°	

From the equation:

$$C_4H_9OH + NaBr + H_2SO_4 \longrightarrow C_4H_9Br + NaHSO_4 + H_2O,$$

it is seen that for one mole of butyl alcohol there is required one mole of sodium bromide and one mole of sulfuric acid. In actual practice, however, it may be found expedient to use some of the reagents in amounts greater than those called for in the equation. The figures in the fourth column of the first table show that in the present case there is more than enough of both sodium bromide and sulfuric acid to react with the alcohol. The latter compound is thus the one on which to base the theoretical molar ratio of reagents, as shown in the next column. The theoretical yield is easily obtained: 0.5 mole of butyl alcohol can give as a maximum 0.5 mole of butyl bromide; multiplying by the molecular weight of the product gives the figure 68.5 g.

A further inference to be drawn from the tables is that any unreacted butyl alcohol will probably distil and contaminate the crude product, for the boiling points are quite close together. Very useful information is given by the specific gravities: butyl bromide is heavier than water, but lighter than concentrated sulfuric acid. These facts should be remembered later in separating the product from each of these reagents.

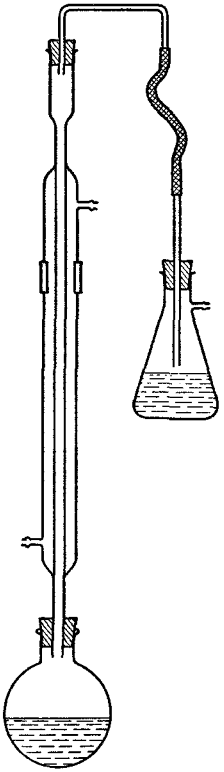

FIG. 9. — Reflux Condenser with Trap

Procedure.[1] — The apparatus is arranged as shown in Fig. 9. A 500-cc. round-bottomed flask is fitted with a reflux condenser which is supported in a vertical position by a clamp attached near the top. No clamp is needed on the flask itself, for this is to rest on an asbestos-centered gauze, and it is indeed a mistake to use a second clamp, for the flask will have to be shaken. The suction flask partly filled with water serves as a trap to catch hydrogen bromide which may escape during the reaction. The

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[1] Kamm and Marvel, "Organic Syntheses," Coll. Vol. I, 26 (1932).

tube extending into this flask should be a few millimeters above the surface of the water; it must on no account extend below the surface, for then water might be sucked back into the reaction vessel. It is convenient to place the filter flask on the shelf; the rubber tubing used to make connection to the condenser should not be of unnecessary length for the rubber deteriorates rapidly after much exposure to hydrogen bromide.

Into the flask (disconnected) there is placed first 60 cc. of water and then 87 g. of finely powdered sodium bromide ($NaBr.2H_2O$) is added with good shaking so that the mixture does not cake. Thirty-seven grams of *n*-butyl alcohol (45.7 cc.) is then added, the condenser is attached, and 50 cc. of concentrated sulfuric acid (92 g.) is poured in through the top of the condenser in about five portions, shaking the flask well between each addition. (This " shaking " is best done by loosening the clamp, supporting the apparatus with the left hand resting on the clamp and condenser, and swirling the flask in a rotary motion with the right hand.)

After adding a piece of porous plate and making connection to the trap, the mixture is boiled gently for two hours, using a small flame. To avoid volatilization of the product the flask is allowed to cool somewhat before it is disconnected, and the condenser is then arranged for downward distillation and connected to the flask by means of a short length of 8 mm. glass tubing bent to an angle of about 70°. The butyl bromide is then removed by distillation, which may be carried out as rapidly as is convenient. The distillation should be continued only as long as water-insoluble material comes over (collect a few drops of the distillate in a test tube, add water, and see if it all dissolves).

The crude distillate usually contains the following impurities (see the discussion above): water, di-butyl ether, butyl alcohol, possibly some dissolved butylene (b.p. $-18°$). The liquid also may be colored from a slight trace of bromine, formed by the oxidizing action of sulfuric acid on hydrogen bromide. Transfer the product to a separatory funnel and wash it once with water;

a pinch of sodium bisulfite added to the wash water will remove the bromine coloration. Separate the butyl bromide, dry the funnel, and wash the product with an equal volume of cold, concentrated sulfuric acid. This reagent removes all of the organic impurities which are likely to be present. Separate from the sulfuric acid, being careful to save the proper layer (see the tables)[1] and to drain the acid thoroughly. Wash the bromide layer carefully with water to remove all but traces of adhering acid and then wash it with an equal volume of 10 per cent sodium bicarbonate solution. After a final washing with water the butyl bromide is poured into a dry flask and dried with about 5 g. of anhydrous calcium chloride, the mixture being allowed to stand with some shaking for about one-half hour.

The dried liquid is filtered through a funnel fitted with a very small, loose plug of cotton into a distilling flask. Add a chip of clay plate and distil with a flame, collecting the fraction boiling in the range of 99–103°. The yield reported in the reference cited is 62 g.; the average yield for beginning students is about 48 g.

The sample of *n*-butyl bromide is to be placed in a narrow-mouth bottle of size appropriate to the amount of material and of the type specially designed for liquids. A neatly printed label is affixed giving the following data: the name of the compound; the formula; the boiling point range actually observed; the yield in grams and, in brackets, the percentage yield, thus: "48 g. (70%)"; the name of the operator. After all the time spent on the preparation, the final product should be worthy of a carefully executed label. First print and dry the label and then press it onto the bottle under a piece of filter paper.

QUESTIONS

1. What experimental method would you recommend for the preparation of *n*-octyl bromide? *tert.*-Butyl bromide?

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[1] The simplest method of telling layers apart is to see which one will mix with water. In the present case one can draw off a few drops of the lower layer into a test tube of water; butyl bromide will not dissolve. sulfuric acid will do so.

2. Explain why the crude product is likely to contain certain definite organic impurities.
3. How does each of these impurities react with sulfuric acid when the butyl bromide is shaken with this reagent?
4. In the early stages of the reaction there often appears an orange or pink coloration due to the formation of free bromine. How is it formed? Why does the coloration later disappear?

EXPERIMENT 10

DIETHYL ETHER

Ethyl alcohol reacts with concentrated sulfuric acid in the cold to form ethyl sulfuric acid and water. At a temperature of 140–150° this reacts with more alcohol with the formation of ether and the regeneration of sulfuric acid. The acid combines with more alcohol and the conversion of freshly added alcohol into ether continues, without the need of adding any further sulfuric acid, until the water formed in the first reaction so dilutes the acid that it loses its activity. It is of particular importance to control the temperature carefully during the reaction, for at only a slightly higher temperature (170°) ethylene becomes the chief product formed instead of ether. Even at 140–150° a considerable amount of ethylene is formed, and this of course decreases the yield. Further losses are due to the volatility of the product and to the distillation of some of the alcohol before it has had an opportunity to enter into reaction. In carrying out the preparation remember that ether is extremely volatile and inflammable; unusual care must be taken in constructing and in operating the apparatus.

It should be noted that the method used for preparing diethyl ether is not one which is generally applicable, and a little reflection will show why this is the case. Sulfuric acid converts ethyl alcohol chiefly into ether at 145° and chiefly into ethylene at 170°. For another alcohol the optimum temperatures for ether-formation and for dehydration may be entirely different. The experience gained in preparing the amylenes (Experiment 7) clearly shows that secondary and tertiary alcohols are dehydrated with great ease for here dilute sulfuric acid was used and the temperature was that of the steam bath. Thus one cannot prepare di-*ter.*-amyl ether or di-*sec.*-amyl ether by heating the alcohols with sulfuric acid for they are converted into amylenes long before a temperature suitable for ether-formation is reached. A further limitation is set by the boiling point of the ether in question. In the preparation of diethyl ether the product can be distilled out of the reaction mixture as soon as it is formed because it is so very volatile. If one attempted to prepare di-*n*-amyl ether by the same method, namely by heating with sulfuric acid at 145°, the reaction product if formed would remain in the flask since it has a boiling point of 169°. To raise the temperature to this point would surely bring about dehydration to an amylene. Since the starting material, *n*-amyl alcohol, boils at 137° and since its conversion into the ether is a reversible reaction, there would be only starting material and amylene in the distillate and no ether could be obtained.

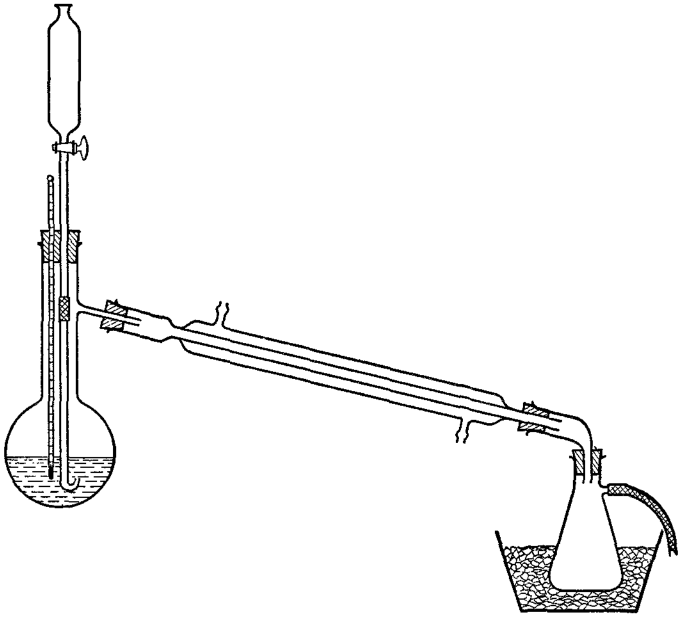

FIG. 10. — *Apparatus for the Preparation of Ether*

Procedure. — The reaction vessel is a 500-cc. distilling flask connected to a long and well-cooled condenser as shown in

Fig. 10. A thermometer is fitted into one hole of the cork stopper and adjusted so that the bulb will be completely immersed when the flask is about one-third filled with liquid, for it is the temperature of the reaction mixture and not that of the vapor which requires controlling. Through the other hole is inserted the stem of a separatory funnel which is to be used for introducing the alcohol underneath the surface of the ethyl sulfuric acid in the flask. (If the alcohol were simply dropped in it would not mix well and it would largely volatilize before having a chance to react.) The stem of the funnel is seldom long enough to reach to the bottom of the flask and so it is pieced out by means of a length of glass tubing attached to it with a short rubber tube (push the two glass ends as close together as possible). It is convenient to draw out the lower end of this tube slightly and bend it upwards in the manner shown, for this gives a better flow of alcohol. Make sure that the stopcock of the separatory funnel fits tightly and that it is properly greased. In turning the stopcock be careful never to loosen it; exert a slight pressure inwards, so as to tighten it. These precautions are very necessary for alcohol might otherwise leak out and take fire.

The distillate is to be collected in a filter flask or distilling flask connected to the end of the condenser by means of an adapter and cooled in a slush of ice and water to minimize volatilization losses. Even with good cooling enough ether vapor will escape to present a fire hazard unless the vapor is led off to the floor through a rubber tube attached to the side arm of the receiver.

Pour 50 cc. of alcohol (95 per cent by volume) into the flask and add cautiously and with good shaking 50 cc. of concentrated sulfuric acid. Heat the mixture on an asbestos wire gauze until the thermometer records a temperature of 140°, measure 100 cc. of alcohol and pour it into the separatory funnel (remove the flame while pouring!). Now turn the stopcock carefully and allow a slow stream of alcohol vapor to bubble up through the liquid in the flask. The temperature must be kept between

140 and 150° throughout the reaction. The alcohol should be added at just the rate at which the ether distils. The addition of the alcohol will require about one hour, and heating should be continued only a few minutes after the addition is complete.

The crude distillate is first shaken in a separatory funnel with one-third its volume of water containing 5 cc. of 10 per cent sodium hydroxide solution to remove traces of sulfurous acid, and then with half its volume of saturated calcium chloride solution, which removes the greater part of the alcohol invariably present. After separating carefully from the aqueous layer the ether is poured out the mouth of the funnel into a dry flask and dried for a few hours with calcium chloride (about 10 g.). It is then decanted into a dry 125-cc. boiling flask and distilled from a water bath, collecting the product in an ice-cooled receiver arranged in the same manner as before (safety tube). Pure ether boils at 35°. The yield of material boiling at 33–38° is seldom better than 40 g.

EXPERIMENT 11

METHYL BENZOATE

The experiment illustrates the procedure most generally used for the esterification of an acid. In the ordinary case the acid is a solid substance and the alcohol with which it is to be combined is one of the inexpensive, common alcohols. In order to bring the solid into a condition in which it can react easily, one employs an excess of the alcohol as the solvent. This has the further advantage of shifting the esterification equilibrium in the direction which favors the more complete conversion of the acid into its ester. As catalyst one can employ either gaseous hydrogen chloride from a generator (see page 394) or concentrated sulfuric acid; the latter reagent obviously is the more convenient one to employ, and it also absorbs some of the water formed in the reaction.

The ester invariably has a lower melting point than the acid from which it is formed, and in many cases it is a liquid substance. In the latter event the ester is best isolated by distributing the reaction mixture between the two solvents water and ether. The sulfuric acid goes to the water layer, the ester dissolves in the ether (since esters and ethers are structurally similar they usually show a mutual solubility). After separating the layers, the ether is easily removed on account of its greater volatility.

The acid chosen for the present experiment is benzoic acid, C_6H_5COOH, a derivative of benzene, C_6H_6. The ester, $C_6H_5COOCH_3$, will serve as the starting material in a later preparation.

Procedure.[1] — In a 500-cc. round-bottomed flask there is

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[1] Method of E. Fischer and A. Speier, *Berichte der deutschen chemischen Gesellschaft*, **28**, 3253 (1895).

placed a mixture of 24.4 g. of benzoic acid (0.2 mole) and 70 cc. of methyl alcohol, and 7 cc. of concentrated sulfuric acid is carefully poured in down the walls of the flask. A boiling chip is added, a reflux condenser is attached, and the mixture is boiled gently on the steam bath for one hour.[1] The condenser is now arranged for downward distillation and the excess alcohol is distilled as long as it comes over easily (the residue should be about one-third to one-half the original volume).

The flask is then cooled well under the tap and the residue is poured into a separatory funnel and treated with 70 cc. of ether, using a part of this to rinse the flask. The ethereal solution is then washed thoroughly with two 50-cc. portions of water in order to remove most of the alcohol and the sulfuric acid. It is then shaken with 50 cc. of 10 per cent sodium bicarbonate solution in order to remove the last traces of sulfuric acid and to separate the ester from any unreacted benzoic acid. After separating the bicarbonate solution, neutralize it with acid and if any benzoic acid precipitates collect the solid, weigh it, and allow for this recovered material in calculating the yield. The washing with bicarbonate is repeated until no precipitate forms on acidification of the aqueous layer. The ethereal solution is then separated carefully, poured into a dry flask (rinse the funnel with a little ether), and dried with about 5 g. of anhydrous potassium carbonate for at least one-half hour.[2]

The dried solution is filtered into a distilling flask, the vessel being rinsed with a little ether. The ether is removed by distillation from the steam bath (porous chip!) using as receiver a flask with a side arm carrying a safety tube running to the floor.

The distillation of the ester itself is now carried out over a free flame (no gauze). The boiling point is so high (199°, corr.) that a water-cooled condenser is not only unnecessary but inad-

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[1] It may be convenient during this period to prepare the bent tube required at the end of the refluxing and the apparatus mentioned below in the "hydrolysis" test.

[2] Anhydrous magnesium sulfate, prepared by heating the hydrate ($MgSO_4 \cdot 7H_2O$) to dryness in a porcelain dish, is also a suitable drying agent. Calcium chloride cannot be used here because it forms molecular compounds with esters.

visable, on account of the danger of cracking the condenser. An air condenser tube (the inner tube of an ordinary Liebig condenser) is employed. A small fore-run should be collected separately and the main fraction taken over the interval 190–196°, most of it boiling over a range of about 2°. The average yield is 20 g.

Test with Sulfuric Acid. — Add a few drops of your ester to about 1 cc. of concentrated sulfuric acid and note the result. Like other oxygen-containing compounds, but unlike hydrocarbons or alkyl halides, the esters are soluble in this reagent, probably because of the formation of oxonium salts. A yellow coloration indicates that the sample is not completely pure.

Hydrolysis. — This is the most useful method of determining that a given substance is an ester (or else a closely related type of compound) and of identifying it, and it will be employed in later work. The hydrolysis is accomplished by boiling the ester with alkali under the reflux condenser, and, when working with a small test sample of material, it is convenient to use the apparatus shown in Fig. 11. A Pyrex test tube serves as the boiling flask and it is supported over a wire gauze by means of a clamp attached near the top. The condenser ("cold finger") is constructed from a filter tube which fits loosely into the test tube and which is supported at the proper level by means of a rubber band. The inlet and outlet for the cooling water are attached as shown.

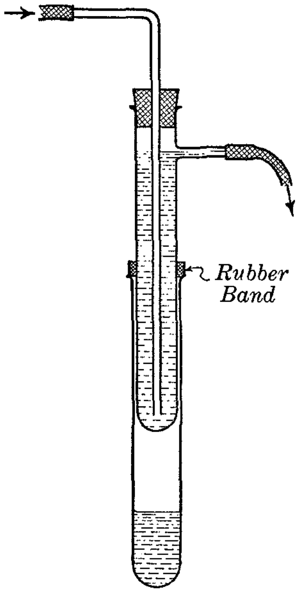

FIG. 11. — Reflux Condenser for a Test Tube ("Cold Finger")

In the boiling tube place 0.5 cc. of the ester, 10 cc. of 10 per cent sodium hydroxide solution and a piece of porous plate and boil the mixture gently until all the oil has disappeared (about 30 minutes). Disconnect the apparatus, cool the solution and make sure that the water-insoluble ester has been completely consumed, and acidify with dilute hydrochloric acid. The separation of the solid (benzoic acid), coupled with the fact that it was before in solution in the alkali (as sodium benzoate), shows that the reaction leads to the formation of an acid.

Optional. — Boil a piece of tallow about the size of a pea with alkali in the manner described above, and determine if this substance has the properties of an ester.

ALTERNATE PREPARATIONS

Methyl Salicylate (Oil of Wintergreen). — This is prepared by the esterification of salicylic acid, a hydroxyl derivative of benzoic acid having the formula $C_6H_4(OH)COOH$. The hydroxyl group is close in space to the carboxyl group and it tends to ward off the esterifying alcohol and so to slow down the reaction. In order to prepare this fragrant ester in good yield, use 0.2 mole of salicylic acid and follow in other details the procedure given above with the one exception that the refluxing with alcohol and sulfuric acid should be continued for at least 5 hours. Even then there may be some unesterified acid and this should be completely removed with sodium bicarbonate. The ethereal solution is in this case best dried with anhydrous magnesium sulfate (see Note 2, page 63). The pure ester boils at 222°, corr.; the yield is 75–80 per cent of the theoretical amount.

Methyl ortho-Benzoyl Benzoate. — This preparation calls for somewhat more skill and care than the other esterifications because the product is a low-melting solid which crystallizes a little slowly and which can be purified by distillation only at diminished pressure, for at the high temperature of atmospheric distillation it undergoes decomposition. The acid concerned is ortho-benzoylbenzoic acid, $C_6H_5COC_6H_4COOH$, and its preparation and properties are described in a later experiment. All that is significant in the present connection is that it has a carboxyl group capable of undergoing esterification. Since the molecular weight is nearly double that of benzoic acid, use only 0.1 mole of the acid. In case the acid is available in the form of the monohydrate, molecular weight 244, place the solid hydrate in a 500-cc. round-bottomed flask, connect the flask to a suction pump and heat it on the steam bath for one-half hour (wrapped with a towel) in order to drive off the water of crystallization. To 0.1 mole of the anhydrous acid add 70 cc. of methyl alcohol and 7 cc. of concentrated sulfuric acid, reflux for one hour and work up the product in the manner described above for methyl benzoate up to the final distillation. Take care that the ether is removed as completely as possible, and then cool the residual oil thoroughly in an ice bath and rub it very vigorously against the walls of the flask with a stirring rod in order to induce crystallization. This may take some time, and it may even be necessary to distil the oil in vacuum. A simple set-up adequate for the purpose is illustrated in Fig. 22, page 241. Once the ester has been obtained in solid form, save a small quantity for seed and crystallize the main portion as follows. Dissolve it in ether, which has been dried previously over calcium chloride and filtered, and add petroleum ether until there is a permanent cloudiness (about an equal volume). Add a little ether to clear the solution and cool slowly (best in an ice chest). If an oil separates rub a seed crystal against the wall of the flask at the surface of the liquid. By careful manipulation the ester can be obtained in the form of large, colorless prisms melting at 49–50°. The yield, barring losses in crystallization, is 75–80 per cent of the theoretical amount.

EXPERIMENT 12

TRIPHENYLCARBINOL

(Grignard Synthesis)

The synthesis of a tertiary alcohol usually is accomplished by allowing a suitable Grignard reagent to react with either an ester or a ketone. An acid chloride may also be used as the carbonyl compound, but it reacts so vigorously that the process is not easily controlled. For the preparation of triphenylcarbinol, $(C_6H_5)_3COH$, it is thus convenient to employ either an ester of benzoic acid, C_6H_5COOR, or benzophenone, $(C_6H_5)_2CO$. Each of these compounds reacts smoothly with phenyl magnesium bromide, C_6H_5MgBr, to give the desired alcohol; but since the ester is only half as expensive as the ketone it is the preferred reagent.

The first part of the preparation, namely the formation of the Grignard reagent from bromobenzene, C_6H_5Br, magnesium and ether, is the most difficult part of the process and it is necessary to follow the directions carefully, particularly in the matter of using dry reagents and dry apparatus, in order to meet with success. The subsequent reaction proceeds well with either methyl or ethyl benzoate. When the methyl ester is used, an intermediate addition product separates as a white solid; the intermediate formed on reaction with ethyl benzoate is more soluble in ether and remains in solution.

The final magnesium compound, $(C_6H_5)_3COMgBr$, is decomposed by treating it with water containing sufficient sulfuric acid to dissolve the basic magnesium bromide, $Mg(OH)Br$, and the triphenylcarbinol is extracted, along with the organic impurities, with ether. The chief impurity, other than unreacted reagents, is the substance diphenyl $(C_6H_5.C_6H_5)$ which is invariably formed by the side reaction:

$$C_6H_5MgBr + C_6H_5Br \longrightarrow C_6H_5.C_6H_5 + MgBr_2$$

The ether is easily removed by volatilization, but the only effective way of removing the diphenyl, together with any unchanged bromobenzene or benzoic acid ester, is by the process of steam distillation. This consists in passing steam into a hot mixture of the crude reaction product with water. The impurities all volatilize and distil along with the steam; triphenylcarbinol has such a low vapor pressure that it remains as a solid residue, to be separated only from the water. For a discussion of the theory of steam distillation see page 153.

Preparation of Phenyl Magnesium Bromide Solution. — The Grignard reagent is prepared in a 200-cc. round-bottomed flask, fitted by means of a well cut cork stopper with an efficient reflux condenser. A calcium chloride drying tube inserted in a cork which will fit either the flask or the top of the condenser is also made ready. The flask and condenser should be as dry as possible to begin with and then, as a further precaution to eliminate a possible film of moisture, the magnesium to be used (3.9 g. = 0.16 mole of magnesium turnings) is placed in the flask, the calcium chloride tube is attached directly, and the flask is heated gently but thoroughly either on the steam bath or, better, by carefully brushing the bottom with a luminous flame. The flask on cooling sucks in dry air through the calcium chloride. Cool to room temperature before proceeding! Extinguish all flames!

Remove the drying tube and insert it in the top of the condenser, and pour into the flask 5 cc. of dry bromobenzene and 10 cc. of absolute ether.[1] There usually is no immediate change and it is necessary to start the reaction before adding further quantities of reagents. A very effective way of doing this is to

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[1] Even when purified as in Experiment 10, ether contains appreciable amounts of water and alcohol, both of which react with the Grignard reagent and hence interfere with its formation. The ether supplied for the experiment should be dried over calcium chloride and then over sodium wire in the manner described on page 361.

insert a dry stirring rod (having a flattened end) and to crush a piece of magnesium firmly against the bottom of the flask under the surface of the liquid, giving a twisting motion to the rod. When this is done properly the liquid suddenly becomes slightly cloudy and ebullition commences at the surface of the turning which has been compressed. Attach the condenser at once, swirl the flask to provide fresh surfaces for contact and allow the reaction to proceed in the cold. (If difficulty is experienced in initiating the reaction, try in succession the expedients mentioned below.[1]) Replace the drying tube at the top of the condenser with a dry separatory funnel supported with a cork provided with grooves to allow for the equalization of pressure. Pour into this 65 cc. of absolute ether and 12.7 cc. of bromobenzene (total of 17.7 cc. or 26.6 g. = 0.17 mole). Run in this solution by drops at such a rate that the ether boils gently from the heat of the reaction alone and without the application of external heating. This takes 25–30 minutes; then replace the separatory funnel by the drying tube and reflux the mixture gently on the steam bath for about one-half hour longer in order to complete the reaction. The magnesium disintegrates and the solution acquires either a cloudy or a brownish appearance. The reaction is complete when there are only a few small remnants of unreacted metal. The solution should be used at once; it deteriorates badly on standing over night.

The Addition Reaction. — The flask is now cooled in a pan of cold water and a solution of 10 g. (9.2 cc.) of methyl benzoate, or 11 g. (10.5 cc.) of ethyl benzoate, in 30 cc. of absolute ether is placed in the separatory funnel and run in slowly with thorough shaking, and with occasional cooling as required. After this is

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[1] (a) Warm on the steam bath with swirling. Then see if boiling continues when the flask (condenser attached) is removed from the heating bath. (b) Try further mashing of the metal with a stirring rod. (c) Add a tiny crystal of iodine as a "starter" (in this case the ethereal solution of the final reaction product should be washed with sodium bisulfite solution in order to remove the yellow color). (d) Add a few drops of a solution of phenyl magnesium bromide or of methyl magnesium iodide. (e) Start in afresh, taking greater care for the dryness of apparatus and reagents.

all added and the reaction subsides,[1] the funnel is exchanged for the calcium chloride tube and the mixture is refluxed on the steam bath for one-half hour. The contents of the flask are now poured onto a mixture of 100 cc. of 10 per cent sulfuric acid and about 50 g. of ice contained in a large beaker. The mixture is well stirred so that the addition compound will be completely hydrolyzed and the triphenylcarbinol will all dissolve in the ether. For this purpose a further quantity of ordinary ether will be required. Use both dilute sulfuric acid and ether to rinse the flask.

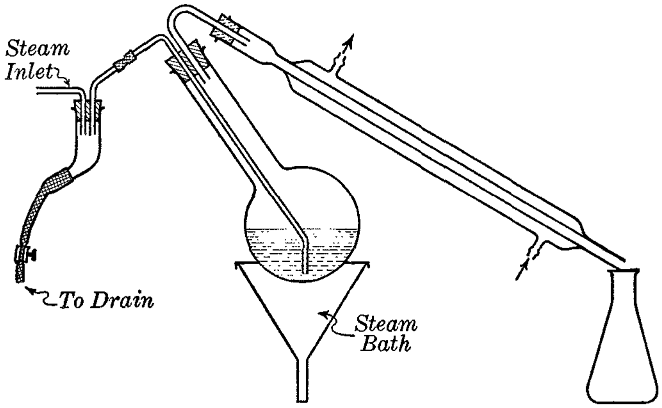

FIG. 12. — Apparatus for Steam Distillation

The solution is poured into a separatory funnel (rinse with ether) and the layers separated. To remove magnesium salts completely, the ethereal solution is washed with 10 per cent sulfuric acid and then with water. The ethereal solution is now poured into a 2-l. round-bottomed flask (rinse) and the bulk of the ether is distilled from a steam bath, taking the usual precautions. The flask is now charged with 100 cc. of water and arranged for steam distillation in the manner illustrated in Fig. 12. An ordinary short-neck flask is adequate, if somewhat less efficient than that shown. When this is arranged at a consider-

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[1] The preparation should be carried at least to this point in one day; the flask may then be left stoppered with a calcium chloride tube.

able angle from the vertical, as shown, little liquid is carried over mechanically even by a very rapid flow of steam. The steam trap is required for the reason that the steam from the supply line is ordinarily so wet that the flask would fill up too rapidly with water if this were not removed. By proper adjustment of the pinch clamp the excess water can be run off to the drain without loss of steam. Since some steam necessarily condenses to maintain the temperature within the flask, it is advisable to heat the flask on the steam bath, or with a small flame, during the distillation.

The steam distillation should be conducted just as rapidly as possible; the only limit being that the liquid must not be carried over mechanically into the distillate. The process is discontinued as soon as there is no appreciable amount of water-insoluble material in the distillate. With the removal of the remaining traces of ether and of the impurities, the triphenylcarbinol separates as a solid. At the end of the process the mixture is cooled and the solid is collected by suction filtration, partially dried by pressing it between filter papers, and crystallized from alcohol (see Experiment 5). The pure material melts at 162° and is colorless.[1] The yield should be about 10 g. Use a wide-mouth ("salt mouth") bottle of suitable size for storing the sample; a bottle with a narrow neck must never be used for a solid sample.

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[1] A small amount of a low melting ether of triphenylcarbinol sometimes is obtained from the mother liquors.

EXPERIMENT 13

BENZOIC ACID AND *n*-VALERIC ACID

(Carbonation of the Grignard Reagent)

The conversion of a halogen compound into a carboxylic acid through the interaction of a Grignard reagent with carbon dioxide is a useful application of the general reaction discovered by Grignard:

$$RMgX + CO_2 \longrightarrow RCOOMgX$$
$$RCOOMgX + H_2O \longrightarrow RCOOH + Mg(OH)X$$

The reaction may be carried out by bubbling dry carbon dioxide into a solution of the alkyl magnesium halide, but this requires a rather elaborate apparatus and it is a little troublesome because of the stoppage of the gas entrance by the MgX-salt. Now that solid carbon dioxide or dry ice has become generally available the method of carbonation can be greatly simplified: the solution of the Grignard reagent is merely poured onto a large excess of dry ice. When the unused dry ice has evaporated, ordinary ice and a mineral acid are added to liberate the carboxylic acid and dissolve basic magnesium salts and the mixture is ready to be worked up.

Two examples are given below to illustrate the different methods used to isolate the acid according to whether it is a solid or a liquid. Whichever preparation is selected or prescribed it will be well to know the scheme used in the alternate experiment. Benzoic acid (C_6H_5COOH) is prepared by the carbonation of phenyl magnesium bromide (C_6H_5MgBr), the Grignard reagent from bromobenzene (C_6H_5Br). The acid is a solid substance soluble in ether and but sparingly soluble in cold water. In the ether-water mixture obtained at the end of the reaction it is found in the ether layer, but along with it are all of the organic impurities, in particular the by-product diphenyl (see page 67). In order to isolate the pure acid most conveniently use is made of the principle illustrated in Experiment 6: it is extracted from the ethereal solution with sodium bicarbonate solution and obtained as a precipitate on acidifying the aqueous extract. The non-acidic by-products and colored impurities are left behind in the ether layer, and very pure benzoic acid can be obtained very easily.

n-Valeric acid is obtained by starting with *n*-butyl bromide, and it is a liquid substance somewhat soluble in water but more soluble in organic solvents. It obviously cannot be precipitated and collected as before and hence it is purified by distillation. The acid, however, retains water tenaciously and if one follows the usual procedure of drying the ethereal solution, evaporating the ether and distilling the product, the result is unsatisfactory. Use is made of another method of drying,[1] namely by distillation with a third solvent immiscible with water, usually benzene. When a mixture of *n*-valeric acid, water, and benzene is distilled a mixture of benzene and water passes over first, then, after all of the water is removed, benzene distils at 80°, followed by the *n*-valeric acid at 186°. This method of drying is very effective and it is used in the procedure given below. The removal of water at a temperature well below the normal boiling point is the result of the principle of steam distillation, as explained more fully on page 153.

Procedure A: Benzoic Acid. — Prepare a solution of phenyl magnesium bromide from 3.9 g. of magnesium according to the directions given on page 68. In a dry 600-cc. beaker place 40 g. (rough weight) of dry ice, keeping it as free from moisture as possible.[2] The material need not be crushed but it should be in the form of 10–15 lumps. Pour the solution of the Grignard reagent slowly onto the solid carbon dioxide while stirring, and

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[1] Adams and Johnson, "Laboratory Experiments in Organic Chemistry," p. 319 (1940).

[2] Handle dry ice with a dry towel or with gloves; if held for long in the bare hand it may cause frost bite. In case of such an injury use the same treatment as for a burn.

retain any unreacted magnesium in the flask. There is at first a vigorous boiling and the Grignard addition compound then sets to a stiff glass. Stir and break up the lumps until the dry ice has all evaporated. Add 100 g. of ice, followed by 50 cc. of water and 15 cc. of concentrated hydrochloric acid, and stir the mixture until most of the solid has dissolved and there is a separation into two layers. Pour the mixture into a separatory funnel, using 50 cc. of ordinary ether to wash in the material adhering to the beaker. Draw off and discard the aqueous layer and wash the ethereal layer with about 50 cc. of water and 5 cc. of concentrated hydrochloric acid. Then shake the ether solution with 100 cc. of 10 per cent sodium bicarbonate solution, being careful to release the pressure developed from liberation of carbon dioxide by inverting the funnel and turning the stopcock. Continue shaking as long as there appears to be a reaction and then separate and save the aqueous bicarbonate layer. Extract again with a 50-cc. portion of bicarbonate solution and this time acidify a few drops of the extract to see if there is an appreciable precipitate of benzoic acid. If so extract further until a test is negative. Stir the combined aqueous extracts with 0.5 g. of animal charcoal, filter by suction, place the filtrate in a large beaker and acidify with concentrated hydrochloric acid. Cool well in ice and collect the precipitate of benzoic acid on the Büchner funnel. Crystallize the crude material, which should be colorless and very nearly pure, from water and record the yield and melting point. Store the product in a wide-mouth bottle.

Pure benzoic acid melts at 121.5°. The yield ordinarily is about 10 g., but the quantity will vary with the condition of the dry ice and with the humidity. Some moisture from the air invariably condenses in the open beaker and this of course decreases the yield by converting the phenyl magnesium bromide into benzene.

Procedure B: *n*-Valeric Acid. — For the preparation of the Grignard reagent follow essentially the procedure given on page 68, but use 5.8 g. of magnesium (in a 200-cc. flask), a total of

27.2 cc. (34.8 g.) of pure *n*-butyl bromide and a total of 85 cc. of ether. After drying the flask containing the magnesium pour in 5 cc. of the *n*-butyl bromide and 10 cc. of ether and start the reaction by pressing the metal against the bottom with a stirring rod. Once the reaction has commenced, run in a mixture of the remaining 22.2 cc. of the halide and 75 cc. of ether in the course of about 30 minutes and while warming the reaction flask very gently on the steam bath. After refluxing for about one hour longer the reaction should be practically complete. Disconnect the flask and slowly decant the solution from any unchanged magnesium onto 60 g. (rough weight) of dry ice contained in a dry 600-cc. beaker (see the footnote on page 73). The vigorous boiling soon subsides and there is formed a stiff glass of the MgBr-salt. When the dry ice has evaporated add 150 g. of ordinary ice and 30 cc. of concentrated hydrochloric acid. Stir until there is a clean separation into two layers and pour the mixture into a separatory funnel, using 25 cc. of benzene to rinse the beaker. Shake well, separate and save both layers. Extract the aqueous layer with 50 cc. of benzene, combine the extract with the benzene-ether solution already collected and give the solution a preliminary (superficial) drying by allowing it to stand over 5 g. of anhydrous magnesium sulfate for 15 minutes.

Filter the solution into a distilling flask (250 cc.) and distil the ether, water, and benzene, stopping the distillation when the boiling point rises sharply and reaches a temperature of 140°. The residue in the flask is then nearly pure *n*-valeric acid. Pour it into a distilling flask of suitable size (50 cc.), connect this to an air condenser, and distil the product into a weighed bottle. The bulk of this should boil in the range 181–185°. Pure *n*-valeric acid boils at 186° (corr.); the uncorrected boiling point is about 5° lower. The yield ordinarily is 10–11 g. (see the remarks at the end of Procedure A). Test the solubility of the substance in water and in sodium bicarbonate solution and compare it in physical properties with acetic acid.

EXPERIMENT 14

ACETYL CHLORIDE

This particular acid chloride is always prepared by the action of phosphorus trichloride on acetic acid, since acetyl chloride (b.p. 51°) is easily separated by distillation from the non-volatile phosphorous acid formed (decomposing at about 200°). Phosphorus pentachloride reacts equally well, but in this case the second reaction product, phosphorus oxychloride (b.p. 107°), distils at a temperature close enough to the boiling point of the desired product so that the separation is not easily accomplished. A similar objection may be raised to the use here of thionyl chloride; an excess of the reagent must be employed, and since it boils at 77° it cannot be removed effectively from the reaction product.

The theoretical equation for the reaction involved is as follows:

$$3CH_3COOH + PCl_3 \longrightarrow 3CH_3COCl + H_3PO_3$$

On carrying out the experiment, however, it will be observed that some hydrogen chloride is evolved and that in the distillation of the product there is a low-boiling fore-run. The more volatile by-products are probably acetates containing phosphorus formed by the splitting out of hydrogen chloride between a molecule of phosphorus trichloride and one or more molecules of acetic acid.

In carrying out the preparation be sure that all flasks used are thoroughly dry and that the cork stoppers are carefully selected and well cut. Be very careful to avoid spilling either acetyl chloride or phosphorus trichloride; they both produce troublesome burns on the skin.

Procedure. — The reaction vessel is a 250-cc. distilling flask supported in a pan of cold water and fitted at the top with a dropping funnel. The side tube is connected to a long condenser carrying an adapter which, in turn, is fitted by means of a cork into the opening of a suction flask, which serves as the receiver. This is surrounded with a container into which ice can be placed when desired, and it is protected against the entrance of moisture from the air by attaching a calcium chloride tube to the side tube with a short section of rubber tubing. Some hydrogen chloride is formed through secondary reactions and this must be caught in a trap connected to the open end of the calcium chloride tube. Insert in the latter a cork carrying a short glass tube and connect this with rubber tubing to a trap of the type shown in Fig. 9 (or to one constructed from an Erlenmeyer flask with a two-hole stopper carrying a glass tube in one of the holes).

Pour 50 g. (48 cc.) of glacial acetic acid into the distilling flask and 40 g. (25 cc.) of phosphorus trichloride into the dropping funnel.[1] Slowly run the contents of the funnel into the flask, while the latter is cooled by immersion in the water bath. Allow the mixture to stand for about one-half hour, then heat the water bath at 40–50° for one hour to complete the reaction, a condition which will be indicated by the separation of the initially homogeneous liquid into two layers. Now heat the water in the bath to boiling so that the upper layer of acetyl chloride distils completely (cool receiver with ice). The product must be distilled from the reaction mixture in the first day.

Redistil the crude product from a clean flask, using the same arrangement of apparatus as before, with the exception that the dropping tube is replaced by a thermometer, and collect the portion boiling at 49–55°. The yield is 35–40 g. The sample should be stored in a glass-stoppered bottle, for it attacks both cork and rubber.

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[1] In case the glass stopper of the phosphorus trichloride bottle is frozen, wrap the bottle in a towel, rest the lip on the edge of the bench and tap the stopper with an oblique, upward blow from a block of wood. If this fails to loosen the stopper place the bottle in a beaker (to catch the liquid in case the bottle breaks), make a file scratch around the neck of the bottle, wrap the shoulder of the bottle with a towel and knock off the top at the file mark with a sharp blow.

REACTIONS

1. Hydrolysis. — Cautiously add a few drops of acetyl chloride to a few cubic centimeters of ice-cold water and then shake the test tube. Note that the acid chloride does not dissolve in the water, but reacts with it to give soluble products.

2. Esters. — Place about 1 cc. of ethyl alcohol in a test tube and add an equal volume of acetyl chloride by drops, while keeping the solution cold by holding the tube under the tap. Dilute the mixture with an equal volume of water, cool it again, and if a layer of fragrant ethyl acetate fails to separate add a few spatulafuls of sodium chloride to salt out the ester.

Repeat the test with one of the following alcohols, noting the characteristic odor: *iso*-butyl alcohol, *n*-amyl alcohol, *iso*-amyl alcohol, *n*-octyl alcohol.

EXPERIMENT 15

ALDEHYDES

1. Acetaldehyde

Of the two methods given below for the preparation of acetaldehyde, the first one represents a general procedure which may be used for a variety of different aldehydes. It consists in the oxidation of a primary alcohol with dichromate mixture. Since an aldehyde is itself attacked by oxidizing agents even more readily than the alcohol from which it is derived, it would be a difficult matter to obtain a satisfactory conversion were it not for the fact that the aldehydes are all much more volatile than the corresponding alcohols. By dropping the alcohol onto the oxidizing mixture and keeping this at a temperature below the boiling point of the alcohol and above the boiling point of the aldehyde, the aldehyde can be distilled from the reaction mixture as soon as it is formed, and it is thus protected from further oxidation. The preparation is a convenient one but the yield is never high and the product usually contains the following impurities: water, alcohol, acid, and the acetal, $RCH(OR)_2$.

The second method, which consists in the depolymerization of paraldehyde, is a special rather than a general method, for only the first two members of the aldehyde series form readily available polymers from which the monomeric aldehyde is easily regenerated. The reaction, however, furnishes the most convenient means of obtaining pure acetaldehyde and it forms the standard method of producing this compound whenever it is required as a reagent in a laboratory preparation.

Acetaldehyde and its trimer, paraldehyde, form an equilibrium mixture of the following composition:

$$\underset{5\%}{3CH_3CHO,\ \text{b p. }21^\circ} \xrightleftharpoons{\text{Catalyst: }H_2SO_4} \underset{95\%}{(CH_3CHO)_3,\ \text{b.p. }124^\circ}$$

Acetaldehyde (water-soluble) is stable when perfectly pure but polymerizes very rapidly in the presence of a trace of catalyst until equilibrium is reached. To obtain pure paraldehyde (insoluble in water), one washes the equilibrium mixture with water to remove both the catalyst and the 5 per cent of monomer and distils the product, which is quite stable in the absence of the catalyst. In order to reverse the reaction a small amount of sulfuric acid is added and the mixture is heated gently. Equilibrium is established when the catalyst is added, but the volatile acetaldehyde is removed from the equilibrium as soon as it is formed, more of the trimer can depolymerize, and eventually the entire product distils as acetaldehyde.

The acetaldehyde prepared by either of the alternate methods is to be employed in making the special tests described below and a part of it should be saved for use in Experiment 16.

Procedure A: Oxidation. — Place 26 g. of sodium dichromate in a 500-cc. distilling flask connected to a long, well-cooled condenser. On the lower end of the condenser is fitted an adapter leading into a 125-cc. Erlenmeyer flask, well cooled in an ice bath. Prepare a mixture of 120 cc. of water and 40 cc. of 95 per cent alcohol and while cooling add cautiously 25 cc. of concentrated sulfuric acid. Pour the cold mixture into a separatory funnel which is fitted with a cork stopper into the top of the distilling flask. Allow the contents of the funnel to drop slowly onto the solid dichromate; the oxidation should begin spontaneously, but if there is a delay the flask may be heated very gently. Acetaldehyde distils, together with some water, alcohol, and acetal.

Procedure B: Depolymerization. — The reaction is carried out in a 200-cc. round-bottomed flask equipped with a fractionating column carrying a thermometer. A long, well-cooled condenser provided with an adapter should be used, and the 125-cc. Erlenmeyer flask which serves as the receiver should be cooled well in a slush of ice. It is well to fit a loose plug of cotton into the space between the adapter and the receiving flask.

Pour 20 cc. (20 g.) of paraldehyde into the reaction flask and add a mixture of 0.5 cc. each of concentrated sulfuric acid and water. Attach the column and warm the flask very gently over an asbestos-wire gauze with a small flame, at such a rate that the acetaldehyde distils at a temperature not higher than 35°. To avoid charring of the mixture, continue only until about half of the material has been converted into acetaldehyde. Dilute 2 cc. of this pure product to a volume of 10 cc. with water, and save this " 20 per cent solution " for use in Experiment 16. The remainder should be stored in the ice bath and used at once for the following tests; it will not keep for more than a few hours.

Special Reactions: (1) Polymerization. — Dip the end of a clean stirring rod into concentrated sulfuric acid and then into 1 cc. of pure acetaldehyde contained in a test tube. Observe the temperature change; add water and see if the product dissolves.

(2) **Metaldehyde.** — This other polymer of acetaldehyde, which appears to be a tetramer, $(CH_3CHO)_4$, is a crystalline solid melting with depolymerization at 112–116°. The formation of metaldehyde is favored by a low temperature and may occur spontaneously in the ice-cooled receiving flask, or better with a salt-ice mixture. The addition of a lump of calcium chloride to a well cooled 1–2 cc. portion in a test tube often aids in the separation of the solid. If these methods are unsuccessful, dissolve 1–2 cc. of acetaldehyde in twice its volume of absolute ether, cool in a freezing mixture, and pass in a few bubbles of dry hydrogen chloride from a generator. With good cooling, the crystals should appear in a short time.

(3) **Action of Alkali.** — Dissolve a few drops of acetaldehyde in 2 cc. of water, add a few drops of 10 per cent sodium hydroxide solution and heat. The solution should become yellow and the formation of crotonaldehyde should be made evident by the characteristic pungent odor of this compound in the boiling solution. Repeat the test, using just a drop of the aldehyde together with 2 cc. of the 10 per cent alkali. The stronger alkali promotes higher condensation to an aldehyde resin.

2. Formaldehyde

Formaldehyde is a gas which liquefies only at −21°, and it polymerizes easily in either the gaseous or liquid state. It is obviously not a reagent which can be stored as such. The commercial preparation known as "formalin," which is an aqueous solution containing 35–40 per cent of formaldehyde and some methyl alcohol, is a convenient source of this reagent for use in reactions and preparations where the presence of water and alcohol are not undesirable. Formalin is of course quite unsuited for use in a Grignard reaction; here the most convenient procedure is to generate gaseous formaldehyde by heating the solid polymer trioxymethylene, $(CH_2O)_3$. The gas is bubbled directly into the solution of the Grignard reagent. Where a small water content is not objectionable, but where formalin is found to contain an excessive amount of this diluent, it is often convenient to employ methylal, $CH_2(OCH_3)_2$ b.p. 42°. In an acidic medium, for example in a glacial acetic acid solution, this substance hydrolyzes easily as follows:

$$CH_2(OCH_3)_2 + H_2O \longrightarrow CH_2O + 2HOCH_3$$

A dilute solution of formaldehyde for test purposes can be made in a minute or two in the manner described in (2) below.

Special Reactions: (1) Hexamethylenetetramine (Urotropine). — This is a characteristic test for formaldehyde and the product, a white crystalline solid, is a useful chemical. The reaction is:

$$6CH_2O + 4NH_3 \longrightarrow C_6H_{12}N_4 + 6H_2O$$

Pour 1 cc. of formalin solution and 2 cc. of concentrated ammonium hydroxide solution onto a watch glass or evaporating dish and evaporate the mixture on the steam bath under the hood. Remember that the two reactants are both volatile.

(2) **Milk Test.** — The test depends upon a coloration which results from some still obscure reaction between ferric chloride, formaldehyde, and a product derived from the casein in the milk. It was once used to detect formaldehyde illegally added to milk

as a preservative. It is now employed sometimes either as a test for formaldehyde or for methyl alcohol (ethyl alcohol gives a negative test).

To oxidize methyl alcohol to the aldehyde, heat a spiral of copper wire in the upper part of the Bunsen flame and plunge it while red-hot into a solution of about 1 cc. of methyl alcohol in 5 cc. of water. Remove the wire, stopper the test tube loosely to prevent burning, cool, and repeat the process two or three times. The oxidation is brought about by the copper oxide formed on the wire.

Pour about 2 cc. of this solution and 5 cc. of milk into a test tube, add 3–4 drops of 10 per cent ferric chloride solution, and then incline the tube and carefully pour 5 cc. of concentrated sulfuric acid down the side of the tube in such a way that it does not mix but forms a layer at the bottom. A violet coloration should develop at the interface; if this is slow in forming the tube may be warmed in hot water to hasten the process.

EXPERIMENT 16

REACTIONS OF ALDEHYDES AND KETONES

These compounds containing the carbonyl group enter into so many different reactions and transformations that it is possible, by the proper application of those reactions which lend themselves well to testing purposes, to obtain in a short time considerable information concerning the structure of an unknown substance falling within the group, or to identify completely some of the simpler members of the series. The first step in the examination of a substance which may possibly be an aldehyde or a ketone is to find out if it actually belongs in this group. One might test the substance with concentrated sulfuric acid, for the great majority of the carbonyl compounds dissolve in this reagent. The polymerization of certain aldehydes (e.g., acetaldehyde) would of course introduce complications, but the most serious objection would be that the test is not specific, for other oxygen-containing compounds such as the alcohols, ethers, esters, and anhydrides give the same test, and this is further true of many unsaturated hydrocarbons. The test really falls down because it is specific for the oxygen atom rather than for the whole carbonyl group.

A reaction which is both specific for the $>C=O$ group and which is very generally applicable is that with phenylhydrazine. All aldehydes and nearly all ketones form phenylhydrazones, and the beauty of the test is that the reaction product is always considerably less soluble than the starting material and usually precipitates or crystallizes from the solution and thus gives an indication that a reaction has occurred. The decrease in solubility undoubtedly is connected with the fact that the molecular weight is increased by 90 units as the result of the condensation.

The next step is to distinguish between aldehydes and ketones, and in many cases this can be done by taking advantage of the fact that only the former, but not the latter compounds (one exception) are easily oxidized and hence show a characteristic reducing action. The permanganate test is not a good one, for many alcohols and unsaturated hydrocarbons likewise reduce this reagent. There are, however, two very mild oxidizing agents which are reduced by aldehydes but not by these other compounds. These reagents, (2) and (3) below, are solutions containing complex cupric ions and complex silver ions, respectively. Though these tests apply quite generally to aldehydes, and in almost all cases do not apply to ketones, there is one type of ketone which responds to the test like an aldehyde: the α-hydroxyketones easily reduce the reagents under discussion.

A further distinction can be made, however, by taking advantage of another property characteristic of the aldehydes, namely, the ease with which they are reduced. They show oxidizing properties not shared by any of the ketones, and it is on this fact that the sensitive Schiff test is based.

A ketone is often recognized simply from the observation that it is found to be a carbonyl compound but does not respond to any of the tests for aldehydes. Positive tests are available, in fact, only for the methyl ketones (e.g., $RCOCH_3$), and even then the reactions must be applied with some discrimination. These tests are listed below as numbers 5 and 6.

While the emphasis in this discussion has been placed on the diagnostic value of the various reactions, the uses of some of them in preparative work should not be overlooked in carrying out the experiments.

1. **Phenylhydrazine.** — The test is varied slightly according to the solubility of the compound to be studied.

(a) *Water-soluble compounds:* To about 3 cc. of water add 5 drops of the phenylhydrazine[1] and 5 drops of glacial acetic acid (dropping tube) and make sure that a clear solution is obtained (add more acetic acid if necessary). Now add 5 drops of the

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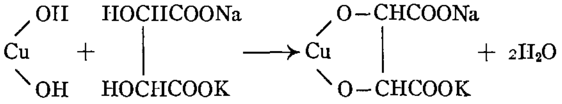
[1] Phenylhydrazine is poisonous; take particular care to avoid getting it on the skin. If spilled, wash it off with dilute acetic acid and then with soap.

substance to be tested and allow the solution to stand until a change is noted (or for one-half hour, before concluding that the test is negative). Test one of the following compounds: acetone; butyraldehyde;[1] furfural, $C_4H_3O.CHO$.[1]

If the phenylhydrazone separates as an oil it usually can be obtained as a crystalline solid by bringing the oil into solution with alcohol and then cooling and scratching. (Acetone phenylhydrazone, however, melts at 16°.)

(b) *Water-insoluble compounds:* Dissolve 5 drops of a liquid sample or a small spatulaful of a solid substance in 2–3 cc. of alcohol and then add water drop by drop until the solution just becomes cloudy. Then add a few drops of alcohol to clear the solution again. To this nearly saturated solution add 5 drops of phenylhydrazine, and if a precipitate does not appear very soon add 5 drops of glacial acetic acid to catalyze the reaction. Test any of the following compounds: benzaldehyde, C_6H_5CHO;[2] acetophenone, $C_6H_5COCH_3$; benzalacetone, $C_6H_5CH = CHCOCH_3$.

2. Fehling's Solution. — This solution is prepared from copper sulfate, sodium hydroxide, and sodium potassium tartrate, and contains a complex compound or ion which is probably produced from the interaction of the cupric hydroxide first formed with the tartrate as follows:



The copper is reduced by the aldehyde from the cupric to the cuprous condition and precipitates as cuprous oxide. The solution does not keep well and hence is prepared when required by mixing a solution of copper sulfate ("solution I") with a solution containing the alkali and the tartrate ("solution II").[3]

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[1] The solubility is not great, but still sufficient.

[2] The benzaldehyde supplied for this and later tests must be free from benzoic acid. See page 224.

[3] *Solution I:* 34.64 g. of $CuSO_4.5H_2O$ dissolved in water and diluted to 500 cc. *Solution II:* 173 g. of sodium potassium tartrate (Rochelle salt) and 65 g. of sodium hydroxide dissolved in water and diluted to a volume of 500 cc. One cubic centimeter of the mixed solutions (1 : 1) is equivalent to 0.005 g. of glucose.

Procedure. — To a mixture of 5 cc. each of solutions I and II in a test tube add 3 drops of the substance to be tested (or a correspondingly greater quantity of a solution), heat the tube in a beaker of boiling water and observe the result.

Carry out parallel tests with the following: acetaldehyde, acetone (special sample[1]), and benzoin ($C_6H_5CHOHCOC_6H_5$, m.p. 133–134°). Use an alcoholic solution of the last-named compound and allow plenty of time for reaction.

3. Silver Mirror Test. — The ammoniacal solution of silver hydroxide required for the test is not stable and is made up fresh as required. The best results are obtained when a large excess of ammonia is avoided and when the test tube used is thoroughly clean (boil it out with nitric acid, wash, let it soak for a minute or two with 10 per cent sodium hydroxide solution, and wash thoroughly).

To 3 cc. of 5 per cent silver nitrate solution add, drop by drop, a very dilute solution of ammonia (1 cc. of concentrated ammonium hydroxide solution to 10 cc. of water) until the first precipitate just dissolves. Add a single drop of a pure liquid to be tested, or 3–4 drops of a solution, quickly mix by shaking, and let the tube stand undisturbed. If the separation of silver is slow the tube may be warmed gently in a beaker of water.

Test the acetaldehyde solution previously prepared and then make parallel tests at room temperature with formaldehyde, acetaldehyde, and benzaldehyde and see if you can distinguish any differences in reactivity. Make enough of the solution to furnish about 2 cc. portions for the three tests. If any of the reactions are unduly slow, try another test solution to which a drop of 10 per cent sodium hydroxide solution is added (and more ammonia, in case there is a precipitate of silver oxide). This is Tollens' reagent.

4. Schiff Test. — The reagent is made by reducing a dilute solution of the dyestuff fuchsin with sulfur dioxide to give a

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[1] To oxidize impurities present even in good grades of acetone, the material is treated with precipitated silver oxide and a small amount of sodium hydroxide solution. See page 363.

colorless solution of the leuko (white) compound.[1] An aldehyde oxidizes the leuko compound to the colored dye and is itself reduced to an alcohol. Dilute about 1 cc. of the colorless Schiff reagent with 5 cc. of water and add one drop of the substance to be tested (or a few drops of a solution), and observe the result.

Try tests with acetaldehyde, acetone (special sample), and benzaldehyde (let the drop float on the surface and observe the under side of the drop).

5. Sodium Bisulfite. — All aldehydes and most methyl ketones react with sodium bisulfite to form colorless, crystalline "bisulfite addition products." (The reason for qualifying the statement with regard to the methyl ketones will be apparent from the experiment which follows.) The reaction is a reversible one, and in order to obtain a high yield of the addition product a large excess of sodium bisulfite is used to displace the equilibrium. This also serves to salt out the water-soluble addition product by the common ion effect. The solubility of the additive compound may be decreased further by adding alcohol. Since the reaction is highly specific, the conversion of a substance into its bisulfite addition compound often serves as a very effective method of purification. To regenerate the carbonyl compound, the solid addition product is dissolved in water, when it dissociates to a certain extent into the two components; the addition of either an acid or a base then displaces the equilibrium by converting the bisulfite into sulfur dioxide or by neutralizing the reagent.

Add slowly 5 cc. of ordinary acetone to 10 cc. of a saturated solution of sodium bisulfite contained in a small Erlenmeyer flask, shaking the mixture thoroughly and cooling it in an ice bath. When the reaction appears complete, add an equal volume of alcohol, collect the crystalline product by suction filtration and wash it with alcohol and then with ether and allow

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[1] A filtered solution of 0 1 g of pure fuchsin (*p*-rosaniline hydrochloride) in 100 cc of distilled water is mixed thoroughly with an equal volume of distilled water saturated with sulfur dioxide, and the mixture is allowed to stand for several hours before use.

it to dry. Dissolve the solid in a little water, and treat half of it with about 5 cc. of 10 per cent sodium carbonate solution and the other half with 5 cc. of 10 per cent hydrochloric acid. Note the odors carefully.

Test: To determine if a substance forms a bisulfite addition product, add 5–10 drops of the material to 1 cc. of a saturated sodium bisulfite solution, shake well and observe if there is any heating effect and if a solid product separates. If the addition product is slow in crystallizing, cool the solution in an ice bath and rub the walls with a stirring rod.

Test either benzaldehyde, furfural, or *n*-butyraldehyde, and make a comparative test with acetophenone, $C_6H_5COCH_3$, noting that the behavior of this methyl ketone is exceptional.

6. Iodoform Test. — On reaction with a solution of iodine in alkali, acetone is converted first into triiodoacetone, CH_3COCI_3, and this is then cleaved by the alkali into sodium acetate and iodoform, CHI_3. Since the latter compound is easily recognized from its highly characteristic odor and from its yellow color, the reaction serves as a convenient test for acetone, as well as for the other ketones having at least one methyl group, for these all undergo iodination and cleavage in the same way. Only one aldehyde has the $-COCH_3$ group essential for the reaction, and this substance, acetaldehyde, is the only one which gives the iodoform test.

Certain alcohols give a positive test, however, for the reason that the active reagent, sodium hypoiodite, has the properties of both an oxidizing agent and an iodinating agent and it oxidizes the alcohols to carbonyl compounds. Thus ethyl alcohol is first oxidized by the reagent to acetaldehyde which in turn yields iodoform; isopropyl alcohol gives the same result through the intermediary formation of acetone. It may be said, then, that a positive iodoform test is an indication that the substance tested is a methyl ketone, acetaldehyde, or some alcohol which yields such a compound on oxidation.

Procedure. — Add 3 drops of the substance to be tested to 3 cc. of water in a test tube, add about 0.5 cc. of a solution of iodine in potassium iodide,[1] and then add 10 per cent alkali drop by drop with shaking until the brown color of the iodine is discharged and the solution is either colorless or faintly yellow. Note the odor; see if there is a crystalline precipitate, which, of course, will be very small. In case the iodoform is not produced at once, warm the test tube for a minute or two in a beaker of water at 60° (alcohols react more slowly than do carbonyl compounds).

Test. — (a) either acetone or acetaldehyde; (b) either ethyl alcohol, isopropyl alcohol, or *sec.*-butyl alcohol; (c) acetophenone, $C_6H_5COCH_3$.

QUESTIONS

1. What conclusions can you draw from the results of your tests concerning the reactivity of compounds containing the phenyl group (C_6H_5-), as compared with the corresponding methyl or ethyl compounds? Make as many comparisons as possible.

2. How does formaldehyde compare in reactivity with the other aliphatic aldehydes?

3. What test would you select for distinguishing between an aldehyde and an α-hydroxy ketone?

4. Only one of the above tests could be used to distinguish between the compounds: $C_6H_5COCH_3$ and $C_6H_5COCH_2CH_3$ (acetophenone and propiophenone). What is the test?

5. How would you proceed to prepare pure acetone, starting with the pure, crystalline bisulfite addition product?

6. Outline the experimental procedure which you would use to separate a mixture of pentanone-2 (b.p. 102°) and pentanone-3 (b.p. 101°).

7. Suppose that it is desired to separate a mixture of an aldehyde and a ketone which does not form a bisulfite addition product, and suppose that they are both solids; how would you proceed? (Recall the procedure used in Experiment 6.)

8. How would you test a sample known to be one of the following compounds: hexanol-1, hexanol-2, or hexanone-2?

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[1] Prepared by dissolving 25 g. of iodine in a solution of 50 g. of potassium iodide in 200 cc. of water; the iodine is largely present in the form of the molecular compound, $KI.I_2$.

EXPERIMENT 17

ACETAMIDE

The conversion of an acid into its amide is an operation which is often carried out as a step in the preparation of an amine according to the method of Hofmann or in transforming an acid into its nitrile. Amides are also of use in the identification of acids, for they are usually crystalline solids of characteristic melting point even though the acids from which they are derived are liquid substances.

Amides are most commonly prepared by the action of ammonia on either the chloride or the ester of the acid in question. In the majority of cases the acid chloride method is preferable because this type of derivative reacts more rapidly with ammonia than do the esters and because an acid chloride can be obtained very rapidly in quantitative yield in a condition suitable for reaction with ammonia. (See page 220.) If the amide is not appreciably soluble in cold water, the ammonium chloride formed in the reaction is easily eliminated by extraction with this solvent. Acetamide, the simplest member of the series, is too soluble in water to permit such a separation and in this case it is best to extract the reaction mixture with alcohol, which dissolves the organic product and leaves a residue of ammonium chloride. Since acetamide is only slightly soluble in ether the reaction can be carried out by saturating absolute ether with dry ammonia gas at $-20°$ and slowly adding acetyl chloride. Reaction takes place at once and the ether is then decanted and the solid residue extracted with alcohol.[1]

When acetamide is prepared from ethyl acetate, as in the procedure given below, the isolation of the product is best accomplished by distillation. The ammonolysis of the ester is much slower than that of the acid chloride and when the reaction

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[1] Govaert, *Chemical Abstracts*, **28**, 740 (1934).

is brought about by shaking ethyl acetate with aqueous ammonia solution a part of the ester is lost by hydrolysis in the alkaline medium. It would seem that the result could be improved by the use of an alcoholic solution of ammonia, and this indeed is an advantageous modification in the preparation of many of the higher amides. In the case of acetamide, however, the ammonolysis in alcoholic solution is too slow to be practical.

For the large-scale production of acetamide the most economical method is by the thermal decomposition of ammonium acetate.[1] The method is seldom used for preparing amides of higher aliphatic acids.

Procedure. — Pour 44 g. (49 cc.) of ethyl acetate and 80 cc. of concentrated ammonia solution (sp. gr. 0.90) into a 250-cc. distilling flask, stopper the flask with loosely-fitting corks[2] and allow the mixture to stand with occasional shaking until ammonolysis of the ester is complete, as indicated by the disappearance of the ester layer. The reagents at first separate into two layers and they react quite slowly if allowed to reach the interface by diffusion alone; thorough mixing of course hastens the reaction. With only a few intermittent periods of shaking the reaction requires 1–2 days; a longer time of standing is in no way harmful.

When the mixture has become homogeneous arrange the flask for distillation, using a thermometer, a water-cooled condenser, and a suction flask for the receiver. A considerable quantity of ammonia is given off in the first part of the distillation and provision for its absorption is made by attaching to the tubulature of the suction flask a short length of rubber tubing which dips under water in a second flask. Remove this tube from the water after the first 30–40 cc. of distillate has collected. Distil rather rapidly the portion boiling up to a temperature of 170°. This contains ammonia, ethyl alcohol, and the bulk of the water and it should be discarded. For the distillation of the remaining

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[1] "Organic Syntheses," Coll. Vol. I, 3 (1932).

[2] The side tube may be closed with a small cork inserted in the end, or else the tube may be fitted into a hole bored part of the way through a larger cork.

fraction use an air condenser and a small, dry beaker as the receiving vessel and collect the material boiling up to 230°. It is well to hold the burner in the hand and to play the flame directly around the sides and bottom of the flask. As the boiling point rises the acetamide may solidify, and if there is danger of the condenser becoming plugged the material lodging here should be melted from time to time by the careful application of a free flame. Cool the distillate well in an ice bath so that the acetamide crystallizes as completely as possible. Scrape out the solid onto a Hirsch or Witt funnel, press it down well and suck it as dry as possible. To remove adhering water and acetic acid wash the material with an ice-cold mixture of 20 cc. of ether and 2 cc. of alcohol, and then with a little ether. The product should then be nearly pure. A considerable additional quantity of acetamide can be obtained by combining the filtrate and washings and any material which can be washed off the funnel and flasks with alcohol, and distilling again with a water condenser to 170° and then from 170–230° with an air condenser. The latter fraction is cooled and treated as before. The total yield of dry material melting not lower than 80° is about 19 g.

Pure acetamide melts at 82° and boils at 222°; it is odorless and not hygroscopic. The crude distillate often contains an impurity having a peculiar odor resembling mice excrement and it also contains a trace of acetic acid which renders the substance difficult to dry. The washing with alcohol-ether should remove both substances. Solvents which have been recommended for the crystallization of acetamide are: chloroform; methyl alcohol-ether (1 : 10); ethyl acetate-benzene (1 : 3).

Hydrolysis. — Boil about 0.5 g. of crude acetamide with (a) 2–3 cc. of 20 per cent sodium hydroxide solution; (b) 2–3 cc. of 10 per cent sulfuric acid. Note the odor of the vapor evolved in each case and account for the results. The hydrolysis of the $-CONH_2$ grouping can be effected also by the action of nitrous acid. To a cold, aqueous solution of acetamide add a few crystals of sodium nitrite and a few drops of dilute hydrochloric acid. Note and account for the results.

EXPERIMENT 18

SYNTHESIS OF MANDELIC ACID

This is an example of the cyanohydrine synthesis:

$$RCHO \longrightarrow RCH(OH)CN \longrightarrow RCH(OH)COOH,$$

in which R is the "phenyl" group C_6H_5, derived from the aromatic hydrocarbon benzene, C_6H_6. The aldehyde used is benzaldehyde, C_6H_5CHO, and the product to be synthesized is mandelic acid, $C_6H_5CH(OH)COOH$. This is a natural substance, obtainable from bitter almonds. The synthetic material, however, is not quite identical with the natural material because the latter is optically active.

Write the equations and study the reactions before commencing, in order that you may work intelligently and so that you will know when to take particular pains to avoid breathing traces of hydrogen cyanide which may be formed.

Caution: Potassium cyanide is extremely poisonous and in contact with an acid it liberates the poisonous gas, hydrogen cyanide. The reagent may be used with perfect safety, but it is necessary to adhere scrupulously to the following rules: Manipulate the solid with great care to avoid spilling and do not touch it with the fingers, particularly if you have an open cut on your hand. Clean up at once any trace of material which may be spilled. Wash the hands after manipulating the solid. Pour any cyanide solutions which are to be discarded directly into the drain pipe and wash down the sink with plenty of water.

Procedure. — To a solution of 16 g. of sodium bisulfite in 40 cc. of water (250-cc. beaker) add 15 g. of benzaldehyde[1] and stir the mixture well until the oily aldehyde is all converted into the

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[1] The benzaldehyde supplied should be free from appreciable quantities of benzoic acid. See page 224.

crystalline bisulfite addition product. Cool the mixture to room temperature but not below, take it to the hood and, in the course of 10 minutes, add a solution of 10 g. of potassium cyanide in 25 cc of water, while stirring vigorously. The mixture should be stirred until practically all of the solid has dissolved and the mandelic nitrile has separated as a thick oil. Disintegration of the solid is facilitated by breaking the lumps with a stirring rod. Incomplete reaction at this point leads to a final product which is contaminated with benzaldehyde.

The oily nitrile now must be separated from the aqueous liquor and treated with hydrochloric acid without delay. If the mixture is allowed to stand for an appreciable length of time at this point, the preparation may be spoiled on account of a rearrangement of the nitrile into an isonitrile. Pour the oil and water into a small separatory funnel, quickly drain the bulk of the oil into a small evaporating dish and stir into it 10 cc. of concentrated hydrochloric acid. Considerable of the oily nitrile adheres to the walls of the beaker and the separatory funnel, while some remains dissolved in the aqueous solution. All of this material may be recovered by extraction with ether; the ethereal extract is placed in a small Erlenmeyer flask connected by means of a bent tube to a condenser, and the ether is evaporated on the steam bath. The oil which remains is added to the other in the evaporating dish and the flask is rinsed into the dish with a mixture of 10 cc. of concentrated hydrochloric acid and 15 cc. of water. The mixture of acid and nitrile is now thoroughly stirred and evaporated on the steam bath under the hood until crystals begin to separate from the hot solution. It is then allowed to cool. Slightly better results are obtained if the mixture is allowed to stand over night before carrying out the evaporation.

The crystals which separate are now brought onto a small suction funnel and washed with a small quantity of water (mandelic acid is quite soluble in water: 16 g. per 100 g.) in order to remove the greater part of the inorganic material. A further quantity of mandelic acid may be obtained from the filtrate by extraction with ether. To this ethereal extract is added the solid acid (still moist) already collected, and the flask is shaken well to bring the acid all into solution. Somewhat more ether may be required, but there will be some ammonium chloride present, and this, of course, cannot dissolve. The ethereal solution is dried with sodium sulfate, filtered and evaporated as before (steam bath, condenser). The mandelic acid is usually left as an oil. Add about 100–200 cc. of benzene and heat on the steam bath until the material is dissolved and set the solution aside to crystallize. Yield, 11–12 g.

Pure mandelic acid in the inactive (*dl*) form melts at 118°; the optically active forms melt at 134°. The *dl*-acid can be resolved by crystallization of the cinchonine salt.[1] Test the solubility of your product in cold water and note the effect of adding sodium carbonate or bicarbonate to the solution.

When mandelic acid which has been crystallized from benzene is allowed to stand at room temperature in contact with the mother liquor for several days the needles gradually change into granular, sugar-like crystals of a molecular compound containing one molecule each of mandelic acid and benzene.[2] These crystals are stable only in contact with benzene and at temperatures below 32.6°; on exposure to the air the benzene of crystallization evaporates and the mandelic acid is left as a white powder.

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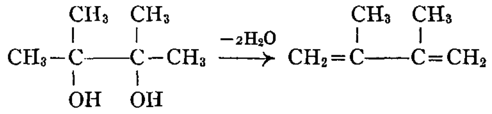
[1] Gattermann-Wieland, "Laboratory Methods of Organic Chemistry," p. 228 (1937).

[2] Zahn, *Recueil des travaux chimique des Pays-Bas*, **44**, 1048 (1925).

EXPERIMENT 19

PINACOL HYDRATE

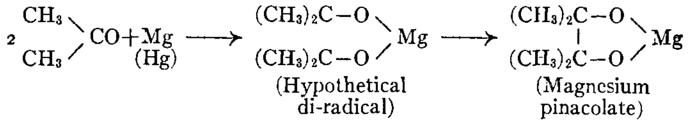
Like most other ketones, acetone is converted by metallic reducing agents largely into a dimolecular reduction product, and a high yield of the normal, monomolecular product is obtained only by catalytic hydrogenation. The " abnormal " product, pinacol, is of considerable theoretical interest both because of the manner of its formation and because of the peculiar rearrangement which it undergoes (see below). It is also of practical interest for it affords a convenient method of preparing dimethyl butadiene:



$$CH_3-\underset{OH}{\overset{CH_3}{C}}-\underset{OH}{\overset{CH_3}{C}}-CH_3 \xrightarrow{-2H_2O} CH_2=\overset{CH_3}{C}-\overset{CH_3}{C}=CH_2$$

Since the diene can be polymerized to a synthetic rubber, the preparation and the dehydration of pinacol have formed the subjects of many investigations.

Of the various reagents used for effecting the dimolecular reduction of acetone, amalgamated magnesium appears to be the best.[1] The reaction probably proceeds as follows:



Magnesium alone is insufficient, but it may be activated adequately by amalgamation with 0.1 mole of mercury. This is done very conveniently by dissolving mercuric chloride in a portion of the acetone; mercury is then liberated by the reaction: $HgCl_2 + Mg \longrightarrow Hg + MgCl_2$. The magnesium pinacolate

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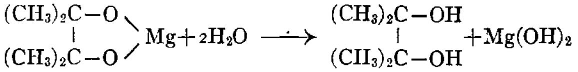
[1] "Organic Syntheses," Coll. Vol. I, 448 (1932).

separates as a voluminous precipitate, and it is converted into pinacol by the action of water:



$$\begin{array}{l} (CH_3)_2C-O \\ \quad | \\ (CH_3)_2C-O \end{array}\!\!>Mg + 2H_2O \longrightarrow \begin{array}{l} (CH_3)_2C-OH \\ \quad | \\ (CH_3)_2C-OH \end{array} + Mg(OH)_2$$

The yield is not good, but this is offset by the cheapness of the reagents.

Pinacol possesses the property, unusual for an alcohol or a glycol, of forming a crystalline hydrate. Pinacol hydrate, which contains no less than six molecules of water of crystallization, is a convenient form in which to isolate the product of the above reaction and to separate it from unreacted acetone and from the isopropyl alcohol formed.

Procedure. — In a 500-cc. round-bottomed flask equipped with an efficient reflux condenser place 8 g. of magnesium turnings[1] and 100 cc. of dry benzene.[2] The apparatus should be thoroughly dry, as in a Grignard reaction. A solution of 9 g. of mercuric chloride in 75 cc. of dry acetone[3] is placed in a small dropping funnel which is fitted into the top of the condenser by means of a grooved cork. Add about one-fourth of this solution, and if the reaction does not start in a few minutes, as indicated by a vigorous ebullition, warm the flask gently on the steam bath, being ready to plunge the flask into cold water if it becomes necessary to moderate the reaction. Once started, the reaction will proceed vigorously at this stage without further heating. Run in the remainder of the acetone solution at such a rate as to keep the reaction in progress. The boiling should be vigorous, but some cooling may be necessary in order to prevent the escape of uncondensed acetone. After 5–10 minutes the reaction slows down, and heat is then applied from the steam bath to keep the mixture boiling briskly for one hour longer. The flask should

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[1] The very fine turnings preferred for a Grignard reaction are not essential; a less expensive grade is adequate.

[2] The benzene is dried by distilling until the distillate is no longer cloudy (10–15 per cent) and rejecting the distillate.

[3] The acetone is refluxed with calcium chloride for 2 hours (or, better, allowed to stand for 2 days with the drying agent) and distilled.

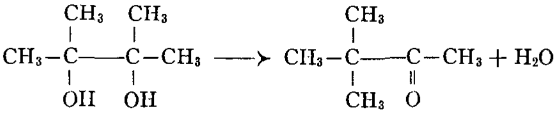
be shaken occasionally during this period and if the magnesium pinacolate forms a mass too stiff for shaking this should be broken up after the first half hour of boiling (cool slightly, disconnect the flask and use a stirring rod).

At the end of the one-hour period pour in 20 cc. of water through the condenser and boil the mixture for one-half hour with frequent shaking. This converts the pinacolate into pinacol (soluble in benzene) and a precipitate of magnesium hydroxide. Filter the hot solution by suction, return the solid magnesium hydroxide to the flask and reflux it with 50 cc. of ordinary benzene for 5–10 minutes, and filter this solution as before. Pour the combined filtrates into a beaker and evaporate the solution on a steam bath under the hood (flames extinguished!) to one-third the original volume. Then add 30 cc. of water, cool well in an ice bath with good stirring and rubbing of the walls of the beaker. The pinacol hydrate separates as an oil which soon solidifies; it should be collected only after thorough cooling and stirring to give the maximum crystallization. Scrape the crude material onto a suction funnel, wash it with a little cold benzene, press it well with a spatula, and let it drain for about 5 minutes in order to remove as much benzene as possible.

The crude material is purified by crystallization from water, in which it is very soluble. Transfer the product to a small beaker, dissolve it in 25 cc. of water by heating, and boil the solution gently for about 5 minutes in order to remove traces of benzene. If the solution is appreciably colored it should be clarified with animal charcoal. Filter the hot solution through a rather large funnel, which has been warmed on the steam bath, into a second beaker and set it aside to crystallize. Cool in ice before collecting the large crystals of pinacol hydrate. The purified product should be dried in a cool place. The yield is 18–20 g.; m.p. 46–47°. The theoretical yield should be based upon the amount of magnesium employed, for the acetone taken is in considerable excess of that theoretically required.

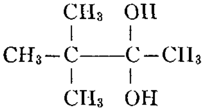
The Pinacolone Rearrangement

When heated with either mineral or organic acids pinacol undergoes a rearrangement with loss of a molecule of water to give a ketone known as pinacolone:



$$CH_3-\underset{OH}{\overset{CH_3}{C}}-\underset{OH}{\overset{CH_3}{C}}-CH_3 \longrightarrow CH_3-\underset{CH_3}{\overset{CH_3}{C}}-\underset{O}{\underset{\|}{C}}-CH_3 + H_2O$$

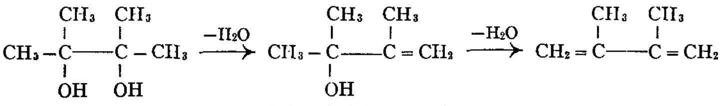
It is possible that the reaction involves the migration of a methyl group from one of the two central carbon atoms to the other, with a migration of a hydroxyl group in the reverse direction to take its place. This would give the substance:



$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-\underset{OH}{\overset{OH}{C}}-CH_3$$

which, by loss of water, would yield pinacolone. There may be still other intermediate steps, and a variety of hypotheses have been advanced to account for the reaction; it is known only that one methyl group shifts its position in the molecule. The reaction is a general one for di-tertiary alcohols of this type and it goes by the general name given in the title.

Pinacol itself, or its hydrate, gives only a poor yield of the rearrangement product (70 per cent), for there is a side reaction which it has not been possible to avoid. Like ordinary tertiary alcohols, pinacol easily undergoes *normal* dehydration, which in this case is progressive:

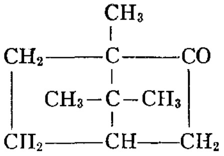


$$CH_3-\underset{OH}{\overset{CH_3}{C}}-\underset{OH}{\overset{CH_3}{C}}-CH_3 \xrightarrow{-H_2O} CH_3-\underset{OH}{\overset{CH_3}{C}}-\overset{CH_3}{C}=CH_2 \xrightarrow{-H_2O} CH_2=\overset{CH_3}{C}-\overset{CH_3}{C}=CH_2$$

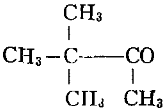
(Dimethyl-*i*-propenyl-carbinol)

The unsaturated alcohol boils at a higher temperature than does pinacolone, the diene is a lower boiling liquid. While a fairly satisfactory separation can be effected by fractionation, this is not practical when operating on a small scale. In the present experiment the pinacolone is thus not purified but it is isolated and identified in the form of the crystalline oxime. Pinacolone, or methyl *tert.*-butyl ketone, reacts only slowly with hydroxylamine or with other " carbonyl reagents," undoubtedly because of the bulky nature of one of the two groups attached to the carbonyl group. The reaction yields a pure product, however, for the reagent does not combine with either the by-products or the unchanged starting material.

Pure pinacolone, as well as its oxime, possesses a marked camphor-like odor. The similarity in structure is shown in the formulas:



Camphor



$$CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-\underset{\underset{CH_3}{|}}{CO}$$

Pinacolone

Aside from being a compound of much theoretical interest, pinacolone is a useful intermediate in the preparation of other substances. Thus trimethyl acetic acid may be prepared from this methyl ketone by the action of sodium hypochlorite.

Procedure. — Into a 200-cc. round-bottomed flask pour 80 cc. of water, followed by 20 cc. of concentrated sulfuric acid and dissolve 20 g. of pinacol hydrate in the warm solution. Attach a reflux condenser and boil the mixture for 15 minutes, observing carefully the changes which take place. Cool until the boiling ceases, connect the flask with a bent tube to a condenser set for downward distillation, and distil until no more pinacolone comes over. Separate the upper layer of crude pinacolone, dry it with calcium chloride, and record the weight. Pour the material not required for the following reaction into the bottle provided for the purpose.[1]

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[1] As a special experiment it may be of interest to fractionate some of the accumulated class preparation (see "Organic Syntheses," Coll. Vol. I, 451) and to use it for the preparation of trimethyl acetic acid (*ibid.*, 512).

Oxime. — Measure into a test tube provided with a cold finger condenser approximately 1 cc. of crude pinacolone[1] and 3 cc. each of 5 *M* hydroxylamine hydrochloride solution and 5 *M* sodium acetate solution, and add 5 cc. of alcohol in order to bring the oil completely into solution. Reflux the solution gently on the steam bath for 2 hours, when sufficient of the oxime should be formed for purposes of identification. The oxime usually separates as an oily layer and on very thorough cooling and by rubbing the walls of the tube with a stirring rod the material can be caused to solidify. Collect the product on a small Witt plate, dry a portion on a filter paper and determine the melting point. Pure pinacolone oxime melts at 77–78°. It is soluble in cold, dilute hydrochloric acid and the fine odor becomes particularly apparent on boiling the solution. The oxime evaporates rather rapidly, even at room temperature, and it should not be left exposed to the air for more than a few hours.

[1] A 2-cm. column in an 11 × 75 mm. test tube is approximately 1 cc.

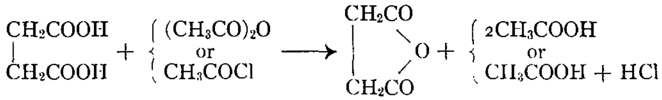
EXPERIMENT 20

SUCCINIC ANHYDRIDE

Acetic anhydride can be prepared by the interaction of sodium acetate and acetyl chloride or by the addition of acetic acid to ketene:

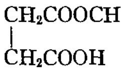
$$CH_3COONa + CH_3COCl \longrightarrow (CH_3CO)_2O + NaCl$$
$$CH_2{=}C{=}O + CH_3COOH \longrightarrow (CH_3CO)_2O$$

The acid also can be treated with a dehydrating agent, and in the case of a dibasic acid of the type of succinic acid this direct method is the only one which is applicable. The dehydration can be accomplished conveniently with the use of either acetic anhydride or acetyl chloride:



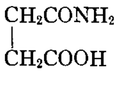
The dehydration is very rapid and when acetyl chloride is used the course of the reaction can be followed from the evolution of gaseous hydrogen chloride. A distinct advantage of the method is that the anhydride formed is not contaminated with any inorganic reagents, and that the acetic acid which is produced serves as a solvent for the crystallization of the anhydride. The procedure may be used for preparing the anhydrides of glutaric, maleic, and phthalic acid, and of many other compounds of the same type.

Succinic anhydride is a useful compound, for it affords a means of obtaining a variety of interesting compounds which cannot be prepared directly from the acid. Thus on alcoholysis succinic anhydride yields the monomethyl ester, I; the acid amide, II,



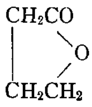
$$\begin{array}{l}CH_2COOCH_3\\|\\CH_2COOH\end{array}$$

I



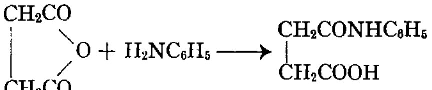
$$\begin{array}{l}CH_2CONH_2\\|\\CH_2COOH\end{array}$$

II



III

is formed on the ammonolysis of the anhydride; reduction gives butyrolactone, III, a typical γ-lactone. A convenient illustration of the reactivity of the anhydride is in the reaction with aniline:

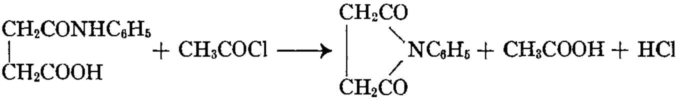


$$\left.\begin{array}{l}CH_2CO\\ |\\ CH_2CO\end{array}\right\rangle O + H_2NC_6H_5 \longrightarrow \begin{array}{l}CH_2CONHC_6H_5\\ |\\ CH_2COOH\end{array}$$

Succinanilic acid

The reaction can be used for the identification of aniline and of other similar primary amines, for the product is a nicely crystalline substance of sharp melting point.

The use of acetyl chloride as a dehydrating agent is further illustrated in the cyclization of the succinanilic acid:



$$\begin{array}{l}CH_2CONHC_6H_5\\ |\\ CH_2COOH\end{array} + CH_3COCl \longrightarrow \left.\begin{array}{l}CH_2CO\\ |\\ CH_2CO\end{array}\right\rangle NC_6H_5 + CH_3COOH + HCl$$

Succinanil

The reaction product has the 5-membered ring characteristic of pyrrole.

Procedure. — In a 100-cc. round-bottomed flask fitted with a reflux condenser closed with a calcium chloride tube place 15 g. of succinic acid and 25 cc. of acetic anhydride.[1] Heat the mixture gently on the steam bath with occasional shaking until a clear solution is obtained and then for one half hour longer to insure completion of the reaction (total time of heating about 1 hour). Remove the flask from the steam bath with the condenser and drying tube still attached and allow it to cool for a time undisturbed, observing the crystallization. Finally cool in an ice bath and collect the crystals on a dry suction funnel, using ether (several small portions) to rinse the reaction flask and wash the crystalline anhydride. The yield is 10–11 g.; m.p. 119–120°. Test the product with cold sodium bicarbonate solution for the presence of any unchanged acid.

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[1] Acetyl chloride (30 cc.) can be used equally satisfactorily; in this case the condenser is provided with an attached tube leading to a gas trap.

Succinanilic Acid. — Dissolve 1 g. of succinic anhydride in 30 cc. of benzene on the steam bath and to the boiling solution add all at once a solution of 0.9 cc. of aniline (measured from a pipette) in about 5 cc. of benzene. The separation of the reaction product occurs in a striking manner. Cool the mixture, collect the crystalline product and wash it with benzene. Determine the yield and melting point and note the action on the substance of cold sodium bicarbonate solution. Pure succinanilic acid melts at 150°.

Note that for test purposes the reaction can be carried out very rapidly and with very small amounts of material. Dissolve a few small crystals of succinic anhydride in 1 cc. of hot benzene in an 11 × 75 mm. test tube, add one small crystal of *p*-toluidine and observe the result.

Succinanil. — Convert the remainder of the succinanilic acid into the cyclization product, using the apparatus employed above. Cover the material (about 1.8 g.) with 5 cc. of acetyl chloride and heat on the steam bath until the reaction is complete (10 minutes). Allow crystallization to take place, collect the product and wash it with ether as before. Test the solubility in bicarbonate solution. The pure material melts at 154°.

QUESTIONS

1. How could succinic acid be converted into β-amino propionic acid?

2. Devise a method for the resolution of a *dl*-alcohol, assuming that an optically active derivative of aniline is available, and noting that the succinanilic acid, like other acids, can be esterified without difficulty.

EXPERIMENT 21

CHARACTERIZATION OF THE AMINES

The amines differ from other organic compounds, even from the various other types of nitrogen-containing substances, in being basic and hence capable of forming salts with acids. Because of this distinctive property it is an easy matter to recognize an amine as such and, further, to separate it from other non-basic substances. In this respect the primary, secondary, and tertiary amines behave in exactly the same manner, but there are fortunately certain other reactions in which the amines differ sharply according as they contain one, two, or three groups in place of the hydrogen atoms of ammonia, and it is thus possible, after determining that a given substance is an amine, to establish the exact class to which it belongs. The reaction with nitrous acid may be used for testing the aromatic amines but in the aliphatic series the changes accompanying the reactions are not always easily visible. A much better test, and one which applies equally well to aliphatic and aromatic amines alike, is given below.

Having classified an amine according to its characteristic type reactions it may be desirable to establish completely the identity of the compound. If it is a solid substance, it may be possible to infer its exact nature from the melting point, and to prove the identity with an authentic sample of the substance in question by a mixed melting point determination. In dealing with a liquid amine, such a complete proof is possible only when the amine can be converted into a solid derivative of characteristic melting point.

A. Testing for Basic Properties. — The amines vary widely in physical properties, for some are gases, some are liquids, and some are solid substances. Those of low molecular weight resemble ammonia both in being soluble in water and in possessing characteristic odors; those of high molecular weight are less soluble in water, less volatile, and they are odorless (a substance must be appreciably volatile in order to possess an odor). A useful rule, which applies well at least to those amines which contain no other functional group, is that the water-soluble compounds are all odoriferous, while the odorless amines are more or less sparingly soluble in cold water. The ability of a compound of the former type to dissolve in dilute acids is obviously no evidence that the substance is basic, but the disappearance of the odor on salt formation does show that a reaction has taken place and hence gives a satisfactory indication that the substance tested has basic properties. With the other type of amine the basic character is easily shown by converting the water-insoluble substance into a water-soluble salt.

In case the amine being studied is present in the form of a hydrochloride, sulfate, or other type of salt, this fact can be ascertained without difficulty. A preliminary indication may be furnished from the observation that the substance is an odorless solid soluble in water, for this combination of properties is characteristic of the amine salts. A proof of the point is given by dissolving the salt in water (hot water, if necessary) and adding alkali; the amine will be set free and it can be recognized either from the odor or by its precipitation from the solution, according to the type to which it belongs.

In order to illustrate the behavior of the various kinds of amines encountered in ordinary practice, the list given below of compounds to be tested includes several substances which may not yet have been discussed in the lectures. For the present purposes, however, the only point of importance is to note if they are primary, secondary, or tertiary amines.

Procedure. — In making solubility tests it is best to employ small test tubes (11 × 75 mm.) and to use just 3–4 drops of a liquid sample; a solid should be finely powdered with a spatula, and a small pinch of material on the rounded tip of the spatula should be sufficient. Add about 0.5 cc. of water and see if the substance dissolves; if a solid substance fails to dissolve easily, rub the material against the walls with a rounded stirring rod and break up the lumps; if it is found not soluble in cold water, see if it will dissolve on heating. Be careful to distinguish between the *melting* and the *dissolving* of a solid.

If the substance *dissolves easily in cold water*, and if the odor is suggestive of an amine, see if the odor disappears on adding to the solution 5–10 drops of 10 per cent hydrochloric acid. If, however, the properties are more like those of a salt, add 5–10 drops of 10 per cent sodium hydroxide solution and observe the result. If the amine does not separate easily, add a small quantity of sodium chloride to decrease its solubility.

If the substance is *not easily soluble even in hot water*, add 5–6 drops of 10 per cent hydrochloric acid to the mixture and see if the material now dissolves (heat the tube, if necessary). Confirmatory test: neutralize the solution with alkali and note if the amine precipitates.

If the substance *dissolves only in hot water*, add 5–6 drops of 10 per cent sodium hydroxide solution and see if an amine precipitates. (If you are in doubt as to whether the solid has dissolved partially, or not at all, add alkali to the supernatant liquid.) Confirmatory test: Add 10–15 drops of 10 per cent hydrochloric acid and 1–2 cc. of water; heat, and note if the amine will again dissolve as the hydrochloride.

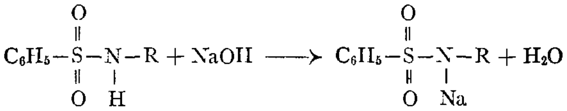
Substances to be tested:

Aniline, $C_6H_5NH_2$, b.p. 184°
p-Toluidine, $CH_3.C_6H_4NH_2$, m.p. 43°
Pyridine, C_5H_5N, b.p. 115° (a tertiary amine)
Methylamine hydrochloride (salt of CH_3NH_2, b.p. $-6.7°$)
Aniline hydrochloride (salt of $C_6H_5NH_2$, b.p. 184°)
β-Naphthylamine hydrochloride (salt of $C_{10}H_7NH_2$, m.p. 112°)

B. Hinsberg Test. — Primary and secondary amines react in the presence of alkali with benzenesulfonyl chloride, $C_6H_5SO_2Cl$, according to the following equations:

1. $C_6H_5SO_2Cl + H{-}NHR + NaOH \longrightarrow C_6H_5SO_2NHR + NaCl + H_2O$
2. $C_6H_5SO_2Cl + H{-}NR_2 + NaOH \longrightarrow C_6H_5SO_2NR_2 + NaCl + H_2O$

The "sulfonamides" formed in these reactions are solid substances and their formation is easily recognized by the separation of a precipitate. A tertiary amine has no replaceable hydrogen attached to the nitrogen atom and hence cannot react with benzenesulfonyl chloride. The two types of amines which do react can be distinguished by the fact that the products of the type indicated in reaction (1) are soluble in alkali, those of the type shown in (2) do not dissolve in this reagent. The sulfonamide from a primary amine dissolves in alkali because of the formation of a water-soluble sodium salt:



$$C_6H_5-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-\underset{\underset{\displaystyle H}{|}}{N}-R + NaOH \longrightarrow C_6H_5-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-\underset{\underset{\displaystyle Na}{|}}{N}-R + H_2O$$

The hydrogen atom is rendered acidic by the strongly unsaturated group which is joined to the nitrogen atom. The sulfonamide from a secondary amine has no such hydrogen atom to confer acidic properties on the molecule and the substance is not soluble in alkali.

Procedure. — To 5 cc. of 10 per cent sodium hydroxide solution in a test tube add 4 drops of the amine and 7 drops of benzenesulfonyl chloride. Shake for 5 minutes and note if there is any heat effect and if any solid precipitates. Warm the tube slightly and shake for a few minutes longer until the odor of benzenesulfonyl chloride is no longer apparent, and cool the mixture. If an oil separates at this point cool the tube in an ice bath, rub the oil against the walls with a stirring rod, and see if this is an oily reaction product which can be caused to solidify or just unreacted amine. Make sure by testing that the solution is still alkaline, and if there is a precipitate at this point it should be collected by suction filtration and a portion tested with dilute alkali to prove that it is actually insoluble in alkali. (An alkali-soluble product may precipitate at this point if the reagents are not taken in the proper amounts.) If there is no precipitate in the alkaline solution, it may contain an alkali-soluble sulfonamide. Acidify with concentrated hydrochloric acid and if a precipitate forms collect it by suction filtration, wash with water, and confirm the solubility in alkali.

It may be pointed out that in case the amine to be tested is supplied in the form of a hydrochloride or other salt, this can be employed directly in the Hinsberg test, for the free amine will be liberated on reaction with the alkali. Simply dissolve the test sample (a small spatulaful) in 1–2 cc. of water, add the alkali (5 cc.) and the benzenesulfonyl chloride (7 drops), and proceed as before. Be sparing of the reagents.

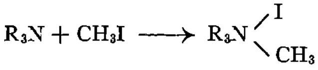
Substances to be tested:

Aniline, $C_6H_5NH_2$
Methylaniline, $C_6H_5NHCH_3$ (b.p. 195.5°)
Dimethylaniline, $C_6H_5N(CH_3)_2$ (b.p. 194°)

Note: There are complications in applying the Hinsberg test to certain amines containing hydroxyl or nitro groups.

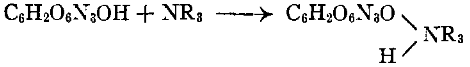
C. Solid Derivatives. — Primary and secondary amines possess hydrogen atoms easily replaceable by acyl radicals, and this is usually the simplest means of converting a liquid amine of either of these two types into a solid derivative. The amine may be acetylated by reaction with acetic anhydride, it may be benzoylated (with benzoyl chloride, C_6H_5COCl, and alkali), or it may be converted into the benzenesulfonamide by reaction with benzenesulfonyl chloride. Thus the two sulfonamides prepared in section B from aniline and from methylaniline are solid substances (m.p. 110° and m.p. 79°, respectively) and they are often used for identifying the amines in question.

Tertiary amines of course form no acylation products and the only way of obtaining solid derivatives is by reactions in which the valence of the nitrogen atom increases from three to five. One way of doing this is by converting the amine into a quaternary ammonium compound, usually the methiodide:



$$R_3N + CH_3I \longrightarrow R_3N\begin{matrix}\diagup I \\ \diagdown CH_3\end{matrix}$$

The only other method available consists in the preparation of some salt. The salts formed with the mineral acids are in some cases easily prepared, sharply melting solids; but it more frequently happens that such a salt is either too soluble in water for its easy isolation or else it is a substance which decomposes when heated, without showing a characteristic melting point. Certain organic acids are more generally useful, for their amine salts are less soluble in water, and usually more easily fusible than the salts from the inorganic acids. Perhaps the best substance for the purpose is the compound known as picric acid ($C_6H_2O_6N_3OH$, m.p. 122°), which reacts thus:



$$C_6H_2O_6N_3OH + NR_3 \longrightarrow \begin{matrix} C_6H_2O_6N_3O \searrow \\ H \nearrow \end{matrix} NR_3$$

It is often possible to identify a tertiary amine from the melting point of its picric acid salt, or picrate, where this is reported in the literature or where it is convenient to prepare a sample for comparison from an authentic source. It should be noted only that the formation of a picrate is not a property peculiar to the tertiary amines, but that it is shared by the other types of amines (and also by certain aromatic hydrocarbons). It is the character of the reaction product, not the fact of reaction, that is important.

Experiments: 1. *Acetyl derivative.* — Mix about 0.5 cc. of aniline in a test tube with about three times its volume of acetic anhydride, shake, and note any heating effect. To complete the reaction, boil the solution gently for a few minutes and then pour it into a small beaker of water (hood). Stir well, so that the excess acetic anhydride will be decomposed by reaction with water, and cool the mixture. The oil should soon solidify. This acetyl derivative is called acetanilide: $C_6H_5NHCOCH_3$, m.p. 114°; it does not form salts with mineral acids. When desired for identification purposes, the solid may be collected and crystallized from water or dilute alcohol.

Repeat the experiment using dimethylaniline and note the differences.

NOTE: To prepare an acetyl amine from an amine hydrochloride, it is only necessary to add to a mixture of the salt with acetic anhydride an amount of fused sodium acetate sufficient to react with the hydrogen chloride present in the salt.

2. *Picrate.* — Dissolve a small spatulaful of picric acid in 1 cc. of alcohol by heating, cool the solution (if the acid crystallizes, add more alcohol) and add two drops of dimethylaniline, mix by shaking and observe the result. Note that this picrate (m.p. 162°) tends to remain in supersaturated solution.

NOTES: (1) Picric acid is an effective dye for proteins; avoid spilling it or getting it on the hands. (2) Certain compounds derived from picric acid, when in the dry form, explode on percussion or on heating; wash your test sample down the sink with plenty of water. (3) The alcoholic solution must be dilute enough so that picric acid itself does not crystallize.

D. Characterization of an Unknown. — Apply to your instructor for an " unknown " sample and determine first if it is an amine or an amine salt, and then determine the class to which it belongs. The complete identification through the preparation of a solid derivative is not required.

QUESTIONS

1. How could you most easily distinguish between samples of β-naphthylamine and of acetanilide?

2. Would you expect the reaction product from benzenesulfonyl chloride and ammonia to be soluble or insoluble in alkali?

3. Is it safe to conclude that a substance is a tertiary amine because it forms a picrate?

4. Why is it usually true that amines which are insoluble in water are odorless?

5. Technical dimethyl aniline contains traces of aniline and of methyl aniline. Work out a method of freeing it completely from these impurities. (Note that acyl derivatives of amines are not basic substances.)

6. How would you prepare aniline from aniline hydrochloride?

EXPERIMENT 22

PHYSIOLOGICAL FORMATION OF HIPPURIC ACID

Hippuric acid appears to be formed in the kidney of an animal by the union of benzoic acid and glycine:

$$C_6H_5COOH + H_2NCH_2COOH \xrightarrow{\text{Enzyme}} C_6H_5CONHCH_2COOH + H_2O$$

Benzoic acid is not attacked by most chemical oxidizing agents and it likewise resists oxidation in the organism. By reaction, or "conjugation," with glycine from the blood stream it is rendered harmless and eventually excreted in the urine in the form of hippuric acid. The mechanism for the elimination of benzoic acid is of importance on account of the fact that certain foodstuffs, particularly vegetables and fruits, contain substances which are converted into this acid by degradation in the body. Benzoic acid apparently can be formed also during periods of fasting by the metabolism of those amino acids which contain aromatic rings.

Hippuric acid occurs abundantly in the urine of the horse, and of other herbivorous animals, and indeed this at one time represented the chief source of commercial benzoic acid, which is easily produced by hydrolysis of the peptide-like acid. Human urine normally contains much smaller quantities of the acid, the average output amounting to about 1 g. per day. The production is considerably increased by special diets; thus one experimenter reports the isolation of 10 g. of hippuric acid after eating 450 g. of prunes, and of 4.7 g. from 305 g. of cranberries. It is believed that quinic acid ($C_6H_{11}O_4COOH$) is the chief precursor of benzoic acid present in these fruits.

Interesting results have been obtained in special feeding experiments with benzoic acid itself, the acid being ingested in the form of a solution of the sodium salt. It requires only about twelve hours for the complete excretion of a 5 g. sample, and the increase in the hippuric acid content of the urine corresponds well with that expected. That the material excreted is actually formed from the benzoic acid taken by mouth has been clearly established by the isolation of chlorohippuric acid following the ingestion of chlorobenzoic acid. That the benzoic acid which normally combines with glycine can arise from the degradation of other benzene derivatives follows from the observed increase in the hippuric acid which results from feeding with benzaldehyde (C_6H_5CHO), toluene ($C_6H_5CH_3$), cinnamic acid ($C_6H_5CH = CHCOOH$), and other similar compounds.

The ingestion of small amounts of sodium benzoate appears to have no harmful effects, but the amount which can be tolerated is of course not indefinite. Experiments with doses as large as 50 g. per day have shown that if the benzoic acid is increased beyond a certain point it is not all conjugated but is excreted as such in the urine (sometimes causing diarrhea). It has been concluded that the body has available for conjugation a maximum of 13 g. of glycine per day (corresponding to 30 g. of sodium benzoate).

Human urine contains a considerable quantity of urea (see Experiment 23), together with various acids (hippuric, uric, phosphoric, sulfuric, and other acids) present largely in combination with basic substances (ammonia, creatinin, purine bases, sodium and potassium salts). The hippuric acid is probably present in the form of a soluble salt, and the simplest method of isolating it is to acidify the urine and to add an inorganic salt to further decrease the solubility of the organic acid. Extraction processes are more efficient but also more tedious.

Procedure.[1] — Ingest a solution of 5 g. of pure sodium benzoate in 200–300 cc. of water (or increase the hippuric acid output through special, measured diet), and collect the urine voided over the following twelve-hour period. If it is to be kept for

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[1] Plimmer, "Practical Organic and Bio-Chemistry," p. 172 (1926); Adams and Johnson, "Laboratory Experiments in Organic Chemistry," p. 343 (1940). For an alternate procedure, see Cohen, "Practical Organic Chemistry," p. 344 (1930).

more than an hour or two before use, add 5–10 cc. of toluene to prevent decomposition, and then separate this when ready to proceed further.

For every 100 cc. of urine add 4 cc. of concentrated hydrochloric acid and note if a precipitate forms. (If some acid separates at this point, collect it and combine it with any further material obtained by the following procedure.) Now add ammonium sulfate (25 g. per 100 cc. of urine) in portions, stirring well so that it will all dissolve. The hippuric acid may separate even before all of the added solid has dissolved, or it may deposit only after the solution has been well cooled and allowed to stand for several hours. Collect the precipitated material by suction filtration, wash it with a small quantity of cold water, and crystallize it from water, using a little animal charcoal to decolorize the solution. Since hippuric acid is fairly soluble in cold water, avoid an excess of solvent and cool the solution at 0° before collecting the crystals. Record the melting point and the yield of the purified product (m.p., pure, 187.5°). The average yield is 3 g.

Identification. — A sample of hippuric acid for comparison is to be prepared synthetically from benzoyl chloride (C_6H_5COCl) and glycine. These reagents combine easily in the presence of alkali, and the reaction is an example of the general type known as the Schotten-Baumann reaction. (Compare the Hinsberg test, Experiment 21.)

In a test tube, or better in a small, stoppered bottle, dissolve 1 g. of glycine in 5 cc. of water, add 1.5 cc. of benzoyl chloride, and then sufficient 10 per cent sodium hydroxide solution to render the mixture alkaline. Shake vigorously, releasing the pressure occasionally and keeping the mixture distinctly alkaline, until there is no longer any odor of benzoyl chloride (open the stopper carefully, smell with caution). When the reaction is complete, pour the alkaline solution into a flask, cool it in an ice bath, and acidify with concentrated hydrochloric acid. The precipitated hippuric acid, which contains a certain amount of benzoic acid, is collected by suction filtration and washed with water. The greater part of the benzoic acid is then washed out with ether; the solvent being poured in portions onto the crystalline cake and allowed to drain before applying the suction. Crystallize the product from water and compare it by melting point determinations with that obtained above.

EXPERIMENT 23

UREA FROM URINE

Urea is the chief nitrogenous end-product of the normal metabolism of proteid bodies in mammals. Though it is formed as a result of a long series of degradations, the immediate reaction by which urea is produced is a synthetic process. It results from the combination in the liver of carbon dioxide and ammonia, the latter compound coming from the hydrolysis of amino acids. The normal output of urea in human urine amounts to about 30 g. (in 1.5 l. of urine) per day; the elimination increases somewhat after a meat diet. In urine voided after consuming large quantities of liquids the concentration may drop from the normal value of 2 per cent to as low as 0.5 per cent.

Urea is most easily isolated from urine in the form of the nitrate, for this salt is considerably less soluble in water than urea itself, and still less soluble in a solution containing an excess of nitric acid (common ion effect). The purified salt is then treated with a suspension of barium carbonate, which neutralizes the nitric acid and liberates the urea. This organic product is then extracted from the evaporated mixture with alcohol, which leaves a residue of barium nitrate. The directions given below include an alternate procedure for the isolation of the purified nitrate, rather than urea itself. If the yield of the crude nitrate is poor it may be well, on advice from the instructor, to follow this less ambitious course.

Procedure. — The first step of the process consists in the evaporation in a porcelain dish of 500 cc. of fresh urine,[1] and this is most conveniently done on the steam bath under a hood at

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[1] Toluene may be added as a preservative if the urine is not to be evaporated until several hours after the collection of the sample. It is not necessary to separate the toluene unless the evaporation is to be conducted over a free flame.

some time preceding the actual working period, for the operation requires no attention but takes some time.[1] To make the evaporation efficient use the largest ring of the steam bath that will support the dish and insert a match stick between the dish and the ring so that the steam will rise around the sides of the dish. The process then can be completed in about 4 hours and without using an excessive amount of steam. The evaporation is to be continued until a thick syrup is obtained.

To this syrup 100 cc. of alcohol is added and the mixture is stirred well and warmed gently on the steam bath so that a good extraction is obtained. After 5–10 minutes the clear solution is decanted and the residue is treated in the same way with a second 100-cc. portion. The combined alcoholic solutions are boiled gently for a few minutes with 1 g. of animal charcoal and filtered through a large paper into a 400-cc. beaker. The alcohol is then evaporated until a thick, brown syrup remains. This can be accomplished very quickly if the beaker is so arranged that it extends through one of the rings *into* the steam bath, and if a towel is wrapped around the beaker so that this will be surrounded by steam and not just heated from the bottom. Use a piece of porous pot and be careful of flames. After removing the alcohol, the residual syrup is cooled thoroughly in a salt-ice bath and 25 cc. of pure, concentrated nitric acid is added by drops from a separatory funnel, the mixture being stirred continually and kept cold. The oil gradually changes to a paste of the solid urea nitrate. This is allowed to stand in ice for fifteen minutes and then the paste is filtered by suction, using a hardened filter paper or a sintered-glass funnel. The filter cake is washed well with ice-cold nitric acid (1 : 1) to remove the yellow mother liquor, and sucked as dry as possible. The filter flask is then cleaned and replaced and the urea nitrate is washed with an ice-cold mixture of 15 cc. of ether and 5 cc. of alcohol. This removes any free nitric acid and hastens the

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[1] In case the hood facilities are limited the evaporation can be carried out in a 2-l. flask evacuated at the water pump and kept warm in a water bath, the level of which is a little higher than that of the liquid in the flask.

drying process without causing much loss of product. The crude urea nitrate is somewhat gray, it retains some of the original odor, and the average yield is 8–11 g.

The crude product is dissolved in about 25 cc. of hot water in a 125-cc. Erlenmeyer flask and the solution is clarified by boiling gently for 5 minutes with 0.5 g. of animal charcoal, resting a funnel in the mouth of the flask so that it will become heated. After filtering the solution the flask and funnel are washed out well with hot water. The filtrate if colorless or nearly so is suitable for use in either of the following procedures. If difficulty is experienced in removing the color it is best to precipitate the material as the nitrate according to Procedure A and to dissolve the dry (weighed) solid in water and repeat the clarification, if this is necessary.

A. Isolation of Urea Nitrate. — The clarified urea nitrate solution is evaporated by boiling to a volume of approximately 20 cc., treated with 20 cc. of concentrated nitric acid, and cooled thoroughly in an ice bath. The colorless crystals of urea nitrate which separate are collected on a hardened filter paper and washed with a little cold 1 : 1 acid. The acid mother liquor is removed from the filter flask and the crystals are washed with a cold ether (15 cc.)-alcohol (5 cc.) mixture. The yield is 7–10 g.

B. Isolation of Urea. — The clarified urea nitrate solution is cooled to room temperature and treated with powdered barium carbonate, using 0.9 g. for every gram of crude urea nitrate, and adding it in small portions and with good shaking. Warm gently with continued shaking and if all of the solid carbonate goes into solution add a small additional quantity so that there is always a slight excess. All of the urea nitrate will then have been converted into free urea and barium nitrate. Add a small amount (0.1 g.) of animal charcoal, boil for a few minutes, filter and evaporate the filtrate on the steam bath, best in a small dish, until a nearly dry residue is obtained. Break up the cake and extract it thoroughly with two or three 10–15 cc. portions of hot alcohol. Evaporate the filtered extract on the steam bath until nearly all of the alcohol is removed and allow the residue to cool in an ice bath. The urea should separate in a colorless and nearly pure condition; the yield is 3-5 g. Pure urea melts at 132.6°.

EXPERIMENT 24

SUGARS

General Characteristics. — The sugars are distinguished from other classes of organic compounds by being highly soluble in water, but practically insoluble in organic solvents, and by their sweet taste. The only compounds which compare at all in water solubility with these polyhydroxy compounds are certain polycarboxylic acids and, of course, the metal salts of acids and the amine salts. The sugars, however, are practically neutral (they are very feebly acidic, but do not, like acids, affect litmus or react with soda), and they are easily distinguished from the salts by being completely combustible and by undergoing no immediate change on treatment with acids or bases. Thus while there are specific tests for carbohydrates (Molisch reaction), a sugar usually can be recognized as such from a few simple solubility and fusion tests.

Regarding physical appearance, the sugars are either colorless, crystalline solids or syrups. Common cane sugar, or sucrose, crystallizes well and can be obtained as beautiful, large crystals (rock candy), but with most sugars it is quite difficult to obtain a crystalline product, particularly in the presence of a slight trace of impurity, and even the best crystals are small and not well formed. Sugars dissolve well only in water, but they are so soluble in this medium that they tend to remain in solution. Alcohol is often added to a water solution to induce crystallization. Some sugars, even when highly purified, have resisted all efforts to obtain them in crystalline condition, and they are known only as viscous syrups.

The term " sugar " is restricted practically to those carbohydrates which contain from one to four monosaccharide units, which possess a sweet taste, and which are easily soluble in water.

The less soluble or insoluble polysaccharides are without taste, and among the sugars the sweetness in a general way decreases with increasing molecular weight. There is no quantitative relationship, and two isomers may differ widely in respect to this property, but it may be said that the sweetest sugars are to be found among the monosaccharides, and that the trisaccharides are only faintly sweet.

Experiments: Test the solubility of glucose[1] in water, in alcohol and in benzene. Compare the taste of equal, small amounts of glucose, fructose[2] and sucrose.

Reduction of Fehling's Solution. — In sugar chemistry this reagent is invaluable for the recognition of those sugars which possess a free (or latent) carbonyl group and for determining the concentration of a known sugar present in an aqueous solution. Even though a sugar such as glucose exists in solution largely in the cyclic forms, these forms are labile and pass into the aldehyde form as this is oxidized by the complex cupric salt. The oxidation does not stop with the conversion of the terminal aldehyde group to a carboxyl radical, for no less than five molecules of cupric salt are reduced by one molecule of glucose. The oxidation presumably proceeds along the carbon chain from the point of first attack, but the exact course of the reaction is not yet known. The ratio of glucose to standard Fehling's solution, if an empirical one, is nevertheless exact, and it forms the basis for quantitative determinations of various kinds. The isomeric hexoses and the reducing disaccharides likewise consume fixed quantities of Fehling's solution.

Experiment: (1) Test each of the three sugars whose formulas are listed below for reducing properties, using a mixture of 2 cc. each of Fehling's solutions I and II, and a small spatulaful of the sample (or a few drops of an aqueous solution) and heating the mixture in a test tube.

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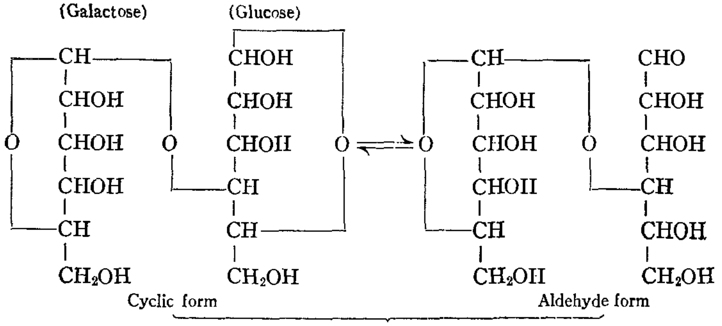
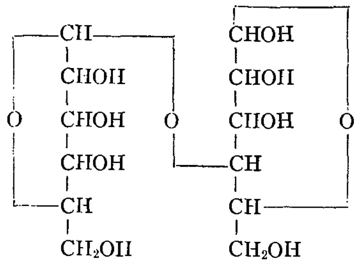
[1] The more specific designation is "*d*-glucose." The compound is also known under the names: dextrose, grape sugar.

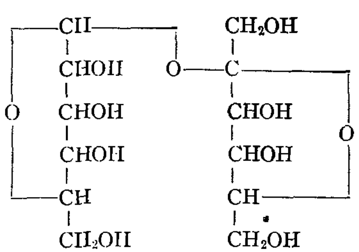
[2] Also called: *d*-fructose, laevulose, fruit sugar.



Lactose
(1-Galactosido [1,5]-4-glucose)[1]



Maltose
(1-Glucosido [1,5]-4-glucose)



Sucrose
(1-Glucosido [1,5]-2-fructoside [2,5])

(2) Pour into a 125-cc. Erlenmeyer flask 5 cc. each of Fehling's solutions I and II, measuring solution I (which contains the copper) carefully from the burette provided. Boil the mixture gently, and while it is hot, add from a burette small portions of the prepared 0.5 per cent solution of glucose.[2] The end of the

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[1] The first part of the name, "galactosido [1,5]," indicates that the half of the molecule shown on the left is a galactose unit and that it has the 1,5-oxide structure, the carbon atoms being numbered from 1 to 6 beginning with the potential carbonyl group at the top. The number in front of "galactosido" indicates that this unit is joined to the other half of the molecule by means of an oxygen bridge at the 1-carbon atom. The ending "4-glucose" indicates the nature of the sugar making up the second half of the molecule and shows that the point of attachment to this unit is at its 4-carbon atom. The position of the oxide ring in the second half of the molecule is only given when it is fixed, as it is in the case of sucrose.

[2] The solution actually contains 0.5 g. of anhydrous glucose in 100 cc. of solution. It is prepared by dissolving 5.49 g. of crystalline glucose, $C_6H_{12}O_6.H_2O$, in water and diluting the solution to a volume of 1 liter.

titration is reached when the deep blue color of the solution just disappears. This should require 10 cc. of the glucose solution. The reaction is not instantaneous and more time must be allowed between successive additions of solution than in an acid-base titration.

Osazones. — The presence or absence of a free carbonyl group in a sugar is most easily demonstrated by testing with Fehling's solution. If a positive test indicates that the substance in question is a reducing sugar, then it can be foretold that the compound will react with phenylhydrazine to form an osazone, and this latter reaction is often of considerable service in furnishing further information concerning the substance under investigation. The reaction is easily carried out and the formation of the osazone becomes apparent by the separation from an aqueous solution of a crystalline, yellow, usually sparingly soluble precipitate. A determination of the melting point or an examination under the microscope of the crystalline form may serve to identify the osazone and hence the sugar from which it was produced. It must be remembered, however, that phenylhydrazine attacks the first two carbon atoms of the sugar and that those sugars which have the same configurations below the second carbon atom yield identical osazones. This is true, for example, of glucose, fructose and mannose, all of which give rise to one and the same osazone. The melting points of the osazones are fairly well defined and characteristic, but they vary considerably with the rate of heating, and it is necessary to adopt a carefully standardized procedure in order to obtain significant results. (The heating bath should rise 1° every two seconds.)

It is often possible to make certain inferences from the osazone reaction without collecting and examining the product. The different sugars vary considerably in the rate with which they react with phenylhydrazine, and it is thus well to follow a standardized procedure and to note the time required for the separation of the crystals. The experiment below will reveal a characteristic difference in the rate of reaction of two isomers, even though they both yield the same product. It is also of significance that the disaccharides form osazones which are distinctly more soluble in water than the osazones from the monosaccharides, and which may separate from the reaction mixture only when the solution is cooled. The many hydroxyl groups of the larger molecule evidently are responsible for the greater solubility. The difference in solubility is so marked that it is often possible to distinguish a monosaccharide from a disaccharide by noting this property of the osazone.

The non-reducing disaccharides, of which sucrose is an example, form no osazones. They do, however, slowly undergo hydrolysis when heated for some time with a solution of phenylhydrazine and acetic acid, particularly if there is an excess of acetic acid, and the monosaccharides produced react to form osazones. It is not always easy to distinguish between reducing and non-reducing sugars by means of the osazone test, and consequently it is advisable to try the osazone reaction only after having tested the sugar for reducing properties with Fehling's solution.

It may be noted that the formation of an osazone is a property characteristic not only of the reducing sugars, but of all α-hydroxyketones. Benzoin, $C_6H_5CHOHCOC_6H_5$, forms an osazone melting at 225°.

Experiment: In separate, labelled test tubes place 10 cc. of 2 per cent aqueous solutions of each of the following sugars: glucose, fructose, lactose, maltose. Prepare a quantity of phenylhydrazine reagent by dissolving 2 cc. of phenylhydrazine and 2 cc. of glacial acetic acid in 5 cc. of water. Mix the solution and dilute it with a small amount of water to some volume easily divided into four equal parts. Pour one-fourth of the solution into each of the test tubes, mix the contents well, note the time, and place the four tubes in a beaker of boiling water. Continue the heating for twenty minutes, shaking the tubes from time to time to prevent the formation of a supersaturated solution, and note the times at which the different osazones separate. At the end of this period cool any of the tubes from which no osazone has yet separated and see if crystallization can be induced by cooling or by rubbing the inner walls of the tube with a stirring rod.

If a microscope is available it will be interesting to compare the crystalline forms of the osazones. A little of the crystalline paste can be transferred with a stirring rod to a microscope slide.

NOTES: (1) If a single osazone test is to be made it is convenient to use a solution of 0.2 g. of a sugar in 10 cc. of water and to add 10 drops each of phenylhydrazine and glacial acetic acid.

(2) Phenylhydrazine is a poisonous substance and should be handled with care. Avoid spilling the reagent or getting it on the skin. In case of such an accident it should be washed off with dilute acetic acid, followed by water.

(3) Phenylhydrazine deteriorates rapidly on storing with access of air, and a pure product is required for the preparation of osazones. Dark-colored material should be distilled *in vacuo.*

(4) Phenylhydrazine hydrochloride is often used in place of the free base for it is easily prepared in pure, colorless condition by dissolving the redistilled base in 10–12 volumes of alcohol and adding concentrated hydrochloric acid as long as a precipitate forms. The hydrochloride is collected and washed with alcohol and then with ether. In place of the mixture of phenylhydrazine and acetic acid specified in the above experiment, one may use a solution of 2.6 g. of the hydrochloride and 2 g. of crystalline sodium acetate in 8 cc. of water.

Silver Mirror Test. — Aldehydes and α-hydroxyketones not only reduce Fehling's solution but they also reduce the complex silver-ammonium salts. Glucose and fructose belong to the two classes mentioned and exhibit a similar reducing action, but, since the free carbonyl forms are present in solution only in small amounts, the reactions are not as rapid as with true aldehydes and ketones. The formation of a silver mirror is the more sensitive of the two reactions and it is more useful in demonstrating small differences in reactivity (but less reliable as a means of distinguishing between reducing and non-reducing sugars).

Experiment: Carry out parallel silver mirror tests with 2 per cent solutions of glucose and fructose, following the procedure given on page 87, and using ammoniacal silver nitrate solution containing a trace of alkali (Tollens' reagent). See if it is possible for you to distinguish between the aldose and the ketose by means of this test. Compare the reactivity of the aldose with simple aldehydes tested in Experiment 16.

Benzoates. — While it is often possible by some combination of the foregoing tests to gain an accurate preliminary indication of the nature of a given sugar, a final proof of identity is best obtained by the preparation of a solid derivative of characteristic melting point. The osazones are often useful, but there is always the difficulty that two or three different isomers may yield the same osazone. This is true, for example, of glucose, fructose, and mannose. The pentaacetates of these sugars, however, are all different, and they might be used for identification purposes if it were not for the fact that they do not crystallize readily. The pentabenzoates (esters of benzoic acid), on the other hand, are considerably less soluble (because of the higher molecular weight), they crystallize well, and they are easily prepared by the Schotten-Baumann method.

Experiment: In a 100-cc. flask or bottle shake vigorously a mixture of 5 cc. of a 10 per cent solution of glucose, 1 cc. of benzoyl chloride and 12 cc. of 10 per cent sodium hydroxide solution until the odor of benzoyl chloride disappears and a crystalline product separates. More alkali may be added to keep the solution alkaline.

NOTE: In carrying out an actual identification the precipitate is collected, crystallized (best from *n*-butyl alcohol), and the sample is compared by melting point and mixed melting point determinations with an authentic sample. Glucose pentabenzoate melts at 179°; fructose pentabenzoate melts at 78–79°.

Hydrolysis of Disaccharides. — That the disaccharides are not easily hydrolyzed by the action of alkali is shown by the experiment above in which sucrose was heated with Fehling's solution; any hydrolytic action of the alkali present in this solution would become evident through the reducing action of the products of hydrolysis. The experiment below will show that a mineral acid, on the other hand, is an effective hydrolytic agent for the rupture of the disaccharide linkage. The reaction is of great importance in determining the structures of the di- and trisaccharides, for it is by cleaving these substances into monosaccharides and identifying the products that the units of which a polysaccharide is composed have been determined. As a test reaction for showing that a given sugar is composed of more than one unit, the reaction may be applied in one of two ways: the sugar after being boiled with hydrochloric acid may develop reducing properties not possessed by the original material; a reducing sugar after hydrolysis will give an osazone or a mixture of osazones, different from that produced from the original material.

Experiment: Add 1 cc. of 10 per cent hydrochloric acid to about 10 cc. of a 2 per cent solution of sucrose and boil the solution for 5 minutes. Neutralize with sodium hydroxide solution and test for a reducing sugar with Fehling's solution.

QUESTIONS

1. What test do you regard as the most satisfactory one for distinguishing between glucose and fructose?

2. Outline the steps which you would take to show that maltose is a reducing sugar, that it is a disaccharide, and that it is composed solely of glucose units.

3. On hydrolyzing a solution of sucrose and then adding phenylhydrazine, there is obtained a single osazone. Would this also be true for lactose?

4. Work out a method for the quantitative determination of sucrose through the use of Fehling's solution.

5. Do your own experiments furnish any indication that glucose does not exist in solution entirely in the aldehyde form?

EXPERIMENT 25

POLYSACCHARIDES

A. Starch

Starch is a complex carbohydrate of high molecular weight having the composition $(C_6H_{10}O_5)_n$. It is known to be composed of glucose units, for this is the sole monosaccharide obtained on complete hydrolysis of the material by means of hydrochloric acid. Under the influence of certain enzymes hydrolysis proceeds just as easily as with a mineral acid but not as far. The enzyme diastase, which is present in malt, brings about hydrolysis to maltose. The saliva contains an enzyme, ptyalin, which likewise converts starch largely into maltose. This disaccharide is susceptible to hydrolysis by hydrochloric acid and hence cannot be isolated in the reaction of starch with this acid although it undoubtedly is an intermediate product. It is probable that starch is made up of a series of maltose units linked together by oxygen bridges by a process akin to a polymerization. Starch occurs in plants in the form of granules and it is not directly soluble in water. When it is boiled with water the granules swell and the material gradually passes into solution, possibly as the result of a partial depolymerization.

Even soluble starch must consist of fairly large molecules, for the solution is colloidal. This can be shown clearly by a simple dialysis experiment. If a solution containing both starch and glucose is placed in a parchment bag and this is left suspended in pure water for some hours, tests will show that glucose has diffused through the parchment and that the starch has not.

Starch is easily recognized, and at the same time distinguished from the other carbohydrates, by the characteristic blue color of some product of unknown nature which is formed by reaction with iodine. The test is very useful in following the progress of a dialysis or a hydrolysis. In the latter case an intermediate stage is reached at which a red color is produced with iodine. At this point the solution contains a certain amount of substances known as dextrins. These are probably tetra- or pentasaccharides, but their exact nature is unknown; a mixture of such products ("dextrin") is used as a mucilage.

Experiment: The hydrolysis of starch by an acid is to be compared with enzymatic hydrolysis. Prepare a colloidal solution of starch by mixing thoroughly 1 g. of starch with 10 cc. of water in a beaker until a uniform paste is obtained, and pour this with stirring into 100 cc. of boiling water.

Since the products of hydrolysis are to be recognized by their reducing properties, it will be necessary to test the starch solution in advance to make sure that no reducing sugars are present prior to the reaction. Use the Fehling test. The disappearance of the starch can be followed by the iodine test, and it will be well to try this in advance. The test consists in adding a drop of a solution of iodine in potassium iodide[1] to a few drops of starch solution (cold). Note that your starch solution can be diluted very highly before the test becomes indistinct, and also that the color fades when the solution is warmed.

Divide the starch solution into two equal parts. Cool one portion to 40° and add 5 cc. of saliva, stir it well, record the time, and test for starch at 1-minute intervals by removing a few drops of the solution and adding one drop of the iodine solution. Add 1 cc. of concentrated hydrochloric acid to the other portion and heat the solution on the steam bath, making tests for starch at 5-minute intervals. Note any changes in the appearance of the solutions and record the time of noting such changes. Record also the time required in each case for complete hydrolysis When the starch is all consumed, neutralize the solution with sodium hydroxide solution and apply the Fehling test to a small portion of the sample.

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[1] Prepared by dissolving 10 g. of iodine in a solution of 20 g. of potassium iodide in 80 cc. of water.

Compare the activity of the two hydrolytic agents used and compare the results of your salivary hydrolysis with those obtained by others in the class. How would you propose to determine if the two methods of hydrolysis give the same, or different, products?

B. Cellulose

Cellulose, like starch, has a composition corresponding to the formula $(C_6H_{10}O_5)_n$, and, like it, is composed entirely of glucose units. It differs distinctly from starch in being insoluble in water and much more resistant to hydrolysis, and from this it is inferred that the molecular size is considerably greater. The digestive enzymes are incapable of bringing about the hydrolysis of ordinary forms of cellulose; hydrolysis by mineral acids is a slow process, but yields of glucose as high as 95 per cent of the theoretical amount have been reported. By carrying out the hydrolysis in the presence of acetic anhydride, the acetate of an intermediate disaccharide has been isolated. This is known as cellobiose and it has the structure of 1-glucosido [1,5]-4-glucose. By reference to page 123 it will be seen that this is also the structure of maltose, the disaccharide obtained from starch. The disaccharides maltose and cellobiose are not identical and the difference between them appears to be of a stereochemical nature: one is derived from α-glucose and the other from β-glucose.

Unlike starch, cellulose is but little affected by being boiled with dilute hydrochloric acid. This stability is probably due both to the insolubility of the material in water and to a low degree of chemical reactivity. Even a strong solution of sulfuric acid prepared from two volumes of concentrated sulfuric acid and one volume of water produces only a superficial change. Filter paper left in such a solution (cold) for just 15 seconds and then washed with water and ammonia is changed somewhat in appearance and in strength without being appreciably hydrolyzed. This is parchment paper. To bring about complete hydrolysis, cellulose is dissolved in concentrated sulfuric acid and the sticky mass is boiled for some time with water.

It is because of the great stability to hydrolysis that cellulose is converted by the action of nitric acid into esters of the acid; this strong mineral acid hydrolyzes such substances as starch and sucrose, and it oxidizes those carbohydrates which have reducing properties.

The preparation of the cellulose nitrates represents one important method of converting the substance into a form in which it can be brought into a solution from which cellulose, or some insoluble derivative, can be reprecipitated. This, of course, is the fundamental principle used in the manufacture of artificial silk and of certain films and lacquers. The following experiments will illustrate the nitration process and two of the three other important methods of rendering cellulose soluble.

Cellulose Nitrate. — The cellulose molecule contains three hydroxyl groups per $C_6H_{10}O_5$ unit, and from one to three nitrate groups can be introduced, depending upon the concentration of the acid and the other conditions of experiment. The following procedure yields a product which, judging from the nitrogen content, consists largely of the dinitrate, and it is called pyroxylin. The directions must be followed carefully in order to avoid the formation of the more dangerous trinitrate (gun cotton).

Preparation. — Prepare a sample of cellulose nitrate by either of the following procedures:

(1) Pour 34 cc. of concentrated sulfuric acid into 5 cc. of water (measure carefully), add cautiously 15 cc. of concentrated nitric acid and cool the solution to 30°. Introduce 0.5 g. of absorbent cotton, stir the mixture, and keep it at a temperature of 30° for twenty minutes. By means of a glass rod transfer the nitrated cotton to a large beaker of water, wash it well here, and then under running water until the material is completely free of acids. Squeeze out the water and allow the cellulose nitrate, or pyroxylin, to dry in the air at room temperature.

(2) Alternate procedure. Add 10 cc. of concentrated sulfuric acid to 10 cc. of concentrated nitric acid and at once introduce to the hot solution 0.5 g. of cotton. Allow it to remain in the mixture for exactly 3 minutes and then transfer the cellulose

nitrate to a beaker of water; wash and dry the product in the manner described above.

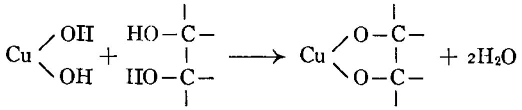
Experiments: (1) Cautiously touch a small bit of the dried pyroxylin, held in tongs, to a flame.

(2) Collodion. In a test tube cover the remainder of the dry nitrate (about 0.5 g.) with a mixture of 5 cc. of alcohol and 7 cc. of ether, shake, and allow the mixture to stand for about 10 minutes. Most of the material should dissolve, giving a viscous solution of the cellulose derivative. See if the solution will leave a skin on drying between the fingers. Pour the solution onto a watch glass and allow the solvent to evaporate. Remove the film, and allow it to dry, and carefully test the inflammability of a small piece.

Destroy any remaining cellulose nitrate or (dried) collodion by cautious burning.

Cellulose and Schweitzer's Reagent. — The "cuprammonium process" for the manufacture of artificial silk depends upon the fact that cellulose dissolves in a concentrated solution of cupric hydroxide in ammonia and precipitates when the solution is acidified. On forcing the solution under pressure through a small opening into a coagulating bath of acid the precipitate takes the form of a long fibre of silk-like appearance.

The solubility of cellulose in Schweitzer's reagent can be accounted for on the basis of certain analogies. Cupric hydroxide forms a complex compound on reaction with sodium potassium tartrate and as a result dissolves in a solution of this reagent to form Fehling's solution. It likewise dissolves in solutions of glycerol or of sucrose. Since these compounds, as well as others which might be mentioned, all contain at least two hydroxyl groups attached to adjacent carbon atoms, it is inferred that this is the essential structural feature and that the reaction probably is to be represented thus:



It is probable that cellulose, since it contains many of these glycol-like groupings, forms similar complexes on reaction with a solution of cupric hydroxide in ammonia.

Experiment: Add a 1 × 3 cm. strip of filter paper to 2–3 cc. of Schweitzer's reagent[1] and stir until most of the material dissolves; then pour the solution into dilute hydrochloric acid and note the result.

Cellulose Acetate. — While glucose is insoluble in non-hydroxylic solvents, its non-hydroxylic derivatives, such as the pentaacetate and the pentabenzoate, dissolve easily in such solvents as benzene or ether. It is thus not altogether surprising that the acetylation of the hydroxyl groups of cellulose yields a derivative which can be dissolved in certain organic solvents, particularly in the halogen derivatives of the aliphatic hydrocarbons. Cellulose acetate can be "precipitated" from such a solution in the form of a film or in the form of a thread by the evaporation of the solvent.

Experiment: To a mixture of 20 cc. of glacial acetic acid and 5 cc. of acetic anhydride contained in a small flask add 3 drops of concentrated sulfuric acid (an effective catalyst for acetylation) and then introduce 0.5 g. of absorbent cotton. Press the cotton against the walls of the flask with a stirring rod so that it stays submerged and in good condition to react, stopper the flask and allow it to stand over night, or until the cotton has all dissolved and a clear solution is obtained.

Pour the solution slowly and with stirring into a large beaker of water, stir for a few minutes longer, and collect the precipitate by suction filtration. Squeeze out as much water as possible by pressing the crude cellulose acetate between filter papers or in the folds of a towel and allow the material to dry.

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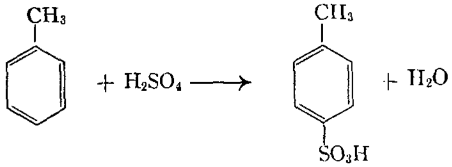
[1] Prepared as follows: dissolve 50 g. of copper sulfate crystals and 5 g. of ammonium chloride in 1 liter of water and add sodium hydroxide solution as long as any precipitate forms. Decant the clear solution, wash the cupric hydroxide several times by decantation and then collect the material on a coarse-grained paper or filter cloth and wash it free of sulfate ion with cold water. Stir the moist material with 100 cc. of concentrated ammonia solution very thoroughly until the greater part is dissolved, transfer the solution to a bottle, shake for a time and allow any undissolved particles to settle.

Cover a portion of the dried product in a test tube with a small quantity of chloroform (3 cc. per 0.1 g.) and allow the mixture to stand with occasional shaking until the solid has dissolved. Pour the solution onto a watch glass and allow it to stand until the solvent has evaporated. The film of cellulose acetate can be removed easily after allowing it to stand under water for a few minutes. The crude film is essentially the same as that now used for moving pictures in place of the more dangerous cellulose nitrate films. Test the inflammability of the material and compare it with the film prepared from collodion.

EXPERIMENT 26

SODIUM *p*-TOLUENE SULFONATE



The conditions required to effect satisfactorily a given sulfonation depend upon the reactivity of the compound in question, and the intensity of the reaction can be adjusted to meet particular needs by varying the temperature and the strength of the sulfuric acid used. The extremely reactive phenols can be sulfonated with dilute acid, naphthalene requires the use of the ordinary " concentrated " sulfuric acid (95 per cent), while benzene is still less easily attacked and hence in order to get a good yield of benzene sulfonic acid one uses fuming sulfuric acid, or " oleum," which in this case consists of a 7 per cent solution of sulfur trioxide in concentrated sulfuric acid. Fuming sulfuric acid containing as much as 30 per cent of the trioxide is sometimes required for a sulfonation; the trioxide has a great affinity for water and so promotes the water-eliminating substitution. An increase in temperature also accelerates the reaction, and an illustration is that, whereas benzene can be monosulfonated with the fuming acid indicated at 40°, in order to obtain the disulfonic acid it is necessary to carry out the reaction at 200°.

In the case of toluene another factor is involved, for three isomeric sulfonic acids can be formed and the proportion in which they are produced is highly dependent upon the temperature of the reaction. The following table gives the results of careful analyses of reaction mixtures obtained at different temperatures:

TOLUENE SULFONIC ACIDS (PER CENT FORMED)

	ortho	*meta*	*para*
0°	45.2	2.5	52.3
35°	33.3	5.3	61.4
100°	17.4	10.1	72.5

In the present experiment in order to obtain as good a yield as possible of the para derivative in a short time the sulfonation is carried out at a still higher temperature (about 170°) with concentrated sulfuric acid. Even so there undoubtedly is some ortho substitution, and perhaps an even greater amount of meta substitution. It is very probable that some disulfonic acids are also produced at the high temperature specified, and this further decreases the yield of the para acid. An excess of sulfuric acid must be avoided for this would favor disulfonation, and a little reflection will show that this is unfortunate. Sulfonation is an equilibrium reaction and the only way to push it to completion in the present case would be to use a special apparatus[1] for the removal of the water formed in the reaction. In the method described below some toluene remains unreacted.

Since the toluene and sulfuric acid are both inexpensive reagents the low yield in the reaction is not a serious handicap provided that the product desired can be separated without difficulty from the other substances in the mixture. This is indeed the case. In the form of the sodium salt, *p*-toluene sulfonic acid crystallizes very well and it can be freed easily from small amounts of isomers and from the much more soluble disulfonates by crystallization in the presence of sodium chloride which, by virtue of the common ion effect, decreases the solubility of the sulfonate. In order to convert the free sulfonic acid obtained in the sulfonation into the sodium salt, it is only necessary to partially neutralize the solution of the acid mixture

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[1] Gattermann-Wieland, "Laboratory Methods of Organic Chemistry," p. 194 (1937).

in water and to add sodium chloride. The acid not neutralized is converted into the salt by the reaction:

$$CH_3.C_6H_4.SO_3H + NaCl \rightleftharpoons CH_3.C_6H_4.SO_3Na + HCl$$

This is much more convenient than the older process in which the solution containing sulfuric acid and the sulfonic acid is first neutralized with barium carbonate. The soluble barium sulfonate is then extracted from the precipitate of barium sulfate and treated with an exactly equivalent amount of dilute sulfuric acid. Barium sulfate again precipitates and the filtered solution of the free sulfonic acid is then treated with just enough sodium hydroxide to form the sodium salt, and the solution is evaporated to obtain the solid.

Where a substitution reaction is likely to give a mixture of products it is of prime importance to be able to determine the purity of the product obtained and to establish its identity. Since the metal salts of the sulfonic acids do not melt but only decompose on being heated to a high temperature, it is necessary to convert them into derivatives characterized by good melting points. The most convenient type of derivative is described at the end of the procedure.

Procedure. — In a 200-cc. round-bottomed flask provided with a reflux condenser place 32 cc. (0.3 mole) of purified toluene[1] and 19.0 cc. of c.p. concentrated sulfuric acid, add a clay boiling chip and heat the mixture on an asbestos gauze while shaking constantly with a rotary motion. The acid should not be thrown onto the cork. When the upper layer of toluene begins to boil cut down the flame to about one inch and note the time. Continue to heat gently and to swirl the mixture very thoroughly every two or three minutes so that the two layers are well mixed and able to react. With proper heating there is little activity in the toluene layer and just a slow dropping from the condenser. When shaken there will be a mild rush of condensate. Too strong heating only drives the toluene out of the reaction

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[1] Ordinary toluene contains thiophene derivatives which cause a blackening of the reaction mixture. The hydrocarbon supplied for the experiment should be purified by the sulfuric acid treatment described on page 364.

zone and favors disulfonation. Thorough shaking will do more to hasten the reaction and favor a good yield. In one hour the toluene layer should have very nearly disappeared and there should be but little return from the condenser. It is not advisable to continue beyond this point.

The reaction mixture, while still warm, is poured into 100 cc. of water and the flask is rinsed with a little water from a wash bottle. (NOTE: If the mixture is allowed to cool before pouring into water it sets to a stiff paste of crystals of *p*-toluene sulfonic acid in the form of a monohydrate. This may be dissolved by warming and treated as above.) The acid solution is partly neutralized by adding carefully and in small portions 15 g. of sodium bicarbonate; 40 g. of sodium chloride is then added and the mixture is heated to boiling, adding a little more water, if necessary, in order to bring the salt completely into solution. Without filtering, cool the saturated solution thoroughly in an ice bath and collect on a Büchner funnel the crystalline sodium *p*-toluene sulfonate which separates. Rinse the crystals out of the beaker with filtered mother liquor, press the cake and wash it with 20 cc. of saturated sodium chloride solution. (The sulfonate is extremely soluble in the absence of sodium chloride and must on no account be washed with water.)

To recrystallize the salt, blow the filter cake out of the funnel into a beaker, wash in the crystals from the paper and funnel with a stream from the wash bottle, and dissolve the product in a total of about 100 cc. of water. Add 40 g. of sodium chloride, heat to boiling, stir and add just enough more water to bring the solid all into solution. Stir for a minute or two with 1 g. of decolorizing carbon and filter the hot solution by suction. Rinse in any material adhering to the beaker, funnel, and paper, but do this efficiently, so as to avoid introducing any more water than is necessary. In case charcoal is visible in the filtrate (or its presence suspected from previous experience with the paper used), refilter through a fresh paper. Transfer the colorless filtrate to a beaker (rinse!) and, since water has been added in the various washings, evaporate the solution by boiling to a volume at which it is saturated (about 170 cc.; pour this amount of water into a beaker of the same size for comparison). Rinse the material which has spattered on the walls, place the beaker in an ice bath and allow crystallization to take place without disturbance. (In case no crystals separate, reduce the volume still further.) Collect and wash the crystals as before.

If dried at room temperature slightly sticky crystals of a hydrate are obtained. The water of crystallization may be eliminated by drying in a dish on the steam bath, or in an oven at 120°. The yield of pure, anhydrous material is 20–25 g.

Identifying and Testing the Purity of the Sulfonate. — A sulfonate may be identified by converting it into a phenol (by alkali-fusion), into a sulfochloride (with PCl_3), or into a sulfonate ester (with $(CH_3)_2SO_4$), but these methods are all rather extravagant of both time and material and they require a dry sample of the sulfonate. A better method is to make a salt with a suitable aromatic amine as follows:

$$RSO_3Na + R'NH_2 + HCl \longrightarrow RSO_3NH_3R' + NaCl$$

While the sodium sulfonate being partly " inorganic " is infusible, the amine salt is completely organic and it has a good melting point.

Dissolve about 1 g. of the sodium sulfonate (if moist product is used, make an estimate) in the minimum quantity of boiling water, add about 0.5 g. of *p*-toluidine and 1–2 cc. of concentrated hydrochloric acid, and bring the material into solution by heating and by adding more water if required. (If there are any oily drops of the amine, more HCl should be added.) The solution is cooled at once in an ice bath and the walls of the flask are scratched until the *p*-toluidine salt crystallizes. The product is collected, washed with a very small quantity of water, and a few crystals are saved for seed. The rest is recrystallized from water, clarifying the solution if necessary, and cooling slowly. If no crystals separate the solution is inoculated with a trace of seed. The pure salt, (*p*) $CH_3.C_6H_4.SO_3NH_3.C_6H_4.CH_3$ (*p*), melts at 197°. A product melting within two or three degrees of this temperature is satisfactory.

This method of identification is very general. *p*-Toluidine salts which are sparingly soluble in water usually crystallize well from alcohol or alcohol-water mixtures.

NOTE: An alternate experiment is to isolate the free *p*-toluene sulfonic acid. To do this the reaction mixture is poured into a beaker, cooled to about 50°, and treated with an equal volume of concentrated hydrochloric acid under the hood (common hydrogen-ion effect). The acid crystallizes nicely. It should be collected on a sintered-glass funnel and washed with concentrated hydrochloric acid. It may be crystallized from a very small quantity of water, after filtering, by adding 3 volumes of concentrated hydrochloric acid. The product must be dried on a porous plate, because it attacks filter paper (compare H_2SO_4). *p*-Toluene sulfonic acid melts at 104–105°.

QUESTIONS

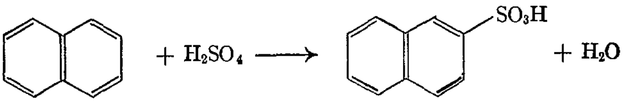
1. Explain why, when the solution saturated at the boiling point with both sodium chloride and sodium *p*-toluene sulfonate cools, it is the latter rather than the former salt which crystallizes.

2. Supposing that you were working with a rare hydrocarbon in place of toluene, how would you recover the unsulfonated material?

3. Potassium *p*-toluene sulfonate is less soluble in water than the sodium salt; how would you proceed to prepare it from your sample of sodium salt?

EXPERIMENT 27[1]

SODIUM β-NAPHTHALENE SULFONATE[2]



For this sulfonation at an elevated temperature it is convenient to use a 200-cc. three-necked round-bottomed flask. This is supported in a position convenient for heating with a free flame and a mechanically driven stirrer is fitted into the middle opening, the shaft turning in a bearing consisting of a glass tube inserted in a cork stopper of suitable size. The bearing may be lubricated with glycerol. The best form of stirrer is a glass rod bent through an angle of 45° about 2 cm. from the end. A thermometer is inserted with a cork in one of the side tubulatures in such a way that the bulb will be immersed when the flask is one-third filled. The sulfuric acid is to be run in from a dropping funnel which should be clamped in such a position that it will deliver into the third tubulature of the flask.

In the flask melt 50 g. of naphthalene, start the stirrer, and adjust the flame until a steady temperature of 160° is maintained. In the course of 3 minutes run in from the dropping funnel 45 cc. of c.p. concentrated sulfuric acid, keeping the temperature at 160° (the flame may be removed). After stirring for 3 minutes longer pour the solution into 400 cc. of water. In a well conducted operation there will be no precipitate of naphthalene, but

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[1] Special experiment; a stirring motor and a special flask are required. It is convenient for two students to work together on the sulfonation, dividing the solution of the sulfonic acid in water.

[2] Method of O. N. Witt, *Berichte der deutschen chemischen Gesellschaft*, **48**, 751 (1915).

there may be 1–2 g. of the water-insoluble di-β-naphthyl sulfone, formed thus:

$$C_{10}H_7SO_3H + C_{10}H_8 \longrightarrow C_{10}H_7SO_2C_{10}H_7 + H_2O$$

To remove it boil the solution with animal charcoal and filter by suction.

Partially neutralize the clarified solution by adding cautiously 20 g. of sodium bicarbonate in small portions. Saturate the solution at the boiling point by adding sodium chloride (30–35 g.) until crystals persist in the hot solution, and then allow crystallization to take place. Recrystallize the material, using this time only a small amount of sodium chloride. Test the purity of the product by examining a sample of the *p*-toluidine salt which, when pure, melts at 217–218°. (See page 140.) The yield is 70–75 g.

EXPERIMENT 28

NITROBENZENE

There are various methods of nitrating organic substances. The compound in question is sometimes stirred into an excess of either concentrated or fuming nitric acid; the acid itself serves as the solvent, for it usually dissolves the nitro compound if not the starting material. At the end of the reaction the mixture is poured onto ice or water to precipitate the product. Another method is to dissolve the substance in glacial acetic acid and add just the calculated quantity of concentrated nitric acid; when the reaction is over the nitro compound, if it has suitable properties, will crystallize on cooling the solution. Concentrated sulfuric acid is a still better solvent for a great many organic compounds, particularly those containing nitrogen or oxygen atoms, and it is used extensively in nitrations. Besides exerting a solvent action it serves another very useful purpose, namely, to absorb the water formed in the nitration:

$$C_6H_6 + HONO_2 \longrightarrow C_6H_5NO_2 + H_2O$$

The sulfuric acid promotes the reaction because it prevents the water formed in the course of the nitration from diluting the nitric acid and decreasing its potency. It is not necessary to use a large excess of nitric acid or to elevate the temperature in order to push the reaction to completion. " Mixed acid," that is a mixture of nitric and sulfuric acids, is employed in the procedure given below and in Experiment 32.

Nitrations usually are run at a fairly low temperature, often at 0°. Otherwise there may be a considerable destruction of the organic material as the result of the oxidizing action of nitric acid. There are ways of increasing the intensity of the reaction other than by elevating the temperature. The concentrated nitric acid may be mixed with fuming sulfuric acid containing up to 60 per cent of sulfur trioxide and a still more potent mixture is made from fuming sulfuric acid and sodium nitrate, for the water introduced with concentrated nitric acid is thus eliminated.

It is sometimes inadvisable to use any but pure, colorless concentrated nitric acid, for the nitrous acid often present in the crude, yellow acid may give rise to secondary reactions. It is easily eliminated, however, by heating the crude acid with a small quantity of urea and passing in a stream of air:

$$2HNO_2 + CO(NH_2)_2 \longrightarrow CO_2 + 2N_2 + 3H_2O$$

Procedure. — To 40 cc. of concentrated sulfuric acid contained in a 500-cc. round-bottomed flask add in portions and with shaking 35 cc. of concentrated nitric acid (sp. gr. 1.4). Cool the nitrating mixture to room temperature and add, in portions of 2–3 cc., 30 cc. (26 g.) of benzene. Shake well after each addition and keep the temperature at 50–60° throughout the reaction, cooling the flask when necessary in a pan of cold water (the reaction is exothermic). The addition of benzene takes about half an hour. To complete the reaction attach a reflux air condenser to prevent volatilization of the benzene and heat the flask in a pan of water at 60° (bath temperature) for one-half hour. Shake well during this period in order to bring the immiscible reacting layers into intimate contact. At the end of the time specified, cool the mixture under the tap, pour it into a separatory funnel, and draw off and discard the lower acid layer. To remove adhering acid shake the crude nitrobenzene thoroughly with about 100 cc. of water, separate the product (lower layer) and wash it with a second portion of water to which about 20 cc. of 10 per cent sodium hydroxide solution is added. After a final washing with water, separate the nitrobenzene carefully, pour it into a small Erlenmeyer flask, and dry it with 6–8 g. of calcium chloride. Since the liquid retains water tenaciously, it is well to warm the mixture on the steam bath with shaking, for this increases the efficiency of drying. After a time the original cloudiness due to emulsified water should disappear. Distil the dried product from a small flask on a wire gauze over a flame, using an air condenser. There may be a fore-run containing benzene and a trace of water. After this is removed, clean the condenser tube before continuing the distillation. Collect the fraction boiling at 200–207° and do not distil quite to dryness, for there may be a residue of *m*-dinitrobenzene and this may decompose explosively if the temperature rises much higher than the boiling point of the chief product.

The yield should be about 30 g. Pure nitrobenzene is a clear, straw-colored liquid boiling at 206–207° (uncor.). It is somewhat poisonous; avoid inhaling the vapor or getting the material on the skin. Like other oxygen-containing compounds, nitrobenzene is soluble in concentrated sulfuric acid (oxonium salt). That it is not found dissolved in the sulfuric acid present at the end of the above nitration is because the acid is so diluted by the water present in the nitric acid and by that formed in the course of the reaction that the oxonium salt is not stable.

NOTE: It is sometimes noted that the product turns brown during the distillation with the evolution of oxides of nitrogen. This is because the nitric acid has not been removed completely by washing and reacts further to produce *m*-dinitrobenzene. In such a case it is best to stop the distillation at once and repeat the washing and drying of the product.

EXPERIMENT 29

ANILINE

Several different methods are available for the reduction of a nitro compound to the corresponding primary amine. The use of iron filings and hydrochloric acid is preferred for the industrial production of aniline on account of the cheapness of the reagents. Much less hydrochloric acid is required than might be expected, for the chlorides of iron formed are largely hydrolyzed to hydroxides and the hydrogen chloride liberated attacks a fresh quantity of iron. Reduction with iron and a small quantity of either hydrochloric or acetic acid is also useful as a general laboratory procedure, as in the alternate experiment on page 152, but it often requires some modification according to the nature of the particular nitro compound which is to be reduced.

A more active combination, and one which furnishes a very generally useful method of reduction, is that of tin and hydrochloric acid. A further refinement consists in the use of a solution of stannous chloride in concentrated hydrochloric acid. This method is particularly useful for the reduction of small amounts of material, or where the dark, insoluble impurities present in metallic tin are objectionable. If a solid nitro compound reacts with difficulty because of a low degree of solubility, alcohol or glacial acetic acid may be added to the reagent.

The process of catalytic hydrogenation sometimes affords a clean method of reducing a nitro compound, but this requires a rather elaborate apparatus and is not easily adapted to any but quite small scale preparations. Reduction with ferrous sulfate and ammonia is likewise useful in certain special cases, but has the disadvantage of requiring a filtration from the colloidal precipitate of ferric hydroxide formed. A reagent which has the specific property of reducing one group of a polynitro compound much more readily than the remaining groups is ammonium sulfide. *m*-Dinitrobenzene, for example, is dissolved in a mixture of alcohol and ammonia, and hydrogen sulfide is introduced in gaseous form until the increase in weight corresponds to that calculated for the required partial reduction; on heating the solution, *m*-nitroaniline is produced in good yield.

The course of the reduction with either tin or stannous chloride can be followed by the disappearance of the yellow color of the nitro compound or from the fact that the reduction product, unlike the starting material, is soluble in dilute hydrochloric acid. The method of isolating the amine depends upon the nature of the amine and the conditions of concentration. Some amines separate from the strongly acidic solution as nicely crystalline hydrochlorides, and this is a very convenient form in which to collect the reduction product. It more often happens, when a crystalline product can be caused to separate by thorough cooling of the reaction mixture, that it is found to contain tin (infusible residue) and is a so-called tin double compound. These double compounds usually contain two molecules each of the amine and of hydrochloric acid and one molecule of either stannous or stannic chloride; they are probably salts of the amine and of either chlorostannous acid or chlorostannic acid, formed, for example, as follows:

$$2HCl + SnCl_2 \longrightarrow H_2SnCl_4$$
$$2RNH_2 + H_2SnCl_4 \longrightarrow (RNH_3)_2SnCl_4$$

Such a substance is most easily decomposed by the action of alkali, which liberates the amine and converts the tin into a water-soluble stannite or stannate (Na_2SnO_2 or Na_2SnO_3). In case the amine is not stable in the presence of alkali or is soluble in this reagent, it is necessary to precipitate the tin as sulfide by saturating the aqueous solution of the double compound with hydrogen sulfide, a somewhat tedious process.[1]

In the present preparation a tin double compound often sepa-

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[1] Other methods of removing the tin are: by displacement with metallic zinc (the chloride of which forms no double compounds with amines); by electrolytic deposition (see Gattermann-Wieland, "Laboratory Methods of Organic Chemistry," p. 317 (1937)).

rates partially at one stage of the process but it is so soluble that the collection of the amine in this form is not practical. Consequently the procedure calls for adding enough alkali to the reaction mixture to neutralize the excess acid as well as to decompose the double compound. Since aniline is volatile with steam, it is easily separated from the inorganic salts and from any residual tin by steam distillation. It is obvious that the insoluble impurities in the metal cannot contaminate the final product and that there is no advantage to be gained in the use of the more expensive stannous chloride in place of tin.

Procedure. — In a 1-l. round-bottomed flask (which is to be used later in the steam distillation) place a mixture of 50 g. of granulated tin and 24.6 g. (20.5 cc.) of nitrobenzene. Fit the flask with a reflux air condenser and add through the condenser in the course of about one-half hour 110 cc. of concentrated hydrochloric acid in the following manner. Pour in about one-tenth of the acid and shake the mixture for a few minutes. The mixture should soon become warm and before long the reaction should become quite vigorous. If this is not the case the flask may be warmed gently; no more acid should be added until the reaction is well under way. The reaction should be allowed to proceed briskly, but when there is danger of the boiling becoming too violent the flask is plunged for a time in a pan of cold water to moderate, without completely suppressing, the reaction. When the ebullition begins to subside of its own accord add a second portion of about 10 cc. of acid and proceed as before, keeping the reaction under control but maintained at a good rate by the action of the fresh acid. The mixture should be shaken well in order to bring the nitrobenzene layer completely into reaction. After the acid is all added the mixture is heated on the steam bath for about one-half hour to complete the reduction. The end of the reaction can be recognized from the disappearance of the odor of nitrobenzene and by diluting a few drops of the solution with water, when a perfectly clear solution should be obtained.[1]

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[1] This is a suitable point at which to interrupt the preparation.

Cool the reaction mixture and add a solution of 75 g. of sodium hydroxide in 150 cc. of water, cooling again during the addition if the boiling becomes too violent. The hydroxides of tin which are first precipitated should all dissolve and the solution should be distinctly alkaline. The flask is now arranged for steam distillation (see Fig. 12). The aniline passes over, along with water, as a nearly colorless oil. Since aniline dissolves in water to the extent of about 3 per cent, some of the product will be present in the distillate even after the latter has lost the original turbidity. It is advisable to collect 100–120 cc. of the clear distillate in addition to that containing droplets of aniline.

The distillate is to be extracted with ether, but the solubility of aniline in water is so appreciable that in order to make the process efficient the distillate is first saturated with sodium chloride to "salt out" the aniline. About 25 g. of salt is required for each 100 cc. of distillate. Use three portions of about 60 cc. each of ether in the extraction. The ethereal extract is dried with crushed sticks of sodium hydroxide, or with pellets of this material. If the solid largely dissolves in the water which it absorbs it is well to decant from the saturated alkaline solution (wash with ether) and to add fresh drying agent to the ethereal solution in a dry flask. It is best to allow several hours for the drying process.

Decant the ethereal solution into a large Erlenmeyer flask and remove the ether by distillation from a steam bath, with the usual precautions. Pour the residual aniline into a small distilling flask, add a pinch of zinc dust, and distil, using an air condenser and collecting the portion boiling at 180–185°. The yield should be close to 80 per cent of the theoretical amount.

Pure aniline is a colorless, refracting liquid boiling at 184.4° and possessing a peculiar odor characteristic also of many of its homologues. The discoloration which occurs on standing, particularly when exposed to the light, is the result of atmospheric oxidation. A sample which has become very red may be purified by adding a pinch of zinc dust and distilling the material.

Note: Calcium chloride cannot be used to dry the ethereal solution because it combines with aniline and with other amines to form molecular compounds, much as it does with hydroxy compounds. Solid sodium hydroxide is an efficient drying agent, potassium hydroxide is even better, but these alkalies react with so many types of organic compounds that their use is limited.

TEST REACTIONS

In addition to the tests already given in Experiment 21 for the recognition of primary amines, there are certain others which are sometimes useful and which apply in particular to the primary aromatic amines. The following tests may be carried out conveniently during the steam distillation. A few drops may be used from the first part of the distillate, or an equivalent amount of water saturated with aniline will suffice.

1. **Bromination.** — To 2–3 cc. of a dilute aqueous solution of aniline add bromine water drop by drop until the solution becomes faintly yellow. The precipitate is tribromoaniline, m.p. 116°, a derivative useful for the identification of the amine.

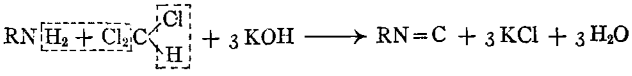
The test is of special value because of the very small amount of material required and because it can be applied to an aqueous solution and does not require the isolation of the dry amine. Most aromatic amines react in a similar fashion: all free positions ortho or para to the amino group are substituted by bromine atoms. Thus *o*-toluidine and *p*-toluidine form dibromo derivatives melting at 50° and 73°, respectively; *m*-toluidine forms a tribromo compound melting at 97°.

2. **Runge's Reaction.** — To a solution of one drop of aniline in about 40 cc. of water add a filtered solution prepared by shaking a few lumps of bleaching powder with 2–3 cc. of water. A violet color is produced.

This sensitive test is peculiar to aniline, and may be used for detecting small quantities of benzene or of nitrobenzene after these have been converted into aniline. The bleaching powder oxidizes this base to a complex dye of structure not yet known.

3. **Isonitrile Reaction.** — To 2 drops of aniline add 2 cc. of alcohol, 10 drops of concentrated potassium hydroxide solution,

and 5 drops of chloroform. Warm very gently under the hood and cautiously smell the mixture. The unpleasant odor is characteristic of phenylisonitrile. Similar isonitriles are formed from primary amines of both the aliphatic and the aromatic series. The reaction is:



$$\mathrm{RN}\boxed{\mathrm{H_2 + Cl_2}}\mathrm{C}\boxed{\begin{matrix}\mathrm{Cl}\\ \mathrm{H}\end{matrix}} + 3\,\mathrm{KOH} \longrightarrow \mathrm{RN{=}C} + 3\,\mathrm{KCl} + 3\,\mathrm{H_2O}$$

Alternate Procedure

(For use when zinc is not available)

To a 1-l. round-bottomed flask (which is to be used later in the steam distillation) add 30 g. of iron powder (reduced by hydrogen) and 40 cc. of water. Warm the liquid to 85°, add $1\frac{1}{2}$ cc. of concentrated hydrochloric acid, attach a reflux air condenser to the flask and through it add a small portion (about 4 cc.) of the total amount of nitrobenzene to be reduced, 24.6 g. (20.5 cc.). Heat the mixture on the steam bath for 2–3 minutes and then, while holding the flask with the condenser in a slanting position, shake quite vigorously; a mirror of oxide quickly appears on the walls of the flask, the mixture becomes very hot, and vapors rise in the condenser. Add the rest of the nitrobenzene in 3- to 4-cc. portions over a period of about 10 minutes, shaking the mixture as above after each addition; occasional cooling of the flask with tap water may be necessary to prevent loss by distillation. After all of the nitro compound has been added, shake the flask until an evident cooling of the mixture indicates that the exothermic reaction has ended (about 5 minutes).

Cool the reaction mixture, arrange the flask for steam distillation, and conduct the distillation and subsequent operations according to the directions beginning with line 6 on page 150. The yield of colorless aniline is 15 g.

STEAM DISTILLATION

This important operation consists in volatilizing an organic compound which is insoluble or sparingly soluble in water by passing steam into a mixture of the substance with a little water. The organic compound, if it has suitable properties, will distil with the steam and, being immiscible with the water in the condensate, it is easily separated whether it is a solid or a liquid substance. Of the compounds which do not dissolve readily in water only a limited number have the added property of being volatile with steam; hence this type of distillation is a highly selective process and wherever it is applicable it usually is found to have certain distinct advantages. It often affords an excellent means of separating an organic reaction product from an aqueous mixture containing inorganic salts, or of separating one compound from a mixture with other organic compounds which do not share the required property. Thus triphenylcarbinol (Experiment 12) is best freed from diphenyl, an unavoidable by-product, by distillation of the latter substance with steam. The isomers *o*-nitrophenol and *p*-nitrophenol are commonly obtained together and separated by steam distillation, since only the former isomer volatilizes under these conditions. A simple way to determine if a substance known to be but sparingly soluble in water is volatile with steam is to boil a mixture of a test sample and water under a cold finger (page 64). A turbidity or cloudiness in the condensate will show that the substance has volatilized.

Another distinct advantage of the process is that the temperature at which a steam distillation occurs is always lower than the boiling point of water under the same conditions, and hence in many cases far below the boiling point of the organic substance which is volatilized in this way. This remarkable fact, which is explained below, makes possible the purification by low-temperature distillation, of substances of high boiling point which are too sensitive to withstand ordinary distillation.

Theory of Steam Distillation. — Benzene, b.p. 80°, and toluene, b.p. 111°, are mutually soluble or miscible liquids and if a mixture of the two is heated distillation begins somewhat above 80° and ends at a temperature near 111°, and the composition of the distillate of course changes progressively during the process. That the boiling point of any mixture lies somewhere between the boiling points of the two pure components is easily understood, but it will be well to think of the process in terms of vapor pressures. Pure benzene has a vapor pressure of 760 mm. of mercury at 80°, the boiling point, but if it is mixed with an equimolecular quantity of toluene the vapor pressure due to the benzene alone (the "partial vapor pressure") is much less than 760 mm. at 80° because the benzene is now diluted and the molecules have only about half the chance to escape from the surface and thus exert a vapor pressure as when uncontaminated. The partial vapor pressure of the benzene in the mixture is not exactly half that of pure benzene because a benzene molecule partially surrounded by toluene has properties slightly different than when surrounded by molecules of its own kind, but the partial pressure is at least in the neighborhood of 380 mm. The toluene present also exerts a pressure against the atmosphere over the mixture and, since pure toluene at 80° has a vapor pressure of 288 mm., the partial pressure in the equimolecular mixture is probably in the order of 144 mm. The total vapor pressure of the mixture is the sum of the partial pressures, or approximately 524 mm. However inaccurate this figure may be, it is clear that the pressure is so far short of that of the atmosphere that boiling can occur only when the temperature is raised to some point above 80°, the normal boiling point of the more volatile constituent. It is inconceivable that boiling should occur at a temperature below 80°.

With an immiscible pair of liquids, however, the situation is entirely different. Toluene and water are almost completely insoluble in each other and they may be considered so for purposes of discussion. Suppose that a mixture of these liquids is heated and kept well agitated so that both substances have ample opportunity for exerting a pressure against the atmosphere of the flask. Although the droplets of the two liquids may be very small they do not even approximate molecular dimensions, and the millions of molecules in each droplet of toluene are in no way diluted because of the presence of water in the same flask, and the toluene exerts its normal vapor pressure for the temperature in question. The same is true of the water; it is not diluted because the toluene is not dissolved in it. The two liquids are thus independent of one another, but of course it is the combined pressure of the two vapors which must overcome the pressure of the atmosphere if boiling is to occur. A little reflection will show that boiling must occur at some temperature *below* the boiling point of either liquid. The lower-boiling liquid is water and it is clear that the addition of any vapor pressure to that of water at 100° would give a combined pressure which would more than suffice to overcome that of the atmosphere; the boiling point will thus be below 100°. To calculate the exact boiling point it is only necessary to find the temperature at which the vapor pressures of toluene and of water add to 1 atmosphere, and this can be done by consulting tables of experimentally determined vapor pressures. Values for the two compounds in question are given graphically in Fig. 13, and it is indicated that at a temperature of 84.6° the sum of the two vapor pressures is just 760 mm. and that this consequently is the boiling point of the mixture. The temperature is easily found by trial additions and interpolations.

It should be noted that the boiling point of the mixture is not dependent upon the relative amounts of toluene and water present so long as there is enough of both to saturate the vapor space in the flask. If toluene is distilled with a large quantity of water the mixture will boil constantly at 84.6° until all of the toluene has been expelled. Also, it is immaterial whether the liquids are heated in a closed flask or whether steam is passed into a flask containing toluene. In the latter case the steam will at first condense until a temperature balance has been established.

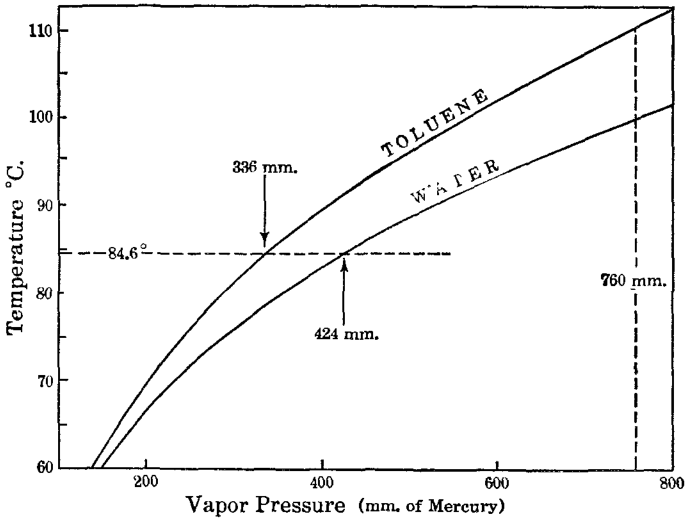


FIG. 13. — Vapor Pressure Curves

It is evident that any water-insoluble compound which has an appreciable vapor pressure in the neighborhood of 100° will distil with water at a temperature below 100°. Toluene distils with steam at a particularly low temperature because it has a high vapor pressure: 557 mm. at 100°. Nitrobenzene has the low vapor pressure of 21 mm. at 100° and steam distillation takes place at 99°. The substance to be distilled may be, on the other hand, more volatile than water. A case in point is that of ethyl iodide, which boils at 72.3°. Data with which to calculate the boiling point are as follows:

VAPOR PRESSURES (MM.) AT:

	62°	63°	64°	65°
Water	164	173	180	187
Ethyl iodide	543	567	587	605
Total	707	740	767	792

The boiling point obviously is somewhat below 64° and by interpolation it can be fixed at 63.7°. In this case the water which distils boils more than 36° below the normal boiling point.

Another important question is with regard to the relative amounts of materials which pass into the distillate, and here there is a simple guiding principle. According to Dalton's law the molecular proportion of the two components in the distillate is equal to the ratio of their vapor pressures in the boiling mixture. The more volatile component contributes a greater number of molecules to the vapor phase. To take the example just cited, the vapor pressures at 63.7° are: water, 177 mm.; ethyl iodide, 583 mm. This means that in the distillate the ratio:

$$\frac{\text{Moles of Water}}{\text{Moles of Ethyl Iodide}} = \frac{177}{583}$$

The weight ratio is then obtained by introducing the molecular weights of water (18) and of ethyl iodide (156):

$$\frac{\text{Weight of Water}}{\text{Weight of Ethyl Iodide}} = \frac{177 \times 18}{583 \times 156} = \frac{1}{28.5}$$

The percentage of water in the distillate is thus:

$$\frac{1 \times 100}{1 + 28.5} = 3.4\%$$

It may also be said that 1 g. of steam carries over with it 28.5 g. of ethyl iodide.

With a less volatile compound more steam is of course required. Thus iodobenzene (b.p. 188°) distils with steam at 98.2°, where its vapor pressure is 48 mm. while that of water is 712 mm. The molecular ratio of water to the organic substance is 712/48 or 14.8/1. About 15 molecules of water are required to carry over one molecule of iodobenzene. It is a fortunate circumstance to the organic chemist that water has a very low molecular weight. Thus when the molecular ratio is converted into a weight ratio it is found that only 1.3 g. of steam is theoretically required for the distillation of each gram of iodobenzene:

$$\frac{712 \times 18}{48 \times 203} = \frac{1.3}{1}$$

Types of Apparatus. — One convenient and efficient assembly for carrying out a steam distillation has been illustrated in Fig. 12 on page 70, and consists, it will be recalled, in a long-necked flask into which steam is passed and which is clamped at an angle to avoid the spattering over of liquid. The only difficulty ordinarily experienced in using this apparatus is encountered in the distillation of a large quantity of a substance of low vapor pressure, as in the recovery of nitrobenzene which has been used as a solvent in some reaction or crystallization. Here the weight ratio in the distillate of water to nitrobenzene is 4 : 1 and a large volume of steam is required for the volatilization of any appreciable quantity of the organic material, and a very rapid flow of steam is required for an efficient operation. The tilted, long-necked flask will accommodate the rapid injection of steam without permitting spattering, but the single condenser, even if reasonably long, will not take care of the violent rush of vapor. A very effective condensing system which is particularly well adapted to the distillation of liquids of low vapor pressure is shown in Fig. 14 (see also Fig. 46, page 320).

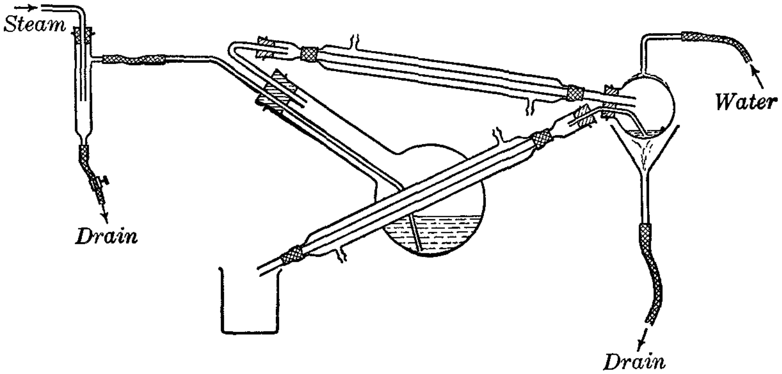


FIG. 14. — Steam Distillation Apparatus with an Efficient Condensing System

For a distillation flask of three liters capacity and having the form already discussed a one-liter flask for condensation is sufficiently large. This is cooled by means of a stream of water which is then caught in a funnel and conducted to the sink. A second condenser is connected as shown by a glass tube running to the bottom of the condensing flask. In operation some vapor condenses at once in the one-liter flask and this forms a liquid seal at the exit tube. Vapor cannot well escape to the second condenser, but simply forces over the condensate as sufficient pressure develops. For purposes of inspection, and in particular to determine when the distillation of organic material is at an end, the one-liter flask can be emptied by diverting for a moment the stream of cooling water to one side of the flask. With this condensing system it is possible to utilize the full force of a good steam line, and one can distil nitrobenzene at the rate of about 400 g. per hour. Before using the apparatus all stoppers should be wired in place. The long-necked flask is heated during the distillation with a flame or on a steam bath so that the flask will not fill with condensed water, and the flask initially should be no more than one-third full. The distillate is collected at the end of the second condenser in a vessel of suitable capacity. One added feature of the set-up shown in Fig. 14 is the simplified steam trap which is easily constructed from a Pyrex test tube with a side arm.

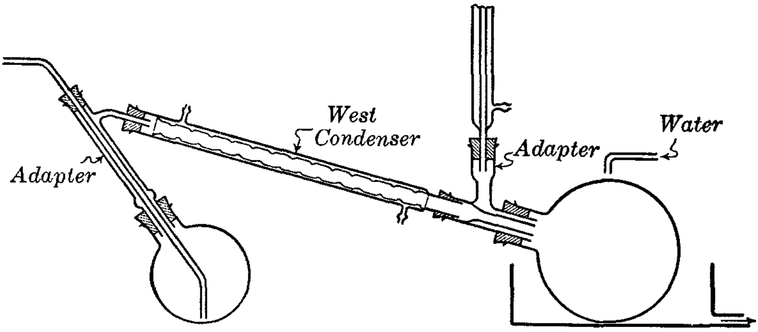


FIG. 15. — Apparatus for the Steam Distillation of Solids

The above condensation system is not suitable for use with a compound which solidifies in the condensate, for the solid would plug the exit tube. In this case it is best to use the arrangement shown in Fig. 15, or one embodying the essential principle. Here a larger receiving flask is required for it must take care of the entire volume of distillate. It is again cooled by a stream of water and a second condenser is provided, but in this case it is connected in such a way as to give free access to the uncondensed vapor. If the condensed solid threatens to plug the system in any part it can be dislodged by interrupting the cooling at an appropriate point. The other features of the assembly are not essential to the operation but they are often useful in this and in other distillations. The West condenser derives its efficiency partly from the indentures in the inner tube, which provide a large cooling surface, and partly from the limited space provided for the cooling water. With the same quantity of water as would be passed through a condenser of the Liebig type the flow past the inner tube is much more rapid and the heat interchange is more efficient. The adapter leading into the receiving flask and the adapter for converting an ordinary flask into one suitable for a steam distillation are useful units designed in the Eastman Kodak Laboratories.

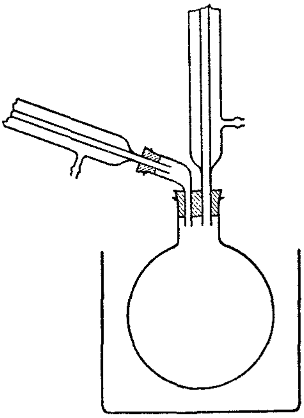


FIG. 16. — Receiving Flask for the Condensation of a Solid Distillate

A simpler cooling system also adapted to the steam distillation of a substance which solidifies is shown in Fig. 16. The receiving flask is cooled in a tub of ice and water, for it is here that the greater part of the condensation takes place. The ice can be renewed as required and the upper part of the flask can be cooled with wet towels.

It is often convenient, particularly in small-scale distillations, to make use of the glassware with standard interchangeable ground joints which is now available in a wide variety of forms

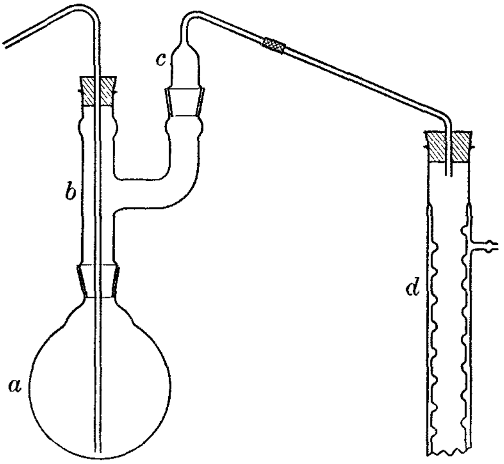


FIG. 17 — Apparatus with Interchangeable Ground Joints

and constructed either of soft glass or of Pyrex. Thus a reaction may be carried out in the flask *a* shown in Fig. 17, which is connected for the purpose to a reflux condenser, an addition tube with mechanical stirrer or other unit having the standard glass joint. In order to remove the solvent or the product by steam distillation at the end of the reaction, the flask *a* is now fitted with the units *b* and *c* and connection is made to condenser *d* (West type), which is conveniently clamped in a vertical position at the side of the desk so that it will not take up desk space.

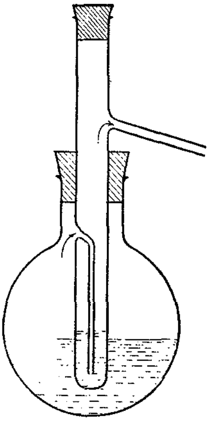


FIG. 18. — Steam Distillation of a Small Quantity of Material

For the steam distillation of very small quantities of material the apparatus shown in Fig. 18 is often useful. The substance to be distilled is placed in the small inner tube and water is boiled in the outer flask. The distilling mixture is bathed in the steam-generating flask and condensation of an unnecessary quantity of water in the inner tube is avoided.

Among other modifications mention may be made of distillation with superheated steam and of steam distillation at diminished pressures. For compounds of extremely low vapor pressure it may be necessary to resort to a combination of these two expedients. One convenient way of obtaining superheated steam is to conduct ordinary steam through a coil of lead or copper tubing which is heated in an oil bath. If a rather long section of metal tubing is used (10–15 ft.) it is not necessary to heat the oil bath more than 20–30° above the temperature of superheating desired. The temperature of the steam itself should be determined by means of a thermometer inserted in the line just before it enters the distillation flask. This flask must also be heated in an oil bath in order to maintain the degree of superheating desired. Another preheater is made from a conical coil of copper wire heated directly in the flame of a burner, but here the temperature is less easily controlled.

If steam is not available from a supply line it is conveniently generated in a kerosene can. The spout is used for the outlet and connected directly (without a trap) to the distillation flask. A safety tube for the equalization of pressure and to prevent a suck-back is fitted into the opening in the top of the can. This is simply a vertical tube about 50 cm. long extending nearly to the bottom of the can. A flask (with a safety tube) may also be used for the boiling vessel.

EXPERIMENT 30

ACETANILIDE

In order to prepare a monosubstitution product of an amine it is often necessary first to convert the amine into its acetyl derivative. Without moderating the directive influence of the amino group of aniline, for example, it is impossible on bromination to prepare satisfactorily any but the tribromo derivative. Acetanilide, on the other hand, gives a good yield of the *p*-bromo compound. Another example is in the nitration of aniline; nitric acid alone acts mainly as an oxidizing agent, and the nitration of the more stable aniline sulfate leads to the production of the meta nitro derivative. The acetylation of the amine both protects the amino group from oxidation and prevents salt formation, and the nitration of this derivative gives the para isomer in good yield. The use of the acetyl derivatives in the identification of amines has been discussed already in connection with Experiment 21.

The most rapid and convenient method of acetylation in general laboratory practice is with the use of acetic anhydride. The formation of an acetate from a hydroxy compound by reaction with this reagent is catalyzed by both acidic and basic substances, and since the amines themselves are basic they react particularly readily with acetic anhydride. Liquid amines often react with such vigor that some care must be exercised in starting the reaction if large quantities are employed. The acetylation of a primary amine may even proceed beyond the formation of a monoacetyl compound, for if either the time or the temperature of reaction is increased beyond a certain point the second amino hydrogen atom can be replaced by an acetyl group:

$$RNHCOCH_3 + (CH_3CO)_2O \longrightarrow RN(COCH_3)_2 + CH_3COOH$$

Thus it is not always easy to obtain a pure monoacetyl derivative by heating the amine with acetic anhydride. Further disadvantages in this method of procedure are that all the impurities in the amine turn up in the reaction product, and that a considerable excess of acetic anhydride is required to act as solvent.

There is another way of using this reagent which obviates all the difficulties mentioned and that is to carry out the acetylation in aqueous solution.[1] This is done by dissolving the amine in water containing one equivalent of hydrochloric acid, dissolving slightly more than one equivalent of acetic anhydride in the solution, and adding enough sodium acetate to neutralize the hydrogen chloride. The free amine liberated is at once acetylated. There is no danger of getting a more highly acetylated product for the desired compound separates rapidly from the solution. By charcoal treatment of the amine hydrochloride solution any colored impurities can be removed before the acetylation and the reaction product often requires no purification. Acetic anhydride of course is subject to hydrolysis by water and it might be thought that the reagent would be largely destroyed when it is stirred into the aqueous solution. At moderate temperature, however, the hydrolysis is quite slow, a 10 per cent solution being destroyed only after several hours at 25°. When the free amine is liberated it reacts with the anhydride very much more rapidly than does water. The preparation of acetanilide by this excellent and general method is described below.

The only disadvantage in the use of acetic anhydride is in the cost of the reagent. This factor is of importance both in industrial operations and in fairly large-scale laboratory preparations, and fortunately there is an alternate method of acetylation for which only glacial acetic acid is required. The principle of the method is to displace the equilibrium:

$$RNH_2 + CH_3COOH \rightleftharpoons RNHCOCH_3 + H_2O$$

in the desired direction by the removal of the water by distilla-

---

[1] Method of Lumière and Barbier, *Bulletin de la Société Chimique de Paris* (3) **33**, 783 (1905).

tion. The preparation of acetanilide by this method is included below as an alternate procedure.

Procedure A: Acetylation in Aqueous Solution. — Pour into 500 cc. of water 16.6 cc. (0.2 mole) of concentrated hydrochloric acid and 18.2 cc. (0.2 mole) of aniline (it is instructive to use material that is somewhat colored). Bring the oil into solution by stirring and if the solution is colored stir it in the cold with 3-4 g. of animal charcoal for 5 minutes and filter by suction. Refilter through a fresh paper in order to remove the charcoal completely. Warm the colorless solution to 50°, measure out 23.3 cc. (0.24 mole) of acetic anhydride, and also prepare a solution of 30 g. (0.22 mole) of crystalline sodium acetate in 100 cc. of water, filtering or clarifying the solution if necessary. To the aniline hydrochloride solution add the acetic anhydride, stir in order to dissolve it, and at once pour in the sodium acetate solution. Stir, cool well in an ice bath, and collect the crystalline acetanilide which separates. The product should be directly pure and the yield is 85-90 per cent of the theoretical amount. If a recrystallization is necessary see the remarks given at the end of Procedure B.

Pure acetanilide is colorless and melts at 114°. Note that the substance dissolves in concentrated sulfuric acid but that it is no more soluble in dilute acids than in water.

Procedure B: Using Acetic Acid. — In a 200-cc. round-bottomed flask equipped with a long reflux air condenser place 18.2 cc. (0.2 mole) of aniline, 25 cc. of glacial acetic acid and a very small pinch of zinc dust (0.1 g.). The purpose of the metal is to reduce colored impurities in the aniline and to prevent oxidation of the amine during the reaction. Heat the mixture to boiling in such a way that the water formed in the reaction is eliminated. This can be accomplished by adjusting the flame so that the ring of condensed vapor in the condenser rises to about 15 cm. from the top of the tube. The water vapor, along with some acetic acid, will then largely escape through the top of the tube. It is well to connect a trap to the mouth of the condenser (see Fig. 9) to prevent the escape of the vapors into the atmosphere. The boiling should be continued for at least four hours, and a somewhat better yield will be obtained if the period of heating is extended for two or three additional hours. Record the actual time of heating.

Since the reaction mixture will set to a hard cake if allowed to cool at the end of the reaction, it is poured in a thin stream while still hot into a liter beaker half-filled with cold water. The flask is rinsed with a little glacial acetic acid. The mixture is stirred well and cooled, and the crude acetanilide is collected on a Büchner funnel and washed with water.

Crystallize the crude product from water, decolorizing the solution with animal charcoal. It should be noted that crude acetanilide melts at a temperature somewhat below 114°, and that water saturated with acetanilide boils somewhat above 100°; the material thus may melt when heated with water. All the material, whether liquid or solid, must be brought into solution, and this requires a rather large amount of water. It is often advisable to add a small quantity of alcohol to assist in the process of solution. Since the product tends to crystallize during the filtration of the hot solution, it is well to select a large funnel and to heat it on the steam bath just prior to use. A hot water funnel and a fluted paper, if available, will greatly facilitate the filtration. Particularly good crystals can be obtained by reheating the filtrate and allowing it to cool slowly and without disturbance.

The yield is 60–65 per cent of the theoretical amount. See the description of properties given at the end of Procedure A.

EXPERIMENT 31

p-BROMOACETANILIDE

To a cold solution of 13.5 g. of acetanilide in 45 cc. of glacial acetic acid contained in a 250-cc. Erlenmeyer flask add in small portions 5 cc. of bromine, measured directly into the flask from the burette provided for the purpose.

Caution: Bromine causes extremely painful and persistent burns. Be very careful in operating the burette to avoid loosening the stopcock. Make sure that there is no leakage, for bromine attacks stopcock grease. Always handle bromine under a good hood and avoid breathing the vapor. If bromine is spilled on the skin, wash immediately with glycerol or alcohol, then with sodium bicarbonate solution, and cover with glycerol, vaseline, or unguentine.

The first few drops of bromine react at once; at the end of the reaction the solution may acquire a yellow color from a slight excess of unused bromine. A part of the reaction product usually separates in a crystalline condition during the course of the reaction. Allow a few minutes after the addition of bromine is complete for any further reaction to occur and then pour the reaction mixture into about 500 cc. of water. Rinse the flask with a little fresh solvent. Stir the mixture well and if it is appreciably colored add a small quantity of sodium bisulfite to reduce the free bromine. Collect and wash the crude material and crystallize it from methanol.

The yield is 14–17 g. Pure *p*-bromoacetanilide forms colorless prisms melting at 167°. It can exist in two distinctly different crystalline forms and the change from one form to the other is very striking. When the substance is crystallized in the ordinary way it separates as well-formed needles and these needles will remain in contact with the mother liquor for days without change if the containing vessel is stoppered and left entirely undisturbed. If, however, the needles are stirred vigorously or if some of them are crushed with a glass rod, they will change completely, after standing for 5–6 hours in contact with the mother liquor, and give place to well-formed prisms of entirely different appearance. The prism-form is thus stable, the needle-form metastable; both forms melt at the same temperature.

HYDROLYSIS

p-Bromoaniline, m.p. 66°, can be obtained by the hydrolysis of the acetyl derivative with either acid or alkali. The reaction is to be carried out here as a test, rather than as a preparation, and there is a slight difference in the conditions most satisfactory in each case. For the preparation of the amine in quantity it is expedient to use considerable alcohol as a solvent; but the presence of much of this solvent is objectionable in a test, for it may obscure the true solubilities of the compounds concerned in water and in acids.

Alkaline Hydrolysis. — Using the cold finger shown on page 64, boil rather vigorously a mixture of 0.2 g. of *p*-bromoacetanilide, 5 cc. of 20 per cent sodium hydroxide solution and 1 cc. of alcohol for 15–20 minutes. Note any change in the appearance of the product and see if it is consistent with the melting points of the compounds concerned. Cool the mixture with shaking; extract a small quantity of the product on the end of a stirring rod and see if the material, or at least a part of it, will dissolve in dilute hydrochloric acid and precipitate again on neutralizing the solution. Such behavior is characteristic of an amine.

Acid Hydrolysis. — In the same apparatus boil a mixture of 0.2 g. of *p*-bromoacetanilide, 5 cc. of 20 per cent hydrochloric acid (equal parts of the concentrated acid and water) and 1 cc. of alcohol for 15–20 minutes, or until the reaction is complete. It is well to shake the tube occasionally in order to dislodge the solid from the walls. When a clear solution is obtained, cool this under the tap and note the character of the crystalline precipitate. This is the hydrochloride of the amine. Pour a few drops of the crystalline paste into a test tube, neutralize with alkali and observe the result. To another small portion add water, dissolve by heating and neutralize the solution. Observe that the amine salt does not dissolve easily in the presence of an excess of hydrochloric acid (common ion effect).

NOTE: It is worth noting that in the hydrolysis of acetyl derivatives of other amines certain changes in the test can be made to advantage. Thus acetanilide is fairly soluble in water, and it is not necessary to add the alcohol. Even so the aniline may not separate easily after alkaline hydrolysis until a small quantity of salt is added. After acid hydrolysis, on the other hand, no crystals will be obtained on cooling because aniline hydrochloride is quite soluble. Aniline should separate as an oil, however, on neutralizing the solution, particularly if some salt is added.

EXPERIMENT 32

p-NITROACETANILIDE

Place 30 cc. of concentrated sulfuric acid in a 125-cc. Erlenmeyer flask, add 13.5 g. of powdered acetanilide in portions, with shaking. Shake the mixture until the solid dissolves, keeping the mixture at room temperature by cooling in an ice bath. Insert a thermometer so that the temperature can be regulated to 15–20° by cooling in the ice bath, and add by drops and with stirring 15 cc. of concentrated nitric acid from a dropping funnel. The temperature should not be allowed to rise above 20° or hydrolysis may occur. After the nitric acid has been added allow the mixture to stand at room temperature for 20 minutes and then pour it into 200–300 cc. of water, with stirring. Collect the crude product, wash it thoroughly with water until free of acids (test the wash water), and crystallize it from alcohol.

The yield is from 80 to 90 per cent of the theoretical amount. The pure material melts at 214–215°.

HYDROLYSIS

p-Nitroaniline, m.p. 146°, can be prepared in satisfactory manner by the acid hydrolysis of the acetyl derivative, but alkaline hydrolysis in this particular case is not advisable for the reason that the *p*-nitroaniline may be partially converted into *p*-nitrophenol by this reagent. The amino group is rendered somewhat mobile by the unsaturated group in the para position, and it is susceptible to alkaline hydrolysis. In the presence of an acid, on the other hand, the amino group is protected by salt formation.

Hydrolyze a test portion of the product by the second method given on page 168.

EXPERIMENT 33[1]

β-NAPHTHOL

$$C_{10}H_7SO_3Na + KOH \longrightarrow C_{10}H_7OK + NaHSO_3$$
$$C_{10}H_7OK + HCl \longrightarrow C_{10}H_7OH + KCl$$

The conversion of a sulfonate into a phenol by the action of molten alkali ordinarily takes place smoothly, but it requires a rather high reaction temperature (about 300°) and the containing vessel must be made of a material resistant to alkali under these drastic conditions. Glass is out of the question. Platinum crucibles are ideal for very small scale fusions, nickel serves well for vessels of intermediate size (up to 500 cc.), and copper, although it is somewhat attacked by the alkali, is the best practical material for use where a one-liter container is required. A silver-plated copper beaker makes an excellent reaction vessel. For still larger operations cast iron kettles are employed. The thermometer used for observing the temperature of the melt must be encased for about two-thirds of its length in a tube of nickel or copper. A large cork placed at the top of the tube as in Fig. 19a makes a good hand grip, and the protected thermometer serves as the stirring rod. The thermometer case shown in Fig. 19b is easily constructed by hammering down the end of a copper tube and folding over the flat part in a vise. A stirrer is abso-

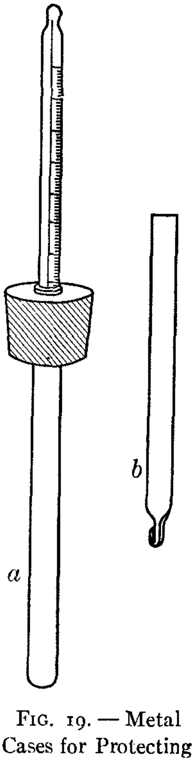


Fig. 19. — Metal Cases for Protecting the Thermometer

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[1] Special experiment.

lutely essential but often, after a little practice or after making a preliminary test, an alkali fusion can be carried out in a quite satisfactory manner without the use of a thermometer, and by simply using a nickel spatula or rod for stirring.

Some spattering of the molten alkali is almost inevitable and the operator must wear goggles, loose cotton gloves, and a laboratory coat with full sleeves. The sulfonate should be pulverized, and it must be thoroughly dry, for moisture in the salt will cause undue spattering. The sodium naphthalene β-sulfonate prepared according to Experiment 27 is a suitable starting material, but it should be dried for a few hours at 110° in a glass or porcelain vessel before being used for the fusion. On the other hand, some water is always added to the solid alkali in order to cause it to melt easily (pure potassium hydroxide melts at 360°). Potassium hydroxide is specified for the present experiment, and recommended in general for any but technical operations, for the reason that it forms a more mobile melt than caustic soda and gives generally more satisfactory results. Mixtures of the two alkalies are sometimes used with success.

Procedure. — Support a 250-cc. nickel crucible on a tripod in rings from the steam bath and melt in it 120 g. of potassium hydroxide sticks or pellets, to which 5 cc. of water is added, by heating over a free flame. When the temperature reaches about 250° remove the flame and stir into the melt without delay 50 g. of sodium β-naphthalene sulfonate. This gives a stiff, pasty mass. Replace the flame, stir the mixture and push down the material from the walls, and bring the temperature to 300° in 5–10 minutes. In order to avoid spattering of the hot alkali, particularly when the paste becomes thinner, the melt must be stirred constantly throughout the fusion. If the stirring has to be interrupted for a moment, remove the flame at the same time; all spattering will at once stop. There is at first some frothing and as the fusion proceeds and the temperature rises to about 300° the mass suddenly separates to a clear, mobile, brown oil of the potassium salt of β-naphthol floating on a pasty, semi-solid mass of alkali. Once the fusion temperature is reached, the reaction is over in about 5 minutes. Bring the temperature to 310°, remove the flame and push down material lodging on the walls, reheat to 310° for a minute or two and then allow the melt to cool.

Do not let the melt solidify, for then it becomes very difficult to handle; as it begins to become pasty, ladle it out in small portions (best with a nickel spatula) into a 1.5-l. beaker half-filled with ice. After scraping the crucible, let it cool and dissolve the remaining material with water. Without filtering the strongly alkaline solution of the melt, precipitate the β-naphthol with concentrated hydrochloric acid. If a finely divided suspension is obtained, heat it with stirring until coagulated to a more easily filterable form (hood; SO_2). Cool well in an ice bath, collect the precipitate, wash it into a beaker of cold water, add just enough alkali to bring it into solution and about one-half gram of sodium hydrosulfite ($Na_2S_2O_4$) to prevent undue oxidation by the air, and filter from traces of insoluble impurities. Precipitate the β-naphthol with acetic acid, heat somewhat to coagulate the precipitate, cool in ice, and collect the product. This material should require no further purification, the yield is 21–24 g.

Pure β-naphthol is colorless, it melts at 122° and boils at 285°. It is moderately soluble in hot water and crystallizes well from alcohol-water, from carbon tetrachloride or from benzene-ligroin. Dissolve a small quantity of β-naphthol in hot sodium carbonate solution, cool until crystals form and add alkali. The result shows that the substance is acidic, but very weakly so. The methyl ether has a delicate orangy odor which can be noted on adding a few drops of concentrated sulfuric acid to a solution of the naphthol in methyl alcohol and heating on the steam bath for 10 minutes.

Notes: Some fusions require temperatures slightly higher or lower than that specified here and the reaction is not always completed in such a short time. Where specific directions are not available it is well to test for the completeness of the reaction after it is judged from the appearance of the melt that this point has been reached. Dissolve a small portion collected on the end of a stirring rod in a little water, acidify, and cool. The precipitate should dissolve completely in ether. When working on a large scale, as in a 1-liter copper beaker, it is of great convenience to stir the melt mechanically. Use a copper rod, or a closed copper tube, with copper wire fastened to the end to form a rough paddle. Instead of ladling out the melt at the end of the reaction it is often convenient to pour it onto a tray made from copper sheeting. When the material cools it can be broken and dissolved in water. With phenols which are very sensitive to oxidation in alkaline solution the melt is best drenched in a mixture of hydrochloric acid and ice.

It is sometimes a convenience to isolate and purify the phenol by steam distillation (see page 182). In other cases it is best to purify the crude product by vacuum distillation, even though the substance in question is a solid.

EXPERIMENT 34

DIPHENYLMETHANE

(The Friedel and Crafts Hydrocarbon Synthesis)

Aluminum chloride is a very active catalyst for the condensation of an alkyl halide with an aromatic hydrocarbon, but this particular application of the Friedel and Crafts reaction suffers from certain distinct disadvantages. Perhaps the most serious difficulty is that the substitution of the alkyl group for an aromatic hydrogen atom cannot be controlled to the point of monosubstitution and some higher substitution products are always formed. The reason for this is clear: the group introduced as a result of the reaction is of the type (saturated, ortho-para directing) which facilitates substitution in the benzene ring. In the preparation of ethylbenzene from a mixture of benzene, aluminum chloride, and either ethyl chloride or ethyl bromide, the primary product reacts more easily than benzene with the ethyl halide and the formation of some diethylbenzenes is inevitable. Indeed it is only because of the concentration effect that ethylbenzene is the chief, if not the sole, reaction product. If one considers the other common substitution reactions it will be seen that in nearly every case the group introduced is of the meta-directing type, and its presence tends to hinder any further substitution.

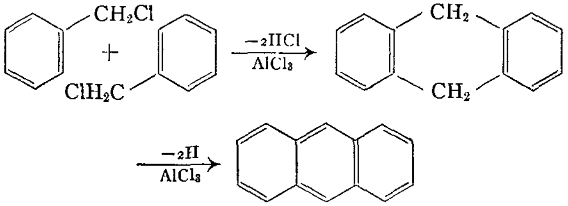
A further difficulty which limits the usefulness of the Friedel and Crafts synthesis of hydrocarbons is that the aluminum chloride employed as catalyst often causes the wandering of an alkyl group from one position in the aromatic nucleus to another, or even to its complete elimination from the molecule. This is a further cause of diminished yields and of impure products.

Another complication, but indeed an interesting one, is that aluminum chloride causes the rearrangement of certain alkyl halides prior to their condensation with the aromatic hydrocarbon. The reaction of *n*-propyl bromide with benzene leads to the production of *iso*-propylbenzene, rather than *n*-propylbenzene. It is inferred that the catalyst first rearranges *n*-propyl bromide into *iso*-propyl bromide, probably by the elimination and readdition of hydrogen bromide, and that the secondary halide then condenses with benzene.

The present preparation of diphenylmethane from benzyl chloride and benzene, according to the equation:

$$C_6H_5CH_2Cl + C_6H_6 \xrightarrow{AlCl_3} C_6H_5CH_2C_6H_5 + HCl$$

is free from some of the complications noted, and it has been selected for the reason that it represents a fairly useful application of the general method. Benzyl chloride is considerably more reactive than the simple, saturated alkyl halides and the reaction proceeds more rapidly than is ordinarily the case. The condensation can be effected at a temperature so low that rearrangements are not likely to occur. Aluminum chloride can be replaced by the less active aluminum mercury couple (strips of amalgamated aluminum foil). The condensation, however, is by no means free from side reactions. If the temperature is allowed to rise above 25° a considerable portion of the benzyl chloride is converted into anthracene through the following series of reactions:



Even at the temperature of the ice bath some anthracene evidently is formed for the solutions of the crude product usually exhibit the fluorescence characteristic of this tricyclic hydrocarbon. This reaction and polysubstitution decrease the yield of diphenylmethane and render it rather difficult to secure a completely pure product. It will be instructive to compare later the results obtained here with those of a Friedel and Crafts ketone synthesis.

Procedure. — In a 500-cc. round-bottomed flask fitted with a reflux condenser place 23 cc. (25.3 g.) of benzyl chloride and 120 cc. of dry benzene.[1] Attach a trap to the top of the condenser to collect the hydrogen chloride produced in the reaction, and cool the contents of the flask very thoroughly in an ice bath. Weigh 10 g. of anhydrous aluminum chloride into a stoppered test tube without exposing it unduly to the action of atmospheric moisture and pour about one-fifth of the material through the top of the condenser into the well cooled liquid. Shake the mixture and keep it cold. A vigorous reaction should set in within a few minutes, with a rapid evolution of hydrogen chloride. After this has subsided there will be little further evidence of reaction. Add the remainder of the aluminum chloride in portions through the condenser and continue to shake at the ice bath temperature for 5–10 minutes; a red, oily substance (aluminum chloride addition product) should have separated by this time. Remove the flask from the cooling bath and allow it to stand at room temperature for one-half hour, when the product may be worked up.

Cool the reaction mixture in an ice bath and cautiously introduce about 50 g. of crushed ice, followed by 100 cc. of water, to decompose the aluminum chloride complex. Stir well and then transfer the mixture to a separatory funnel where the water layer can be drawn off from the upper layer of benzene containing the diphenylmethane. Wash the benzene solution with dilute hydrochloric acid to remove basic aluminum salts and then with water to remove the acid. Dry the benzene solution by warming it with about 5 g. of calcium chloride until it is clear, shake for a

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[1] Thiophene-free benzene is not required here, as impurities arising from it are removed by distillation. If the ordinary benzene available contains moisture this may be removed by distilling until the distillate is no longer cloudy and using the residue

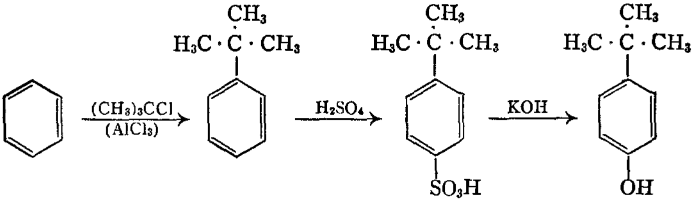
minute or two with 0.5 g. of animal charcoal, and filter the solution into an Erlenmeyer flask. Remove the bulk of the benzene by distillation from the steam bath, using a bent tube to make connection to the condenser. Let the flask rest below the rings and wrap it with a towel. Distil the oil which remains from a small distilling flask over a free flame using an air condenser. The fore-run will contain some benzene and must be kept away from the flame. Pure diphenylmethane boils at 262°, crystallizes to a colorless solid melting at 26-27°, and has a pleasant orange odor. Collect the fraction boiling at 250–275° and see if it can be caused to solidify by cooling in ice and scratching, or by seeding with a crystal of the pure material. If this is not the case redistil the product, collecting the fraction boiling at 255–265°. Allow the solid to melt while stirring it with a thermometer. The temperature rises steadily at first and then remains essentially constant for a time until most of the solid has melted; this is the melting point. Material prepared as above usually melts in the range 20-23°; yield 15–20 g.

Note that there is a considerable quantity of high-boiling residue. This is known to contain anthracene (m.p. 217°), *o*-dibenzylbenzene (m.p. 78°), and *p*-dibenzylbenzene (m.p. 86°); these hydrocarbons all boil in the range 350–380°.

EXPERIMENT 35[1]

tert.-BUTYLBENZENE AND *p-tert.*-BUTYLPHENOL

Tertiary aliphatic compounds, and aromatic compounds containing tertiary alkyl groups, often possess unusual properties. *tert.*-Butyl alcohol can be converted into the chloride by the action of cold, concentrated hydrochloric acid (see below), whereas most primary and secondary alcohols react with this acid only at temperatures well above their boiling points. The so-called " nitro musk," a synthetic substitute used to some extent in the perfume industry in place of natural musk, has the structure of 2,4,6-trinitro-3-methyl-*tert.*-butylbenzene. The delicate odor disappears if the *tert.*-butyl group is replaced by a methyl group. *p-tert.*-Amylphenol recently has been placed on the market on an industrial scale. It is used in the production of special aldehyde resins, as a plasticizer for cellulose nitrate and cellulose acetate, and as a germicide. It is said to be seventy-five times stronger than phenol in this last respect.



p-tert.-Butylphenol has similar properties. The compound can be obtained from *tert.*-butylbenzene, prepared by the Friedel and Crafts synthesis, by sulfonation, followed by the alkali

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[1] Special series of experiments. The preparation of *tert.*-butylbenzene may be substituted for the Friedel and Crafts reaction of Experiment 34. The preparation of *p-tert.*-butylphenol by an entirely different method has been described by Smith, *Journal of the American Chemical Society*, **55**, 3718 (1933)

fusion of the sulfonate. The reactions are described below in somewhat brief form; for further details consult the literature.[1] It may be noted that *tert.*-butylbenzene can be prepared by the reaction with benzene and aluminum chloride of either *tert.*-butyl chloride or isobutyl chloride. It is of interest that the sulfonation of *tert.*-butylbenzene leads exclusively to the production of the para isomer (compare toluene). The bulky alkyl group hinders substitution in the adjacent, ortho position.

***tert.*-Butylbenzene.** — The *tert.*-butyl chloride required for the reaction is prepared by shaking vigorously in a separatory funnel a mixture of 50 cc. of *tert.*-butyl alcohol and 250 cc. of concentrated hydrochloric acid. After agitating very thoroughly for 10 minutes the conversion should be complete and the lower acid layer should be perfectly clear. Separate carefully the *tert.*-

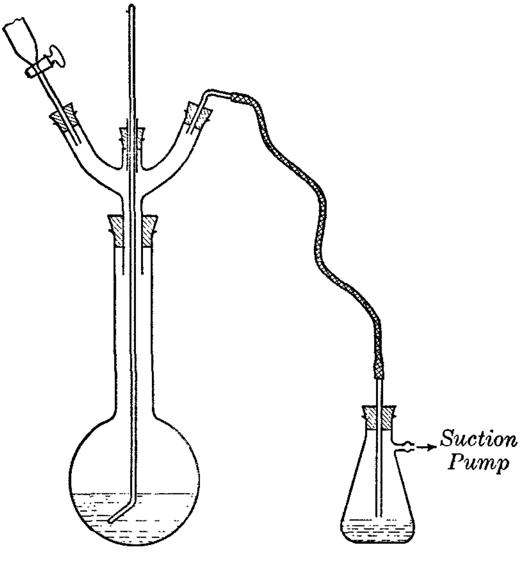

FIG. 20. — Apparatus for Carrying Out the Friedel and Crafts Reaction at a Low Temperature

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[1] Schramm, *Monatshefte fur Chemie*, **9**, 618 (1888); Senkowski, *Berichte der deutschen chemischen Gesellschaft*, **23**, 2412 (1890); Beilstein-Prager-Jacobson, "Handbuch der organischen Chemie," V, p. 415 (1922).

butyl chloride layer, dry the liquid over calcium chloride, and purify it by distillation. Yield, 45–50 g.; b.p. 50–51°.

The Friedel and Crafts reaction is best carried out in a 1-l. long-necked, round-bottomed flask which can be used later for steam distillation and which is fitted with a mechanical stirrer and a dropping funnel fitted into a three-way addition tube as shown in Fig. 20. By applying a very gentle suction the hydrogen chloride can be drawn into the trap and it is not necessary to use a gas seal for the stirrer. For 50 g. of *tert.*-butyl chloride use 50 g. of aluminum chloride and 175 cc. of dry benzene. Place the halide in the dropping funnel and introduce the other reagents to the reaction flask. Clamp the flask in a salt-ice bath, set the stirrer in motion, and at once run in 2–3 cc. of the halide from the dropping funnel in order to prevent the benzene from freezing. Cool the mixture thoroughly before proceeding further. It is well to stir the ice bath occasionally by hand. Add the *tert.*-butyl chloride in portions over a period of 6 hours, stirring continuously and keeping the mixture at a temperature of 0–5°.

Continue the stirring for one hour longer and then remove the stirrer and add in small portions 150–200 g. of ice (hood), shaking the mixture in an ice bath during the process. Add 50–100 cc. of cold water to complete the decomposition of the intermediate product and then steam distil the mixture. After separating the upper layer of benzene and *tert.*-butylbenzene, extract the water layer with two small quantities of ether and combine the extract with the benzene solution. Dry thoroughly over calcium chloride and fractionally distil the mixture twice, using a column. In the second distillation retain the fraction boiling at 164–168°. The pure material boils at 167°. Yield, 35–45 g.

Sodium *p-tert.*-Butylbenzene Sulfonate. — To 40 g. of *tert.*-butylbenzene in a 250-cc. round-bottomed flask add slowly in the course of 20 minutes 45 cc. of fuming sulfuric acid containing 15 per cent of sulfur trioxide. Keep the mixture at a temperature of 25° (thermometer in the liquid), shaking frequently.

Then heat the mixture slowly to a temperature of 80° and shake thoroughly. The layer of oil should be completely dissolved by this time.

Pour the reaction mixture into 300 cc. of water, partially neutralize the acid by adding carefully 15 g. of sodium bicarbonate, and remove any particles of char by suction filtration. To salt out the sodium sulfonate, add 30 g. of clean sodium chloride and heat the solution until the solid is all dissolved. Cool thoroughly in an ice bath, collect the crystalline product, and wash it well with a saturated solution of sodium chloride. Dry the product thoroughly (best in an oven at 120°).

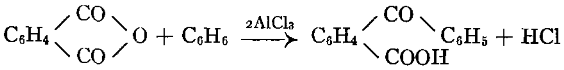
The salt crystallizes with one molecule of water of crystallization. The *p*-toluidine salt melts at 240°. Yield, 50 g.

***p-tert.*-Butylphenol.** — In carrying out the alkali fusion of the sulfonate follow the directions given on page 171 for the preparation of β-naphthol, using the same apparatus and, for 50 g. of sodium *p-tert.*-butylbenzene sulfonate, the same quantities of alkali and water. The fusion in this case occurs at a slightly higher temperature: 320–330°. It is of advantage to work up the reaction product in a different way from that specified for β-naphthol. When the melt has been dissolved in water pour the alkaline solution into a long-necked flask suitable for steam distillation. Then acidify with hydrochloric acid and steam distil the *p-tert.*-butylphenol liberated. This separates as a solid on cooling the distillate, and it may lodge in the condenser. To prevent it from clogging the tube, dislodge it occasionally by allowing the water to run out of the condenser jacket until the product is melted.

Cool the distillate well before collecting the product. Dry the product and crystallize it from petroleum ether. Yield, 18–20 g.; m.p. 98.5°. Note the odor and solubility of this phenol and compare it with *p*-cresol. Add a drop of ferric chloride to dilute aqueous and alcoholic solutions. Add sodium carbonate to the test in aqueous solution. Are any of these tests characteristic?

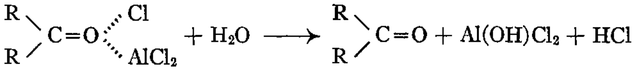
EXPERIMENT 36

o-BENZOYLBENZOIC ACID



$$C_6H_4\begin{array}{c}\diagup CO \diagdown\\ \diagdown CO \diagup\end{array}O + C_6H_6 \xrightarrow{2AlCl_3} C_6H_4\begin{array}{l}\diagup CO \diagdown C_6H_5\\ \diagdown COOH\end{array} + HCl$$

The usual method of carrying out the synthesis of a ketone by the Friedel and Crafts reaction consists in bringing into reaction a mixture of the acid chloride, the hydrocarbon, and aluminum chloride in the presence of some inert solvent such as carbon bisulfide, tetrachloroethane, or nitrobenzene. Either the acid chloride or the aluminum chloride usually is added in portions to a mixture of the other reagents and the solvent. If the hydrocarbon in question is an inexpensive liquid, an excess of this substance is used in place of some other solvent. At the end of the reaction the aluminum chloride addition compound is decomposed by adding ice and enough hydrochloric acid to dissolve any basic aluminum salts, and the product is isolated by the method best suited to the ketone in question. The addition compound formed in the synthesis of a simple ketone, $R_2C=O$, appears to be an oxonium salt and it may be represented as a matter of convenience by the formula given below in an equation indicating the decomposition of the salt by water:



$$\begin{array}{l}R\diagdown\\ R\diagup\end{array}C=O\begin{array}{l}\cdot\cdot\, Cl\\ \cdot\cdot\, AlCl_2\end{array} + H_2O \longrightarrow \begin{array}{l}R\diagdown\\ R\diagup\end{array}C=O + Al(OH)Cl_2 + HCl$$

(Actually the addition compound has twice the molecular weight indicated, and aluminum chloride in most solutions has the formula Al_2Cl_6.[1])

The example given in the present experiment, selected because

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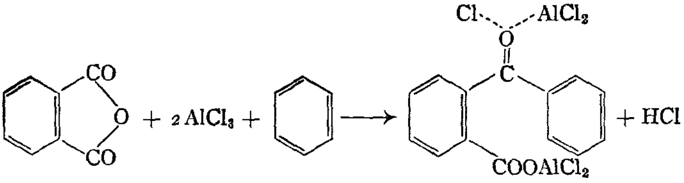
[1] Kohler, *American Chemical Journal*, **24**, 385 (1900); **27**, 241 (1902).

of the speed of the reaction and the excellent yield, utilizes a cyclic anhydride and the product is a keto acid rather than a simple ketone. The only difference in the procedure, but an important one to note in practice, is that two molecules of aluminum chloride are required instead of one, for the intermediate addition product in this case probably is to be represented as follows (or by a "double" formula):



It is well to remember that one molecule of aluminum chloride is required for every carbonyl group in the acid chloride or anhydride, whether or not this is cyclic. In the Friedel and Crafts hydrocarbon synthesis, on the other hand, there are no carbonyl groups in the halogen compound to bind aluminum chloride, and a small fraction of a molecular equivalent is often sufficient to catalyze the reaction.

Procedure. — The Friedel and Crafts reaction is carried out in a 500-cc. round-bottomed flask equipped with a short condenser. A trap for collecting the hydrogen chloride liberated is connected to the top of the condenser by means of a piece of rubber tubing sufficiently long to make it possible to heat the flask on the steam bath or to plunge it into an ice bath. The most convenient form of trap is a suction flask half filled with water and with a delivery tube inserted to within 5 mm. of the surface of the water.

Fifteen grams of phthalic anhydride and 75 cc. of thiophene-free benzene[1] are placed in the flask and this is cooled in an ice bath until the benzene begins to crystallize. This serves to

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[1] The thiophene present in small amounts (0.03 per cent) in ordinary benzene interferes with the Friedel and Crafts reaction because it is converted into a tar by aluminum chloride. Material suitable for the reaction (end-desk) is prepared by shaking crude benzene with concentrated sulfuric acid (see page 363).

moderate the vigorous reaction which otherwise might be difficult to control. Thirty grams of anhydrous aluminum chloride[1] is added, the condenser and trap are connected, and the flask is shaken well and warmed for a few minutes by the heat of the hand. If the reaction does not start, the flask is warmed very gently by holding it for a few seconds over the steam bath. At the first sign of vigorous boiling, or evolution of hydrogen chloride, the flask is held over the ice bath in readiness to ice it if the reaction becomes too vigorous. This gentle, cautious heating is continued until the reaction is proceeding smoothly enough so that the mixture may be refluxed on the steam bath. This point can be reached in about 5 minutes. The mixture should then be shaken well (rotary motion) and the refluxing continued for one-half hour. It is generally noted that, after about 5 minutes of refluxing, the aluminum chloride nearly all dissolves and the colorless addition product suddenly separates.

At the end of the time specified the flask is cooled well in ice (hood) and the aluminum compound is decomposed by the cautious addition of ice and then water. While shaking the flask in the ice bath, small pieces of ice are added, one at a time, waiting after each addition until the last piece has reacted. (Too rapid addition of ice may cause very vigorous boiling.) When the ice no longer produces much reaction and about 100 cc. has been added, 20 cc. of concentrated hydrochloric acid is added,[2] together with enough water to make the flask half full. The excess benzene is then removed by steam distillation, and it is separated from the water layer and placed in the bottle marked " Wet Thiophene-free Benzene."

The benzoylbenzoic acid is left as an oil which partially solidifies on cooling in ice. The aqueous solution containing aluminum chloride is decanted through a suction funnel, the residue is washed once with water, and the material collected is returned to the flask. In order to remove traces of aluminum

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[1] This is best weighed from a freshly opened bottle into a stoppered test tube.

[2] The acid serves to dissolve $Al(OH)_3$ and $Al(OH)_2Cl$ and thus to facilitate their elimination.

the acid is dissolved in soda solution. This is done by adding 75 cc. of 10 per cent sodium carbonate solution and enough water to half fill the flask, and then passing in steam as in a steam distillation until all of the solid material except particles of Al_2O_3 or $Al(OH)_3$ has become dissolved. The solution of the sodium salt of the acid is then cooled well in ice, stirred with 1 g. of animal charcoal, filtered by suction, and placed in a 600-cc. beaker. The acid is then precipitated by cautious neutralization with hydrochloric acid, adding a little at a time and stirring well. The reason for this caution and for the large beaker is that the evolution of CO_2 may carry the material over the top of the vessel. The *o*-benzoylbenzoic acid usually separates as an oil, but it soon solidifies on stirring and cooling. The material obtained in this way consists largely of the rather unstable monohydrate (m.p. 94.5°).

For the preparation of pure, anhydrous *o*-benzoylbenzoic acid the still moist precipitate of the crude hydrate is transferred to a 250-cc. Erlenmeyer flask, 125 cc. of ordinary benzene is added, and the mixture is heated to boiling on the steam bath. After the acid has dissolved in the benzene the mixture is transferred to a separatory funnel and the aqueous layer is drawn off and extracted with 25 cc. of benzene. The combined benzene solutions are placed in a dry 250-cc. Erlenmeyer flask and 2–3 g. of charcoal is added. The benzene need not be dried, since the charcoal absorbs the small amount of water present. The solution is boiled for 2–3 minutes, filtered by gravity, and concentrated to a volume of 50–60 cc. Ligroin is added slowly to the hot solution until a slight turbidity is produced, and at this point crystals begin to separate. After spontaneous cooling to room temperature, and then in an ice bath to 5°, the colorless, well-formed crystals are collected and dried. The yield is 17–20 g. (74–88 per cent); m.p. 127–128°.

o-Benzoylbenzoic acid forms a nicely crystalline ammonium salt which, on dehydration, yields the amide. By means of the Hofmann reaction, the amide may be converted into *o*-aminobenzophenone. Benzophenone itself may be prepared in good yield by heating *o*-benzoylbenzoic acid with 1 per cent of copper powder. Write equations for these reactions.

QUESTIONS

1. What molecular proportion of aluminum chloride would you use and what solvent would you employ for the Friedel and Crafts condensation of (a) acetic anhydride with toluene; (b) succinic anhydride with naphthalene?

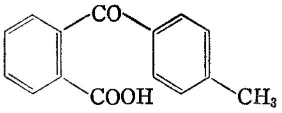
2. Would you expect that anisole, $C_6H_5OCH_3$, would be capable of forming a complex compound with aluminum chloride?

3. Why, in the purification of the crude *o*-benzoylbenzoic acid, is the product dissolved in sodium carbonate solution rather than in alkali?

4. What is the objection to the use of alcohol as solvent in the Friedel and Crafts reaction? Ether?

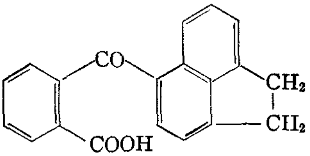
ALTERNATE PREPARATIONS

o-(*p*-Toluyl)-benzoic Acid. —



Use a good grade of toluene (75 cc.) in place of benzene and proceed according to the above directions. The heating should be done on the steam bath as above although the solvent in this case will not reflux. The addition compound is more soluble and will not separate from the solution as in the experiment with benzene. The crude *o*-(*p*-toluyl)-benzoic acid usually separates in a partly hydrated condition and it is best to dry it in a dish on the steam bath. A yield as high as 96 per cent of the theoretical amount can be obtained and the crude product, m.p. 138–139°, is sufficiently pure for conversion into an anthraquinone according to the procedure given in the next experiment, or for decarboxylation as in Experiment 39. Pure crystals melting at 139–140° can be obtained from benzene or toluene.

o-(3-Acenaphthoyl)-benzoic Acid. —

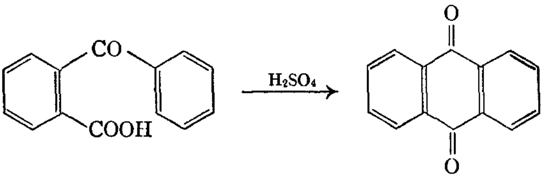


Acenaphthene is a solid melting at 95° and in order to condense it with phthalic anhydride a solvent inert to aluminum chloride must be used. Dissolve 15 g. of acenaphthene and 15 g. of phthalic anhydride in 75 cc. of purified tetrachloroethane (see page 366) by heating in a 500-cc. long-necked, round-bottomed flask designed for efficient steam distillation. No condenser is required during the reaction but the flask should be provided with a tube to conduct hydrogen chloride to a gas trap. Cool the solution until the temperature registers 5° (some solid may separate) and, keeping the flask in the ice bath, add 30 g. of aluminum chloride and connect the trap. Shake thoroughly with good cooling for 10 minutes, remove the flask from the cooling bath and allow the reaction to proceed at room temperature for one-half hour with frequent shaking, when the addition compound should have separated as a stiff paste. To complete the reaction place the flask in a beaker of water heated to 50° and allow it to stand for one-half hour. Work up the product according to the procedure given above, making such slight changes as appear advisable. Record your own procedure and observations carefully.

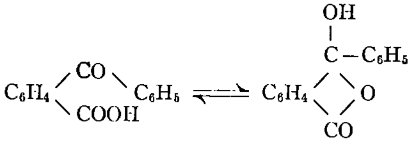
Pure *o*-(3-acenaphthoyl)-benzoic acid forms colorless, anhydrous crystals melting at 200°. If mechanical losses are minimized by careful and thorough work (wash and rinse all flasks, funnels!), it is possible to achieve a 96 per cent yield of material melting within one or two degrees of the correct temperature. This keto-acid is reported to undergo ring closure to an anthraquinone only with great difficulty.

EXPERIMENT 37

ANTHRAQUINONE



This very useful reaction is also a remarkable one, for carboxylic acids usually do not condense with aromatic rings under the influence of sulfuric acid, particularly when the ring is to be entered in a position ortho to the unsaturated carbonyl group. It is known that *o*-benzoylbenzoic acid can exist in two forms:

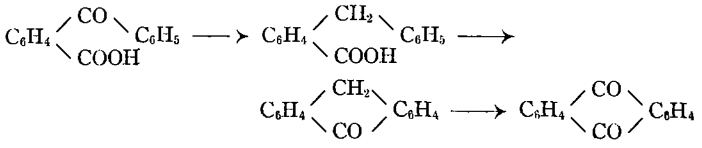


$$C_6H_4\left\langle\begin{matrix}CO\\COOH\end{matrix}\right.\!\!-C_6H_5 \rightleftharpoons C_6H_4\left\langle\begin{matrix}C(OH)-C_6H_5\\CO\end{matrix}\right\rangle O$$

Keto acid Lactol form

and it is possible that it is the lactol form which is responsible for the ready ring closure to anthraquinone.

The ring closure can be accomplished by heating with concentrated acid at a low temperature or with dilute acid at a high temperature, and both procedures are illustrated below. Other dehydrating agents are sometimes used but if, with a particular derivative of *o*-benzoylbenzoic acid, it is found difficult to close the ring it is best to reduce the keto group (with zinc dust and alkali), treat with sulfuric acid, and oxidize:



$$C_6H_4\left\langle\begin{matrix}CO\\COOH\end{matrix}\right.\!\!-C_6H_5 \longrightarrow C_6H_4\left\langle\begin{matrix}CH_2\\COOH\end{matrix}\right.\!\!-C_6H_5 \longrightarrow C_6H_4\left\langle\begin{matrix}CH_2\\CO\end{matrix}\right\rangle C_6H_4 \longrightarrow C_6H_4\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle C_6H_4$$

The reduction of the unsaturated ketone group gives a group of the ortho-para directing type which facilitates attack by the carboxyl radical.

Procedure. — Two grams of *o*-benzoylbenzoic acid (either hydrated or anhydrous) is heated with 10 cc. of concentrated sulfuric acid in a small Erlenmeyer flask for 1 hour on the steam bath. The mixture should be shaken at the start so that all of the solid dissolves rapidly. The color changes from red to brown. The anthraquinone formed is precipitated by pouring the hot solution onto about 100 g. of ice. Digestion of the precipitate, accomplished by heating the mixture for a short time at the boiling point, gives a more granular product. This is collected by suction filtration, washed well with water and then with a little dilute ammonia in order to remove traces of unchanged starting material. The product, which need not be dried, is crystallized from glacial acetic acid. To do this the material is transferred to a 250-cc. flask, covered with 60–80 cc. of glacial acetic acid, and boiled under the reflux condenser (free flame) until the solid is dissolved. It is usually not necessary to filter the solution; if this is done, it must be carried out under the hood. The melting point need not be recorded, since it is at about the upper limit of the sulfuric acid bath (m.p. 286°, corr.).

β-Methylanthraquinone (m.p. 173°) can be prepared by the same method from *p*-toluylbenzoic acid and it crystallizes well from alcohol.

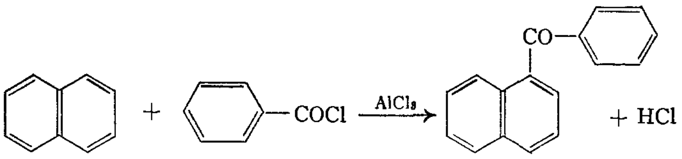
Vatting Test. — A small quantity of anthraquinone is placed in a test tube and covered with about 5 drops of sodium hydroxide solution and a little water. A very small pinch of sodium hydrosulfite, $Na_2S_2O_4$, is added and the mixture is warmed until a strong vat color is produced (alkaline solution of anthrahydroquinone). The solution is then shaken with the air until the vat color disappears. This is a general test for anthraquinones.

Ring Closure with Dilute Acid. — Pour 3 cc. of concentrated sulfuric acid onto 1 cc. of water and cover about 0.05 g. of *o*-benzoylbenzoic acid in a small test tube with 0.5–1 cc. of this dilute acid. Heat the tube very gently over a small "soft" flame until the yellow solution turns darker and somewhat red and crystals of anthraquinone begin to separate (this occurs at about 160°). Allow the tube to cool to room temperature, dilute with water, force a wad of crystals into the end of the tube with a stirring rod, decant the acid solution and wash by decantation. Perform a vat test. By this simple procedure it is an easy matter to determine if a given acid is of the type represented by *o*-benzoylbenzoic acid.

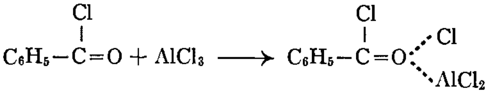
EXPERIMENT 38[1]

1-BENZOYLNAPHTHALENE

(The Perrier Modification of the Friedel and Crafts Reaction)



An excellent modification of the usual ketone synthesis was introduced in 1904 by Perrier,[2] but as yet it has attracted little attention. The application of the method is limited, to be sure, to benzoyl chloride and to closely related substances. Perrier heated a mixture of equivalent quantities of benzoyl chloride and aluminum chloride, with or without a solvent, and obtained an addition compound having the composition of the sum of the reactants. It is probably an oxonium salt (the molecular weight is actually twice that indicated):

(1) 

$$C_6H_5-\overset{\overset{\displaystyle Cl}{|}}{C}=O + AlCl_3 \longrightarrow C_6H_5-\overset{\overset{\displaystyle Cl}{|}}{C}=O\begin{smallmatrix}\cdot\cdot Cl\\ \cdot\cdot AlCl_2\end{smallmatrix}$$

Though aluminum chloride itself is quite insoluble in carbon bisulfide, this addition product dissolves easily in the solvent named. On adding to this solution one equivalent of some hydrocarbon, such as naphthalene, there is an immediate, but not a violent, reaction, and a crystalline solid separates at once from the solution. This solid contains aluminum, and from its composition and from the fact that hydrogen chloride is evolved

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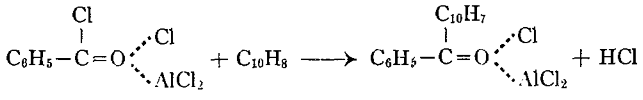
[1] On account of the fire hazard attending the use of carbon bisulfide, this preparation is to be carried out only as a special experiment by selected students.

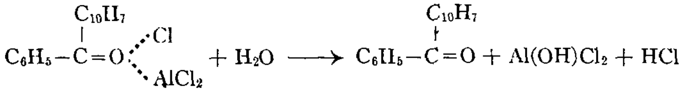
[2] Perrier, *Bulletin de la Société Chimique de Paris*, [3], **31**, 859 (1904).

during its formation, it is concluded that the reaction takes the following course:

(2) 

$$\mathrm{C_6H_5-\overset{\overset{Cl}{|}}{C}=O\begin{smallmatrix}\cdot Cl\\ \cdot AlCl_2\end{smallmatrix} + C_{10}H_8 \longrightarrow C_6H_5-\overset{\overset{C_{10}H_7}{|}}{C}=O\begin{smallmatrix}\cdot Cl\\ \cdot AlCl_2\end{smallmatrix} + HCl}$$

The solid is collected by filtration, dried and treated with water, when it at once decomposes:

(3) 

$$\mathrm{C_6H_5-\overset{\overset{C_{10}H_7}{|}}{C}=O\begin{smallmatrix}\cdot Cl\\ \cdot AlCl_2\end{smallmatrix} + H_2O \longrightarrow C_6H_5-\overset{\overset{C_{10}H_7}{|}}{C}=O + Al(OH)Cl_2 + HCl}$$

The ketone is separated from the aqueous mixture by filtration or ether extraction.

The rapidity with which the preparation can be completed will be appreciated on carrying out the experiment. Another distinct advantage of the Perrier procedure is that it furnishes very pure products. The 1-benzoylnaphthalene obtained as a crude product must be freed by crystallization from traces of insoluble material coming from the commercial aluminum chloride, but it is already free from the organic tar which ordinarily accompanies a Friedel and Crafts reaction product, and, above all, it is free from isomers. Regardless of the procedure used, benzoyl chloride attacks naphthalene in both the α and β positions, and from 5 to 15 per cent of 2-benzoylnaphthalene is formed in the course of the reactions under discussion. In the ordinary procedure this isomer appears in the final product, and the separation of the two isomers is a difficult process. In the Perrier method the addition product containing the 2-isomer, formed as indicated in Equation (2), is eliminated easily and completely on account of its solubility in carbon bisulfide. The solid which is collected contains only the 1-isomer; the 2-isomer remains entirely in solution in the mother liquor. It should be noted that the mother liquor also retains, and eliminates from the main product, any organic tars which may be formed.

Procedure. — The Perrier addition product is prepared by carefully heating together in a dry 500-cc. Erlenmeyer flask a mixture of 11.5 cc. (14 g.) of pure benzoyl chloride[1] and 14 g. of fresh aluminum chloride (hood). It is well to grind the aluminum chloride to a fine powder and to sprinkle it slowly into the benzoyl chloride, while rotating the flask to mix the contents thoroughly. The mixture warms of itself and a part of the solid dissolves without the application of external heat. In order to complete the reaction hold the flask by the neck and heat it gently over a " soft " free flame, being careful to avoid overheating. When the particles of aluminum chloride have nearly all disappeared the melt should be deep yellow or brown in color, but it should not show signs of decomposition. Allow the flask to cool (using an air blast if desired) and do not proceed further until all parts of the vessel, including the contents, are thoroughly cold. The addition compound sets to a yellow or orange crystalline product. Add 80 cc. of carbon bisulfide, warm gently and cautiously on the steam bath with shaking until the solid is all dissolved.

Caution: Carbon bisulfide is very volatile (b.p. 46°) and extremely inflammable. Be very careful throughout the experiment to keep it well out of the reach of any flames.

Allow the solution to cool somewhat, but without causing the addition compound to crystallize, and set the flask in a well ventilated hood. Add in portions 12.8 g. of solid naphthalene. This may be done just as rapidly as the vigorous evolution of hydrogen chloride permits. Note that the solution does not become warmer; the activity observed is due to gas evolution rather than to boiling. Warm the mixture for a few minutes on the steam bath to complete the reaction and then cool it thoroughly in an ice bath and rub the material against the walls of the flask to cause the dark oil to solidify. Collect the dark-colored solid material by suction filtration, being careful to use a perfectly dry funnel and flask.

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[1] Even the best grades of benzoyl chloride may give inferior results and the material supplied should be freshly distilled from an all-glass apparatus in the hood (lachrymator; attacks corks!).

Wash the precipitate with a small quantity of fresh solvent, let it drain well, and then stir it in portions into about 300 cc. of water containing 20 cc. of concentrated hydrochloric acid. Heat the mixture on the steam bath (hood) for about 10 minutes in order to decompose completely the aluminum complex and to expel adhering carbon bisulfide, cool to room temperature and extract the oily or semi-solid product with ether. Dry the ethereal solution with calcium chloride, adding a small quantity of decolorizing carbon, filter, and distil the solvent from the steam bath. The residual oil should solidify on thorough cooling, and the product is best purified by taking it up in ethanol or methanol and allowing crystallization to proceed slowly. If the product " oils out " on cooling to room temperature more solvent should be added.

Pure 1-benzoylnaphthalene, also called phenyl α-naphthyl ketone, melts at 76°. The yield is about 18 g. The isomeric 2-benzoylnaphthalene melts at 82°.

NOTES: The experiment can be varied by using acenaphthene or β-methylnaphthalene in place of naphthalene. The Perrier procedure is applicable to the benzoylation of various other hydrocarbons, for example the 1,6-, 2,3-, 2,6-, and 2,7-dimethyl derivatives of naphthalene. Phenanthrene gives a mixture of several isomers in the Friedel and Crafts reaction, the 2- and 3-isomers ordinarily predominating; the otherwise difficultly accessible 1-benzoylphenanthrene can be isolated through the crystalline Perrier complex in a pure condition, if in low yield (8 per cent). The final aluminum chloride reaction product corresponding to that in Equation (2) may not in every case separate from the solution. In such an event it is necessary to pour the solution at this point onto a large volume of ice and to remove the solvent by steam distillation. The naphthalene derivatives react with the Perrier compound from benzoyl chloride much more rapidly than does benzene, and with the latter compound it is necessary to reflux the solution for some time in order to complete the reaction.

An alternate method of preparing the double compound from benzoyl chloride and aluminum chloride is to reflux a mixture of these materials in carbon bisulfide solution until the aluminum chloride is all dissolved (10–15 minutes). A refinement is to filter the solution through a sintered glass funnel, thus eliminating a trace of dark impurity. Moisture should be excluded during the operation, however, and this makes the process somewhat troublesome.

EXPERIMENT 39

BENZOPHENONE

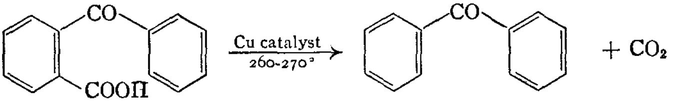
Like other aromatic ketones this compound can be prepared by the general method of Friedel and Crafts:

$$C_6H_5COCl + C_6H_6 \xrightarrow{AlCl_3} C_6H_5COC_6H_5 + HCl$$

It also can be obtained by an interesting modification of the alkylation reaction, carbon tetrachloride being condensed with two molecules of benzene and the benzophenone dichloride being hydrolyzed by steam:

$$C_6H_6 + CCl_4 + C_6H_6 \xrightarrow{AlCl_3} C_6H_5CCl_2C_6H_5 + 2HCl$$
$$C_6H_5CCl_2C_6H_5 + H_2O \longrightarrow C_6H_5COC_6H_5 + 2HCl$$

When run on a large scale where careful control is possible as, for example, when 500 g. of benzophenone is to be prepared, the method is practical and economical, for an 85 per cent yield of a fairly good grade of the ketone can be obtained. Still a third method is utilized in the present experiment and it consists in the decarboxylation of *o*-benzoylbenzoic acid:[1]



The acid is heated in a distilling flask with a small amount of catalyst until no more carbon dioxide is evolved, and the ketone is then distilled. The yield and quality of the benzophenone are both good and the method has the further advantage of being inexpensive and rapid.

The preparation illustrates the manner in which aromatic acids usually are decarboxylated. The elimination of carbon

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[1] Dougherty, *Journal of the American Chemical Society*, **50**, 571 (1928).

dioxide takes place more readily with the aromatic acids than with the ordinary aliphatic acids, probably because the carboxyl group is attached to another unsaturated group, that is, the benzene nucleus. Oxalic acid, $(COOH)_2$, has the somewhat similar structural feature that two unsaturated carboxyl groups are directly connected, and it likewise loses carbon dioxide readily. The ortho-keto acid used here is decarboxylated with particular ease, the reaction commencing at about 150°. It should be noted that the catalyst is all-important, for without it *o*-benzoylbenzoic acid is converted on heating (at 300–350°) chiefly into anthraquinone, water being eliminated rather than carbon dioxide. One per cent of copper is enough to change the entire course of the reaction, but the exact way in which it functions is not yet clear. The metal itself is not the active catalyst, for it is effective only after it has dissolved in the molten acid to form a copper salt. In fact, since it dissolves rather slowly, it is better to introduce the copper in the form of the normal copper salt of *o*-benzoylbenzoic acid $(C_6H_5COC_6H_4COO)_2Cu$, for this dissolves at once. It might be supposed that this is the true catalyst, but observation of the color changes in the course of the reaction will show that this cannot be the case. The matter still awaits solution.

The unpurified, hydrated *o*-benzoylbenzoic acid prepared as in Experiment 36 is suitable for use as the starting material. It is well to drive off the water of crystallization before adding the catalyst for otherwise this water will cause trouble at the high temperature and interfere with the even heating. The decarboxylation must be carried to completion, for any unchanged *o*-benzoylbenzoic acid will be converted into anthraquinone when the temperature is raised for the distillation. Overheating will also lead to contamination with yellow anthraquinone.

It is of interest that benzophenone exists in two different forms. The ordinary, or stable form crystallizes easily and forms opaque prisms melting at 48°; the labile form solidifies only very slowly and gives transparent crystals melting at 26°.

The two forms have identical chemical properties and they are interconvertible. If the stable form is introduced carefully into a distilling flask in such a way that no tiny particles (" seed ") lodge in the side tube or above it, and if the material is slowly distilled from clean, seed-free apparatus, the distillate is a water-clear liquid which can be cooled to 0° without solidifying. This is the labile form in liquid condition. If the liquid is rubbed against the containing walls, or if it is inoculated with a trace of the stable form of benzophenone, it suddenly changes to the stable form and solidifies. There is a considerable temperature rise, due to a combination of the heats of isomerization and of crystallization. If the liquid labile form is allowed to stand in an ice chest for several hours or days it sometimes solidifies, and it then remelts at 26°. The solid material, however, is not easy to obtain since it appears inadmissible to try to induce crystallization either by rubbing or by the use of solvents, for this only leads to a change to the more stable form.

Procedure. — Place 24.4 g. (0.1 mole) of *o*-benzoylbenzoic acid monohydrate in a 50-cc. distilling flask supported by means of a clamp fitted with a strip of asbestos paper (no rubber!). Heat the flask gently with a free flame (no gauze) with shaking until the solid is all melted and some of the water is expelled. Then insert a cork stopper carrying a thermometer so arranged that the bulb is completely submerged in the molten acid. Connect the side tube of the flask to the suction pump and again heat gently for a few minutes in order to eliminate the water. Bring the temperature of the liquid to 200° and play the flame gently over the upper parts of the flask in order to expel any water which may condense here. Then disconnect the tube leading to the suction pump, remove the stopper and add 2 g. (0.004 mole) of the copper salt of *o*-benzoylbenzoic acid (end desk[1]),

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[1] Enough copper salt for 12 runs is prepared as follows: Dissolve 24.4 g. of *o*-benzoylbenzoic acid monohydrate and 5.3 g. of anhydrous sodium carbonate in 300 cc. of water by boiling, cool to 50° by the addition of ice and add a solution of 12.5 g. of copper sulfate crystals in 25 cc. of water. The voluminous blue-green precipitate is a hydrate; heat and stir the suspension until this changes to the granular, anhydrous salt. Collect and wash this material and dry it at 110°;

using a dry funnel or a paper cone so that the salt cannot lodge in or above the side tube. Replace the thermometer and connect the outlet of the flask by means of a section of rubber tubing to a glass tube resting in a graduate in which there is just enough water to seal the tube, so that the evolution of carbon dioxide can be followed. More water may be dangerous in case of a suck-back. Heat the flask with a small free flame and bring the temperature of the liquid to 265° without delay, and by constant adjustment maintain a temperature as close to this as possible throughout the reaction. There should be a steady, vigorous evolution of gas and in 20–25 minutes metallic copper should separate from the clear solution. In another 5 minutes, with the temperature still at 265°, the bubbling in the trap should cease. When this point is reached the trap is disconnected, the flame is removed, and the thermometer is raised to the usual position for distillation. Using an air condenser, distil the benzophenone into a weighed 50-cc. Erlenmeyer flask, using a free flame and no gauze. The true boiling point of benzophenone is 306°, but with so much of the thermometer thread extending out of the heated area the uncorrected boiling point may be as low as 294°. The condensate is usually colorless or light yellow. Continue the distillation until there is a marked rise in the boiling point (4–5°) or until the distillate becomes dark yellow.[1]

Record the weight of the crude benzophenone (15–18 g.) and see if it will solidify on cooling under the tap or on being rubbed with a stirring rod. Unless the laboratory air carries sufficient ordinary benzophenone to act as seed, one usually obtains at this point the labile form, which (particularly since it is not quite pure) is very reluctant to solidify. If this is the case fix a barely visible particle of ordinary benzophenone on the end of a stirring rod and rub it into the liquid against the side of the

yield, 24–25 g. (The salt separates as an oil if the solution is at the boiling point when the copper sulfate is added.)

[1] The dark residue in the flask can be loosened and the mass of copper dislodged by adding benzene and heating the flask on the steam bath for one-half hour. The dark solution is decanted and if necessary the process is repeated.

flask. When crystallization sets in note the warming against the palm of the hand. Save a trace of seed. Benzophenone crystallizes well from ligroin, b.p. 60–90° (alcohol leaves too much material in the mother liquor). Without removing the material from the original receiving flask, cover it with the ligroin, using 1.5 cc. per gram of solid, and dissolve by heating on steam bath. Without using charcoal or filtering, cool the solution in an ice bath until it becomes cloudy and the product "oils out." Then remove the flask, allow liquid to come to rest, and add seed. As crystallization progresses return flask to the bath and eventually stir the mixture and cool it thoroughly. Collect crystals on a suction funnel and use 30–40 cc. of fresh, ice-cold solvent to wash any yellow material into the mother liquor. Recrystallize the product if it is not white; very large crystals can be obtained by allowing the solution to cool slowly and without seed; yield, 13–16 g., m.p. 47–48°. In calculating the yield for crude and purified material, consider the theoretical yield 0.108 mole, since 0.008 mole was used to make the catalyst.

Methods of Decarboxylation. — Instead of 2 g. of copper salt as catalyst, one can use 0.3 g. of copper powder or 0.5 g. of basic copper carbonate. In the first case the flask should be shaken during heating until the metal is dissolved. Copper carbonate should be added carefully and the mixture shaken and gently heated until the neutralization reaction subsides and the water formed is expelled. Most of the substituted benzoylbenzoic acids obtainable by the phthalic anhydride synthesis can be decarboxylated with the use of basic copper carbonate as catalyst.

Decarboxylation can be accomplished also (1) by using the copper chromite catalyst employed in high-pressure hydrogenations (page 453), (2) by heating the acid with copper powder in quinoline solution,[1] and (3) by heating the barium salt of the acid in vacuum with sodium methoxide.[2]

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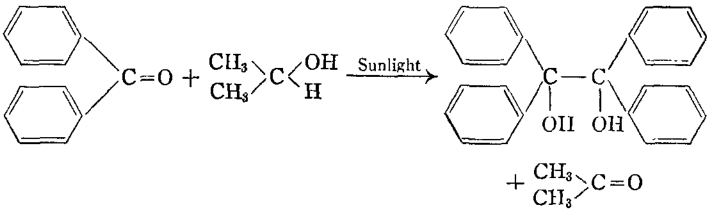
[1] Shepard, Winslow and J. R. Johnson, *Journal of the American Chemical Society*, **52**, 2083 (1930).

[2] Mai, *Berichte der deutschen chemischen Gesellschaft*, **22**, 2133 (1889); see Case, *Journal of the American Chemical Society*, **56**, 715 (1934).

EXPERIMENT 40

BENZOPINACOL

(Photochemical Reduction)



Although benzophenone is a colorless substance and absorbs no light in the visible region of the spectrum, it does have an unsaturated carbonyl group which is paired, or " conjugated " with the double bonds of the two phenyl groups and hence it is not surprising that the compound absorbs ultraviolet rays. The loosely held electrons of the unsaturated centers are set in vibration by rays of short wave-length through a resonance effect. When the molecule acquires energy in this way from the sunlight it becomes activated and in this state it is capable of entering into reactions which are not otherwise possible. Under ordinary conditions benzophenone is not at all easily reduced; it is in fact one of the least reactive of the simple ketones. Isopropyl alcohol, on the other hand, is certainly not a powerful reducing agent. When, however, a mixture of these two relatively unreactive substances is exposed to the sunlight benzophenone is reduced by isopropyl alcohol with remarkable ease to benzopinacol, according to the equation given above. It is interesting to note that the aliphatic ketones are not capable of undergoing a similar bimolecular reduction under the influence of photocatalysis, presumably because they lack the extensive unsaturation and conjugation of the di-aryl ketones. Acetone is a product of the above reaction and yet it is not affected by the exposure.

The experiment described below is quite simple, but it is best carried out during warm weather and when there is some prospect for continued bright sunshine. Otherwise the reaction is slow and the benzophenone may have to be brought into solution by periodic heating.

Procedure.[1] — In a 100-cc. round-bottomed flask dissolve 10 g. of benzophenone in 60–70 cc. of isopropyl alcohol by warming, fill the flask to the neck with more of this alcohol and add one drop of glacial acetic acid. (If the acid is omitted enough alkali may be derived from the glass to destroy completely the reaction product by the alkaline cleavage described below.) Stopper the flask with a well-rolled, tightly-fitting cork which is then wired in place. Invert the flask in a 100-cc. beaker, leave it in the desk over night to see that there is no "dark" reaction, and then expose it to the best available sunlight. Since benzopinacol is but sparingly soluble in the alcohol, its formation can be followed from the separation around the walls of small, colorless crystals (benzophenone forms large, thick prisms). In the bright August sunlight of Cambridge the first crystals separate in about 5 hours, and the reaction is practically complete (95 per cent yield) in four days. In the winter the reaction may take as long as two weeks, and any benzophenone which crystallizes must be brought into solution by warming on the steam bath. When the reaction appears to be at an end, chill the flask if necessary and collect the product. The material should be directly pure, m.p. 188–189°. In case the yield is poor more material can be obtained by further exposure of the mother liquor. The filtrate can be used for the reduction of several further batches of benzophenone.

Alkaline Cleavage. — Suspend a small test sample of benzopinacol in alcohol, heat to boiling and make sure that the amount of solvent is insufficient to dissolve the solid. Add one drop of sodium hydroxide solution, heat for a minute or two and observe

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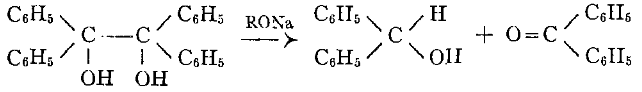
[1] Bachmann, *Journal of the American Chemical Society*, **55**, 391 (1933).

the result. The solution contains equal parts of benzhydrol and benzophenone, formed by the following remarkable reaction:

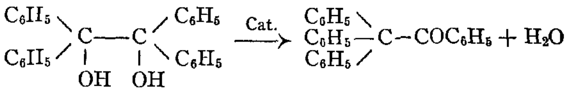


Benzopinacol, m.p. 189° Benzhydrol, m.p. 68° Benzophenone, m.p. 48°

The low-melting cleavage products are much more soluble than the starting material. For an explanation of the transient color see the paper of Bachmann cited above.

Benzophenone may be converted into benzhydrol in nearly quantitative yield by following the procedure outlined above for the preparation of benzopinacol with one change: instead of adding a drop of glacial acetic acid, dissolve a very small piece of sodium (0.05 g.) in the isopropyl alcohol. The reaction is complete when, after exposure to the sunlight, the greenish-blue color disappears. The solution is diluted with water, acidified and evaporated. What happens, of course, is that benzopinacol is produced as before by photochemical reduction, but it is at once cleaved by the sodium alcoholate; the benzophenone formed by cleavage is converted into more benzopinacol, cleaved and eventually consumed.

Pinacolone Rearrangement. — This further remarkable reaction of benzopinacol is characterized by its speed and by the high yield obtainable:



Benzopinacolone, m.p. 179–180°

There is no possibility here for the formation of by-products, as is the case with the aliphatic pinacols (see page 100). Iodine serves as a very effective catalyst.[1]

In a 125-cc. Erlenmeyer flask place 5 g. of benzopinacol, 25 cc. of glacial acetic acid and two or three very small crystals of iodine (0.05 g.). Heat to the boiling point for a minute or two

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[1] Bachmann, "Organic Syntheses," **14**, 12 (1934).

under a reflux condenser until the crystals are all dissolved, and then reflux the red solution for 5 minutes. On cooling the pinacolone separates to form a stiff paste. Thin this with alcohol, collect the product and wash it free from iodine with alcohol. The material should be directly pure; yield, 95 per cent.

EXPERIMENT 41

AZO DYES

The coupling of benzene diazonium chloride with phenol, or with one of the cresols or naphthols, gives rise to a type of azo compound which is highly colored, but which contains no acidic or basic groups, which is not soluble in water, and which thus lacks two of the properties ordinarily required of a direct dyestuff. The introduction of a sulfonic acid group is sufficient to confer on the substance the desired properties, but the direct sulfonation of an azo compound often presents some difficulties. A much simpler method is to use a sulfonic acid derivative of one of the two components of the coupling reaction. Many azo dyes are prepared by the coupling of phenols and amines with diazotized sulfanilic acid.

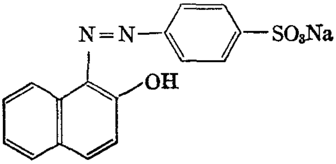
Since sulfanilic acid in the form of the inner salt is not very soluble in water, it is converted into the soluble sodium salt prior to diazotization:

$$2H_3\underbrace{N.C_6H_4.SO_3} + Na_2CO_3 \longrightarrow 2H_2N.C_6H_4.SO_3Na + CO_2 + H_2O$$

On adding sodium nitrite to the solution and treating the mixture with a mineral acid, diazotization occurs and the diazonium compound soon separates as a colorless solid which probably has the structure of an inner salt:

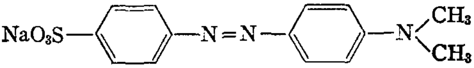
$$H_2N.C_6H_4.SO_3Na + 2HCl + NaNO_2 \longrightarrow N{\equiv}\underbrace{N.C_6H_4.SO_3} + 2NaCl + 2H_2O$$

The coupling of the inner diazonium salt with a phenol takes place best in the presence of alkali in which, of course, the phenol is readily soluble. β-Naphthol, for example, reacts in alkaline solution to form the dyestuff known as Orange **II,** which is isolated as the sodium salt:



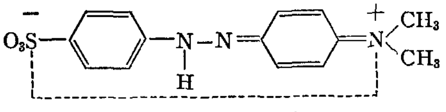
It is a direct dye for wool or silk.

Primary and secondary amines do not always couple directly but form diazoamino compounds: RNH.N=N.C_6H_4.SO_3Na. Tertiary amines, having no replaceable hydrogen in the amino group, couple readily in the para position. The tertiary amines usually are not soluble in alkali, and a solution in hydrochloric acid cannot be used because the coupling reaction is inhibited by a high concentration of hydrogen ion. The slightly ionized acetic acid, however, serves to dissolve the amine without being so strongly acidic as to prevent the reaction. This is the method used in coupling diazotized sulfanilic acid with dimethylaniline to give a product which, in the form of the sodium salt, is known as Methyl Orange, or Helianthin:



(Alkali-stable form)

This particular compound is more useful as an indicator than as a dye, for it changes color at a certain concentration of hydrogen-ion (*p*H 3.2 – 4.4). Acidification of a solution of the orange sodium salt converts the substance into a red form. This is an inner-salt best represented by the following formula:



(Acid-stable form)

The change from one chromophoric group to another accounts for the change in color.

Directions are given below for the diazotization of sulfanilic acid and for coupling this with both β-naphthol and dimethylaniline. Select one or the other of these two for preparation, but in either case perform the test experiments given below with both dyes (exchange samples with a neighbor). Remember that the compounds are active dyes for proteid materials and take special care to avoid spilling the substances or getting them on the hands.[1]

Diazotization of Sulfanilic Acid. — In a 250-cc. Erlenmeyer flask dissolve 10.5 g. (0.05 mole) of sulfanilic acid crystals (dihydrate) in 100 cc. of 2.5 per cent sodium carbonate solution (or use 2.65 g. of anhydrous soda and 100 cc. of water) by boiling. Cool the solution under the tap, add 3.7 g. of sodium nitrite and stir until it is dissolved. Pour the solution into a beaker or flask containing about 50 g. of ice and 10 cc. of concentrated hydrochloric acid. In a minute or two a powdery white precipitate of diazobenzene sulfonate should separate and the material is then ready for use. The product is not collected but is used in the form of the suspension. It is more stable than most diazonium salts, and it will keep for a few hours, but not indefinitely.

A. Orange II (1-*p*-Sulfobenzeneazo-2-Naphthol Sodium Salt). — In a 600-cc. beaker dissolve 7.2 g. (0.05 mole) of β-naphthol in 40 cc. of cold 10 per cent sodium hydroxide solution and pour into this solution, with stirring, the suspension of diazotized sulfanilic acid (rinse). Coupling occurs very rapidly and the dyestuff, being a sodium salt, separates easily from the solution on account of the presence of a considerable excess of sodium ion (from the soda, the nitrite, and the alkali added). Stir the crystalline paste thoroughly to effect good mixing and after 5–10 minutes heat the mixture until the solid is all dissolved. Add 20 g. of sodium chloride to further decrease the solubility of

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[1] In case of an accident the hands can be cleaned by soaking them in a warm, dilute, slightly acidic (H_2SO_4) solution of potassium permanganate until they are quite black with manganese dioxide stain, and then removing this in a bath of warm, dilute sodium bisulfite solution.

the product, bring this all into solution by heating and stirring, set the beaker in a pan of ice and water and let the solution cool undisturbed.[1] Eventually cool thoroughly by stirring and collect the product on a Büchner funnel. Use saturated sodium chloride solution, rather than water, for rinsing the material out of the beaker and for washing the filter cake free from the dark-colored mother liquor. The filtration is somewhat slow.[2]

The product dries only slowly and it contains about 20 per cent of sodium chloride. The crude yield is thus not significant and the material need not be dried before being purified. This azo dye is too soluble to be crystallized from water; it may be obtained in a fairly satisfactory form by adding saturated sodium chloride solution to a hot, filtered solution of the dye in water and cooling, but the best crystals are obtained from aqueous alcohol. Transfer the filter cake to a beaker, wash the material from the paper and funnel with water, and bring the substance into solution at the boiling point. Avoid a large excess of water but use enough to prevent separation of solid during filtration (volume: about 100 cc.). Filter by suction through a Büchner funnel which has been preheated on the steam bath (wash). Pour the filtrate into a beaker (wash), estimate the volume and if this is greater than 120 cc. evaporate by boiling. Cool to 80°, add 200–250 cc. of alcohol, and allow crystallization to proceed. Cool well before collecting. Rinse the beaker with mother liquor and wash finally with a little alcohol. The yield of pure, crystalline material is 13–16 g. Orange II separates from aqueous alcohol with two molecules of water of crystallization and allowance for this should be made in calculating the percentage yield. When the water of

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[1] This gives a more easily filterable product. If time permits it is still better to allow the solution to cool in the air.

[2] If the filtration must be interrupted, close the rubber suction tubing while the pump is still running with a screw pinch clamp placed close to the filter flask and then disconnect the tubing from the pump. Fill the funnel and set the unit aside; if the rubber stopper fits properly the suction will be maintained and filtration will continue. See the discussion on page 321 of the use of a rubber dam or balloon in slow filtrations.

hydration is eliminated by drying at 120° the material becomes fiery red.

B. (Alternate.) Methyl Orange (Helianthin, *p*-Sulfobenzene-azo-4-Dimethylaniline Sodium Salt). — In a test tube mix well 6.3 cc. (0.05 mole) of dimethylaniline and 3 cc. (0.05 mole) of glacial acetic acid. To the suspension of diazotized sulfanilic acid contained in a 600-cc. beaker add with stirring the solution of dimethylaniline acetate (rinse). Stir and mix thoroughly and within a few minutes the red, acid-stable form of the dye should separate. A stiff paste should result in 5–10 minutes and 35 cc. of 20 per cent sodium hydroxide solution is then added to produce the orange sodium salt. Stir well and heat the mixture to the boiling point, when a large part of the dye should dissolve. Place the beaker in a pan of ice and water and allow the solution to cool undisturbed (see Note 1 on page 209). Then cool thoroughly, collect the product on a Büchner funnel, using saturated sodium chloride solution rather than water to rinse the flask and to wash the dark mother liquor out of the filter cake.

The crude product need not be dried but may be crystallized at once from water after making preliminary tests to determine the proper conditions. The yield is 10–12 g.

TESTS

1. Solubility and Color. — Compare the solubility in water of Orange II and Methyl Orange and account for the difference in terms of structure. Treat the first solution with alkali and notè the change in shade due to salt formation; to the other solution alternately add acid and alkali.

2. Reduction. — Characteristic of an azo compound is the ease with which the molecule is cleaved at the double bond by the action of reducing agents to give two amines. Since the amines are colorless, the reaction is easily followed by the color change. The reaction is of use in the preparation of hydroxy-amino and similar compounds, in the analysis of azo dyes by titration with a reducing agent, and in the identification of azo compounds from an examination of the cleavage products.

(a) *Acid Reduction.* — Dissolve about 0.5 g. of stannous chloride in 1 cc. of concentrated hydrochloric acid, add a small quantity of the azo compound (0.1 g.) and heat. A colorless solution should result and no precipitate should form on adding water. The amino phenol or the diamine derivative is present as the soluble hydrochloride, the other product of cleavage, sulfanilic acid, is sufficiently soluble to remain in solution unless this is very concentrated. A modification of this method of reduction is used in quantitative analysis.

(b) *Neutral Reduction.* — Suspend a small spatulaful of the azo dye in 1 cc. of water, add a small quantity of sodium hydrosulfite and heat the mixture until no further change occurs. Test the precipitate formed in the reduction of Orange II and see if it dissolves in alkali, as would be expected. If after the reduction of Methyl Orange a clear solution is obtained, cool the solution and see if a solid can be caused to crystallize. If not, repeat the test with a somewhat greater amount of material.

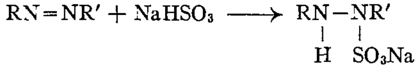
The reduction with sodium hydrosulfite proceeds as follows:

$$RN{=}NR' + 2Na_2S_2O_4 + 4H_2O \longrightarrow RNH_2 + H_2NR' + 4NaHSO_3$$

The reaction is of great value where it is desired to isolate the aminophenol or the diamine derivative and where the sulfanilic acid is to be discarded, for the separation of the cleavage products is very easily accomplished. The sulfanilic acid forms a sodium salt and remains in solution, the more valuable component will either crystallize or else it can be extracted from the solution with ether. Write the formulas of the substances produced in the present tests.

If in the test it is desirable to prove that the substance which separates is an amine, the material should be collected before testing the solubility in hydrochloric acid, for the addition of acid to the reduction mixture causes the decomposition of the hydrosulfite with the separation of sulfur.

3. Addition of Bisulfite. — That a given colored compound yields an amine on reduction is not sufficient evidence that the substance in question is an azo compound; it might be a nitro compound. A further characteristic test is furnished by the reaction with sodium bisulfite, which probably proceeds as follows:



$$\mathrm{RN{=}NR' + NaHSO_3 \longrightarrow \underset{\displaystyle H}{RN}{-}\underset{\displaystyle SO_3Na}{NR'}}$$

The $N{=}N$ group resembles the $C{=}O$ group in this addition reaction. The addition product is either colorless or else quite faintly colored in comparison to the original azo compound. Nitro compounds do not react with sodium bisulfite.

Add two drops of 10 per cent sodium hydroxide solution to 1 cc. of saturated sodium bisulfite solution, heat the mixture, add a few drops of an aqueous solution of the azo compound, heat again, and if no change is apparent at once allow the mixture to stand under observation for several minutes.

EXPERIMENT 42

o-CHLOROTOLUENE

The Sandmeyer Reaction

The replacement of the diazonium-salt group by chlorine, bromine, or by the nitrile group takes place only in the presence of a cuprous salt (Sandmeyer) or copper powder (Gattermann). The iodine atom alone can be introduced without the use of a catalyst. In the present preparation the amino group of *o*-toluidine is to be replaced, after diazotization, by a chlorine atom. Since cuprous chloride is insoluble in water, it is brought into a form suitable for reaction in a solution in concentrated hydrochloric acid. Since the salt either in the dry form or in this solution is susceptible to air oxidation, fresh material must be made up for each preparation. Of the many methods which have been used for preparing the acid solution of cuprous chloride required for the Sandmeyer reaction, two have been selected as being particularly satisfactory: (a) reduction of copper sulfate by sodium sulfite in the presence of sodium chloride, followed by solution of the product in hydrochloric acid; (b) reduction of cupric chloride by zinc and hydrochloric acid. Either method may be employed.

For the diazotization the amine must be converted into the hydrochloride. In the presence of at least two additional equivalents of hydrochloric acid, this is treated with sodium nitrite. The nitrous acid liberated brings about the diazotization and the end of the reaction can be ascertained by testing for the presence of free nitrous acid with starch-potassium iodide paper. Nitrous acid oxidizes the iodide to iodine which forms a blue compound with the starch. The test should be applied only after allowing 3–4 minutes for the reagent to be consumed, and the drop of solution to be tested should be diluted with a few drops of water on a watch glass, for very strong hydrochloric acid alone produces some coloration.

The third equivalent of hydrochloric acid specified for the diazotization is to keep the solution sufficiently acidic to prevent certain side reactions. The most important of these is the interaction of some of the diazonium salt with unchanged amine to form a diazoamino compound, a reaction which occurs readily in a neutral solution. The mixture must be kept very cold during the diazotization for otherwise the diazonium salt may be partially hydrolyzed to the corresponding hydroxy compound, *o*-cresol.

The remainder of the reaction consists in mixing the two solutions, allowing the intermediate addition product containing cuprous chloride and the diazotized amine to decompose under regulated conditions, and working up the product. The reaction mixture usually represents a most unpromising-looking product for it invariably contains, in addition to a large number of different inorganic products, a considerable amount of tar. The reason for this is that the occurrence of certain side reactions is unavoidable: a part of the diazonium compound is hydrolyzed to the corresponding phenol, a part of the latter couples with unreacted diazonium salt to give an azo compound. Fortunately, however, the desired product, *o*-chlorotoluene, is volatile with steam and can be separated from the inorganic products and from most of the tar by steam distillation. Except for slight traces, the azo compound, having a high molecular weight and a low vapor pressure, remains and the only organic by-product which passes over in the distillate in appreciable quantities is the *o*-cresol. This, however, is easily removed by virtue of its solubility in concentrated sulfuric acid (or in alkali).

It is important to note that both the cuprous chloride and the toluene diazonium chloride are sensitive substances which cannot be kept much longer than an hour without deterioration. The solutions must be prepared and mixed in a single period; only after the Sandmeyer reaction proper has subsided is it safe to interrupt the preparation.

Preparation of the Cuprous Chloride Solution. (a) From Cupric Sulfate.[1] — In a 2-liter round-bottomed flask (to be used later in the steam distillation) dissolve 125 g. of copper sulfate crystals ($CuSO_4.5H_2O$) in 400 cc. of water by vigorous boiling. In the hot solution dissolve 35 g. of sodium chloride, which may cause a precipitate of basic copper chloride to form. Prepare a solution of sodium sulfite from 27 g. of sodium bisulfite, 18 g. of sodium hydroxide and 200 cc. of water and add this, not too rapidly, to the hot solution containing copper sulfate. When the solution has become decolorized, or nearly so, cool to room temperature, allow the colorless cuprous chloride to settle, and decant the supernatant liquid. Wash the precipitate once by decantation and dissolve the material in 175 cc. of crude concentrated hydrochloric acid. Keep the flask stoppered until the solution is to be used.

(b) (Alternate) From Cupric Chloride.[2] — In a 2-liter round-bottomed flask dissolve 65 g. of cupric chloride crystals ($CuCl_2.2H_2O$) in 120 cc. of crude concentrated hydrochloric acid and to the green solution add 25 cc. of water and 25 g. of granular (or mossy) zinc. Heat at the point of very gentle boiling for one-half hour, when the reduction should be complete. Stopper the flask loosely and set it aside. Just before use the solution is to be cooled in an ice bath.

Diazotization. — Pour 100 cc. of concentrated hydrochloric acid (1.2 moles) and 50 cc. of water into a 500-cc. Erlenmeyer flask, add 43 g. (43 cc.) of *o*-toluidine (0.4 mole) and shake well in order to convert the amine into the hydrochloride. Cool with shaking in a salt-ice bath and for further cooling during the reaction add to the mixture about 50 g. of ice. The amine hydrochloride should separate as fine crystals, in which form it is in good condition to react. Keeping the mixture at a temperature of 0–5° by vigorous shaking in the salt-ice bath and by adding a few lumps of ice, if necessary, add over a period of about 10 minutes a solution of 28 g. of sodium nitrite in 80 cc. of water

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[1] Marvel and McElvain, "Organic Syntheses," Coll. Vol. I, 163 (1932).

[2] Ullmann, "Travaux Pratiques de Chimie Organique," p. 189 (1922).

with shaking. The hydrochloride should dissolve as the more soluble diazonium salt is formed, and at the end of the addition of the nitrite the solution should contain a trace of nitrous acid. Test with starch-KI paper. The material is now ready for use.

Sandmeyer Reaction. — Cool the solution of cuprous chloride, prepared by either of the above methods, in an ice bath until well below room temperature. Pour in the cold solution of toluene diazonium chloride with shaking and allow the mixture to come to room temperature. After about 10 minutes warm the mixture gradually on the steam bath with good shaking. As the temperature rises the brown addition product begins to decompose with the evolution of nitrogen and with the formation of an oily layer of *o*-chlorotoluene.

When the decomposition reaction is at an end, steam distil the mixture, continuing the process only as long as oily droplets are present in the distillate, for the product is not appreciably soluble in water. Separate the layer of *o*-chlorotoluene carefully and wash it twice with an equal volume of concentrated sulfuric acid, which removes both the *o*-cresol and the azo compound. Then wash with water to remove the acid. Dry over calcium chloride and distil, using an air condenser and collecting the product boiling at 153–158°. Pure *o*-chlorotoluene boils at 157°. The yield is 25–30 g.

NOTE: *p*-Toluidine can be substituted for the ortho isomer without essential change in the procedure (except that in converting the amine to its hydrochloride it is well to heat the mixture in order to get complete interaction). *p*-Chlorotoluene boils at 162° and freezes at 7.4°. Determine the melting point of the sample, cooling enough of the liquid in a test tube to cover the bulb of a thermometer and noting the temperature when, with good stirring, the two phases are in equilibrium.

EXPERIMENT 43

BENZOIC ACID AND PHENYLGLYOXYLIC ACID

The oxidation of the side chain of an aromatic compound to a carboxyl group is a reaction of some importance in preparative work, and it often is of particular assistance in determining the structure of a new compound or in establishing the position of the side chain. The oxidation of toluene, which gives a 90 per cent yield of benzoic acid, would form a good illustration of the reaction were it not for the fact that the oxidation is complete only after eight hours of heating. While the methyl or ethyl group is attacked only slowly, a group which contains oxygen and which is thus already partially oxidized, is converted much more readily into a carboxyl group. To shorten the time required (to 10–15 minutes!) the example selected to illustrate the reaction is the oxidation of mandelic acid (prepared in Experiment 18):

$$C_6H_5CH(OH)COOH + 2[O] \longrightarrow C_6H_5COOH + CO_2 + H_2O$$

The oxidizing agents most commonly employed for such a reaction are potassium permanganate, potassium dichromate (or chromic anhydride), and dilute nitric acid. When potassium permanganate is used in neutral or alkaline solution it is converted into the insoluble manganese dioxide while the organic oxidation product, being an acid, remains in solution in the form of the potassium salt. The product may be isolated by acidifying the aqueous solution after it has been filtered from the precipitated manganese dioxide. This often is a good method, but it has the disadvantage that the voluminous precipitate is of such a character as to render filtration tedious and to retain a considerable quantity of the oxidation product unless it is washed repeatedly. The large filtrate then has to be evaporated.

Consequently an alternate procedure which expedites the isolation is often very useful. This consists in treating the reaction mixture with sulfur dioxide, which first reduces the manganese dioxide to a water-soluble salt:

$$MnO_2 + SO_2 \longrightarrow MnSO_4,^1$$

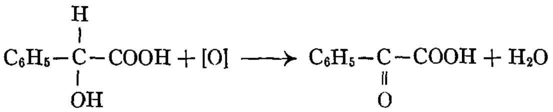
and then liberates the acid from its salt:[2]

$$RCOONa + SO_2 + H_2O \longrightarrow RCOOH + NaHSO_3$$

No extra water is required and the acid is much less soluble in the solution containing manganous sulfate than it is in water, and it usually separates easily.

Even in an acid permanganate oxidation some manganese dioxide often separates unless the solution is strongly acidic and very dilute, and it is convenient to eliminate it by the use of sulfur dioxide or, better, by adding sodium bisulfite, from which sulfur dioxide is liberated by the acid present. This is the method used below.

The oxidation of mandelic acid affords a good illustration of the difference often noted according to whether an acidic or an alkaline medium is used. It is probable that in any case the first step is the oxidation of the secondary alcohol to the keto acid, phenylglyoxylic acid (benzoylformic acid):



$$C_6H_5-\underset{\displaystyle OH}{\overset{\displaystyle H}{\underset{|}{\overset{|}{C}}}}-COOH + [O] \longrightarrow C_6H_5-\underset{\displaystyle O}{\underset{\|}{C}}-COOH + H_2O$$

When this keto acid is formed in the course of the acid oxidation it is converted rapidly to benzaldehyde:

$$C_6H_5CO\boxed{COO}H \longrightarrow C_6H_5CHO + CO_2$$

Oxidation of the aldehyde then yields benzoic acid. In an alkaline medium, however, phenylglyoxylic acid is far more stable. In a hot solution in alkali it is slowly oxidized by

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[1] Manganese dithionate, MnS_2O_6, is also formed.

[2] Some polycarboxylic acids separate at this point as manganous salts which can be collected and decomposed with hydrochloric acid.

permanganate to benzoic acid, but by working in the cold and with just the proper amount of oxidizing agent it is possible to isolate the keto acid in quite good yield. Since phenylglyoxylic acid is extremely soluble in water the actual isolation is rather time-consuming and this is omitted in the experiment below. Instead the product is to be identified as the sparingly soluble phenylhydrazone. It should be noted that permanganate has a more intensive action in an acidic solution than in the presence of alkali.

Acid Oxidation: Benzoic Acid. — Pour 20 cc. of concentrated sulfuric acid into 200 cc. of water in an 800-cc. beaker, dissolve 7.6 g. of mandelic acid in the hot solution, cool to room temperature, and add in small portions and with good stirring 15 g. of potassium permanganate crystals. Note the odor of the oil which separates in the early stages of the reaction. After the permanganate has been added, wash the walls of the beaker and heat the mixture with good stirring for 10 minutes on the steam bath. Some benzoic acid may be noted at this point, mixed with manganese dioxide. Make a "spot test" for permanganate, the color of which may be obscured by the brown dioxide: touch a drop of liquid to a filter paper and hold this to the light. The liquid rim around the brown spot will clearly reveal any color in the solution. If there is no unchanged permanganate, transfer the beaker to the hood and stir in 20 g. of sodium bisulfite ($NaHSO_3$) in small portions. A small additional quantity of the reducing agent may be added if the precipitate of benzoic acid is still brown,[1] but a few hard particles of manganese dioxide in the white product should cause no alarm for they will be removed later in crystallization. Cool well in an ice bath, collect the material and wash it with water. The crude product (about 4.5 g.) need not be dried but may be crystallized at once from about 200 cc. of water; yield, 3.8 g.

Pure benzoic acid melts at 121.5°; the solubility in water at 0° is about 0.2 g. per 100 cc. It sublimes easily, and this is inter-

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[1] After this experience with acidified bisulfite it should not be necessary to ask the instructor how to remove brown stains of manganese dioxide from glassware.

esting to observe. Place a little of the material in a 100-cc. beaker and on the top of this rest a 100-cc. round-bottomed flask filled with cold water. Heat the beaker gently with a small flame for some time and note the character of the sublimate.

Conversion to the Acid Chloride and the Amide. — Place about 0.1 g. of benzoic acid in a test tube (150 mm.) and cover it with enough thionyl chloride to wet the solid and form a thin paste. Heat gently on the steam bath under the hood, when sulfur dioxide and hydrogen chloride are evolved. Heat more strongly for 10 minutes on the steam bath to volatilize the excess thionyl chloride (b.p. 77°), then cool the tube and add a little water. Note the oily appearance and the characteristic odor of benzoyl chloride. Pour off the water, add 1 cc. of concentrated ammonia solution, and shake. The white solid formed is benzamide, $C_6H_5CONH_2$. It melts at 128°, crystallizes well from alcohol, and is easily hydrolyzed by a boiling, aqueous alkali solution.

Alkaline Oxidation: Phenylglyoxylic Acid. — Dissolve 1 g. of mandelic acid in a mixture of 3 cc. of 10 per cent sodium hydroxide solution and 15 cc. of water and add 150 g. of crushed ice. Measure 73 cc. of 1 per cent potassium permanganate solution, add a few cubic centimeters of it to the iced solution and wait a few minutes for a color change. Add the rest of the permanganate, stir, and allow the mixture to stand for about 7 hours, or over night. Then note if there is any unchanged permanganate, making a spot test if in doubt. If the solution is at all pink stir in very small quantities (0.01 g.) of sodium bisulfite until the color is completely discharged (spot test). Filter from the precipitated manganese dioxide by suction, refiltering the first portion in case it is not clear. Make the solution weakly acid to litmus (HCl) and add a solution of 1 g. of phenylhydrazine hydrochloride in a little hot water. Heat nearly to the boiling point for 15 minutes (or else allow the mixture to stand for 2 hours at room temperature), cool and collect the crystalline, yellow phenylhydrazone. Yield, 1 g.; m.p., 159°, with decomposition (loss of CO_2).

Since benzaldehyde is a possible oxidation product, and since its phenylhydrazone melts at 156°, it is necessary to prove that this is not what has been isolated. Write the formulas of the phenylhydrazones of benzaldehyde and of phenylglyoxylic acid and carry out some simple test which will distinguish between them.

EXPERIMENT 44

ACETYLSALICYLIC ACID (Aspirin)

This experiment illustrates a very useful method of acetylating phenols: the phenolic substance is suspended in acetic anhydride and a small quantity of concentrated sulfuric acid is added to serve as a catalyst. The strong mineral acid is very effective in accelerating the reaction and frequently no external heating is required. Certain basic substances may also be employed as catalysts, the commonest ones being fused sodium acetate and pyridine (a tertiary amine). It should be observed that phenols (unlike amines) cannot be acetylated satisfactorily in aqueous solution; the hydroxyl group of a phenol is not attacked much more rapidly by acetic anhydride than is the hydroxyl group of water, with which the phenol would be competing.

Procedure. — Place 1 g. of precipitated salicylic acid[1] in a 50-cc. Erlenmeyer flask and add 2 cc. of acetic anhydride, using the liquid to wash any material lodging on the walls of the flask. Note that there is no visible reaction. Add 2 drops of concentrated sulfuric acid and rotate the flask for a minute or two in order to mix the contents and bring the salicylic acid all into solution. Allow the solution to stand for 5 minutes or longer and whether or not crystals of the acetate have begun to separate rub the mixture well with a stirring rod and cool in ice until a stiff crystalline paste is obtained. Add 20 cc. of water, rub to a thin paste, cool well in an ice bath and collect the white powder on a Witt filter plate. Note the dry weight and the melting point: the yield is about 0.9 g. (the remainder of the material separates slowly from the aqueous mother liquor).

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[1] The material supplied should be precipitated from a sodium bicarbonate solution and dried at 110°.

The product is practically pure, but to obtain it in a nicely crystalline condition dissolve it in dry ether, add about an equal volume of petroleum ether and allow the solution to cool undisturbed in an ice bath.

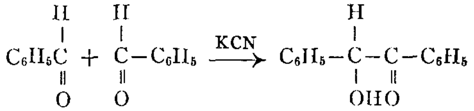
Acetylsalicylic acid decomposes when heated and does not have a true, clearly defined melting point. Decomposition points ranging from 128° to 137° are recorded in the literature. Some decomposition may occur on crystallization if a high-boiling solvent is used.

Test the solubility of your sample in benzene and in hot water, noting the peculiar character of the aqueous solution when it is cooled and when it is then rubbed against the tube with a stirring rod. Note also that the substance dissolves in cold sodium bicarbonate solution and is precipitated by adding an acid. Procure a tablet of commercial aspirin and compare it with your sample. Test the solubility in water and in benzene, observing if it dissolves completely. Note the behavior on heating the product in the melting point apparatus, and determine further if it is all combustible. If an " impurity " is found present this probably is simply some substance used as a binder for the tablets. Is it organic or inorganic? What harmless, edible type of substance do you suppose it is, judging from the various properties?

EXPERIMENT 45

BENZOIN AND BENZIL

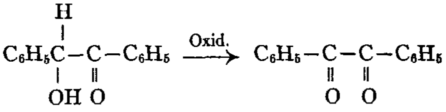
Benzoin is prepared by causing two molecules of benzaldehyde to condense under the influence of potassium cyanide, which acts as a very specific catalyst:



$$C_6H_5\underset{\underset{O}{\|}}{\overset{\overset{H}{|}}{C}} + \underset{\underset{O}{\|}}{\overset{\overset{H}{|}}{C}}-C_6H_5 \xrightarrow{KCN} C_6H_5-\underset{\underset{OH}{|}}{\overset{\overset{H}{|}}{C}}-\underset{\underset{O}{\|}}{C}-C_6H_5$$

The yield in the reaction is highly dependent upon the quality of the benzaldehyde used. Unless benzaldehyde is stored in the complete absence of light and air it rapidly deteriorates as the result of auto-oxidation to benzoic acid. Even though crystals of the acid are not visible in the reagent bottle there may be a considerable quantity in solution in the liquid. The benzaldehyde supplied for the present experiment should give but little gas when a test portion is shaken with sodium carbonate solution.[1]

Benzoin can be oxidized to benzil by means of nitric acid, as in the procedure given below:



$$C_6H_5\underset{\underset{OH}{|}}{\overset{\overset{H}{|}}{C}}-\underset{\underset{O}{\|}}{C}-C_6H_5 \xrightarrow{Oxid.} C_6H_5-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-C_6H_5$$

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[1] Crude benzaldehyde should be shaken with equal volumes of 5 per cent sodium carbonate solution until no further carbon dioxide is evolved. The upper layer is dried over calcium chloride and distilled, the fraction boiling at 178–180° is collected in a well cooled receiver, avoiding undue exposure of the hot liquid to the air. If the purified product is to be stored for any length of time it is well to dissolve in it about 0.1 per cent of hydroquinone, for this acts as an efficient antioxidant and greatly retards the deterioration. A brown bottle should be used and there should be little air space.

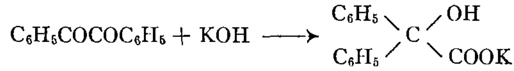
It is not necessary to employ completely pure, dry material or to know the exact amount in order to obtain a good result and time can be saved by using for the reaction the crude moist benzoin. Another oxidizing agent often used is Fehling's solution. Note the structural similarity between benzoin and a reducing sugar.

Benzoin. — Place 3 g. of potassium cyanide (handle with care!) in a 200-cc. round-bottomed flask, dissolve it in 20 cc. of water and add 24 cc. (25 g.) of pure benzaldehyde and 50 cc. of alcohol. Attach a reflux condenser and boil the solution for one-half hour on the steam bath. On cooling well in an ice bath a thick paste of benzoin crystals is obtained. Collect the product on a Büchner funnel, remove the color with a little alcohol and then wash thoroughly with water. (Wash the cyanide-containing mother liquor down the sink with plenty of water.) If convenient dry the product and determine the yield (18–20 g., m.p. 133–134°). In any case set aside about 1 g. of the crude benzoin and use the rest for the oxidation to benzil.

Properties. — Pure benzoin forms colorless prisms melting at 137° and it crystallizes well from alcohol. This α-hydroxy ketone reduces Fehling's solution, best in alcoholic solution, and forms an osazone (m.p. 225°).

Benzil. — Place the crude benzoin in a 200-cc. round-bottomed flask, add 30 cc. of concentrated nitric acid (sp. gr. 1.4), and heat the mixture on a steam bath under a reflux condenser connected at the top to a gas trap in which the gas-escape tube is just above the surface of a mixture of about 100 cc. of water and 10 cc. of 10 per cent sodium hydroxide solution. Use cork stoppers at both ends of the condenser as rubber is even more subject to attack by the acid. The benzoin at first dissolves and there is a vigorous initial reaction. Oxides of nitrogen are evolved and a yellow oil soon separates. After heating for 2 hours with occasional shaking the reaction is practically complete. Pour the contents of the flask into 300–400 cc. of cold water, stir well to coagulate the solidified yellow material, and collect it at the suction pump. Wash with water and then to remove the nitric acid completely suspend the crude benzil in about 100 cc. of water, heat until the solid melts, remove the flame and add 10 per cent sodium carbonate solution until it no longer produces an effervescence. The addition of the cold solution causes the oil to solidify, and the material is again collected after some stirring. The yellow lumps need be dried only superficially before being crystallized from alcohol. Yield, 14–17 g.; m.p. 94–95°.

Properties. — Benzil forms yellow prisms melting at 95°. It reacts with the usual ketone reagents such as phenylhydrazine and the Grignard reagent, and as an α-diketone it exhibits certain special reactions characteristic of this more limited group of compounds. On treatment with alcoholic potassium hydroxide it undergoes the benzilic acid rearrangement:

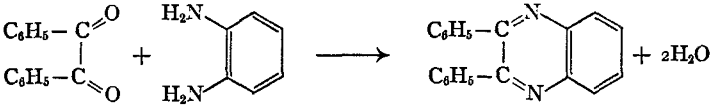


$$C_6H_5COCOC_6H_5 + KOH \longrightarrow \begin{matrix}C_6H_5\\ C_6H_5\end{matrix}\!\!>C<\!\!\begin{matrix}OH\\ COOK\end{matrix}$$

On boiling a solution of a small quantity of benzil in alcohol with a fragment of potassium hydroxide there is produced a violet solution containing this potassium salt of benzilic acid. (Test your product in this way.) The acid can be prepared in good yield under properly controlled conditions, but it is not easily isolated in a small-scale, test experiment.

In being attacked by alkali with the production of a colored solution, benzil bears some resemblance to quinone, and a further similarity is in the color of the two compounds. Benzil furthermore is of a structure somewhat comparable to that of an ortho-quinone, for this type of compound can be regarded as a cyclic α-diketone. These resemblances, however, are superficial and a simple reduction test (heat with $Na_2S_2O_4$ and water) is sufficient to show that benzil does not possess the property, characteristic of the quinones, of undergoing very ready reduction. It can be reduced, to be sure, but only under much more drastic conditions than are required for the conversion of a quinone into a hydroquinone.

Like other α-diketones and indeed like the ortho-quinones, benzil reacts with *o*-phenylenediamine in glacial acetic acid solution to form a quinoxaline derivative (m.p. 124°):



Auto-Oxidation of Benzoin. — In the presence of alcoholic alkali benzoin is slowly oxidized by the oxygen of the air and eventually converted completely into benzil. In the course of the reaction the solution develops a striking color, which fades on shaking the solution and reappears when the solution is at rest. The color is due to the formation of an intermediate product which is very sensitive to air and which Michaelis and Fetcher[1] regard as a free radical having a univalent oxygen atom. The fact that the color develops most rapidly when benzil is present suggests that the intermediate may form a colored complex with benzil. With pure benzoin there is an induction period before the color develops, presumably a period during which the requisite amount of benzil is being formed. Pure benzil does not give the color at all.

Tests. — In a test tube dissolve about 0.1 g. each of benzoin and benzil in 10 cc. of alcohol and add 3–4 drops of 10 per cent sodium hydroxide solution. Alternately shake the solution vigorously with the air (stopper and shake end to end) and allow it to stand. The color change can be repeated until the benzoin originally present is all oxidized. Test the behavior in alcoholic alkali of your samples of benzoin and benzil.

QUESTIONS

1. What product would you expect to obtain from the reaction of benzil with phenylhydrazine? What is the melting point?

2. How could you most easily detect the presence of any unchanged benzoin in the crude benzil?

3. If benzoin were present in the crude material in appreciable amount (5–10 per cent), how could you determine the exact quantity?

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[1] *Journal of the American Chemical Society,* **59,** 1246 (1937).

EXPERIMENT 46

QUINONES

SPECIAL EXPERIMENTS: The first three preparations are alternative, while the remainder constitute a series of experiments which can be completed in two or three working periods.

***p*-Benzoquinone ("Quinone").** — Quinone usually is prepared by the oxidation of aniline in acid solution with sodium dichromate. The many intermediate stages give opportunity for the loss of material through side reactions, and the product desired is itself fairly susceptible to further oxidation. On a laboratory scale the yield is only about 35 per cent of the theoretical amount and the process is somewhat lengthy. In the industrial process the quinone itself is not isolated and purified but instead the crude material is converted into hydroquinone. The latter compound is available at a reasonable figure and it is a more satisfactory starting material than aniline for the laboratory production of quinone, for the yield in the oxidation is much better. A rapid method of preparing pure quinone is that described by Clark[1] and given in the following procedure. It consists in oxidizing hydroquinone with manganese dioxide in an acid medium and removing the product from the reaction mixture by steam distillation.

Procedure. — The reaction is carried out in a 2-liter flask having a long neck or an adapter suitable for steam distillation and equipped with the following special condensing system to prevent the loss of quinone, for this substance is very volatile with steam and sublimes easily. Use a long water condenser and fit the lower end of the condenser tube, connected by means of an adapter, to a 2-liter round-bottomed, short-necked flask submerged as far as possible in a large tub of ice and water. Through a

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[1] Clark, *American Chemical Journal*, **14**, 565 (1892).

second hole in the stopper of this receiving flask insert the end of a second condenser clamped in a vertical position. (The arrangement is shown in Fig. 16, page 160.) The main condensation takes place in the receiving flask. The whole apparatus must be ready for immediate use, with the cooling water running and the ice in place, before mixing the reagents.

Disconnect the reaction flask and pour into it 240 cc. of water and then 45 cc. of concentrated sulfuric acid, followed by 55 g. of hydroquinone. Mix these reagents well and then add 70 g. of powdered manganese dioxide, mix the contents quickly, and at once connect the flask with the receiving system and steam distil. The oxidation is a brisk reaction and the quinone distils so rapidly at first that it may clog the tube of the first condenser. Watch this tube and when it begins to fill, run the water out of the condenser until the yellow solid is all melted. The distillation requires from one-half to three-quarters of an hour.

Push any material lodged in the two condensers into the receiver with a long rod, cool the distillate thoroughly and collect the product. Spread it out on a paper until dry but no longer, or material will be lost through sublimation.

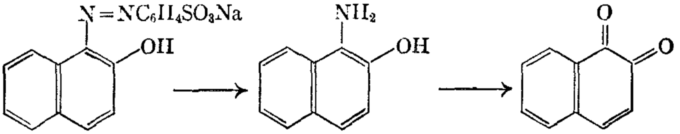
The yield is 35–40 g. and the product usually requires no further purification. Pure quinone melts at 116° and darkens when exposed to the light.

Toluquinone. — *o*-Toluidine is the best starting material available for the preparation of this homologue of quinone. The yield is not good, but Clark's method of oxidation furnishes a means of preparing the compound which in other respects is quite satisfactory.

Procedure. — Follow in detail the above procedure for the preparation of quinone, using the following quantities and reagents: 280 cc. of water, 45 cc. of concentrated sulfuric acid, 20 g. (20 cc.) of *o*-toluidine, 70 g. of manganese dioxide.

The yield is about 11 g. Toluquinone melts at 68–69° and resembles quinone in most of its properties.

β-Naphthoquinone. — One of the most generally applicable methods of preparing a quinone is to start with a phenol (or a naphthol, anthrol, or phenanthrol), couple it with a diazotized amine, reduce to an aminophenol, and oxidize the last named substance. The quinone-imine first formed is at once hydrolyzed in an acid medium to produce the quinone. β-Naphthoquinone may be obtained most conveniently from the class preparation of Orange II, for this yields 1-amino-2-naphthol on reduction with sodium hydrosulfite, along with sulfanilic acid, which remains in solution as the sodium salt whereas the product desired precipitates easily (see page 211). The substance is purified in the form of the hydrochloride and then oxidized:



Procedure. — In a 1-liter beaker dissolve 38.6 g. (0.1 mole) of Orange II (dihydrate) in 500 cc. of water and bring the solution to a temperature of 40–50°. Add with stirring 45 g. of sodium hydrosulfite, which soon discharges the red color and gives a pink or cream colored precipitate of 1-amino-2-naphthol. In order to complete the reaction and coagulate the product, heat the mixture nearly to boiling and until it begins to froth badly; then cool to 25° in an ice bath, collect the product on a Büchner funnel and wash it with water. Prepare a solution of a small spatulaful (0.4 g.) of stannous chloride[1] and 10 cc. of concentrated hydrochloric acid in 200 cc. of water in a beaker, and warm it to 30°. Transfer the precipitate to this acid solution and wash in the material adhering to the funnel. On good stirring all the aminonaphthol should dissolve, leaving a suspension of a small amount of dark, fluffy material. Stir the solution for 5 minutes with 2 g. of animal charcoal, and then filter by suction. (If crystalline material should begin to sepa-

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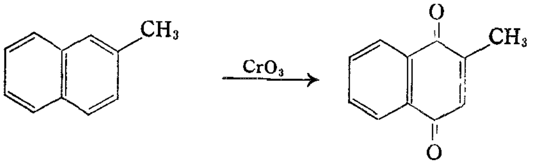
[1] Aminonaphthol is very sensitive to air oxidation and a solution of the hydrochloride in water rapidly darkens. Stannous chloride, however, is an effective antioxidant and it protects the compound from undergoing this change.

rate at any point, bring it into solution by heating. More water may be used, but in this case add later a correspondingly greater amount of acid.) Transfer the clarified solution to a beaker, add 40 cc. of concentrated hydrochloric acid and heat to the boiling point until the precipitated material has been brought into solution. The solution may be allowed to cool in the air, or directly in an ice bath; in any event the mixture should be cooled to 0° before collecting the crystals. Collect the aminonaphthol hydrochloride, which forms colorless or very nearly colorless crystals, using a cold mixture of 10 cc. of concentrated hydrochloric acid and 40 cc. of water to rinse the vessel and for washing. (The salt dissolves easily in water; the solubility is greatly decreased in the presence of chloride ion.) Leave the crystalline product draining in the funnel while making preparations for the oxidation; this reaction must be carried out rapidly in order to obtain a good result, and both the oxidizing solution and the apparatus required should be made ready in advance. Prepare the oxidizing solution by dissolving 55 g. of ferric chloride crystals in a mixture of 20 cc. of concentrated hydrochloric acid and 50 cc. of water by heating, cool to room temperature by the addition of about 50 g. of ice, and filter the solution by suction.

Wash the crystalline aminonaphthol hydrochloride into a 1-l. beaker with water, add 300 cc. of water and dissolve the material quickly by stirring, warming to about 35° and, if necessary, adding more water. Filter the solution quickly by suction from a trace of residue, transfer it to a 1-l. round-bottomed flask, and add the ferric chloride solution all at once, shaking the flask very vigorously. The β-naphthoquinone separates at once as a voluminous mass of microcrystalline, golden yellow material. Collect the product by suction filtration and wash it very thoroughly to remove all traces of acid. Dry the product at room temperature, best in an atmosphere free from acid fumes. The yield is 75 per cent of the theoretical amount, provided of course that the Orange II is pure and salt-free.

The material should be directly pure, and examination under a microscope will reveal a nicely crystalline structure. This is a fortunate circumstance, for this particular quinone is so very sensitive and reactive that it has not been possible to crystallize it without some decomposition. The substance has no melting point, but decomposes at about 145–147°. Test the color in concentrated sulfuric acid; make a thin suspension of the quinone in hot water and add concentrated hydrochloric acid. Dissolve a small sample in cold alcohol, add a drop of aniline and observe the result; the red product is 4-anilino-1,2-naphthoquinone.

2-Methyl-1,4-naphthoquinone. — On oxidation with chromic acid naphthalene is converted largely into phthalic acid, and even with the most careful control the reaction affords no more than 16 per cent of α-naphthoquinone. A β-alkyl group has an activating influence and promotes selective attack at the α-positions, as shown by the observation that β-methylnaphthalene can be converted into 2-methyl-1,4-naphthoquinone in reasonably good yield (38–42 per cent).



The β, β-disubstituted naphthalenes obtainable from coal tar likewise give quinones in 45 to 55 per cent yield when oxidized by the procedure given below. The resulting 1,4-naphthoquinone derivatives have the following properties: 2,3-dimethyl, m.p. 126.5–127°; 2,6-dimethyl, m.p. 138.5–139°; 2,7-dimethyl, m.p. 114–115°. Anthracene can be oxidized in the same way, except that the amount of solvent should be doubled, and gives anthraquinone in nearly quantitative yield. Phenanthrene can be converted by this procedure in 45 per cent yield into pure phenanthrenequinone, m.p. 206.5–207.5°, corr. In the latter case the crude, moist oxidation product is best treated with saturated sodium bisulfite solution to produce the bisulfite addition compound, a colorless substance which can be extracted with hot water and thus separated from unchanged hydrocarbon and tars. Addition of sodium carbonate solution to the filtrate precipitates the purified phenanthrenequinone.

Procedure. — In the hood, clamp a separatory funnel in place to deliver into a 600-cc. beaker which can be cooled in an ice bath when required. The oxidizing solution to be placed in the funnel is prepared by dissolving 50 g. of chromic anhydride (CrO_3) in 35 cc. of water and diluting the dark red solution with 35 cc. of glacial acetic acid.[1] In the beaker prepare a mixture of 14.2 g. of β-methylnaphthalene and 150 cc. of glacial acetic acid and, without cooling, run in small portions of the oxidizing solution and stir with a thermometer until the temperature rises to 60°. At this point ice cooling will be required to prevent a further rise. By alternate addition of reagent and cooling the temperature is maintained close to 60° throughout the addition, which can be completed in about ten minutes. When the temperature begins to drop spontaneously the solution is heated gently on the steam bath (85–90°) for one hour to complete the oxidation.

Dilute the dark green solution with water nearly to the top of the beaker, stir well for a few minutes to coagulate the yellow quinone, collect the product on a Büchner funnel, and wash it thoroughly with water to remove chromous acetate. The crude material may be crystallized from methanol (40 cc.) while still moist (without filtering), giving 6.5–7.3 g. of satisfactory 2-methyl-1,4-naphthoquinone, m.p. 105–106°. The substance must be kept out of the light, for on exposure it is converted into a pale yellow, sparingly soluble polymer.

Note: α-Naphthoquinones are often conveniently purified by charcoal treatment in ether solution. The solid substance need not be dried but may be taken up directly in ether and the solu-

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[1] The anhydride is hygroscopic; weigh it quickly and do not leave the bottle unstoppered. The substance dissolves very slowly in acetic acid — water mixtures and solutions always should be prepared by adding the acetic acid only after the substance has been completely dissolved in water.

tion decanted and dried over calcium chloride or magnesium sulfate. The solution is then shaken for several minutes with a liberal quantity of decolorizing carbon (Norit) and filtered by gravity, using fresh ether to wash the flask and paper clean. The ether is then distilled from the steam bath until yellow crystals of the quinone begin to separate; the product is collected after ice cooling and washed with a little fresh ether. Additional crops are obtained by concentration of the mother liquor, which is further clarified if required. By this method quinone samples having a dull color due to persistent contaminants are easily purified with little loss. Other useful methods of purification are by distillation *in vacuo*, using the flask shown in Fig. 28 (page 250), and by sublimation, using the unit illustrated in Fig. 21.

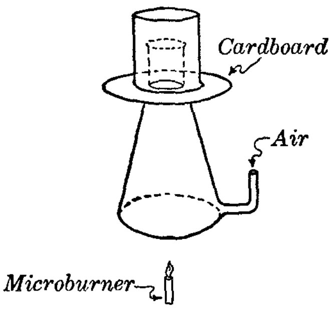

FIG. 21. — Sublimation Apparatus

2-Methyl-1,4-naphthohydroquinone. — In an Erlenmeyer flask dissolve 2 g. of the quinone in 35 cc. of ether [1] by warming, pour the solution into a separatory funnel, and shake with a fresh solution of 4 g. of sodium hydrosulfite in 30 cc. of water. After passing through a brown phase (quinhydrone) the solution should become colorless or pale yellow in a few minutes; if not, add more hydrosulfite solution. After removing the aqueous layer shake the ethereal solution with 25 cc. of saturated sodium chloride solution and 1–2 cc. of saturated hydrosulfite solution to remove the bulk of the water and filter the ethereal layer by gravity through a paper moistened with ether and about one-third filled with magnesium sulfate.[2] Evaporate the filtrate on the steam bath until nearly all of the solvent has been removed, cool and add petroleum ether. The hydroquinone separating as a white or

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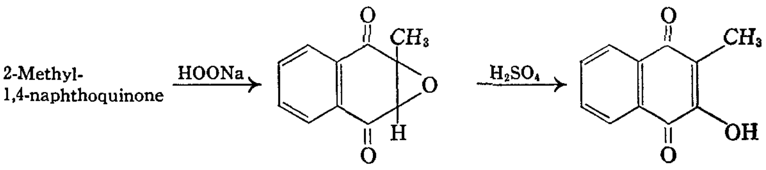
[1] With large quantities it is not necessary to use enough ether to dissolve the quinone; satisfactory amounts per g. of quinone are 3 cc. of ether and a solution of 0.7 g. of sodium hydrosulfite in 2 cc. of water.

[2] Anhydrous sodium sulfate may be used but is slightly less satisfactory.

grayish powder is collected, washed with petroleum ether and dried; yield 1.9 g. (the substance has no sharp m.p.).

Phthiocol (2-Methyl-3-hydroxy-1,4-naphthoquinone). — This quinone has been isolated from human tubercular bacilli and also as a cleavage product of vitamin K_1. The best synthesis consists in converting 2-methyl-1,4-naphthoquinone into the oxide and treating this with sulfuric acid. The oxide is obtained from the quinone and sodium hypochlorite or, better, with a mixture in which the active agent probably is sodium hydrogen peroxide.

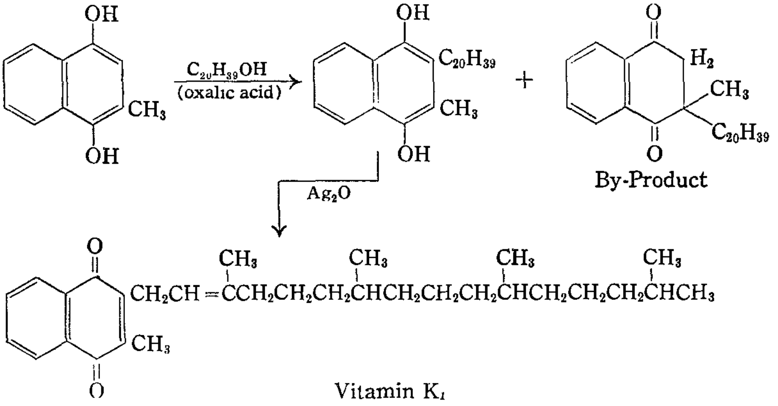
Dissolve 1 g. of 2-methyl-1,4-naphthoquinone in 10 cc. of alcohol by heating, and let this stand while the second reagent is prepared by dissolving 0.2 g. of anhydrous sodium carbonate in 5 cc. of water and adding (cold) 1 cc. of 30 per cent hydrogen peroxide solution. Cool the quinone solution under the tap until crystallization begins, add the peroxide solution all at once, and cool the mixture. The yellow color of the quinone should be discharged at once. Add about 100 cc. of water, cool in ice, and collect the colorless, crystalline oxide; yield 0.97 g., m.p. 93.5–94.5° (pure: 95.5–96.5°).



Oxide Phthiocol

To 1 g. of the dry oxide in a 25-cc. Erlenmeyer flask add 5 cc. of concentrated sulfuric acid; stir if necessary to produce a homogeneous deep red solution, and after ten minutes cool this in ice and slowly add 20 cc. of water. The precipitated phthiocol may be collected, washed and crystallized by dissolving in methanol (25 cc.), adding a few drops of hydrochloric acid to give a pure yellow color, treating with Norit, concentrating the filtered solution, and diluting to the saturation point. Alternately, the yellow suspension is washed into a separatory funnel and the product extracted with a mixture of 25 cc. each of benzene and ether. The organic layer is dried over magnesium sulfate and evaporated to a volume of about 10 cc. for crystallization. The total yield of pure phthiocol, m.p. 172–173°, is 0.84–.88 g.

Vitamin K_1 (2-Methyl-3-phytyl-1,4-naphthoquinone). — The synthesis of the vitamin is accomplished by condensing phytol ($C_{20}H_{39}OH$) with 2-methyl-1,4-naphthohydroquinone, separating the substituted hydroquinone from the reaction mixture and oxidizing it to the corresponding quinone. The condensation proceeds readily in the presence of oxalic acid as catalyst, but gives in addition to the desired vitamin hydroquinone a considerable amount of a ketonic by-product of the same composition.



A separation must be made from this substance, from unreacted phytol and its dehydration product phytadiene, and from unchanged starting hydroquinone. The latter is removed completely by extraction from ether with dilute alkali; the substituted hydroquinone with its long alkyl side chain is a cryptophenol (hidden phenolic properties) and remains in the ether phase. Since hydroquinones are very sensitive to air oxidation in the presence of alkali, sodium hydrosulfite is added to keep the substances in the reduced form during the extraction operation. When the material recovered from the ether layer is treated with petroleum ether, the ketonic by-product, the phytol, and phytadiene all dissolve readily, while the vitamin hydroquinone, being phenolic, is less soluble in the hydrocarbon solvent and separates as a solid. By suitable centrifugation and washing, it is easily obtained in such a form that completely pure vitamin K_1 is obtained on oxidation.[1]

Procedure.[2] — In a 50-cc. Erlenmeyer flask prepare a mixture of 1.48 g. of phytol, 1.5–2.0 g. of 2-methyl-1,4-naphthohydroquinone (preferably the larger amount), 1 g. of anhydrous oxalic acid,[3] and 10 cc. of dioxane. Warm and stir until the solids are dissolved, stopper the flask with a cork carrying a thermometer, and heat the solution on the steam bath for 4 hours at a temperature of 90–95°. Cool to 30°, wash the solution into a separatory funnel with 40 cc. of ether, and wash the orange-colored ethereal solution with two 40-cc. portions of water to remove oxalic acid and dioxane. To extract unchanged hydroquinone, add a freshly prepared solution of 2 g. of sodium hydrosulfite in 40 cc. of 2 per cent aqueous potassium hydroxide and 10 cc. of saturated sodium chloride solution (which helps break the resulting emulsion). Shake vigorously for a few minutes, when any red color should disappear and the alkaline layer should acquire a bright yellow vat color. After releasing the pressure through the stopcock, keep the funnel stoppered until the layers separate as a precaution against oxidation. Draw off the yellow liquor and repeat the extraction a second and a third time, or until the alkaline layer remains practically colorless. Separate the faintly colored ethereal solution and dry it over magnesium sulfate, filter into a tared flask and evaporate the filtrate on the steam bath, eventually with evacuation at the water pump. The total oil, which becomes waxy on cooling, amounts to 1.7–1.9 g.

Add 10 cc. of petroleum ether (b.p. 20–40°) and boil and manipulate with a spatula until the brown mass has given place to a paste of white solid. Wash the paste into small centrifuge tubes with 10–20 cc. of fresh petroleum ether, make up the volume of

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[1] If phytol is not available one can use an equal weight of geraniol and obtain a substance very similar to the natural vitamin and having pronounced antihemorrhagic activity. The geranyl-substituted hydroquinone forms a voluminous precipitate which requires repeated washing.

[2] Fieser, *Journal of the American Chemical Society*, **61**, 2559, 3467 (1939).

[3] Prepared by heating the dihydrate at about 140° until a dry solid is obtained. This condensing agent can be replaced by 1 cc. of 85 per cent phosphoric acid.

paired tubes to the same point, cool well in ice and centrifuge. Decant the brown supernatant liquor into the original tared flask, fill the tubes with fresh solvent and stir the white sludge to an even suspension, cool, centrifuge, and decant as before. Evaporation of the liquor and washings gives 1.1–1.3 g. of residual oil, the difference giving an indication of the yield of vitamin to be expected. Dissolve the portions of washed sludge of vitamin K_1 hydroquinone in a total of 10–15 cc. of absolute ether, and add a little Norit for clarification if the solution is at all pink or dark. Add 1 g. of silver oxide and 1 g. of magnesium sulfate. Shake for 20 minutes, filter into a tared flask, and evaporate the clear yellow solution on the steam bath, removing traces of solvent at the water pump. Undue exposure to light should be avoided when the material is in the quinone form. The residue is a light yellow, rather mobile oil consisting of pure vitamin K_1; yield 0.55–0.65 g.

To observe a characteristic color reaction, transfer a small bit of vitamin on the end of a stirring rod to a test tube, stir with 1 cc. of alcohol, and add 1 cc. of 10 per cent alcoholic potassium hydroxide solution; the end pigment responsible for the red color is phthiocol. A sample for preservation is transferred with a spatula, or with a dropper made by drawing out a piece of glass tubing, into a small specimen vial which is sealed, labeled, and wrapped in metal foil or black paper to exclude light.

TESTS FOR QUINONES

Reduction. — Suspend a small sample of the quinone in a little water, add a small pinch of sodium hydrosulfite ($Na_2S_2O_4$) and heat. A green quinhydrone is sometimes observed as an intermediary product. The hydroquinone may separate as a colorless solid or it may remain dissolved in the hot solution. If it does not crystallize on cooling, add more materials. To the suspension of the hydroquinone add sodium hydroxide solution and note that the substance dissolves easily in this reagent.

Action of Alkali. — Suspend a small quantity of the quinone in 1–2 cc. of water and add a drop of 10 per cent sodium hydroxide solution. If there is no change, heat to the boiling point.

The test illustrates the great reactivity and sensitivity of some of the quinones. The changes involved in the reaction of the benzoquinones are not yet understood. The 1,4-naphthoquinones which carry no substituent in the 2-position are probably hydroxylated, with the formation of the corresponding 2-hydroxy-1,4-naphthoquinones.

Quinhydrone Formation. — Dissolve about 0.3 g. each of quinone and of hydroquinone in small volumes of alcohol in separate test tubes, and mix the cold solutions. Green crystals of the molecular compound, quinhydrone, separate.

VACUUM DISTILLATION

There are a great many substances which cannot be distilled satisfactorily in the ordinary way either because they boil at such high temperatures that some decomposition occurs during the process or because the hot liquid is sensitive to attack by the oxygen of the air. In such cases it is found almost invariably that a purification can be accomplished very satisfactorily by distillation at a diminished pressure. By operating at a pressure of 20 mm. of mercury or below, the boiling point can be lowered very decidedly, and there is much less chance for the destruction of material by oxidation in the rarefied atmosphere. Vacuum distillation finds countless applications in the organic laboratory and the operation is almost as common as distillation at the pressure of the atmosphere. A few of the many forms of apparatus are described in the following pages. It may be said at the outset that it is essential to employ apparatus which is particularly designed to withstand the external pressure. A flat-bottomed flask of thin, soft glass is almost certain to collapse. With round-bottomed Pyrex ware and with the specially constructed, thick-walled suction flasks there is likely to be little trouble but even so the beginner should always wear goggles in carrying out a vacuum distillation.

Distillation Assemblies. — One of the simplest arrangements for distillation *in vacuo* is illustrated in Fig. 22 and the assembly is sometimes useful where great refinement of operation is not required. It is constructed of two distilling flasks, one of which serves as the receiver. The side arm of the first flask must extend well beyond the tube in the other flask which serves to make connection to the suction pump. It is usually necessary to cool the receiving flask in an air blast or, better, with running water in the manner to be described below. Liquids bump very badly when boiled at reduced pressure and clay boiling chips lose all their activity in an evacuated system; it is therefore essential to make special provision for controlling the bumping. This is done by allowing a fine stream of air bubbles to be sucked

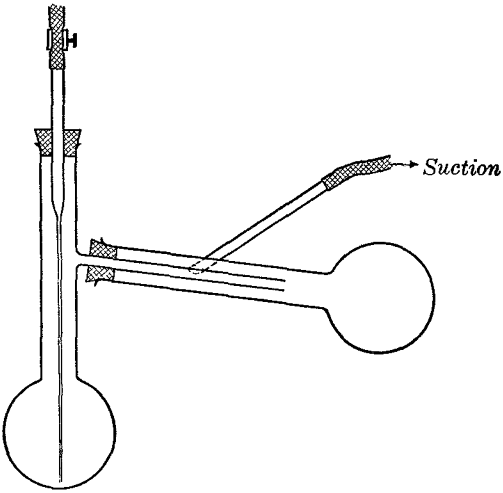

FIG. 22. — Arrangement of Flasks for Distillation at Reduced Pressure

into the boiling liquid through a glass tube drawn out to a fine capillary and provided at the top with a section of suction tubing which can be closed with a screw pinchcock which serves to regulate the flow of air. The pinchcock is closed at the beginning of the operation and carefully opened after the system has been evacuated until there is a steady stream of bubbles. Some further adjustment is required usually during the heating in order to secure even boiling with a minimum amount of air. The capillary should extend to the very bottom of the flask and for the best results it should be slender and flexible so that it will whip back and forth in the boiling liquid. Another method of preventing bumping is to introduce sufficient glass wool into the flask to fill a part of the space above the liquid.

To remove a fraction it is necessary to break the vacuum and change the receiving flask, and certain precautions must be observed in order to do this properly. If the suction is released at the end of the system next to the pump, liquid may be drawn up into the evacuated capillary and even into the rubber tubing. Consequently, after allowing the hot liquid to cool somewhat, the pressure is released as much as possible at the other end by gradually opening the pinchcock; the connection to the pump is then broken, also gradually. After a clean flask has been put in place and the pinchcock closed, the system is evacuated and the air flow is regulated before heating is recommenced.

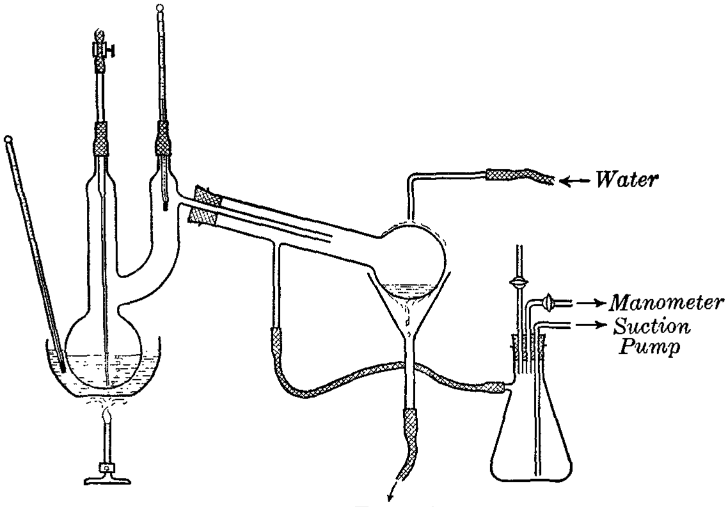

FIG. 23. — Vacuum Distillation Assembly

The simple apparatus just described has certain faults which may be corrected by using the assembly shown in Fig. 23. Here provision is made for a thermometer, which is of course essential in most distillations, by using a Claisen flask with two necks as shown. This form of flask has the further advantage of minimizing the chance of liquid being carried over into the distillate by frothing or spattering. The particular Claisen flask shown has constricted necks into which the tube drawn out to a capillary and the thermometer are inserted and held in place by sections of suction tubing. The rubber tubing is first coated on the inside with a thin film of glycerol and slipped over the constricted neck, and the tube of the thermometer is then inserted. The purpose of this construction is to prevent contact of the hot vapor with rubber. The stopper which makes connection to the receiving flask does not constitute a serious source of contamination for little hot vapor ordinarily reaches it. A rubber stopper is usually employed in order to secure the best vacuum, but there is the limitation that if the distillation occurs at a temperature much above 160° the rubber may melt from the heat of the tube passing through it. In this case it is advisable to use a cork stopper although much care is required in order to provide a vacuum tight connection. The cork should be selected carefully for quality and fit, it should be cleanly cut, and the system should be evacuated and tested with a manometer before use. A slight porosity sometimes may be corrected by lightly charring the cork surfaces which are to come in contact with the glass, or by painting the cork with a thin coating of collodion after the system has been evacuated.

It will be noted that the drawing calls for the use of a heating bath rather than a free flame. This is a distinct advantage in promoting even boiling and in making possible an accurate determination of the boiling point. The bath is filled with a suitable oil or a fusible metal (see page 306) and heated to a temperature about 20° higher than that at which the substance in the flask distils, and the bath temperature is kept constant throughout the distillation. The surface of the liquid in the flask should be below that of the heating liquid for this condition lessens the tendency to bump. It is important to note that the heating of the flask is begun only after the system has been evacuated; otherwise the liquid might boil too suddenly on reduction of the pressure.

The condensing flask is conveniently cooled by means of a stream of water so directed that the bulb is completely bathed. The overflow is caught in a funnel in the manner shown.

The connection to the suction pump must be made with the special suction tubing capable of withstanding the external pressure without collapsing, and it is of great convenience to introduce in the line a suction flask fitted as shown in the drawing. This serves as a reservoir to equalize the pressure and as a trap to catch and return to the pump any liquid which may be drawn back by a sudden fluctuation in pressure in the system. This is very likely to occur when a water pump is used as the source of suction. A stopcock which may be opened to the atmosphere provides a convenient means of releasing the pressure. The stopcock to the manometer is kept closed except when taking a pressure reading.

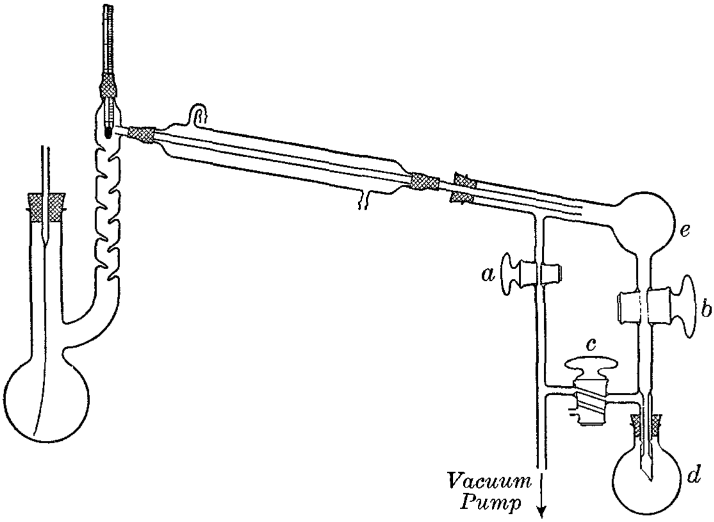

FIG. 24. — Apparatus for Fractional Distillation *in Vacuo*

Some additional features of design in vacuum distillation apparatus are shown in Fig. 24. The Claisen flask is modified in several respects. The distillation neck is longer than before and it has a series of indentures made from the four sides so that the points nearly meet in the center and it thus serves as a fractionating column. The side arm outlet extends for a short distance into the neck, preventing any condensate which has become contaminated by contact with the rubber connection at the top from running down into the side arm and finding its way into the receiver. With this construction, indeed, it is hardly necessary for this neck of the flask to be constricted, and it may be finished like an ordinary flask and the thermometer inserted through a stopper. Both arrangements are about equally satisfactory. It is a great convenience, on the other hand, to have the neck of the flask which carries the capillary open rather than constricted, for this facilitates both the filling and the cleaning of the flask. Unless the liquid to be distilled is extremely destructive to the stopper this construction is preferable to that illustrated in Fig. 23. Another feature of the flask under discussion is that it is provided with a particularly long side arm to serve as the inner tube of a condenser. A cooling jacket is slipped over it and held in place by sections of rubber tubing. It will be noticed that the capillary tube in the distilling flask is not supplied with a pinchcock, as in the previous cases. The flow of air is determined by the bore of the capillary. The glass tube is first drawn out in a flame to a fairly slender capillary and this is drawn out again in a smaller flame to a very fine thread. This is tested by blowing into the tube with the capillary tip submerged in a little ether. If a fine stream of bubbles can be produced the capillary should prove satisfactory. This is much the best form of capillary.

The flask shown in Fig. 24 is fitted also with a special adapter for the taking of successive fractions without interrupting the distillation or breaking the vacuum.[1] Stopcock *b* has a particularly wide bore to allow the free passage of condensate into the receiver *d*, and the two-way stopcock *c* if turned through an angle of 180° makes connection to the outside atmosphere. At the beginning of the distillation the stopcocks are adjusted

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[1] Adapter and receiver devices of improved design are described by Noonan, *Industrial and Engineering Chemistry, Analytical Edition*, **10**, 34 (1938), Dunicz, *ibid.*, **11**, 28 (1939), and Cloke, *ibid.*, **12**, 329 (1940).

to the positions shown and the distillate collects in *d*. When this fraction is to be removed *b* is closed and *c* is turned in such a way as to open *d* to the atmosphere. With the suction released *d* can be removed and replaced by a fresh flask. Stopcock *a* is then closed, *c* is turned to the original position (that shown) and air now present in the closed system below *a* and *b* is pumped out. When a good vacuum has been attained *a* and *b* are again opened. The original condition is restored and the liquid which has collected in the reservoir *e* runs down into the second receiver. Successive fractions are collected in the same way and there is only one limitation to the smooth course of the fractionation: while the lower part of the system is being evacuated with *a* and *b* closed, air is being sucked into the flask through the capillary and the pressure in the upper part of the system thus rises. Although the vacuum is later reëstablished it is clearly impossible to conduct the entire distillation at an entirely constant pressure with the apparatus shown.

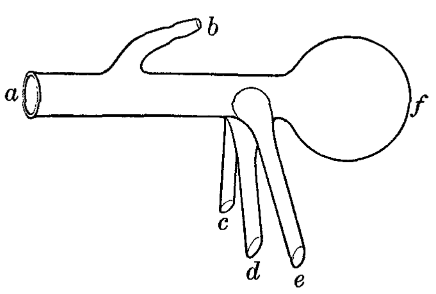

Fig. 25. — Adapter for Collecting Fractions at Constant Pressure

A fractionation at strictly constant pressure may be accomplished with the use of the adapter shown in Fig. 25. The end of the condenser tube is fitted into a stopper lubricated with glycerol at *a*, the suction line is connected at *b*, and flasks for receiving fractions are attached to the arms *c*, *d*, and *e*. By turning the adapter through the proper angle a small fore-run can be caught in the bulb of the adapter (*f*) and then three successive fractions can be caused to run into the receivers at *c*, *d*, and *e*. With low-boiling liquids this method suffers from the disadvantage that the three receiving flasks are all open to the same vapor space and there may be some interchange of vapors between the three fractions. It is, however, a very handy piece of apparatus and it is particularly useful in the distillation of moderate quantities of liquid where only two or three fractions are to be collected.

For the distillation of a very small amount of material it is often advantageous to use the type of flask shown in Fig. 26. Toward the end of a distillation the liquid draining from the walls is confined to a small area by the conical construction of the bulb and little material is lost as undistilled residue. Without describing other modifications it may be noted that many other assemblies may be constructed to meet special requirements by making various combinations of the features of design already discussed and, further, by building onto the distilling flask special fractionating columns. A refinement which may be applied in any case is to introduce an inert gas (nitrogen, hydrogen, carbon dioxide) into the capillary instead of air in order to protect fully a substance particularly sensitive to oxidation, but this is seldom necessary. One of the best of the reasonably simple columns, and one well adapted to vacuum work, is

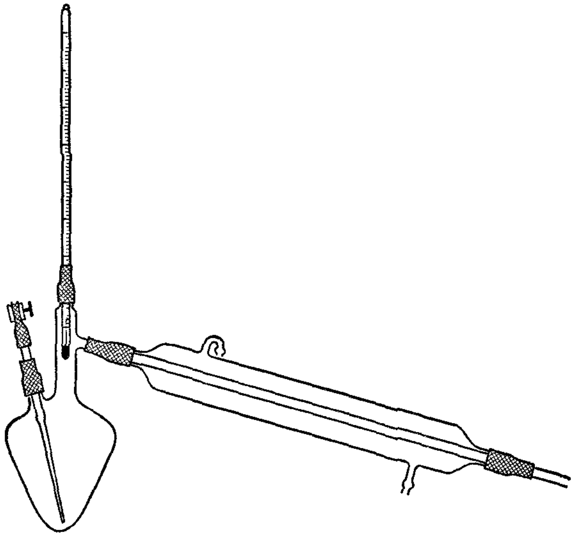

FIG. 26. — Pointed Flask for the Distillation of Small Quantities

that of Widmer (page 20). Another highly efficient column is one packed with glass spirals of special construction.[1]

Suction Pumps. — A water pump cannot give a suction better than the vapor pressure of water at the temperature of flow, but with a good pump it is possible to approach this limit. With the tap water at 10° a pressure as low as about 10 mm. of mercury can be attained, while the limit is about 25 mm. if the water is at 25°. While a water pump provides a vacuum which is in some cases adequate, an oil pump is in general to be preferred because of its greater effectiveness and because the pressure is steadier. A good oil pump in perfect condition may establish a pressure as low as 0.1 mm., and one which has had more wear will go to 2–3 mm. if it is treated properly. It is an act of gross negligence to use the pump when a corrosive gas (HCl) is likely to be given off (use a water pump), and the commonest cause of poor operation is the contamination of the oil with low-boiling solvents, particularly ether and alcohol. These substances of high vapor pressure obviously impose a limit to the suction obtainable. The removal of solvent by evaporation on the steam bath of a liquid to be distilled should be regarded as a purely preliminary operation and the solvent which almost invariably remains should be eliminated further, by distillation at the water pump until the main product begins to boil, before making connection to the oil pump. Water in the oil causes particularly bad performance (foaming), and a drying tower of solid potassium hydroxide always should be placed in the line to protect the pump from unavoidable or unsuspected moisture. This also will take care of traces of acids which would otherwise corrode the metal. It is a very good practice to provide also a trap surrounded by a dry ice and ether mixture to condense any vapors which may escape from the distillation system. The satisfaction of having a pump always ready for superior service will more than make up for the time spent in taking these precautions. It is a good plan to test the pump with a manometer before and after each usage, particularly if

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[1] Wilson, Parker and Laughlin, *J. Am. Chem. Soc.*, **55**, 2795 (1933).

the pump is shared with others. If the prevention has been inadequate the cure is to change the oil. Contaminated oil sometimes may be restored to usefulness by heating it for some time on a hot plate.

The Relationship between Boiling Point and Pressure. — It is not possible to calculate the boiling point of a substance at some reduced pressure from a knowledge of the boiling temperature at 760 mm., for the relationship between boiling point and pressure varies from compound to compound and it is unpredictable. It is true, however, that the boiling point curves for organic substances have much the same general disposition, as illustrated by the two lower curves in Fig. 27. These are of similar, if not identical form, and they do not differ greatly from that of water. As a useful approximation it may be said that with substances boiling in the region 150–250° at 760 mm. the boiling point at 20 mm. is 100–120° lower than at 760 mm. Benzaldehyde, which is very sensitive to air oxidation at the normal boiling point of 178°, distils at 76° at 20 mm. pressure and the concentration of oxygen in the rarefied atmosphere is

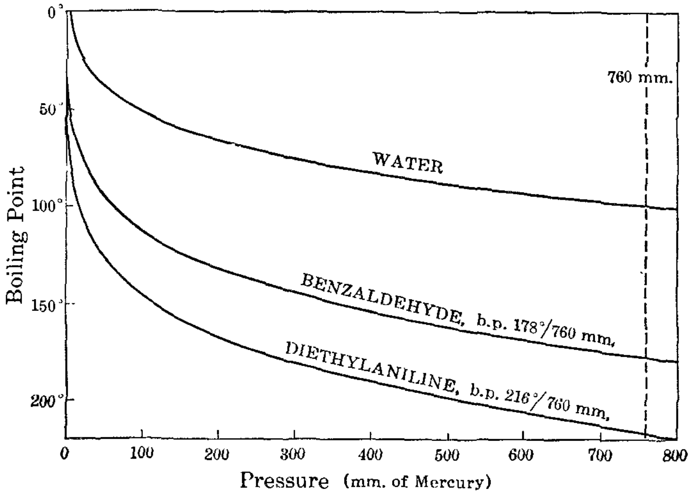

Fig. 27. — Boiling Point Curves

just 20/760, or 3 per cent, of that encountered in an ordinary distillation.

It will be observed that the curves all show a sharp upward inclination in the region of very low pressure. The lowering of the boiling point attending a reduction in pressure is much more pronounced at low than at high pressures. A drop in the atmospheric pressure of 10 mm. lowers the normal boiling point of an ordinary liquid by less than a degree, but a reduction of pressure from 20 mm. to 10 mm. causes a drop of about 15° in the boiling point. The effect at pressures below 1 mm. is still more striking and, with the development of practical forms of the highly efficient mercury vapor pump, distillation at a pressure of a few thousandths or ten thousandths of a millimeter has become a standard operation in many research laboratories. High vacuum distillation, that is at a pressure below 1 mm., affords a very useful means of purifying substances which are extremely sensitive or very slightly volatile. High vacuum technique now

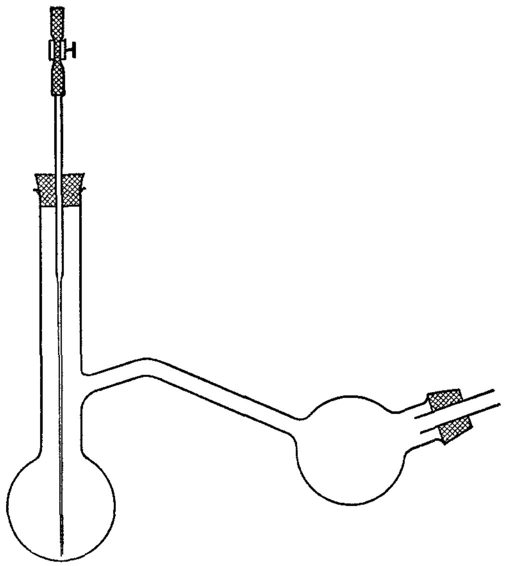

FIG. 28. — Two-bulb Flask for the Distillation of Solids

presents no great difficulties and requires only slight refinement of the methods of ordinary vacuum distillations.[1] The following table indicates roughly the order of magnitude of the reduction in boiling point which can be attained by operating in different ways, and it illustrates clearly the importance of keeping suction pumps in good repair.

DISTILLATION OF A (HYPOTHETICAL) SUBSTANCE AT VARIOUS PRESSURES

METHOD		PRESSURE (MM.)	B.P.
Ordinary distillation		760	250°
Water pump	Summer	25	144°
	Winter	15	134°
Oil pump	Poor condition	10	124°
	Good condition	3	99°
	Excellent condition	1	89°
Mercury vapor pump		0.01	30°

Distillation of Solids. — Vacuum distillation is by no means confined to the purification of substances which are liquid at the ordinary temperatures and the method often can be used to advantage in dealing with solid organic substances. The purpose of the operation and the technique are, however, slightly different. A solid is seldom distilled with the object of effecting a separation of constituents of different degrees of volatility, for such a separation usually can be achieved much more easily and completely by crystallization. The object in view is rather to cleanse the solid, for it is often possible to remove in one vacuum distillation all of the foreign coloring matter and tar without appreciable loss of product, whereas several more or less wasteful crystallizations might be required to attain the same purity. It is often good practice to distil a crude product and then to crystallize it. Time is saved in the latter operation because the hot solution usually requires neither filtration nor clarification with charcoal. The solid must be dry and a test should be made to determine if it will distil without decom-

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[1] For a description of methods and apparatus see Bernhauer, "Einführung in die organisch-chemische Laboratoriumstechnik," pp. 22–28 (1934).

position at the pressure of the pump which is available. That a compound will lack the required stability at high temperatures may sometimes be foretold from the structure, but a high melting point should not be taken as an indication that the distillation will fail. Substances melting as high as 300° have been distilled with complete success at the pressure obtained with an ordinary oil pump.

It is not necessary to observe the boiling point in distillations of this kind because the purity and identity of the distillate can be checked with much greater accuracy by melting point determinations. The omission of the customary thermometer greatly simplifies the technique. A very simple and useful assembly is shown in Fig. 28; this apparatus is adequate for all ordinary purposes.[1] A rather stout capillary tube carrying an adjustable vent at the top is fitted into the neck of the two-bulb flask by means of a rubber stopper, and the suction pump is connected through a trap at the other bulb. It is not necessary to insert in the mouth a rubber stopper of just the right size; a somewhat larger stopper may be put on backwards as shown and held in place by the suction. The same scheme can be used for the other stopper or for both of them. Water cooling is unnecessary and it is also inadvisable on account of the danger of cracking the glass. If some cooling of the receiving bulb is required it is best to use an air blast. Since the connection between the distilling and the receiving flask is of glass any material which solidifies and tends to plug the side arm can be melted by application of a free flame. A heating bath should not be used; it is best to heat the flask with a rather large flame. Hold the burner in the hand and play the flame in a rotary motion around the side walls of the flask. This allows less bumping than when the flask is heated from the bottom. If there is much frothing at the start it is even advisable to direct the flame upon the upper walls and the neck of the flask. If the

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[1] For a modified design see Diels and Riley, *Berichte der deutschen chemischen Gesellschaft*, **48**, 901 (1915).

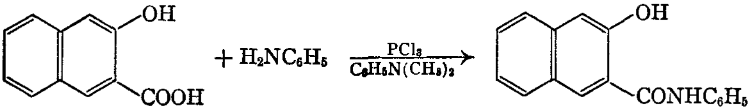
liquid froths over into the receiving bulb the flask is tilted to such a position that this bulb can drain through the connecting tube back into the distillation bulb when suitably warmed.

At the end of the distillation the vacuum is broken by the careful opening of the pinchcock and the contents of the receiving bulb may be melted and poured out. This method of emptying the bulb is sometimes inadvisable, however, because the hot, molten material may be susceptible to air oxidation. In such a case the material is allowed to solidify and cool completely before breaking the vacuum. The solid is then chipped out with a clean knife or with a strong nickel spatula and the last traces recovered with the solvent to be used in the crystallization. The bad tar usually remaining in the distillation bulb is best removed by adding small quantities of concentrated nitric and sulfuric acids, mixing the layers well, and heating the mixture while the flask is supported by a clamp under the hood. After cooling and pouring the acid mixture down the drain, loose char is removed with water and a brush and the process is repeated.

EXPERIMENT 47[1]

NAPHTHOL-AS

(Anilide of 2-Hydroxy-3-Naphthoic Acid)



This compound is used extensively as a coupling component in the preparation of azo dyes. Cotton is impregnated or printed with an alkaline solution of Naphthol-AS and then dipped into a bath of diazotized *p*-nitroaniline (or other amine); coupling occurs on the fibre and a bright red dyeing is produced. β-Naphthol formerly was used, giving with *p*-nitroaniline the dyestuff known as Para Red, but it had the disadvantage of being too soluble, allowing the color to run. The introduction of Naphthol-AS and of similar amides represents a distinct advance. These compounds not only are less soluble, but they possess a distinct affinity for the cellulose fibre, probably by virtue of the $-CONH-$ group. With the phenolic component firmly held to the cloth by adsorption, clearly defined printing of great fastness is possible.

Naphthol-AS, the "Anilid" (anilide) of a certain "Säure" (acid), is prepared according to the method indicated above. The 2-hydroxy-3-naphthoic acid is converted by the action of phosphorus trichloride into the acid chloride and this reacts with aniline to form the anilide. Dimethylaniline is added to the mixture partly to serve as solvent and partly to bind the hydrogen chloride which is produced and which otherwise would neutralize some of the aniline.

[1] Special experiment; the preparation is required for class use in Experiment 48.

Procedure.[1] — Use as the reaction vessel a 200-cc. three-necked flask fitted with a small dropping funnel and a hand stirrer made by bending a glass rod through an angle of 45° about 2 cm. from the end. Good stirring can be accomplished by twirling this rod between the thumb and forefinger. Place in the flask a mixture of 18.8 g. (0.1 mole) of 2-hydroxy-3-naphthoic acid, 10 cc. (0.11 mole) of aniline and 30 cc. of dimethylaniline and immerse the flask in an oil bath, the temperature of which is maintained at 100–105° (hood!). Stir the mixture until the acid is dissolved, then from the dropping funnel add 10 cc. (0.12 mole) of phosphorus trichloride drop by drop and with good stirring (10 minutes). Continue to heat at the temperature indicated for one-half hour after the addition is complete, stirring the mixture occasionally. Then lift out the flask, using the clamp as a holder, wipe the bottom with an old towel, and pour the brown, syrupy liquid while still hot in a very thin stream into a hot mixture of 100 cc. of concentrated hydrochloric acid and 400 cc. of water while stirring. If this operation is done properly the resinous material is at once disintegrated to a white powder. The material left in the flask can be removed by adding water and boiling, and by dislodging the solid with the bent stirrer.

Collect the product without cooling and then in order to complete the extraction of water-soluble impurities, as well as to remove any unchanged 2-hydroxy-3-naphthoic acid, wash the solid into a beaker, add 20 g. of sodium carbonate and 300 cc. of water and boil the mixture for a few minutes. Collect the undissolved material and for further purification suspend it in 300–400 cc. of water, heat to 60°, and add 10 per cent sodium hydroxide solution slowly and with good stirring so that the naphthol derivative can be brought into solution without using a great excess of alkali. There may be a small amount of insoluble material which will give the yellow solution a cloudy appearance; do not continue to add alkali in the hope of dissolving the impurity. Stir in a little animal charcoal and filter

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[1] Based upon the Swiss Patent No. 108072.

the solution under gentle suction (to avoid breaking the paper). On acidifying the filtrate with hydrochloric acid the product separates as a very fine precipitate and in order to facilitate filtration it is well to digest the suspension close to the boiling point for about 10 minutes. Filter hot and wash well with water. If the product should be colored by a trace of green material this impurity may be removed by extraction with hot alcohol, in which the Naphthol-AS is only very slightly soluble. This should be done before the product is dried by stirring it with alcohol on the steam bath and filtering. Yield, 15–17 g.; m.p., 244–246°.

The Naphthol-AS should be quite pure enough for the dyeing experiment, but it will be of interest to try a few crystallization tests. The following solvents should be tried, for they are often of service in dealing with compounds sparingly soluble in the usual organic solvents: nitrobenzene, *s*-tetrachloroethane ($CHCl_2CHCl_2$).

The experiment can be varied by substituting for aniline other common primary aromatic amines.

EXPERIMENT 48

DYES AND DYEING

In carrying out the following experiments keep in mind the fact that considerable damage to the laboratory or the clothing may result from careless work. It is entirely possible to avoid staining the working space or the person and this is a case in which neat manipulation will be clearly evident to the instructor. Stirring rods are nearly as convenient as the fingers for manipulating dyed cloth until it is thoroughly washed, and they are more easily cleaned. In case of an accident see the note on page 208.

Most cotton cloth available contains inorganic material in the form of a filler or of sizing and this may have a mordanting action which will obscure the true behavior of cellulose material toward some of the dyestuffs. The cotton supplied for the experiment should be freed of sizing by boiling it with soda solution.[1]

Unless otherwise specified the small quantities of dyes and reagents called for may be estimated, and it is better to use too little material rather than too much.[2]

(1) **Picric Acid.** — (Direct to wool and silk.[3]) Dissolve 0.5 g. of the acid in a little hot water to which a few drops of sulfuric acid have been added. Heat pieces of wool, silk, and cotton in this bath for one minute, then remove them with a stirring rod, rinse well, wring, and dry. Describe the results.

(2) **Congo Red, a Benzidine Dye.** — Dissolve 0.1 g. of Congo Red in 400 cc. of water, add about 1 cc. each of 10 per cent solu-

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[1] Boil for 2 hours with 2 per cent sodium carbonate solution, repeat with fresh solution and wash thoroughly.

[2] The dyes required are best supplied in individual waxed envelopes.

[3] Picric acid stains on the skin can be removed by applying a coating of collodion and, after 10 minutes, peeling this off with a knife blade.

tions of sodium carbonate and sodium sulfate, heat to a temperature just below the boiling point, and introduce pieces of cotton, wool, and silk. At the end of 10 minutes remove the fabrics and wash in warm water as long as the dye is removed. Place pieces of the dyed material in very dilute hydrochloric acid solution and observe the result. Rinse and wash with soap.

(3) **Orange II.** — The dye bath is prepared from 0.5 g. of Orange II, 5 cc. of sodium sulfate solution, 300 cc. of water, and 5 drops of concentrated sulfuric acid. Dye wool, silk, and cotton for 5 minutes at a temperature near the boiling point.

Replace the dyed wool in the bath, make the solution alkaline with sodium carbonate, and add sodium hydrosulfite ($Na_2S_2O_4$) until the color of the bath is discharged. Account for the result.

(4) **Eosin.** — (Direct to silk or wool.) Dissolve 0.1 g. of sodium eosin in 200 cc. of water and dye a piece of silk by heating it with the solution for about 10 minutes.

(5) **Triphenylmethane Dyes.** — Mordant pieces of cotton cloth by allowing them to stand in a hot solution of 0.5 g. of tannic acid in 500 cc. of water for 5 minutes. The mordant must now be fixed to the cloth, otherwise it would wash out. For this purpose, transfer the cloth to a hot bath made from 0.2 g. of tartar emetic (potassium antimonyl tartrate) in 200 cc. of water. After 5 minutes, wring the cloth. A dye bath is prepared by dissolving 0.1 g. of one of the following dyes in 200 cc. of water (boiling). Dye the mordanted cloth in this bath for 5–10 minutes at a temperature just below the boiling point.

Dyes: Malachite Green, Crystal Violet, Methyl Violet.

Try further dyeings with unmordanted cotton and with untreated wool or silk.

NOTE: The stains on glass produced by triphenylmethane dyes can be removed with concentrated hydrochloric acid, which forms a di- or tri-hydrochloride more soluble than the original mono-salt.

(6) **A Developed Dye: Primuline.** — Dye three pieces of cotton cloth in a solution of 0.2 g. of primuline and 5 cc. of sodium

carbonate solution in 500 cc. of water, at a temperature just below the boiling point for 15 minutes. Wash the cloth twice in about 500 cc. of water. Prepare a diazotizing bath by dissolving 0.2 g. of sodium nitrite in 500 cc. of water containing a little ice and, just before using the bath, add 5 cc. of concentrated hydrochloric acid. Allow the cloth dyed with primuline to stay in this diazotizing bath for about 5 minutes. Now prepare three baths for the coupling reaction. Dissolve 0.1 g. of β-naphthol in 2 cc. of 5 per cent sodium hydroxide solution and dilute with 100 cc. of water; prepare similar baths from phenol, resorcinol, Naphthol-AS (page 254), or other phenolic substances.

Transfer the cloth from the diazotizing bath to a beaker containing about 500 cc. of water and stir. Put one piece of cloth in each of the developing baths and allow them to stay for 5 minutes.

(7) **Para Red, an Ingrain Color.** — Prepare a solution of *p*-nitrobenzene diazonium chloride as follows: dissolve 1.4 g. (weighed) of *p*-nitroaniline in a mixture of 30 cc. of water and 6 cc. of 10 per cent hydrochloric acid, by heating. Cool the solution in ice (the hydrochloride of the amine may crystallize), add all at once a solution of 0.7 g. (weighed) of sodium nitrite in a little water and filter the solution by suction. The material to be dyed (cotton cloth, filter paper) is first soaked in a solution prepared by suspending 0.5 g. of β-naphthol in 100 cc. of water, stirring well and adding alkali, a drop at a time, until the material all dissolves. This solution may also be painted onto the cloth. The cloth is then dried and dipped into the solution of the diazotized amine, after diluting the latter with about 300 cc. of water.

Better results can be obtained by substituting Naphthol-AS for β-naphthol; in this case it is necessary to warm with alkali and to break the lumps with a flattened stirring rod in order to bring the material into solution.

(8) **Vat Dyes.** — Use 0.2 g. of a solid dye; if a dye is available in the form of a paste use as much as will adhere to about 1 cm. of the end of a stirring rod. Boil the dye with 100–200 cc. of water, 5 cc. of 10 per cent sodium hydroxide solution and about

1 g. of sodium hydrosulfite until it is reduced. Introduce a piece of cotton cloth and boil the solution gently for 10 minutes. Rinse the cloth well in water and allow it to dry.

Dyes: Indigo, Indanthrene Brilliant Violet, Indanthrene Yellow.

FORMATION OF DYESTUFFS

(1) **Phenolphthalein.** — Mix 0.1 g. of phthalic anhydride and 0.1 g. of phenol in a test tube, add 2 drops of concentrated sulfuric acid, and heat gently over a small flame with constant agitation for about 2 minutes. The melt will become dark red but should not blacken. When cool, treat with 5 cc. of water and then add very gradually, with shaking, a dilute solution of sodium hydroxide until a permanent pink color is obtained. Then test the suitability of the material as an indicator by adding first a trace of acid and then a trace of alkali.

(2) **Fluorescein.** — Heat gently for 2 minutes a mixture of 0.1 g. each of phthalic anhydride and resorcinol to which 3–4 drops of concentrated sulfuric acid have been added. Allow to cool, add 5 cc. of water, make alkaline with sodium hydroxide. Add a drop of this solution to a test tube full of water.

(3) **Crystal Violet, a Triphenylmethane Dye.** — Michler's ketone has the structure of *p,p'*-tetramethyldiamino-benzophenone: $(CH_3)_2N.C_6H_4.CO.C_6H_4.N(CH_3)_2$. In the presence of phosphorus oxychloride, aniline adds to this compound in such a way that the para carbon of aniline becomes joined to the carbon of the carbonyl group, while the para hydrogen becomes attached to the oxygen. In the presence of an acid, here derived from the phosphorus oxychloride, a dye is formed.

Place 0.1 g. of Michler's ketone, 5 drops of dimethyl aniline, and 2 drops of phosphorus oxychloride in a test tube, and heat the tube in boiling water for one-half hour. Add 10 cc. of water and stir.

Add several drops of this solution to 20 cc. of water and treat with a little ammonia. Let stand until the color has disappeared and then add hydrochloric acid.

Write the formula for crystal violet and account for the color changes noted.

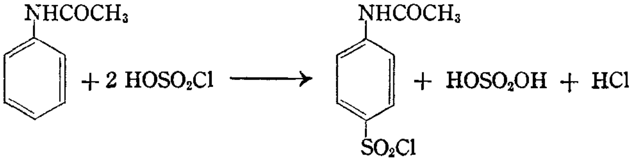
If the original solution is allowed to stand over night, crystals of crystal violet should separate.

EXPERIMENT 49

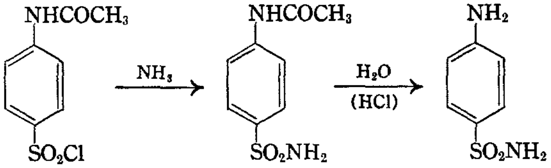
SULFANILAMIDE

The amide of an acid having no interfering groups can be obtained by converting the acid to the acid chloride by means of either phosphorus pentachloride or thionyl chloride and treating the reaction product with ammonia. This direct process cannot be used for the preparation of the amide of sulfanilic acid unless the amino group is protected by acetylation against attack by the halogenating agent. Since the amino group of sulfanilic acid is not free but is bound in an inner salt or dipolar ion structure, the substance must be converted into the sodium salt prior to treatment with acetic anhydride. The salt, however, is not soluble in acetic anhydride, and the reaction proceeds so poorly that the preparation of *p*-acetaminobenzenesulfonyl chloride by this method leaves much to be desired.

A much better route to this intermediate consists in the treatment of acetanilide with excess chlorosulfonic acid. The sulfonyl chloride group is thereby substituted into the para position and the water formed reacts with more of the reagent to form sulfuric and hydrochloric acids. *p*-Acetaminobenzenesulfonyl chloride (m.p. 148–149°) can be obtained in this way in excellent yield and purity. (Chlorosulfonic acid is very corrosive to skin and clothing and reacts with water with great violence; a graduate used to measure the reagent should be drained thoroughly into the reaction vessel and then cautiously held under the tap in a slanting position.)



Conversion to the amide is accomplished conveniently by warming the crude acid chloride with aqueous ammonia. Purified *p*-acetaminobenzenesulfonamide melts at 212–213°. The protecting acetyl group must now be removed without hydrolyzing the sulfonamide group, and this can be accomplished by the action of boiling dilute hydrochloric acid. The liberated sulfanilamide goes into solution in the form of the hydrochloride, $H_2NSO_2C_6H_4NH_3Cl$, and the free base is obtained by neutralization with sodium bicarbonate.

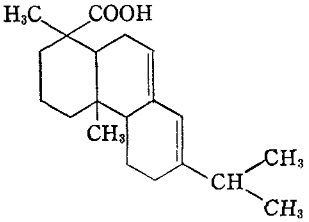


Procedure. — The chlorosulfonation is conveniently carried out without solvent in a 250-cc. Erlenmeyer flask fitted with a stopper which is connected by means of a section of rubber tubing to a gas trap (page 54) to entrain the liberated hydrogen chloride. The reaction is more easily controlled when the acetanilide employed is in the form of a hard cake than when it is in a powdered condition. Place 10 g. of acetanilide in the flask, melt it over a free flame, and cause the material to solidify over the lower walls of the flask by swirling and cooling in an air blast. Cool thoroughly in an ice bath, measure 25 cc. of chlorosulfonic acid into a dry graduate, add the reagent all at once, and put in place the stopper connected to the gas trap. The flask is now removed from the ice bath and swirled until a part of the solid has dissolved and the evolution of hydrogen chloride is proceeding at a rapid rate. Occasional cooling in ice may be required to prevent a too brisk reaction. In 5 to 10 minutes the reaction subsides and only a few lumps of acetanilide remain undissolved. When this point has been reached, heat the mixture on the steam bath for 10 minutes to complete the reaction, cool the flask under the tap, and pour the oily mixture slowly in a thin stream with stirring into 150 cc. of ice water contained in a 600-cc. beaker which is cooled in an ice bath (hood). Rinse the flask with cold water and stir the precipitated *p*-acetaminobenzenesulfonyl chloride for a few minutes until an even suspension of granular white solid is obtained, and then collect and wash this on a Büchner funnel. After pressing and draining the filter cake, transfer the solid to the rinsed reaction flask, add 30 cc. of concentrated aqueous ammonia solution and 30 cc. of water, and heat the mixture over a free flame with occasional swirling (hood) and maintain it just below the boiling point for 5 minutes. During this treatment a change can be noted as the sulfonyl chloride undergoes transformation to a more pasty suspension of the amide. Cool the suspension well in an ice bath, collect the *p*-acetaminobenzenesulfonamide by suction filtration, making sure to press the cake on the funnel and to drain it thoroughly from excess water, which otherwise will unduly dilute the acid used in the next step.

Transfer the still moist amide to the well drained reaction flask, add 5 cc. of concentrated hydrochloric acid and 20 cc. of water, boil the mixture gently over a free flame until the solid has all dissolved (5–10 minutes), and then continue the heating at the boiling point for 10 minutes longer. The solution when cooled to room temperature should deposit no solid amide, but if this is not the case heating should be continued for a further period. The cooled solution of sulfanilamide hydrochloride is shaken with Norit for a few minutes and filtered by suction, giving a colorless filtrate. Place the solution in a 400 cc. beaker and cautiously add 8 g. of sodium bicarbonate with stirring. After the foam has subsided, test the suspension with litmus and if it is still acidic add more bicarbonate until the neutral point is reached. Cool thoroughly in ice and collect the granular, white precipitate of sulfanilamide. The crude product (6.5–7.5 g., m.p. 161–163°) on crystallization from alcohol or water affords pure sulfanilamide, m.p. 163–164°, with about 90 per cent recovery.

EXPERIMENT 50[1]

ABIETIC ACID



The viscous yellow oleoresin which exudes from an incision made in the trunk of a pine tree affords two commercially important products which are separated by steam distillation. The steam-volatile portion constitutes oil of turpentine, a mixture of terpene hydrocarbons, and the non-volatile residue sets on cooling to an amber colored, glassy mass known as rosin or colophony. When rosin is heated with acetic acid, or with alcoholic hydrochloric acid, various labile resin acids originally present are isomerized to abietic acid, which crystallizes in a crude form when the solution is cooled. The once recrystallized acid (" Steele's acid ") contains a small amount of the isomer *d*-pimaric acid, and possibly traces of other isomers; the melting point is about 158–163° and the optical rotation, which affords a better index of purity, is α_D −77°. The best method of effecting a further purification is by crystallization of the quarter-sodium salt, a stable molecular compound of the formula $C_{19}H_{29}COONa.3C_{19}H_{29}COOH$. After extensive purification the sodium salt melts at 195–198° and on acidification yields substantially pure abietic acid, α_D −100° (" Palkin's acid "). Even the purest acid melts over a wide temperature range (165–170°, variable). The free acid

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[1] Special experiment; if large amounts of the acid are to be prepared suitable provision must be made for the disposal of the resinous mother liquor.

slowly deteriorates as the result of air oxidation, and it is stored in the form of the air-stable quarter-sodium salt.

Procedure. — Place 70 g. of light yellow rosin (or " commercial abietic acid "), 50 cc. of glacial acetic acid, and 1 cc. of water in a 200-cc. round-bottomed flask and boil the mixture gently under a reflux condenser for 2 hours. Decant the brown solution into a 250-cc. beaker (hood), cool, and scratch the walls of the vessel well in order to induce the abietic acid to crystallize. When this has formed a thick meal and the process of crystallization appears complete, the crude acid is collected on a Büchner funnel, pressed well, and washed carefully with an ice-cold mixture of 100 cc. of alcohol and 20 cc. of water. To wash the material efficiently, disconnect the suction, cover the cake with a portion of the wash liquid, break up the cake with a spatula and mix it with the wash liquor, and then apply suction. After the process has been repeated once or twice, a granular, nearly colorless product is obtained. Without drying the crude acid, crystallize it once from 30 cc. of glacial acetic acid and 1 cc. of water in a 250-cc. beaker (cool rapidly) and wash the collected crystals as before. The product (Steele's acid) should be dried and carefully weighed; yield 25–30 g.[1]

For conversion into the quarter-sodium salt the acid is placed in a 400-cc. beaker and dissolved in alcohol, using 2.5 cc. per gram. The solution is then treated with just the calculated amount of 10 per cent sodium hydroxide solution (0.33 cc. per gram of acid) and warmed on the steam bath with stirring until the salt separates and sets to an almost dry powder. Alcohol is added (7 cc. per gram of crude acid), the salt is brought into solution by heating, and the solution is set aside for crystallization. Collect the fibrous white needles and recrystallize the product at least once more from alcohol. The yield of salt melting at 188–191° is 7–9 g.

Dissolve 1 g. of the quarter-sodium salt in 10 cc. of hot alcohol, add dilute hydrochloric acid by drops until a test with moistened litmus paper shows the solution to be acidic, and dilute the solu-

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[1] The glassware can be washed free of resinous material with acetone.

tion slowly with water at the boiling point until a cloudiness persists and the abietic acid begins to crystallize. Cool, collect the product and dry it; yield 0.9 g., m.p. 162–166°. Test the substance for unsaturation to bromine and to permanganate. Save the sample and observe its character from time to time.

EXPERIMENT 51

THE IDENTIFICATION OF ORGANIC COMPOUNDS

This experiment is designed to provide experience in carrying out tests which will establish the presence or absence of various functional groups in an unknown compound as an aid in its identification. A method of attacking the problem of determining the nature of an unknown substance is presented in the procedure outlined below. This gives a series of observations and tests which may be applied to advantage and it indicates a rational order in which to try them. In the interest of economy of time the procedure is limited to a rather small group of aromatic compounds, for the problem would become far too complicated if a distinction were to be made between all of the many organic types. The aromatic hydrocarbons and their halogen derivatives, as well as the phenol ethers, have been omitted from consideration for the reason that they are comparatively inert substances for which there are no simple, general tests. The types for which provision is made include acids, bases, salts, and the reactive carbonyl and nitrogen-containing compounds. With the exceptions noted, nearly any of the aromatic compounds whose preparation, properties, or uses as reagents have been discussed up to this point in the manual may be taken as " unknowns." Other substances suitable for the experiment may be found in the list of aromatic compounds ordinarily considered in an introductory lecture course in organic chemistry. The instructor may elect to attain some further variety by including halogen, alkyl, or alkoxyl derivatives of the simpler types, and compounds containing more than one functional group will of course present problems of special difficulty and interest.

Each unknown should be examined with the aim of determining its exact structure. If a substance has been classified by means of tests as belonging to a certain limited group, it may be possible to make a rational hypothesis as to the exact identity by comparing the physical constants of the substance with those recorded for the various members of the group in text books, manuals, or works of reference.[1] The hypothesis then should be tested by carrying out some further specific reactions and by the preparation of characteristic derivatives. It is particularly important to obtain solid derivatives of characteristic melting points when dealing with a substance which is a liquid, and a complete proof of identity can be established by means of a mixed melting point determination with an authentic sample of the substance or derivative.

In some cases the complete identification may take more time than it is wise to spend on any one compound, and the instructor should be consulted as to the advisability of carrying the investigation beyond any reasonable stopping point. It may be considered sufficient in a given case to report correctly that the unknown is " an ester of benzoic acid," " a hydrochloride of a secondary amine," " an aldehyde, possibly one of the tolualdehydes." While a complete identification always should be undertaken, it may not be deemed expedient to complete it, for it is desirable that time be available for the examination of several different substances.

It may be observed that the kind of testing indicated below is exactly that which is constantly employed by the research worker. A known reaction applied to some new case may be expected to yield a certain type of compound; after the reaction product has been isolated the next step is to see if it has the expected properties, that is, if it responds to characteristic group tests. If this is not the case, and the situation is by no means unusual, other tests have to be applied according to whatever system appears most rational until the nature of the product is revealed and the course of the unexpected reaction has been

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[1] Shriner and Fuson, "The Systematic Identification of Organic Compounds"; Kamm, "Qualitative Organic Analysis"; Clarke, "Handbook of Organic Analysis."

established. The only essential difference from the present work is that a quantitative analysis of the unknown substance is then included in the study. The problem may be in some respects more difficult, but it is even more limited, for the investigator has all the clues provided by a knowledge of the nature of the starting materials.

In the present work any reasonable clues or guesses may be followed without regard to the formal procedure. Any order or method of experiment which gives fair promise of quick success may be worthy of trial. If you think that you recognize the unknown from the odor or from some other characteristic property, it would be wise to carry out at once some specific test, or a mixed melting point determination (of a suitable derivative, in case the compound is a liquid). The only rigid stipulation is that any conclusions must be supported by adequate experimental evidence. In most cases it will be found convenient to adopt the following order of observation.

PROCEDURE

(1) **Note the color, odor, physical state, crystalline character.** — Try to distinguish between a characteristic, pure color and an " off " shade or tint which may be due to an impurity. The samples available may contain traces of foreign coloring matter and still be sufficiently pure for purposes of the tests. Even the best grades of the liquid amines may become discolored on storage, as your own experience with various grades of aniline probably has shown, but the color is dull and not full-bodied.

Crystals are usually classified as needles, plates, or prisms, but if they are too small for a recognition of the form the solid is described as microcrystalline in order to distinguish it from amorphous material.

(2) **Examine the behavior on heating.** — If the unknown is a *solid*, heat a small sample carefully on a knife blade. If it melts nicely, determine the melting point; if not, see if it leaves a large residue of inorganic material when burned, indicating a metal salt. (A slight residue is not significant; see page 9.)

In case the unknown is a *liquid* determine the approximate boiling point: carefully heat about 1 cc. in a test tube supported with a clamp until a ring of vapor rises part of the way up the tube. Hold a thermometer in the vapor and read the boiling point (two or three trials). The liquid may be colored from impurities; observe whether the condensed vapor is colored or colorless. NOTE: Boiling points given in reference books represent corrected values; those found by the above method are uncorrected and they may be appreciably lower than the true values.

(3) **Classify the unknown by its solubility,** according to the Tables given below. Note that these solubility tests should be made in the cold, unless otherwise stated. In making the tests use just 3–4 drops of a liquid unknown; a solid should be *finely* powdered with a spatula, and a small pinch on the rounded tip of the spatula should be sufficient. Use about 0.5 cc. of solvent and rub the mixture with a rounded stirring rod. Where the Table calls for " dilute NaOH," it is best to use 3–4 drops from the reagent bottle (10 per cent solution) and 0.5–1 cc. of water. Remember that small test tubes conserve both time and material; also that a 2-cm. column of liquid in an 11 × 75 mm. test tube gives an approximate measure of 1 cc. Use clean dropping tubes for the addition of reagents.

In case a substance is found to be more soluble in an acidic or basic solution than in water it is always advisable to confirm the observation by seeing if the original material will precipitate on neutralizing the solution. The experience gained in testing amines and amine salts (page 106) should be recalled in this connection. Many of the tests included in the Tables have been discussed in connection with previous experiments and the references given to these discussions should be consulted for fuller information. If the tests lead you to suspect some type of compound with which you are not familiar it will be helpful to refer in this book or elsewhere to a description of the properties and reactions of some representative member of the class suspected.

It is to be noted that this " system " of analysis is designed for use in studying a very limited number of relatively simple aromatic compounds, and that the classifications would be greatly extended if aliphatic substances were included. The " system," moreover, is not infallible; it is offered as an aid and a guide, but careful thought will be required for its successful application.

(4) **Determine the sub-group** to which the unknown belongs (e.g., " IV B," " VI A ").

(5) **Qualitative tests for N, S, halogen.** — These may not be necessary, and should be tried only if you think that they will give additional information. A test for nitrogen is useful in distinguishing between groups V and VI.

(6) **Report to your instructor** the group and sub-group suspected and find out if your inferences thus far are correct. This will save unnecessary work in a wrong direction.

(7) **Attempt a more complete identification.** — Try to distinguish between the various possibilities in the sub-group.

Finally, if so advised by the instructor, try to establish the complete identity. If your unknown is a solid, look up the melting point of representative members of the type found. If it is a liquid, there may be some easily prepared solid derivative whose melting point will furnish suggestive information.

CLASSIFICATION

Groups I and II

Soluble in Cold Water[1]

I	II Insoluble in Ether[2]	
Soluble in Ether	A	B
	Acid to Litmus, Fusible	Neutral
Some Phenols (See IV B, below.) **Some Hydroxy Acids**	**Sulfonic Acids** **Polycarboxylic Acids** **Amine Salts** (weakly acidic)	**Metal Salts** (infusible) **Ammonium Salts** (fusible)

NOTES

1. If the compound is not *easily* soluble in cold water, treat it as a water-insoluble substance.

2. The addition of hydrochloric acid to a water solution of the unknown may give a precipitate of a carboxylic acid (solid); sodium hydroxide may precipitate an amine (oil or solid), particularly if the solution is concentrated or if solid sodium chloride is added, or it may cause the liberation of ammonia (odor). In either case the material (from a larger sample of the unknown) should be collected (either by filtration or by extracting with ether) and the carboxylic acid or the amine then can be studied further as in IV A or III. The salt of a sulfonic acid is not affected by adding hydrochloric acid. If such a salt is suspected, it should be analyzed for sulfur. A sulfonic acid or its salt often can be identified from the melting point of the *p*-toluidine salt (prepared as on page 140).

Groups III and IV

Insoluble in Cold Water

III Soluble in Dil. HCl[1]	IV Soluble in Dil. NaOH[2] A	B
	Soluble in $NaHCO_3$	Insoluble in $NaHCO_3$
Amines (3 classes) (See Expt. 21, p. 106.)	**Carboxylic Acids**[3] **Nitrophenols** (colored) **and similar phenols, e.g., vanillin, salicylaldehyde** **Amino Sulfonic Acids**	**Phenols**[4]

NOTES

1. Use very dilute acid (2–3 drops of 10 per cent hydrochloric acid and 1–2 cc. of water). Some amines dissolve only when the mixture is heated; if solution then occurs, neutralize with alkali and see if this precipitates the amine. If a part of the solid appears to dissolve, decant and neutralize the supernatant liquor.

2. If the unknown is colored, be careful to distinguish between the *dissolving* and the *reacting* of the sample. Some quinones (colored) *react* with alkali and give highly colored solutions. On the other hand, some phenols (colorless) dissolve *and then* become oxidized to give colored solutions. Some compounds (e.g. benzamide) are hydrolyzed with such ease that careful observation is required to distinguish them from acidic substances.

3. A good test consists in making the ester, which is *not* soluble in sodium hydroxide solution and which sometimes has a characteristic odor. Cover about 0.2 g. with 2–3 cc. of methyl alcohol, add 4 drops of concentrated sulfuric acid, and boil 5–10 minutes (steam bath). Cool, add 10 cc. of water, smell, and see if the solid or oily precipitate fails to dissolve when the cold mixture is made alkaline with sodium hydroxide. A better conversion to the ester can be obtained by refluxing the mixture

with alcohol and catalyst under the cold finger condenser (page 64).

4. Phenols frequently impart to their dilute aqueous or alcoholic solutions characteristic colors on the addition of a drop of ferric chloride solution. This color test may be useful for the identification of a particular phenol. The test is negative with nitrophenols, and with meta and para phenol carboxylic acids.

A typical test reaction of polyhydric phenols having ortho or para hydroxyl groups is the oxidation of an alkaline solution by exposure to the air. The reaction is evidenced by a development of color.

A further useful test for phenols, as well as for amines, is the reaction with bromine. Shake an aqueous solution of the unknown with bromine water and if a solid precipitate forms, determine the melting point (see the test for aniline with bromine water, page 151).

Groups V and VI

Insoluble in Cold Water (*Continued*)

Soluble in Cold, Concd. H_2SO_4[1, 2]				
V Carbonyl Compounds			VI Neutral Nitrogen Compounds	
A	B	C	A	B
Colored Compounds	React with Phenylhydrazine[4]	Hydrolyzed by Hot NaOH[5]	Reducible,[6] Colored	Hydrolyzable[7] Usually Colorless Solids
Quinones[3] **Diketones** (See tests for benzil, p. 226.)	**Aldehydes** **Ketones** (Try Schiff test, iodoform test, see pp. 84–90.)	**Esters** **Anhydrides**	**Polynitro Compounds** (yellow) **Azo Compounds** (orange or red)	**Amides** ($RCONH_2$) **Acetyl Amines** ($RNHCOCH_3$)

NOTES

1. This is a general property of oxygen- and nitrogen-containing compounds and depends upon the formation of oxonium or ammonium salts. The test gives a means of distinguishing such inert compounds (not included here) as the phenol ethers, which dissolve, from the hydrocarbons, which do not dissolve.

2. Test for the presence of nitrogen.

3. Quinones (colored) can be recognized by their easy reduction to hydroquinones (usually colorless). Suspend a small sample in a little water, add a small pinch of sodium hydrosulfite ($Na_2S_2O_4$) and heat. A green quinhydrone is sometimes observed as an intermediary product. The hydroquinone may separate as a colorless solid or it may remain dissolved in the hot solution. If an anthraquinone is suspected (high melting point, slight solubility, slow reduction) add sodium hydroxide solution along with the hydrosulfite and keep the solution alkaline. A characteristic red vat will then develop if the quinone belongs

to the anthracene series. (See pp. 228–235 for further properties characteristic of benzo- and naphthoquinones.)

4. Dissolve about 0.2 g. in about 2 cc. of alcohol, add water drop by drop until the solution (cold) is nearly saturated but clear (if too much water is used, add more alcohol). Add 5 drops of phenylhydrazine and see if a precipitate of the sparingly soluble phenylhydrazone forms (a few drops of acetic acid will catalyze the reaction). The melting point of the solid may help in identifying the unknown. See page 85 for further particulars of the test.

5. Reflux about 0.2 g. of the sample, using the cold finger (page 64), with 5 cc. of 10 per cent sodium hydroxide solution for 10–20 minutes. If a clear solution is then obtained, cool and acidify the solution. If the acid fails to separate, use a more concentrated solution. See page 64.

6. On reduction in the presence of hydrochloric acid these compounds form amine hydrochlorides (soluble in water). Dissolve about 0.5 g. of stannous chloride in 1 cc. of concentrated hydrochloric acid, add about 0.1 g. of the unknown, and warm. The material should dissolve with disappearance of the color and give a clear solution when diluted with water. See pp. 210–212.

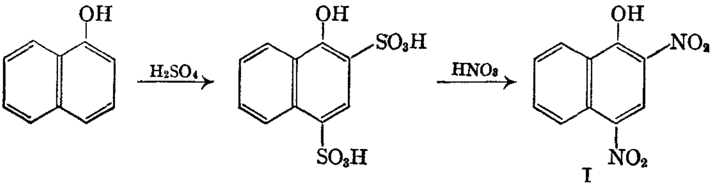
7. Most amides can be hydrolyzed by short boiling with dilute sodium hydroxide solution; the acid dissolves and one smells ammonia. An acetyl derivative of an amine may be hydrolyzed by either an acid or an alkali. Using the cold finger, reflux for 15–20 minutes a mixture of 0.2 g. of the sample and 5 cc. of either 20 per cent sodium hydroxide or 20 per cent hydrochloric acid (equal parts of the concentrated acid and water). If hydrolysis occurs, determine if the product is an amine. See page 168.

EXPERIMENT 52

MARTIUS YELLOW AND ITS REDUCTION PRODUCTS

The series of experiments described below illustrates certain operations of general importance and application and it further should afford the student an opportunity of gaining some experience in the rapid handling of small quantities of materials. Starting with 5 g. of α-naphthol, a skilled operator familiar with the procedures can prepare pure samples of the seven compounds listed below in four hours.[1] In a first trial of the experiment, a particularly competent student who plans his work in advance and who makes intelligent use of all of his time can complete the program in about six hours. The series of transformations of course can be carried to any point considered desirable. The wide choice is offered for the reason that it is not often possible to obtain in a simple manner so many nicely crystalline and for the most part beautifully colored compounds of unusual structure from one of the commonly available starting materials.

Description of the Reactions. — The first compound of the series, 2,4-dinitro-1-naphthol (I), is prepared by sulfonating α-naphthol and treating the disulfonic acid with nitric acid in dilute aqueous solution:



I

The exchange of groups occurs with remarkable ease, and it is not necessary to isolate the disulfonic acid. The advantage of

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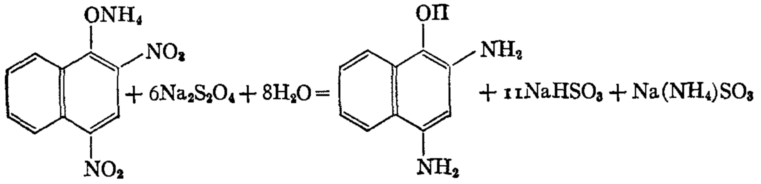
[1] Actual working time. Some of the crystallizations are allowed to proceed over night.

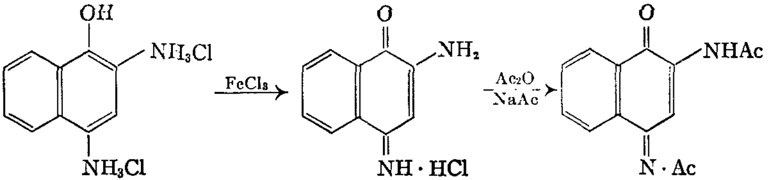
introducing the nitro groups in this indirect way is that the naphthol is very sensitive to oxidation and would be partially destroyed on direct nitration, whereas the disulfonic acid, on account of its two unsaturated groups, is much more resistant to attack by oxidizing agents. The same method is used in the preparation of picric acid. Dinitronaphthol further resembles picric acid in being a strongly acidic substance and in having the properties of an acid dye. It was discovered and introduced to the dyestuff industry in 1868 by Karl Alexander von Martius, who prepared it by the action of nitric acid on diazotized α-naphthylamine. The substance comes on the market in the form of the sodium or the ammonium salt, both of which are known as "Martius Yellow." One gram of this material dyes about 200 g. of wool.

Dinitronaphthol is conveniently purified in the form of the ammonium salt, and for the present purposes this has the further advantage of bringing the substance into a form well suited for reduction to diaminonaphthol according to the equation:



The particular advantage of using sodium hydrosulfite as the reducing agent is discussed below in a note. The ammonium salt is reduced easily at room temperature in an aqueous suspension and the diaminonaphthol separates in the free condition, rather than as an ammonium salt, because the diamine, unlike the highly unsaturated nitro compound, is only a very weakly acidic substance.

2,4-Diamino-1-naphthol is exceedingly sensitive to air oxidation, but by proper handling it can be converted without loss into a solution of the dihydrochloride, in which form it is considerably more stable. By adding an oxidizing agent to the solution there is obtained in a beautifully crystalline condition the second compound of the series: aminonaphthoquinone-imine hydrochloride, II.

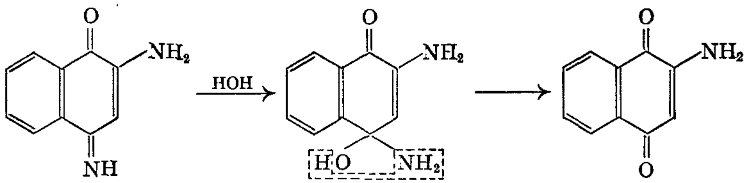


II

III

Since this substance, like many other salts, has no melting point, it is converted for identification into the diacetate, III.

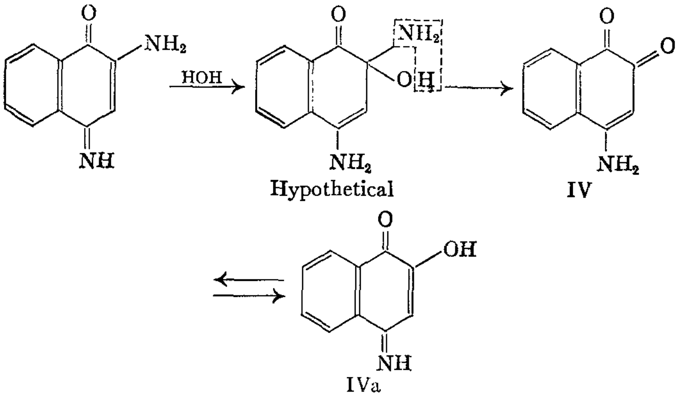
Aminonaphthoquinone-imine (II) is remarkable in that it is one of the very few quinone-imines which are stable enough to be isolated. While most quinone-imines (and di-imines) are hydrolyzed to quinones almost instantly by water, the present compound can be crystallized from an acidic solution. Hydrolysis occurs more easily in a weakly alkaline medium, but even here a boiling temperature must be maintained. One would perhaps expect that the hydrolysis product would be amino-α-naphthoquinone, and that it would result from the addition of water to the $\rangle C{=}NH$ grouping, as follows:



Hypothetical

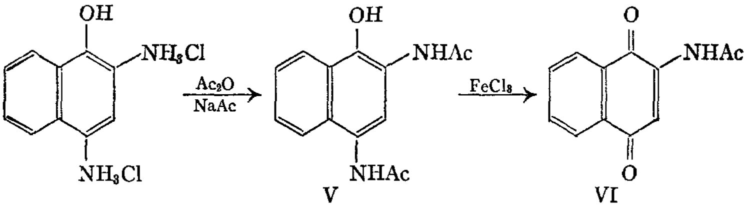
Amino-α-naphthoquinone

This substance is indeed formed, but in very small amount, for the chief reaction product is the amino-β-naphthoquinone, IV. This probably results from the addition of a molecule of water not to the $\rangle C{=}NH$ group but to the ends of the conjugated system: $\rangle C{=}CH{-}C{=}NH$, in the following manner:



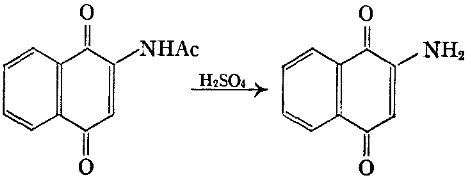
The β-quinone (IV) is easily separated from the small amount of the isomer by taking advantage of the fact that in a strongly alkaline medium it undergoes a tautomeric change to hydroxynaphthoquinone-imine (IVa). This being acidic, the substance dissolves in alkali; the isomer undergoes no such change and remains undissolved.

The remaining compounds of the series are obtained by starting with another portion of the acid solution of diaminonaphthol. By adding acetic anhydride and sodium acetate to the solution the amino groups can be acetylated without affecting the hydroxyl group (for comments on the reaction, see the note below). This yields 2,4-diacetylamino-1-naphthol, V.



This is converted by oxidation smoothly and in quantitative yield into acetylamino-α-naphthoquinone, VI. One acetylamino group is hydrolyzed in the course of the reaction, but the mechanism of the change is still obscure. The last product of this series of transformations is amino-α-naphthoquinone (VII).

This is obtained by the hydrolytic action of concentrated sulfuric acid on VI:



VII

General Instructions. — Use a horn-pan balance or a triple-beam balance accurate to 0.1 g. for weighing the small quantities of the solid reagents and a 10 cc. graduate for measuring the liquids. Record yields and melting points wherever conveniently possible. As each stage in the series of transformations is reached, save for purification and testing a small amount of the product (about 0.3 g.). The remainder of the material is to be used without further purification, often without drying, for the next step in the series of reactions. In case the dry weight is known and does not correspond exactly to that called for, suitable adjustments should be made in the amounts of the various reagents.

The purification of the small samples requires little time and usually can be carried out along with the rest of the preparative program. Remember that a substance which crystallizes well from a solvent miscible with water does not have to be dried before crystallization from such a solvent. One should aim to obtain well formed crystals of clear and pure color or with no color at all. The amount of the final sample should represent a reasonable fraction of the material purified, but the exact recovery is not of great importance and it usually is not worth while to work up the mother liquors. Preserve the purified sample in a neatly labeled specimen tube.

Each pure sample is to be fully characterized in the manner ordinarily used by the investigator on discovering a new compound. This includes an observation of (1) the melting point (or other behavior on heating); (2) the crystalline form: needles, plates, prisms, leaflets, etc., perhaps with some further descriptive adjectives; (3) the color and shade; (4) the approximate solubility in a few typical solvents; i.e., " readily," " moderately," or " sparingly " soluble, or " insoluble " in a solvent of the hydrocarbon type (benzene, ether, or ligroin) and in a hydroxylic solvent (water, alcohol, or glacial acetic acid); (5) any characteristic properties noted, such as a reaction with either dilute acids or bases, or a distinctive color test with concentrated sulfuric acid (use a minute fragment and a drop of reagent), with alkali (1–2 drops of 10 per cent sodium hydroxide in about 1 cc. of water), or with alcoholic alkali (1–2 drops of 10 per cent sodium hydroxide in about 1 cc. of alcohol). Though this may seem a somewhat long list of observations, the characterization requires little time or material and it can be reported quite concisely. For example it may be noted that a certain substance " crystallizes from alcohol, in which it is moderately soluble, in the form of cottony clusters of fine, lemon-yellow needles melting at 154°. The compound is very readily soluble in benzene and insoluble in aqueous alkali. It imparts an intense purple color to concentrated sulfuric acid and forms a clear blue solution in alcoholic alkali."

Rather than try at random a number of tests of the kind mentioned in (5), one may save time by applying only those which are likely to be of significance. Some suggestions in this direction have been included below.

The following procedures give information sufficient for the preparations, but a thorough description of the reactions as well as of the products, is purposely omitted. The student should note carefully all color changes and other occurrences, and he is expected to record all pertinent observations.

(1) **Preparation of Martius Yellow.** — Pour 10 cc. of c.p. concentrated sulfuric acid onto 5 g. of finely powdered α-naphthol[1] in a 50-cc. Erlenmeyer flask, stir the mixture for a few

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[1] If the α-naphthol available is crude or dark in color it should be purified by distillation at atmospheric pressure. The colorless distillate is most easily pulverized before it has completely cooled and hardened.

minutes until most of the solid has dissolved, and then heat it for just 15 minutes on the steam bath, stirring well at the start in order to bring the remaining particles into solution. Toward the end of the period specified the disulfonic acid should begin to separate on the walls of the flask, particularly on scratching. Cool well in an ice bath, dissolve the product in 25 cc. of water, cool the solution and place it in a small dropping funnel. This should be supported by a clamp in such a way that the solution can be run into a 250-cc. beaker which is cooled in an ice bath. Place 6 cc. of concentrated nitric acid (sp. gr. 1.42) in the beaker and, while rotating this in the bath to effect good cooling, add the solution of naphthol disulfonic acid by drops in the course of about 10 minutes (1 drop per second until one-half is added, then at twice this rate[1]). When the addition is complete, warm the mixture very gently on the steam bath in such a way that the maximum temperature is reached only in about 5 minutes. Stir well and watch for a vigorous reaction. After applying the full heat for 5–10 minutes longer there should be no noticeable increase in the amount of the yellow nitration product. Dilute the mixture with several volumes of water, collect the crude dinitronaphthol and wash it well with water.

Without drying the precipitate, wash it into a beaker and dissolve the crude material in 200 cc. of water containing 4 cc. of concentrated ammonia solution (sp. gr. 0.90) at the boiling point. Filter the hot solution by suction and add 10 g. of ammonium chloride in order to salt out the ammonium salt (Martius Yellow). Cool the mixture by stirring in an ice bath and collect the precipitate. This should be washed with a solution containing about 1 per cent of ammonium chloride.

Save about 0.3 g. of the crude Martius Yellow for purification. This sample may be precipitated again as the ammonium salt, but it should eventually be converted to the free 2,4-dinitro-1-naphthol (Compound I). This may be crystallized from alcohol; m.p. 138°.

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[1] In working with larger quantities it is well to insert a thermometer and keep the temperature below 10°.

(2) **Reduction to Diaminonaphthol.** — Wash the remainder of the moist precipitate of Martius Yellow[1] into a beaker, dilute with water to a volume of about 200 cc., add gradually 45 g. of solid sodium hydrosulfite and stir the mixture well for 5–10 minutes, when reduction should be complete. This is judged by the disappearance of the original color and by the formation of a crystalline tan precipitate. Cool well in ice before collecting, and also make ready about 100 cc. of a freshly prepared 1 per cent solution of sodium hydrosulfite for use in washing, and a beaker containing a mixture of 6 cc. of concentrated hydrochloric acid and 25 cc. of water. Now collect the precipitate on a small Hirsch or Witt funnel, being very careful to avoid exposing the material to the air in the absence of the reducing agent, for it will become oxidized (and darken) with extreme rapidity. Use the hydrosulfite solution and not water for washing the material out of the beaker. Before the mother liquor is drained completely, cover the filter cake with hydrosulfite solution. When the material is all assembled, allow the cake to suck nearly dry for an instant and at once transfer the precipitate into the dilute acid and quickly wash in the material adhering to the funnel with water. Once the diaminonaphthol is converted into the dihydrochloride it is considerably less sensitive to oxidation and may be handled at some leisure. Be careful to stir the mixture well so that the amine dissolves as rapidly as possible.

The acid solution is usually somewhat dark and cloudy and it contains some suspended sulfur. If the solution were treated with decolorizing carbon and exposed unduly, the carbon would catalyze the air oxidation of the material. A clarification is effectively accomplished, however, by filtering the solution through a 2–3 mm. layer of decolorizing carbon. This is prepared by dusting the carbon onto the moistened paper of a Hirsch or Witt funnel with the suction applied, and then washing the mat with water, the washings being discarded.

The filtered solution of diaminonaphthol dihydrochloride may be divided into approximately equal parts, and one of these used

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[1] The dry weight is usually 7 g. (80% yield).

for reactions 3–5, the other for the series 6–8. The whole of the solution may of course be used for either series (using double the quantities of the reagents). In either event the solution should be completely utilized as soon as possible. Notice that both reactions 3 and 6 can be carried to a suitable stage within a few minutes.

(3) **Aminonaphthoquinone-imine** (II). — To one half of the acid solution of diaminonaphthol add 27 cc. of 1 *N* ferric chloride solution, followed by 8 cc. of concentrated hydrochloric acid to decrease the solubility of the red oxidation product (common ion effect). The quinone-imine hydrochloride should begin to crystallize within a few minutes on cooling the solution in an ice bath and scratching the walls of the vessel very thoroughly with a stirring rod.[1] Collect the product and wash it with a small quantity of 10 per cent hydrochloric acid (not water!). Yield, about 2 g.

The material not required for use in Sections 4 and 5 should be purified as follows: dissolve the sample by gentle warming in a few cubic centimeters of water containing 2–3 drops of concentrated hydrochloric acid, shake for a minute or two with animal charcoal, filter by suction, add concentrated hydrochloric acid to induce crystallization and cool in ice. Test the action of alkali and of sodium hydrosulfite on aqueous solutions of the substance.

(4) **Aminonaphthoquinone-imine Diacetate** (III). — A mixture of 0.3 g. of the dry aminoquinone-imine, II, and 0.3 g. of fused sodium acetate is treated in a test tube with 2 cc. of acetic anhydride and the mixture is warmed gently (not above 80°) over the steam bath and stirred thoroughly until red particles are no longer discernible. Acetylation is then complete. Pour the mixture into a small beaker of water and stir until the excess acetic anhydride has either dissolved or become hydrolyzed.

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[1] In order to induce crystallization most effectively the glass must be rubbed until there is a visible scratch. The rubbing should be confined to one spot and this should be slightly above the surface of the liquid, where there is a liquid film.

Collect the crystalline solid on a Witt plate, wash it with water and then with a little alcohol. Yield, 0.3 g.

The diacetate crystallizes well from alcohol and melts at 189°. Note the color reactions of the substance with concentrated sulfuric acid and with alcoholic alkali.

(5) **4-Amino-1,2-Naphthoquinone** (IV). — Dissolve 1 g. of aminonaphthoquinone-imine hydrochloride (II) in 25 cc. of water, add 1.5 cc. of concentrated ammonia solution (sp. gr. 0.90) and heat to boiling. The ammonia neutralizes the salt and the free aminoquinone-imine first precipitates and then is converted in the hot solution to a mixture of the quinones IV and VII. After boiling for 5 minutes the reaction should be complete. Cool and collect the precipitate. Suspend this in about 50 cc. of cold water, add 25 cc. of 10 per cent sodium hydroxide solution, stir for a few minutes and filter by suction from the small amount of undissolved amino-α-naphthoquinone. Acidify the filtrate with acetic acid, collect the precipitate of amino-β-naphthoquinone, wash the product while still wet into a large beaker, and crystallize it from 500–600 cc. of water (the separation is slow). Yield, 0.4 g. The substance shows no characteristic melting point but rather decomposes (at about 270°). Test the solubility in dilute hydrochloric acid (heat to boiling, then cool) and the action of sodium hydrosulfite.

(6) **2,4-Diacetylamino-1-Naphthol** (V). — One-half of the diaminonaphthol dihydrochloride solution prepared as in Section 2 is employed as follows for the preparation of the diacetate, V, (see Note 2). Add 3 cc. of acetic anhydride to the acid solution at room temperature, then add with stirring a solution of 5 g. of crystalline sodium acetate (trihydrate) and about 0.1 g. of sodium hydrosulfite in 20–30 cc. of water. The diacetate often separates at first in an oily condition, but on good stirring it gradually changes into a nearly colorless solid. Collect this material, suspend it in 30 cc. of water, add 5 cc. of 10 per cent sodium hydroxide solution, and stir well without heating until the solid is dissolved. The addition of a trace of sodium hydrosulfite may serve to give a somewhat brighter solution. Filter

the alkaline solution by suction and acidify with hydrochloric acid. The substance may remain for a time in super-saturated solution, and it is advisable to stir well, rub the walls of the vessel with a stirring rod, and cool in ice before collecting the purified diacetate. Dry the material in an oven or on a watch glass heated on the steam bath. Yield, 2 g.

The sample to be saved (0.3 g.) is best purified as follows. Dissolve the sample in the requisite amount of glacial acetic acid at the boiling point, add a solution of a small crystal of stannous chloride in a few drops of dilute hydrochloric acid (this will effectively arrest any oxidation and consequent darkening of the product), and then gradually add 4–5 volumes of water, while keeping the solution at the boiling point. If crystals do not appear in the course of this process, allow the solution to stand in a cold place over night. The pure substance melts with some decomposition at 224°.

Use the remainder of the preparation for the following reaction.

(7) **2-Acetylamino-1,4-Naphthoquinone** (VI). — Dissolve 1.5 g. of diacetylaminonaphthol (V) in 10 cc. of glacial acetic acid (hot), dilute with an equal volume of water and to the hot solution add 13 cc. of 1 *N* ferric chloride solution. The oxidation product separates in a crystalline and a nearly pure condition. Cool, collect the product, and wash it well with water and then with a little alcohol (so that it will dry quickly). Yield, 1.2 g.

Crystallize a small sample (0.3 g.) from alcohol. The pure material melts at 204°.

(8) **2-Amino-1,4-Naphthoquinone** (VII). — In a small flask or test tube cover 0.5 g. of the acetylaminoquinone, VI, with 1 cc. of concentrated sulfuric acid and heat the mixture for just 15 minutes on the steam bath, stirring well until the solid has dissolved completely. Pour the highly colored solution into water, collect the precipitated aminoquinone, wash well with water, and crystallize the moist sample from alcohol. Yield, 0.3 g.; m.p., 206°. Test the action on the substance of sodium hydrosulfite and of alcoholic alkali. Determine if the amine is as strongly basic as its isomer, IV.

NOTES

1. *Reduction with Sodium Hydrosulfite.* — In the early investigations of the reduction of Martius Yellow the reduction was accomplished by the use of stannous chloride and the tin was removed from the acid solution by displacement with metallic zinc. The process, however, is both tedious and uncertain, and the use of sodium hydrosulfite as the reducing agent represents a great simplification of the method. Since this reagent is not soluble in the organic solvents and can be used only in an aqueous medium, it is evident that it is a distinct advantage that the dinitro compound which is to be reduced is an acidic substance and forms water-soluble salts. The ammonium salt is more soluble than the alkali metal salts and is better suited for the reaction. The experiment shows that the reduction is very rapid and easily carried out.

It is also possible, if somewhat less convenient, to reduce dinitronaphthol itself, rather than the salt, with sodium hydrosulfite. In this case it is best to suspend the yellow solid in alcohol and to add an aqueous solution of the reducing agent at the boiling point. The same procedure is recommended for the reduction of other compounds which are not appreciably soluble in water, while the simpler method described above serves well in the alternate case, or where the substance can be obtained as a salt.

Sodium hydrosulfite serves as a convenient reagent for the reduction of many other nitro compounds as well as azo compounds (page 210) and quinones (page 238).

2. *Acetylation in aqueous solution.* — An amine is always more easily acetylated than a phenol of similar structure, and if an aminophenol is treated in the dry condition with acetic anhydride the amino group is the first to be attacked. It is not easy, however, to stop the reaction at this stage and the pure *N*-acetate is not readily prepared by this method. A much better method is to conduct the acetylation in aqueous solution (see page 164). The amino group again reacts very rapidly to

form an acetylamino group, but the hydroxyl group does not react with acetic anhydride much more rapidly than does water, and the concentration is of course much less than that of the substance with which it competes. The anhydride not required for the acetylation of the amino group undergoes slow hydrolysis, and much of it probably remains as such in solution in the mother liquor when the reaction product is collected.

The value of purifying the crude reaction product by dissolution in alkali and reprecipitation with acid is that, besides removing any foreign, insoluble particles, this converts any higher acetylation products which may be present into the product desired. An acetyl group attached to nitrogen is not influenced by cold, dilute alkali, but this reagent easily hydrolyzes such a group when it is attached to oxygen. The diacetate of *p*-aminophenol, for example, dissolves rather rapidly on being stirred with dilute alkali in the cold, and *p*-acetylaminophenol precipitates in a pure condition on neutralization of the solution.

PART II

CHAPTER I

SUGGESTIONS FOR ADVANCED WORK

There is no great difference in the nature of advanced and of elementary work in the organic laboratory and it is a change in the attitude of the student rather than his registration in a new course which will mark his development beyond the ranks of the beginners. In order to make reasonably rapid progress in a strange field the beginner has to be told a great many things, provided with suitably prepared reagents and given highly detailed directions, and the responsibility for the successful outcome of the experiments properly rests with the instructor. As soon as the student is able to assume at least a large part of this responsibility and to work without fully standardized directions he has reached a definite stage of advancement. He will still have much to learn, but if he will undertake to lay his own plans and attempt to correct his own faults of manipulation or procedure through reflection and further trial, he will be headed in the right direction.

With difficult preparations, or preparations for which no more than an outline of the procedure can be found in the literature, it is too much to expect an entirely satisfactory result on the first trial. It is well to make a preliminary run, planned as intelligently as possible but limited to a small amount of material, in order to test the reagents and conditions and to gain first-hand experience with the reaction before risking an appreciable quantity of the starting material. If the result is poor, without the trouble being readily apparent, it may be well to investigate the purity of the reagents and solvents, for traces of impurities often exert a marked influence on the course of a reaction by virtue of either a catalytic or a poisoning (anticatalytic) effect. It may be necessary to vary systematically the temperature, the proportion of the different reagents, the solvent, or the dilution. Remember that a bimolecular reaction proceeds faster in a concentrated than in a dilute solution, but that the velocity of a monomolecular reaction is independent of the concentration.[1] Several preliminary, small-scale runs may be necessary in order to perfect the process, and each repetition, whether of a trial nature or for the purpose of obtaining more material, should be looked upon as an opportunity for improvement. It is often possible by working in this way to simplify or improve methods found in the literature, and exactly the same procedure is followed in studying reactions which have never before been tried.

It is of the utmost importance to record all observations directly in a laboratory notebook, for data supplied from memory cannot be relied upon in scientific work. It is a good plan to use a strong book with the pages numbered for purposes of cross reference and indexing. The nature of each experiment should be made clear by a suitable heading, and the date likewise should be included. This is particularly important in research work, for it is impossible to anticipate the occasions on which such information may acquire real importance. It is equally impossible to foretell the future history of the operator, and one should endeavor to keep an original notebook which will be perfectly intelligible to others and which will require neither explanation nor transcription. Clarity and completeness are of much greater importance than a neat appearance.

In case of patent claims, laboratory notes ordinarily are accepted as valid evidence of priority of invention only when they have been recorded in ink in a bound notebook with accompany-

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[1] See Ziegler's striking application of the dilution principle to the problem of preparing large-ring compounds: *Ann.*, **504**, 94 (1933); compare Adams and Kornblum, *J. Am. Chem. Soc.*, **63**, 188 (1941). Kuhn and Brockmann, *Ber.*, **66**, 1319 (1933), were able to isolate a very sensitive primary oxidation product from β-carotene by working at the extremely high dilution obtained by mixing two solutions on a rotating glass rod.

ing notations indicating the dates of the observations; significant notes should bear the signature or initials of a competent witness to whom the results have been revealed.

When, in planning an experiment, the physical constants and molecular weights of the reagents have been looked up or computed they should be recorded at once in the notes where they will be easily available at any future time. References to the literature or to a literature notebook also are to be included, and one should make clear the procedure that is being followed or the points of departure from a given procedure. If the possibility of a repetition of the experiment at some later date is anticipated it is well to leave space for additional notes, but if the record has to be continued in other parts of the book the various scattered accounts can be connected by suitable page references. From time to time it is desirable to summarize the results and page references in the form of a table.

A careful record should be kept of the weight and physical constants of a given product at each stage in the process of purification, for this information may be helpful in tracing the loss of material and it is essential for purposes of making a report or publication of the results. A report of a yield can be accepted as valid only when it specifies clearly the degree of purity of the material upon which the yield is based. The following statement is unambiguous and complete: "The yield of crude product, m.p. 83–85°, was 3.9 g. (79%); two recrystallizations afforded pure material, m.p. 87–88°, in yield of 3.6 g. (73%)." It would be incorrect to say: "The product crystallized in needles, m.p. 87–88°; the yield was 3.9 g. (79%)," and to say either "the yield was 73%" or "the yield was 79%" would be ambiguous. The accuracy of weighing should be commensurate with the quantity of material and the significance of the yield. For weighing 1–50 g. with an accuracy of 0.05 g. or better either a triple-beam or a horn-pan balance (with selected fractional weights) is satisfactory. The knife-edges of all laboratory balances should be coated with vaseline to protect them from rust.

USE OF THE LITERATURE

Excellent guides are fortunately available to the very voluminous and ever expanding literature of organic chemistry. Richter's "Lexikon der Kohlenstoffverbindungen" lists in four volumes all of the organic compounds known up to the time of publication (1910). Compounds are listed according to their empirical formulas, the commoner elements being given in the order: C, H, O, N. A notation at the top of each page gives the number of carbon atoms (Arabic) and the number of other atoms combined with carbon (Roman) for the compounds listed. To look up benzamide, $C_6H_5CONH_2$, the formula is written: C_7H_7ON and this will be found on the page marked "7 III." Once the empirical formula has been located the compound itself may have to be picked from a long list of isomers by the name, or names, the Geneva-system name (slightly abridged) often being supplemented by one or more common ("trivial") names. Richter gives melting point ("Sm." = Schmelzpunkt) or boiling point ("Sd." = Siedepunkt) data and references to the original literature. References are also given (in Roman numerals) to the various volumes of the third edition of Beilstein's "Handbuch der organischen Chemie," but this edition is now quite out of date (see below).

Stelzner's "Literatur-Register der organischen Chemie" forms a continuation of Richter's formula index and in five volumes covers the period 1911–1921 (inclusive). The system follows much the same plan as Richter's but gives in addition some classification of the references. Different symbols are used to indicate melting point ("F.") and boiling point ("Kp."), and in the case of the latter constant the pressure in millimeters of mercury is included as a subscript. The most important groupings of the references are as follows: (1) "E." (Eigenschaften), properties; (2) "B." (Bildung), formation (methods not regarded as having preparative value); (3) "Darst." (Darstellung), preparation.

The Richter-Stelzner index has been continued since 1922 by the "Chemisches Zentralblatt" and the system used is practically that of Stelzner. Each year the Zentralblatt contains a formula index and these are then combined in volumes covering a 3–5 year period. The collective indexes, as rapidly as they become available, form convenient extensions of Richter and Stelzner.

For a systematic search of the literature for all available references regarding a given organic compound the following works should be consulted in order:

Richter's "Lexikon," to 1910
Stelzner, 5 vols., 1911–1921
"Chemisches Zentralblatt," Collective Indexes: 1922–1924, 1925–1929, 1930–1934
"Chemisches Zentralblatt," Formula Index, 1935, 1936, etc.

The most extensive compilation of information on organic compounds is the great work of Beilstein, the fourth edition of which is now nearing completion: Beilstein-Prager-Jacobson, "Handbuch der organischen Chemie." By 1938 twenty-seven volumes of the main work had appeared, together with the index. The literature is reviewed thoroughly to January 1, 1910, and later references occasionally are included. Supplementary volumes, of which thirty-one have been published, will cover the literature of the period 1910–1919. The material of "Beilstein" is beautifully organized. The indexing is by names rather than formulas and it follows simple and rational principles. While there is no indication of the character of a given group of isomers, the page references are listed in the order: ortho, meta, para; or α, β, and γ, etc.[1] With some experience "Beilstein" is easy to use and it provides a wealth of admirably organized information and references. One finds references and discussions not only with regard to the properties, reactions, formation, and methods of preparation of organic compounds, but also pertaining to questions of theory and to points of historical interest.

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[1] The beginner can derive assistance from the following guide books: Huntress, "Introduction to the Use of Beilstein" (1938); Prager, Stern, and Ilberg, "System der organischen Verbindungen" (1929).

Much valuable information concerning the laboratory methods of organic chemistry is to be found in the following comprehensive treatises on the subject:

Houben, "Die Methoden der organischen Chemie," 3rd edition (1925).

Hans Meyer, "Lehrbuch der organisch-chemischen Methodik. I, Analyse und Konstitutions-Ermittlung organischer Verbindungen," 6th edition (1931).

Lassar-Cohn, "Arbeitsmethoden," 5th edition (1923).

Abderhalden, "Handbuch der biochemischen Arbeitsmethoden," several volumes.

These works, which are of much the same character but which cover somewhat different subjects, give exhaustive discussions of the various standard operations of the organic laboratory, and of the methods and procedures used for carrying out reactions of a great many different types. Their greatest value lies in the systematic organization of the literature, but they often further provide authoritative suggestions and opinions. Books of more modest proportions but more modern are those of Bernhauer, "Einführung in die organisch-chemische Laboratoriumstechnik" (1934), Morton, "Laboratory Technique in Organic Chemistry" (1938), and Weygand, "Organisch-Chemische Experimentierkunst" (1938).

"Organic Syntheses" is in a different category, since it is an annual publication giving tested directions for the preparation of various compounds. The first nine volumes were combined, revised, provided with extensive references, and published as a Collective Volume in 1932. The procedures not only are of use for the preparation of specific compounds, but they also serve as models for the adaptation of a known reaction to a new case.

Too much emphasis cannot be placed on the necessity for consulting the original literature. "Beilstein" and the other secondary sources mentioned serve an admirable purpose, but they in no sense supplant the original papers to which they furnish so convenient a guide. One who is satisfied with books of reference alone will miss many points of interest and importance in the writings of the investigators. It is impossible to include all material of value in a secondary source and there is a wealth of forgotten ideas and suggestive concepts to be unearthed by anyone who will study with diligence both the early and the recent literature of organic chemistry.

BENZENE-RING STAMPS

Satisfactory hexagons can be cut from rubber stoppers by the following method, and after a little practice it is possible to make stamps of different styles for rings varying from 3 mm. to 20 mm. in height. The small stamps are useful in labelling specimen tubes, the large ones in preparing reports and manuscripts. The cutting is done with razor blades, and a particularly sharp blade is reserved for the finer work. A hard (usually old) rubber is preferred both because it is more easily cut than a soft, elastic rubber and because it gives a stamp of firmer edge.

On the small end of the stopper two parallel cuts, lines 1 and 2 in Fig. 29*a*, are first made by placing the razor edge flat on the surface of the rubber and slowly drawing the blade back and forth with steady pressure. After each line has been cut to a depth of 2–3 mm. the stopper is cut away roughly with an older blade in the manner shown in Fig. 29*b* to give a tapered slice. The distance between cuts 1 and 2 determines the dimension indicated, and the symmetry of the final ring is largely dependent upon the accuracy with which the cuts are made parallel in this and in the following operations.

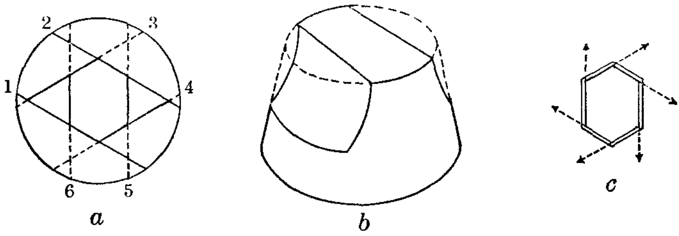

FIG. 29. — Cutting Benzene-ring Stamp from a Stopper

The next two parallel cuts, 3 and 4, are made at a suitable angle to the first two and care must be taken to make the distance between the cuts exactly the same as that between cuts 1 and 2. Cuts 5 and 6 are then made; they should be equidistant from and parallel to the long axis of the ring, and the distance between them determines the width of the hexagon. The stopper is then cut away on all sides.

To clear out the inside of the hexagon and leave an outline, make cuts about 1 mm. deep in the positions indicated by the lines of Fig. 29*c*, working the rubber carefully with a sharp blade. The cut in each corner of the ring usually does not show in the completed stamp and it greatly facilitates the sharp cutting of the outline and the removal of the center. The edges should be about 0.5 mm. wide. The rubber in the center is carefully cut away by folding back each edge, laying the razor flat and cutting horizontally at a depth of 1 mm. A feature of the construction is that with the long taper the edges are open to view when the stamp is in use, thus facilitating a proper alignment.

PURIFICATION OF A SAMPLE FOR ANALYSIS

When a substance has been obtained in a very nearly pure condition and it is desired to effect a final purification which will give a sample suitable for quantitative analysis, one proceeds in a manner slightly different from that of an ordinary crystallization. The analysis is an operation which may require several hours for its completion, and it is obviously a great mistake to employ any but the best sample obtainable. The sample may be of good appearance, it may melt sharply, and it may be entirely suitable for use in certain reactions, and yet it may be unsuitable for analysis because of the presence of traces of dust, of solvent, of an inorganic salt, or of other contaminant which would affect the analytical results. One always should consider the possibility of such contamination and take steps to avoid the source of error suspected.

The glassware used for such a crystallization must be scrupulously clean. Even though the hot solution of the sample appears to be perfectly clear, it always should be filtered before being set aside to crystallize, for it may contain particles not easily visible. After the filtration heat the solution again to boiling but do not introduce a chip of porous plate, for a small piece might break off and contaminate the sample. Inspect the solution very carefully for foreign particles which may have come from the filter or receiving flask, and then allow crystallization to take place. If solvent is to be added after the filtration, it should be introduced through the filter. Decolorizing carbon never should be used in the final crystallization for some of it invariably gets through the filter paper. If clarification is deemed desirable, always reheat and refilter the solution through a fresh paper. With an analytical sample small crystals are preferable to large ones for they are less likely to occlude solvent and they are more easily handled in the weighing.

Similar care as to cleanliness should be taken in the collecting, drying, and bottling of the sample. It is well to dry the sample in a glass dish or on a filter paper covered with a watch glass just until it appears to be dry and to carry out any more extensive drying required after transference to a specimen tube. The filter paper should have a smooth surface and it should be brushed or blown free of lint. Before drying, it is often advisable to grind the sample in an agate mortar to insure removal of occluded solvent, particularly if the crystals are large.

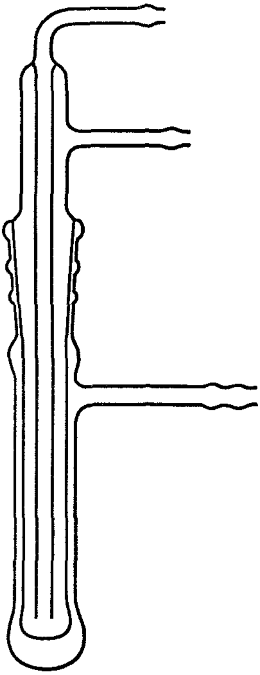

FIG. 30. — Apparatus for Sublimation in Vacuum

It is often advantageous to sublime the sample in vacuum prior to analysis, for persistent traces of occluded solvent or of solvent of crystallization usually are eliminated completely by this process. Where applicable, sublimation can be conducted with little loss of product and provides added assurance of purity. An all-glass assembly for conducting the sublimation of small amounts of material is illustrated in Fig. 30; this may be used in conjunction with a water, oil, or mercury vapor pump. A simpler unit suitable for sublimations at 2–20 mm. pressure can be constructed by inserting a cold finger (page 64) through a rubber stopper into a wide test tube with a side arm.[1]

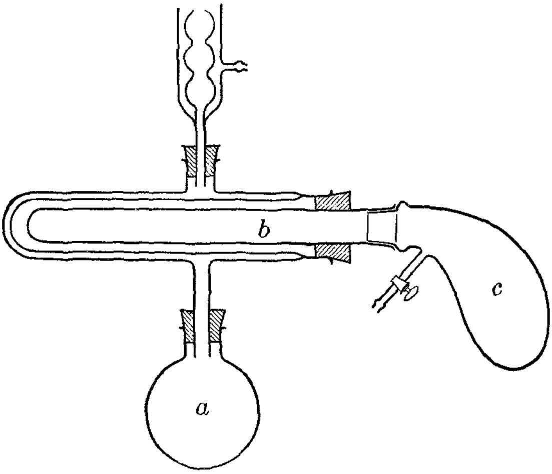

Fig. 31. — Drying Pistol

A convenient form of specimen tube is a 50 × 12 mm. vial which is flat on one end; a screw cap vial is still more satisfactory. To transfer the dried sample, stand the tube on a clean paper, fold the paper holding the sample, and with the aid of a spatula tap the crystals down the crease and into the vial. If a corked specimen tube is used, cut out a circle of clean paper or of cellophane of about twice the diameter of the small end of the cork and force this into the mouth of the tube on the end of the cork, thus providing a neat covering which prevents contamination from the cork.

The sample is best dried in the "pistol" shown in Fig. 31. Vapor from a boiling liquid in *a* rises through the jacket sur-

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[1] Efficient large-scale sublimation units are described by Morton, Mahoney and Richardson, *Ind. Eng. Chem., Anal. Ed.*, **11**, 460 (1939).

rounding the drying chamber *b* and is returned by the condenser. The open specimen tube containing the sample is slid into *b* with a wire and vessel *c*, containing phosphorus pentoxide distributed on glass wool, is put in place and connected to the suction pump. By proper selection of the heating liquid, drying can be accomplished at any temperature desired. The drying pistol also can be heated electrically. Usually a period of 1–2 hours will be sufficient, but some compounds retain solvent very tenaciously and more time may be required. Where there is any doubt the sample should be dried to constant weight. For the thorough elimination of a hydrocarbon solvent it may be advisable to charge the container *c* with lumps of paraffin to absorb the vapors; solid potassium hydroxide may be used for the removal of acetic acid.

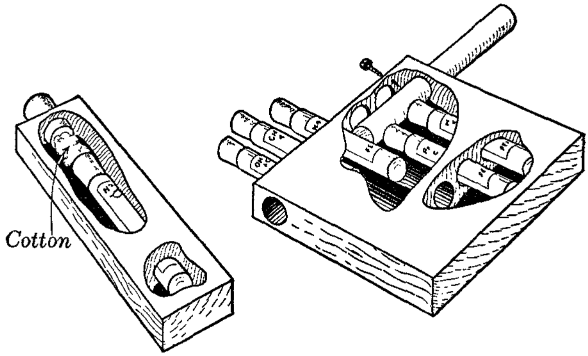

FIG. 32 — Containers for Mailing Samples

The label should reflect in some measure the care which has been taken in the preparation. It is a good plan to include both the name and the formula of the compound, if this can be done conveniently, and the label also should bear the melting point of the sample and the worker's name. If the substance is likely to undergo any change on storage, it is well to include the date. In order to affix the carefully printed and blotted label, moisten one end first and press this firmly onto the tube with the aid of a filter paper. Moisten the rest of the glue and roll the label onto the tube with the filter paper, and continue to press somewhat longer than may appear necessary. After the glue has dried, coat the label with a suitable lacquer such as vinylite, collodion, or paraffin; rub off the excess material with a towel while it is still soft.

For a discussion of the characterization of a new compound see pages 282–283.

Samples which are to be sent through the mails can be packed securely in a block of wood with holes bored to accommodate the specimen tubes. A piece of cotton introduced either at the bottom of the hole or on top of the cork or screw cap will hold this in place and prevent the tube from rattling; the hole is closed with a cork or with the dowel arrangement shown in Fig. 32. The block can be labelled and stamped, or inclosed in a manila envelope.

CHAPTER II

APPARATUS AND METHODS

Equipment for the Laboratory Bench. — In addition to an adequate supply of the usual pieces of apparatus, the following items of equipment may be desirable:

Bottle or tube (stoppered) of chips of **porous plate**

Closed tube or box for **melting point capillaries.** The capillary can be cut twice the required length, sealed at both ends, and stored in this form; a cut in the middle then gives two tubes. Some substances give more sharply defined and higher melting points in Pyrex capillaries than in soft glass, and it may be desirable to evacuate and seal the tube. Fine capillary tubes can be cut most readily with the sharp edge of a piece of unglazed clay plate.

Scissors, knife

Glycerol bottle with a glass rod inserted through the stopper (lubricating rubber tubing and stoppers, boring rubber stoppers, lubricating the bearing of a mechanical stirrer)

Acetone (for drying apparatus, washing out tars)

Decolorizing carbon (e.g., Norit, Darco)

Spatulas: small one of silver or platinum for analytical weighing; 18-cm. silver spatula (page 27); 25-cm. nickel spatula; flat, "pressing" spatula of nickel or of Allegheny metal

Dropping tubes

Test solutions in small bottles provided with droppers mounted in screw cap tops: dilute solutions (distilled water!) of sodium hydroxide, sodium carbonate, sodium bicarbonate, and hydrochloric acid; concentrated sulfuric acid (all-glass container)

Rack for graduates of various sizes (inverted; best over the sink)

Stand for small test tubes (11 × 75 mm.): block of wood with holes

Traps for all water pumps (suction flask with a two-hole rubber stopper carrying a stopcock). A glass water pump can be joined securely to a screw faucet by means of a short length of garden hose fitted with a coupling and a hose clamp.

Sectioned drawers for filter paper, test tubes, corks, etc. (filter paper lining for drawers containing flasks, beakers)

Towels, including old, wet, dry, and oiled ones for wiping the desk

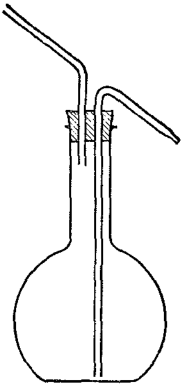

FIG 33. — Solvent Wash Bottle

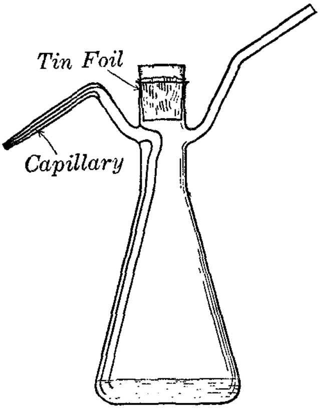

FIG 34 — Solvent Wash Bottle

Suberite rings for supporting round-bottomed flasks

Wash bottles: 500-cc. for water; 125-cc. for alcohol and benzene (see Figs. 33 and 34)

Support for separatory funnels: see Fig. 35

Acid Bath for Cleaning (shared with other workers). — A 14-inch porcelain dish (no larger) is supported on a strong tripod over a large enamelled pan of capacity greater than that of the evaporating dish. The pan rests on a large square of asbestos board placed under the hood and as near to a sink as possible. The asbestos board is saturated with hot paraffin before use. The dish is filled with crude concentrated sulfuric acid and crude concentrated nitric acid is added from time to time in order to clarify the liquor by oxidation of organic material. The nitric acid is added by drops, while the bath is hot, in amount just sufficient to give a clear solution. A little copper sulfate added to the acid liquor (2–3 g. per liter) greatly accelerates the digestion of resinous material. The dish is heated with a burner connected by means of a soldered lead pipe to the gas line. For the best performance it is essential that the bulk of the organic tar be removed with acetone, acid, alkali, water, or with a little of the acid liquor, or mechanically, before vessels are placed in the acid bath. Water or other solvent must be drained thoroughly from a vessel before it is introduced to the hot bath. Avoid the introduction of inorganic material, charcoal, boiling chips. The tongs used to remove the vessels to a porcelain dish for cooling are first rinsed in a bottle of water, then in a bottle of crude soda solution. The vessels when cold must be washed with great thoroughness (warm water) to remove all traces of acids. A laboratory coat and goggles always should be worn when using an acid cleaning bath. The operation of these baths is attended with risk and the utmost care must be taken in their use.

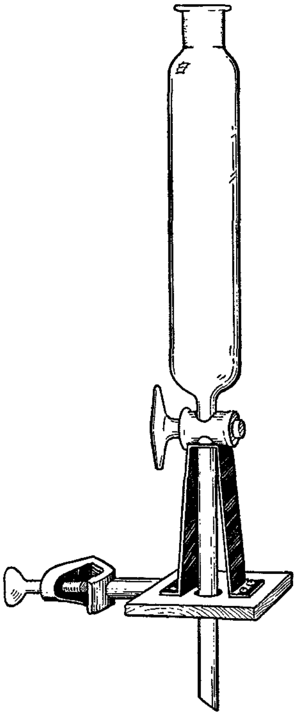
FIG. 35. — Stand for Holding Separatory Funnels

Heating Baths. — One of the most satisfactory of the inexpensive materials commonly used for oil baths is stearic acid. Other materials often used are: commercial hydrogenated oils, cotton seed oil, rape seed oil, lubricating oil, Nujol, and paraffin. All these substances begin to smoke badly at 250–300° and they may catch fire. Both the smoking and the fire hazard are greatly reduced by using as a cover an asbestos sheet with a hole in it to fit the vessel being heated. The oil bath should be placed under the hood whenever possible. On removal from the oil bath the flask should be allowed to drain into the bath and then wiped with an old, dry towel.

A shallow iron dish filled with sand (or graphite) is sometimes useful where a fairly high temperature is desired; a beaker filled with iron filings can be used to maintain temperatures up to 350°. A bath of a fusible metal alloy allows better temperature control. The commonest alloys and their compositions by weight are: *Wood's metal* (m.p. 71°): bismuth, 4; lead, 2; cadmium, 1; tin, 1; *Rose's metal* (m.p. 94°): bismuth, 2; lead, 1; tin, 1. The metal can be kept from sticking to a flask by coating the glass with graphite. Otherwise the metal is removed by scraping the flask with a rod when it is first removed from the bath and then wiping it with a dry towel. The metal baths should not be used at temperatures much above 350° on account of the rapid oxidation of the alloy. When a temperature in the range 250–350° is to be maintained for some time, as in a pyrolysis or a selenium dehydrogenation, a mixture of 10 parts of potassium nitrate and 7 parts of sodium nitrite (m.p. 145°) forms an excellent heating bath. Care must be taken to avoid the spattering of the hot nitrate onto organic material or cracking of the reaction vessel, as this may result in an ignition. The container for the fused salt bath must be of metal (iron, stainless steel), for the melt expands sufficiently on solidification to crack a glass or porcelain vessel. A glass thermometer must be withdrawn before the melt solidifies, or it may be cracked. When not in use, the nitrate-nitrite bath should be kept covered with a flat crystallizing dish, for if left exposed it will absorb moisture and subsequently spatter when heated. A pot made from a block of aluminum may be used in place of a liquid heating bath.[1]

For laboratories not equipped with steam the gas-heated steam bath constructed of metal and provided with a constant level device is convenient. Electrically heated steam baths are also

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[1] Morton, *Ind. Eng. Chem.*, *Anal. Ed.*, **11**, 592 (1939).

available in commercial types, and the electric hot plates and cones are very useful, although not free from fire hazard. A heater for distilling small quantities of ether can be made by building a suitable housing over an electric light bulb. A boiling-water bath is easily constructed by providing a vessel of suitable size with one of the constant level siphons described in the literature.[2]

A convenient way of heating a reaction mixture at a constant temperature for prolonged periods is to heat a small amount of some liquid of appropriate boiling point in a three-necked flask equipped with a condenser, and to insert test tubes containing the reaction mixture in the other two openings[3] (see also Fig. 61, page 335).

Cooling Baths. — The ordinary ice bath, for the most efficient service, actually should consist of a slush of crushed ice or snow with enough water to cover the solid and to provide contact with the vessel to be cooled. Thorough stirring of the mixture is also required to maintain the lowest possible temperature. The commonest freezing mixture for producing temperatures below 0° is that of ice or snow with salt; with one part of sodium chloride and 3 parts of ice, temperatures to $-20°$ can be reached. A mixture of concentrated hydrochloric acid and ice (in a glass vessel!) provides still more effective cooling. Finely crushed ice with 1.5 parts of crystalline calcium chloride (powdered) gives temperatures to about $-50°$. If cooling is required when ice is temporarily not available, advantage can be taken of the cooling effect accompanying the solution of certain salts and salt mixtures in water. A reduction from 10° to about $-20°$ can be obtained from 1 part each of ammonium chloride and sodium nitrate and 1–2 parts of water; also with sodium sulfate decahydrate, concentrated hydrochloric acid, and water. Solid carbon dioxide, m.p. $-78.8°$, is used for temperatures as low

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[2] Yohe and Keckler, *J. Chem. Ed.*, **11**, 462 (1934); Bernhauer, "Laboratoriumstechnik," p. 14 (1934).

[3] This is similar to the heating bath described by Meisenheimer, Schmidt and Schäfer, *Ann.*, **501**, 134 (1933).

as −85°. Bath temperatures in the range 0° to −30° can be maintained by adding pieces of dry ice as required to alcohol; the evolution of gaseous carbon dioxide keeps the bath stirred. Effective cooling of a trap for a mercury vapor pump, or of a receiver in which a gaseous product is to be condensed, is accomplished by adding dry ice cautiously to a mixture of equal parts (by weight or volume) of carbon tetrachloride and chloroform. An advantage of this mixture is that solid carbon dioxide floats on the surface and does not tend to produce excessive initial frothing.

Stirring Motor. — An electric stirring motor of rugged construction which develops ample power at both low and high speeds is described by Hershberg.[4] Inexpensive motor units satisfactory for intermittent use with light and constant loads can be made from the motor of a discarded vacuum cleaner, fan, or other device. A speed regulator can be made from resistance coils and dials obtainable from a radio store. A discarded speedometer cable can be used as a flexible driving shaft. An easily constructed air-pump shaker driven by compressed air is described by Morton.[5]

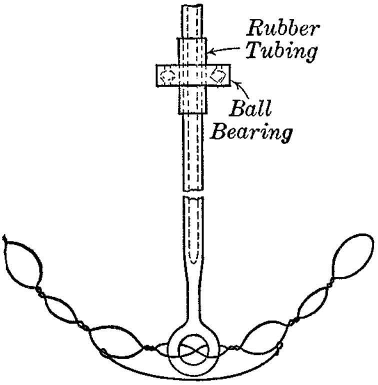

Fig. 36. — Hershberg Stirrer

Stirring. — Efficient agitation of even very pasty mixtures can be accomplished with the use of the Hershberg wire stirrer[6] illustrated in Fig. 36. A glass tube is used for the stirrer shaft in preference to a rod because of its light weight, strength, and straightness. A glass ring is sealed to the shaft by a technique described in a later section (page 354) and threaded with stiff wire; a second threaded ring placed at right angles to the

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[4] *Ind. Eng. Chem., Anal. Ed.*, **12**, 293 (1940).

[5] *Ind. Eng. Chem., Anal. Ed.*, **6**, 469 (1934).

[6] *Ind. Eng. Chem., Anal. Ed.*, **8**, 313 (1936).

first gives still better efficiency but usually is not required. Very smooth operation of a stirrer is obtained by using a ball-bearing mounting. A short piece of rubber tubing is inserted in the bearing, moistened with glycerol, and slid over the shaft (Fig. 36). It is generally advisable to use two ball bearings placed a few inches apart, as in the assembly shown in Fig. 52 (page 327). Nichrome or chromel wire is satisfactory for use in condensations with sodium or in the Friedel and Crafts or Blanc reaction, but should be employed in Grignard reactions only when the stirrer is reserved exclusively for such use. Tantalum wire is still better and can be used for all ordinary purposes, for it resists corrosion by strong acids, bases, alkali metals, or chlorine. The wire threading is easily inserted through a narrow opening in a flask and in operation it follows the contour of the flask without scratching the glass.

Where only moderate agitation is required, stirrers of the bent rod (Fig. 20, page 180) and propeller type (Fig. 38, page 310) may be adequate. On occasion, mixing can be accomplished most satisfactorily by hand stirring with a glass rod or by swirling the flask; this may offer the best opportunity for control and observation, and also for inducing crystallization.

Stirrer Seals. — Where it is desired to prevent the escape of gas or vapor during mechanical stirring a mercury seal of the form shown in Fig. 37 is often useful. Mercury is poured into the space between the outer tube (*a*) and the bearing tube (*b*) up to the level *c*. Tube *d* revolves with the stirrer shaft in the mercury and entraps the gas. The stopper (*e*), with an additional glass bearing, is not required but prevents the spattering of mercury during operation and the spilling of the metal when the

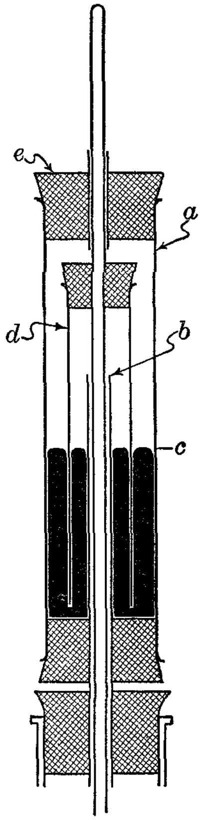

Fig. 37. — Mercury Seal for a Stirrer

seal is disconnected. The bearings are lubricated lightly with glycerol. Compact seals of glass operating on the same principle are illustrated in Fig. 75 (page 404) and Fig. 76 (page 405). Mercury-sealed stirrers made of stainless steel and well adapted for high-speed operation have been described by Rogers.[7] A vapor-proof stirrer having an oil-impregnated bronze bearing is described by Calingaert.[8]

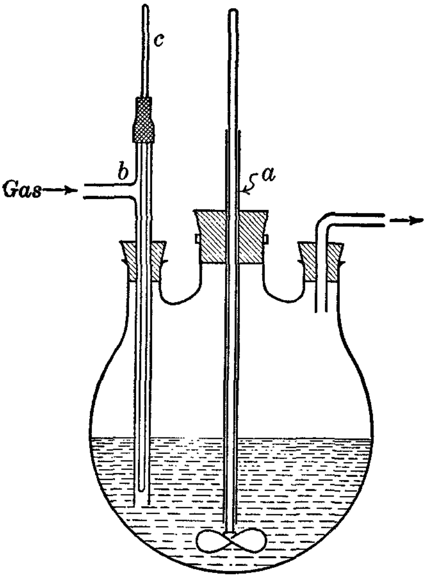

FIG. 38. — Liquid-sealed Stirrer and Special Gas-delivery Tube

While the mercury seal usually is found to be satisfactory, it represents in some cases a needless complication of the apparatus. Where a noxious gas is to be eliminated during stirring it is often sufficient to run the stirrer through a rather close-fitting glass sleeve and to apply gentle suction at the gas outlet of the flask in order to draw the gases into a trap. This arrangement is illustrated in Fig. 20 (page 180). Another method, often useful where a gas is to be absorbed in a stirred liquid, is shown in Fig. 38. The stirrer sleeve (*a*) is extended well into the flask so that the liquid itself serves to seal the stirrer. A simple rubber slip joint is also serviceable. A stirrer sleeve similar to tube (*a*) of Fig. 38, but extending only a short distance into the flask, is provided with a 2-cm. section of rubber tubing which projects above the end of the tube and fits snugly around the stirrer shaft. The point of contact between the shaft and the rubber is lubricated with glycerol. The seal operates satis-

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[7] *J. Am. Chem. Soc.*, **55**, 4901 (1933); *J. Chem. Ed.*, **11**, 427 (1934).

[8] *Ind. Eng. Chem., Anal. Ed.*, **12**, 51 (1940).

factorily even in partial vacuum (10 mm.). More elaborate devices for stirring in vacuum employ an agitating rod driven by an eccentric and operating through a flexible seal in the neck of the flask.[9] A seal consisting of a finely ground glass shaft-and-sleeve will retain fluids and hold a moderate vacuum.

Addition Tubes. — The assembly of Fig. 38 includes a gas-delivery tube (*b*) of useful construction: the glass rod (*c*) slips through a section of suction tubing and can be used to clear the lower end of the delivery tube in case it becomes plugged with solid reaction product.

For the addition of a solid reagent in small portions to a reaction mixture while this is being refluxed or stirred, one can use either a three-necked flask or an ordinary flask with an addition tube and add the reagent through one of the openings, from which the stopper is temporarily removed. Where vigorous refluxing is desired, or where the reagent is very sensitive to the moisture of the atmosphere (powdered potassium hydroxide, aluminum chloride) this procedure has obvious disadvantages. A convenient improvement is to add the reagent from an Erlenmeyer flask which is fitted to one of the tubulatures of a three-necked flask by means of a section of rubber tubing of large diameter (Fig. 39). The intermittent addition of the solid is accomplished by raising the containing flask, which can then be cut off from the system by kinking the rubber tube.

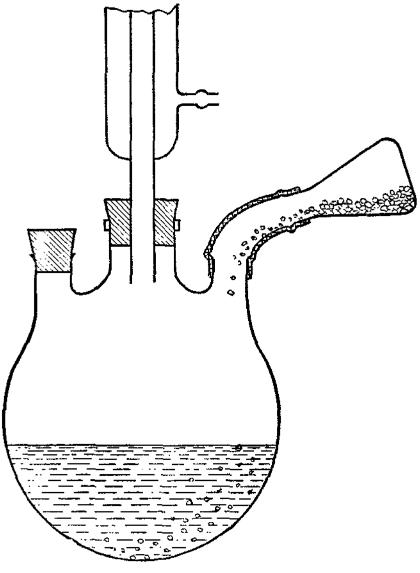

FIG. 39. — Method of Adding a Solid Reagent

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[9] Powell, *Ind. Eng. Chem., Anal. Ed.*, **8**, 488 (1936); Maude, *ibid.*, **9**, 196 (1937); Joseph, *ibid.*, **9**, 212 (1937).

The addition of a solid also may be accomplished with the use of a hopper provided with a glass valve,[10] and this is particularly useful where contact of the reagent with rubber is undesirable. A hopper type of tube for the addition of a liquid can be made from a long-stem funnel which can be stoppered by means of a rubber bung (small rubber stopper) on the end of a glass rod.[11]

When an ordinary dropping funnel is used for the addition of a liquid, difficulty is often experienced in adjusting the stopcock to a sufficiently slow or steady rate of flow. The difficulty is obviated by using a funnel of the type designed by Hershberg[12] and shown in Fig. 40. The flow of liquid is easily regulated by varying the distance to which the wire protrudes into the capillary. The rate of flow can be kept constant throughout the entire addition by connecting the funnel, through the side opening, to a gas reservoir of constant positive pressure. In case the liquid is to be added extremely slowly to a refluxing or stirred mixture, the funnel should be mounted in such a way that the tip touches a side wall and drop formation is prevented.

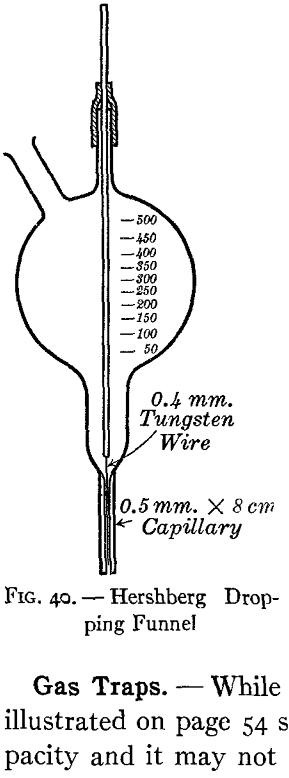

FIG. 40. — Hershberg Dropping Funnel

Gas Traps. — While the simple form of gas absorption trap illustrated on page 54 serves many purposes, it is of limited capacity and it may not always take care of a rapid rush of gas. Two satisfactory and efficient traps are shown in Fig. 41.

When a gaseous reagent is to be absorbed in a reaction mixture, the excess gas is often caught in an absorption trap or else conducted to the fume chamber. Another method of caring for the

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[10] Webster and Dennis, *J. Am. Chem. Soc.*, **55**, 3234 (1933).

[11] Clarke and Hartman, "Organic Syntheses," Coll. Vol. I, 228 (1932).

[12] "Organic Syntheses," **18**, 16 (1938).

unabsorbed gas is to attach a small rubber balloon to the gas-exit tube of the flask and to run in gas until it is inflated. The slight pressure thus established assists the process of absorption, and the condition of the balloon gives an indication of the course of the absorption.

It is sometimes desirable to be able to follow the progress of the evolution of gas from a reaction mixture with the use of a bubbler connected either directly to the reaction vessel or to the top of a reflux condenser. This must be constructed in such a way that the liquid cannot be sucked back into the reaction flask in case of a momentary drop in the temperature. A simple and safe bubbler can be made by supporting an empty calcium chloride tube in a vertical position with the small end dipping just below the surface of 5 cc. (no more) of water in a beaker or a 10-cc. Erlenmeyer flask. Connection is made to a section of rubber tubing and suction is applied by mouth to make sure that the capacity of the calcium chloride tube cannot be exceeded.

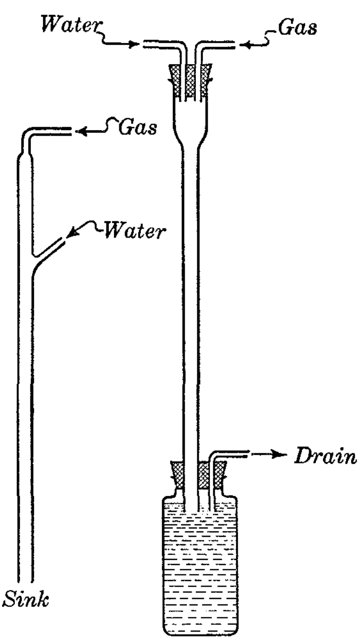

FIG. 41. — Gas Absorption Tubes

A trap suitable for the protection of an oil pump consists in a pair of glass towers connected near the bottom by means of a glass tube bent upwards into a vertical loop about one fourth the height of the towers. The first tower is filled with pellets of potassium hydroxide and connected to the pump by means of a glass tube inserted in a rubber stopper. The second tower, which is closed with a rubber stopper making connection to the system to be evacuated, is filled with pieces of porous plate or lump pumice and provided at the bottom with a stopcock to permit draining. The filling is impregnated with concentrated sulfuric acid; from time to time, as this is observed to darken, the spent liquor is drawn off and fresh acid added.

Pressure Reactions. — Certain reactions proceed satisfactorily only at a temperature well above the boiling point of one or more of the reagents and must be carried out in a vessel capable of withstanding the sometimes excessive total pressure due to vaporized materials initially present and gaseous products which may be formed. In the case of exhaustive oxidations with nitric acid, high temperature reductions with hydriodic acid and red phosphorus, and other reactions developing high pressures and giving corrosive products, the only suitable vessel is a sealed glass tube. Since the use of a sealed tube is attended with evident danger, such reactions should be carried out only on a very small scale and with great caution. When the mixture is not corrosive to steel, a choice between an autoclave, if one is available, and a sealed tube can be made on the basis of the scale of operation. With small amounts of material, or where a number of pilot runs are to be made, the sealed tube method may be preferable because it takes less time than is required for operating an autoclave. Safety, however, should not be sacrificed for speed. That a reaction has been conducted in a sealed tube without trouble on a 1–2 g. scale offers no assurance that a larger run can be made with safety. There is no way of telling how close one is to the danger point, and there is no warning. The use of large amounts of material not only increases the risk of a damaging and wasteful explosion but adds to the force of the explosion. It is evident that the preparation of a significant quantity of material should be conducted either in an autoclave or in a series of small-scale sealed tube reactions.

A stout tube of Pyrex glass should be used and the seal should be drawn out to a thick-walled, tapered capillary some 4–5 cm. long. The heating is best done in a special bomb room, or at least in an unoccupied room. A steam bomb can be made from a strong iron tube mounted vertically and provided with steam inlet and outlet tubes inserted in rubber stoppers. Satisfactory control at other temperatures is best achieved with an electrically heated furnace (page 383). The entire unit must be allowed to cool to room temperature before the tube is opened. Ordinarily, the proper method of opening the tube is to stand at the side of the furnace and well in back of the front end and direct a Bunsen flame at the projecting tip of the capillary. If the tube is under pressure, a small hole is blown out at the end of the tip and the tube can be withdrawn. If the tip bends over, indicating that there is no excess pressure, the capillary can be filed and cut.

If one of the components of the reaction mixture is a gas at room temperature, the tube is cooled in a bath of ice or dry ice, the substance is poured or distilled into the chilled tube, and the sealing operation is performed with the closed end still resting in the cooling bath. If some of the gaseous material is still present at the end of the reaction, the tube when cooled to room temperature will be under pressure. If the reaction is of a type which definitely cannot produce a permanent gas, it is sometimes permissible to withdraw the thoroughly cooled tube (Pyrex), while keeping it covered with several layers of towelling, and insert it at once into a cooling bath corresponding to that used in the sealing operation. In the initial experiment the capillary of the chilled tube should be melted in a flame, as above; if the absence of pressure has been established, the capillary can be opened by a file scratch.

A suitably constructed and fully tested autoclave provides a safe method of conducting large-scale pressure reactions. An autoclave is also applicable to operations with small amounts of valuable materials, for methods are available for confining a small volume of reaction mixture and preventing losses. One is to seal the mixture into a glass tube, place the tube in an autoclave, and introduce nitrogen or other inert gas into the autoclave chamber sufficient to give a pressure substantially higher than that which will be developed in the sealed tube. Another method, introduced by Grosse,[13] consists in using a glass reaction

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[13] *J. Am. Chem. Soc.*, **60**, 212 (1938).

flask having an outlet constructed of a long piece of capillary tubing wound into a spiral. Figure 42 illustrates a Grosse flask which has been modified by the inclusion of a ground joint of the ball and socket type held in place by a metal clamp. This joint has the great advantage that it will not freeze when subjected to high pressures. The assembled flask containing the reaction mixture is placed in the autoclave in a beaker, and nitrogen is admitted very slowly, to avoid breaking the capillary, to give a pressure considerably higher than that anticipated from the reaction mixture. Gases under pressure diffuse through capillaries so very slowly that there is little chance for the escape of a volatile reagent or solvent into the autoclave chamber. With this device, the use of autoclave heating can be extended to mixtures which are corrosive to metals, except in those cases where a considerable amount of gas is produced in the reaction. When a Grosse flask is used, the autoclave should be vented very slowly, for otherwise the capillary may be broken.

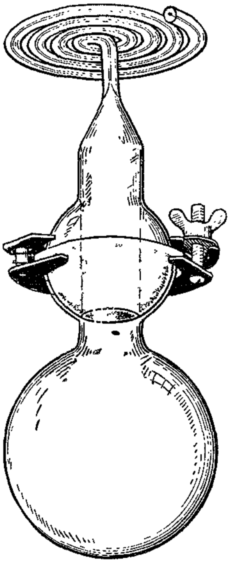

FIG. 42.—Pressure Vessel for Retaining Gas or Vapor

A useful method of conducting reactions at moderate temperatures and pressures is to use as the container a bottle or tube closed with a metal bottle cap which is crimped in place with an ordinary capping machine. A thick-walled soda bottle has sufficient strength and capacity for many purposes; for example, for carrying out diene addition reactions in alcohol or benzene in the temperature range 50–100°. Small amounts of materials are conveniently manipulated in a short pressure tube of the type illustrated in Fig. 43. The tube is made of heavy-walled Pyrex glass and is provided with a thick rim to hold the cap (for construction, see page 348). For capping, the tube is inserted in a hole in a wooden block of suitable height. Caps lined with various metal foils may be obtained commercially and are useful for special purposes. In experiments with aluminum alkoxides, for example, a liner of aluminum foil can be used. The liner should extend only to about $\frac{1}{8}''$ of the edge of the cork disc.

Ultraviolet Lamp. — An inexpensive source of ultraviolet light suitable for observing the fluorescence of samples or for following the passage of a fluorescent substance through a chromatographic adsorption column may be constructed by mounting a Photoflood lamp (110 volt, size A) into the screw cap of a large tin box and cutting in the base of the box a window over which is fitted a purple glass filter (Corning, H. R. Red Purple Ultra No. 587, molded) to retain visible light. The lamp should be kept on only intermittently and for brief periods because it otherwise becomes hot, and also because the life of the bulb is limited.

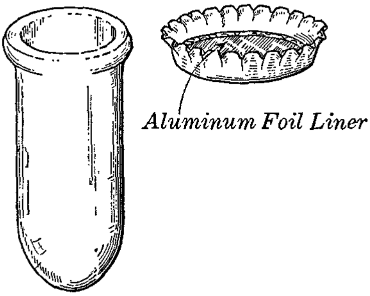

FIG. 43. — Pressure Tube and Cap

Distillation. — A number of distillation assemblies are described in Part I (pages 240–253). An improved method of mounting a thermometer in a distillation flask is illustrated in Fig. 44. The sealed-in thermometer well obviates all possibility of contamination or leakage attending the use of a stopper at this point, and is a generally useful modification of the Claisen type flask. The flask shown has a conical bulb, and the capillary has been drawn out twice. The receiver is attached by means of a ground glass joint to the side tube, which is provided with a simple but effective cooling device. This apparatus is useful for the distillation of high-boiling liquids and of substances which may solidify.

For a discussion of some of the many ramifications of the technique of fractional distillation at atmospheric or reduced pressure the reader is referred to the manual by Morton.[14] Efficient

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[14] "Laboratory Technique in Organic Chemistry," pp. 73–123 (1938).

columns of not too elaborate design and suitable for general use are as follows: a modified Widmer column[15]; a simplified Podbielniak column[16] embodying features of the highly efficient apparatus developed by Podbielniak[17] for precise fractional distillation analysis; a column of the partial condensation type designed for general laboratory use[18] (the column is packed with

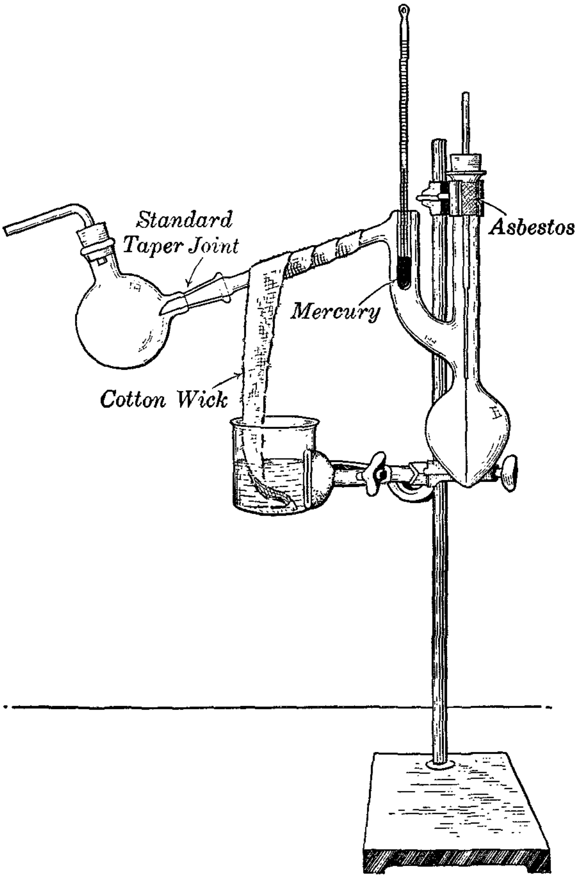

FIG. 44. — Apparatus for the Distillation of High-boiling Substances

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[15] M. E. Smith and Adkins, *J. Am. Chem. Soc.*, **60**, 662 (1938).

[16] Jacobs, *J. Am. Chem. Soc.*, **58**, 2272 (1936).

[17] *Ind. Eng. Chem., Anal. Ed.*, **3**, 177 (1931); **5**, 119 (1933).

[18] Laughlin, Nash and Whitmore, *J. Am. Chem. Soc.*, **56**, 1396 (1934).

glass helices, as in the high-efficiency stills developed by Fenske [19]). Baker, Barkenbus and Roswell [20] describe a spinning-band column with very little holdup for the fractionation of small quantities of liquid.

A number of satisfactory manometers are on the market, but many of these are rather expensive, particularly if supplied filled with mercury. Where a general utility manometer is required, it is well to purchase or construct a simple and inexpensive U-tube and to fill and mount it. One type of tube which is satisfactory and easily filled is illustrated in Fig. 45; another is that having a constriction at the bottom of the bend in place of the sealed-in tip. The tube is cleaned in an acid bath, washed very thoroughly, and dried well in an oven. The closed arm is filled with mercury to the middle of the bend and the mercury is boiled out as follows. The tube is inverted and connected to the water pump, and it is then held in a nearly horizontal position with the closed end slightly depressed. A 2–3 cm. section of mercury at the closed end is heated in a Bunsen burner flame until it begins to boil, and the tube is given a sharp jerk or whip in the direction of its length to dislodge gas; the mercury on returning to its original position should click against the glass. A second short section of mercury immediately above the first is boiled as before and shaken free of gas, and the whole column is similarly treated. Sufficient mercury is eventually added to fill the bend and the boiling out at this point is completed by heating. The manometer is mounted on a wooden frame, with a backing of millimeter coordinate paper to serve as the scale.

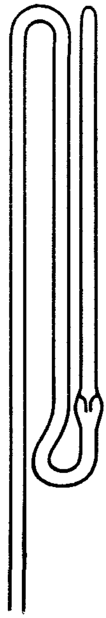

FIG. 45. — Manometer Tube

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[19] Fenske, Tongberg and Quiggle, *Ind. Eng. Chem.*, **26**, 1169 (1934); Tongberg, Quiggle and Fenske, *ibid.*, **26**, 1213 (1934).

[20] *Ind. Eng. Chem., Anal. Ed.*, **12**, 468 (1940).

The Zimmerli[21] manometer has certain desirable features but requires a large amount of mercury. Pressure regulators for precision work are of rather elaborate construction (see Morton, *loc. cit.*); a simple and easily constructed regulating device is described by Newman.[22]

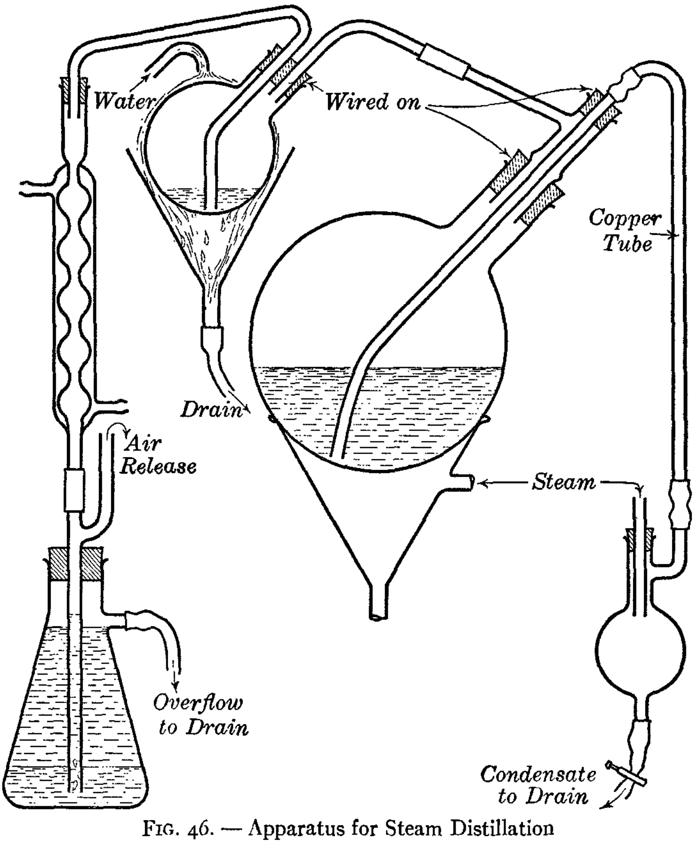

Fig. 46. — Apparatus for Steam Distillation

Steam Distillation (see pages 153–162). — The steam distillation of difficultly volatile substances can be accomplished rapidly with the compact unit shown in Fig. 46. This embodies the efficient liquid-sealed condensing flask described earlier (pages 158–159).

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[21] *Ind. Eng. Chem., Anal. Ed.*, **10**, 283 (1938).

[22] *Ind. Eng. Chem., Anal. Ed.*, **12**, 274 (1940).

Filtration. — While the collection of a finely divided precipitate by suction filtration is often an unavoidably tedious operation, there are certain remedies and aids which in some cases greatly expedite the process. It is almost always worth at least trying to coagulate the fine particles by digesting the suspension at or near the boiling point, and stirring also may help to increase the particle size. If the solid is a crystalline product obtained by precipitation or by salting, it may be found that better crystals can be obtained by a slower addition of the reagent or by operating at a higher temperature. In many cases, however, all such methods fail and the filtration requires many hours for completion; the difficulty also is increased by the development of cracks in the filter cake which break the vacuum. In such a case the rubber dam [23] is of invaluable assistance. After all the suspension has been transferred to the Büchner funnel, a piece of rubber sheeting is laid over the top of the funnel and the edges are folded over and held down by strong rubber bands to give an air-tight fit. The unit is then allowed to stand for a few hours, or overnight, with the suction pump running. As soon as a crack develops the rubber is drawn down onto the filter cake to the position shown in Fig. 47 and the vacuum is maintained. The solid is thus subjected to the full pressure of the atmosphere and a hard cake containing very little mother liquor is obtained without any attention on the part of the operator. For small funnels it is often convenient to use a partially inflated toy balloon pressed down onto the top of the funnel by means of an iron ring.

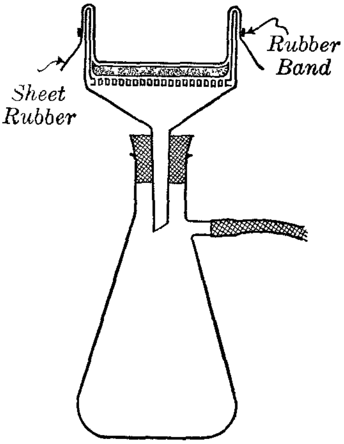

Fig. 47. — Rubber Dam for Pressing the Filter Cake

In working with substances sensitive to the air it is sometimes

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[23] Gortner, *J. Am. Chem. Soc.*, **36**, 1967 (1914).

necessary to filter hot, saturated solutions, or to collect crystals, in an indifferent atmosphere. Several forms of apparatus have been developed for performing either or both of these operations, but the design depends greatly upon the special requirements to be met in each case. The assemblies described in the references given below will be found suggestive.[24]

A convenient device for collecting the filtrate of a suction filtration directly into an Erlenmeyer flask is shown in Fig. 48. The flat rubber ring accommodates funnels of different sizes, and some range is also possible in the size of flask; a series of cork or wood supports can be kept on hand and labelled according to the size of flask with which they are to be used.

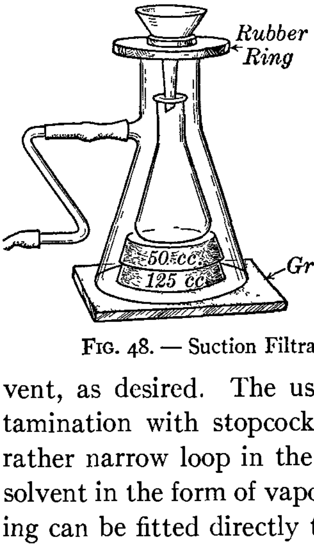

FIG. 48. — Suction Filtration

Evaporation of Solvent. — A useful condenser with a take-off tube[25] is shown in Fig. 49. With this device it is possible to reflux a solution or distil the solvent, as desired. The use of a Nolub stopcock obviates contamination with stopcock grease, and a carefully constructed, rather narrow loop in the delivery tube prevents the escape of solvent in the form of vapor. The condenser shown in the drawing can be fitted directly to a flask by means of a ground glass joint or connected to a stoppered flask with the use of the adapter. The drawing also illustrates a simple stand of adjustable height and shows the construction of a boiling tube. This is made by sealing an inverted glass cup to a rod which is provided with a hook to facilitate its withdrawal for rinsing. This device for promoting boiling is preferred by some workers to a piece of porous pot because of the possibility that the latter

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[24] Steinkopf, *Ber* , **40**, 400 (1907), v Euler, Karrer and Rydbom, *ibid* , **62**, 2449 (1929), Scholl and Bottger, *ibid* , **63**, 2124 (1930); Bernhauer, "Laboratoriumstecknik," p 97 (1934)

[25] Designed by Dr E B Hershberg

may become chipped in use. The boiling tube operates satisfactorily in a vacuum so long as the reduction in pressure is maintained.

The take-off condenser is of distinct aid in carrying out crystallizations. A substance which dissolves slowly can be refluxed with excess solvent and the excess subsequently removed by distillation. If the solution is to be clarified with activated charcoal, the best technique is to do this under reflux with a large excess of solvent, filter the hot solution, and remove the excess solvent by distillation. The space-saving assembly of

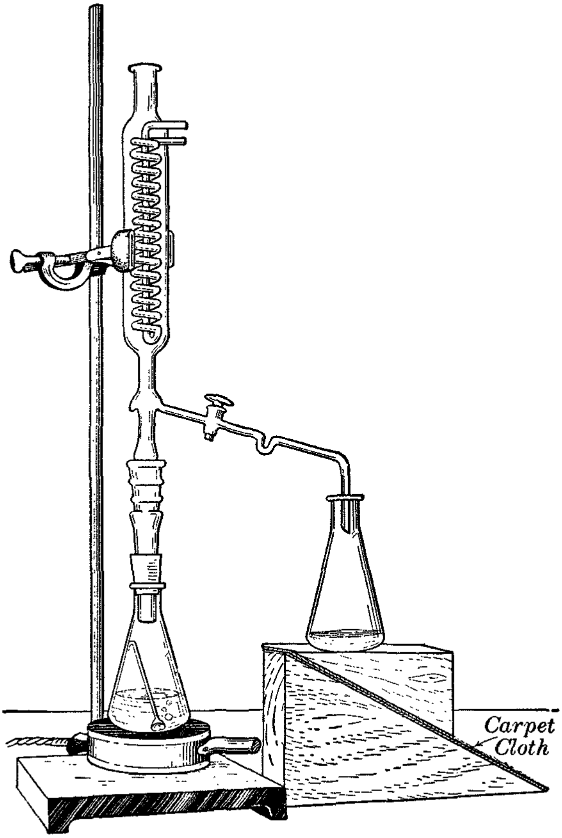

FIG. 49. — Reflux Condenser with a Take-off Tube

Fig. 49 affords a convenient unit for this or other distillation of solvent.

When a crystallization is conducted in a small Erlenmeyer flask (10–25 cc.) the excess solvent can be removed by introducing a boiling chip or boiling tube and heating the flask on a hot plate under a glass tube extending nearly to the mouth of the flask and connected to the suction pump for withdrawal of the vapors.

The apparatus shown in Fig. 50 is useful for the rapid evaporation of a solution to dryness.[26] The tube at the right is connected to a suction pump and dry air or nitrogen is admitted at reduced pressure by operation of the screw clamp. The flask can be heated as required in a water bath. The gas stream should make a slight ripple on the surface of the liquid.

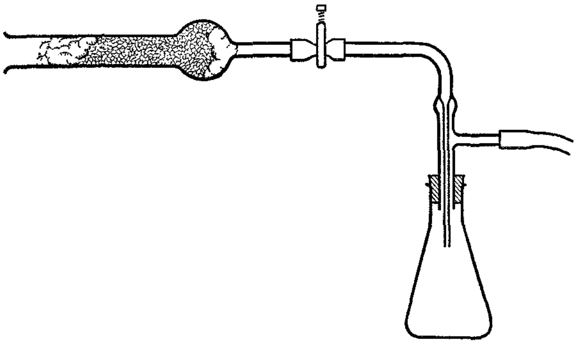

FIG 50. — Evaporation at Reduced Pressure

Polarizing Microscope. — The usefulness of an inexpensive, low-power microscope can be increased greatly by transforming it into a polarizing instrument as follows. A disc of Polaroid film is mounted in the eyepiece in a position near the uppermost lens and displaced from the focal point. A second sheet of Polaroid is mounted in a fixed position below the stage of the microscope in the path of the light source; this serves as the polarizer. The eyepiece can be rotated and functions as the analyzer of the improvised polariscope. In operation, the analyzer is turned to a position of minimum light transmission,

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[26] R. R Williams and T. D. Spies, "Vitamin B_1", p. 141 (1938).

indicating that the two Polaroid "prisms" are optically crossed. A doubly refractive crystal when examined between crossed prisms shows a white or colored image against a black field. Such behavior is positive evidence of crystallinity, and this method of observation is of great value in distinguishing between crystalline and amorphous substances or in detecting the presence of minute crystals in an oil. Nearly all organic crystals are doubly refractive, although there are rare instances of organic substances which are isotropic and which therefore do not give a lighted image.

The brilliant color phenomena observed with doubly refractive substances under polarized light are highly characteristic of the crystalline nature of the material. The observation is sometimes improved by suspending the crystals in a suitable liquid vehicle such as aqueous glycerol or paraffin oil, depending on the solubility relationships. Plates are sharply differentiated from needles, and a pure individual can be distinguished without difficulty from a mixture of substances. When an oil has been inoculated with seed, one can easily determine by examination of the material under polarized light if new crystals form, and if these correspond to the substance used as seed or to a different compound.[27]

DETERMINATION OF MELTING POINTS

The long-necked flask with a round bulb described in Part I (page 26) constitutes a convenient form of tube for the rapid determination of uncorrected melting points. A slightly modified tube fitted with further accessories is shown in Fig. 51. The bulb is provided with two small openings (*a*) for the insertion of capillaries, and it is heated by a microburner provided with a chimney (*b*) which furnishes protection from drafts. The clamp holding the burner is mounted on a metal collar (*c*) which fits loosely over the ring stand and rests on a washer; the burner is always ready for use, but may be swung out of the heating

[27] Chamot and Mason, "Handbook of Chemical Microscopy," I, pp. 261–326 (1938).

position when desired. A test tube (*d*) provides a convenient receptacle for used capillaries, and a lens (*e*) hooked onto a wire carriage which can be slipped up and down on the neck of the heating flask may be useful for observing either the sample or the thermometer stem.

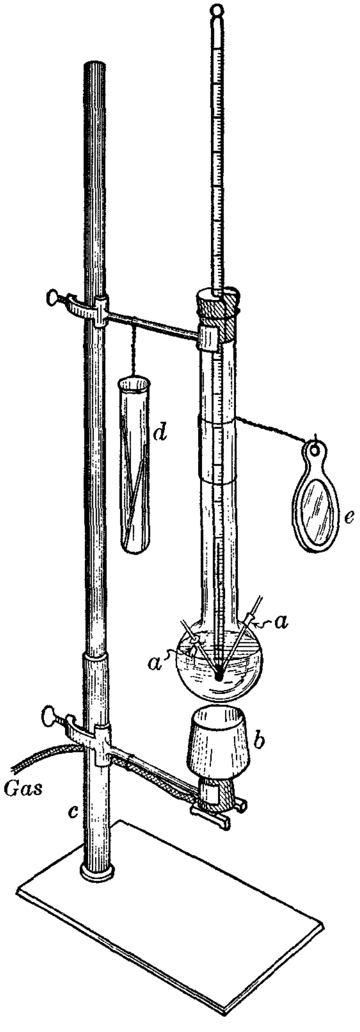

FIG. 51. — Melting Point Apparatus

Although uncorrected melting points may be adequate for student experiments and in certain preliminary phases of research work, the best modern practice in research calls for the accurate determination of the corrected melting points of all final samples of fully purified products. The method of estimating the stem correction to be applied to a melting point determination in which a part of the mercury column is exposed above the bath (page 29) gives only rough approximations and is inadequate in accurate work. A well constructed thermometer which has been calibrated for immersion to a specified point is capable of furnishing reasonably accurate corrected melting points if it is used carefully. The thermometer should first be checked at several points by reference to fully purified samples whose melting points have been determined with a precision instrument.

Precision Apparatus. — The most accurate method of determining corrected melting points is with an apparatus designed to accommodate a set of short thermometers (Anschütz) which can be immersed in the heating bath over the entire length of the mercury column. The principle of total immersion is embodied in Hershberg's[1] precision apparatus, an improved form of which is illustrated in Fig. 52. The heating fluid (sulfuric acid[2]) is circulated rapidly in an electrically heated Thiele tube by means of a glass stirrer driven by a shaded pole motor.[3]

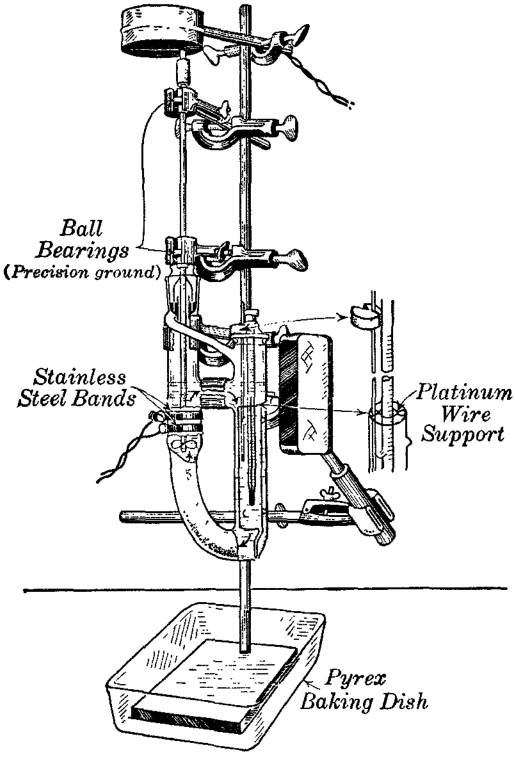

FIG. 52. — Hershberg Melting Point Apparatus

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[1] *Ind. Eng. Chem., Anal. Ed.*, **8**, 312 (1936).

[2] When the acid has absorbed an undue amount of water, a portion can be removed and the remainder fortified with fuming (20 per cent) acid.

[3] The Model 1 stirrer and rheostat of the Eastern Engineering Co., New Haven, Conn., is satisfactory. The unmounted motor may be obtained at low cost from the Barber-Colman Co., Rockford, Ill. (Model YAa No. 707, 0.0004 H.P.), and a 1000-ohm, 10- or 20-watt rheostat connected in series is suitable for speed control.

The propeller-type stirrer is mounted in the longer of the two vertical compartments. The thermometer and melting point capillary are inserted through holes drilled in a ground glass cap and pass through guiding loops of platinum wire; in the body of the heating tube[4] they are surrounded by an insulating glass sleeve resting on a leg which fits into a depression at the bottom of the tube. The thermometer is supported by a permanently affixed rubber disc and the capillary is held in the jaws of a fastener made by cutting slots in opposite sides of a section of a rubber stopper or heavy walled tubing (inset, Fig. 52). A feature of the improved design not specified for the original apparatus is the addition of a mercury seal and a pressure equalizing tube connecting the two arms; with this arrangement there is little escape of fumes and the liquid level remains the same in both arms. The apparatus is mounted in a Pyrex dish to catch the acid in case of breakage. The Anschütz thermometers are conveniently mounted when not in use in a wire rack with provision for drainage (Fig. 53).

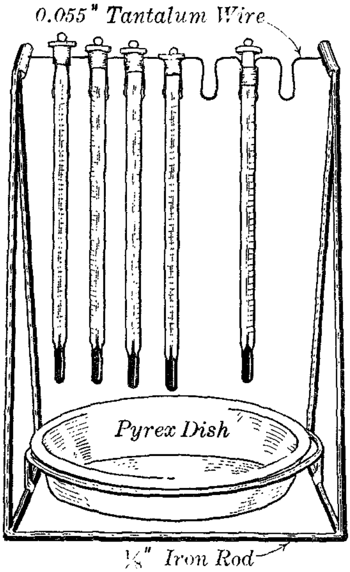

FIG. 53. — Thermometer Rack

Melting Point Blocks. — A metal block apparatus is useful for the determination of melting points above 300°. The block

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[4] A simplified method of winding the heating element is as follows. Two ½" strips of asbestos paper are wetted and stuck to the upper and lower walls of the curved part of the tube, leaving the side walls bare. The resistance wire is attached at one end to a stainless steel strap and wound over the partly dried asbestos strips with $\frac{1}{16}$" spacings. When the lower end of the curve is reached, the winding is covered with a spiral of asbestos tape for insulation and the wire is returned in three or four turns to the second binding post. The wiring is then wrapped with a thin layer of asbestos paper, and this is moistened and worked into a smooth, adherent covering.

of Berl and Kullmann[5] consists in a copper cylinder with vertical holes for the thermometer and the melting point capillary and horizontal windows for illumination and observation. Modifications include illumination of the capillary from above at an angle[6] and by transmission of light through bent Pyrex tubes.[7]

A melting point block which has given good service in the author's laboratory is illustrated in Fig. 54.[8] The heating unit is made from a solid cylinder of aluminum, 11 cm. long and 9 cm. in diameter. A well is drilled in the center to a depth corresponding exactly to the immersion point of a 500° thermometer, and a second well of the same diameter is drilled close to this and at a slight angle sufficient to cause the two holes to meet, or nearly meet, at the bottom. The offset well is closed at the top with an aluminum plug drilled with two or three small holes for the insertion of melting point capillaries. Observation is made through a horizontal hole drilled in the plane of the two vertical wells and extending just to that carrying the thermometer; the side hole is closed with a screw plug fitted with a mica window. Illumination is provided through a second horizontal hole drilled at an angle of 60° to the first and plugged with a piece of Pyrex rod. The sample in the capillary is seen clearly in its natural color. The large size of the block contributes

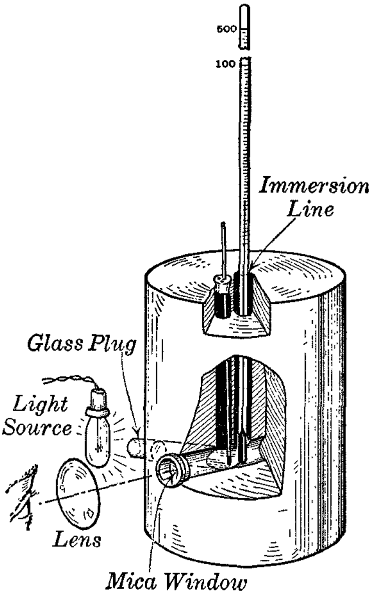

FIG. 54. — Aluminum Melting Point Block

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[5] *Ber.*, **60**, 811 (1927); see also Walsh, *Ind. Eng. Chem., Anal. Ed.*, **6**, 468 (1934).

[6] Bergstrom, *Ind. Eng. Chem., Anal. Ed.*, **9**, 340 (1937).

[7] Eastman Kodak Co., "Synthetic Organic Chemicals," **10**, No. 2 (1937).

[8] Designed by Dr. J. Cason and Dr. H. J. Creech.

to the uniform distribution of the heat supplied by a Bunsen burner, and the inclusion of the thermometer bulb and the sample in the same inner compartment provides assurance that they will reach the same temperature.

An alternate device for characterizing high-melting substances is the differentially heated melting point bar of Dennis and Shelton;[9] the substance is dusted onto the hot surface and the melting point is determined from the line of demarkation between the solid and liquid phases.

Microdetermination of Melting Points. — In some types of experimentation it is of distinct value to be able to make accurate melting point determinations with no more than a single tiny crystal of the substance in question. Although the usual capillary-tube method may not seem unduly wasteful of material, the total sample of about 1 mg. (including losses in transfer) in some cases represents enough material for extensive characterization (for example, determination of the absorption spectrum, polarographic analysis, or bio-assay). The micromethod of Kofler[10] consists in placing a minute fragment of material on a cover glass centered over a small hole in a metal stage of controllable temperature and establishing the point of melting by observation under the microscope. The determinations can be made rapidly and with a high degree of precision. Mixed melting point determinations can be made after rubbing minute amounts of the two substances together on a cover glass, without the necessity of making a transfer. The original apparatus is rather elaborate, as are some of the later modifications designed for special studies. It is possible, however, to construct at very moderate expense a simplified instrument suitable for general use which retains the chief advantages of the more complicated designs. A microscope is not necessary, for the observation can be made satisfactorily with an ordinary lens. A satisfactory hot-stage assembly can be made by building an

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[9] *J. Am. Chem. Soc.*, **52**, 3128 (1930).

[10] Kofler and Hilbck, *Mikrochemie*, **9**, 38 (1931); see Pregl, "Quantitative Organic Microanalysis," 3rd English Ed., pp. 222–223 (1937); Chamot and Mason. "Handbook of Chemical Microscopy," I, pp. 200–204 (1938).

aluminum block, welled to accommodate a thermometer, along the lines of the simplified design described by Dunbar,[11] and equipping it with an electrical heating element of the type specified by Zscheile and White.[12] The thermometer used should have a rather short stem and should be provided with an armor. Calibration can be made with a series of compounds whose corrected melting points have been determined with a precision capillary-tube apparatus. The instrument can be made still more useful by providing it with facilities for optical polarization. This is done by interposing one piece of Polaroid in the eyepiece and another in the path of the light source which is directed at the sample through the narrow hole in the hot-stage. When the optical axes of the two Polaroid pieces are crossed, a minute crystal of the sample gives a luminous image on a dark field, and the melting point is easily discerned by the disappearance of luminosity.

MANIPULATION OF SMALL QUANTITIES OF MATERIAL

Much of value can be accomplished in experiments conducted with quantities of materials well below the usual level (about 0.1 mole) but still not in the micro range (1–2 mg.). Reactions often can be carried out with 25–500 mg. of starting material by essentially the same technique as in operations on a larger scale, and where some modifications are required these usually represent convenient improvements. Weighings of appropriate precision should be made on an analytical balance, and the accuracy of the yield data may well surpass that of macro experiments. A given operation often can be performed more rapidly with small than with large quantities, and the intelligent use of simple semimicro technique where it is appropriate effects a great saving of valuable starting materials or intermediates and expands enormously the scope of practical experimentation.

A useful suction filter for the collection of small amounts of

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[11] *Ind. Eng. Chem., Anal. Ed.*, **11**, 516 (1939).

[12] *Ind. Eng. Chem., Anal. Ed.*, **12**, 436 (1940).

solids is shown in Fig. 55. A slender filter rod long enough to project beyond the end of the funnel is provided with a flattened nob on which a circle of filter paper rests. These circles can be prepared in quantity with the use of a cork borer or a steel die and are manipulated most easily with a pair of tapered tweezers. The drawing illustrates a method of weighting the suction flask to avoid its being tipped over. A small suction filter of another form is made by sealing a Witt porcelain plate into a Pyrex test tube, sealing a delivery tube to the bottom, and cutting off the top.[1] The filter illustrated in Fig. 56 is designed for the collection of very small amounts of solids. The capillary drainage tube is of such small diameter that no support is required for the filter paper, and the paper is of so limited an area that little product is lost by adherence to the paper. The construction permits filtration directly into a small Erlenmeyer flask or centrifuge tube.

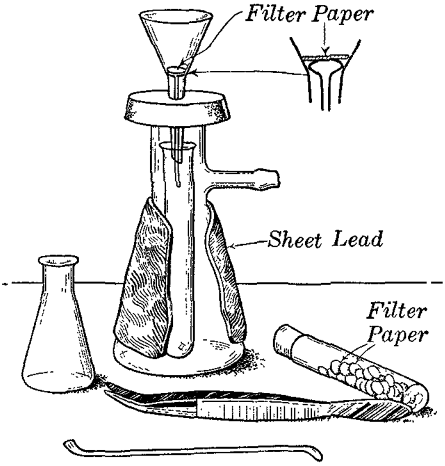

FIG. 55. — Apparatus for Suction Filtration

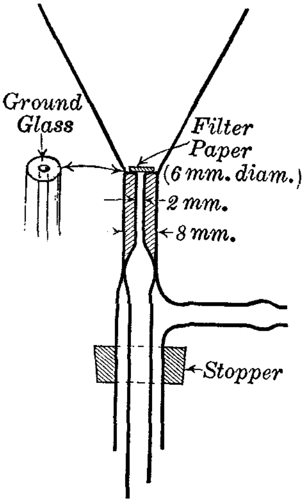

FIG 56. — Suction Filter

An excellent and easily constructed microburner utilizes as the regulator a stopcock mounted in a base consisting of a large rubber stopper,[2] as shown in Fig. 57. The exit

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[1] Roswell, *Ind. Eng. Chem., Anal. Ed.*, **12**, 350 (1940).

[2] C. L. Wilson, "An Introduction to Microchemical Methods," p. 41 (1938).

tube is bent upwards to a vertical position and drawn out to a small tip which serves as the burner.

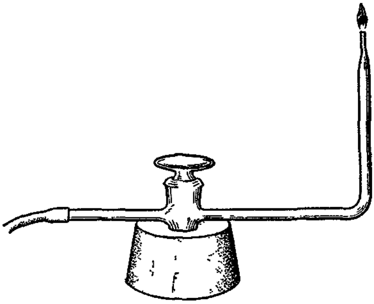

Fig. 57. — Microburner

The filtration of a small volume of solution can be done very conveniently and with little loss of material by the use of a filter stick. This is a capillary tube, or other tube of small bore, bent in the form of an inverted U. One lĕg, which is long enough to extend to the bottom of the vessel or tube containing the solution, is provided with a sintered glass disc, a filter paper held in place by a glass ring and a wire (Craig[3]), or other filtering device.[4] The second leg is shorter and delivers into a receiver to which suction can be applied by mouth or with a water pump. A suitable assembly is illustrated in Fig. 58. The filter stick[5] shown in the drawing has the advantage of simplicity of construction and ease of cleaning. It is an adaptation of the Schwinger funnel[6] and is made by grinding the exposed ends of the sectioned limbs until a small circle of filter paper fits snugly between them; a short piece of rubber tubing is slipped over the joint to hold the ends in place.

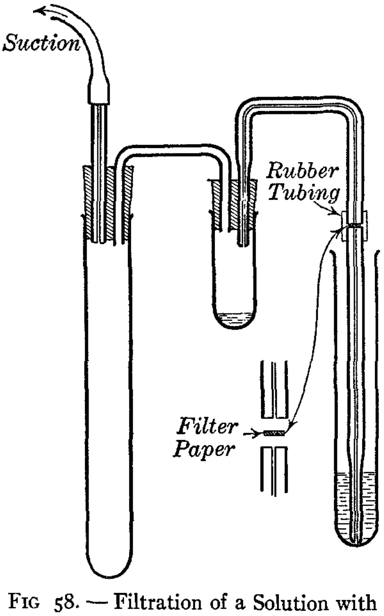

Fig 58. — Filtration of a Solution with the Use of a Filter Stick

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[3] *Ind. Eng. Chem., Anal. Ed.*, **12**, 773 (1940)

[4] Morton, "Laboratory Technique in Organic Chemistry," pp. 166–167 (1938).

[5] Designed by W. von E. Doering.

[6] Emich, "Microchemical Laboratory Manual," p. 30 (1932).

Small quantities of solids can be collected and washed by centrifugation rather than by suction filtration. The ordinary 15-cm. tapered centrifuge tube serves as a convenient crystallization vessel and indeed can be used for carrying out the majority of small-scale operations. A solution can be evaporated quickly in a tared conical tube using the attachment shown in Fig. 59, a stream of dry air is admitted through a tube of easily adjustable height and directed at the surface of the liquid at a sufficient distance to produce a ripple. When a crystallizate or precipitate is obtained it can be packed down by centrifugation, and the clear liquid decanted into another tared tube for further concentration. The solid product can be washed, dried, and weighed in the original tube, and there is little chance for loss of material. Various solvents may be tried in succession for crystallizing the substance, for a solvent which proves unsatisfactory can be evaporated quickly and replaced by another one.[7] The evapora-

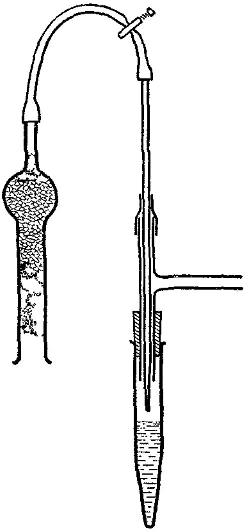
FIG. 59. — Evaporation at Reduced Pressure in a Centrifuge Tube

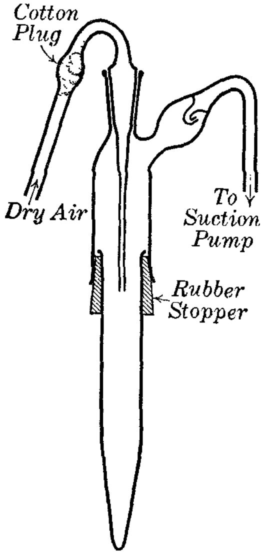

FIG. 60. — Evaporation Head for a Centrifuge Tube

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[7] Williams and Spies, "Vitamin B_1", 140–142 (1938).

tion head shown in Fig. 60 is designed to prevent possible contamination of the contents of the tube from contact with rubber and is useful in the preparation of an analytical sample. The convenient adapter arrangement can, of course, be combined with the adjustable gas inlet device of Fig. 59.

The construction of a constant temperature boiler for heating a reaction mixture in a centrifuge tube or test tube is shown in Fig. 61 (J. C. Cline).

The technique of centrifuge filtration in a Skau tube [8] is very useful for the rapid collection of low-melting substances and for separating a product which can be crystallized most advantageously from a small volume of a solvent in which it is readily soluble.[9] The Skau tube is a device for making a sharp separation of crystals and liquid in which the mixture is brought onto a filter in a tube permitting centrifugation. Modifications of the technique have been introduced by Hershberg,[10] Perrine and Kump,[11] and Craig.[9] The modified tube devised by Hershberg is shown in Fig. 62 in the position in which the filtering operation is performed. Initially, the unit is assembled in the inverted position, with the crystallization mixture contained in the rounded inner tube. The filter paper and plate are put in place and covered with the funnel tube with its attached receiver, and

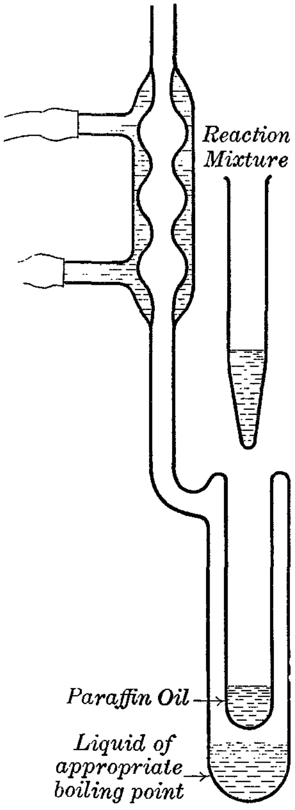

FIG. 61. — Constant Temperature Boiler

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[8] Skau, *J. Phys. Chem.*, **33**, 951 (1929); Skau and Rowe, *Ind. Eng. Chem., Anal. Ed.*, **3**, 147 (1931).

[9] Craig, *Ind. Eng. Chem., Anal. Ed.*, **12**, 773 (1940).

[10] Morton, "Laboratory Technique in Organic Chemistry," pp. 177–178 (1938)

[11] *Ind. Eng. Chem., Anal. Ed.*, **11**, 658 (1939).

the whole unit is quickly inverted and filtration accomplished by centrifugation.

CHROMATOGRAPHIC ADSORPTION

The selectivity with which even closely related substances are adsorbed from solution on the active surface of certain finely divided solids affords the basis for a very effective method of separating mixtures. When a solution containing a mixture of pigments is passed slowly through a column packed with a white adsorbent such as alumina, the individual constituents tend to be retained in different colored zones, the most strongly adsorbed pigments being held at the top of the column and the ones having less affinity for the adsorbent appearing at lower levels. Although the initial separation of the different colored layers may not be very distinct, the zones often become much more sharply differentiated on filtering through the column a fresh portion of the original solvent or a quantity of a second solvent. This operation constitutes the development of the chromatogram. The process of development is continued until the zones are spread over the entire length of the column. When the operation is conducted in a tower of the type shown in Fig. 63, the variegated column can be pushed carefully out of the open end of the tube with a plunger onto a clean paper. It is then cut into sections with a knife or spatula and each highly pigmented zone is eluted separately with a solvent capable of stripping the colored substance from the adsorbent, the pigment being obtained by filtration and evaporation.

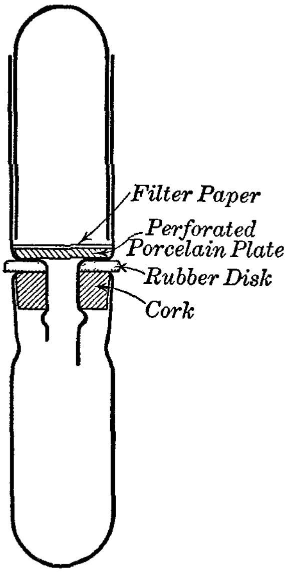

FIG. 62. — Modified Skau Tube

The effectiveness of the separation is strikingly demonstrated by passing an extract from a few green leaves through a tower packed with layers of alumina (bottom), calcium carbonate, and powdered sugar; the developed chromatogram is resolved into zones of chlorophyll b (top), chlorophyll a, xanthophyll, and carotene.[1] In general an organic compound is adsorbed most strongly from a solution in a nonpolar solvent such as hexane or benzene and is but loosely held when the adsorbent is in contact with alcohol, or other polar solvent, for this itself has a strong affinity for the active surface of the solid and tends to displace the much less plentiful pigment present. Therefore hexane is an effective solvent for the preparation and development of the chromatogram, and alcohol, or benzene containing a little alcohol, serves well for the elution.

The chromatographic method was discovered by the botanist Tswett and heretofore the most prominent applications have been in the investigation of plant pigments. The method, however, can be employed extensively in various simplified and convenient forms in many problems of general laboratory practice, and the following notes apply particularly to the more general uses of the adsorption procedure. A substance does not have to be very highly colored to give a distinctly visible adsorption band, particularly since the adsorbate may be a complex of accentuated color and also because the material retained in a section of the column is in a concentrated form. A pale yellow reaction product may be resolvable by adsorption analysis into a yellow component and a colorless one, or it may be found that the slight color is due to a trace of

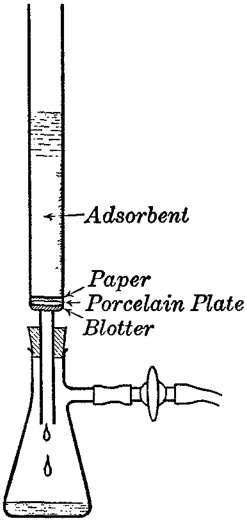

FIG. 63 — Adsorption Column, Suction Filtration

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[1] Zechmeister and Cholnoky, "Die Chromatographische Adsorptionsmethode," J. Springer, Vienna, 1937.

a persistent colored impurity which is not eliminated by crystallization, or by using decolorizing carbon in the ordinary way, but which will be adsorbed on the column while the main product passes through into the filtrate. Such a purification is favored by the general tendency of colored substances to be adsorbed more strongly than related substances which are less highly colored, or less unsaturated. Certain colorless substances exhibit a brilliant fluorescence in ultraviolet light, and the pas-

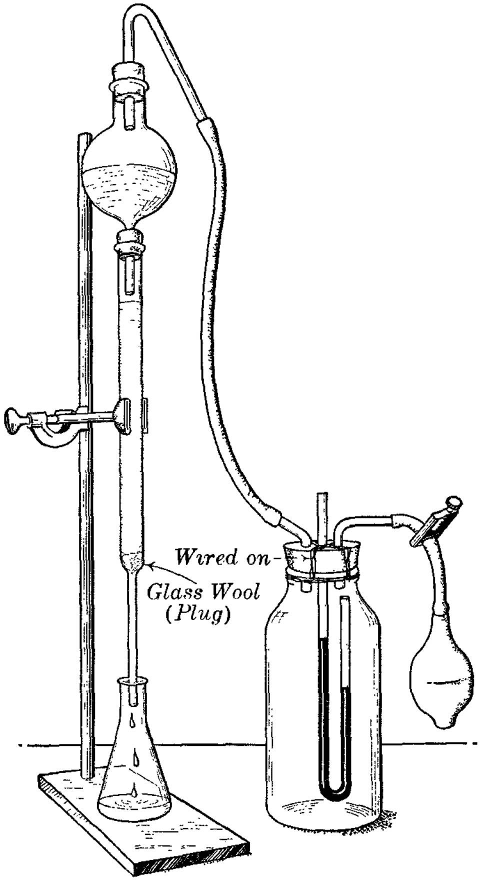

FIG 64 — Adsorption Column, Pressure Filtration sage of such a compound through an adsorption column in an ordinary Pyrex tube can be followed readily in a partially darkened room with the use of the simple lamp described on page 317.[2] Methods elaborated in special cases for processing colorless and nonfluorescent compounds include the use of a colored indicator,[3] location of the zones by streaking the column with a test reagent which will give a color reaction,[1] and conversion of the materials under investigation to colored derivatives[4] (separation of glucose and fructose in the form of the *p*-phenylazobenzoyl esters[5]). A very effective method of fractionation by adsorption which is entirely independent of any color phenomena is mentioned below.

Two satisfactory methods of supporting the adsorbent in a glass tube are shown in Figs. 63 and 64. A plug of glass wool serves adequately in tubes up to about 2 cm. in diameter, while a perforated porcelain plate resting on a cushioning piece of blotting paper on a shoulder in the glass tube and covered with a circle of filter paper provides a convenient means of support in larger tubes (at least up to 5 cm.). Sealed-in porous plates are not easily cleaned and do not permit removal of the column for sectioning. Sectioned tubes requiring rubber gaskets should be used only when the scale of operation necessitates this construction;[6] one should make sure that a rubber is employed which is capable of resisting attack by the solvent to be used. An adsorbent such as alumina, calcium carbonate, magnesium sulfate or magnesium oxide is employed in the form of a light powder. This is introduced into the tube and packed evenly by tapping the walls of the tube; when using the assembly shown in Fig. 63 it is convenient to apply suction and then tap the tube around

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[2] Winterstein and Schön, *Z. physiol. Chem.*, **230**, 139, 146 (1934); Winterstein, Schön and Vetter, *ibid.*, **230**, 158 (1934); Karrer and Schöpp, *Helv. Chim. Acta*, **17**, 693 (1934).

[3] Brockmann, *Z. physiol. Chem.*, **241**, 104 (1936).

[4] Strain, *J. Am. Chem. Soc.*, **57**, 758 (1935).

[5] Reich, *Biochem. J.*, **33**, 1000 (1939); *Compt. rend.*, **208**, 589, 748 (1939).

[6] A serviceable form is constructed of flanged Pyrex piping. Bruce, *Science*, **81**, 179 (1935).

its circumference, for this helps to give an even packing not subject to subsequent channelling. A loose plug of cotton or a circle of filter paper placed at the top of the column protects the solid from disturbance when liquid is poured in. The column is washed with some of the solvent to be used and the rate of flow observed under moderate suction or pressure. The solvent should percolate at the rate of about 5–10 cc. per minute in a 2-cm. tube and at the rate of about 20–40 cc. per minute in a 5-cm. tube. When suction is used (Fig. 63) the stopcock of the suction flask should be closed after a suitable pressure has been established, both in order to avoid evaporation and to maintain a steady suction. The pressure method (Fig. 64) is preferable when a very volatile solvent is employed and perhaps in any case gives a somewhat more even flow of liquid. Once the column has been wetted, the level of solvent or solution should not be allowed to fall below the top of the adsorbent, for this may lead to channelling or oxidation of the adsorbate.

Alumina is probably the most generally useful adsorbent and has a high affinity for many organic substances dissolved in hexane, benzene, or carbon tetrachloride. Material of particularly high quality is the "aluminum oxide standardized according to Brockmann," which is now manufactured in this country (Merck and Co.). Very satisfactory results are obtainable with the inexpensive "activated alumina, Grade A, minus 80 mesh" obtainable from the Aluminum Ore Co. (Illinois). Prior to use, this must be fully activated by heating it until free from moisture. A 1-l. Erlenmeyer flask half filled with the alumina is heated in an oil bath maintained at 225–250° and the powder, which at first appears to boil, is stirred with a thermometer until this registers a temperature of 210°, at which point the boiling ceases ($\frac{1}{2}$–$\frac{3}{4}$ hour). Any moisture which has condensed on the walls of the flask is driven out by gentle heating with a free flame, and the flask is stoppered loosely and allowed to drain on a paper and cool. When stored in a screw-capped bottle the activated alumina can be kept for prolonged periods without deterioration.

The designation "minus 80 mesh" indicates that the material will all pass an 80-mesh sieve but may contain much powder considerably finer than the 80-mesh size. When a lot of alumina is found by trial to contain sufficient very fine material to impede the free flow of liquid, the situation is remedied easily by mixing the adsorbent with one of the commercial filter aids, consisting of a heat-treated siliceous earth [7] (Johns-Manville, Dicalite Company). Thus a mixture of equal volumes of the above activated alumina and Hyflo Super-Cel gives a uniform packing permitting a free flow of liquid. The filter aid, which does not itself act as an adsorbent of organic compounds, contains very little moisture and can be mixed with the alumina either before or after the activating operation.

Because of its basic character, alumina cannot be used satisfactorily for processing substances as acidic as carboxylic acids, for a direct chemical interaction detracts from the selectivity of true adsorption. Alumina is also sufficiently basic to be destructive to sensitive quinones (e.g. vitamin K_1). Among the neutral if weaker adsorbents, one of the most serviceable is magnesium sulfate. The commercial powdered material is satisfactory but should be activated by heating it at 200° for about one hour.

The nonpolar solvent employed for distributing the material on the column should be dried just as scrupulously as the adsorbent, for mere traces of water or other hydroxylic solvent markedly detract from the efficacy of the adsorption process. Fortunately drying is easily accomplished with the usual solvents: hexane, petroleum ether, benzene, carbon tetrachloride.

One significant use of the chromatographic method is in effecting purifications, and frequently this can be done by a simple filtering operation and without recourse to the sectioning of the column. Thus an essentially homogeneous preparation of a polynuclear aromatic hydrocarbon contaminated with a trace of impurity giving it an extraneous yellow color or a dull ap-

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[7] Strain, *J. Biol. Chem.*, **105**, 523 (1934); Cassidy, *J. Am. Chem. Soc.*, **62**, 3076 (1940).

pearance can be dissolved in an ample amount of benzene, and the solution passed through a previously washed column of alumina, or of alumina and Super-Cel. The impurity is often retained in a narrow colored zone at the top of the column while under the ultraviolet lamp the hydrocarbon is observed to pass into the filtrate (blue fluorescence). After washing the column with enough benzene to remove all fluorescent material, the filtrate is concentrated and the purified hydrocarbon recovered. It is sometimes advantageous to purify a dark colored reaction mixture by similar percolation through an adsorption tower in order to remove extraneous coloring matter prior to fractional crystallization. Similar processing affords an effective method of removing traces of colloidal selenium following a selenium dehydrogenation, or of rendering an oily unsaturated compound capable of undergoing catalytic hydrogenation. Advantage can be taken of the fact that oxygen-containing compounds generally are more strongly adsorbed than related hydrocarbons. For example, a carbinol obtained from a ketone by the Grignard reaction as an intermediate in the synthesis of a hydrocarbon may be contaminated with unchanged ketone. If the total reaction mixture is dehydrated, the ketone is easily separated from the hydrocarbon by selective adsorption on alumina. Hydroxy compounds invariably exhibit a very marked affinity for the active surface of an adsorbent. Alcohols are adsorbed considerably more strongly than ketones or esters of similar molecular complexity. Phenols are adsorbed readily by neutral materials, including carbon, and are held very firmly by alumina (basic).

A further application of the chromatographic method is in recovering hydrocarbons from their picrates or trinitrobenzene derivatives.[8] When a benzene solution of the complex is passed through a tower packed with activated alumina the nitro component usually is adsorbed in a narrow orange or red zone while the hydrocarbon can be washed through into the filtrate (ex-

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[8] Plattner and St. Pfau, *Helv. Chim. Acta*, **20**, 224 (1937); Fieser and Hershberg, *J. Am. Chem. Soc*, **59**, 2502 (1937); **60**, 945, 1664 (1938).

amples: anthracene, 3,4-benzpyrene). Occasionally the hydrocarbon itself is so strongly adsorbed that an efficient separation cannot be accomplished (example: methylcholanthrene).

The method of fractionally eluting material adsorbed on a column constitutes a highly effective means of separating mixtures of compounds, whether or not they are colored. The mixture is adsorbed on a column arranged for pressure filtration (Fig. 64) and eluted with successive fractions of solvent or solvent mixture. The fractions are collected separately for evaporation and examination. Although the method is empirical, the selective distribution of the constituents of the mixture over several fractions is often very effective. The elution method, furthermore, offers greater opportunities for intelligent manipulation than the alternate scheme of sectioning the column arbitrarily. An early procedure[9] has been modified to considerable advantage by the Callows[10] and employed by them with distinct success for the separation and isolation of steroids of the sex hormone group from urinary extracts. In the Callow procedure, about 1 g. of a neutral keto-alcohol gum is dissolved in 25 cc. of carbon tetrachloride and adsorbed on a 1.5 × 27-cm. alumina column; this is eluted first with 1–2 liters of pure carbon tetrachloride and then with seven or eight 250-cc. portions of carbon tetrachloride containing 0.1 per cent of ethanol, followed by similar portions containing 0.2 per cent or more of ethanol. Certain of the fractions on evaporation are found to give well-defined crystallizates of individual steroids, while intermediate fractions afford gums. About one third of the total hormone gum can be accounted for in the form of three pure constituents. Reichstein[11] has made use of a similar process of fractionation in his work on cortical hormones. Material adsorbed on alumina is eluted in some 30–50 fractions, using first pentane containing

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[9] Holmes, Cassidy, Manly and Hartzler, *J. Am. Chem. Soc.*, **57**, 1990 (1935).

[10] N. H. Callow, *Biochem. J.*, **33**, 559 (1939); N. H. Callow and R. K. Callow, *ibid.*, **33**, 931 (1939); for a further example, see Wolfe, Fieser and Friedgood, *J. Am. Chem. Soc.*, **63**, 582 (1941).

[11] Reichstein and Montigel, *Helv. Chim. Acta*, **22**, 1212 (1939); Reichstein and Euw, *ibid.*, **22**, 1222 (1939).

increasing amounts of benzene and then, in succession, benzene, benzene with added ether, ether, and ether containing acetone.

Experiments: (1) *Chromatographic adsorption of leaf pigments.* — For detailed procedure see Zechmeister and Cholnoky[1] or Gattermann-Wieland.[12]

(2) *Purification of anthracene.*[2] — Dissolve 100 mg. of crude yellowish anthracene in 150 cc. of hexane and pass the solution through a 1.5–2 cm. column packed to a height of 7–10 cm. with activated alumina — Super-Cel. Develop the chromatogram with 50–100 cc. of hexane, using an ultraviolet lamp to follow the progress of the hydrocarbon. Carbazole (m.p. 238°, corr.) if present is retained at the top of the column in a sharp, deep blue fluorescent (lamp) zone. Naphthacene (m.p. 337°, corr.), the chrysogen responsible for the color, appears next in a narrow yellow nonfluorescent zone, and the anthracene forms a broad, blue-violet fluorescent zone in the lower part of the column. Continue the development with hexane until fluorescent material begins to pass into the filtrate, remove the first filtrate (containing soluble impurities), and elute the column with benzene-hexane (1 : 1) until the anthracene has been largely removed or until the yellow zone invades the bottom region of the column. Concentration of the filtrate and crystallization from benzene-hexane should yield pure anthracene, m.p. 215–216°, corr., which is blue fluorescent in daylight. The beautiful fluorescence of dilute solutions of the pure hydrocarbon is completely obliterated by the presence of $\frac{1}{30,000}$ per cent of naphthacene.

(3) *Purification of anthracene through the picrate.* — Dissolve 1 g. of crude anthracene and 1.5 g. of picric acid in 10 cc. of benzene at the boiling point and allow the solution to cool slowly without disturbance. Anthracene picrate crystallizes in thick, dark red prisms, m.p. 142°, while carbazole picrate may appear as fine, reddish orange needles, m.p. 186°. Separate the crystals roughly by hand and recrystallize the anthracene picrate from benzene. To recover the hydrocarbon, dissolve the picrate in 20–30 cc. of benzene and pass the solution through a column

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[12] "Laboratory Methods of Organic Chemistry," pp. 410–411 (1937).

prepared as specified in (2). Wash down the column with 40–50 cc. of benzene, concentrate the filtrate to a volume of about 10 cc., and add an equal volume of hexane. Anthracene should be obtained in fluorescent plates.[13]

GLASS BLOWING[1]

By E. B. Hershberg

Types of Glass. — Laboratory tubing made of soft glass (soda-lime glass) softens at a comparatively low temperature (400–450°) and can be worked most satisfactorily using an air-gas blast lamp with a quiet blue flame just tipped with yellow. With soft glass, simple practice operations can be carried out in the flame of a Bunsen burner; a microburner of the type shown in Fig. 51 (page 326) is useful for learning the technique of joining pieces of 6–8 mm. tubing. Soft glass has a high coefficient of expansion and must be brought to the working temperature slowly in a yellow flame in order to avoid cracking; the temperature during working should not be too high or the surface may become frosted as the result of volatilization of alkali. After the blowing operation has been completed, the glass should be annealed, in order to relieve strains, by rotating

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[13] A convenient method for the purification of anthracene in quantity consists in distilling a mixture of 50 g. of the crude hydrocarbon and 700 cc. of ethylene glycol from a 1-l. distilling flask directly (without a condenser) into a second flask which is cooled when required with a stream of water. The distillation is continued until about 50 cc. of residue is left, and the mixture of anthracene and ethylene glycol in the receiver is redistilled as before. With a good grade of crude anthracene, blue-fluorescent material is obtained on two distillations in 70–80 per cent yield. — Communicated by W. W. Hartman, Eastman Kodak Co.; see Yule, U. S. Patent 2,213,755 (1940).

[1] Reference books:

Frary, Taylor and Edwards, "Laboratory Glass Blowing," McGraw-Hill Book Co., New York (1928).

Morey, "The Properties of Glass," Reinhold Publishing Corp., New York (1938).

Vigreux, "Le soufflage du verre," Dunod, Paris (1930).

Woytacek, "Lehrbuch der Glasbläserei," J. Springer, Vienna (1932).

Useful pamphlets giving instructions for blowing Pyrex glass are distributed by the Corning Glass Works.

the piece in a luminous flame until it is coated evenly with a layer of soot.

Pyrex, Glasbake, or other similar borosilicate glass has a higher softening point (820°) than soft glass and a lower coefficient of expansion. The proper working temperature is easily obtained with a blast lamp provided with valve-controlled inlets for gas, oxygen, and air; a gas-oxygen flame is preferred by some workers. A suitable gas mixture can be obtained by first adjusting the gas and air valves to give a soft, nonluminous flame and then feeding in enough oxygen to produce a sharp, light blue inner cone (considerable noise). The hottest part of the flame is at the tip of the blue cone, the diameter and length of which is determined by the size of the orifice of the burner and the composition of the gas mixture. A hand torch with a trigger-type gas regulator is useful in mounting and assembling apparatus; a satisfactory type which is quiet in operation is that fueled with premixed gas and oxygen (without air). Pyrex glass tubes up to a diameter of 10 mm. can be plunged directly into the flame of the blast lamp without cracking; larger pieces are preheated with a soft gas-air flame. Less time and care is required at the beginning of the glass blowing operation than when soft glass is used. The annealling operation is important and with any but the simplest articles requires a careful and skillful technique, for the annealling point (560°) is not much below the temperature of softening. The worked portion is rotated in a soft, bushy flame until it is heated uniformly to a just visible red, and the temperature is then gradually lowered by manipulating the glass in the cooler parts of the flame and by reducing the flame temperature.

Cutting Glass Tubing. — Considerable care should be taken in the initial operation of making a fine, straight scratch extending about a quarter of the way around the tube. A triangular file is rather unsatisfactory because after only brief use it becomes worn and produces too wide a scratch. Hardened steel knives and knives with tungsten carbide cutting edges perform excellently but are expensive. A 6-inch flat Swiss pattern pillar file (cut No. 4) is very satisfactory and inexpensive. The four sharp edges formed at the junctions of the broad abrading surfaces and the smooth, narrow sides are all available for cutting and make clean, fine scratches in glass. The file is easily sharpened by light regrinding of the narrow edges. The scratch is best made by pressing one edge of the file firmly against the tube and slightly rotating the tube away from the body while filing in the same direction. Only one stroke should be made; a fine scratch gives a much better opportunity for a clean break than a wide groove sawed in the tube at the expense of dulling the file. After the scratch has been made, the tube (up to about 15 mm.) is grasped with the scratch away from the body and the thumbs pressed together at the near side of the tube just opposite the scratch. Slight pressure is exerted outwards with the thumbs and at the same time the tube is forcefully pulled apart. A straight, clean break should result.

Tubing of larger sizes can be cut with an electrically heated wire [2] or by touching the scratch lightly but firmly with a hot piece of glass rod. This produces a deep crack which can be led around the tube by further applications of the heated rod. With soft glass the rod should be of small diameter (2 mm.) and only moderately hot, for otherwise it may start a number of cracks radiating from the point of contact. In the case of Pyrex tubing it is well to use a 2–4 mm. rod of soft glass heated at the tip to bright redness. A large bottle may be cut by the same method except that a slender flame is applied tangentially at

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[2] A simple hot-wire cutting device is made as follows. A 6- to 8-inch length of No 22 chromel A wire is suspended in a loop from two supports and a 660-watt bowl heater element is partly unwound, a short section judged to be equivalent in resistance to the cutting wire is removed, and the remainder is connected in series with this wire. If the looped wire does not then reach bright red heat, the element is further shortened. The tube to be cut is scratched, laid firmly into the loop, and rotated until the entire circumference has been heated. Soft glass usually cracks at once; with Pyrex glass it is usually necessary to apply water to the heated portion with a small brush or dropper. Pyrex tubes of large diameter are best chilled by immersion in a stream of water. In another design the heated wire is suspended from the ends of a pair of tongs and can be made to encircle the tube (see the glass blowing manual of the Corning Glass Works).

right angles to the tube in order to lead the crack around the circumference.

Flaring of Glass Tubing. — A simple flaring tool is made from a 4″ × 1″ × $\frac{5}{8}$″ charcoal block by cutting it at one end to a smooth, uniform conical point, using a grinding wheel or a knife and sandpaper. Untreated charcoal does not tend to stick to glass as does a triangular metal reamer or an arc-light carbon rod, both of which must be rubbed while hot into beeswax prior to use. Charcoal is too fragile to be used for flaring tubes of small diameter and in this case carbon rods are preferable.

In forming a flare, the tube, stoppered or sealed at one end, is rotated in an oblique position in a rather narrow flame which impinges on both the front and the back edge at the same time without heating much of the body of the tube. When the glass is sufficiently plastic the tube is removed from the flame and the charcoal reamer is pressed lightly into the opening and rotated with sufficient pressure to turn out the edge. A reinforcing rim, such as that shown on the Pyrex pressure vial of Fig. 43, page 317, can be formed by reheating the flare in exactly the same manner until the turned edge flows together into a rim, when the reamer is again applied. The process is repeated enough times to give a beaded edge of the desired thickness.

Bends. — For the production of a successful bend it is important to apply heat uniformly to the entire section of tubing necessary for the bend. As in all comparable manipulations, the tube is grasped in the left hand with the palm down, and in the right hand with the palm up, for these positions make it possible to swing the right-hand end of the tube into a position for blowing without interruption of the steady process of synchronized rotation of the two ends. The rotating is best done in the direction in which the top of the tubing moves away from the body. Facility in the rotation of the two ends at exactly the same rate is gained only with careful practice; in the beginning stages it may be helpful to make a chalk mark on each side of the heated portion in order to indicate the proper alignment. If a U-bend or a sharp right-angle bend is to be made, one end of the tube is closed and the tube is heated to a higher temperature than required for a right-angle bend. With soft glass, the heating is best done with a Bunsen burner supplied with a fish-tail adapter; heating is continued until the tube begins to sag of its own weight and the flame has become strongly tinged with yellow sodium light. In the case of Pyrex glass, the section to be bent is rotated evenly in a long, brushy flame, the tube being held at a slight angle to the flame. Because of the higher temperature required and the narrower temperature range over which Pyrex retains plasticity, the operation must be carried out more rapidly than with soft glass. When the heated section has become thoroughly plastic, the tube is removed and bent in a vertical plane, with the ends upwards and the central portion of the bend at the bottom. If the bend is sharp, the tube usually becomes somewhat constricted, and in this case pressure is applied by mouth to the open end of the tube immediately after completion of the bend until the tube is expanded to its full size and irregularities are eliminated. If a very sharp bend is to be made it is advisable to thicken a short section of the tubing to about two thirds its original diameter and, while forming the bend, to pull out the tube and apply air pressure.

Round Ends. — The first step in closing a tube is to pull it down to a section of small diameter. This is known as a "point." A tube is often "pulled to a point" in order to provide a handle for its manipulation, and in this case a short section is heated strongly until pliable, and the tube is removed and pulled slowly, while being constantly rotated, to a length of about 8 inches. In making a round tube-end, the tube is heated in the same way but pulled out more rapidly, in order to produce greater constriction. The point *a* (Fig. 65) is then sealed with a sharp flame as in *b*. The thick lump is spread out evenly by heating the tip of the tube, blowing it out as in *c*, and heating the whole tube-end until a thick, even seal is produced (*d*); the tube is then blown to the final form *e*.

Straight Seals. — When two tubes of the same diameter are to be joined, one piece is stoppered[3] and held in the left hand with the palm over the tube and the open piece is held in the right hand with the palm upwards. Both ends should be squared, if necessary by making fresh cuts. The tubes are held at a slight angle from the horizontal and the ends are rotated simultaneously in opposite zones of the flame in such a way that only the cut edges are brought to the fusion point and very little constriction occurs. The tubes are removed a short distance above the flame (soft glass) and the ends pressed lightly and evenly together on the same axis and then pulled slightly to reduce the thick ring of glass at the joint. (With Pyrex glass these operations are performed without complete removal of the tube from the flame.) The flame is adjusted quickly to a narrow point and the tube is rotated in such a way as to heat only the welded section and cause it to shrink in diameter and increase in wall thickness. The tube is withdrawn and blown, without pulling, until the heated section is expanded slightly beyond the normal diameter. The bulbous part is heated in a softer flame and gently pulled enough to reduce the diameter of the seal to that of the tube. In order to secure the correct wall thickness it may be necessary to reheat the seal and repeat the shrinking and enlarging operations.

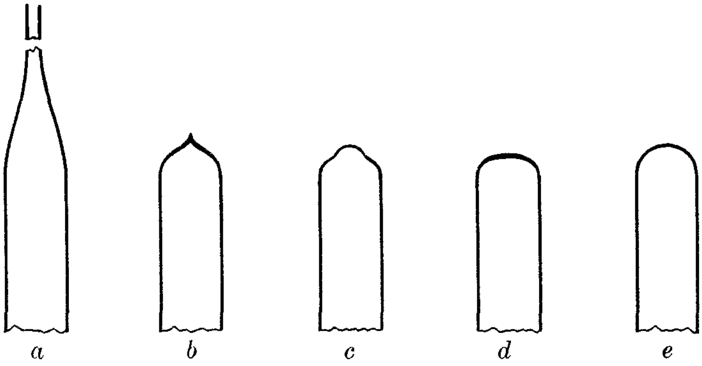

FIG. 65. - Blowing a Round End

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[3] Tapered corks useful for stoppering small tubes are available in the following sub-sizes (below No. 1): 0, 00, 00½, 000, 000½.

Tubes of unequal size can be joined by drawing out the larger tube, cutting it at a point where the diameter corresponds to that of the smaller tube, and making the seal essentially as described above. Another method is to make a round end on the larger tube, heat the central spot on the bottom with a sharp flame, and blow out a bulb of fragile glass which is brushed off with a file until a flared opening remains of diameter corresponding to that of the tube to be joined. By the same method, capillary tubing can be provided with a flared opening suitable for making a seal to a piece of ordinary tubing of the same diameter.

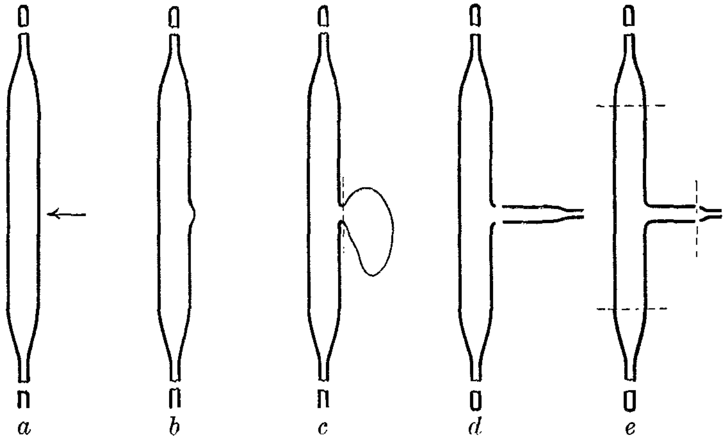

Fig. 66. — *Construction of a T-Seal*

T-Seals. — The tube which is to form the straight part of the joint is sealed or stoppered at one end and a small spot in the middle is heated with a sharp flame (Fig. 66*a*) and blown out so as to form a bulge (*b*) of diameter somewhat less than that of the tube which is to be sealed at this point. The bulge is heated carefully at its tip and blown out to a thin-walled bulb (*c*). The thin glass is brushed away with a file until a short side tube is left which can be joined to the second tube by the method described above for making a straight seal (*d* and *e*).

Bulbs. — Small flasks suitable for microdistillations can be blown from Pyrex tubing as follows. The tube is sealed at the bottom and the end is heated strongly until it shrinks and the glass thickens. It is blown out slightly, reshrunk, and the process is repeated until sufficient glass has been accumulated to produce the bulb. The thickened end is then heated until it is very soft, the tube is held in a horizontal position and rotated slowly and steadily, and a bulb is blown to the desired diameter. A tendency of the bulb to sink on one side can be corrected by quickly rotating this section to the opposite side and puffing. Similarly, a bulb can be formed at the middle of a piece of tubing by alternately shrinking and expanding a portion of the tube while pushing slightly on the ends. When a sufficiently thick section has been formed, the bulb is blown to final shape.

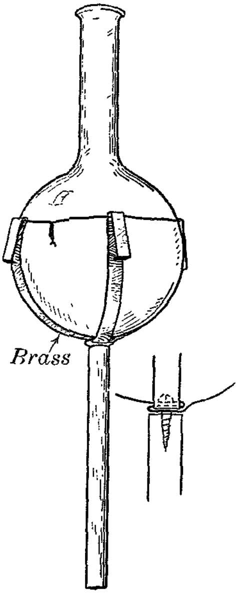

FIG. 67. — Flask Holder

When bulbs of more than about 25-cc. capacity are required it is best to use the flasks available commercially in various sizes and shapes. The manipulation of a flask in a glass blowing operation is greatly facilitated by having available a holder with which the bulb can be grasped firmly and rotated along the central axis. A flask holder which can be made easily from a round piece of wood and flexible strips of brass is shown in Fig. 67. One of the brass strips is bent to a smooth hemisphere and the second strip is crimped around the first in order to maintain the right-angle position. The ends can be bent over at various positions to hold the tightening wire, and hence the holder is adjustable to flasks of different sizes.

Ring Seals. — One of the standard methods of making ring seals may be illustrated by a description of the blowing of an all-glass condenser of the cold finger type. The method can be employed in the construction of thermometer wells (Fig. 44, page 318), mercury seals (Fig. 75, page 404; Fig. 76, page 405), and similar apparatus. The large tube which is to constitute the body of the condenser is provided with a rounded bottom (alternately, this tube can be pulled to a point). The inner tube of the seal is flared slightly at the end, inserted in the larger tube, and maintained in a centered position by means of a smaller tube which slips into it and which is secured in a cork stopper, as shown in Fig. 68*a*. The assembled unit is rotated in a nearly

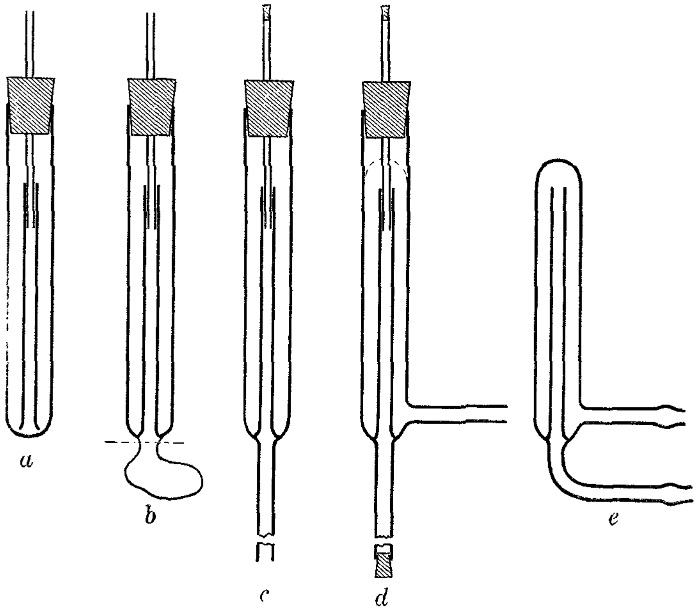

FIG. 68. — Construction of a Condenser with a Ring Seal

horizontal position and a small, sharp flame is directed at the rounded bottom of the large tube at the point of contact between this and the flared tube. The two pieces of glass soon fuse and a clear ring can be discerned. The flame is then centered at the bottom of the large tube, and a bulb is blown, as in *b*. The thin glass is removed, the guide tube leading through the cork stopper is closed, and a terminal tube is sealed on as in *c*. As soon as this operation has been completed, and before the ring seal has a chance to cool, a side tube is joined to the condenser body (*d*), and the lower part of the piece, including the ring seal, is annealed carefully. The stopper is then removed from the large tube, and this is sealed to a rounded end. The final operation consists in making a right-angle bend in the terminal tube, giving the completed condenser *e*. If the water inlet and outlet tubes are to be finished as shown in the drawing with slight bulges for the retention of rubber tubing, these are best blown into the tubes before they are joined to the condenser body; sufficient tubing is left on both sides of the bulge for purposes of manipulation and the excess glass is cut off after the piece is assembled. Alternately, the side tubes can be finished, after assembly of the piece, by flaring them slightly.

Rings. — The ringed shaft of a wire stirrer of the type illustrated in Fig. 36, page 308, is constructed as follows. A glass rod is sealed to the end of the section of tubing, which is to form the shaft of the stirrer, and cut off at a length sufficient to make the ring. The rod is heated thoroughly and bent around with tweezers into a rough circle until the end meets the base of the rod, to which it is then fused. The crudely formed ring is softened uniformly, and a $\frac{1}{4}''$ carbon rod which has been rubbed in beeswax is inserted in the hole and employed to spread the ring evenly. The ring is reheated until it shrinks, and spread again, and the operations are repeated until a symmetrical ring of uniform diameter is obtained.

Use of Asbestos. — Asbestos, in the form of thin paper or special woven tape, is a useful accessory in glass blowing. An inexpensive roll of $1'' \times 0.015''$ asbestos paper is quite satisfactory. When the paper is to be used in the dry form, traces of organic matter should be burned prior to use by passing the asbestos strip through a Bunsen flame until it is momentarily red. Standard taper joints can be held together securely during a glass blowing operation by covering the male member with a strip of asbestos paper and thrusting it into the outer joint; without the paper the dry joint might be damaged. Another use is in making a holder for a short length of tubing which is to be heated close to the point of support (see pressure flask, Fig. 43, page 317). A tube of diameter slightly smaller than the tube to be supported is wrapped with one or two layers of asbestos paper and forced securely into the open end of the larger tube; the small tube forms a handle and the joint can be made tight enough for blowing.

Wet asbestos paper can be molded to fit a glass piece of irregular form and gives a protective covering which subsequently can be removed without damage to the glass. When a seal is to be made a short distance from a stopcock, this is first wrapped with a few layers of wet asbestos paper and the covering is molded with the fingers. When a reaction mixture is sealed into a rather short tube, it is often convenient to provide a collar of wet asbestos just below the portion to be heated.

Glass Grinding. — Glass grinding is done by rubbing together two pieces of glass, or a piece of glass and one of metal, in the presence of an abrasive powder such as silicon carbide (carborundum, corundum) or fused aluminum oxide (alundum, aloxite). The grinding powder is wetted with a suitable fluid, which provides better distribution of the abrasive and helps dissipate the heat. Water serves satisfactorily in most operations; turpentine and other nonvolatile oils are used for drilling holes and in special polishing operations. The satiny finish on ground joints is achieved by performing the final grinding operation with fine powder (500–800 mesh), with water as the vehicle. A stopcock which will hold without lubricant or solvent is surfaced carefully in a final grinding with rouge as the abrasive.

The end of a glass tube can be squared by sprinkling a little 200- or 400-mesh grinding powder (0.2–0.4 g.) onto a flat piece of glass (preferably plate glass), moistening it with water, and grinding with a circular rubbing motion until the end is planar and smooth. An example of the process is in the construction of the suction filter flask and plate shown in Fig. 48, page 322. The plate is prepared by grinding together two squares of $\frac{1}{4}''$ plate glass, using 600-mesh aloxite as the abrasive, until a suitable finish is obtained. One of these plates is saved for the final apparatus and the other may be employed for the initially rough grinding of the flask. The filter flask (Pyrex) can be cut by making a scratch, starting the crack with a piece of hot rod, and continuing it around the flask with a long, sharp oxygen-gas flame. A satisfactory cut can be made more easily and surely with a hot-wire device. The grinding is started with 220-mesh carborundum and finished with 600-mesh aloxite. This gives a satin-smooth surface capable of holding a vacuum without the use of lubricating grease.

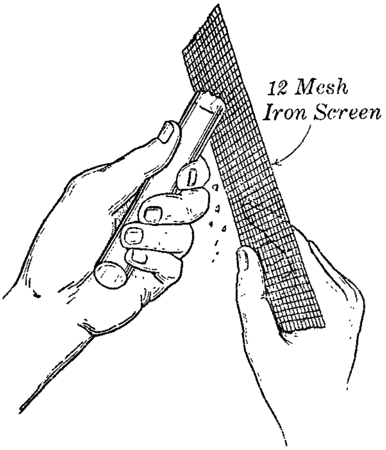

FIG. 69. — Chipping an Edge with Wire Gauze

Chipping a Rough Surface. — It is sometimes desirable to square the jagged end of a tube roughly, or to smooth the uneven edge of a cut flask, in preparation for a grinding or sealing operation. One method is illustrated in Fig. 69. A 5-inch square of heavy iron gauze (12-mesh) is held at an angle of slightly less than 90° to the axis of the tube, or nearly in the plane of the end which is to be formed, and the rough edge is hit with a quick striking and rubbing motion. The glass is removed partly as coarse chips and partly as dust; the refuse should be caught in waste jar and care taken not to breathe the dust. Professional glass blowers often use a pair of iron tweezers for removing jagged ends. The operation, illustrated in Fig. 70, consists in grasping the wall of the tube firmly with the tweezers and withdrawing the tool with a quick motion.

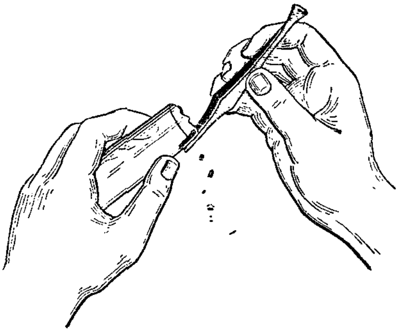

FIG. 70. — Smoothing a Surface with Tweezers

CHAPTER III

SOLVENTS, REAGENTS, AND GASES

Preparations reported in the original literature usually are described in a somewhat abbreviated form, and details of importance to the success of the operation may be omitted for the reason that the communication is addressed primarily to trained chemists who can supply these details from their own experiences. To the uninitiated worker this presents a real difficulty. He is directed to use a "suitably purified" reagent, an "alcohol free" or a "strictly anhydrous" solvent, or to work up the reaction mixture "in the usual way," without being told how to effect the purifications or operations called for. The aim of the present chapter is to provide answers to some of the many questions which may arise in the course of "literature preparations" or other advanced work. Notes are given on the preparation, purification, or uses of compounds and materials of general utility which fall into the classification given in the title.

It is well to keep in mind two general considerations with regard to the use of solvents and reagents. The first is that impurities in the starting materials not only may turn up in the reaction product but they may also have either a retarding effect on the main reaction or a catalytic influence on side reactions. A product often is no better than the materials put into the reaction and frequently it is incomparably worse. This would mean that all reactants should be subjected to high purification before use, were it not for a second consideration of importance: the purification of reagents beyond the state actually necessary in order to achieve the best results is a waste of time. A proper balance between these two considerations can be attained only by study and thought and by making preliminary trials.

SOLVENTS

Absolute Alcohol (b.p. 78.4°). — The complete dehydration of the constant-boiling mixture which ethyl alcohol forms with water and which contains 95.6 per cent alcohol by weight is best accomplished in two steps. The bulk of the water can be removed conveniently in the laboratory by the reaction with quicklime, but this gives at best a product containing about 99.5 per cent of alcohol and the small trace of water may interfere seriously in some reactions and operations. Commercial grades of absolute alcohol likewise may contain traces of water, for pure alcohol is extremely hygroscopic and easily picks up moisture during transfer or storage. (The industrial method consists in the distillation of the azeotropic mixture: alcohol, water, benzene. A mixture of all three components distils first, then benzene and alcohol, then absolute alcohol.) Of the many methods which have been suggested for the removal of the last traces of water the two outlined below appear to be the simplest and most reliable.

Alcohol of approximately 99.5 per cent purity is prepared as follows: A round-bottomed flask is charged about two thirds full with 95 per cent alcohol and (fresh) quicklime broken into lumps, using enough lime so that the pieces project above the surface of the alcohol. A reflux condenser equipped with a calcium chloride tube is attached and the mixture is refluxed gently for about 1 hour and then allowed to stand for 2 or 3 days, when the lumps should have largely disintegrated to a powder. The alcohol is then refluxed for 1 hour and distilled into a suction flask fitted by means of an adapter and protected with a calcium chloride tube against the entrance of moisture. The distillation is rather slow and considerable alcohol is retained by the solid residue.

For the further dehydration of this material or of commercial absolute alcohol a method has been developed by Smith[1] which

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[1] *J. Chem. Soc.*, 1288 (1927).

makes use of the irreversible reaction of an ethyl ester with sodium ethoxide and water:

$$RCOOC_2H_5 + C_2H_5ONa + H_2O \longrightarrow RCOONa + 2C_2H_5OH$$

The ester must be one of low volatility so that it will not distil with the alcohol when used in excess. Smith selected ethyl succinate and Manske[2] substituted the still higher-boiling and less expensive ethyl phthalate. Thus 7 g. of sodium is dissolved in small portions in 1 liter of "absolute" alcohol, 27.5 g. of ethyl phthalate (or 25 g. of ethyl succinate) is added and the solution is refluxed for 1 hour in a system protected from moisture. The anhydrous alcohol is then distilled through a short column with careful exclusion of moist air. Alcohol containing less than 0.05 per cent of water can be obtained by this method.

In the process of Lund and Bjerrum[3] the water is removed by reaction with magnesium ethoxide:

$$Mg(OC_2H_5)_2 + 2H_2O \longrightarrow Mg(OH)_2 + 2C_2H_5OH$$

Since the magnesium hydroxide formed is insoluble in alcohol the reaction proceeds to completion. A mixture of 5 g. of magnesium turnings, 60 cc. of absolute alcohol, and 0.5 g. of iodine is refluxed in a large flask until a vigorous reaction ensues and until the magnesium nearly all has been converted into the ethoxide. (If the reaction is slow in starting an additional 0.5 g. of iodine is added.) Nine hundred cc. of absolute alcohol is added, the mixture is refluxed for 1 hour and the anhydrous alcohol is distilled. The quality of the product depends upon the success with which moisture is excluded from the apparatus.

A convenient test capable of detecting 0.05 per cent of water in ethyl alcohol is given by Henle:[4] a voluminous precipitate is formed on adding a solution of aluminum ethoxide in benzene to a test portion of the alcohol.

Methyl Alcohol (b.p. 65.6°). — In a number of cases this may be substituted for the more expensive ethyl alcohol and the slight difference in properties sometimes renders the lower homo-

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[2] *J. Am. Chem. Soc.*, **53**, 1106 (1931).

[3] *Ber.*, **64**, 210 (1931).

[4] *Ber.*, **53**, 719 (1920).

logue more suitable for a given reaction or crystallization. The synthetic methanol now available is suitable for most purposes without further purification but it usually contains traces of acetone (less than 0.1 per cent) and formaldehyde. Acetone may be eliminated by treatment with a hypohalite and the formaldehyde presents no difficulties. An interesting method of purification has been developed by Morton and Mark:[5] methyl alcohol (500 cc.) is refluxed for several hours with furfural (25 cc.) and 10 per cent sodium hydroxide solution (60 cc.), thereby forming a resin which carries down all of the carbonyl compounds present. The alcohol is then carefully fractionated through an efficient column and separated from water and furfural with 95 per cent recovery. A highly sensitive test for acetone with Nessler's reagent is described in this paper.

When water is the chief objectionable impurity, and when it is present in quantities of only 1–2 per cent, a process similar to that of Lund and Bjerrum[6] is very useful. A good grade of methyl alcohol is placed in a large flask provided with an efficient condenser and 5–15 g. of magnesium turnings is added, the amount being adjusted according to the quantity of water probably present. If there is but little water in the alcohol the reaction will start after a short time and it may become so vigorous as to require cooling of the flask. On this account the mixture should not be heated at the outset. If much water is present the reaction may be slow in starting and it is often helpful to treat a small amount of magnesium with purer methyl alcohol in a small vessel and, after the formation of magnesium methoxide has commenced, to pour the solution into the main reaction flask. Once the first vigorous reaction is over and the magnesium has been largely dissolved, the mixture is refluxed for 2–3 hours to complete the dehydration, and the dry alcohol is then distilled from the residue of magnesium hydroxide and magnesium methoxide.

Absolute Ether (b.p. 34.6°). — Ether of the U.S.P. grade

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[5] *Ind. Eng. Chem., Anal. Ed.*, **6**, 151 (1934).

[6] *Ber.*, **64**, 210 (1931).

manufactured by the sulfuric acid process contains 2.5–4 per cent of alcohol and water, and the bulk of these materials should be removed prior to treatment with sodium in order to eliminate all traces of hydroxylic contaminants. Of a large number of methods available for the preliminary purification,[7] the following alternate procedures can be recommended for their rapidity and efficiency. A procedure convenient for *small-scale* operation consists in washing the ether in a separatory funnel with one sixth its volume of 1 : 1 sulfuric acid and drying with solid calcium chloride, then with sodium. Purification on a *large scale* by the following procedure [8] should be conducted only by an experienced worker mindful of the safety precautions necessary. A 12-l. flask equipped with an efficient spiral-type reflux condenser is mounted on a steam bath and charged with 6 kg. of commercial ether. Six hundred cc. of C.P. concentrated sulfuric acid is run in through a dropping funnel at such a rate that the reflux capacity of the condenser is not exceeded (about 45 minutes), and the resulting two-phase mixture is refluxed for 1 hour. The condenser is then replaced by a distilling head bearing a thermometer and fitted to a condenser for downward distillation and the ether is distilled until the temperature of the vapor has reached 40°; the yield is 5 kg.

For removal of the last traces of alcohol and water the ether is placed in a dry bottle or flask connected by means of an inverted U-tube to a drying tube containing calcium chloride or anhydrous calcium sulfate, and sodium wire (2–3 g. per kg.) is run in from a press. If there is an appreciable evolution of hydrogen, fresh sodium wire is added after an interval of about 12 hours. When all reaction has ceased and the wire remains bright, the bottle is stoppered with a cork and stored in a cool place remote from flames.

The Carbide and Carbon Chemicals Corporation currently supplies, at approximately the regular price, ether containing so little

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[7] MacArdle, "Solvents in Synthetic Organic Chemistry," pp. 83–88, D. Van Nostrand Co., New York, 1925; see also Bruce, *Science*, **87**, 171 (1938).

[8] Procedure of E. B. Hershberg and M. S. Newman.

alcohol and water that it can be treated directly with sodium without preliminary purification.

A laboratory group will often find it convenient to maintain jointly a ready supply of ether of assured Grignard quality in a 5-l. flask mounted on a steam bath and connected to an offset 5-cm. vertical tube into the top of which a copper condensing coil is affixed by means of a stopper carrying a drying tube. The lower part of the vertical tube should have a receiver capacity of about 250 cc. (calibrated) and is provided at the bottom with a delivery tube which can be closed by operation of either a mercury valve or a silver-clad stopcock. The flask is charged with sodium-dried ether and sufficient *n*-butylmagnesium bromide solution, or other available Grignard reagent, is added to maintain anhydrous conditions. After refluxing for a time and returning to the flask a few portions caught in the receiver, the ether is satisfactory for use and will remain so. In practice the dry solvent is measured directly into the reaction flask or dropping funnel.

Ordinary (impure) ether which has stood for some time in contact with the air usually contains peroxides, which may give to the solvent a pungent odor, and which may lead to an explosion if a large volume is evaporated to dryness. The dangerous peroxides are particularly likely to be present in recovered ether and should be destroyed prior to distillation by shaking the ether with a dilute, weakly acidic solution of ferrous sulfate.

Acetone (b.p. 56.5°). — Commercial acetone is useful for the rapid drying of glassware [9] (see page 17) and for the preliminary cleaning of reaction vessels, because it has a great solvent power for many organic substances and for reaction tars. It is also a good solvent for some crystallizations, although the low boiling point is somewhat of a disadvantage. The next higher homologue, **methyl ethyl ketone,** b.p. 80°, is only slightly more expensive and it is an excellent solvent, particularly for fractional

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[9] A more rapid drying action is obtained with a mixture of equal volumes of acetone and ether; the mixture has a greater solvent action for stopcock grease and will tolerate 13 per cent of water.— Markham, *Ind. Eng. Chem., Anal. Ed.*, **12**, 748 (1940).

crystallizations. In the crude condition both ketones are likely to contain water and alcohol, neither of which ordinarily interferes with a crystallization except in the case of an easily esterified acid. Where the impurities are undesirable the method of purification should be chosen according to the purpose in view.

(1) Acetone suitable for reduction to pinacol (page 97) or for use in the Oppenauer oxidation reaction should be dried thoroughly over calcium chloride or potassium carbonate (page 98, note 3).

(2) When a quantity of pure, dry acetone or methyl ethyl ketone is required for use as a reagent it is best purified through the bisulfite compound (see page 88), dried over calcium chloride or potassium carbonate, and distilled.

(3) For test purposes, where a trace of water is immaterial but where an alcohol might interfere with the test, destruction of the alcohol by means of silver oxide is perhaps the most convenient method. To 700 cc. of acetone add a solution of 3 g. of silver nitrate in 30 cc. of water, then add 8 cc. of 10 per cent sodium hydroxide solution and shake for 10 minutes; filter and distil.

(4) Acetone is often used as a solvent in oxidations with potassium permanganate, for it dissolves the inorganic as well as the organic reactant. For this purpose it is sufficient to reflux the acetone and add very small quantities of permanganate until the violet color persists. Potassium carbonate is then added for drying and the purified product is distilled.

Benzene, Thiophene-free (b.p. 80.4°). — Stir mechanically a mixture of crude benzene and crude concentrated sulfuric acid (80 cc. per liter of benzene) at room temperature for one half hour, decant from the dark acid liquor and repeat the process twice with fresh portions of acid. The acid should darken only slightly during the last agitation. Remove the acid layer by siphoning, decant the benzene into a clean flask, taking care to avoid inclusion of any remaining acid, and distil. (The stirring with acid can be done in a large separatory funnel and the acid liquor removed through the stopcock.)

Test for Thiophene. — Dissolve about 10 mg. of isatin in 1 cc. of concentrated sulfuric acid (C.P.), shake the red solution with 3 cc. of benzene and let the mixture stand. Thiophene if present produces a blue-green coloration. A more sensitive test is described by Holmes and Beeman.[10] These authors describe an improved process for the removal of thiophene by means of aluminum chloride, a method which entails less loss of benzene but one which is somewhat less convenient than the sulfuric acid process.

Toluene, Free from Sulfur Compounds (b.p. 110.6°). — Crude toluene may be purified with sulfuric acid as in the case of benzene, but it is more subject to sulfonation and some control of the temperature is required. Stir mechanically for one-half hour a mixture of 1 l. of toluene and 80 cc. of crude, concentrated sulfuric acid, keeping the temperature from rising above 30° by occasional cooling. Decant from the acid layer, repeat the process once or twice, separate the acid, and proceed as in the purification of benzene.

Ethyl Acetate (b.p. 77.5°). — Commercial material may contain traces of water, ethyl alcohol, and acetic acid. Purification may be accomplished by washing with an equal volume of 5 per cent sodium carbonate solution, then with saturated calcium chloride solution, drying over anhydrous potassium carbonate, and distilling. Phosphorus pentoxide may be used for a final drying, after which the ethyl acetate is filtered and distilled with protection from moisture of the atmosphere.

Ligroin and Petroleum Ether. — These refined fractions from petroleum usually contain unsaturated hydrocarbons which ordinarily do not interfere with the use of the solvents for crystallizations but which are sometimes undesirable because of their reactivity. The bulk of the unsaturated substances can be removed by shaking with concentrated sulfuric acid, after which a test should be made with acid permanganate and, if there is any reaction, the hydrocarbon fraction should be shaken with a solution of potassium permanganate and sulfuric acid until all

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[10] *Ind. Eng. Chem.*, **26**, 172 (1934).

oxidizable substances have been destroyed. The solvent is then washed with water, dried over calcium chloride, and distilled. It is not advisable to use a fraction boiling over a range of more than 30° because in dissolving a solid there is some loss of the more volatile part of the solvent, and the substance, being more soluble in the higher-boiling residue, may not crystallize. Hexane fractions of narrow boiling range are available commercially and are particularly serviceable.

Carbon Bisulfide (b.p. 46.2°). — This common solvent (Friedel and Crafts reaction) and reagent is extremely inflammable and it has been known to ignite from being overheated on the steam bath. For the distillation of appreciable quantities it is advisable to use a pan of water warmed on the steam bath to just the required temperature. For the purification of crude carbon bisulfide Wieland and Bettag[11] recommend shaking with mercury, then with a cold, saturated solution of mercuric chloride followed by cold, saturated potassium permanganate solution, drying over phosphorus pentoxide, and distilling the product.

Carbon Tetrachloride (b.p. 76.7°). — Commercial material often contains carbon bisulfide, which may be removed by shaking at 60° with about one-tenth volume of a mixture of concentrated potassium hydroxide solution and alcohol. After two or three repetitions the carbon tetrachloride is washed with water, stirred at 25° with small portions of concentrated sulfuric acid until there is no further coloration, washed with water, dried over calcium chloride, and distilled. Phosphorus pentoxide may be used for a final drying.

As with other solvents which are immiscible with water, moisture may be removed effectively by distilling the wet solvent until the distillate is clear; the residue will then be completely anhydrous.

Carbon tetrachloride is a useful fire extinguisher but should not be applied to a sodium fire, for this may lead to an explosion.

Chloroform (b.p. 61.2°) may contain a trace of alcohol and it is purified by shaking with concentrated sulfuric acid, washing with

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[11] *Ber.*, **55**, 2249 (1922).

water, drying with calcium chloride, and distilling. (Do not dry with sodium as there is danger of an explosion.)

Methylene Chloride, CH_2Cl_2 (b.p. 40–41°), is a convenient substitute for ether where it is desired to employ an extraction solvent heavier than water.

Ethylene Chloride, CH_2ClCH_2Cl (b.p. 83–84°), has a selective solvent action which makes it an effective solvent for the extraction of steroids from biological materials.

s-Tetrachloroethane, $CHCl_2CHCl_2$ (b.p. 147°). — This is an excellent solvent for many substances which dissolve with difficulty in benzene, glacial acetic acid, etc., although it does not equal nitrobenzene. The pure liquid is inert to aluminum chloride and it serves as an excellent solvent for the Friedel and Crafts reaction, particularly since the solvent is very easily volatile with steam. A convenient method of removing a trace of colored impurity often persisting through several crystallizations of a higher aromatic hydrocarbon (e.g., chrysene) is to shake a solution of the substance in tetrachloroethane (warmed if necessary) with successive portions of concentrated sulfuric acid until no further color is extracted. A crude reaction product which does not dissolve well in the commoner solvents and which is likely to contain char is often conveniently purified by dissolving it in the solvent in question, clarifying the solution with active charcoal, and removing the solvent by steam distillation (example: benzanthrone prepared by the Bally-Scholl method). Here crude tetrachloroethane is satisfactory; for the other operations mentioned it is essential to use purified material.

For purification the crude liquid is warmed on the steam bath with crude, concentrated sulfuric acid (80 cc. per liter) and either shaken or stirred mechanically for one-half hour. After decanting the upper layer, the process is repeated once or twice until the acid liquor does not become discolored. The solvent is then separated, washed with water (or, better, steam distilled), dried with calcium chloride, and distilled.

Chlorobenzene (b.p. 132°) has a solvent action similar to that of benzene and toluene but considerably greater, and it is used for crystallizing sparingly soluble substances. It has been recommended as a solvent for carrying out the Fries rearrangement of a phenol acetate with aluminum chloride. Effective use has been made of the higher boiling and still more inert polychlorobenzenes in conducting reactions with polynuclear aromatic compounds.[12] **o-Dichlorobenzene** (b.p. 179°) serves well as solvent in the conversion of hydrocarbons into aldehydes by interaction with methylformanilide and phosphorus oxychloride,[12, 13] and **1,2,4-trichlorobenzene** (b.p. 213°) can be used in chlorinations.[12] The anthraquinone ring closure reaction has been conducted with **α-chloronaphthalene** (b.p. 259°) as the solvent and benzoyl chloride as the dehydrating agent.[12]

Nitrobenzene (b.p. 210°). — Nitrobenzene is a liquid of extremely great solvent power for many organic compounds and it often serves as a useful solvent for the crystallization of substances which dissolve to only a slight extent in the usual solvents. After the crystalline product is collected it should be washed thoroughly with benzene, alcohol, or ether in order to remove the nitrobenzene, for this otherwise adheres tenaciously to the crystals during attempted drying. The heating of the solution should be done on a hot plate under the hood as the vapor of the solvent is somewhat poisonous. One limitation to the use of this solvent is that at the boiling point it has a rather pronounced oxidizing action. Aluminum chloride is moderately soluble in nitrobenzene and does not attack it (except to form a labile molecular compound), and this is a good solvent for many Friedel and Crafts reactions, particularly at temperatures ranging from −15° to 25°.

Crude nitrobenzene may contain dinitrobenzene, and recovered solvent may contain aniline. Both substances, along with other impurities, are effectively removed by steam distillation from a mixture with dilute sulfuric acid. The solvent is then dried over calcium chloride and distilled.

Pyridine (b.p. 115°) is sometimes useful as a special solvent on

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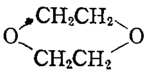
[12] Vollmann, Becker, Corell and Streeck, *Ann.*, **531**, 1 (1937).

[13] Fieser, Hartwell and J. E. Jones, "Organic Syntheses," **20**, 11 (1940).

account of its great dissolving power. It is an excellent solvent for use in the Zerewitinoff determination of the number of active hydrogen atoms in a compound through the measurement of the methane evolved on reaction with methylmagnesium iodide, or in the modified method[14] in which the amount of Grignard reagent consumed by an addition reaction is also determined. Anhydrous pyridine can be prepared by the distillation of commercial material from barium oxide with careful exclusion of moist air. Another method is to add phenylmagnesium bromide solution to the pyridine, evaporate the ether, and distil the pyridine. An alternate solvent for use in the modified Zerewitinoff determination of sparingly soluble substances consists in a mixture of diphenyl ether (solid) and xylene.[15]

Quinoline Substitute. — Because it is a basic substance and has a high boiling point (236°), quinoline has been found useful as a solvent in which to carry out decarboxylations,[16] and in the purification of low-boiling liquids containing traces of acids (e.g., thionyl chloride, page 381). The same purposes are well served by the much less expensive coal tar base fractions of suitable boiling-point range supplied by the Barrett Co., Philadelphia.

Dioxane, 
$O\left\langle\begin{matrix}CH_2CH_2\\CH_2CH_2\end{matrix}\right\rangle O$
(b.p. 101.3°, m.p. 11.8°). — Dioxane is an effective solvent for organic compounds of a wide variety of types; the solvent action is similar to that of ether but more pronounced. The fact that the substance is also miscible with water in all proportions renders it extremely useful for a number of special purposes. Although dioxane usually behaves as a neutral, indifferent solvent, it is capable of forming complexes of considerable stability which in some instances may interfere with the normal course of a reaction. Thus dioxane added to an ethereal solution of a Grignard reagent quantitatively precipitates the RMgX and MgX_2 components as complexes and

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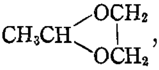
[14] Kohler and Richtmeyer, *J. Am. Chem. Soc.*, **52**, 3736 (1930).

[15] Schmitz-Dumont and Hamann, *Ber*, **66**, 71 (1933).

[16] Shepard, Winslow and Johnson, *J. Am. Chem. Soc.*, **52**, 2083 (1930).

leaves a solution of the MgR_2.[17] Phenolic substances when crystallized from dioxane frequently are found to separate in the form of more or less stable solvated complexes.

Commercial dioxane usually contains a certain amount of glycol acetal,  $CH_3CH\left\langle\begin{array}{l}OCH_2\\ \vert\\ OCH_2\end{array}\right.$, together with some water. On storage the acetal tends to undergo hydrolysis, and the liberated acetaldehyde gives rise to rapid peroxide formation. While the commercial solvent is entirely adequate for some purposes (vitamin K_1 synthesis, page 236; some crystallizations), other uses call for anhydrous, peroxide-free dioxane (high-pressure hydrogenations, sodium reactions). If the material contains only very small amounts of impurities, it may be possible to effect a satisfactory purification by refluxing the solvent for a day or two with adequate amounts of sodium, but if some of the glycol acetal escapes conversion into aldehyde gum, it may subsequently give rise to peroxide formation. Usually it is best to employ the process described below,[18] in which the glycol acetal is hydrolyzed and the acetaldehyde eliminated before the drying operation.

A mixture of 2 l. of commercial dioxane, 27 cc. of concentrated hydrochloric acid, and 200 cc. of water is refluxed for 12 hours, during which time a slow stream of nitrogen is bubbled through the solution to entrain the acetaldehyde. The solution is cooled and potassium hydroxide pellets are added slowly with shaking until they no longer dissolve, and a second layer has separated. The dioxane is decanted, treated with fresh potassium hydroxide pellets to remove adhering aqueous liquor, decanted into a clean flask, and refluxed with sodium for 10–12 hours, when the metal should remain bright. The solvent is then distilled from the sodium and best stored out of contact with air.

Ethylene Glycol Monomethyl Ether (Methyl Cellosolve), $CH_3OCH_2CH_2OH$ (b.p. 125.0°). — This solvent is miscible with

[17] Schlenk and Schlenk, *Ber.*, **62**, 920 (1929).

[18] Hess and Frahm, *Ber.*, **71**, 2627 (1938); see also Eigenberger, *J. prakt. Chem.*, **130**, 75 (1931).

water in all proportions, a property shared even by the commercially available *n*-butyl Cellosolve (b.p. 171.2°).

Ethylene Glycol Dimethyl Ether, $CH_3OCH_2CH_2OCH_3$ (b.p. 85°). — Like the analogously constituted dioxane, this substance is an effective solvent for water-insoluble organic compounds and is at the same time miscible with water. The interaction of aromatic hydrocarbons with metallic sodium is greatly facilitated by employing either this solvent or dimethyl ether (less conveniently handled, b.p. $-25°$).[19] Even naphthalene and diphenyl will add sodium in the presence of either of these special solvents, whereas no reaction occurs when diethyl ether is used.

Ethylene glycol diethyl ether (diethyl Cellosolve), b.p. 121.4°, dissolves in water to the extent of 21 per cent at 20°.

Diethylene Glycol Monomethyl Ether (Methyl Carbitol), $CH_3OCH_2CH_2OCH_2CH_2OH$ (b.p. 194.1°). — This solvent is miscible with water, as is the homologue butyl Carbitol (b.p. 230.7°).

DRYING AGENTS

The common drying agents are listed below together with some of the considerations which are of importance in the selection of one which will be suitable for a given purpose.

Calcium Chloride: large capacity for the absorption of water (forms the hexahydrate below 30°), not very efficient, particularly useful for preliminary drying. *Usually unsuitable for drying:* alcohols and amines (forms molecular compounds), phenols, esters, acids (contains lime).

Potassium Hydroxide (solid): very efficient and rapid, but limited almost entirely to use with amines.

Sodium (wire): very efficient but of use only with inactive, neutral compounds (ethers, saturated and aromatic hydrocarbons). The liquid or solution should be dried first with calcium chloride to remove the bulk of the water.

Caution: Every precaution must be taken in using sodium for drying purposes or as a reagent, for on no account must the

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[19] Scott, Walker and Hansley, *J. Am. Chem. Soc.*, **58**, 2442 (1936).

metal come in contact with water. A serious explosion may result from a leaky condenser or a flask which cracks when heated over a steam or water bath, and the apparatus must be tested in advance as to soundness. Sodium residues and cuttings should be transferred at once to a bottle provided for the purpose and filled with kerosene, and scraps must not be allowed to remain exposed and on no account are they to be thrown into the sink or the waste jar. From time to time the residues accumulating should be destroyed by adding the scraps in *small* portions to a rather large quantity of alcohol. After *all* the metal has reacted the solution is washed down the drain. Wire remaining after a drying operation is destroyed in the same way and *not* by pouring alcohol onto the wire.

Lead-sodium alloy [1] can be used in place of sodium for drying ether and other inflammable liquids. The alloy is easily prepared in a finely divided form and is less hazardous to handle than sodium.

Phosphorus Pentoxide: very efficient and rapid; for hydrocarbons, ethers, esters, nitrites, alkyl halides; not for alcohols, acids, amines, ketones.

Anhydrous Potassium Carbonate: fair efficiency and capacity (forms the dihydrate); for esters, nitriles, ketones; not for use with acidic substances.

Neutral Anhydrous Salts: Na_2SO_4, $MgSO_4$, $CaSO_4$. Being neutral, inert, and insoluble in organic liquids, these salts can be used for all types of compounds, including those which are sensitive to the other drying agents. *Sodium sulfate* is inexpensive and has a high capacity of absorption, since at temperatures below 33° it forms the hydrate $Na_2SO_4.10H_2O$, but the drying action is slow and not thorough. Anhydrous *magnesium sulfate* is somewhat more rapid and effective and it forms the heptahydrate below 48° and is thus capable of absorbing considerable quantities of water. Both the sodium and the magnesium salts may be obtained in an anhydrous condition by heating hydrated or partially hydrated material in a casserole over a wire gauze.

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[1] Soroos, *Ind. Eng. Chem., Anal. Ed.*, **11**, 657 (1939).

Anhydrous *calcium sulfate* prepared in a special way [2] is marketed under the trade name Drierite. An indicating form is available which turns from blue to red when exhausted. The reagent, which is called "soluble anhydrite" to distinguish it from the insoluble mineral of the same composition but different behavior, is prepared by heating either the dihydrate or the hemihydrate in an oven at 235° for 2–3 hours, and used material may be regenerated by the same process. The soluble salt reverts in drying to the hemihydrate, $CaSO_4 \cdot \frac{1}{2}H_2O$, and its capacity is limited to the absorption of only 6.6 per cent of its weight of water. The rapidity and efficiency of drying, however, are both very great. Added to a moist liquid, such as ordinary alcohol, the salt produces a marked rise in the temperature. In completeness of drying, Drierite stands between phosphorus pentoxide and concentrated sulfuric acid, and it is surpassed only by the former of these reagents. The reagent should find many uses, particularly when employed in combination with a primary drier.

Absorbent Cotton: an excellent drying agent [3] well suited for use in drying tubes placed at the top of reflux condensers or dropping funnels.[4] The cotton can be dried by heating it in an oven at 100°.

ALKYLATING AGENTS

Alkyl Iodides. — Methyl and ethyl iodide deteriorate rapidly with the liberation of iodine if exposed to the light, and commercial preparations which have been kept long in storage are often found to be quite dark and unsuitable for use. Such material can be purified, however, by shaking it with successive portions of a dilute solution of either sodium thiosulfate or sodium bisulfite until the color is completely bleached, washing with water, drying over calcium chloride, and distilling the product. The colorless distillate should be stored in a brown bottle and kept out of the direct sunlight. As a further pro-

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[2] Hammond and Withrow, *Ind. Eng. Chem.*, **25**, 653, 1112 (1933).

[3] Obermiller and Goertz, *Z. physik. Chem.*, **109**, 162 (1924).

[4] Adkins and Rainey, "Organic Syntheses," **20**, 9 (1940).

tective measure a few drops of clean mercury may be added, for the alkyl iodide will then keep almost indefinitely without becoming discolored, providing that it is not exposed for long periods to the light. Prolonged exposure in this case presents a certain danger, for appreciable quantities of the poisonous methylmercuric iodide may result from the photochemical reaction of the halide with the metal. With ordinary care no difficulty is experienced. A little mercury may be used also to remove a slight purple or pink color from a sample of an iodide which has just begun to decompose. Hartman[1] has described a convenient procedure for the preparation of methyl iodide from methyl sulfate and potassium iodide (90–94 per cent yield).

Alkyl bromides should be washed thoroughly with concentrated sulfuric acid and then with water, dried over calcium chloride, and distilled through a column.

***tert.*-Butyl Chloride.** — See page 180 for a method of preparation.

Alkyl Sulfates, $(RO)_2SO_2$. — Commercial methyl and ethyl sulfate are sometimes dark in color and often contain considerable amounts of the alkyl sulfuric acid $ROSO_2OH$, formed by hydrolysis. In the latter case a test portion shaken with cold water will diminish in volume and give at once a strong acid reaction. The acid sulfate does not interfere with the alkylating action of the remainder of the product, unless it is an alkylation involving the use of the Grignard reagent, but it makes uncertain the quantities of materials to be used. The acid sulfate is not volatile but undergoes decomposition to the normal sulfate on being heated:

$$2ROSO_2OH \longrightarrow (RO)_2SO_2 + H_2SO_4$$

The normal sulfate can be distilled satisfactorily at a somewhat reduced pressure, and a good method for the purification of either methyl or ethyl sulfate is to distil the crude material slowly at the pressure of a good water pump. The purified product should be stored in a glass-stoppered bottle sealed with paraffin, for it attacks corks.

Both methyl and ethyl sulfate are somewhat poisonous.

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[1] "Organic Syntheses," **18**, 88 (1938).

though not dangerously so. They should be kept off the skin and manipulated under the hood. They are of particular service for the alkylation of phenols and react only with difficulty with the more strongly acidic carboxylic acids. The alcoholic groups of a sugar can also be alkylated by this method. To convert a phenol into the methyl ether it is dissolved in a slight excess of warm alkali, dimethyl sulfate is added, and the mixture is heated on the steam bath and shaken or stirred mechanically. When the solution becomes acid to litmus more alkali is added, followed by a little dimethyl sulfate. The reagents are added alternately, allowing the solution to become acid frequently, until eventually no phenol precipitates on acidifying a test portion of the alkaline solution. An alternate method is to add the alkali slowly to a stirred mixture of the phenol and dimethyl sulfate.

Higher alkyl sulfates are likewise good alkylating agents, but they cannot be prepared satisfactorily by heating the alkyl sulfuric acid, as in the case of the methyl and ethyl derivatives. A method described by Barkenbus and Owen [2] involves the preparation of the corresponding alkyl sulfite as an intermediate. The process is generally applicable to the preparation of the neutral normal primary alkyl sulfates, regardless of the length of the carbon chain. The materials required are: the appropriate alcohol, sulfuryl chloride, and thionyl chloride.

Alkyl *p*-Toluene Sulfonates, *p*-$CH_3C_6H_4SO_2OR$. — Esters of this type may be obtained by the reaction of an alcohol with *p*-toluenesulfonyl chloride.[3] The esters are useful for certain alkylations and have been found to give good results where more usual reagents present certain difficulties.[4]

Diazomethane is an invaluable reagent for the methylation of carboxylic acids or other substances which are strongly or moderately acidic. It is a yellow gas and is ordinarily employed

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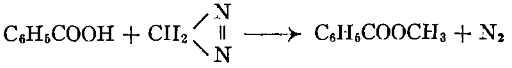
[2] *J. Am. Chem. Soc.*, **56**, 1204 (1934); Suter and Gerhart, "Organic Syntheses," **19**, 27, 29 (1939).

[3] Roos, Gilman and Beaber, "Organic Syntheses," Coll. Vol. I, 139 (1932); Sekera and Marvel, *J. Am. Chem. Soc.*, **55**, 345 (1933).

[4] Kanevska, *Arch. Pharm.*, **271**, 462 (1933).

in the form of an ethereal solution. When a substance such as benzoic acid is added to the solution there is an immediate evolution of gas and if enough is used the point of equivalence is apparent from the bleaching of the yellow color, the reaction being as follows:



$$C_6H_5COOH + CH_2{<}\begin{matrix}N\\ \| \\ N\end{matrix} \longrightarrow C_6H_5COOCH_3 + N_2$$

In practice an excess of diazomethane is employed and at the end of the very rapid reaction the unused material is removed by boiling off a part or all of the ether on the steam bath. Although the reagent is expensive, it provides a rapid and elegant method for the preparation of a small quantity of an ester in a very pure condition. The method is applicable in certain cases where other methods fail.

The rate of the reaction appears to be a function of the acidity of the hydroxyl group which is being methylated. The sulfonic and carboxylic acids and the nitrophenols react at once, ordinary phenols react only very slowly, and with alcohols the reaction usually is too slow to be useful. Catalysts, however, have a marked influence on the reaction. Although *n*-butyl alcohol is attacked but slightly by pure diazomethane, it can be methylated in good yield in the presence of a small amount of aluminum *n*-butoxide.[5] Diazomethane is an actively unsaturated compound capable of entering into many reactions other than that of methylation. It reacts with certain aldehydes, ketones, and acid chlorides, and with compounds containing a particularly reactive ethylenic linkage. When a rather strongly acidic group and an active point of unsaturation are both present in the molecule, the acidic group usually reacts so much more rapidly than the other that the compound can be methylated without difficulty.

Liquid diazomethane, b.p. −24°, is an explosive substance, and explosions may occur in the gaseous state if the material is

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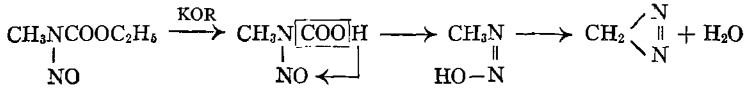
[5] Meerwein and co-workers, *Ber.*, **61**, 1840 (1928); **62**, 999 (1929); *Ann.*, **484**, 1 (1930).

dry and undiluted. The liquid is not required for ordinary work, however, and the gas can be handled with safety by diluting it with nitrogen. However it is prepared, diazomethane is best dissolved at once in ether, for the ethereal solution is entirely safe and this is the most convenient form in which to employ the reagent. The ethereal solution if anhydrous can be kept for a day or two, but it undergoes gradual decomposition with the liberation of gas; the containing vessel must not be stoppered tightly but should be protected with a calcium chloride tube and kept in a cold place. It is well to prepare fresh reagent when required and to use it at once. Diazomethane is poisonous, but with reasonable care no difficulty should be experienced in handling an occasional small quantity. In work requiring the continued use of the reagent there is danger of developing a supersensitivity to attacks of asthma and fever. Special care must also be taken in handling nitrosomethylurethane (see below).

Several good methods have been described for the preparation of diazomethane and the choice depends somewhat upon the availability and current prices of the starting materials. The method listed below as 1(a) is perhaps the simplest when only small quantities are required and when the presence of methyl alcohol and moisture in the ethereal solution is not objectionable; methods 1(b) and 2 yield an absolute ethereal solution of the reagent. In some cases, as in ordinary methylations, methyl alcohol acts as a catalyst, and where two or more modes of reaction are possible the presence or absence of this catalyst may control the course taken. Method 4 is applicable to the preparation of higher diazohydrocarbons.

1. From Nitrosomethylurethane, $CH_3N(NO)COOC_2H_5$ (also called Ethyl Nitrosomethylcarbamate). — The conversion of this substance into diazomethane by the action of a potassium alcoholate may be represented as follows:



$$\begin{array}{l}CH_3NCOOC_2H_5\\ \ \ \ \ \mid\\ \ \ \ NO\end{array} \xrightarrow{KOR} \begin{array}{l}CH_3N\boxed{COO}H\\ \ \ \ \ \mid\\ \ \ \ NO\end{array} \longrightarrow \begin{array}{l}CH_3N\\ \ \ \ \ \|\\ HO-N\end{array} \longrightarrow CH_2\left\langle\begin{array}{c}N\\ \|\\ N\end{array}\right. + H_2O$$

The procedures below differ only in that the alcohol used as solvent is a volatile one in the first case and a non-volatile one in the second case.

(a) *Method of v. Pechmann.*[6] — The reaction is carried out in a 100-cc. distilling flask with a high side arm connected to an efficient condenser (a bulb or coil condenser set in the vertical position). In the flask is placed 1.2 cc. of 25 per cent methyl alcoholic potassium hydroxide and about 10 cc. of ether (ordinary). The flask is provided with a small dropping funnel with the stem extending well below the side arm and in this is placed 15–20 cc. of ether, followed by 1 cc. of nitrosomethylurethane (*caution*, see below). The flask is heated gently on the steam bath and the solution is run in from the dropping funnel at about the rate at which ether distils from the reaction vessel. The diazomethane formed is carried over with the ether and the yellow distillate is collected in a flask cooled in an ice bath. Some additional ether is used to rinse the dropping funnel and the distillation is continued until the condensate becomes colorless. The diazomethane in the ethereal solution amounts to about 0.2 g. or 0.005 mole (56 per cent yield). The solution contains methyl alcohol and moisture. Quantities up to about five times this amount can be prepared in a flask of the size specified. For the production of 10 g. of diazomethane about 57 g. of nitrosomethylurethane is required.

NOTE: Nitrosomethylurethane, b.p. 60°/10 mm., density 1.133 at 20°, is a commercial product. A satisfactory method of preparation is given by Hartman and Phillips.[7] This substance is an extremely active skin irritant and it must be manipulated with great care. It produces no immediate sensation on the skin, but a troublesome, painful rash develops after a few hours. If applied soon enough, alcohol will wash off most of the material.

(b) *Modification of Meerwein.*[8] — Nitrosomethylurethane (5 cc.) is dropped into 10 cc. of a 6 per cent solution of sodium in

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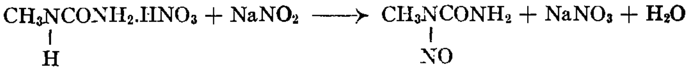
[6] *Ber.*, **28**, 855 (1895).

[7] "Organic Syntheses," **13**, 84 (1933).

[8] Meerwein and Burneleit, *Ber.*, **61**, 1845 (1928).

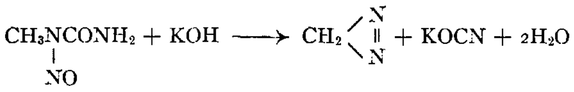
glycol and a stream of nitrogen is passed through the apparatus in order to sweep the diazomethane produced into absolute ether or else directly into the reaction vessel.

2. **From Nitrosomethylurea.** — This substance may be obtained by the action of sodium nitrite on methylurea nitrate (commercially available):



$$\mathrm{CH_3}\underset{\substack{| \\ \mathrm{H}}}{\mathrm{N}}\mathrm{CONH_2.HNO_3} + \mathrm{NaNO_2} \longrightarrow \mathrm{CH_3}\underset{\substack{| \\ \mathrm{NO}}}{\mathrm{N}}\mathrm{CONH_2} + \mathrm{NaNO_3} + \mathrm{H_2O}$$

Nitrosomethylurea is a rather unstable compound but enough of it for several batches of diazomethane can be prepared at one time and, if proper precautions are taken, the material can be stored for several months. For conversion to diazomethane the nitrosomethylurea is shaken in the cold with a mixture of aqueous potassium hydroxide solution and pure ether. The reaction is complete in 1–2 minutes and the yellow ethereal solution is decanted and dried over solid potassium hydroxide. As an alternate procedure, the diazomethane may be distilled with ether from the aqueous layer. The reaction may be represented as follows:

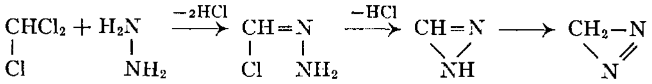


$$\mathrm{CH_3}\underset{\substack{| \\ \mathrm{NO}}}{\mathrm{N}}\mathrm{CONH_2} + \mathrm{KOH} \longrightarrow \mathrm{CH_2}\left\langle \begin{array}{c}\mathrm{N} \\ \| \\ \mathrm{N}\end{array}\right. + \mathrm{KOCN} + 2\mathrm{H_2O}$$

The yield is good (65 per cent) and this is an excellent method for the preparation of a dry solution of the reagent in pure ether. Full details of the procedure, together with directions for the preparation of nitrosomethylurea starting with ammonia, methylamine, or acetamide are given by Arndt.[9] About 90 g. of methylurea nitrate is required to produce 10 g. of diazomethane.

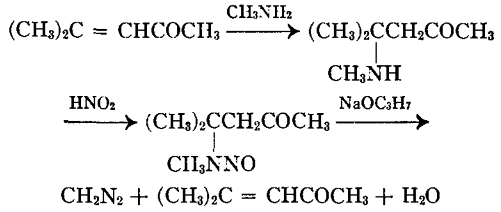
3. **From Hydrazine and Chloroform.** — In the presence of alcoholic potassium hydroxide solution these reagents combine in the following manner:

[9] Arndt and Amende, *Z. angew. Chem.*, **43**, 444 (1930); Arndt and Scholz, *ibid.*, **46**, 47 (1933); Arndt, "Organic Syntheses," **15**, 3 (1935).



Chloroform is run into a hot solution of hydrazine hydrate and potassium hydroxide in absolute alcohol and the diazomethane is swept out of the reaction mixture with a current of hydrogen and dissolved in absolute ether, the solvent being largely retained by a reflux condenser.[10] The yield is about 20 per cent of the theoretical amount, and 60 g. of anhydrous hydrazine hydrate is required for the preparation of 10 g. of diazomethane.

4. From the Addition Product of Mesityl Oxide and Methylamine.[11] — The reaction sequence is indicated in the formulas:



$$(CH_3)_2C = CHCOCH_3 \xrightarrow{CH_3NH_2} (CH_3)_2\underset{CH_3NH}{\underset{|}{C}}CH_2COCH_3$$

$$\xrightarrow{HNO_2} (CH_3)_2\underset{CH_3NNO}{\underset{|}{C}}CH_2COCH_3 \xrightarrow{NaOC_3H_7}$$

$$CH_2N_2 + (CH_3)_2C = CHCOCH_3 + H_2O$$

The methylamine addition product of mesityl oxide is not isolated but is neutralized with acetic acid and converted into the nitroso derivative. This is cleaved by the action of sodium isopropoxide into mesityl oxide and diazomethane, which is obtained in overall yield of about 45 per cent. Other primary amines can be employed in place of methylamine and the method is thus well adapted to the preparation of higher diazohydrocarbons.

Determination of the Diazomethane Content. — The amount of reagent in an ethereal solution can be determined by diluting an aliquot portion of the solution and adding it slowly to a cold, measured quantity of a 0.2*N* solution of benzoic acid in absolute ether, the benzoic acid solution used being more than sufficient to react with all of the diazomethane (colorless at the end). Water is added and the excess benzoic acid is titrated with 0.1*N* sodium hydroxide solution.

[10] Staudinger and Kupfer, *Ber.*, **45**, 505 (1912).

[11] E. C. S. Jones and Kenner, *J. Chem. Soc.*, 363 (1933); Adamson and Kenner, *ibid.*, 286 (1935).

ACYLATING AGENTS

Acetic Anhydride (b.p. 136.4°). — The reagent often deteriorates as the result of improper storage and it is well to test it either in a preliminary, small-scale run or by shaking a sample with ice-water and rapidly titrating the free acetic acid. A satisfactory purification can be effected by careful fractionation, and if the material is of a practical grade it is well to distil it first from fused sodium acetate in order to eliminate halogen compounds and metals.

Acetyl Chloride (b.p. 51°). — Student preparations of this reagent are likely to contain free hydrogen chloride and low-boiling esters containing phosphorus. After a preliminary distillation, in case it is very crude, the material is mixed with about one tenth its volume of dimethylaniline and fractionated. This removes both types of impurities and gives a clear product which will not react with sodium.

Benzoyl Chloride (b.p. 197°). — See page 194.

Benzenesulfonyl Chloride (m.p. 14.5°, b.p. 120°/10 mm.). — Three methods of preparation are described in "Organic Syntheses."[1] Benzenesulfonyl chloride solidifies at 13–14°; impure material should be distilled at the water pump.

***p*-Toluenesulfonyl Chloride** (m.p. 69°, b.p. 146°/15 mm.). — The crude (technical) material can be purified by dissolving it in benzene, shaking the solution with dilute alkali, drying it over potassium carbonate, removing the solvent, and distilling the product at the pressure of the water pump.

Other Acid Chlorides. — Probably the most generally applicable method of converting an acid into the acid chloride is by treatment with phosphorus tri- or pentachloride (page 76). Thionyl chloride (page 76) sometimes proves to be a slightly more convenient reagent, particularly when the product can be distilled, but in some instances it gives rise to side reactions. It is difficult to remove traces of thionyl chloride from a nonvolatile acid chloride, and the material retained may cause difficulties

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[1] "Organic Syntheses," Coll. Vol. I, 77 (1932).

in a subsequent reaction. Commercial phthaloyl chloride, employed in combination with a trace of zinc chloride as catalyst, has been used with success for the preparation of succinoyl chloride and fumaryl chloride.[2]

OTHER REAGENTS

Thionyl Chloride (b.p. 77°). — Commercial preparations of this reagent often contain traces of acids and other impurities which interfere with the smooth conversion of an acid into an acid chloride, and a dark, tarry product may result unless they are removed by the following simple and effective process. The crude thionyl chloride (50 cc.) is mixed thoroughly in a round-

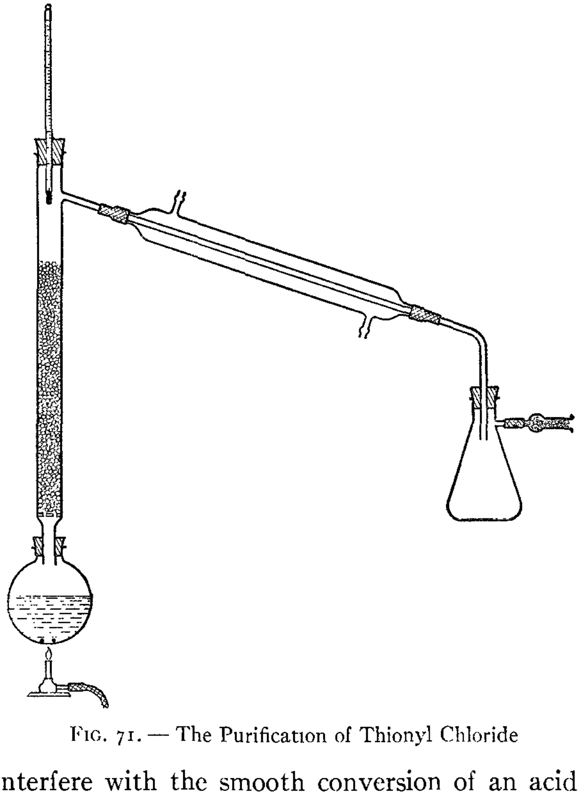

FIG. 71. — The Purification of Thionyl Chloride

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[2] Kyrides, *J. Am. Chem. Soc.*, **59**, 206 (1937); "Organic Syntheses," **20**, 51 (1940).

bottomed flask with 10 cc. of quinoline or a suitable substitute (see page 368), a boiling chip is added and the flask is arranged for distillation with a column in the manner shown in Fig. 71. The distillate is kept out of contact with corks and is protected with a calcium chloride tube. After distillation from the quinoline, which removes acids, the thionyl chloride is mixed in a clean flask with 20 cc. of raw linseed oil (refined grade, unboiled) and fractionated from it in the above apparatus. The distillate is colorless and of a high degree of purity.

Ethyl Formate (b.p. 54°). — When required for use in the Grignard synthesis of a dialkyl carbinol,[1] the commercial ester should be dried over potassium carbonate, then over phosphorus pentoxide, and distilled.

Dimethylaniline (m.p. 2°, b.p. 193°). — Monomethylaniline, the usual contaminant, can be eliminated, if present in small amounts, by adding a small quantity of acetic anhydride and fractionally distilling. The secondary amine present is converted into the less volatile acetyl compound and the acetic acid formed is retained as a salt. A rise in temperature on adding the acetic anhydride indicates the presence of the secondary (or even primary) amine; with the pure tertiary amine there is a lowering in the temperature. The acetylation also can be followed by extraction of the tertiary amine with dilute mineral acid.

Aniline (b.p. 184.4°). — The color can be removed from old samples most effectively by distilling the material from a small amount of zinc dust.

Ethylene Oxide (b.p. 14°). — This is available in small cylinders. The gas is passed through a short tower filled with soda lime and then either passed directly into the reaction mixture or condensed to a liquid in a spiral condenser packed with salt and ice.

Acetylene. — For the purification and technique of handling this gas see Reichert and Nieuwland.[2]

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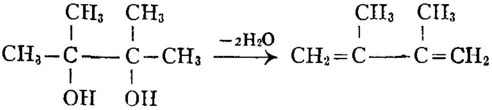
[1] For an example see Coleman and Craig, "Organic Syntheses," **15**, 16 (1935).

[2] "Organic Syntheses," Coll. Vol. I, 224 (1932).

Aldehydes: formaldehyde, page 82; acetaldehyde, page 79; benzaldehyde, page 224. For the recovery of aldehydes or ketones from their bisulfite addition compounds in cases where a mineral acid or a base might lead to side reactions, the addition compound can be cleaved smoothly by warming a solution of the substance at 100° with a slight excess of formaldehyde.[3]

2,3-Dimethylbutadiene-1,3 (b.p. 70°). — This diene can be prepared easily by the dehydration of pinacol (page 97):



$$CH_3-\underset{OH}{\overset{CH_3}{C}}-\underset{OH}{\overset{CH_3}{C}}-CH_3 \xrightarrow{-2H_2O} CH_2=\overset{CH_3}{C}-\overset{CH_3}{C}=CH_2$$

The dehydration can be accomplished by the catalytic method of Kyriakides:[4] slow distillation in the presence of a small amount of hydrobromic acid. With any but small quantities, however, careful temperature control over a long period is required, the catalyst may distil out of the reaction mixture, and the procedure is in general unreliable. A much better method is by the rapid distillation of anhydrous pinacol over alumina at 450–470°, preferably at diminished pressure.[5] A 70 × 3 cm. Pyrex tube packed with 8-mesh alumina is inserted in an electrically heated furnace[6] and connected at one end to a distillation flask and at the other to a vertical coil condenser delivering into a suction flask, cooled in salt-ice, to catch the bulk of the water formed. The side tube of this flask is connected by means of a short length of suction tubing to a wide tube delivering into a second suction flask cooled in a bath of

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[3] Barbot, *Compt. rend.*, **203**, 728 (1936).

[4] *J. Am. Chem. Soc.*, **36**, 992 (1914).

[5] Improved procedure developed by L. W. Newton and R. C. Coburn.

[6] A suitable furnace can be constructed by wrapping a 3-ft. length of 1½-inch iron pipe with asbestos paper and winding on about 48 ft. of No. 18 B. and S. gauge nichrome resistance wire. The whole is enclosed in a length of steam pipe insulation and mounted in a wooden frame. The temperature is recorded with a thermometer or thermocouple inserted alongside the alumina tube. When used in conjunction with a Variac, the winding specified will provide for a temperature of 470° with a Variac setting of about 90 volts. The furnace can be made more generally serviceable by adding another winding of resistance wire (40 ft., No. 28 B. and S. gauge) to provide for low heat.

dry ice and methanol contained in a Dewar flask. The assembly is completed by connecting the receiving flask through a manometer to a water pump, with which the whole system is evacuated. The alumina tube is heated to 470° and pinacol is distilled through it at the rate of about 100 g. in 15 minutes, while more heat is applied in order to keep the temperature from falling below 420°. The bulk of the water formed is caught in the ice trap and the dimethylbutadiene condenses and solidifies in the dry ice trap. At the end of the reaction the receiver is removed and the hydrocarbon allowed to melt; the flask is then reinserted in the cooling bath just long enough to freeze the water present, and the hydrocarbon layer is decanted, dried over sodium sulfate, and distilled through a column. The yield of dimethylbutadiene, b.p. 67–70°, is 84–87 per cent of the theoretical amount. The alumina darkens somewhat in usage but is easily regenerated. At the end of each run the tube is maintained at a temperature of 450–470° and a slow stream of air is drawn through it until the catalyst is white (2–3 hours).

When the dehydration is conducted at atmospheric pressure the yield is only 60–70 per cent and pinacolone (b.p. 106°) usually is obtained as a by-product. When pinacolone is distilled through the tube in vacuum as above the yield of dimethylbutadiene is 70–77 per cent. The crude pinacolone accumulating from the student preparation (page 100) may be used as a convenient source of dimethylbutadiene. If pinacol is available in the form of the hydrate (page 97), the water can be removed by slow fractionation up to a temperature of about 115° (rework the distillate); the anhydrous material is then distilled, b.p. 170°. Since dimethylbutadiene polymerizes rather easily, the material should be treated with a little hydroquinone (antioxidant) and stored in a refrigerator.

Piperylene (b.p. 43–45°) can be prepared by the same procedure in 84 per cent yield from the carbinol resulting from the addition of methylmagnesium chloride to crotonaldehyde. **Butadiene** (b.p. −5°) is available commercially in small cylinders.

Sodium ethoxide (alcohol-free) is conveniently prepared by the method of Brühl,[7] with a slight modification. About 25 cc. of purified xylene is poured into a 100-cc. round-bottomed, long-necked flask and 11.5 g. of cleanly cut sodium is quickly weighed and added. A cork is inserted loosely and the flask is placed in a sand bath and heated until the rim of boiling xylene rises to the top of the neck. The flask is removed and wrapped in towels, the stopper is inserted, and the flask is shaken five or six times in the direction of its length, giving a sharp whip to each stroke. A little air is admitted and the mixture is allowed to cool. Too much shaking often causes the particles to coalesce. In a successful operation a very finely divided, even powdery, metal results and it has a bright appearance. Often the product is more properly described as "bird shot" sodium, and it is rather gray. If larger lumps are present the heating and shaking should be repeated.

When the flask has cooled the xylene is decanted and the sodium is washed twice with absolute ether by decantation. The flask is filled with fresh absolute ether and the contents poured into a 1-liter round-bottomed flask. Enough more ether is added to bring the volume to about 300 cc., a condenser provided with a tube packed with calcium chloride and soda lime is attached, and 29.2 cc. of absolute alcohol is added in 5–6 portions through the condenser. When all the alcohol has been added a Bunsen valve is attached at the top of the system and, when the reaction begins to subside, the mixture is refluxed for 6–7 hours to complete the reaction and to use up all the sodium. The hydrogen evolved serves to protect the metal from becoming oxidized (yellow color). After cooling, the flask is transferred to a large vacuum desiccator containing calcium chloride and the ether is removed completely at the pump. The sodium ethoxide is obtained as a white powder. Sodium methoxide may be prepared by the same procedure; the reagent is available commercially

Sodium Ethoxide Solution (10 per cent).[8] — A 2-l. flask

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[7] *Ber*, **35**, 3516 (1902), **37**, 2067 (1904)

[8] Communicated by Dr Max Tishler

equipped with a dropping funnel and an efficient condenser protected with a calcium chloride tube is charged with 23 g. (1 mole) of freshly cut sodium (it is advantageous, if not essential, to pass a slow stream of dry nitrogen into the flask during the reaction). Three hundred cc. of absolute alcohol is allowed to run in intermittently, the rate of addition being such that rapid refluxing is maintained. After all the alcohol has been added, the mixture is heated on the steam bath until the sodium has reacted completely. The process takes 2–3 hours. Sodium methoxide solution can be prepared in the same way.

Fused Sodium Acetate. — Anhydrous sodium acetate is available commercially in a colorless grade of high purity and suitable for most purposes. Freshly dehydrated material is best prepared by fusion of the crystalline hydrate, $CH_3COONa.3H_2O$. This is heated in a casserole over a flame, when the salt first dissolves in its own water of crystallization and then, as the water evaporates, solidifies. Heating is continued carefully, to avoid charring the product, but strongly enough to melt the solid and drive off all remaining water. The hot melt is then poured onto a square of Transite board or other clean surface and broken and pulverized while it is still warm and easily ground. It is stored in a tightly stoppered bottle.

Anhydrous Hydrogen Cyanide. — Although hydrogen cyanide is an active poison, the reagent can be prepared in quantities up to 0.5 kg. without difficulty or undue danger if a good hood is available and if proper care is taken in the operation. Satisfactory methods are described by Ziegler[9] and by Slotta.[10]

Anhydrous hydrogen cyanide is used chiefly in the synthesis of hydroxyaldehydes according to Gattermann:

$$\text{HC}\equiv\text{N} + \text{HCl} \longrightarrow \text{ClCH}=\text{NH}$$

$$\text{HO.C}_6\text{H}_5 + \text{ClCH}=\text{NH} \xrightarrow[-\text{HCl}]{\text{ZnCl}_2} p\text{-HO.C}_6\text{H}_4\text{.CH}=\text{NH}$$

$$\xrightarrow{\text{H}_2\text{O}} p\text{-HOC}_6\text{H}_4\text{.CH}=\text{O} + \text{NH}_3$$

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[9] "Organic Syntheses," Coll. Vol. I, 307 (1932).

[10] *Ber.*, **67**, 1028 (1934).

The phenol is treated in anhydrous ether solution with anhydrous hydrogen cyanide and dry hydrogen chloride; the imide separates as a hydrochloride and is hydrolyzed by an aqueous acid. Phenol ethers, as well as some phenols, react with difficulty unless the zinc chloride is replaced by the more active aluminum chloride, when a satisfactory transformation usually is accomplished.

Adams[11] modified the Gattermann synthesis in such a way as to avoid the use of anhydrous hydrogen cyanide. In this method hydrogen chloride is passed into a mixture of the phenol and zinc cyanide in ether. The reagent, hydrogen cyanide, and the catalyst, zinc chloride, are produced in the reaction flask at the time required. Anhydrous aluminum chloride can be added where a more active catalyst is required. This modified method usually, if not invariably, gives as good results as the original one.

Liquid Hydrogen Fluoride (b.p. 19.4°). — Liquid hydrogen fluoride containing only 0.1–0.2 per cent water is available commercially in steel cylinders. The liquid reagent has a powerful solvent action for many organic compounds, particularly for oxygen-containing substances and for aromatic hydrocarbons and their derivatives. It is an effective dehydrating and condensing agent, often exhibiting an action comparable with that of concentrated sulfuric acid, and it is less prone than the latter acid to give rise to secondary or side reactions, such as enolization and aromatic substitution. Liquid hydrogen fluoride functions similarly to aluminum chloride or boron fluoride as a catalyst for certain alkylations and acylations, and it sometimes serves as a promoter for polymerization reactions.[12] One important synthetic use of the reagent is in the preparation of ketones of the α-hydrindone, α-tetralone, and anthrone types by cyclization of the appropriate acids.[13] Other significant applications arise from the fact that the orientation in both intramolecular cycliza-

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[11] Adams and Levine, *J. Am. Chem. Soc.*, **45**, 2373 (1923); Adams and Montgomery, *ibid.*, **46**, 1518 (1924).

[12] See review by Simons, *Ind. Eng. Chem.*, **32**, 178 (1940).

[13] Fieser and Hershberg, *J. Am. Chem. Soc.*, **61**, 1272 (1939); **62**, 49 (1940).

tions and intermolecular acylations is sometimes different from that in the Friedel and Crafts procedure.[13]

Hydrogen fluoride is highly corrosive to tissue and should be handled with care and not breathed. When spilled on the skin it produces severe burns which only become apparent through pain some 5–8 hours later. Parts known or suspected to have been in contact with the reagent should be treated immediately, first by thorough washing with water and then by application of a paste of magnesia, water, and glycerol. When these precautions are kept in mind, hydrogen fluoride can be handled safely and easily and is a very useful addition to the usual list of research reagents.

Reactions which proceed satisfactorily at room temperature can be carried out in a platinum crucible or, with larger amounts, in an open copper flask. The hydrogen fluoride cylinder is stored in a cold place (5°) until required, when it is removed and fitted with a copper delivery tube. The vessel containing the organic reactants is tared on a rough balance in the hood, the tank is inverted and the required weight of hydrogen fluoride is run in (use goggles and rubber gloves). The material usually dissolves at once or on brief stirring with a metal spatula, and the reaction may be complete in 10–20 minutes, or at least before the bulk of the reagent has evaporated. The excess reagent may be evaporated by gentle heating over a steam bath or in a current of air, or the solution may be poured into water and a little ice in a beaker and the product quickly collected by suction filtration or by ether or benzene extraction, followed immediately by a washing with soda solution. For use at higher temperatures (100°), a pressure vessel can be constructed from a welded steel cylinder fitted with a stainless steel condenser tube carrying a glass water jacket and connected through the condenser to a stainless steel gauge and a steel receiver into which the excess reagent can be distilled at the end of the reaction.[13]

Cyanogen Bromide. — The reagent is of use in the degradation of nitrogen-containing ring compounds by the method of

v. Braun.[14] Although the substance is toxic, and may become extremely unpleasant when improperly handled, it can be prepared easily and without difficulty if proper care is taken. The molten material should be manipulated in a hood and it is best to wear a gas mask when working with large quantities. Improved methods of preparation are described by Hartman and Dreger [15] and by Slotta.[16]

Iodine monobromide is a mild brominating agent and has been employed for effecting aromatic substitutions. A solution suitable for use is prepared by the interaction of bromine and iodine in acetic acid at 50°.[17]

Iodine monochloride, prepared by passing chlorine into iodine,[18] is an iodinating agent. An example of its use is in the iodination of anthranilic acid in acetic acid solution.[19]

Boron Fluoride (b.p. −101°). — The reagent is available in cylinders and can be bubbled into a reaction mixture. Aromatic hydrocarbons can be alkylated by condensation with an alcohol in the presence of boron fluoride.[20] The reaction resembles the Friedel and Crafts condensation in that normal and iso alkyl groups are isomerized in the process to secondary and tertiary substituents, respectively. In the dialkylation of benzene, however, boron fluoride leads to the formation of the *p*-isomer as the chief product, whereas with aluminum chloride as catalyst the *m*-dialkylbenzene predominates.

Another use of the reagent is illustrated by the preparation of acetylacetone by the condensation of acetone with acetic anhydride in the presence of boron fluoride.[21]

Sodium Aluminum Chloride. — Certain condensations and dehydrations requiring rather drastic conditions can be accom-

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[14] *Ber.*, **40**, 3914 (1907); **42**, 2219 (1909); **44**, 1252 (1911).

[15] "Organic Syntheses," **11**, 30 (1911).

[16] *Ber.*, **67**, 1028 (1934).

[17] Militzer, *J. Am. Chem. Soc.*, **60**, 256 (1938).

[18] Sandin, Drake and Leger, "Organic Syntheses," **12**, 29 (1932).

[19] Wallingford and Krueger, "Organic Syntheses," **19**, 52 (1939).

[20] McKenna and Sowa, *J. Am. Chem. Soc.*, **59**, 470 (1937).

[21] Meerwein and Vossen, *J. prakt. Chem.*, **141**, 149 (1934); Denoon, "Organic Syntheses," **20**, 6 (1940).

plished effectively with the use of fusible mixtures of sodium chloride and aluminum chloride. A procedure employed for effecting the cyclodehydration of γ-keto acids,[22] for conducting the Scholl condensation of a *peri*-aroylnaphthalene to a benzanthrone,[23] and for the synthesis of naphthazarin by the condensation of hydroquinone with maleic anhydride,[24] consists in heating a mixture of 1 part of sodium chloride with 5 parts of aluminum chloride over a free flame until molten, allowing the melt to cool until it begins to solidify (about 100°), adding the substance or substances to be condensed, and heating the mixture in an oil bath with occasional stirring at the desired temperature (120–180°). A preformed reagent of the composition $NaCl.AlCl_3$ may be employed for the dehydration of amides.[25] One part of sodium chloride and 2.28 parts (1 equiv.) of aluminum chloride are heated in a flask at 230–250° for 1 hour and the melt is poured into a beaker and stirred to a meal as it solidifies; the solid is kept in a well-stoppered bottle and powdered before use. An aromatic or aliphatic amide is heated cautiously with 0.03–0.20 mole of sodium aluminum chloride over a free flame until the evolution of hydrogen chloride nearly ceases and the nitrile is then distilled from the charred residue (60–90 per cent yields).

INORGANIC GASES

Ammonia. — The gas may be obtained from a cylinder of liquid ammonia or generated in the apparatus shown in Fig. 72. Concentrated ammonia water (sp. gr. 0.89) is heated in *a* with a very small flame at first and then more strongly and the gas evolved is dried in a tower of soda lime (*b*). A trap (*c*) is introduced just before the flask (*d*) in which the ammonia is to be

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[22] I. G. Farbenind., English Patent 303,375 (1930); French Patent 636,065 (1928); Swiss Patent 131,959 (1929); Gruene, U. S. Patent 1,759,111 (1930); Fieser, *J. Am. Chem. Soc.*, **53**, 3546 (1931); Fieser and Peters, *ibid.*, **54**, 3742, 4347 (1932); Fieser and Fieser, *ibid.*, **55**, 3342 (1933).

[23] Fieser and Hershberg, *J. Am. Chem. Soc.*, **60**, 1658 (1938).

[24] Zahn and Ochwat, *Ann.*, **462**, 81 (1928).

[25] Norris and Klemka, *J. Am. Chem. Soc.*, **62**, 1432 (1940).

absorbed in the reaction mixture or in a solvent, and the tubes are so arranged that any liquid sucked back into the trap will eventually find its way again into the absorption vessel.

Carbon Dioxide. — Gaseous carbon dioxide suitable for some purposes but containing air may be obtained from a cylinder of the liquid material or by the evaporation of dry ice from a bottle wrapped with a towel and fitted with a stopper carrying a gas outlet and a Bunsen valve for the release of excess pressure. The gas also may be generated by dropping hydrochloric acid (1 : 1) onto lumps of marble, as shown in Fig. 73, or, where small amounts of gas are required over a long period, with the use of a Kipp, Ostwald, or other standard form of generator. For use in the Dumas method for the determination of nitrogen, where traces of air are objectionable, the marble is boiled with water before use or replaced by either potassium carbonate or sodium bicarbonate. A convenient dry ice generator suitable

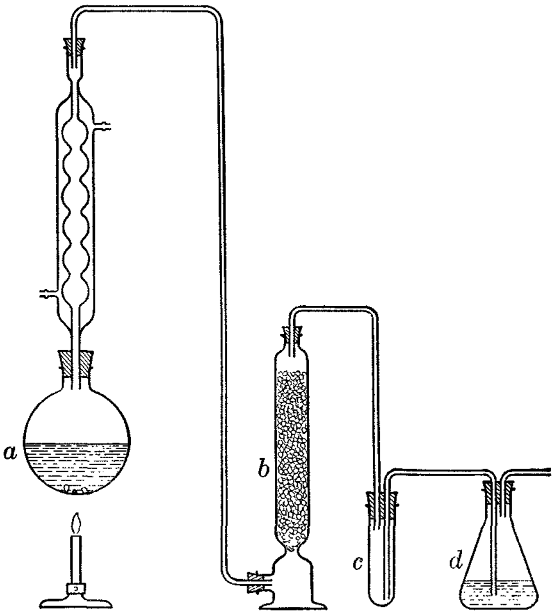

FIG. 72. — The Preparation of Dry Ammonia

for use in the micro-Dumas determination of nitrogen is described by Hershberg and Wellwood.[1]

Carbon monoxide is conveniently prepared by dropping 85–90 per cent formic acid into concentrated sulfuric acid contained in a 1-liter distilling flask which serves as the generator. A condenser tube fitted with a dropping funnel and extending 2 cm. below the surface of the acid provides for good mixing. The flask is heated in a water bath kept at 60–70° in order to promote an even flow of gas on dropping in the formic acid. The gas is passed through a drying tower filled with potassium hydroxide pellets.

Chlorine. — When 25–50 g. of gaseous chlorine is to be passed into a reaction mixture it is convenient to use one of the small cylinders of liquid chlorine and to follow the addition by the loss in weight of the cylinder. For smaller quantities, or where more exact control is required, it is preferable to generate the chlorine according to the method of Graebe.[2] The calculated amount of solid potassium permanganate is placed in a distilling flask with a high side arm which serves as the gas exit tube. Concentrated hydrochloric acid diluted with one fourth its volume of water is added from a dropping funnel, the stem of which runs nearly to the bottom of the flask and is drawn down and bent upwards at the extremity. The chlorine evolved is passed through a wash bottle containing water to remove hydrogen chloride and then it is dried in a sulfuric acid wash bottle. A safety trap to relieve excessive gas pressure, consisting of a T-tube with a long arm dipping into concentrated sulfuric acid, comes next in line and the gas is then passed into the reaction vessel. The acid solution is run in slowly at room temperature

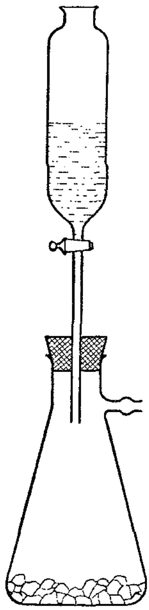

FIG. 73. — Carbon Dioxide Generator

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[1] *Ind. Eng. Chem., Anal. Ed.*, **9**, 303 (1937).

[2] *Ber.*, **35**, 43 (1902).

until about half of it has been added; when the gas evolution begins to slacken the mixture in the generating flask is heated with a small flame at first and then nearly to boiling in order to complete the reaction. For each gram of potassium permanganate 6.2 cc. of concentrated hydrochloric acid is used (excess), and the theoretical yield is 1.12 g. of chlorine. The actual yield does not fall far short of this amount and the recovery is practically quantitative if the chlorine is swept out of the flask and bottles with a stream of carbon dioxide.

Hydrogen Bromide. — Gaseous hydrogen bromide may be prepared by dropping bromine into boiling tetralin,[3] but the removal of traces of bromine and of hydrocarbon from the gas stream is rather troublesome. A better method is by the direct combination of the elements. Claisen and Eisleb [4] heated bromine to a temperature of about 40°, where the vapor pressure is 0.5 atmosphere, and passed in a stream of hydrogen. The gas mixture issuing from the flask contained approximately equimolecular quantities of the two elements, and combination was effected by passing the mixture through a hot tube packed with platinized quartz or asbestos. Any excess bromine was removed in a tube charged with beads moistened with red phosphorus. The method has been improved by Ruhoff, Burnett and Reid,[5] whose description should be consulted for details. These authors find the catalyst to be unnecessary and simply pack the combustion tube with clay chips and heat it with the full force of a burner. Excessive bromine is removed in a tube filled with copper turnings. According to Ionescu and Radulescu,[6] pure dry hydrogen bromide can be prepared in 80–90 per cent yield by dropping bromine onto petroleum ether in the presence of aluminum bromide.

Hydrogen Chloride. — Hydrogen chloride is available in cylinders. Small quantities of the gas are conveniently generated by dropping concentrated sulfuric acid onto sodium chloride covered

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[3] Houben, "Methoden d. org. Chem.," 3rd Ed., III, 1156.

[4] *Ann.*, **401**, 28 (1913).

[5] "Organic Syntheses," **15**, 35 (1935).

[6] *Bul. soc. chem. România*, **17**, 309 (1935).

with concentrated hydrochloric acid in the apparatus shown in Fig. 73. This arrangement is not satisfactory for the production of larger quantities, because in order to get the full yield of gas the flask has to be shaken carefully to mix the contents and this is not easily done without producing a too rapid rush of gas. A better generator is shown in Fig. 74. A charge of concentrated sulfuric acid is run into the large separatory funnel and the concentrated hydrochloric acid is placed in the dropping funnel and run in when required through the long stem. Entering in this way at the bottom of the layer of heavier liquid, the hydrochloric acid becomes thoroughly mixed with it. The capillary construction permits the stem to remain filled with liquid so that the flow is continuous. The connection between the gas exit and the top of the dropping funnel serves to equalize the pressure

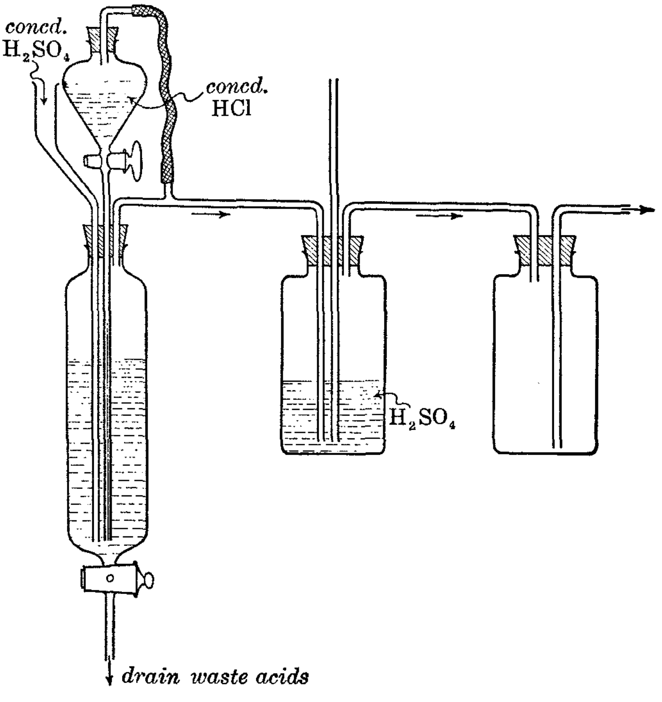

Fig. 74. — Hydrogen Chloride Generator

in the system, allowing the hydrochloric acid to flow in under gravitational pressure. The sulfuric acid wash bottle is provided with a safety tube to prevent a suck-back. The empty bottle next in line is a trap to catch any liquid which may suck back from the absorbing flask, and it will return such liquid to the flask when the flow of hydrogen chloride is resumed. The spent acid liquor can be run out and the separatory funnel recharged without dissembling the apparatus. If the rubber stopper at the top of the separatory funnel is coated heavily with varnish after it has been put in place it will remain gas-tight for many months; after the surface of a stopper has been corroded by hydrogen chloride the rubber becomes impervious to further attack.

Nitrogen.—For many purposes, prepurified nitrogen containing less than 0.1 per cent oxygen is satisfactory as an inert gas. If nitrogen of this quality is not available, or if a still purer gas is required, the oxygen can be removed by absorption in Fieser's solution:[7] an alkaline sodium hydrosulfite solution to which sodium β-anthraquinone sulfonate is added as catalyst. The quinone is at once reduced to the hydroquinone, which absorbs oxygen with great rapidity and which is kept in the reduced condition by the reserve of hydrosulfite present. The solution is prepared by dissolving 20 g. of potassium hydroxide in 100 cc. of water and adding 2 g. of sodium anthraquinone β-sulfonate and 15 g. of sodium hydrosulfite ($Na_2S_2O_4$) to the warm solution. The mixture is stirred until a clear, blood-red solution is obtained; this is ready for use after it has been cooled to room temperature. Nitrogen from the tank is passed through two or three wash bottles containing this solution and then into a wash bottle of saturated lead acetate solution, the latter to absorb traces of hydrogen sulfide sometimes present. Since the absorbent functions on a catalytic principle the original efficiency is retained to the point of exhaustion and the wash bottles do not require refilling as long as the solution remains clear and bright. When the color changes to dull red or brown,

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[7] *J. Am Chem. Soc.*, **46**, 2639 (1924).

or when a precipitate appears, the solution should be replaced. With fresh commercial hydrosulfite (about 85 per cent) the efficient capacity of the above quantity of solution is 788 cc. of oxygen.

For some purposes, as in working with free radicals, completely dry, oxygen-free nitrogen is required. Nitrogen purified in the manner described above and dried with sulfuric acid will often give satisfactory service, but as an added precaution the gas may be washed with a solution in absolute ether of the metal ketyl from benzophenone and sodium, $(C_6H_5)_2CONa$ (or the bimolecular form). This substance is extremely sensitive to both oxygen and moisture. If the vapor of ether in the gas stream is objectionable a higher-boiling liquid such as xylene may be employed and in this case it is well to use the liquid sodium-potassium alloy. To fill a wash bottle of ordinary size 5 g. of sodium is covered with a little xylene and 5 g. of potassium is dropped in. If the metals do not alloy they are pushed together with a glass rod until liquefaction occurs. The liquid alloy is transferred with a pipette under a layer of solvent to a suitable amount of xylene contained in the wash bottle. Ten grams of benzophenone is added and the bottle is sealed with wax at the top. Before each period of use the bottle should be shaken vigorously. To remove the small amount of hydrocarbon vapor, and to seal the metal ketyl bottle from the air, the gas is next passed into a wash bottle containing liquid paraffin.

Sulfur dioxide is available in cylinders; it may be generated by dropping 1 : 1 hydrochloric acid onto sodium bisulfite (Fig. 73).

Nitric Oxide, NO. — The generation of this gas from sodium nitrite and sulfuric acid is described by Gattermann-Wieland.[8]

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[8] "Laboratory Methods of Organic Chemistry," p. 357 (1937).

CHAPTER IV

REACTIONS

ACYLATION

Acetylation with acetic anhydride is sometimes accomplished by refluxing the hydroxy or amino compound for an extended period with an excess of acetic anhydride, but the more usual practice is to take advantage of the marked catalytic influence exerted by a trace of either sulfuric acid or a basic reagent such as sodium acetate or pyridine. The addition of a few drops of concentrated sulfuric acid to a suspension of the substance in acetic anhydride at room temperature usually initiates a reaction, as evidenced by a marked temperature rise, and the material may all go into solution without application of heat and then separate in the form of the acetate (example: acetylsalicylic acid, page 222). Acetylations often can be initiated similarly with pyridine. Sodium acetate functions less spectacularly because it does not dissolve readily in cold acetic anhydride; in this case the mixture is warmed for a time on the steam bath or heated at the reflux temperature. Acetic anhydride is such an effective solvent for acetylated compounds that it is usually best to decompose the excess reagent with water even though some of the product has separated from the mixture in a crystalline condition. The mixture can be poured into a large volume of water and stirred until the oily anhydride has disappeared, although with a large batch this may take several hours. With any but a highly sensitive acetyl derivative the following rapid method of decomposition is often satisfactory. The acetylation mixture is boiled steadily under a reflux condenser and water is added cautiously by drops through the condenser. Although the hydrolysis is exothermic, the reaction proceeds rapidly but without turbulence when steady boiling is deliberately maintained. In the case of a solid acetyl derivative, it is often convenient to continue the addition of water until a saturated solution of the substance in dilute acetic acid results and then to allow crystallization to proceed.

Acetylations can be conducted satisfactorily **in dilute aqueous solution.** Typical procedures for conducting the N-acetylation of amines and aminophenols are given in the preparation of acetanilide (pages 164–165) and of 2,4-diacetylamino-1-naphthol (page 287, see discussion, pages 289–290). In an initially neutral aqueous solution acetic anhydride preferentially attacks amino groups and does not readily acetylate phenolic hydroxyl groups. In a weakly alkaline medium, however, phenols can be acetylated very smoothly.[1] Thus phenol is dissolved in an aqueous solution of 1.5 equivalents of sodium hydroxide, ice is added, acetic anhydride (1.25 equivalents) is added rapidly, and the mixture shaken. Phenyl acetate separates in a few seconds and is obtained, after distillation, in 98.5 per cent yield.[1]

The **Schotten-Baumann method** of acylation consists in shaking an aqueous solution or suspension of the hydroxy or amino compound with an acid chloride, while adding sufficient dilute sodium hydroxide solution to keep the mixture basic (examples: pages 109, 115, 127). A variation consists in using pyridine or quinoline as the basic reagent (which functions both to bind the liberated hydrogen chloride and as a catalyst). The substance can be dissolved in pyridine and the solution treated at room temperature with either an acid chloride or an anhydride and the reaction conducted without application of heat. While often effective, this method sometimes suffers from the disadvantage that the crude product has a persistent yellow impurity not encountered in the Schotten-Baumann procedure.[2]

Kaufmann's procedure[3] for the acetylation of phenols and amines consists in treating the substance with one equivalent of acetic anhydride in an indifferent solvent such as benzene, ether,

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[1] Chattaway, *J. Chem. Soc.*, 2495 (1931).

[2] See preparation of tricaprylin, Hershberg, *J. Am. Chem. Soc.*, **61**, 3587 (1939).

[3] Kaufmann, *Ber.*, **42**, 3481 (1909).

or carbon tetrachloride. The reaction usually commences spontaneously with some warming and is completed by short boiling; if there is any delay it may be well to employ an acid catalyst.[4] Thus *o*-nitroaniline (0.5 mole) is suspended in benzene (75 cc.) in an evaporating dish and treated with acetic anhydride (0.6 mole) and 3–5 drops of concentrated sulfuric acid, which initiates a vigorous reaction. On evaporating the solvent and crystallizing the residue the pure product is obtained in 93 per cent yield.[4]

The process of **reductive acetylation** is applied to the preparation of stable acetyl derivatives of air-sensitive reduction products of quinones, benzanthrones, α-diketones, and similar compounds. One satisfactory procedure consists in suspending the substance in acetic anhydride (5–6 cc. per gram), adding 1 part of zinc dust and 0.2 part of fused, powdered sodium acetate, and warming the mixture gently until the colored material has disappeared and the supernatant liquid is colorless or pale yellow, depending upon the purity of the starting material. After short boiling to complete the reaction, acetic acid is added to dissolve the product and a part of the zinc acetate which has separated, the solution is filtered by gravity at the boiling point from zinc and zinc acetate, the residue is washed with fresh hot solvent, and the total filtrate is boiled under a reflux condenser and treated cautiously with sufficient water to hydrolyze the excess acetic anhydride and then to produce a saturated solution.

Tetramethylammonium bromide (0.2 part) can be used in place of sodium acetate and is an even more effective catalyst. Certain tertiary amines also can be employed, one of the most satisfactory being triethylamine (b.p. 89.4°). For example, a suspension of 0.5 g. of 2-methyl-1,4-naphthoquinone and 0.5 g. of zinc dust in 3 cc. of acetic anhydride is treated at 25° with 1 drop of triethylamine and shaken; a transient red color appears, the temperature rises, and in about 2 minutes the color is discharged. The mixture is boiled for a minute or two and extracted with a total of 10 cc. of hot acetic acid in portions. A boiling stone is added to the filtered solution and this is kept

[4] Fieser and Martin, *J. Am. Chem. Soc.*, **57**, 1838 (1935).

at the boiling point while water is added slowly to the saturation point (20–25 cc.); the colorless solution on cooling deposits 0.6 g. of pure 2-methyl-1,4-naphthohydroquinone diacetate, m.p. 112–113°. A variation of the procedure which is of convenience in the preparation of low-melting substances (e.g. vitamin K_1 hydroquinone diacetate [5]) is to extract the reaction mixture with ether, wash the filtered extract with dilute hydrochloric acid, and then shake it thoroughly with three or four portions of dilute alkali to destroy the acetic anhydride; the product is obtained on evaporation of the dried ethereal solution. Earlier procedures specified the use of pyridine as catalyst,[5, 6] but this has the distinct disadvantage that the reaction mixture tends to acquire a yellow color due to a side reaction between pyridine, acetic anhydride, and zinc. The difficulty is completely obviated by the use of the aliphatic tertiary amine. **Reductive benzoylation** has been accomplished by adding benzoyl chloride dropwise to a cooled mixture of the quinone and zinc dust in pyridine.[6]

Ketene. — This is a useful reagent for the acetylation of amino acids, proteins, and other sensitive compounds. It is a gaseous substance (b.p. −56°) made by the pyrolysis of acetone. The most convenient form of laboratory ketene generator consists of a boiling flask with a heated filament suspended in the vapor space and a condenser for the return of acetone. Three satisfactory designs are reported in the recent literature.[7, 8, 9] The ketene may be condensed in a cooling trap (CO_2) or passed directly into the reaction mixture through a delivery tube provided with a sintered glass plate.[8] Since amines react with ketene more rapidly than water does, an amino acid can be acetylated by passing ketene into an alkaline solution of the substance at room temperature.[10] In the case of an optically active acid, the solution must be kept alkaline throughout the

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[5] Fieser, *J. Am. Chem. Soc.*, **61**, 3473 (1939).

[6] Fieser, Campbell, Fry and Gates, *J. Am. Chem. Soc.*, **61**, 3219 (1939).

[7] Hershberg and Ruhoff, "Organic Syntheses," **17**, 25 (1937).

[8] Li, *Science*, **90**, 143 (1939).

[9] Williams and Hurd, *J. Org. Chem.*, **5**, 122 (1940).

[10] Bergmann and Stern, *Ber.*, **63**, 437 (1930).

reaction or racemization may occur.[11] Sensitive, water-insoluble substances often can be acetylated by adding excess liquid ketene to a cold solution or suspension of the material in an organic solvent (e.g., acetone).

Formylation. — Hydroxy and amino compounds frequently can be converted into the formyl derivatives by direct interaction with formic acid. This acid is a more reactive acylating agent than the other members of the series and the formyl derivatives are much more easily hydrolyzed than the acetyl or benzoyl compounds, and for these reasons formylation often constitutes a convenient method of temporarily protecting a reactive hydroxyl or amino group. Cholic acid, which has three secondary alcoholic groups, can be converted into the triformyl derivative in 60–75 per cent yield by heating it with 88 per cent formic acid (sp. gr. 1.2, 2 cc. per gram) at 50–55° for 5 hours.[12] The yield is not improved by using more concentrated acid. The formylation of amino acids was initially accomplished by a rather laborious process calling for repeated treatment with anhydrous formic acid.[13] A much more convenient method[14] is illustrated by the following procedure for the formylation of *dl*-cystine: a mixture of 40 g. of the amino acid and 600 cc. of 85–90 per cent formic acid is heated to 60°, stirred mechanically, and treated with 200 cc. of acetic anhydride, added at such a rate as to maintain a temperature of 60°.

Carbobenzoxylation. — The elegant method developed by Bergmann[15] for the introduction of a protective acyl group which can be removed by a process more selective and gentle than that of hydrolysis utilizes as the effective reagent the acid chloride resulting in good yield from the interaction of benzyl alcohol with phosgene in toluene solution (a). The reagent is

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[11] Jackson and Cahill, *J. Biol. Chem.*, **126**, 37 (1938).

[12] Cortese and Bauman, *J. Am. Chem. Soc.*, **57**, 1393 (1935).

[13] E. Fischer and Warburg, *Ber.*, **38**, 3998 (1905). Steiger, *J. Biol. Chem.*, **86**, 695 (1930), introduced an improvement consisting in the addition of toluene and the removal of the water formed by distillation.

[14] du Vigneaud, Dorfmann and Loring, *J. Biol. Chem.*, **98**, 577 (1932).

[15] Bergmann and Zervas, *Ber.*, **65**, 1192 (1932).

condensed by the Schotten-Baumann procedure with an alcohol,

(a) $C_6H_5CH_2OH + ClCOCl \longrightarrow C_6H_5CH_2OCOCl + HCl$
(b) $C_6H_5CH_2OCOCl + H_2NCH_2CO_2H \longrightarrow C_6H_5CH_2OCONHCH_2CO_2H + HCl$
(c) $C_6H_5CH_2OCONHCH_2CO\text{-}A + H_2(Pd) \longrightarrow C_6H_5CH_3 + CO_2 + H_2NCH_2CO\text{-}A$

amine or amino acid, as shown for glycine (b). The resulting carbobenzoxy derivative can then be put through certain synthetic operations not affecting the protected group, for example, the glycine derivative can be linked through the acid chloride to a second amino acid residue. In the final step (c) the covering group is eliminated by hydrogenation, when the derivative is split into toluene, carbon dioxide, and the free amino derivative without disturbance of a peptide linkage.

Acylation of Tertiary Alcohols. — Tertiary alcohols are so resistant to acylation by ordinary methods that they usually can be distinguished from primary and secondary alcohols on the basis of their behavior in the reaction. Thus a compound having alcoholic groups of all three types can be converted by mild treatment with acetic anhydride and sodium acetate into a partially acetylated derivative in which the free hydroxyl groups are all tertiary. The use of acid catalysts is likely to give rise to dehydration. The reaction of a tertiary alcohol with acetyl chloride in benzene solution, or with a large excess of acetylchloride alone, results in the replacement of the hydroxyl group by chlorine, often in excellent yield,[16] as in the example:

$$(C_6H_5)_3COH + CH_3COCl \longrightarrow (C_6H_5)_3CCl + CH_3COOH$$

Acetyl bromide gives the corresponding bromide, and the reactions have distinct preparative value where the halides are desired.

This abnormal reaction is considered by Norris and Rigby[17] to involve the formation of the acetate and the cleavage of this reactive intermediate by the hydrogen halide liberated in the initial phase. By introducing an amine to bind the acid formed, these investigators were able to obtain the acyl derivatives in

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[16] Gomberg and Davis, *Ber.*, **36**, 3924 (1903).

[17] *J. Am. Chem. Soc.*, **54**, 2088 (1932).

excellent yields. *Tert.*-butyl alcohol can be acetylated smoothly by treatment with acetyl chloride and dimethylaniline, and *tert.*-butyl benzoate is obtained equally well using benzoyl chloride and pyridine (86 per cent yield). Another procedure introduced by Norris and Rigby is to use acetic anhydride in combination with either magnesium, zinc dust, or zinc chloride. The method has been studied further by Spassow,[18] who reports yields of about 55 per cent in the reaction of a tertiary alcohol with acetyl chloride and magnesium in ether: $2(CH_3)_3COH + 2CH_3COCl + Mg \longrightarrow 2(CH_3)_3COCOCH_3 + MgCl_2 + H_2$. The metal destroys the hydrogen chloride as formed and also seems to exert a catalytic influence.

THE GRIGNARD REACTION

Apparatus. — Certain elaborations of the technique of carrying out the Grignard reaction are generally of distinct value, and sometimes are essential to the success of the operation. A suitable assembly of apparatus which meets most requirements is illustrated in Fig. 75. A three-necked flask, preferably one having ground glass openings, is mounted on a removable steam cone and provided with an efficient coil-type condenser, a dropping funnel with a pressure-equalizing side tube, and a mercury sealed stirrer of the Hershberg type made of tantalum wire. Dry nitrogen is introduced at the top of the condenser and initially can be allowed to sweep through the apparatus and escape at the mouth of the dropping funnel; when the funnel is closed a very slight positive pressure is maintained at the nitrogen tank, as indicated by the level of mercury in the escape valve. This gas-trap arrangement[1] is economical of nitrogen and has the further advantage over the use of a continuous stream of inert gas that it obviates evaporation of the solvent. Tank nitrogen ordinarily can be used without purification, particularly if it is of the prepurified grade.

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[18] Spassow, *Ber.*, **70**, 1926 (1937); "Organic Syntheses," **20**, 21 (1940).

[1] Gilman and Hewlett, *Rec. trav. chim.*, **48**, 1124 (1929).

One reason for providing a nitrogen atmosphere is to prevent destruction of the Grignard reagent by air oxidation. Both aliphatic and aromatic Grignard reagents interact more or less readily with molecular oxygen in ether solution with the formation of the hydroxy derivatives:[2] $2RMgX + O_2 \rightarrow 2ROMgX$. The oxidation is a chemiluminescent reaction and a beautiful demonstration is furnished by pouring a solution of *p*-chlorophenylmagnesium bromide from one flask to another in the dark.

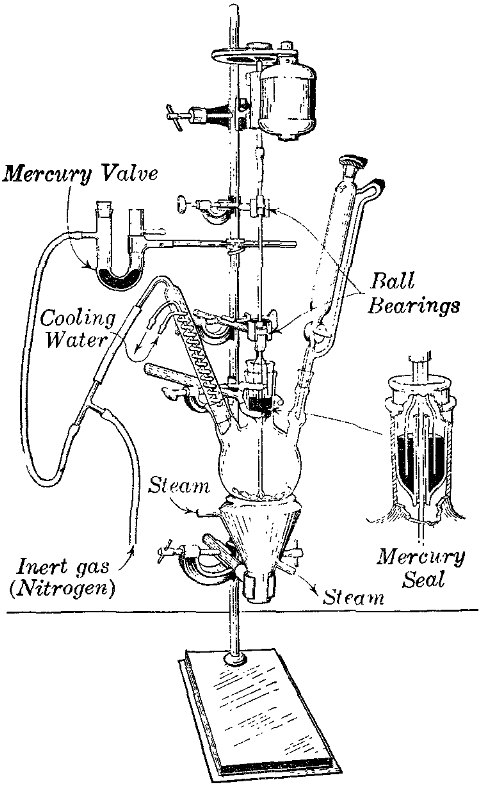

FIG. 75. — Apparatus for the Grignard Reaction

Another useful form of reaction flask is illustrated in Fig. 76. The mercury seal and condenser shown in the drawing are fitted

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[2] Gilman and Wood, *J. Am. Chem. Soc.*, **48**, 806 (1926).

into the appropriate openings by means of rubber stoppers, and a dropping funnel of the ordinary form is mounted in the same way in the shorter side neck. Inlet and outlet tubes are provided for flushing the system with nitrogen.

Starting the Reaction. — In conducting a reaction, the required amount of magnesium[3] is placed in the flask and the apparatus is assembled and swept with nitrogen, the gas being used to flush both parts of the empty dropping funnel. When the air has been displaced the flask is heated gently with a free flame under continued flow of nitrogen in order to insure the elimination of any moisture adhering to the surface of the glass or the metal. The baking-out process is much more effective when conducted under a flow of dry gas than when done in a static system (page 68), and the use of nitrogen precludes the possibility of surface oxidation of the warm metal. When the flask has cooled completely, the nitrogen flow is reduced to a barely perceptible rate and small portions of the ether and halogen compound are introduced through the funnel. The stirrer is started, even though very little liquid is present, for the crushing of pieces of light magnesium foil in contact with the liquid is a very effective method of initiating the reaction. Indeed, if stirring alone is insufficient, it may be well to try the expedient of inserting a flattened stirring rod and crushing a piece of metal with a twisting motion against the bottom of the flask (page 69). If the reaction still fails to start, the addition of a small crystal of iodine or a few drops of methyl iodide may

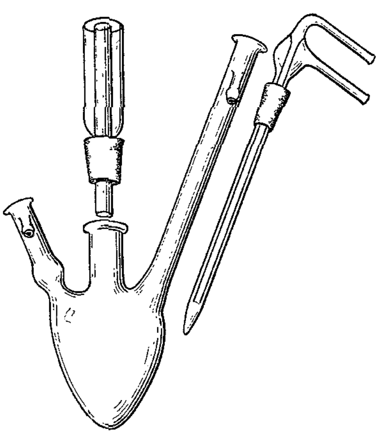

FIG. 76. — Grignard Reaction Flask

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[3] Magnesium of high purity gives very clear Grignard solutions; with less pure metal the solutions are dark. Rods of pure metal can be turned in a lathe or reduced to granules in a grinding machine.

be effective. Gilman's catalyst,[4] prepared by the interaction of magnesium and iodine in ether-benzene, is often serviceable. An expedient for converting the less reactive halogen compounds into their magnesiohalide derivatives which was introduced by Grignard[5] consists in adding one equivalent of ethyl bromide to the ethereal solution of the refractory halide and dropping this mixture slowly onto sufficient magnesium to react with both halides. The auxiliary halide may function in part by keeping the surface of the magnesium in a clean and active condition but probably is effective chiefly by virtue of an exchange reaction. In any case the second halide is often induced to react. The resulting solution contains a mixture of the two Grignard reagents, and when used in a synthesis it must be treated with two equivalents of the second component. The presence of the reaction product from the ethylmagnesium bromide usually does not interfere with the isolation of the desired reaction product, particularly if this is of significantly higher molecular weight.

The difficulty experienced in starting a previously unexplored Grignard reaction not infrequently is due to inadequate purification of the halide rather than to its lack of reactivity. Traces of impurities not detectable by analysis or from the physical constants of the halide may exert a marked poisoning action. Such impurities often can be eliminated effectively either by washing the halide with concentrated sulfuric acid or by steam distillation of the substance, preferably from an alkaline medium. It is to be noted further that certain halides will form Grignard derivatives satisfactorily if given sufficient time; hence the trials should include heating and stirring under nitrogen for a period of one or two days before concluding that a suitably purified halide cannot be used in the proposed synthesis.

For the preparation of small amounts of methylmagnesium bromide, a sealed vial of methyl bromide (b.p. 4.5°) is cooled in ice, opened, and fitted with a length of rubber tubing connected

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[4] Gilman and Kirby, *Rec. trav. chim.*, **54**, 577 (1935).

[5] Grignard, *Compt. rend.*, **198**, 625 (1934). See also Clément, *ibid.*, **198**, 665 (1934); Urion, *ibid.*, **198**, 1244 (1934).

through a calcium chloride drying tube to a glass delivery tube leading into the reaction flask. The reagent is then introduced as required by warming the vial in the hand. With larger amounts it may be well to generate the methyl bromide required. Methyl chloride (b.p. $-24°$) is obtainable in steel cylinders, from which it can be run directly into the mixture of magnesium and ether. In the preparation of small batches the difficulty sometimes experienced in starting the reaction usually can be overcome by stirring and heating the mixture while passing in a slow stream of methyl chloride. When a large quantity of methylmagnesium chloride is to be prepared it is desirable to conserve the reagent. This can be accomplished by providing the flask with a mercury valve or balloon or, more advantageously, with a cold-finger condenser inserted in a side tubulature consisting of a test tube filled with dry ice. The latter scheme avoids any difficulty from back pressure and makes it possible to build up an initial high concentration of methyl chloride favorable for starting the reaction. With a highly reactive halide such as allyl bromide, the preparation of the Grignard reagent should be conducted in a very dilute solution in order to minimize coupling.

Analysis and Detection of the Reagent. — With the halides most commonly used the yield of Grignard reagent in a well-conducted operation ordinarily is in the neighborhood of 90 per cent of the theoretical amount, and if a slight excess is not likely to be harmful the quantity of halide required can be estimated on this basis. A very large excess may lead to unexpected complications and is to be avoided. When a selective action is desired, or when an effort is being made to improve the overall yield in a synthesis, a knowledge of the exact concentration of the reagent may prove useful.

The most convenient method of analysis is by titration:[6] an aliquot portion (5 cc.) of the ethereal solution is poured slowly into 20 cc. of water, excess standard hydrochloric acid is added

[6] Gilman, Wilkinson, Fishel and Meyers, *J. Am. Chem. Soc.*, **45**, 150 (1923); Houben, Boedler and W. Fischer, *Ber.*, **69**, 1766 (1936).

(to react with the Mg(OH)X), and the excess acid titrated with standard sodium hydroxide solution, using methyl orange as the indicator.

For determining when a Grignard compound has been completely consumed, as when gaseous formaldehyde is passed into the ethereal solution, Gilman's test[7] for the presence of the Grignard reagent is useful: about 0.5 cc. of the ethereal solution is pipetted and treated with an equal volume of a 1 per cent solution of Michler's ketone in dry benzene, and then, slowly, with 1 cc. of water. The addition of several drops of a 0.2 per cent solution of iodine in glacial acetic acid then produces a characteristic greenish blue color if Grignard reagent has been present.

The Reaction Proper. — The usual, or direct, reaction is one in which a given component of a synthesis is caused to react as completely as possible with a Grignard reagent, and the ordinary procedure is to prepare a slight excess of the reagent as described above and to stir this under reflux in the original apparatus while slowly adding a solution of the second component in ether. Some addition reactions, however, do not proceed satisfactorily at the boiling point of ether and require forcing conditions, that is, a more elevated temperature. The desired conditions are obtained by preparing a solution of the Grignard reagent in ether, adding a dry hydrocarbon solvent of higher boiling point, and removing the bulk of the ether by distillation. By using benzene, toluene, or xylene for displacing the ether the temperature obtainable in the subsequent reaction can be varied over a considerable range. Air should be excluded with nitrogen during the operation, for oxidation may occur rapidly at the high temperatures. It is sometimes desirable to dispense entirely with the use of diethyl ether in order to facilitate the isolation of a reaction product boiling in the same range as this solvent. In the preparation of *n*-pentane, b.p. 35.5°, Noller[8] used di-*n*-butyl ether, b.p. 141°, as the solvent.

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[7] Gilman and Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925); Gilman and Heck, *ibid.*, **52**, 4949 (1930).

[8] "Organic Syntheses," **11**, 84 (1931).

The procedure for conducting an inverse Grignard reaction consists in adding slowly one equivalent of a Grignard reagent in ether to a stirred solution of the second component in ether or a dry hydrocarbon solvent. The inverse method is required whenever the desired reaction product is capable of reacting further with the Grignard reagent, and is employed in the synthesis of ketones from acid chlorides or esters, or of keto acids from cyclic anhydrides. It is not advisable to pour a Grignard solution from one vessel to another in the open, for the exposure to moist air is attended with considerable loss through both hydrolysis and oxidation. A satisfactory technique consists in preparing the reagent in the apparatus shown in Fig. 75, replacing the dropping funnel by a siphon tube held by a cork or a glass joint and bent to extend to the bottom of the flask, and transferring the solution under nitrogen pressure to a dry dropping funnel flushed with nitrogen. The funnel is then attached to a reaction flask containing a solution of the second component.

Not infrequently the addition of a Grignard reagent to a carbonyl compound is attended with some reduction to a carbinol.[9] Methyl and aryl Grignard reagents are less prone to give rise to reduction than are higher alkylmagnesium halides, particularly those having a secondary alkyl group and those containing iodine. Allen and Bell[10] have reported an instance where extensive reduction was found to be promoted by the minute traces of magnesium remaining in the Grignard reagent mixture. When the reagent was carefully filtered to remove all traces of metal, addition proceeded smoothly and no reduction was noted. The filtration can be accomplished by introducing a carefully arranged plug of glass wool into the bottom of a siphon tube (5–7 mm. bore) inserted as above for transference of the solution under nitrogen pressure.

Hydrolysis of the Reaction Mixture. — At the end of the reaction the MgX-derivative can be decomposed by adding 25 per

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[9] Conant and Blatt, *J. Am. Chem. Soc.*, **51**, 1227 (1929); Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 209 (1936); Whitmore, *Rec. trav. chim.*, **57**, 562 (1938).

[10] *J. Am. Chem. Soc.*, **62**, 2408 (1940).

cent sulfuric acid dropwise with cooling under reflux, or by pouring the reaction mixture onto ice and dilute acid. In the event that the reaction product is sensitive to the dehydrating action of mineral acids it is best to effect the hydrolysis with aqueous ammonium chloride solution. One procedure is to add a sufficiently large excess of saturated ammonium chloride solution to bring the precipitated basic salts of magnesium into solution. A much better method is to add just enough of the solution to precipitate the magnesium and leave a nearly anhydrous supernatant solution of the reaction product in ether. Where applicable, this method has the advantage of convenience over the sulfuric acid procedure whether or not the presence of a mineral acid is objectionable. The reaction mixture is cooled and stirred under reflux in the original flask and a saturated solution of ammonium chloride in water (25°) is added slowly from the dropping funnel at a rate controlled by the rapidity of refluxing. Usually 150–170 cc. of the saturated solution per mole of magnesium is required to reach a point where a clear separation occurs, and this point should not be passed. The solution at first becomes cloudy and opaque and then, when sufficient ammonium chloride solution has been added, the solution suddenly becomes clear and a white salt separates as a tough cake which is likely to stop the stirrer. The mixture is allowed to settle for several minutes, the supernatant solution is decanted, and the dense precipitate is washed with one or two portions of fresh ether. The ethereal solution requires no drying and can be evaporated directly for recovery of the product. The procedure is applicable to reaction mixtures in which as much as one third of the solvent is benzene.

Lithium Derivatives. — Alkyl and aryl derivatives of lithium behave very much like the corresponding Grignard reagents and often can be used to accomplish the same syntheses as obtained with the magnesiohalide derivatives.[11] The usual method of preparation consists in treating a halide with lithium metal in dry ether by essentially the same technique as employed in

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[11] Ziegler and Colonius, *Ann.*, **479**, 135 (1930).

preparing a Grignard reagent, and the yields are excellent.[12] The reaction with lithium starts more readily and proceeds at a greater rate than that with magnesium. Lithium metal should not be warmed in a nitrogen stream for it tends to form the nitride. Phenyllithium may be prepared from either bromobenzene or chlorobenzene by interaction with lithium in the presence of ether:

$$C_6H_5Cl + 2Li \longrightarrow C_6H_5Li + LiCl$$

Lithium alkyls can be prepared not only in the presence of ether but also with low-boiling petroleum ether as the sole solvent;[13] the hydrocarbon solvent has advantages over ether and makes possible the preparation of organolithium compounds (e.g., isopropyllithium) otherwise difficultly obtainable.

The lithium derivatives are somewhat more reactive than the corresponding Grignard reagents[14] and, in the reaction with an α,β-unsaturated ketone, differ from the magnesiohalides in giving rise to a much higher proportion of the 1,2-addition product.[15] One of the most useful applications of organolithium derivatives is in the utilization of aromatic chloro compounds in syntheses which cannot be accomplished by the Grignard method because the aryl chlorides do not react satisfactorily if at all with magnesium under ordinary conditions. If an aromatic bromide and a chloride are about equally available, it usually is preferable to employ the former in the form of the Grignard derivative, but if the chloride is much more readily obtainable it can be utilized in the form of the lithium compound.

Another use is illustrated by the conversion of anisole or an analogue into the *o*-lithium derivative by reaction with an alkyl or aryllithium and carbonation of the metal derivative to give the *o*-carboxylic acid.[16]

Several procedures for the manipulation of lithium are de-

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[12] Gilman and co-workers, *J. Am. Chem. Soc.*, **54**, 1957 (1932); **55**, 1262 (1933).

[13] Gilman, Langham and Moore, *J. Am. Chem. Soc.*, **62**, 2327 (1940).

[14] Gilman and Kirby, *J. Am. Chem. Soc.*, **55**, 1265 (1933).

[15] Lüttringhaus, *Ber.*, **67**, 1602 (1934).

[16] Wittig and co-workers, *Ber.*, **71**, 1903 (1938); **72**, 89 (1939); **73**, 1197 (1940); Adams and Hunt, *J. Am. Chem. Soc.*, **61**, 1132 (1939).

scribed by Gilman.[13] One convenient method is as follows.[17] The lithium available in the form of small blocks is pressed into a wire with a sodium press equipped with a 3-mm. die. The wire is collected under heavy paraffin oil and cut into uniform 12-cm. lengths which are placed in a test tube having a stopcock at the bottom and a nitrogen inlet near the rubber stopper. The sticks of metal are washed with successive portions of benzene and ether under nitrogen, the wash liquor being drained out through the stopcock under nitrogen pressure. The average relationship of weight to length is determined by weighing a few of the wires, so that subsequently a given total length of wire can be measured for use in a reaction. The lithium is introduced to the reaction flask after this has been flushed with nitrogen, and with the gas streaming from the widest opening of the flask. While the opened lithium container is being flushed with nitrogen, it is held at right angles to the mouth of the flask, a length of lithium wire is withdrawn, and short cylinders are cut with scissors and allowed to drop into the flask. Fresh, silvery surfaces are thus exposed and protected. Powdered lithium can be prepared by heating the metal in mineral oil at 250° under nitrogen with vigorous stirring; this gives fine, shiny particles.

THE FRIEDEL AND CRAFTS REACTION

Some of the more prominent applications of the Friedel and Crafts reaction are indicated in Part I. The hydrocarbon synthesis (pages 175–177), consisting in the condensation of an alkyl halide with an aromatic hydrocarbon in the presence of a catalytic amount of aluminum chloride, is illustrated by the preparation of diphenylmethane (pages 176–178) and *tert.*-butylbenzene (pages 180–181). In the ketone synthesis (pages 183–184) the procedure differs to the extent that at least one full molecular equivalent of aluminum chloride must be used to satisfy the requirements for complex formation. When an acid chloride is used as one of the components it initially combines

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[17] Fieser and Hershberg, *J. Am. Chem. Soc.*, **59**, 396 (1937).

with aluminum chloride to form a molecular complex, and as the reaction proceeds this is transformed into an aluminum chloride complex of the ketone produced. The Perrier procedure for carrying out Friedel and Crafts benzoylations utilizes the preformed complex of benzoyl chloride and aluminum chloride, as illustrated for the preparation of 1-benzoylnaphthalene (pages 192–196). When phthalic anhydride is employed as the acylating agent the amount of aluminum chloride must be sufficient to allow for complex formation with both carbonyl groups (2 equivalents), as specified in the procedures for effecting condensations with benzene, toluene, and acenaphthene (pages 184–188). Condensations of succinic anhydride with aromatic hydrocarbons are conducted similarly in the presence of 2 equivalents of aluminum chloride; a typical example is in the preparation of β-benzoylpropionic acid.[1] In the succinoylation of the more reactive hydrocarbons of the naphthalene, phenanthrene, and pyrene series it is often advantageous to employ nitrobenzene as the solvent, for this holds the aluminum chloride in solution in the form of a labile complex and makes it possible to conduct the reaction at such a low temperature (–15° to 25°) that even a highly sensitive hydrocarbon is protected against damaging side reactions; example: β-(3-acenaphthoyl)-propionic acid.[2] Aluminum chloride also forms complexes with ether groups, but these are labile and do not restrain the reagent from exerting a catalytic action. Thus the condensation of succinic anhydride with either anisole or veratrole is carried out with the use of 2 equivalents of aluminum chloride.[3] Since ethers readily undergo hydrolysis under the influence of aluminum chloride at moderate temperatures (about 80°), Friedel and Crafts reactions with ethers are best carried out in the cold with the use of sufficient nitrobenzene to keep the complexes in solution. A convenient general procedure[3] consists in using as solvent a combination of nitrobenzene and tetrachloroethane.

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[1] Somerville and Allen, "Organic Syntheses," **13**, 12 (1933); Martin and Fieser, *ibid.*, **15**, 92 (1935).

[2] Fieser, "Organic Syntheses," **20**, 1 (1940).

[3] Fieser and Hershberg, *J. Am. Chem. Soc.*, **58**, 2314 (1936).

The orientation in Friedel and Crafts substitutions is sometimes influenced to a marked extent by the nature of the solvent. When naphthalene is condensed with acetyl chloride in carbon bisulfide solution at temperatures ranging from −15° to 25°,[4] the product is a mixture of α- and β-acetonaphthalene in the ratio of about 3 to 1;[5] when the same reaction is carried out in nitrobenzene solution β-acetonaphthalene is the chief product and can be isolated easily in excellent yield by crystallization.[6]

When the aromatic component of the condensation is so reactive that it is subject to the destructive polymerizing action of aluminum chloride, this catalyst is advantageously replaced by the milder stannic chloride. The use of this reagent is illustrated in a procedure for the preparation of methyl 2-thienyl ketone from acetyl chloride and thiophene.[7]

One method of cyclizing β-arylpropionic acids and γ-arylbutyric acids to ketones of the α-hydrindone and α-tetralone types is by converting the acid to the acid chloride and carrying out an intramolecular Friedel and Crafts reaction. Thionyl chloride is sometimes used for the preparation of the intermediate acid chloride, but it may give rise to side reactions.[8] Furthermore, any trace of thionyl chloride not removed prior to the cyclization step is likely to enter into destructive combination with the organic material under the influence of the catalyst.[9] No such difficulties have been encountered when phosphorus pentachloride is employed, and this reagent is therefore to be preferred. A convenient cyclization procedure consists in heating the acid with phosphorus pentachloride in benzene solution and, after allowing sufficient time for conversion to the chloride, adding aluminum chloride to effect ring closure.[10] When the

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[4] Caille, *Compt. rend.*, **153**, 393 (1911).

[5] St. Pfau and Ofner, *Helv. Chim. Acta*, **9**, 669 (1926); Fieser, Holmes and Newman, *J. Am. Chem. Soc.*, **58**, 1055 (1936).

[6] Chopin, *Bull. soc. chim.*, [4] **35**, 610 (1924); Riwkin and Meerson, *Chem. Zentr.*, II, 2208 (1935).

[7] J. R. Johnson and May, "Organic Syntheses," **18**, 1 (1938).

[8] Fieser and Desreux, *J. Am. Chem. Soc.*, **60**, 2253 (1938).

[9] Fieser, Hershberg, Long and Newman, *J. Am. Chem. Soc.*, **59**, 475 (1937).

[10] Adelson and Bogert, *J. Am. Chem. Soc.*, **59**, 399 (1937).

compound possesses a sensitive and reactive aromatic nucleus, stannic chloride can be employed to advantage as the condensation catalyst.[11]

REDUCTION

In the following notes concerning processes of reduction, typical uses of some of the common reducing agents are considered first.

Tin and Hydrochloric Acid. Nitrobenzene ⟶ aniline (page 147).

Stannous Chloride Crystals ($SnCl_2.2H_2O$). Reduction of azo dyes (page 211) and nitro compounds (pages 147, 277).

Iron Powder and Hydrochloric or Acetic Acid. Reduction of nitro compounds (page 147): 2,4-dinitrotoluene ⟶ 2,4-diaminotoluene.[1]

Ferrous Sulfate and Ammonia. Reduction of nitro compounds (page 147).

Ammonium (Sodium) Sulfide. Partial reduction of polynitro compounds (page 147).

Magnesium Amalgam. Pinacol reduction of acetone (page 97).

Sodium Hydrosulfite ($Na_2S_2O_4$). Reduction of quinones (pages 190, 234), azo compounds (pages 211, 230), nitro compounds (page 289).

Zinc Dust and Alkali.

(a) $o\text{-}C_6H_5COC_6H_4CO_2H \longrightarrow o\text{-}C_6H_5CH_2C_6H_4CO_2H$ (page 189)

(b) $C_6H_5COC_6H_5 \longrightarrow C_6H_5CHOHC_6H_5$[2]

(c) $2C_6H_5NO_2 \longrightarrow C_6H_5NHNHC_6H_5$[3]

(d) $o\text{-}O_2NC_6H_4NH_2 \longrightarrow o\text{-}H_2NC_6H_4NH_2$[4]

(e) Anthrone ⟶ Anthracene.[5] The zinc dust is activated by treatment with copper sulfate solution and the reaction conducted with a layer of added toluene. Pure, fluorescent anthracene is obtained in 93 per cent yield; the yield of hydrocarbon from anthraquinone is 80 per cent.

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[11] Fieser and Novello, *J. Am. Chem. Soc.*, **62**, 1855 (1940).

[1] Mahood and Schaffner, "Organic Syntheses," **11**, 32 (1931).

[2] Marvel and Hansen, "Organic Syntheses," Coll. Vol. I, 84 (1932).

[3] E. Fischer, "Anleitung zur Darstellung org. Präparate," p. 23 (1905).

[4] Martin, "Organic Syntheses," **19**, 70 (1939).

[5] Martin, *J. Am. Chem. Soc.*, **58**, 1441 (1936).

Zinc Dust and Hydrochloric Acid. Cetyl iodide ⟶ *n*-Hexadecane [6] (85 per cent yield).

Zinc Dust and Ammonium Chloride. Nitrobenzene ⟶ β-Phenylhydroxylamine.[7]

Zinc Dust and Calcium Chloride. 2-Nitrofluorene ⟶ 2-Aminofluorene.[8]

Zinc Dust–Zinc Chloride Melt.[9] Reduction of polynuclear quinones and hydroxy compounds to aromatic hydrocarbons.

Zinc Dust–Pyridine–Acetic Acid. Reduction of polyene carboxylic acids and cyanine dyes [10] (at room temperature, with a trace of water or alcohol present).

Sodium.

(a) $n\text{-}C_4H_9CN \xrightarrow{Na + C_2H_5OH} \underset{n\text{-Amylamine}}{n\text{-}C_4H_9CH_2NH_2}$ [11]

(b) $n\text{-}C_4H_9COOC_2H_5 \xrightarrow{Na + C_2H_5OH} \underset{n\text{-Amyl alcohol}}{n\text{-}C_4H_9CH_2OH}$ [11]

(c) β-Naphthylamine $\xrightarrow{Na+C_5H_{11}OH}$ *ac*-Tetrahydro-β-naphthylamine [12]

Tin-Mercury Couple.

$$\underset{\text{Benzoin}}{C_6H_5COCHOHC_6H_5} \xrightarrow[HCl]{Sn - Hg} \underset{\text{Desoxybenzoin}}{C_6H_5COCH_2C_6H_5}$$ [13]

Copper-Zinc Couple.[14]

$$RX \xrightarrow[\text{alcohol}]{Cu-Zn} RH$$

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[6] Levene, "Organic Syntheses," **15**, 27 (1935).

[7] Kamm, "Organic Syntheses," Coll. Vol. I, 435 (1932).

[8] Kuhn, "Organic Syntheses," **13**, 74 (1933).

[9] Clar, *Ber.*, **72**, 1645 (1939).

[10] Kuhn and Winterstein, *Ber.*, **65**, 1737 (1932).

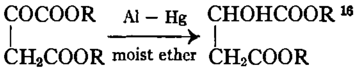
[11] Adams and Marvel, *J. Am. Chem. Soc.*, **42**, 310 (1920).

[12] Waser and Möllering, "Organic Syntheses," Coll. Vol. I, 486 (1932).

[13] Ballard and Dehn, *J. Am. Chem. Soc.*, **54**, 3970 (1932).

[14] Preparation: Houben, 3rd Ed., II, 304 (1925).

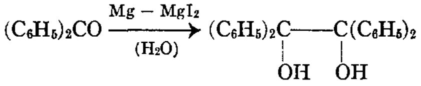
Aluminum Amalgam.[15]



$$\begin{array}{l}COCOOR\\ |\\ CH_2COOR\end{array} \xrightarrow[\text{moist ether}]{Al-Hg} \begin{array}{l}CHOHCOOR^{16}\\ |\\ CH_2COOR\end{array}$$

Oxalacetic ester Malic ester

Magnesium-Magnesium Iodide.[17]

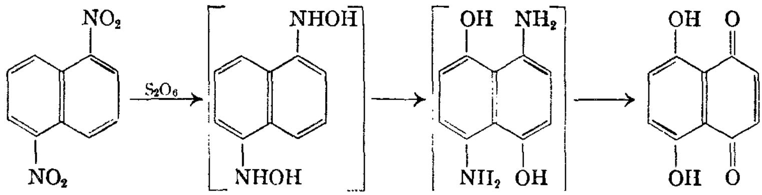


$$(C_6H_5)_2CO \xrightarrow[(H_2O)]{Mg-MgI_2} (C_6H_5)_2\underset{OH}{\underset{|}{C}}-\underset{OH}{\underset{|}{C}}(C_6H_5)_2$$

Sodium Sulfite. Benzenediazonium chloride ⟶ Phenylhydrazine.[18]

Formic Acid (anhydrous). $Ar_3COH \longrightarrow Ar_3CH$.[19]

Sulfur Sesquioxide, S_2O_6 (sulfur dissolved in fuming sulfuric acid). — In special cases this converts a nitro compound into a *p*-aminophenol derivative:[20]



Naphthazarin

Titanous Chloride, $TiCl_3$. — A titrating agent for nitro and azo compounds.[21]

Vanadous Chloride (VCl_2) and Chromous Chloride ($CrCl_2$).[22] — Titrating agents of very low potential. Chromous chloride is

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[15] Preparation: *ibid.*, 256 (1925).

[16] Wislicenus, *J. prakt. Chem.*, **54**, 60 (1896).

[17] Gomberg and Bachmann, *J. Am. Chem. Soc.*, **49**, 241 (1927).

[18] Coleman, "Organic Syntheses," Coll. Vol. I, 432 (1932).

[19] Kauffmann and Pannwitz, *Ber.*, **45**, 766 (1912); Kovache, *Ann. chim.*, [9] **10**, 184 (1918).

[20] German Patent 71,386; Charrier, *Gazz. chim. ital.*, **53**, 431 (1923); Fieser, *J. Am. Chem. Soc.*, **50**, 459 (1928).

[21] Knecht and Hibbert, "New Reduction Methods in Volumetric Analysis," pp. 41–42 (1925).

[22] Preparation: Conant and Cutter, *J. Am. Chem. Soc.*, **48**, 1023 (1926).

used for the reduction of imidochlorides, in the preparation of α,β-unsaturated aldehydes.[23]

Alkaline Formaldehyde. — The deamination of amines can be accomplished by the reduction of diazonium salts with this reagent.[24] This method often gives particularly satisfactory results where the classical method of reduction with alcohol is unsatisfactory (largely due to ether formation), and vice versa.

Hypophosphorous acid has been used for the reduction of diazonium salts to hydrocarbons.[25] An improved procedure described by Adams and Kornblum [26] has given excellent results with certain amines of the diphenyl series.

Anhydrous Stannous Chloride. — This reagent is employed in an ether solution saturated with hydrogen chloride for the reduction of imidochlorides of the types —C(Cl) = NH and —C(Cl) = NC_6H_5 to the hydrogen compounds —CH = NH and —CH = NC_6H_5. These are the respective intermediates in the Sonn-Müller [27] and Stephen [28] methods of preparing aldehydes. The reagent is prepared by heating hydrated stannous chloride for one hour in a bath maintained at 195–200°, pulverizing the cooled melt and storing it in a desiccator or a tightly stoppered bottle.

Sodium Amalgam. — The amalgams usually employed contain from 1 to 3 per cent of sodium. The 1.2 per cent amalgam is semisolid at room temperature and is melted completely at 50°; amalgams of higher concentration are solids which can be pulverized. The reaction can be carried out (1) by pushing successive pieces of sodium impaled on a pointed glass rod under the surface of mercury warmed to 40°, but the process is attended with flashes of flame and spattering and should be conducted from behind a protecting shield. Protection of the warm amal-

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[23] von Braun and Rudolph, *Ber.*, **67**, 269, 1735 (1934).

[24] Brewster and Poje, *J. Am. Chem. Soc.*, **61**, 2418 (1939).

[25] Mai, *Ber.*, **35**, 162 (1902).

[26] *J. Am. Chem. Soc.*, **63**, 188 (1941).

[27] Sonn and Müller, *Ber.*, **52**, 1929 (1919); Sonn and Meyer, **58**, 1096 (1925).

[28] Stephen, *J. Chem. Soc.*, **127**, 1874 (1925); see also Williams, *J. Am. Chem. Soc.*, **61**, 2248 (1939).

gam from air is desirable and can be achieved (2) by conducting the reaction in a nitrogen atmosphere, or (3) by using a covering layer of toluene. The nitrogen method (2) gives a superior product and is particularly recommended because of the ease of manipulation and the complete safety of the process. Procedures for the preparation of 2 per cent amalgam by methods (2) and (3) are given below. Clean mercury is used; the crust is cut from the sodium and any adhering kerosene is removed from the surface with a dry filter paper.

(2) [29] The sodium (6.9 g., 0.3 mole) is placed in a 250-cc. round-bottomed three-necked flask fitted with nitrogen inlet and outlet tubes in the side openings and a dropping funnel in the center opening. The flask is flushed out with nitrogen and the funnel is charged with 340 g. of mercury. About 10 cc. of the mercury is added and the flask is warmed slightly with a free flame until the reaction starts. Once this point is reached little further heating is required, for the reaction can be kept in progress by the slow addition of mercury until the total amount has been added. At the end, the still hot, molten amalgam is poured onto a piece of Transite board.. While it is still warm and soft, the silvery amalgam is crushed in a mortar and transferred to a tightly stoppered bottle.

The method is equally well applicable to the preparation of 3 per cent amalgam. In this case the mixture begins to solidify when about half of the mercury has been added, and the mixture is then kept in a molten condition by external heating, with occasional shaking.

(3) [30] The sodium (6.9 g.) is placed in a 250-cc. Erlenmeyer flask, covered with 10–15 cc. of toluene and cautiously melted by heating on a hot plate or over a free flame. All flames are extinguished and the mercury (340 g.) is added cautiously by drops with some shaking. After 2–3 cc. of mercury has been introduced the reaction becomes less vigorous and the mercury is added more rapidly so that the toluene boils continuously.

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[29] Communicated by Dr. Max Tishler.

[30] Holleman, "Organic Syntheses," Coll. Vol. I, 539 (1932).

At the end of the addition the toluene is allowed to evaporate completely or else decanted in case the amalgam solidifies. If necessary the amalgam is melted over a free flame or on a hot plate and then poured onto a Transite board and pulverized.

A typical example of the use of sodium amalgam is in the reduction of cinnamic acid to hydrocinnamic acid.[31]

The Clemmensen Method. — Clemmensen [32] discovered that a great many ketones and aldehydes can be reduced to hydrocarbons by the action of amalgamated zinc and hydrochloric acid, the change accomplished being: $>C{=}O \longrightarrow\ >CH_2$. Acetophenone yields ethylbenzene, benzil yields dibenzyl, salicylaldehyde yields *o*-cresol. The reduction proceeds particularly well with aromatic or aromatic-aliphatic ketones; purely aliphatic ketones also can be reduced to hydrocarbons but considerably more time is required for the completion of the reaction. Cyclic ketones usually are reducible by the Clemmensen method and the reaction finds many applications in the sterol and bile acid series. A steroid having one or more secondary alcoholic groups is oxidized with chromic acid and the ketonic product is then reduced with zinc and acid; the steroid alcohols themselves are seldom susceptible to Clemmensen reduction, possibly because they tend to undergo dehydration with consequent resinification. Derivatives of benzyl alcohol, benzhydrol, and triphenylcarbinol are not subject to dehydration and are reducible. Carboxyl and phenolic hydroxyl groups offer no special interference to the reaction except when they produce an unfavorable modification in the solubility relationships. Aromatically bound chlorine ordinarily withstands the reaction; with a bromide some loss of halogen may be anticipated.[33] The methyl ethers of phenolic compounds often suffer some

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[31] Gattermann-Wieland, "Laboratory Methods of Organic Chemistry," p. 234 (1937).

[32] Clemmensen, *Ber.*, **46**, 1838 (1913); **47**, 51, 681 (1914).

[33] β-(*p*-Bromobenzoyl)-propionic acid gives 75 per cent of the bromophenylbutyric acid and 14 per cent of the bromine-free acid; Fieser and Seligman, *J. Am. Chem. Soc.*, **60**. 173 (1938).

demethylation in the course of the reaction, and in working with such substances it is usually advisable to submit the crude material to remethylation before isolating the reaction product.[34]

Either mossy or granulated zinc may be used and is conveniently amalgamated[34] by placing 100 g. of the metal in a round-bottomed flask suitable for the reduction and shaking it for 5 minutes with a mixture of 150 cc. of water, 5 cc. of concentrated hydrochloric acid, and 10 g. of mercuric chloride; the supernatant solution is decanted and the other reagents added. In a typical reduction by the original Clemmensen procedure, the amalgamated zinc is covered with 100 cc. of water, 100 cc. of concentrated hydrochloric acid, and 50 g. of the compound to be reduced (e.g., acetophenone). The mixture is then heated under the reflux and maintained at a steady boil for a period varying from 4 to 10 hours. Two or three additions of fresh concentrated hydrochloric acid are made during this period and more amalgamated zinc is used if required. The product may be isolated by extraction with ether or by steam distillation, according to its properties.

Martin[34] found that improved results often are obtained by adding a layer of toluene to the reaction mixture. The toluene keeps otherwise undissolved material out of contact with the metal, which retains a bright surface throughout the reaction. The actual reduction doubtless occurs in the lower aqueous layer, and, since the ketonic material is distributed into this layer in a condition of high dilution, polymolecular side-reactions tend to be inhibited. It is well to maintain vigorous boiling in order to promote interchange of material between the two layers, and even so a prolonged period of refluxing is required (1 to 2 days). Improvements in the yield and in the quality of the product usually more than compensate for the added time required, and the Clemmensen-Martin procedure of reduction has found widespread use.

A typical procedure[34] applicable to a number of cases calls for

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[34] Martin, *J. Am. Chem. Soc.*, **58**, 1438 (1936).

amalgamating 100 g. of mossy zinc as above and adding the other reagents in order as follows: 75 cc. of water, 175 cc. of concentrated hydrochloric acid, 100 cc. of toluene, and 50 g. of the carbonyl compound (0.2–0.3 mole). The flask is fitted with an efficient reflux condenser, preferably by means of a ground glass joint, and the mixture is refluxed briskly for 24 to 36 hours, three 50-cc. portions of concentrated hydrochloric acid being added at intervals of about 6 hours. The flask must not be shaken during the refluxing, for this may cause a dangerous surge of vapor from the superheated mixture. In the preparation of γ-phenylbutyric acid[35] and other substances readily soluble in toluene, the reaction mixture is cooled, the toluene layer separated, and the aqueous layer diluted with water and extracted with benzene. The solvent is then removed and the product distilled in vacuum. In case a methoxy compound is to be remethylated, it is often convenient to mix the combined toluene and benzene solutions with alkali, steam distil, and add dimethyl sulfate at about 80°, using a little sodium hydrosulfite if necessary to prevent darkening of the solution. In isolating higher melting compounds, the layers are separated after slight cooling, benzene is used for the extraction, and the solution is clarified with Norit while wet, concentrated, and allowed to cool for crystallization.

Further modifications of the procedure are sometimes desirable. In the case of substances very sparingly soluble in water the reduction is greatly facilitated by the addition of a small amount (3–5 cc.) of glacial acetic acid along with the toluene. Good results have been obtained, for example with β-acetonaphthalene (50 g.), by using a combination of benzene (150 cc.), methanol (300 cc.), and concentrated hydrochloric acid (200 cc., plus three 20-cc. portions).[36] In isolated instances Clemmensen reduction has been accomplished most successfully in homogeneous solutions prepared by mixing hydrochloric acid with alcohol, glacial

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[35] Martin and Others, "Organic Syntheses," **15**, 64 (1935); Martin, *ibid.*, **17**, 97 (1937).

[36] Fieser, Campbell, Fry and Gates, *J. Am. Chem. Soc.*, **61**, 3218 (1939); see also Fieser, Fry and Jones, *ibid.*, **61**, 1852 (1939).

acetic acid,[37] or dioxane. Occasionally there is some advantage in the use of unamalgamated zinc.[38] Another means of moderating the reaction is to operate at a lower temperature.[39] Thus ketones derived from thiophene are highly sensitive to strong hydrochloric acid at the boiling point, but can be reduced satisfactorily by allowing a mixture of the substance with 1 : 1 acid and amalgamated zinc to stand at room temperature for 1–2 days and then to reflux the mixture for 1–2 hours to complete the reaction.

The reduction of a β-aroylpropionic acid sometimes presents difficulties because the substance neither dissolves readily nor melts at the reaction temperature. A useful expedient is to employ for the reduction a lower melting and more soluble ester derivative of the acid. The ester eventually is hydrolyzed in the acid mixture, but often survives hydrolysis long enough to promote reaction. Keto acids melting in the region of 200° have been reduced satisfactorily in the form of their methyl esters melting about 100° lower.[40]

In those rare instances where all variations of the Clemmensen method fail, alternate methods probably will also present difficulties but may afford at least some of the desired product. The Wolff-Kishner method, or reduction with zinc and alkali, is sometimes effective. High pressure hydrogenation over copper-chromite catalyst[41] is perhaps the most generally applicable method and with some ketones and keto acids gives better yields than the Clemmensen procedure. While fully aromatic keto acids have been hydrogenated as such without solvent,[42] difficulty

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[37] Example: reduction of an aromatic γ-lactone in 76 per cent yield; Fieser and Newman, *J. Am. Chem. Soc.*, **58**, 2381 (1936). An alternate method giving even better results (91 per cent yield) consists in opening the lactone ring with alcoholic alkali and reducing the hydroxy acid with zinc (copper-activated) and alkali; Newman, *ibid.*, **60**, 1369 (1938).

[38] Reduction of dehydrodesoxycholic acid to 12-ketocholanic acid; Wieland and Schlichting, *Z. physiol. Chem.*, **150**, 267 (1925).

[39] Krollpfeiffer and Schäfer, *Ber.*, **56**, 624 (1923); Anschütz and Wenger, *Ann.*, **482**, 32 (1930); Fieser and Kennelly, *J. Am. Chem. Soc.*, **57**, 1611 (1935).

[40] Fieser and Peters, *J. Am. Chem. Soc.*, **54**, 4373 (1932).

[41] Connor, Folkers and Adkins, *J. Am. Chem. Soc.*, **54**, 1138 (1932).

[42] Fieser and Hershberg, *J. Am. Chem. Soc.*, **59**, 1028, 2331 (1937).

is sometimes experienced with β-aroylpropionic acids owing to a tendency of the free acid to attack and deactivate the catalyst. In this case the hydrogenation can be conducted satisfactorily with a weakly alkaline aqueous solution of the sodium salt.[43]

The Wolff-Kishner Method. — This excellent method of reducing a carbonyl group to a methylene group depends upon the catalytic decomposition of a hydrazone in the presence of alkali and it involves the following sequence of reactions:

$$R_2C{=}O + H_2NNH_2 \longrightarrow R_2C{=}NNH_2 + H_2O$$

$$R_2C{=}NNH_2 \xrightarrow{\text{KOH or KOR}} R_2CH_2 + N_2$$

The reaction is one of wide application and usually gives good results with both aromatic and aliphatic ketones, with aldehydes, with cyclic ketones and keto acids, and with unsaturated carbonyl compounds. Wolff [44] originally isolated the hydrazone and heated it in a sealed tube with a solution of sodium ethylate to effect the decomposition, while Kishner [45] heated the hydrazone with solid potassium hydroxide. It is also possible to carry out both reactions together, as follows: 1 g. of sodium is dissolved by warming on the steam bath in 12 cc. of absolute alcohol in the tube which is to be used for the heating. The solution is cooled, 1.25 cc. (0.0255 mole) of pure hydrazine hydrate and 0.025 mole of the compound to be reduced (e.g., 4.55 g. of benzophenone) are added, the tube is sealed and heated in the bomb furnace at 160° for 6–8 hours.

On opening the tube it is sometimes found that the reduction product is contaminated with a small amount of a yellow, sparingly soluble product. This is the azine, formed by the side reaction: $R_2C{=}NNH_2 + O{=}CR_2 \longrightarrow R_2C{=}NN{=}CR_2 + H_2O$. The presence of water in the reaction mixture favors the formation of the azine and, since a molecule of water is formed in the reaction of the carbonyl compound with hydrazine, it is some-

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[43] Observation of H. Heymann; for examples, see Fieser and Cason, *J. Am. Chem. Soc.*, **62**, 1293 (1940); Fieser and Clapp, *ibid.*, **63**, 319 (1941).

[44] *Ann*, **394**, 86 (1912).

[45] *J. Russ. Phys. Chem. Soc.*, **43**, 582 (1911) [*Chem. Zentr.*, **2**, 363 (1911)].

times preferable to isolate the hydrazone in a crude but dry condition and either (1) to heat the material (0.025 mole) with a solution of sodium (1 g.) in absolute alcohol (12 cc.) in a sealed tube, or (2) to heat a mixture of the hydrazone with 5 per cent of its weight of dry, pulverized potassium hydroxide in an open flask in an oil bath to a temperature (160°–180°) at which nitrogen is rapidly evolved.[46] Where pure hydrazine hydrate is not available or is unreasonably expensive, this method has the further advantage of economy, for the hydrazone usually can be prepared with the use of an aqueous solution of hydrazine or with a solution prepared by warming a suspension of hydrazine hydrochloride (1.05 g., 0.01 mole) and fused sodium acetate (1.64 g., 0.02 mole) in alcohol and filtering from the sodium chloride formed. If, on the other hand, a sealed tube or autoclave has to be used for the preparation of the hydrazone, the other method is to be preferred.

Another variation which is equally satisfactory is to heat the semicarbazone of the carbonyl compound with sodium ethylate. This is converted first into the hydrazone: $R_2C=NNHCONH_2 \longrightarrow R_2C=NNH_2 + CO_2 + NH_3$ and the latter substance then undergoes the usual decomposition to the hydrocarbon.

Reduction with Aluminum Alkoxides (Meerwein-Ponndorf Method [47]). — Aldehydes and ketones can be reduced very smoothly to the corresponding alcohols by treatment with aluminum isopropoxide in a suitable solvent and displacement of the resulting equilibrium by distillation of the acetone formed.

$$3\,\begin{matrix}R_1\\R_2\end{matrix}\!>\!C=O + Al\left(OCH\!<\!\begin{matrix}CH_3\\CH_3\end{matrix}\right)_3 \rightleftharpoons \left(\begin{matrix}R_1\\R_1\end{matrix}\!>\!CHO\right)_3 Al + 3O=C\!<\!\begin{matrix}CH_3\\CH_3\end{matrix}$$

The alcoholic reduction product is recovered from the reaction mixture after acidification. Aluminum ethoxide and aluminum derivatives of other primary alcohols were used in the early work [47] but have been found much less efficacious than alumi-

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[46] Rabe and Jantzen, *Ber.*, **54**, 928 (1921).

[47] Meerwein and Schmidt, *Ann.*, **444**, 221 (1925); Ponndorf, *Z. angew. Chem.*, **39**, 138 (1926); see also Verley, *Bull soc. chim.*, [4] **37**, 537 (1925).

num isopropoxide.[48, 49] The reagent can be prepared by heating aluminum turnings (from aluminum alloy such as "2–ST" or from pure aluminum) with dry isopropyl alcohol (distilled over sodium, 15–25 cc. per gram of aluminum). In order to insure prompt starting of the reaction it is well to place the aluminum in the reaction flask and to heat it in an atmosphere of nitrogen over a free flame prior to the addition of the isopropyl alcohol. A small amount of mercuric chloride is then added and the mixture is refluxed. In case the reaction does not commence in 5–10 minutes, as evidenced by a cloudy appearance followed by a marked darkening of the solution, it may be found helpful to add (1) a small crystal of iodine, followed by a pinch of copper bronze,[50] or (2) a few drops of carbon tetrachloride.[51] Once started, the reaction proceeds vigorously and the metal usually is all dissolved after refluxing for a few hours. The resulting gray-black solution may be used as such or the aluminum isopropoxide may be collected by removal of the solvent and purified by distillation[48] (b.p. 145–150° at 5 mm.). In the former case[49, 50] the compound to be reduced is added and the solution is boiled in a flask equipped with a column in such a way as to allow the acetone formed and the solvent to distil slowly in the course of 2–3 hours; fresh isopropyl alcohol is added and the slow distillation repeated. For the efficient reduction of ketones[51] it is well to distil the bulk of the isopropyl alcohol from the aluminum isopropoxide, take up the residual dark, syrupy product in toluene, add the ketone and reflux for 2–3 hours, slowly distil the acetone and a part of the solvent, add fresh toluene, and slowly distil the bulk of the solvent. In any case the final reaction mixture is acidified in the cold with 10 per cent sulfuric acid and the product collected by extraction with ether. Sufficiently volatile products may be purified by distillation, while with substances of higher molecular weight it is often convenient to submit the product to steam distillation in order

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[48] Young, Hartung and Crossley, *J. Am. Chem. Soc.*, **58**, 100 (1936).

[49] Lund, *Ber.*, **70**, 1520 (1937).

[50] Schenck, *J. prakt. Chem.*, **134**, 241 (1932).

[51] Bachmann and Struve, *J. Org. Chem.*, **4**, 456 (1939).

to remove the solvent and traces of mesityl oxide and other odoriferous condensation products of acetone which may be present.

The yields usually are excellent, and the Meerwein-Ponndorf method of reduction has the great advantage of being specific for the carbonyl group and without influence on other centers of unsaturation, as illustrated in the following examples:

$$\begin{array}{lcl} \mathrm{CH_3CH=CHCHO} & \xrightarrow{\mathrm{Al(OC_3H_7)_3}} & \mathrm{CH_3CH=CHCH_2OH}\ \text{[48]} \\ \text{Crotonaldehyde} & & \text{Crotyl alcohol (85–90\% yield)} \\ o\text{-}\mathrm{O_2NC_6H_4CHO} & \xrightarrow{\mathrm{Al(OC_3H_7)_3}} & o\text{-}\mathrm{O_2NC_6H_4CH_2OH}\ \text{[50]} \\ o\text{-Nitrobenzaldehyde} & & o\text{-Nitrobenzyl alcohol (90\% yield)} \end{array}$$

Hydrogen Iodide — Red Phosphorus. — The combination of concentrated hydriodic acid (57 per cent) and red phosphorus when employed in a sealed tube at 150–200° constitutes a powerful method of reduction which at one time found application for the conversion of alcohols into hydrocarbons and of aromatic hydrocarbons into hydroaromatic derivatives.[52] Only small amounts of material can be used, however, and even so the tubes frequently do not survive the heating. Although the original method has been supplanted by other processes, the following modifications are of distinct preparative value.

The use of a refluxing solvent at atmospheric pressure was introduced by Zinsser,[53] who obtained diphenylacetic acid in excellent yield by refluxing benzilic acid in acetic acid with hydriodic acid and red phosphorus. The method was further improved [54] by using red phosphorus and iodine in 98 per cent acetic acid, the amount of iodine being only a small fraction of the equivalent amount. Miescher and Billeter [55] have pointed out that iodine or an iodide functions merely as a hydrogen carrier and that phosphorus is the true reducing agent.

$$\mathrm{(C_6H_5)_2C(OH)CO_2H} \longrightarrow \mathrm{(C_6H_5)_2CHCO_2H}$$

These investigators describe a number of satisfactory variations of the procedure calling for the use of either potassium iodide or

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[52] Houben, 3rd Ed., II, 451–452 (1925).

[53] *Ber*, **24**, 3556 (1891).

[54] Marvel, Hager and Caudle, "Organic Syntheses," Coll. Vol. I, 219 (1932).

[55] *Helv. Chim. Acta*, **22**, 601 (1939).

iodine in an amount corresponding to 5–10 per cent of one equivalent. Dilute hydrochloric acid may be used as the reaction medium if a moderate temperature (100°) is adequate; and progressively higher temperatures are obtained by using acetic acid or propionic acid. Phosphoric acid serves as a particularly good medium, and temperatures between 100° and 150° can be attained by using mixtures of commercial phosphoric acid and water. Reduction occurs readily even though the starting material dissolves in the acid to only a slight extent.

A *typical procedure*[55] consists in refluxing for six hours a mixture of 15 g. (0.1 mole) of mandelic acid, 2.07 g. of potassium iodide, 6 g. of red phosphorus, 70 cc. of phosphoric acid (90 per cent), and 10 cc. of water. A little water is added to dissolve precipitated salts and the cooled mixture is extracted with ether. The extract is decolorized by extraction with sodium bisulfite solution, and is then washed, dried, and evaporated. Distillation of the residue gives phenylacetic acid in 90 per cent yield.

Other applications of the method are indicated in the formulas:

$C_6H_5CH = CHCO_2H \longrightarrow C_6H_5CH_2CH_2CO_2H$

Cinnamic acid → Hydrocinnamic acid (80% yield)

$$o\text{-}C_6H_4\begin{cases}CO_2H\\COCO_2H\end{cases} \longrightarrow o\text{-}C_6H_4\begin{cases}CO_2H\\CH_2CO_2H\end{cases}$$

Phthalonic acid → Homophthalic acid (86% yield)

$p\text{-}CH_3C_6H_4SO_2Cl \longrightarrow p\text{-}CH_3C_6H_4SH$

p-Toluenesulfonyl chloride → *p*-Tolylmercaptan (87% yield)

o-Benzoylbenzoic acid is reduced in only moderate yield (71 per cent), and the method is considerably less satisfactory when applied to the reduction of β-benzoylpropionic acid to γ-phenylbutyric acid. The procedure can be adapted to the cleavage of phenol ethers by using a full molecular equivalent of iodine.

OXIDATION

Potassium Permanganate. Mandelic acid → phenylglyoxylic acid → benzoic acid (page 217).

Sodium Dichromate. Ethyl alcohol → acetaldehyde (page 80).

Nitric Acid. Benzoin ⟶ benzil (page 225).

Manganese Dioxide. Hydroquinone ⟶ quinone (page 228).

Sodium Chlorate with Vanadium Pentoxide as Catalyst. Hydroquinone ⟶ quinone [1] (92–96 per cent yield).

Fehling's Solution. Preparation: page 86. Example: Benzoin ⟶ benzil.[2]

Ferric Chloride. Aminonaphthols ⟶ naphthoquinones (page 231).

Gold Chloride. α-Tocopherol ⟶ α-tocopherylquinone.[3]

Chromic Anhydride in Acetic Acid. Aromatic hydrocarbons ⟶ quinones (page 232).

Chromic Anhydride in an Acetylating Mixture.[4] — The solvent medium is prepared by adding concentrated sulfuric acid (1 cc.) to an ice-cooled mixture of acetic acid (5 cc.) and acetic anhydride (5–10 cc.). After the introduction of the toluene derivative to be oxidized, the solution is stirred and treated at 5–10° with chromic anhydride, added in portions. The aldehyde resulting as the primary product of oxidation is at once converted to the diacetate and thus protected from further oxidation; the aldehyde subsequently is liberated by acid hydrolysis. The reaction is applicable to nitro-, halo-, and hydroxy-derivatives of toluene, and the xylenes are convertible to dialdehydes. The yields usually are in the range 30–55 per cent.

$$ArCH_3 \longrightarrow ArCH(OCOCH_3)_2 \longrightarrow ArCHO$$

Potassium Permanganate in Pyridine. — This combination has been employed for the quantitative determination of the oxygen equivalent of unsaturated substances [5] and in degradative studies.[6]

Silver Oxide. — For the preparation of completely anhydrous silver oxide suitable for use where the oxidation product is ex-

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[1] Underwood and Walsh, "Organic Syntheses," **16**, 73 (1936).

[2] Clarke and Dreger, "Organic Syntheses," Coll. Vol. I, 80 (1932).

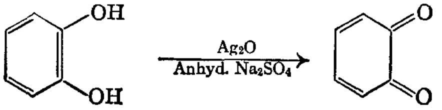
[3] Karrer and Geiger, *Helv. Chim. Acta*, **23**, 455 (1940).

[4] Thiele and Winter, *Ann.*, **311**, 353 (1900).

[5] J. H. C. Smith and Spoehr, *J. Biol. Chem.*, **86**, 87 (1930).

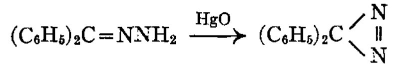
[6] Bucher, *J. Am. Chem. Soc.*, **32**, 374 (1910).

tremely sensitive to traces of moisture, the paper of Willstätter and Pfannenstiel[7] should be consulted. Example:



For the use of the reagent in the preparation of vitamin K_1 see page 238.

Mercuric Oxide (Yellow). — A useful reagent for oxidations in non-aqueous solvents, thus:[8]



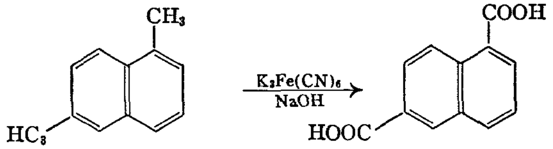
$$(C_6H_5)_2C{=}NNH_2 \xrightarrow{HgO} (C_6H_5)_2C{\langle}\overset{N}{\underset{N}{\|}}$$

Diphenyldiazomethane

Similar oxidations have been conducted with the addition of anhydrous calcium sulfate to absorb the water formed.[9]

Lead Dioxide, PbO_2,[10] is used for the oxidation of the leuko bases of triphenylmethane dyes.

Potassium Ferricyanide. — This is a mild oxidizing agent which sometimes attacks a side chain (slowly) without affecting the aromatic ring, thus:[11]



(The reaction is useful for structure determination but is hardly of preparative value.)

Oxides of Nitrogen (N_2O_3, NO_2, etc.). — The preparation of the gas from arsenious oxide and nitric acid and its use in the following oxidation:

$$CH_2(COOC_2H_5)_2 \longrightarrow CO(COOC_2H_5)_2$$

Ethyl oxomalonate

are described in detail by Dox.[12]

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[7] *Ber.*, **37**, 4744 (1904).

[8] Staudinger, Anthes and Pfenninger, *Ber.*, **49**, 1932 (1916).

[9] L. I. Smith and Hoehn, "Organic Syntheses," **20**, 47 (1940).

[10] Preparation: Gattermann-Wieland, "Methods," p. 325 (1937).

[11] Weissgerber and Kruber, *Ber.*, **52**, 352 (1919); Ruzicka and co-workers, *Helv. Chim. Acta*, **9**, 976 (1926); **14**, 238 (1931).

[12] "Organic Syntheses," Coll. Vol. I, 261 (1932).

Ceric Sulfate, $Ce(SO_4)_2$. — An aqueous solution of this substance, which is useful as a titrating agent on account of the very high oxidation-reduction potential, is conveniently prepared by dissolving ceric ammonium sulfate in sulfuric acid and diluting to a volume at which the concentration is $0.1N$.[13]

Mercuric Acetate. Ergosterol ⟶ dehydroergosterol.[14]

Oxygen. Tetralin ⟶ peroxide ⟶ α-tetralone[15] (50 per cent yield).

Hypochlorite Solution. — An approximately 1 normal solution of this reagent may be prepared as follows.[16] A solution of 100 g. of sodium hydroxide in 500 cc. of water is cooled in an ice bath, 400 g. of crushed ice is added and, while cooling well in the ice bath, chlorine gas is passed in from a tank until 71 g. has been added. (The chlorine also may be generated as described on page 392, using 32.3 g. of potassium permanganate.) The solution is diluted to one liter, filtered if necessary, and kept in the dark. An excess of sodium hydroxide is used to prevent decomposition to sodium chlorate and sodium chloride, and the solution will keep for over a week without appreciable decrease in strength.

It is sometimes a convenience to make use of the preparations sold for household use under various trade names and containing about 5 per cent of sodium hypochlorite.

Another method of preparation[17] is to dissolve 250 g. of commercial calcium hypochlorite ("HTH") in 1 l. of warm water, add a warm solution of 175 g. of potassium carbonate and 50 g. of potassium hydroxide in 500 cc. of water, shake vigorously until the semisolid gel becomes fluid, and filter the solution through a large Büchner funnel. The solid is washed with 200 cc. of water and pressed well with the use of a rubber dam. The filtrate of approximately 1500 cc. contains about 200 g. (2.3 moles) of potassium hypochlorite.

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[13] Willard and Furman, "Elementary Quantitative Analysis," p. 254 (1940).

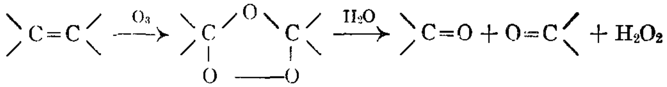
[14] Windaus and Linsert, *Ann.*, **465**, 148 (1928).

[15] Thompson, "Organic Syntheses," **20**, 94 (1940).

[16] Graebe, *Ber.*, **35**, 2753 (1902); Raschig, *ibid.*, **40**, 4586 (1907); Adams and Brown, "Organic Syntheses," Coll. Vol. I, 302 (1932).

[17] Newman and Holmes, "Organic Syntheses." **17**, 66 (1937).

Ozone. — The cleavage of an ethylenic linkage by ozonization, followed by the decomposition of the ozonide with water, may be represented as follows:



Useful forms of laboratory ozonizers have been described by Smith[18] and by Whitmore and associates.[19] By far the best method known for decomposing ozonides is F. G. Fischer's process of hydrogenation in the presence of palladium–calcium carbonate catalyst.[20] The amount of hydrogen absorbed gives a measure of the extent of the ozonization, and the hydrogenation stops with the formation of the aldehydic or ketonic reaction products.

Sodium Hydrogen Peroxide. — A slightly alkaline solution containing approximately 3.8 per cent of hydrogen peroxide can be prepared from inexpensive starting materials as follows:[21] 80 g. (1 mole) of sodium peroxide powder is added slowly to 650 g. of a mixture of ice and water which is stirred mechanically in a salt-ice bath; 142 cc. (1.7 moles) of concentrated hydrochloric acid is then added by drops, and the temperature is kept from rising above 5° by stirring and by adding more ice if necessary. If the resulting solution is to be used in an alcoholic medium it is advisable to add 50 cc. of alcohol to it at once, for this stabilizes the solution and also helps to prevent the precipitation of the organic reactant. For the preparation of the oxide of benzalacetophenone[21] the above solution, after the alcohol has been added, is poured rapidly into a solution of 0.5 mole of the unsaturated ketone in 2 liters of alcohol at 35°.

An alternate and simpler method of preparing a water-alcohol solution in which the active reagent probably is sodium hydrogen peroxide consists in adding hydrogen peroxide and aqueous sodium carbonate solution to a solution of the unsaturated com-

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[18] L. I. Smith, *J. Am. Chem. Soc.*, **47**, 1844 (1925); L. I. Smith and Ullyot, *ibid.*, **55**, 4327 (1933). See also Gross and Phillips, *J. Assoc. Official Agr. Chem.*, **21**, 326 (1938).

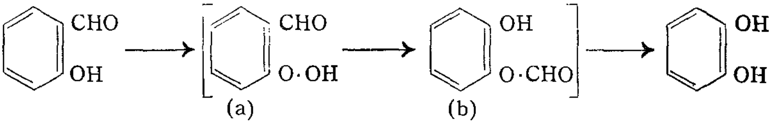
[19] Church, Whitmore and McGrew, *J. Am. Chem. Soc.*, **56**, 176 (1934).

[20] F. G. Fischer, Düll and Ertel, *Ber.*, **65**, 1467 (1932).

[21] Kohler, Richtmyer and Hester, *J. Am. Chem. Soc.*, **53**, 213 (1931).

pound in alcohol[22] (example: 2-methyl-1,4-naphthoquinone oxide, page 235).

Alkaline Hydrogen Peroxide (Dakin Reaction [23]). — On treatment with 3 per cent hydrogen peroxide in alkaline solution at room temperature *o*- and *p*-phenolic aldehydes and ketones are converted smoothly into the dihydroxy compounds with cleavage of the formyl or acyl group. Salicylaldehyde and *p*-hydroxybenzaldehyde yield catechol and hydroquinone, respectively. *o*-Aminobenzaldehyde similarly affords *o*-aminophenol on oxidation with Caro's acid in a weakly alkaline solution.[24] The presence of a hydroxyl or amino group ortho or para to the carbonyl group is essential; the *meta*-compounds are merely oxidized to the corresponding acids. Recent evidence [25] indicates that the Dakin reaction probably involves the formation of a peroxide (a) and its rearrangement (b). An intermediate of the second type (b) has been isolated from the reaction with *o*-aminobenzaldehyde.[24]



When applied to substances sparingly soluble in aqueous alkali, the reaction is best conducted by adding perhydrol and concentrated alkali to a solution of the material in pyridine; example: 3-phenanthrol-4-aldehyde ⟶ morphol.[26]

Hydrogen Peroxide — Acetic Acid. — One use for the reagent is in the hydroxylation of an olefinic compound to the corresponding glycol. The reaction may be conducted at room temperature over a period of several days.[27] An improved procedure [28] consists in heating a mixture of acetic acid and 30 per

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[22] Fieser, Campbell, Fry and Gates, *J. Am. Chem. Soc.*, **61**, 3216 (1939); Tishler, Fieser and Wendler, *ibid.*, **62**, 2866 (1940).

[23] Dakin, *Am. Chem. J.*, **42**, 477 (1909).

[24] Bamberger, *Ber.*, **36**, 2042 (1903).

[25] v. Waeck and Eppinger, *Ber.*, **73**, 644 (1940).

[26] Barger, *J. Chem. Soc.*, **113**, 218 (1918).

[27] Hilditch, *J. Chem. Soc.*, 1828 (1926).

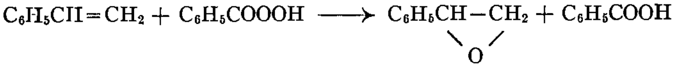
[28] Scanlan and Swern, *J. Am. Chem. Soc.*, **62**, 2305, 2309 (1940).

cent hydrogen peroxide at 85° for one hour, cooling to 25°, adding the unsaturated compound, and allowing the reaction to proceed exothermally (75°) until completed (4–5 hours). Hydrogen peroxide in acetic acid also cleaves phenanthrenequinones smoothly to diphenic acids,[29] and the reagent oxidizes hydrocarbons such as β-methylnaphthalene and anthracene to the *p*-quinones in about the same yields as obtained with chromic acid.[30]

Hydrogen Peroxide — *tert.*-Butyl Alcohol — OsO_4. — An anhydrous solution of hydrogen peroxide in *tert.*-butyl alcohol with a trace of osmium tetroxide as catalyst converts olefinic substances at 0° into glycols in yields of 30–60 per cent.[31]

Nitric Acid — Hydrogen Peroxide.[32] — A mixture of nitric acid (sp. gr. 1.26) and 30 per cent hydrogen peroxide (perhydrol) in acetic acid constitutes an excellent reagent for the oxidation of aromatic nitroso compounds to the nitro derivatives (62–88 per cent yields), as in the example shown. The method is advantageously applied to methylated compounds, for more drastic methods result in some attack of the alkyl substituents.

Perbenzoic Acid (Benzoyl Hydrogen Peroxide), C_6H_5COOOH. The preparation of the reagent has been described by various investigators.[33] An illustration of its special function is in the preparation of styrene oxide [34] (Prileschajew reaction):



$$C_6H_5CH{=}CH_2 + C_6H_5COOOH \longrightarrow C_6H_5\underset{\diagdown\,O\,\diagup}{CH{-}CH_2} + C_6H_5COOH$$

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[29] Diphenic acid is obtained in 70 per cent yield by refluxing 50 g. of phenanthrenequinone in 150 cc. of acetic acid with 500 cc. of 6 per cent hydrogen peroxide for 3 hours; Linstead and Walpole, *J. Chem. Soc.*, 855 (1939).

[30] Arnold and Larson, *J. Org. Chem.*, **5**, 250 (1940).

[31] Milas and Sussman, *J. Am. Chem. Soc.*, **58**, 1302 (1936).

[32] Kuhn and van Klaveren, *Ber.*, **71**, 779 (1938).

[33] Tiffeneau, "Organic Syntheses," Coll. Vol. I, 422 (1932); Braun, *ibid.*, **13**, 86 (1933); Brooks and Brooks, *J. Am. Chem. Soc.*, **55**, 4309 (1933). For observations concerning the stability of different preparations of perbenzoic acid, see Calderwood and Lane, *J. Phys. Chem.*, **45**, 108 (1941).

[34] Hibbert and Burt, "Organic Syntheses," Coll. Vol. I, 481 (1932).

Monoperphthalic Acid. — The reagent may be used in place of perbenzoic acid for the conversion of unsaturated compounds into oxides. It is more easily and cheaply prepared than perbenzoic acid and has greater stability. The sparing solubility of phthalic acid in chloroform is sometimes of advantage in working up the reaction mixture. The peracid is prepared by the action of alkaline hydrogen peroxide on phthalic anhydride.[35]

Selenium Dioxide. — Since Riley's discovery[36] of the oxidizing action of this reagent on certain types of organic compounds it is finding many uses in the organic laboratory. Selenium dioxide has the specific property of converting a compound containing an active methylene group adjacent to a carbonyl group into an α-keto aldehyde or an α-diketone. Thus glyoxal is conveniently prepared by the reaction:

$$CH_3CHO + SeO_2 \longrightarrow OHC.CHO + Se + H_2O$$

Phenylglyoxal can be prepared in a similar manner starting with acetophenone.[37] Selenium dioxide has been employed also for effecting the introduction of a hydroxyl group at a position adjacent to the double bond or diene system of an unsaturated compound. The reaction ordinarily is carried out in a boiling solution in alcohol or dioxane, in both of which solvents the selenium dioxide is soluble. The separation of red selenium furnishes an indication of the progress of the reaction. Commercial selenious acid (H_2SeO_3) may be used in place of the dioxide, but in any case the selenium should be recovered and converted into the dioxide for further use. The dioxide is poisonous and the following operations are to be carried out under the hood.

Seventy cc. of concentrated nitric acid is heated in a 1-l. beaker on a hot plate and 50 g. of selenium (pure or recovered) is stirred in, in small portions. When the material is all dissolved the solution is evaporated in a porcelain dish on the hot plate and heated at a temperature not exceeding 200° until the selenious

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[35] Böhme, *Ber.*, **70**, 379 (1937); "Organic Syntheses," **20**, 70 (1940).

[36] Riley, Morley and Friend, *J. Chem. Soc.*, **1932**, 1875.

[37] Riley and Gray, "Organic Syntheses," **15**, 67 (1935).

acid is completely dehydrated. For purification the dioxide is sublimed from a porcelain crucible upon which is placed a Pyrex Erlenmeyer flask, with tap water running through it, to act as a condenser.

Lead Tetraacetate. — This substance is a very powerful oxidizing agent having properties which make it particularly serviceable for bringing about certain specific transformations. The solvent usually employed is glacial acetic acid, in which lead tetraacetate is readily soluble, but a suspension of the material in benzene also can be used. Although the reagent is hydrolyzed rapidly by water, it can under certain conditions be employed in an aqueous medium,[38] and the velocity of oxidation in acetic acid is greatly increased on adding water or alcohol.[39]

In the first of the two procedures given below lead tetraacetate is prepared by warming red lead with acetic acid in the presence of enough acetic anhydride to combine with the water formed:

$$Pb_3O_4 + 8HOAc \longrightarrow Pb(OAc)_4 + 2Pb(OAc)_2 + 4H_2O$$

In the second procedure more acetic acid and acetic anhydride are used and chlorine is passed into the solution to oxidize a part of the bivalent lead to the tetravalent state:

$$2Pb(OAc)_2 + Cl_2 \longrightarrow Pb(OAc)_4 + PbCl_2$$

The second method is preferred for the preparation of large amounts of material because the yield is better and because a colorless product is more easily obtained.

Procedure 1: [40] A mixture of 600 cc. of glacial acetic acid and 400 cc. of acetic anhydride in a wide-mouthed or three-necked flask is heated to 55° with mechanical stirring, and 700 g. (1.02 moles) of dry red lead powder is added in portions of 15–20 g. A fresh addition is made only after the color due to the preceding portion has largely disappeared, and the temperature is kept

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[38] Baer, Grosheintz and H. O. L. Fischer, *J. Am. Chem. Soc.*, **61**, 2607 (1939); Baer, *ibid.*, **62**, 1597 (1940).

[39] Criegee and Büchner, *Ber.*, **73**, 563 (1940).

[40] This is essentially the procedure of Dimroth and Schweizer, *Ber.*, **56**, 1375 (1923), as modified by Hellmuth, *Dissertation*, Würzburg (1930).

between 55° and 80°. At the end of the reaction the thick and somewhat dark solution is cooled and the crystalline lead tetraacetate which separates is collected and washed with acetic acid. The crude product without being dried is dissolved in hot acetic acid and the solution is clarified with Norit, filtered, and cooled. The colorless crystalline product is dried in a vacuum desiccator over potassium hydroxide and stored in the desiccator; yield 320–350 g.

Procedure 2:[41] A 5-liter three-necked flask fitted with a mechanical stirrer (tantalum wire or glass, no seal required), a thermometer, and a 10-mm. gas inlet tube is charged with 2500 cc. of glacial acetic acid and 700 cc. of acetic anhydride and the mixture is warmed to 60° on the steam bath (hood). Dry chlorine gas is passed into the solution with stirring and 700 g. of dry red lead powder is added in 15–20 g. portions, each addition being made only after the color due to the previous portion has faded. The temperature is maintained at 60–75° throughout the addition, which takes about 2 hours. When the reaction is complete, 1–2 g. of Norit is added to the hot mixture containing precipitated lead chloride and the suspension (at 75°) is filtered rapidly by suction using a large preheated Büchner funnel. The residue consisting largely of lead chloride is extracted by digesting it with 100 cc. of warm acetic acid, filtering, and repeating the process with two successive 100-cc. portions of solvent. The combined filtrates on cooling deposit the lead tetraacetate in colorless needles, and the product is collected, dried in a vacuum desiccator, and stored out of contact with moist air; yield 500–550 g. This material is found by titration to be 94–95 per cent pure; it contains a small amount of lead chloride but is entirely satisfactory for most purposes. A purer product can be obtained by recrystallization, but the process is attended with considerable loss. Distillation of the filtrate gives acetic acid satisfactory for use in another preparation.

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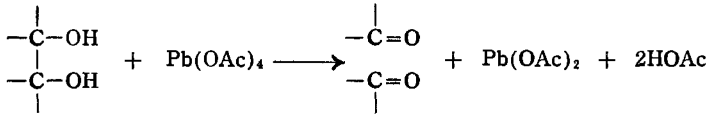
[41] Procedure of Oesper and Deasy, *J. Am. Chem. Soc.*, **61**, 972 (1939), with slight modifications.

Lead tetraacetate rapidly turns brown at the surface on exposure to moist air. Slightly brown material may be used in combination with acetic acid with little disadvantage, for the color eventually disappears. Very dark material should be purified by refluxing it gently with acetic acid until the color is discharged (1–2 hours), adding Norit, filtering the hot solution by gravity, and allowing crystallization to take place.

In using lead tetraacetate in an oxidation reaction, a small portion of the material is added and given an opportunity to react, and the solution is then tested for the presence of tetravalent lead by placing a drop on a moistened starch-iodide paper. If the test is positive (blue coloration), more time is allowed, or the temperature is raised. In case excess reagent persists after completion of the oxidation, it is often convenient to destroy the excess by the addition of the requisite amount of glycerol, added dropwise, before adding water and working up the reaction mixture. For standardization of a solution of lead tetraacetate in acetic acid, an aliquot portion is run into an aqueous solution of sodium acetate and excess potassium iodide and the liberated iodine is titrated with standard sodium thiosulfate solution.[42]

An important reaction of lead tetraacetate of wide application is the cleavage of glycols to aldehydes and ketones.[43] The hydroxyl groups of the glycol must be in a free, unacylated condition. The reaction has been extended to α-keto acids and α-keto alcohols by operating in a solution containing water or methanol;[44] the hydroxylic component adds to the carbonyl group to give a pseudoglycol, which then undergoes quantitative oxida-



$$\begin{matrix} | \\ -\text{C}-\text{OH} \\ | \\ -\text{C}-\text{OH} \\ | \end{matrix} + \text{Pb(OAc)}_4 \longrightarrow \begin{matrix} | \\ -\text{C}=\text{O} \\ \\ -\text{C}=\text{O} \\ | \end{matrix} + \text{Pb(OAc)}_2 + 2\text{HOAc}$$

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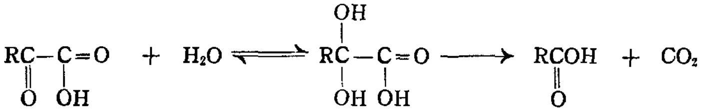
[42] Hockett and McClenahan, *J. Am. Chem. Soc.*, **61**, 1670 (1939).

[43] Criegee, Kraft and Rank, *Ann.*, **507**, 159 (1933).

[44] Baer. *J. Am. Chem. Soc.*, **62**, 1597 (1940).

tive cleavage. Lead tetraacetate has been employed also for effecting the cleavage of the carbon chain of glycosides.[45]



$$\underset{\overset{\|}{\mathrm{O}}}{\mathrm{RC}}-\underset{\overset{|}{\mathrm{OH}}}{\mathrm{C}}=\mathrm{O} + \mathrm{H_2O} \rightleftharpoons \overset{\underset{|}{\mathrm{OH}}}{\underset{\overset{|}{\mathrm{OH}}}{\mathrm{RC}}}-\underset{\overset{|}{\mathrm{OH}}}{\mathrm{C}}=\mathrm{O} \longrightarrow \underset{\overset{\|}{\mathrm{O}}}{\mathrm{RCOH}} + \mathrm{CO_2}$$

Another use of lead tetraacetate is in the acetoxylation of compounds having a reactive hydrogen atom. Malonic ester may be converted into acetyltartronic ester,[46] $CH_2(CO_2C_2H_5)_2 \xrightarrow{Pb(OAc)_4} CH_3COOCH(CO_2C_2H_5)_2$, and acenaphthene is attacked in the ace-ring and gives 7-acenaphthenyl acetate in good yield.[47] When such an oxidation is to be conducted in acetic acid solution on a large scale, it often is convenient to dispense with the preparation of lead tetraacetate and simply add red lead in portions to an acetic acid solution of the compound to be oxidized.[47, 48] Certain uniquely reactive hydrocarbons such as 3,4-benzpyrene can be acetoxylated in excellent yield by interaction with lead tetraacetate at a low temperature.[49] Anthracene affords 9-acetoxyanthracene in moderate yield[50] as the result of an addition to the diene system.[51]

Both open-chain and cyclic unsaturated hydrocarbons are susceptible to attack by lead tetraacetate. Usually the chief reaction consists in the introduction of an acetoxyl group on a carbon atom adjacent to the center of unsaturation, but since addition to the unsaturated system may also occur a complex mixture of products often results. Ketones can be acetoxylated in the α-position with moderate success with lead tetraacetate.

Another use for the reagent is in the preparation of quinones of very high potential. Diphenoquinone separates in a crystalline

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[45] McClenahan and Hockett, *J. Am. Chem. Soc.*, **60**, 2061 (1938); Hockett and McClenahan, *ibid.*, **61**, 1667 (1939).

[46] Dimroth and Schweizer, *Ber.*, **56**, 1375 (1923); Bak, *Ann.*, **537**, 291 (1938).

[47] Fieser and Cason, *J. Am. Chem. Soc.*, **62**, 434 (1940).

[48] Ward, *J. Am. Chem. Soc.*, **60**, 325 (1938); Scanlan and Swern, *ibid.*, **62**, 2305 (1940).

[49] Fieser and Hershberg, *J. Am. Chem. Soc.*, **60**, 1893, 2542 (1938).

[50] K. H. Meyer, *Ann.*, **379**, 73 (1911).

[51] Observation of S. T. Putnam.

condition in good yield on adding lead tetraacetate to a solution of *p,p'*-dihydroxydiphenyl in glacial acetic acid.

Periodic Acid (Malaprade Reaction[52]**).** — Treatment with periodic acid in aqueous solution constitutes a general method of cleaving glycols to carbonyl-containing products, and the results parallel those obtainable with lead tetraacetate. The carbon chain of a polyalcohol suffers fission between each pair of hydroxylated positions. Thus glycerol yields two moles of formaldehyde and one of formic acid. Dihydroxyacetone, presumably reacting in the hydrated form, gives formaldehyde and glycolic acid:

$$CH_2(OH)COCH_2OH + HIO_4 \longrightarrow CH_2(OH)COOH + CH_2O + HIO_3$$

For some purposes it is satisfactory to employ the aqueous solution of the acid obtained by treatment of a solution of potassium periodate with an equivalent amount of sulfuric acid. A large volume of water is required, however, to dissolve the potassium salt, and in applying the reaction in the sugar series the presence of potassium ion is often objectionable. Such difficulties are obviated by using the commercially available crystalline periodic acid[53, 54] ($HIO_4.2H_2O$), which is readily soluble in water. The oxidation of compounds difficultly soluble in water, such as glycols of the steroid series, is best accomplished by adding the aqueous periodic acid to a solution of the substance in purified dioxane.[54] The reaction proceeds to completion at room temperature in a period of several hours. Excess reagent can be destroyed with glycerol. Alcohol is a less satisfactory solvent because of the tendency to form acetals with aldehydic products.

Silver Benzoate–Iodine Complex.[55] — An alkene is converted by treatment with silver benzoate and iodine in boiling benzene into the corresponding glycol dibenzoate, often in excellent yield.

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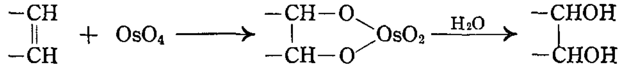
[52] Malaprade, *Bull. soc. chim.*, [5] **1**, 833 (1934).

[53] Jackson and Hudson, *J. Am. Chem. Soc.*, **59**, 994 (1937).

[54] Miescher, Hunziker and Wettstein, *Helv. Chim. Acta*, **23**, 400 (1940).

[55] Prévost, *Compt. rend.*, **196**, 1129 (1933); **197**, 1661 (1933); Hershberg, *Helv. Chim. Acta*, **17**, 351 (1934).

Osmium Tetroxide. — An elegant method for the hydroxylation of a double bond consists in the addition of this reagent to the ethylenic component in a non-aqueous solvent at room temperature and reductive fission of the resulting osmic ester.[56]



Because of the high yields and the freedom from side reactions which might occur under less mild conditions, the reaction has advantages for application to valuable compounds which may well outweigh the consideration that the reagent is both poisonous and expensive. The metal, however, is recoverable. Extensive use has been made of this method of hydroxylation in the hormone series.[57, 58, 59] The reaction is conducted in absolute ether [58, 59] or pure dioxane [57] at room temperature and is complete in 2–4 days. The osmic ester, which either precipitates or is obtained by evaporation of the solvent, may be converted to the glycol by refluxing with aqueous-alcoholic sodium sulfite,[56, 58] or with sodium sulfite and zinc dust.[57] A still better method of cleavage is to treat the ester with alkaline formaldehyde or ascorbic acid in the cold.[59]

Caro's Acid [60] (Sulfomonoperacid, $H_2S_2O_8$). — This is a specific reagent for the oxidation of aromatic primary amines to nitroso compounds; [60] the three nitroanilines, for example, may be converted rapidly into the nitronitroso derivatives in good yield by treatment with Caro's acid in an acidic aqueous solution.[61] When required for such an oxidation, the reagent is conveniently prepared [62] by stirring finely powdered potassium persulfate (10 g.) into ice cold concentrated sulfuric acid (6–8 cc.) and, when the mixture is homogeneous, adding ice (40–50 g.). The

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[56] Criegee, *Ann.*, **522**, 75 (1936).

[57] Serini and Logemann, *Ber.*, **71**, 1362 (1938); Serini, Logemann and Hildebrand, *ibid.*, **72**, 391 (1939).

[58] Butenandt, Schmidt-Thomé and Paul, *Ber.*, **72**, 1112 (1939).

[59] Reich, Sutter and Reichstein, *Helv. Chim. Acta*, **23**, 170 (1940).

[60] Caro, *Z. angew. Chem.*, **11**, 845 (1898).

[61] Bamberger and Hübner, *Ber.*, **36**, 3803 (1903).

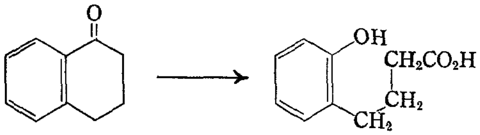
[62] Baeyer and Villiger, *Ber.*, **32**, 3625 (1899); **33**, 858 (1900).

amine is then added and the reaction allowed to proceed at 25–40° for a period of a few hours or until the separation of the nitroso compound is complete.

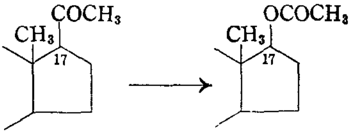
Caro's acid is also employed for effecting the fission of the carbon-carbon linkage of ketones. Cyclic ketones of the cyclohexanone type are converted into lactones[62] (a), even in the case of the many-membered ring compounds,[63] the reaction resulting in the insertion of an oxygen atom in the ring. When there is an aromatic nucleus adjacent to the carbonyl group, as in α-tetralone, cleavage occurs adjacent to this nucleus and gives a phenol-acid[64] (b). The reaction has been applied in the steroid series for the elimination of the 17-acetyl group of pregnanone derivatives and its replacement by the acetoxyl group[65] (c); the methyl group is acetoxylated to some extent, and acidic by-products are also formed.

(a)

(b)



(c)



The oxidative cleavage of ketones has been carried out in ligroin solution at 50–65° with Caro's acid prepared by the method described above,[63] in a solution containing more sulfuric acid, less water, and no organic solvent,[62] and by refluxing the ketone with a mixture of potassium persulfate (4 g.) and concentrated sulfuric acid (1 cc.) in 90 per cent acetic acid (150 cc.).[66] A particu-

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[63] Ruzicka and Stoll, *Helv. Chim. Acta*, **11**, 1159 (1928).

[64] Schroeter, German Patent 562,827 (1928) [*Chem. Zentr.*, **1**, 127 (1933)].

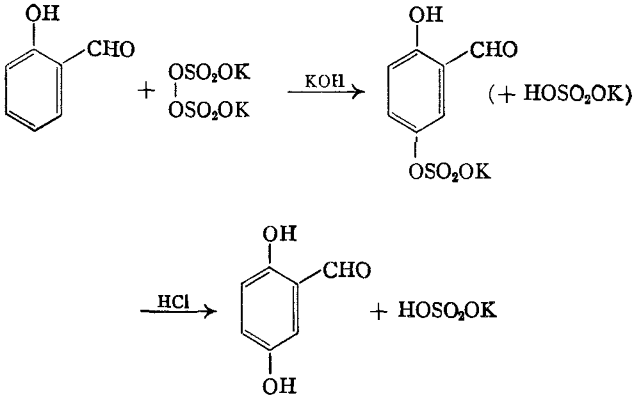
[65] Marker and co-workers, *J. Am. Chem. Soc.*, **62**, 525, 650, 2543, 2621 (1940).

[66] Rollett and Bratke, *Monatsh.*, **43**, 685 (1922).

larly satisfactory method consists in the use of Baeyer and Villiger's[62] dry reagent, prepared by grinding 10 g. of potassium persulfate thoroughly in a mortar with 6 cc. of concentrated sulfuric acid, adding 30 g. of potassium sulfate, and grinding the mixture to a dry powder. This may be stored for some time in a stoppered bottle without deterioration. The dry reagent is added to a cold solution of the ketone in glacial acetic acid and the reaction allowed to proceed at room temperature for 7–10 days.[65]

A similar reagent which can be employed for the oxidative cleavage of ketones is prepared by cautiously mixing acetic anhydride (65 g.), concentrated sulfuric acid (30 g.) and perhydrol (25 g.).[67] Benzophenone (20 g.) added to this solution is converted, after standing for several days at 0°, into phenyl benzoate in nearly quantitative yield.

Potassium Persulfate, $K_2S_2O_8$. — Reaction of Neubauer and Flatow:[68]



Gentisaldehyde

This is sometimes a convenient method for the introduction of a para hydroxyl group into a phenolic compound having an oxidizable side chain, but the reaction is not entirely general and the yields are often low.

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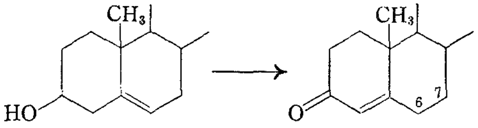
[67] Dilthey, Inckel and Stephan, *J. prakt. Chem.*, **154**, 219 (1940).

[68] *Z. physiol. Chem.*, **52**, 380 (1907).

Aluminum *t*-Butoxide (Oppenauer Oxidation). — Treatment with this reagent in combination with acetone or other hydrogen acceptor provides an invaluable method for the oxidation of secondary alcohols to ketones:[69]

$$>\mathrm{CHOH} + (\mathrm{CH_3})_2\mathrm{C{=}O} \xrightleftharpoons{\mathrm{Al[OC(CH_3)_3]_3}} >\mathrm{C{=}O} + (\mathrm{CH_3})_2\mathrm{CHOH}$$

The actual reaction is between acetone and the aluminum derivative of the alcohol being oxidized; this is formed by interchange with the aluminum derivative of another alcohol, usually one which itself is stable to oxidation. The reaction is an equilibrium, and represents the reversal of the Meerwein-Ponndorf method of reduction; the oxidation can be pushed practically to completion by the simple expedient of employing a large excess of acetone. The method is particularly valuable for the oxidation of unsaturated alcohols without attack of the double bond and finds wide application in the field of the steroids. With β,γ-unsaturated alcohols the double bond migrates to a position conjugated with the newly formed carbonyl group in the course of the reaction. Thus cholesterol affords cholestenone (80–86 per cent yield[69]). When quinone is used as the hydrogen acceptor an additional double bond is introduced at the 6,7-position.[70]



The reagent is best prepared from aluminum turnings made in a lathe from "fast cutting rods" consisting of an alloy ("17ST") containing copper, manganese, and magnesium. Once some of the reagent is on hand, further batches are easily prepared by using the preformed alkoxide as starter. The preparation is facilitated by amalgamating the aluminum as follows.[71] After

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[69] Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).

[70] Wettstein, *Helv. Chim. Acta*, **23**, 388 (1940).

[71] Adkins, *J. Am. Chem. Soc.*, **44**, 2178 (1922).

repeated washings with dilute hydrochloric acid and with alkali, the metal is immersed for 1½ minutes in 0.5 per cent mercuric chloride solution, washed with water, alkali, and water; immersed once more, washed well with water, alcohol, and ether, and used at once. After some experience has been gained, unamalgamated aluminum alloy usually will be found to give satisfactory results.

In case the reaction fails to start, as evidenced by a dark coloration, the addition of a small amount of one of the following reagents may prove helpful: (1) mercuric chloride with shaking,[72] (2) aluminum isopropoxide [69] (easily prepared), (3) aluminum activated with iodine; [69] the reagent obtained after any of these treatments is not suitable for use in an oxidation but serves as a catalyst for preparing reagent which is adequate for such use.

Preparation: [69, 72] A dry flask with a ground glass joint carrying a reflux condenser protected with a calcium chloride tube is charged with 40 g. of amalgamated aluminum alloy turnings and 200 cc. of *t*-butyl alcohol (distilled over sodium) and heated in an oil bath. If the reaction does not begin after refluxing for 1 hour, as shown by darkening of the solution, about 5 g. of aluminum *t*-butoxide or other starter is added. Once in progress, the reaction proceeds to completion after gentle refluxing for 10–15 hours, during which time sufficient benzene (500–600 cc.) is added to keep the alkoxide in solution. When hydrogen evolution has stopped, the warm mixture is centrifuged and the sediment is stirred with hot benzene and centrifuged; the addition of a little moist ether may be of assistance in obtaining a clear solution. The clear extracts are combined and evaporated on the steam bath, at first at ordinary pressure and then at the water pump to remove traces of solvent. The colorless aluminum *t*-butoxide weighs 155–165 g.; it keeps indefinitely in a well-stoppered bottle.

Oxidation procedures: The usual method of conducting the reaction [69] consists in dissolving the alcoholic substance to be oxidized in about equal volumes of acetone and benzene, adding

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[72] Adkins and Cox, *J. Am. Chem. Soc.*, **60**, 1158 (1938).

a solution of aluminum *t*-butoxide (1.2–1.4 molecular equivalents) in hot benzene, refluxing the mixture for 8–10 hours, and adding dilute sulfuric acid to the cooled reaction mixture. The crude product often contains mesityl oxide (odor) and other condensation products of acetone. The yields usually are excellent and there is no danger of overoxidation. With sensitive compounds the reaction can be conducted at room temperature over a period of 2–3 weeks.[73] The reaction can be completed in a shorter time (1 hour) by operating at the higher reaction temperature provided by using cyclohexanone as the hydrogen acceptor in combination with toluene.[74] Aluminum *t*-butoxide can be replaced by the more easily prepared aluminum phenolate [75] or by aluminum isopropoxide.[74]

CATALYTIC HYDROGENATION

The methods available for the hydrogenation of organic compounds may be classified as follows according to the nature of the catalyst and the conditions employed for promoting the reaction: (1) liquid phase, noble-metal catalyst (Pt, Pd), low temperature (25–60°), pressures slightly above one atmosphere (Willstätter); (2) vapor phase, base-metal catalyst (Ni), high temperature (300°), atmospheric pressure (Sabatier); (3) liquid phase, base-metal catalyst (Ni, Cu-Cr), moderate temperature (150–200°), high pressure (Ipatiev).

The **low temperature method** is very generally useful in ordinary laboratory work, and a particularly satisfactory type of catalyst and a serviceable form of apparatus were developed by Adams and co-workers and are described in detail in "Organic Syntheses."[1] A bottle or a long-necked flask often serves as a satisfactory vessel in which to conduct the hydrogenation. A flask

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[73] Reichstein and Euw, *Helv. Chim. Acta*, **23**, 136 (1940).

[74] Inhoffen, Logemann, Hohlweg and Serini, *Ber.*, **71**, 1032 (1938).

[75] Kuwada and Joyama, *J. Pharm. Soc. Japan*, **57**, 247 (1937) [*Chem. Zentr.*, **2**, 1612 (1938)].

[1] Preparation of Adams platinum oxide catalyst: Adams, Voorhees and Shriner, "Organic Syntheses," Coll. Vol. I, 452 (1932); apparatus for hydrogenation at 2–3 atm. pressure: *ibid.*, p. 53.

having certain special features of design is shown in Fig. 77 (Hershberg; see note 16, page 451). Hydrogen is admitted through a flexible brass spiral connected to the flask by means of a two-way glass trap which prevents possible contamination with the metal and which can be cleaned by means of the capped side opening. The flask is provided with a sealed-in coil which can be used for heating the reaction mixture with hot water or steam or for cooling it with tap water or with brine circulated by a small pump. The tube suspended from the rubber stopper is provided with a series of baffles to prevent the splashing of liquid into the hydrogen inlet and to aid in the washing down of any catalyst or solid organic substance which tends to lodge in the neck of the flask. The same baffle construction is employed in the flask shown in Fig. 78; this all-glass unit is designed for use in special cases where it is considered desirable to avoid contact of the reaction mixture with rubber. The baffling is made by cutting staggered $\frac{1}{16}''$ slots in the wide glass tube with a grinding wheel and heating the glass above each cut until it draws in.

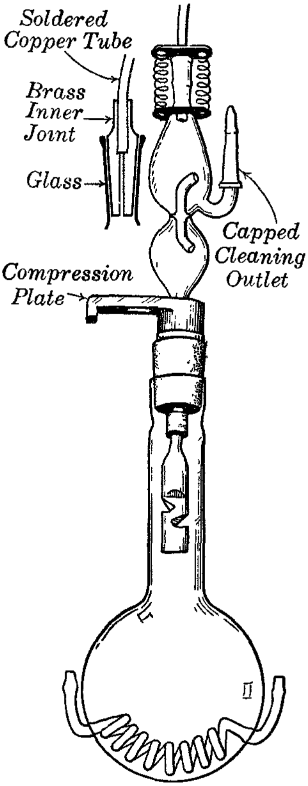

FIG 77. — Hydrogenation Flask with Coil for Heating or Cooling

Certain useful modifications have been introduced in the procedure for the preparation of Adams platinum oxide catalyst, which consisted originally in fusing chloroplatinic acid with sodium nitrate in a casserole over a free flame at 500–550°. Cook and Linstead[2] found that fusion with potassium nitrate gave a somewhat more active catalyst. The temperature of the melt

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[2] *J. Chem. Soc.*, 952 (1934).

is a factor of considerable importance in determining the character of the product and should be controlled carefully. In the author's laboratory the best results are obtained by controlling the temperature during fusion to 550–565°, corr., as determined with a glass inclosed thermocouple used as the stirrer. Short [3] recommends that the fusion be conducted in a Pyrex beaker resting in a suitably shaped cavity in a copper block heated with a burner and provided with a thermometer well, the thermometer reading required to give a catalyst of maximum activity being determined by trial. Bruce [4] found that the fusion can be conducted just as satisfactorily with ammonium chloroplatinate as with chloroplatinic acid. The salt, which yields just half its weight of catalyst, has the advantage of being nonhygroscopic and easily handled, and it is available as an intermediate in the most effective procedure for purifying scrap platinum or recovering the metal from spent catalyst.[5] The spent platinum or platinum charcoal catalyst residues accumulated on filter papers are digested with aqua regia and the solution is diluted, filtered, and evaporated three times to dryness with added hydrochloric acid to remove nitric acid. The crude chloroplatinic acid is dissolved in water, saturated ammonium chloride solution is added to precipitate the salt, $\frac{1}{3}$ volume of alcohol is added, and the precipitate is collected, washed with ammonium chloride solution, dried at 100°, and ignited in a casserole. The spongy platinum is redissolved in aqua regia, the above process is repeated, and the

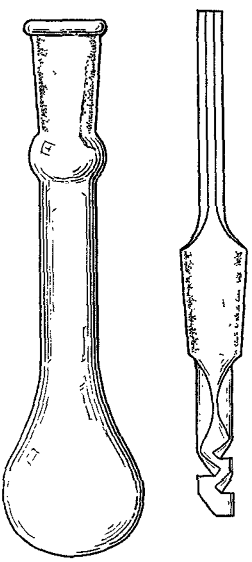

FIG 78 — All-Glass Hydrogenation Flask

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[3] *J Soc Chem Ind*, **55**, 14T (1936)

[4] "Organic Syntheses," **17**, 98 (1937)

[5] Wichers, *J Am. Chem Soc*, **43**, 1268 (1921); Baldeschwieler and Mikeska, *ibid.*, **57**, 977 (1935)

ammonium chloroplatinate obtained is fused with 10 parts of sodium or potassium nitrate, the mixture being stirred and heated gently at first and then for one-half hour at a higher temperature (e.g. 550–565°).

Palladium oxide catalyst is prepared according to Adams[1] by fusion of the chloride with sodium nitrate as in the preparation of the platinum catalyst, the optimum fusion temperature being given as 600°. For recovery of the metal,[6] spent palladium catalyst is extracted with aqua regia, the solution is evaporated three times to dryness with hydrochloric acid, the residue is dissolved in very dilute hydrochloric acid and the solution treated with ammonia and warmed until the precipitate redissolves. The solution is filtered from any precipitate (iron) and hydrogen chloride gas is passed in to precipitate palladium diammonium chloride. The salt is collected, redissolved in dilute ammonia, reprecipitated, and reduced to the metal with hydrogen or with formaldehyde and alkali.

Palladium is a less effective catalyst than platinum for the low pressure hydrogenation of carbon-carbon double bonds, and is therefore preferred as catalyst for the elimination of halogen from the aromatic nucleus by catalytic hydrogenation.[7, 8] With palladium this can be done with little danger of attacking the nucleus; with the more active platinum the secondary reaction is less easily avoided. The supported type of catalyst is favored for the halogen replacement reaction, and it is necessary to use some 2–3 parts of 5 per cent material. Palladinized calcium carbonate[7] is prepared by warming the precipitated and washed carbonate with an aqueous solution of palladium chloride until the metal is all precipitated in the form of the hydroxide (which becomes reduced in use). Palladinized barium sulfate is prepared according to Schmidt[9] by reducing palladium chloride with formaldehyde and alkali in the presence of precipitated barium sulfate. The hydrogenation of the aromatic halide may

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[6] Keiser and Breed, *Am. Chem. J.*, **16**, 20 (1894).

[7] Busch and Stöve, *Ber.*, **49**, 1065 (1916).

[8] Rosenmund and Zetsche, *Ber.*, **51**, 578 (1918).

[9] *Ber.*, **52**, 409 (1919).

be conducted in alcohol, usually with alkali or ammonia present to bind the liberated acid, or in glacial acetic acid containing sodium acetate as the acceptor.[10] Palladium-barium sulfate (Schmidt [9]) is employed as catalyst in the hydrogenation of acid chlorides to aldehydes (method of Rosenmund [11]). A sulfur-quinoline poison [12] is often used to prevent the hydrogenation from proceeding too far, although this is not required if the acid chloride is hindered.

The substance to be hydrogenated should be purified with great care before attempts are made to carry out the reaction, for a mere trace of impurity often acts as an effective poison for platinum and palladium catalysts. A persistent anti-catalytic impurity present in minute amounts often can be eliminated effectively by shaking the substance (liquid), or a solution of the substance, with Raney nickel catalyst (see below) and filtering; this pretreatment with nickel usually conditions the substance for hydrogenation with this or other catalyst. Purification by chromatographic adsorption also may be effective. If a solvent is employed, this should be purified just as scrupulously as the compound. In general, the solvents most useful for low pressure hydrogenations are alcohol, glacial acetic acid, ethyl acetate, and ether. Most hydrogenations proceed more rapidly and extensively in glacial acetic acid or other acidic medium than in neutral solvents. Since a suspension of the Adams catalyst in alcohol is faintly basic,[13] the character of the medium is not altered by employing added alkali. The addition of a few drops of hydrochloric acid, however, markedly changes the nature of the medium and increases the effectiveness of the catalyst,[14] particularly for the hydrogenation of aromatic

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[10] Fieser and Holmes, *J. Am. Chem. Soc.*, **60**, 2553 (1938).

[11] Rosenmund *et al.*, *Ber.*, **51**, 585, 594 (1918); **54**, 425, 2888 (1921); **55**, 609 (1922).

[12] Rosenmund and Zetsche, *Ber.*, **54**, 436 (1921).

[13] Miescher and Scholz, *Helv. Chim. Acta*, **20**, 263 (1937), found that oestrone acetate can be hydrolyzed by shaking a solution of the substance in absolute alcohol with reduced Adams catalyst at room temperature.

[14] Brown, Durand and Marvel, *J. Am. Chem. Soc.*, **58**, 1594 (1936).

rings or other comparatively inert centers of unsaturation. When oestrone is hydrogenated in the presence of Adams catalyst in glacial acetic acid or in alcohol containing hydrochloric acid the aromatic nucleus is attacked rapidly, in part even in preference to the carbonyl group; by the use of a neutral solvent the carbonyl group can be reduced smoothly and the nucleus remains untouched.[15] It is sometimes advantageous to use a combination of two solvents, one of which is desirable because of its favorable solvent action, while the other promotes the reaction. For example, ethyl acetate has been employed in combination with 17 per cent of acetic acid[16] or 8 per cent of alcohol[17] as promoters.

Ferrous chloride, at an optimum concentration of 0.0001 mole in 100 cc. of the reaction mixture, markedly promotes the hydrogenation of aldehydes and counteracts the tendency of the catalyst to lose its activity[18] (hydrochloric acid in this case is ineffective). Both ferrous chloride and hydrochloric acid have been found to exert a promoter action in the hydrogenation of polynuclear aromatic hydrocarbons.[19] Zelinsky, Packendorff and Leder-Packendorff[20] added aqueous palladium chloride solution along with platinum charcoal catalyst to a solution of the substance to be reduced in methanol or ethanol and found that by this method acetophenone and mandelic acid can be hydrogenated smoothly to ethylbenzene and phenylacetic acid, respectively. The effectiveness of the reagent may be due in part to the promoting action of the hydrogen chloride liberated, for Packendorff[21] found the activity of platinum charcoal for the reduction of the carbonyl to the methylene group to be increased

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[15] Dirscherl, *Z. physiol. Chem.*, **239**, 53 (1936).

[16] Fieser and Hershberg, *J. Am. Chem. Soc.*, **60**, 940 (1938). This paper includes a description of a serviceable all-glass (and metal) apparatus designed by Hershberg with which the hydrogen absorption can be measured accurately even in hydrogenations extending over a period of several days.

[17] Fieser and Hershberg, *J. Am. Chem. Soc.*, **62**, 1640 (1940).

[18] Carothers and Adams, *J. Am. Chem. Soc.*, **45**, 1071 (1923); **47**, 1047 (1925).

[19] Fieser and Hershberg, *J. Am. Chem. Soc.*, **59**, 2502 (1937).

[20] *Ber.*, **66**, 872 (1933); **67**, 300 (1934).

[21] *Ber.*, **67**, 905 (1934).

by the addition of chloroplatinic acid to the reaction mixture. The combination of the two metals also seems to lead to an enhancement of the catalytic activity. Hershberg [19] observed that platinum catalyst containing 1–2 per cent of palladium, which was dissolved with the platinum in aqua regia, absorbed twice as much hydrogen as Adams catalyst prepared from the same lot of platinum and was considerably more active for aromatic hydrogenations. Palladium alone has been found by Hartung [22] to be a very effective catalyst for the hydrogenation of certain ketones and oximes. Propiophenone was reduced easily and completely to *n*-propylbenzene in the presence of palladium charcoal, whereas similarly prepared platinum charcoal was tried and found inactive.[23] Added hydrochloric acid had no effect on the rate or extent of reduction of propiophenone but proved very advantageous in hydrogenations affording primary amines. Hartung's general procedure [22, 24] for reducing such substances consists in using as the solvent absolute alcohol containing three equivalents of hydrogen chloride and conducting the hydrogenation in the presence of palladium charcoal. Both benzaldoxime and benzonitrile are converted smoothly into benzylamine, and oximino ketones of the type $ArCOC(R)=NOH$ afford amino alcohols, $ArCH(OH)CH(R)NH_2$ (as the hydrochlorides). The mineral acid greatly increases the rate of reduction and prevents the formation of secondary and tertiary amines.

The technique of conducting **high-pressure hydrogenations** according to Adkins is described fully by this author in an excellent monograph [25] which should be consulted by anyone employing or considering this highly useful method. Fully standardized and safe high-pressure equipment of convenient design is available from American firms. The apparatus should be operated only by those who are fully instructed in its proper

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[22] *J. Am. Chem. Soc.*, **50**, 3370 (1928).

[23] Hartung and Crossley, *J. Am. Chem. Soc.*, **56**, 158 (1934).

[24] Hartung, *J. Am. Chem. Soc.*, **53**, 2248 (1931).

[25] Adkins, "Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts." The University of Wisconsin Press (1937).

use, for certain parts are easily damaged by inexpert or careless handling.[26] One of the most useful catalysts is the copper chromite catalyst (copper-chromium oxide) of Adkins and co-workers, particularly the preparation designated 37KAF.[27] Apart from its many uses in promoting hydrogenations, copper chromite is a very effective catalyst for decarboxylations (see pages 197–201). A second very useful catalyst is the Raney nickel catalyst,[28] prepared by the action of warm alkali on a commercial alloy of equal parts of nickel and aluminum, as described by Covert and Adkins.[29] The aluminum dissolves, leaving the nickel as a finely divided black suspension. The well-washed catalyst is stored under absolute alcohol in an air-free container and measured in the form of the suspension; it must be handled under a solvent at all times, for it is highly pyrophoric. The outstanding characteristic of Raney nickel is its remarkable activity at low temperatures and pressures; for example, both acetone and styrene can be hydrogenated at 23° and 2–5 atmospheres. The activity of the catalyst in low pressure hydrogenations is enhanced markedly by the addition of a small amount of platinic chloride.[30] For some purposes Adkins' much less active nickel catalyst supported on kieselguhr [31] has advantages.

The copper chromite and nickel catalysts supplement one another, for each has special uses for which the other is unsuited. The following statements by Adkins [25] indicate some of the prominent applications of each catalyst. "Copper-chromium oxide is particularly active for the hydrogenation of aldehydes and ketones to alcohols, of esters to alcohols, and of amides to amines. It is notably inactive for the hydrogenation of the (isolated) benzenoid nucleus and so may be used for the hydrogenation

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[26] A convenient form of glass liner for the metal bomb is described by Hershberg and Weiner, *Ind. Eng. Chem., Anal. Ed.*, **11**, 93 (1939).

[27] Connor, Folkers and Adkins, *J. Am. Chem. Soc.*, **54**, 1138 (1932); Lazier and Arnold, "Organic Syntheses," **19**, 31 (1939).

[28] Raney, U. S. Patent 1,839,974 (1932).

[29] *J. Am. Chem. Soc.*, **54**, 4116 (1932). See also Adkins.[25]

[30] Lieber and G. B. L. Smith, *J. Am. Chem. Soc.*, **58**, 1417 (1936).

[31] Covert, Connor and Adkins, *J. Am. Chem. Soc*, **54**, 1651 (1932).

of aryl compounds without much danger of saturating the ring.[32] Nickel is inactive, or nearly so, for the hydrogenation of amides to amines and of esters to alcohols; but it is by all odds the preferred catalyst for the hydrogenation of carbon to carbon double bonds in alkenes and in benzenoid, furanoid, and pyridinoid rings, as well as for the hydrogenation of oximes, cyanides, nitro compounds, etc."

DEHYDROGENATION

The principal methods available for effecting the dehydrogenation of hydroaromatic compounds consist in heating the substance in question with sulfur, selenium, or palladium charcoal, aromatization being attended with the formation of hydrogen sulfide, hydrogen selenide, or elementary hydrogen. Sulfur acts more rapidly than selenium, it is effective at a lower temperature, and it is less prone to give rise to the pyrolytic cleavage of alkyl substituents from reactive positions.[1] On the other hand sulfur, by virtue of its great reactivity, may give rise to troublesome side reactions or even yield a sulfur-containing compound as the chief product.[2] The less reactive selenium requires a higher temperature and a longer reaction period but has less tendency to combine with the organic material[3] and sometimes is found to operate very smoothly and cleanly. The reaction temperature is so high, however, that the aromatization may be attended with the loss or migration of alkyl groups and the elimination or alteration of other substituents.[4] Cata-

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[32] Certain polynuclear hydrocarbons are sufficiently reactive to undergo ready partial hydrogenation over copper. Phenanthrene can be converted smoothly to the 9,10-dihydride at low temperatures, and the remaining, isolated benzenoid rings are attacked only slowly: Burger and Mosettig, *J. Am. Chem. Soc.*, **58**, 1857 (1936); Durland and Adkins, *ibid.*, **59**, 135 (1937); **60**, 1501 (1938); Fieser and Johnson, *ibid.*, **61**, 168 (1939).

[1] Fieser and Hershberg, *J. Am. Chem. Soc.*, **59**, 1028, 2331 (1937); Fieser and R. N. Jones, *ibid.*, **60**, 1940 (1938).

[2] Fieser, *J. Am. Chem. Soc.*, **55**, 4977 (1933).

[3] A by-product containing selenium, however, was encountered by Ruzicka, *Helv. Chim. Acta*, **19**, 419 (1936), in the dehydrogenation of *trans*-β-decalone.

[4] For a discussion of normal and abnormal dehydrogenations, see Linstead, "Annual Reports of the Chemical Society," **33**, 294–312 (1936).

lytic dehydrogenation in the presence of platinum or palladium can be conducted at moderate or elevated temperatures and, since the process is more subject to control than the selenium method and is free from the side reactions attending the use of sulfur, this constitutes the most generally satisfactory method.

Sulfur.[5] — The general technique of the process is to heat the compound at 230–250° with the theoretical amount of sulfur required to bring the substance to the fully aromatic condition. Thus 2 equivalents of sulfur are required for the conversion of tetralin to naphthalene (70 per cent yield[6]): $C_{10}H_{12} + 2S \longrightarrow C_{10}H_8 + 2H_2S$. The mixture is placed in a two-bulb distillation flask (page 250), or in a Claisen flask with a sealed-on receiver, and this is introduced into a nitrate bath (page 306) maintained initially at 200–230°.[7] The globule of sulfur dissolves after some shaking, hydrogen sulfide is evolved copiously for a time (hood), and then the bubbling begins to slacken (about 30 minutes). The bath temperature is raised to 250° in the course of 30 minutes, when the reaction is essentially complete. The isolation of a sulfur-free reaction product is facilitated by heating the melt at 250° for 1–2 hours longer or by adding a small amount of zinc dust and heating the mixture for 5–10 minutes. The product is then distilled in vacuum and crystallized.

The sulfur method has found only limited use in the dehydrogenation of hydroaromatic ketones to phenols.[8] Aromatic methoxy compounds have been prepared successfully by sulfur dehydrogenation without elimination of the methoxyl group.[9]

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[5] Method of Vesterberg, *Ber.*, **36**, 4200 (1903).

[6] Ruzicka and Rudolph, *Helv. Chim. Acta*, **10**, 915 (1927).

[7] See preparation of 1,2-naphthalic anhydride, Hershberg and Fieser, "Organic Syntheses," **18**, 59 (1938).

[8] α-Tetralone ⟶ α-naphthol (40% yield), Darzens and Lévy, *Compt. rend.*, **194**, 181 (1932); 4-keto-1,2,3,4-tetrahydro-3,4-benzpyrene ⟶ 4′-hydroxy-3,4-benzpyrene (30% yield), Fieser, Hershberg, Long and Newman, *J. Am. Chem. Soc.*, **59**, 475 (1937).

[9] Fieser and Fieser, *J. Am. Chem. Soc.*, **57**, 1679 (1935); Fieser and Holmes, *ibid.*, **58**, 2319 (1936); Darzens and Lévy, *Compt. rend.*, **200**, 469 (1935); Haberland, *Ber.*, **69**, 1380 (1936).

Selenium.[10] — Selenium dehydrogenations are best carried out by heating the compound with a large excess of selenium at 300–330° for 36–48 hours; higher temperatures are likely to lead to extensive rearrangements. With substances not volatile at the required temperature the reaction can be conducted in a test tube or, with larger amounts, in a long-necked flask of the type used for melting point determinations (page 26). An inert atmosphere usually is not required but can be provided by passing in a slow stream of nitrogen; the reaction vessel is stoppered with a cork carrying a glass tube either drawn out to a capillary or making connection to a small bubble counter from which the gas is led into a flask containing moist calcium hypochlorite. The hydrogen selenide may be allowed to escape into a well-ventilated hood but should not be breathed, since even small amounts may cause illness. The presence of hydrogen selenide in the gas stream can be detected with a piece of filter paper moistened with lead acetate solution. Temperature control over the long period is facilitated by using a nitrate bath mounted in an electric bowl-type heater controlled by a Variac. For insulation against drafts, the bath can be surrounded by a sheet metal cylinder with a sectioned Transite cover provided with holes to accommodate the neck of the reaction vessel and the thermometer. Selenium is weighed out for a reaction most conveniently when in the powdered form although, since the substance is molten at the reaction temperature, the initial physical state or allotropic modification is unimportant. An excess of selenium is used largely because some of the material invariably sublimes out of the reaction vessel. Although most published procedures call for adding the selenium in portions, there seems to be no disadvantage in adding the entire lot at the outset. At the end of the reaction the product can be extracted with ether or benzene from the residual selenium, which is present partly in the form of a hard button and partly in a somewhat gelatinous condition. The filtered solution has a cloudy appearance due to the presence of colloidal selenium. The colloidal material usually can be

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[10] Method of Diels and Karstens, *Ber*, **60**, 2323 (1927).

eliminated easily by shaking a benzene solution of the mixture with Norit or, if the extraction has been made with ether, by diluting the solution with petroleum ether and treating it with Norit. The adsorption of colloidal selenium by Norit is still more effective if done in a solution of petroleum ether or hexane alone. If difficulty is experienced, the last traces of selenium can be removed by refluxing the product in benzene solution with sodium or by passing the benzene solution through a column of activated alumina.

An example of the use of selenium to effect a normal dehydrogenation is in the conversion of 1′,2′,3′,4′-tetrahydro-3,4-benzpyrene into 3,4-benzpyrene[11] (1.6 parts of selenium, 36 hours at 330°, 79 per cent yield); in this case palladium charcoal has been observed to give equally good results.[12] Selenium has been found very serviceable for the preparation of the highly reactive methylcholanthrene from bile acid degradation products, a process requiring the elimination of angular methyl groups and the retention of a sensitive alicyclic ring.[13] The high temperature of the selenium reaction tends to promote elimination of oxygen-containing groups. Instances are known, however, in which the methoxyl group survives the selenium reaction;[14] in one case[15] the substituent was retained only when the temperature was kept below 300°. Cyclic ketones in a few instances have been dehydrogenated with selenium to phenols, and with better results than when sulfur was employed.[16] In other cases, treatment of a cyclic ketone with selenium has

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[11] Cook and Hewett, *J. Chem. Soc.*, 398 (1933); Fieser and Fieser, *J. Am. Chem. Soc.*, **57**, 782 (1935).

[12] Observation of Dr. J. L. Wood.

[13] Wieland and Dane, *Z. physiol. Chem.*, **219**, 240 (1933); Cook and Haslewood, *J. Chem. Soc.*, 428 (1934); Fieser and Newman, *J. Am. Chem. Soc.*, **57**, 961 (1935).

[14] Hill, Short and Higginbottom, *J. Chem. Soc.*, 317 (1936); Short, Stromberg and Wiles, *ibid.*, 319 (1936); Fieser and Holmes, *J. Am. Chem. Soc.*, **60**, 2548 (1938).

[15] Kon and F. C. J. Ruzicka, *J. Chem. Soc.*, 187 (1936).

[16] Darzens and Lévy, *Compt. rend.*, **194**, 181 (1932); Lévy, *ibid.*, **194**, 1749, 1952 (1932); Ruzicka, *Helv. Chim. Acta*, **19**, 419 (1936).

yielded the hydrocarbon as the sole product.[17] Selenium not only functions as a weak dehydrogenating agent but also is capable of promoting hydrogenations and disproportionations. Thus cholesterol is converted by selenium at 230° into cholestanone and small amounts of cholestanol and cholestenone.[18] A still more striking instance is in the reduction of cyclic anhydrides to dimethyl compounds.[19] Treatment of 2,3-naphthalic anhydride with selenium in the presence of *p*-cyclohexylphenol as a hydrogen donor affords 2,3-dimethylnaphthalene.

Platinum and Palladium Catalysts. — Dehydrogenations over metal catalysts can be conducted in both the liquid and vapor phase at temperatures ranging from about 180° to 450°. The conditions required in a given case are determined to some extent by the properties of the substance in question, but even more by the nature of the transformation to be accomplished. A given catalyst is just as satisfactory for low as for high temperature work and is not specific to any one type of compound or transformation. Platinum and palladium catalysts can be used either with or without a charcoal or asbestos carrier. Such differences in effectiveness as exist between platinum and palladium catalysts are so minor that the choice can safely be made on the basis of the availability and current prices of the two metals. Raney nickel and other base metal catalysts have not proved sufficiently effective for practical use.

Charcoal supported catalysts are favored for liquid phase operations because material in this form is easily weighed out for a reaction and subsequently recovered. Charcoals are employed containing from 10 to 30 per cent of the metal, and the general practice is to employ 0.1 to 0.2 part by weight of 10 per cent charcoal or 0.1 part of 30 per cent material. Although in special studies it is customary to submit the charcoal to acid washing, followed by a careful drying or degassing operation,

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[17] Cook and Hewett, *J. Chem. Soc.*, 398 (1933); Peak and R. Robinson, *ibid.*, 760 (1936); Winterstein and Vetter, *Z. physiol. Chem.*, **230**, 169 (1934).

[18] Dorée and Petrow, *J. Chem. Soc.*, 1391 (1935).

[19] Windaus and W. Thiele, *Ann.*, **521**, 160 (1935); W. Thiele and Trautmann, *Ber.*, **68**, 2245 (1935); see also Ruzicka, footnote 16.

in order to insure reproducibility of results, this elaborate pretreatment can be dispensed with in ordinary practice. Norit and other charcoals are usually supplied in acid-washed form, and if there is any uncertainty on this score the charcoal may be heated on the steam bath for 5 hours with 10 per cent nitric acid, collected and washed free of acid, and employed for the preparation of the catalyst without being dried. Catalysts prepared essentially according to Zelinsky and Turowa-Pollak [20] were found particularly satisfactory by Linstead and co-workers [21] in their extensive studies of dehydrogenation phenomena. These authors describe the procedure for the preparation of 30 per cent catalysts as follows.[21b] A solution of the nitrate-free dichloride, prepared from or equivalent to 5.0 g. of platinum or palladium, in 50 cc. of water and 5 cc. of concentrated hydrochloric acid is cooled in an ice bath and treated with 50 cc. of formalin (40 per cent formaldehyde) and 11 g. of charcoal (Norit) or Gooch asbestos (acid-washed). The mixture is stirred mechanically and a solution of 50 g. of potassium hydroxide in 50 cc. of water is added slowly at 0–5°. After the addition the temperature is raised to 60° for 15 minutes and the catalyst is then washed thoroughly by decantation with water and finally with dilute acetic acid, collected on a suction filter, and washed with hot water until free from alkali (when colloidal material begins to pass into the filtrate). The catalyst is dried thoroughly, best in vacuum at 100°.

A convenient alternate method of preparing 10 per cent palladium charcoal [22] consists in adding a solution of 5 g. of palladium chloride in the minimum amount of hot water to a paste of 27 g. of charcoal in 50 cc. of water, stirring or shaking the mixture at 50° for 2 hours, and passing in a rapid stream of hydrogen as long as it is absorbed. The catalyst is collected,

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[20] *Ber.*, **58**, 1295 (1925).

[21] (a) Linstead, Millidge, Thomas and Walpole, *J. Chem. Soc.*, 1146 (1937); (b) Linstead and Thomas, *ibid.*, 1127 (1940); (c) Linstead and Michaelis, *ibid.*, 1134 (1940); (d) Linstead, Michaelis and Thomas, *ibid.*, 1139 (1940).

[22] Diels and Gädke, *Ber.*, **58**, 1231 (1925); Ott and Schröter, *ibid.*, **60**, 633 (1927). See also Kaffer, *ibid.*, **57**, 1263 (1924).

washed well with water and dried. Platinum charcoal can be prepared similarly by reduction with hydrogen at 135°.[23] Satisfactory catalysts containing no carrier are the palladium black of Willstätter and Waldschmidt-Leitz[24] and the platinum catalyst of Adams (page 447). At the end of a reaction the catalyst should be collected carefully for either recovery of the metal (page 448) or re-use; frequently a given batch of catalyst is found to function satisfactorily in several successive runs.

The procedure heretofore usually employed for the dehydrogenation of intermediates in the synthesis of polynuclear aromatic hydrocarbons consists in heating the intermediate with 0.1 part of 10 per cent palladium (or platinum) charcoal in a test tube flushed at the start with nitrogen or carbon dioxide and connected either to a gas bubbler or to an assembly for collecting the evolved gas over water. The heating is done in a nitrate bath maintained initially at about 220°. The temperature is raised slowly in such a way as to initiate and maintain a steady gas evolution and, if the theoretical amount of hydrogen has not been evolved, the temperature is brought to 310–320° before terminating the operation (total time about 1–1½ hours). After cooling, the product is extracted with ether and purified by distillation, crystallization, or conversion to the trinitrobenzene derivative or the picrate. In a synthesis involving the addition of a Grignard reagent to a cyclic ketone, dehydration of the carbinol, and dehydrogenation, a useful simplification consists in heating the intermediate carbinol with palladium charcoal, which accomplishes the last two steps of the synthesis in one operation.[25] The degradative dehydrogenation of a natural product is illustrated by the conversion of abietic acid (page 265) to retene (loss of angular methyl and carboxyl) in excellent yield by the action of palladium charcoal at 350°.[26]

The investigations of Linstead[21] have cast much new light on the process of dehydrogenation. Tetralin (b.p. 207°) when

[23] Packendorff and Leder-Packendorff, *Ber.*, **67**, 1388 (1934).

[24] *Ber.*, **54**, 123 (1921).

[25] Bachmann and Wilds, *J. Am. Chem. Soc.*, **60**, 624 (1938).

[26] Ruzicka and Waldmann, *Helv. Chim. Acta*, **16**, 842 (1933).

boiled with a charcoal-supported catalyst was found [21a] to evolve less than the theoretical amount of hydrogen, due to a reversal of the reaction, but when the hydrogen was swept from the system with a stream of carbon dioxide the conversion to naphthalene proceeded smoothly to completion. Later,[21c] the striking observation was made that tetralin is dehydrogenated readily in the liquid phase only when it is actually boiling. Reaction failed to occur in the tranquil liquid at 200° but proceeded rapidly when the liquid was made to boil at 185° either by employing diminished pressure or by adding a diluent. The phenomenon is a general one, and the technique of conducting the dehydrogenation in an actively boiling medium makes it possible to bring about aromatization at considerably lower temperatures than by the older procedure, with the consequent advantage of avoiding rearrangements and the elimination of substituents. Compounds of high molecular weight can be dehydrogenated by maintaining ebullition in a suitable solvent. Substances which serve satisfactorily as solvents or diluents are mesitylene (b.p. 165°), *p*-cymene (b.p. 177°), naphthalene (b.p. 218°), and α-methylnaphthalene (liquid, b.p. 242°).

In conducting liquid phase dehydrogenations it is clearly advantageous both to maintain active boiling in the medium and to provide for the elimination of the hydrogen as it is evolved. Linstead [21a] employed carbon dioxide for sweeping the system, for this gas could then be retained with an absorbent and the residual volume of hydrogen measured. A convenient apparatus [27] for conducting small-scale dehydrogenations according to this scheme is shown in Fig. 79. The boiling tube (3.5 × 24 cm.) is provided with a ground glass condenser, an inlet tube for the admission of pure, dry carbon dioxide, and a gas exit tube placed as near the top of the boiling tube as possible. The issuing gases are conducted to a 100-cc. nitrometer filled with 30–50 per cent potassium hydroxide solution. After the substance to be dehydrogenated (1–2 g.), the solvent, and the catalyst have been introduced, the system is flushed with carbon

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[27] Designed by H. Heymann.

dioxide until micro-bubbles are obtained, and boiling is then commenced. If the volume of hydrogen exceeds the capacity of the nitrometer, successive portions can be measured and allowed to escape.

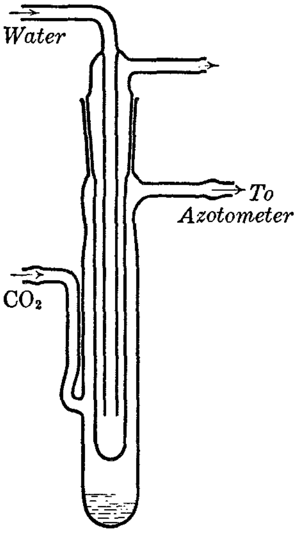

FIG. 79.—Apparatus for Catalytic Dehydrogenations

The liquid phase method is not satisfactory for the dehydrogenation of hydrocarbons which boil below 300° and which are almost or entirely saturated, or in which an angular methyl group is present.[21a, 21d] Cis and trans decalin are only very slowly attacked at the boiling point (ca. 190°), the octalins suffer disproportionation, and when an angular methyl group is present neither dehydrogenation nor disproportionation occurs at moderate temperatures. With compounds of these types, full aromatization is accomplished most effectively by dehydrogenation in the vapor phase[21] (method of Zelinsky[28]). As described by Linstead, the reaction is conducted by introducing the substance in question, together with hydrogen, into the top of an inclined reaction tube[21a] packed with platinum or palladium charcoal mixed with asbestos,[21b] or with metalized asbestos,[21b] at temperatures usually in the range 300–350°.

Hydroaromatic ketones and alcohols often can be dehydrogenated to phenols very satisfactorily with a metal catalyst in a boiling liquid medium.[21c, 29] 4-Phenanthrol can be obtained from 4-ketotetrahydrophenanthrene in about 60 per cent yield with palladium black[29] or palladium charcoal[21c] in boiling xylene[29] or *p*-cymene[21c]; the 1-isomer is produced in yields up to 86 per cent with naphthalene as the solvent.[29] Carvone

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[28] *Ber.*, **56**, 1723 (1923).
[29] Mosettig and Duvall, *J. Am. Chem. Soc.*, **59**, 367 (1937).

(b.p. 229°) can be isomerized to the aromatic carvacrol (b.p. 238°) in 95 per cent yield by boiling it with palladium charcoal for 12 hours.[21d]

High temperatures, of course, favor loss of oxygen-containing substituents. 2-Methyltriphenylene was obtained in 73 per cent yield by heating a ketotetrahydride derivative with palladium charcoal at 310° in a sealed tube filled with nitrogen,[30] but in another instance the yield by this method was only 19.5 per cent.[31] An acetoxytetrahydrobenzpyrene was found to be aromatized (70 per cent) with loss of the acetoxyl group when heated at 300° with palladium catalyst and acetic acid.[32]

Other Methods. — The method of *bromination* and elimination of hydrogen bromide [33] has found occasional use, particularly for the conversion of hydroaromatic ketones into phenols.[34] The ketone is brominated in carbon bisulfide solution, the solvent removed, and the crude α-bromoketone refluxed in dimethylaniline solution. The yields are better than when sulfur or selenium is used but inferior to those obtainable by the catalytic process described above. In preparing pentacene (*lin.*-dibenzanthracene) and hexacene, Clar and John employed the following methods for effecting the dehydrogenation of the dihydrides of these hydrocarbons: *sublimation over copper powder* in a carbon dioxide atmosphere at reduced pressure and at temperatures from 300 to 400°; [35] heating the dihydride with *phenanthrenequinone in nitrobenzene* solution; [36] and refluxing with *chloranil in xylene* solution.[36] The method of dehydrogenation with chloranil in boiling xylene is reported to give moderately good yields as applied to dihydrides of the biphenyl and terphenyl series and to tetra-

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[30] Fieser and Joshel, *J. Am. Chem. Soc.*, **61**, 2960 (1939).

[31] Fieser and Cason, *J. Am. Chem. Soc.*, **62**, 1293 (1940).

[32] Fieser and Hershberg, *J. Am. Chem. Soc.*, **61**, 1565 (1939).

[33] Baeyer, *Ber.*, 2429 (1899).

[34] Examples: 1-phenanthrol (50%), Mosettig and Burger, *J. Am. Chem. Soc.*, **57**, 2189 (1935); 6- and 7-methyl-1-naphthol (70%, 40%), Fieser and Dunn, *ibid.*, **58**, 572 (1936); 3-methyl-1-naphthol (65%), Tishler, Fieser and Wendler, *ibid.*, **62**, 2871 (1940).

[35] Clar and John, *Ber.*, **62**, 3021 (1929); Clar, *ibid.*, **72**, 1817 (1939).

[36] Clar and John, *Ber.*, **63**, 2967 (1930); *ibid.*, **64**, 981 (1931).

hydrophenanthrene.[37] Another method,[38] which thus far has been tested only in two cases, consists in heating the hydroaromatic hydrocarbon with *isoamyl disulfide* at 250–260° and removing by distillation the isoamyl mercaptan (b.p. 115°) formed, for example: $C_{10}H_{12} + 2RS.SR \longrightarrow C_{10}H_8 + 4RSH$. Naphthalene was obtained in 70 per cent yield from tetralin, and ionene afforded 1,6-dimethylnaphthalene in 32 per cent yield. The latter reaction involves the loss of methyl from a quaternary carbon atom, and it was established that this is eliminated as methane, whether the dehydrogenation is done with isoamyl disulfide or with sulfur.

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[37] Arnold and Collins, *J. Am. Chem. Soc.*, **61**, 1407 (1939); Arnold, Collins and Zenk, *ibid.*, **62**, 983 (1940).

[38] Ritter and Sharpe, *J. Am. Chem. Soc.*, **59**, 2351 (1937).

CHAPTER V

THE SEMIMICRODETERMINATION OF CARBON AND HYDROGEN

The most important methods for the analysis of organic compounds are as follows: Liebig's determination of carbon and hydrogen by burning the sample with oxygen and copper oxide, absorbing separately and weighing the carbon dioxide and the water formed; Dumas's determination of nitrogen by burning the sample with copper oxide in an atmosphere of carbon dioxide, absorbing this gas in potassium hydroxide solution and measuring the volume of nitrogen; the Carius method for determining either halogen or sulfur by oxidizing the sample with nitric acid in the presence of either silver nitrate or barium chloride and weighing the silver halide or the barium sulfate formed. The ordinary procedures for carrying out these determinations have been thoroughly standardized, and detailed directions for carrying out the analyses are to be found in several readily available books. There are in addition a number of special types and methods of analysis designed to meet particular requirements, including the elegant micromethods of Pregl.[1] The method indicated in the title of this chapter has been singled out for description for the reason that, although the method is gaining rapidly in popularity both in advanced courses of instruction and in research laboratories, the only account of it which has been published is in a rather inaccessible journal. The method, which is an adaptation of Pregl's microcombustion procedure, was worked out by Lauer and Dobrovolny[2] at the University of Minnesota and has been modified in some details in other laboratories.

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[1] Pregl, "Quantitative Organic Microanalysis" (Third English Edition, 1937); Emich, "Microchemical Laboratory Manual" (translation by Schneider, 1932).

[2] *Mickrochemie*, Sonderband "Pregl-Festschrift," 243 (1929).

In the ordinary macrocombustion according to Liebig a sample weighing 100–120 mg. is burned in each analysis, while with the technique developed by Pregl it is possible to analyze with accuracy a sample weighing as little as 2–3 mg. The method of Pregl is an extreme refinement of Liebig's original scheme of analysis and it has been of the utmost aid in modern investigations of natural products and in other researches where all possible conservation of material has been desirable. It is, however, not well adapted to routine analysis in laboratories for advanced or graduate work because a too elaborate outlay of equipment is required, because the technique can be mastered only after a somewhat extensive period of training, and because the method loses in efficiency when the usage is discontinuous. It is essentially a method for the specialist in analysis.

The macromethod is far more rugged and easily learned, but even when the size of the sample is not an important consideration it suffers from the disadvantage that the operation requires the use of a large and rather costly combustion furnace which must be mounted on a heat-resistant bench, usually in a special room. The semimicromethod not only has some special merits of its own but it also combines to a large degree the advantages of both the other methods. The sample required is not large, for with an ordinary analytical balance a 50 mg. sample can be analyzed satisfactorily and, if a fairly good microbalance is available, no more than 10 mg. of material is required for an analysis. The combustion is more rapid than in the macromethod, and the procedure is standardized in such a way that the manipulation is easily learned. The method further gives reliable results in discontinuous use without restandardization of the apparatus; the equipment is not elaborate and it requires but little desk space in an ordinary laboratory.

The procedure given below is that preferred for research work; for work of a less advanced degree the procedure can be simplified by making the few changes indicated in the footnotes.

DESCRIPTION OF THE APPARATUS

The various units of the combustion train are illustrated in Fig. 80 and they are to be assembled in the order A to H. The special (Pyrex) pieces marked B, C, D, E, and F must be of accurate construction and it is of the utmost importance that the seals be free from pin holes and that the ground glass joints be gas tight.

Drying Train and Pressure Regulator (A, B, and C in the Figure). — Oxygen from a low pressure tank is passed through A, a large calcium chloride tube containing pellets or small lumps of potassium hydroxide held in place by plugs of glass wool. The drying tube (A) is connected by rubber tubing to the pressure regulator (B), which consists of a delivery tube with a collar dipping in a large test tube containing concentrated sulfuric acid. This is mounted in such a manner as to allow the test tube to be raised or lowered with respect to the delivery tube.

The bubbler tube (C) is connected to the pressure regulator by rubber tubing and to the rear end of the combustion tube through a rubber stopper. Just enough sulfuric acid is introduced into the bubble counter to make the bubbles visible; if too much acid is used the bulb blown into the bubbler tip will not be large enough to accommodate the acid in case of a suck-back. The body of the tube is filled with layers of Dehydrite (magnesium perchlorate trihydrate) and Ascarite (a granular sodium hydroxide — asbestos absorbent) held in place between plugs of cotton. A layer of Dehydrite is introduced first, then one of Ascarite, and finally a second layer of Dehydrite. With ordinary tank oxygen the drying train can be used for over five hundred determinations without being refilled.

The Combustion Tube, D. — The combustion tube is filled in the following manner, special care being taken not to pack the tube too tightly. First (section 1 in the figure) there is a 3-cm. wad of fine silver wire (No. 28); second, a 4-cm. basket of copper gauze filled with lumps of lead chromate (about the size of a small pea); third, a 3.5-cm. layer of copper oxide asbestos prepared by impregnating acid-washed asbestos with saturated cupric nitrate solution, drying, and igniting in a porcelain crucible; fourth, a 3-cm. layer of platinized asbestos prepared by impregnating asbestos with 10 per cent chloroplatinic acid solution, drying, and igniting; fifth, a second 3.5-cm. layer of copper oxide asbestos; sixth, a second 3-cm. layer of platinized asbestos.[1]

A 3–4 cm. copper spiral, made by wrapping a strip of copper gauze around a hooked wire, is used behind the boat containing the sample. A stout platinum wire (No. 22) is inserted in the small end of the tube, with one end flush with the tip of the tube and the other extending well into the tube filling. The conduction of heat along the wire helps to prevent the condensation of water vapor in the tip of the tube. Since asbestos retains water very tenaciously, all the material used for filling should be ignited very thoroughly before being introduced. With ordinary care the combustion tube will give long service and the filling materials can be used repeatedly. The boat is an 11 × 7 mm. tray about 4 mm. deep, easily made from a 19 × 15 mm. sheet of medium platinum foil.[2] A lip is convenient but not essential.

The combustion tube is supported in a trough made from a 12-inch piece of $\frac{3}{4}$-inch angle iron, with the ends bent upward slightly about 3 inches from each end to diminish warping. The trough is supported in V-bends at the ends of a piece of $\frac{3}{8}$-inch iron rod which is bent into the shape of a wide U. The base of the U is attached to a ringstand by means of an ordinary clamp holder. The trough is lined with two thicknesses of asbestos paper, and small covers for the combustion tube are made from bent pieces of the same paper. Three Bunsen burners

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[1] Simplified procedure: The first and second sections (7 cm. in all) are packed loosely with glass wool, the remainder of the tube is filled in the manner described. The simplified filling is entirely adequate for the analysis of compounds containing neither halogen nor sulfur. If such compounds are to be burned, silver wire is introduced to retain halogen and lead chromate to combine with oxides of sulfur.

[2] Simplified procedure: A larger boat is required, about 14 × 7 mm. at the base and 5 mm. deep, made from a 23 × 17 mm. piece of platinum foil.

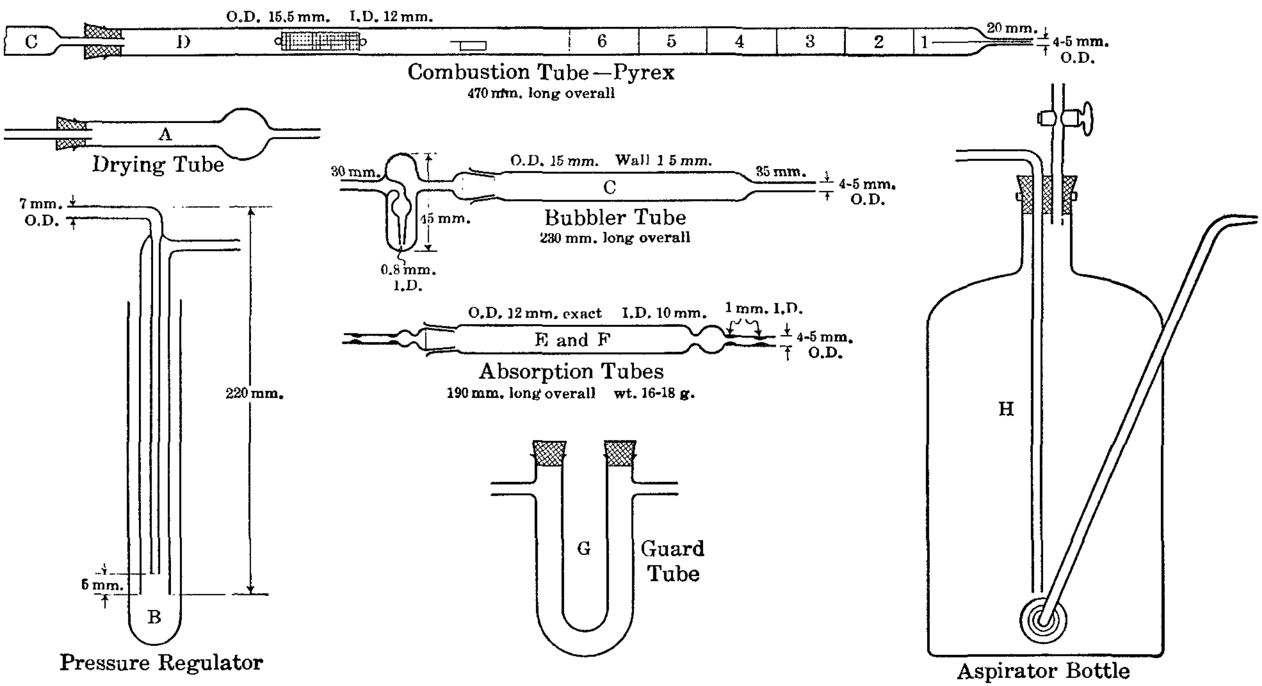

FIG. 80. — Apparatus for Semimicrocombustion

fitted with wing tops furnish heat for the combustion. Asbestos sheets are used at the ends of the combustion tube to diminish the diffusion of heat. When the combustion is to be conducted on a wooden bench the burners are mounted on a large piece of asbestos board raised about one inch from the bench on wooden runners.

The Absorption Train. — This consists of tubes for the absorption of water (E) and carbon dioxide (F), a guard tube (G), and an aspirator bottle (H). Tube E is filled with Dehydrite held in place by plugs of cotton, and tube F is similarly filled with Ascarite and a terminal 1-cm. layer of Dehydrite. The ground glass joints are wiped and carefully sealed with stopcock grease.[3] The Ascarite tube can be used until about one third of the filling has been exhausted, as indicated clearly by the color change (about 25 analyses). The Dehydrite tube should be refilled when about a 1-cm. layer of the solid becomes noticeably mushy (about 50 analyses).

Absorption tube E is attached to the combustion tube with the lubricated joint away from the source of heat. For convenience in handling, tube F is attached in the opposite position, and it is connected in turn to the guard tube (G). These connections are made by means of one-inch pieces of heavy walled rubber tubing ($\frac{1}{8}$ by $\frac{1}{4}$ inch), which is prepared by rubbing out the sulfur, moistening with glycerol and wiping dry. The ends of the glass tubes should meet inside the rubber connections. The absorption tubes are conveniently supported by hooks of aluminum wire suspended from a straight piece of glass rod held in a clamp on a ringstand. Caps are provided for the ends of the absorption tubes made from short lengths of rubber tubing cleaned and treated with glycerol as above and plugged with short sections of glass rod.

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[3] The grease may be replaced by a glass cement made by melting together one part of white wax and four parts of colophony resin. (Pregl, *loc. cit.*, p. 35.) The cement is applied to the warmed joint and the excess is removed mechanically and by wiping with a cloth moistened with benzene. The tube is opened by warming the joint and after it has cooled the contents can be removed and replaced without disturbance of the hardened cement.

The guard tube (G) is a small U-tube filled with potassium hydroxide pellets. It is connected to the absorption tube by a piece of the cleaned, heavy walled tubing and to the aspirator bottle with ordinary rubber tubing. When the tube is not in use the ends are closed by means of caps. It is still more convenient to use a U-tube with ground glass stoppers with which the tube can be sealed to the outside when desired.

The aspirator bottle (or Mariotte flask) connected next in line has a capacity of about 2 liters, and is graduated in units of 50 cc. marked on a strip of paper. The bottle is fitted with a gas-tight rubber stopper carrying a stopcock extending a short distance through the stopper and a glass tube extending to within about one inch of the bottom of the bottle. This tube is connected to the guard tube, G, by means of rubber tubing. The outlet of the bottle is fitted with a rubber stopper carrying a piece of glass tubing which is bent at an angle of 90° so that it passes up along the side of the bottle to the top, where the end is bent over and drawn down to a fairly small opening. This tube turns in the stopper and, with the bottle filled with water, oxygen can be drawn through the absorption train at a slightly diminished pressure which can be adjusted by swinging the tube down to the proper level. The reason for providing the bottle with a stopcock is that, if there is a temporary stoppage of the gas flow and a suck-back in the water delivery arm, the flow of water can be started again by opening the stopcock for a moment to the atmosphere.

The head of sulfuric acid in the pressure regulator should be such as to provide just sufficient pressure to overcome the resistance of the packed combustion tube to the flow of gas, and this pressure should not be increased when the absorption tubes are in place for the purpose of overcoming the added resistance, for this would tend to promote leakage. Instead, adjustment is made in such a way that the gas is delivered to the absorption train at atmospheric pressure and drawn through the absorption tubes by the aspirator. The adjustment is made while the tube is hot. With the end of the tube open to the air, oxygen is admitted at a rate of two bubbles per second. The aspirator bottle is then connected directly to the end of the tube, the delivery arm is adjusted to the specified rate of bubbling, and the volume of oxygen delivered in a given time is determined. The absorption tubes are next put in place, the aspirator bottle is connected at the end of the assembly, and the regulator arm is lowered until the oxygen delivery is the same as in the preceding operation. In this way one determines the amount of aspiration required to draw the gas through the absorption train when it is delivered at the end of the tube without excessive pressure.

PROCEDURE

Burning Out the Combustion Tube. — The absorption train is attached, the three Bunsen burners with wing tops are lighted, and a slow stream of oxygen is passed through the tube; the pressure regulator and the aspirator bottle are adjusted to maintain a constant slight pressure in the apparatus, with excess oxygen bubbling out slowly around the pressure regulator. A new tube should be burned out for a day or more and then tested by making a blank determination in which the regular procedure given below is followed in all details except for the use of a sample. The carbon dioxide tube should remain practically constant in weight, but the water tube gains about 0.1 mg. for every 300 cc. of oxygen passed through. Correction is not made for this, however, since the error seems to be partially compensated in the actual combustion. For an old tube the burning out requires from one-half to one hour, depending on the length of time the tube has been standing unused.

When the combustion tube has been burned out sufficiently the absorption tubes are disconnected and capped and a cap is placed over the tip of the combustion tube. The stream of oxygen need not be stopped; the gas may be allowed to escape at the pressure regulator. The burner nearest the bubble counter is turned off and the others are adjusted to allow the rear part of the tube to cool while the filling is kept warm.

Weighing the Tubes and the Sample. — About 10–12 mg. of the sample is weighed on a microbalance to the nearest 0.01 mg.[1] into the platinum boat which previously has been ignited, and allowed to cool in a small desiccator. Although the boat may vary little in weight in successive determinations, the actual weight of the empty boat is determined each time. A volatile liquid sample can be weighed in the manner described by Pregl.[2]

In weighing the absorption tubes it is of the greatest importance to adopt a uniform procedure and to adhere to it strictly. The following method has given good results. Shortly after being disconnected from the combustion tube the capped absorption tubes (Ascarite tube first) are wiped very thoroughly with a towel which has been wrung out of clean water. This is followed by a lighter wiping with a dry towel in the same order, being careful not to let the fingers touch the glass, and the tubes are allowed to stand near the balance for ten minutes. The Ascarite tube is then uncapped, the ends are wiped with a dry towel, and the tube is placed on the balance. The weights are adjusted and the final reading made as quickly as possible, for in spite of the capillary constrictions at the ends of the tubes oxygen diffuses fairly rapidly and this of course changes the weight. The Dehydrite tube is weighed immediately afterwards in the same way. The weights are recorded to the nearest 0.01 mg.[3]

The Combustion. — When the end of the combustion tube has cooled sufficiently the oxidized copper spiral is removed by means of a long, hooked wire and it is grasped with forceps and hung for the moment on a conveniently located hook. The boat containing the sample is slid into position; the oxidized copper spiral is replaced and the drying tube connected. The cap is removed from the tip of the combustion tube and the

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[1] Simplified procedure: Weigh about 50 mg. of the sample, using an analytical balance.

[2] Pregl, *loc. cit.*, pp. 51–52.

[3] Simplified procedure: Weigh to 0.1 mg. It is convenient to use a small cradle made from aluminum wire for holding the absorption tubes on the pan of the balance.

absorption train is connected. The oxygen, which until this time has been escaping at the pressure regulator, now resumes its course through the entire train.

The burner which was turned off is now lighted, after removing the wing top, and placed under the oxidized copper spiral. The heating of the sample should be carried out in such a manner as to allow about 50 cc. of oxygen to pass through before the substance starts to burn, the rate of flow being no more than two bubbles per second and no less than one bubble every two seconds. The wing top is then replaced on the rear burner and the heating is continued until the boat has burned clean. At no time should there be more than two bubbles of oxygen per second passing through the bubble counter. Any moisture which may collect in the end of the Dehydrite tube is removed by grasping the end between the warm prongs of a pair of crucible tongs. About 100 cc. of oxygen (at the rate of two bubbles per second) is now passed through the tube to sweep out the last traces of carbon dioxide and water. The whole operation, from the attaching to the disconnecting of the absorption train, requires about 45 minutes and a total of 250 cc. to 350 cc. of oxygen is employed.[4]

When this point has been reached the flow of water from the aspirator bottle is discontinued, the absorption tubes are disconnected, capped, and weighed in the manner described. The combustion tube is now ready for another analysis.

When burning compounds containing nitrogen it usually is sufficient merely to use air in place of oxygen and to proceed in the manner indicated above, using a somewhat larger volume of gas.

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[4] Simplified procedure: The combustion takes slightly over one hour and the total oxygen consumed is 350–450 cc. (50 cc. of the gas is used before the actual burning and 100 cc. is used for sweeping).

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