Lecture note- 8

Organic Chemistry CHE 502

NATURAL PRODUCTS

(Basic Concepts)

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UNIT- 13 NATURAL PRODUCTS

CONTENTS

13.1 OBJECTIVES

A natural product is a chemical compound or substance produced by a living organism - that is found in nature. In board sense, natural products can also be prepared by chemical synthesis (both) semi synthesis and total synthesis and have played a central role in the development of field of organic chemistry by providing challenging synthetic targets. Natural products has also been important to study as they extended for commercial/purposes to refer to cosmetics, dietary supplements and food produced from natural sources with out added. Artificial ingredients.

"These some times have pharmacological or biological activity that can be of therapeutic benefit in treating disease. For example-Terpenoid are well known natural products for essential oils having a strong and pleasant odour? Due to their pleasant odour these essential oils, have been used as perfumes since long. Some essential oils, eg. Lemon, orange and turpentine oil are almost exclusive mixtures of terpenoids.

In alkaloids; the poisonous and therapeutic properties of various plants have been known and utilized form early times, the first alkaloid (morphine) was isolated by Serturner only in 1817 from opium, this was further following by discovery strychnine (1818), burcine (1819), quinine (1820) and many other alkaloids.

So many of the Natural products possess curative properties and are of great value in medicine. In this unit we are discuss the natural product especially terpenoid & alkaloids. Objective of this unit is the study of occurrence synthesis and chemistry of terpenoids and alkaloids.

13.2 INTRODUCTION

TERPENOIDS

Terpene was employed to describe a mixture of isomeric polyhydrocarbons of the molecular formula $C_{10}H_{16}$ occurring in the turpentine and many essential oils which are obtained from in sap and tissues of certain plants and trees. The oxygenated derivations like alcohols, aldehydes, ketones etc at that time were called camphor's.

13.3 CLASIFICATION

Terpenoid polyhydrocarbons with few exceptions have the molecular formula $(C_5H_8)_n$ and the value of n have been used as a basis for the classification of terpenoids.

S.No.	**Value of n**	**formula**	**classes**
1.	2	$C_{10}H_{16}$	monoterpenoid
2.	3	$C_{15}H_{24}$	sesquiterpenoid
3.	4	$C_{20}H_{32}$	diterpenoid
4.	5	$C_{25}H_{40}$	sester terpenoid
5.	6	$C_{30}H_{48}$	triterpenoid
6.	8	$C_{40}H_{64}$	tera terpenoid (carotenoids)
7.	>8	$(C_5H_8)_n$	Polyterpenoids

The simpler mono-and sesqui-terpenoid and the related oxygen containing substance are highly widespread in the plant kingdom. Volatile oils contained in different parts of the plants are separated by steam distillation. These are called essential oils and have a strong and. Pleasant odour. This oil is responsible for the odour and flavour associated with plants. Essential oils are mixtures of terpenoid hydrocorbons and their oxygenated derivatives. Some essential oil, for e.g. lemon, orange and turpentine oil, are almost exclusive mixtures of terpenoids.

Terpenoids are most widespread, chemically interesting and provide structures of great diversity. Although the majority of terpenoids occur in the plant kingdom a few of them have also been obtained from other sources.

13.4 GENERAL PROPERTIES OF TERPENOIDS

Terpenoids are lighter than water and boil between 410K and 460K. A few of them are solids these are usually lighter than water, volatile in steam usually high refractive index. These are insoluble in water but soluble in organic solvent. Most of the terpenoids are optically active.

The various general chemical properties of terpenoids are as follows:

1. They are unsaturated compounds (open chain or cycles) with one or more carbon atom rings having one or more double bonds. Consequently, terponids undergo addition reaction with hydrogen, halogens, halogen acids etc. some of them forms hydrates. They also form characteristic addition products with NO_2, NOCl and NOBr. These addition proudest are found to be useful in the identification of terpenoid. A number of addition products have antiseptic properties.

2. They undergo polymerization, also dehydrogenation in the ring.

3. As they have olifinic bonds, they are very easily oxidized nearly by the entire oxidizing agent.

4. A number of terpenoid are labile and hence readily isomerised in the presence of and into more stable forms.

5. On thermal decomposition, most of the terpenoids yield isoprene as one of the products.

Isoprene Rule:

Wallach, in 1887 enunciated the famous isoprene rule, which stated as follows: "The skeleton structures of all naturally occurring terpenoids are built up of isoprene units."

From the above rule it follows that the divisibility into isoprene units is regarded as a necessary condition to be satisfied by every naturally occurring terpenoid. The isoprene rule has been deduced from the following facts.

a) The empirical formula of almost all the naturally occurring terpenoid is C_5H_8.

$$\left(C_5H_8\right)_n \quad \frac{distructive}{distilation} \quad nC_5H_8 \ isoprene$$

b) The thermal decomposition of almost all terpenoids gives isoprene as one of the products. For example rubber on destructive distillation field isoprene as one of the decomposition products.

$$\left(C_5H_8\right)_n \quad \frac{distructive}{distilation} \quad nC_5H_8 \ isoprene$$

Isoprene rule has been confirmed by the fact that under special experimental condtions, isoprene undergoes polymerisation to yield various terpenoids. For example.

i) Isoprene when heated to 280^{0}C gets dimerised to yield a widely distributed terpenoid called dipentene.

$$2C_5H_8 \quad \frac{Heat}{280^0C} \quad C_{10}H_{16}$$

ii) Isoprene may be polymerised to yield a rubber like product

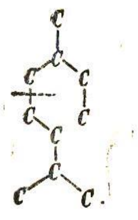
$$nC_5H_8 \ \xrightarrow{Polymerisation} \ (C_5H_8)_n$$

Special isoprene rule: - According to Ingold (925) molecules of terpenoids are built of isoprene units joined head to tail. The branched and of the isoprene molecule is termed the head and the other end is called the tail.

C-C-C-C C-C-C-C-C-C-C-C

This divisibility of terpenoids into isoprene units and their head to toil union is referred to as Ingold's special isoprene rule: this rule is a very suitable tool to limit the number of carbon skeletons of the structure of unknown terpenoids.

Monocyclic monoterpenoid contain a six membered ring. Inglod point out that the presence of a gem-dialkyls group renders the cyclohexane ring more stable this gem-dialkyle rule, stated by Inglod, limits the number of possible structures obtained by classing the open chain to a cyclohexane ring. Thus the monoterpenoid open chains give rise to only one monocyclic monoterpenoid like p-cymene structure. Most of the naturally occurring monocyclic monoterpnoids are derivations of P- cymene.

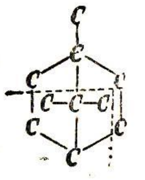
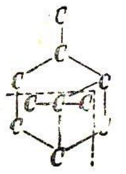
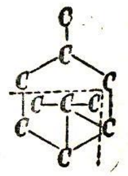


Acyclic structure

p-Cymene structure

The acylic structure written above is also presented in the conventional ring shape.

Bicyclic monterpenoids contain a six member ring along with another three, four or five member ring. Presence of a gem-dimethyl group in these cyclo propane and cyclobutane ring is essential to render them sufficiently stable for occurrence in nature. Three possible skeletons of a bicyclic montoerpoid are:

The dotted lines in the above skeletons indicate the two isoprene units.

Terpenoids with all the three types of skeletons given above are known. Thus gem-dialkyl group tends to render the cyclohexane ring unstable whereas it stabiles the three four and five membered rings.

13.5 EXTRACTION AND GENERAL METHODS OF STRUCTURE DETERMINATION OF TERPENOIDS

Due to their wide occurrence in nature, all the terpenoids could not be isolated and separated by a general method. However, mono-and sesqui-terpenoids have a common source, i.e., essential oils and, therefore, their isolation has been generalised. This is carried out in two steps as follows:

1. Isolation of essential oils.

2. Separation of terpenoids from essential oils.

Let us discuss these steps one by one.

a) **Extraction by means of volatile solvents.** This method is widely used in perfume industry. This method is generally used for such plants which yield an oil or give low quantities of oil on steam distillation due to decomposition of essential oils. In such cases, the plant material is directly treated with light petrol at 50^0C. Under these conditions the oil is taken up by the solvent along with the soluble colouring materials. The essential oils from this extract are separated by removing the solvent by distillation under reduced pressure.

(b) Adsorption in purified fats. This method is also known as enfleurage method and is widely employed in France. By this method, the yield of the essential oil is generally higher. This method is used to extract a large number of essential oils like rose and jasmine.

In this method, the fat is warmed to 50^0C in glass plates. Then, the surface of the fat is covered with flower petals and it is allowed to be kept as such for several days until it becomes saturated with essential oils. Then, the old petals are replaced by fresh petals and this process is repeated. After removing the petals, the fat is digested with ethyl alcohol when all the oil present in fat is dissolved in alcohol. Some quantity of fat is also dissolved in alcohol. This can be removed by cooling the alcohol extract to 20^0C, when the fat separates out. The alcoholic distillate is then finally fractionally distilled under reduced pressure to remove the solvent.

Recently, the fat has been replaced by coconut charcoal due to its greater stability and higher adsorptive capacity. After keeping the coconut charcoal in contact with petals for a number of days, the charcoal is submitted to steam to get essential oils. This method is superior to the enfleurage method.

2. **Separation of Terpenoids from Essential Oils.** The essential oils obtained from the step 1 generally contain a number of terpenoids and these are separated by various physical and chemical methods.

a) Physical methods. The various physical methods are as follows:

(i) Fractional distillation methods. The various terpenoids present in essential oils are separated by fraction distillation method. The terpeniod hydrocarbons distil over first followed by the oxygenated derivatives. Distillation of the residue under reduced pressure yields the sesquiterpenoids and these are separated by fractional distillation.

On an industrial scale, specially designed stills are employed and an efficient condensing system is necessary to minimize loss of more volatile hydrocarbons.

(ii) Chromatography More recently chromatography in its various forms has been widely used both for isolation and separation of terpenoids.

In adsorption chromatography, the essential oil is made to flow through a particular adsorbent when the different types of terpenoids are adsorbed at different places on the adsorbent to form different chromatograms. Then, the various chromatograms are eluted by different solvent systems to get different eluates (each eluate is having terpenoids of a single group). Each eluate is then subjected separately to adsorption chromatography when different subjected separately to adsorption chromatography when different bands due to the various terpenoids present in eluate are obtained which are them eluted to yield different terepenoids.

In adsorption chromatographic method, alumina and silica gel are generally used as adsorbents for separating the terpenoids, particularly triterpenoids.

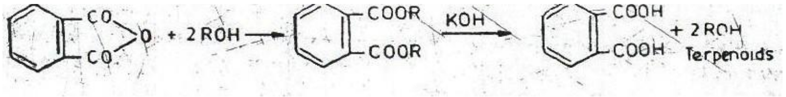
Gas chromatography has been particularly useful for isolating pure configurationally forms of a given terpenoid from mixtures produced by synthesis.

b) Chemical methods. These methods are not used these days to separate various terpenoids from essential oils. However, the various chemical methods are as follows:

i) When essential oils containing terpeniod hydrocarbons are treated with nitrosyl chloride in chloroform, crystal line adducts of hydrocarbons having sharp melting points are obtained. These are separated and decomposed into their corresponding hydrocarbons.

ii)When essential containing alcohols are treated with phthalic anhydride to form diesters, the primary alcohols react with phthalic anhydride readily, secondary alcohols less readily and tertiary alcohol does not react at all.

After extracting with sodium bicarbonate, diesters are decomposed by alkali to the parent terpenoid alcohols.



iii)Terpenoid aldehydes and ketones are separated from essential oils by forming their adducts with the common carbonyl reagents like $NaHSO_3$, 2-dinitrophenylhydrazine, phenylhydrazine, semincarbazide, etc. After separation, these are decomposed to regenerate terpeniod aldehydes and ketones.

6. General methods for the determination of structure of terpenoids.

The fundamental researches done by Wallach, Baeyer, Perkin, Semmler, Simonson, Ruzicka, etc. are of great importance in elucidating the complicated structures of terpenoids. All the methods used for these have been grouped into four classes:

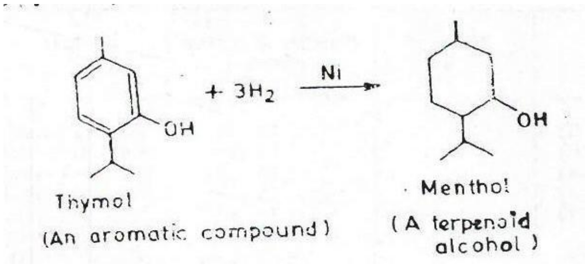
1. Analytical methods.
2. Synthetical methods.
3. Physical methods.
4. Knowledge of a molecular rearrangement.

5. Synthesis.

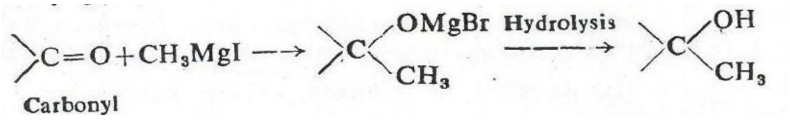
We will discuss these some methods

1. Synthetically Method: the following synthetical reactions have been found to be great value in elucidating the structure of terpeniods.

a) **Catalytical hydrogenation:** When aromatic compounds are hydrogenated catalytically under suitable conditions, It is possible to obtain synthetic terpenoids. For example, a terpeniod alcohol menthol may be prepared from thymo0l, an aromatic compound, by catalytic hydrogenation.

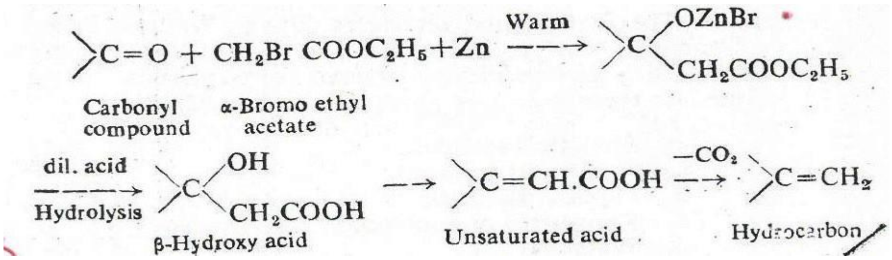


(b) Grignard's reaction. This reaction is of wide importance in the chemistry of terpenoids. This reaction was successfully employed by Perkin et al. to synthesise a large number of compounds which are related to terpenoids. By Grignard's reagent, methyl or isopropyl groups can be introduced into a compound having carbonyl group.



By the direct application of Grignard's reaction, $\alpha-$terpineol, a naturally occurring terpenoid tertiary alcohol, can be readily prepared.

(c) Reformatsky reaction. Similar to Grignard's reaction, Reformatsky reaction is very useful in synthesising many terpenoids this reaction; x- halogen substituted ester is treated with a carbonyl compound (aldehyde, ketone or ester) in the presence of zinc to form a $\beta-$hydroxy ester. The latter compound when treated with dilute acid yields $\beta-$hydroxy acid which may be further converted into an unsaturated acid or a hydrocarbon.



$$>C=O + CH_2Br\,COOC_2H_5 + Zn \xrightarrow{Warm} >C<^{OZnBr}_{CH_2COOC_2H_5} \xrightarrow[Hydrolysis]{dil.\ acid} >C<^{OH}_{CH_2COOH} \longrightarrow >C=CH.COOH \xrightarrow{-CO_2} >C=CH_2$$

2. Physical Methods

A number of physical methods have been employed in elucidating the structure of natural terpenoids. All complicated structural problems in terpenoids have been solved successively by physical methods. These methods also help to confirm the results of degradative studies.

The various methods for elucidating the structures of terpenoids are as follows:

(a) Ultraviolet spectroscopy. This technique is widely used in terpeniod chemistry for the detection of conjugation. The values of λmax for various types of terpenoids have been calculted. Thus:

(i) For simple acyclic dynes, λmax has been found to be 217-228 nm. If the conjugated double bonds are not present in the same ring. i.e. heteroannular diene, λmax has been found to be 230-240mn. If the diene is homoannular in which both double bonds are present in the same ring, λmax has been found to be 256-265 nm.

(ii) For B unsaturated carbonyl systems, λmax has been found to be 220-250 nm. Such systems also show a weak band at λmax 315-330 nm.

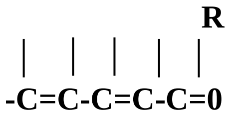
The values of for various polyenes and the increment values for substituents are given in Table:

TABLE

Absorption value for Various Polyenes and the increment values for substituent's

S.No.	Polyenes	Absorption value
1	Basic value of homoannular dienes	253 nm
2	Basic value of heteroannular (and acyclic) dienes	214 nm
3	Increment for each C-substituent	5 nm
4	Increment for each exocyclic double bond	5 nm
5	Increment for each double bond that extends conjugation	30 nm

The general formula of α, β unsaturated ketenes is



$$\begin{array}{c} \qquad\qquad\quad\ \mathbf{R} \\ |\quad|\quad|\quad|\quad| \\ \mathbf{-C{=}C{-}C{=}C{-}C{=}0} \end{array}$$

Where R is an alkyl group or a ring residue and the parent system. The various values of these systems are given in Table

Absorption Values of Unsaturated Ketones and Increment Absorption Values for Various Substituents'

S.No.	Polyenes	Absorption value
1	Basic value of homoannular dienes	215 nm
2	Basic value of heteroannular (and acyclic) dienes	10 nm
3	Increment for each C-substituent	12 nm
4	Increment for each exocyclic double bond	5 nm
5	Increment for each double bond that extends conjugation	30 nm

The above mentioned rules have been successfully applied to various terpeniods. For example,

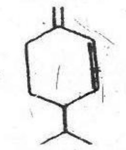
i)The observed $\lambda \max$ value for mycrene is 224 nm whereas the calculated $\lambda \max$ value (an cyclic diene with one C-substituent) is 214+5-219 nm.

ii)The observed $\lambda \max$ value for phellandrene is 232 nm whereas the calculate $\lambda \max$ value (a heteroannular diene with two substituents and one exocyclic double bond) is 214+2×5+5 or 229 nm.

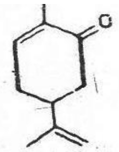
iii)The observed $\lambda \max$ value for carvone is 235 nm whereas the calculated $\lambda \max$ value is 237 nm which is obtained as follows:

Parent system	215 nm
C-substituent at $\alpha - c$	10 nm
C-substituent at $\beta - c$	12 nm
	λmax 237 nm

Myrcene



β-Phellandrene

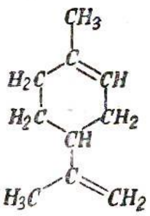


Carvone

Ultraviolet spectroscopy has also been used to recognize unsaturated acids esters and lactones. These compounds have in the region of 220 nm.

13.5.1 LIMONENE:

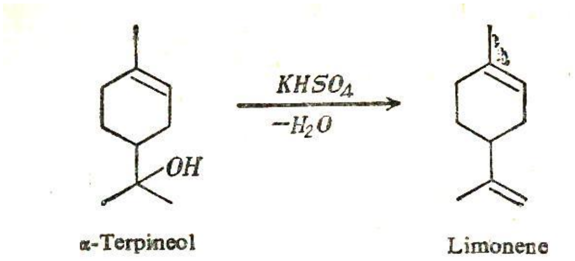
Introduction: It is the most important monterpenoid which is widely distributed in nature. Its +). form occurs in lemon and orange oils the (-). form occurs in peppermint oil where as the (+). form occurs in turpentine oil. The racemic modification of limonene is known as dependence. This name was give to the inactive form before its relation to the active form (limonene) was established.



Limonene

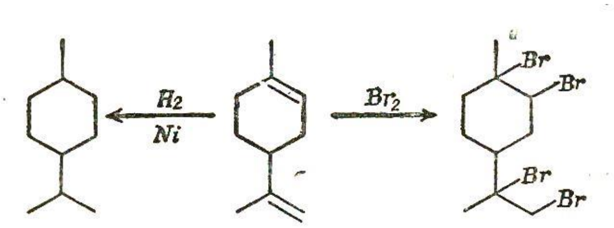
Preparation (i) From Essential Oils. (+) - Limonene is obtained from oranges. Dipentene is extracted from turpentine oil.

(ii) By dehydration of α - terpineol with $KHSO_4$.

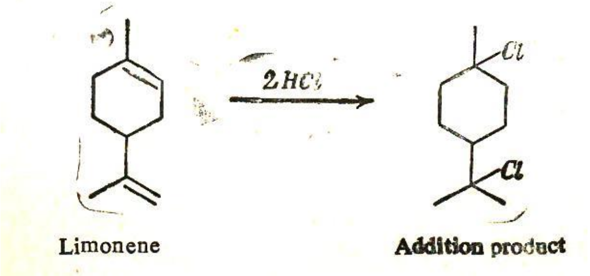


Properties: Limonene is a pleasant-smelling liquid with citrus-like odour (b.p. 450K). It is insoluble in water. Chemically it gives the reactions of a diolefin. For example,

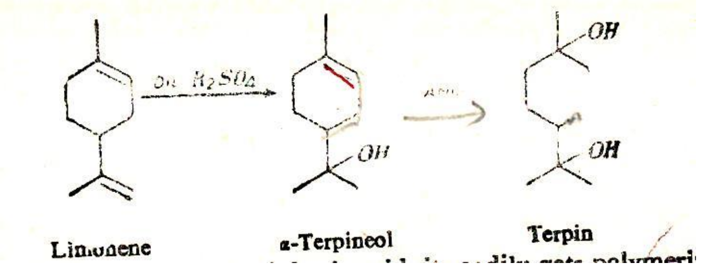
(i) It forms addition products with hydrogen and bromine to give p-menthane and its crystalline tetrabromide respectively.



(ii) It gives an addition product with two molecules of halogen acid.



(iii) With dilute sulphuric acid, it gives α -terpineol and terpin hydrate.



Uses: (i) Limonene is used as flavoring agent in beverages and foods.

(ii) Dipentene is used in medicine and in making synthetic resings and high pressure lubricating oil additives.

(iii) It is also used in the synthesis of isoprene, cymene and menthane.

Constitution of limonene: This has been elucidated on the basis of following analytical and synthetic evidences.

1. Molecular formula. From analytical data, the molecular formula of limonene has been found to $C_{10}H_{16}$.

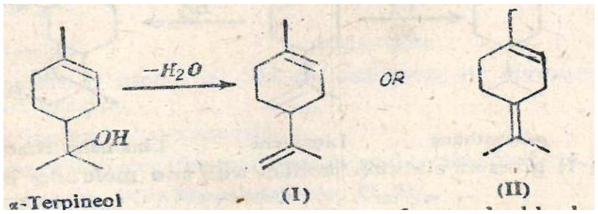
2. Presence of two olefinic bonds. This has been revealed on the basis of following facts.

(a) It adds on four bromine atoms to form a tetra bromide.

(b) On catalytic reduction, it adds on four atoms of hydrogen to form tetrahydro derivative.

c) With hydrochloric acid, a dihydrochloride is formed.

d) With hydrobromic acid, it yields a dihydrobromide.

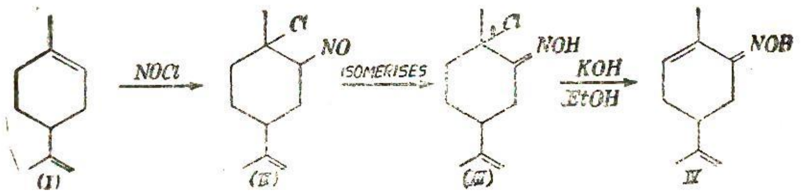


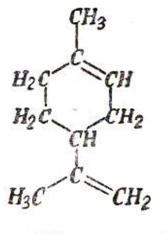
3. As a monocyclic derivative. The molecular formula of the saturated parenthy drocarbon corresponding to limonene is $C_{10}H_{20}$ which corresponds to the general formula C_nH_{2n} (n=10) for the monocyclic compound. Hence, the limonene contains monocyclic system.

4. Position of the double bonds. Chemical proof for double bond at position-8(9) is afforded by the following reactions

$$\underset{\text{(I)}}{\text{Limonene}} \xrightarrow{\text{NOCl}} \underset{\text{(III)}}{\text{Limonene nitrosochloride}} \xrightarrow[\text{EtOH}]{\text{KOH}} \underset{\text{(IV)}}{\text{Carvoxime}}$$

Structure of carvoxime is known and it has a double bond in Position 8(9). It, therefore, follows that limonene must have the structure I with double bond in position 8(9). Thus the above reaction may be written as follows:





Limonene

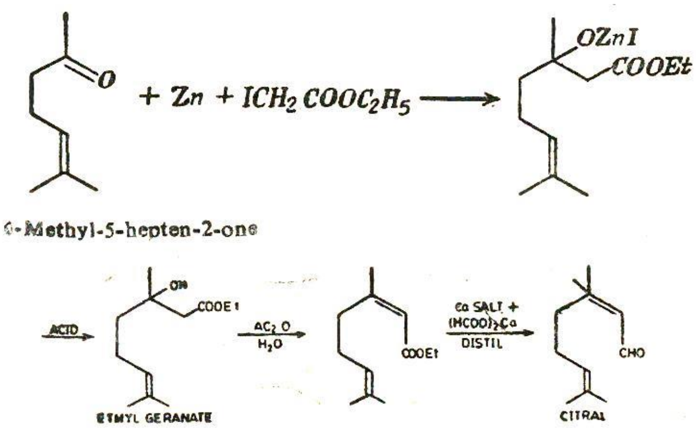
Thus Structure of limonene is 1, 8(9) menthadiene (I).

13.5.2 Citral ($C_{10}H_{16}O$):

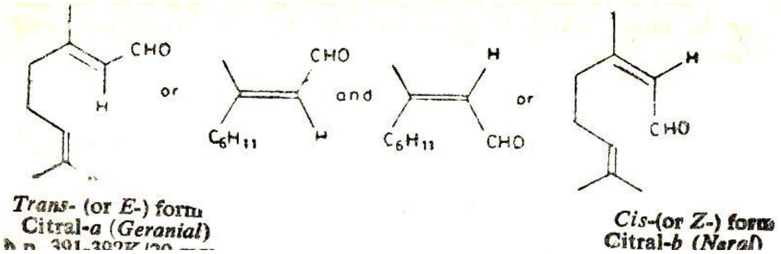
This is the most important acyclic terpenoids since the structures of most of the other monoterprenoids are based on the structure of citral. It occurs in oil of lemon grass (70-80%) and oils of lime, lemon, citronella, etc.

Extraction: It is obtained from lemon-grass oil by fractional distillation under reduced pressure and purified though the formation of bisulphite compound which is decomposed with sodium carbonate to get free citral.

Synthesis: Citral may be synthesied from 6-methyl-5- hepten 2 one by Reformatsky reaction using Zn+ICH2COOEt, as follows:



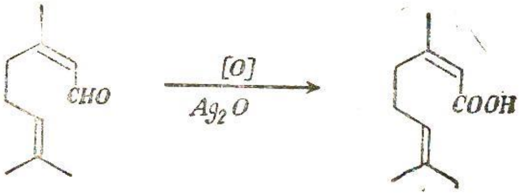
Properties: Citral is a pale yellow oily liquid (b.p. 497-501 K) with a pleasant odour of lemons. Chemical formula of citral is.

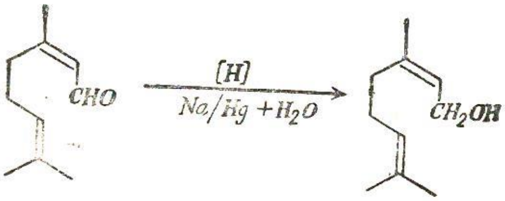


Chemical Properties: Some chemical reactions of citral are:

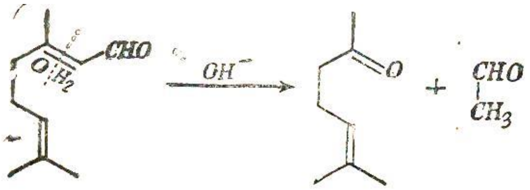
(i) **Reduction** Citral on reduction with sodium amalgam and water gives geranial.

ii) **Oxidation.** On oxidation with silver oxide, it gives geranic acid.

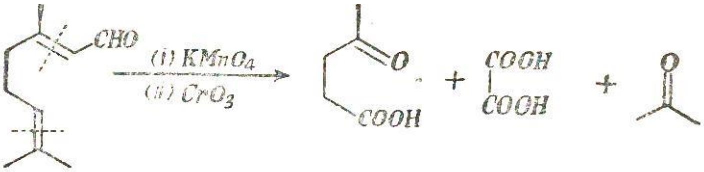




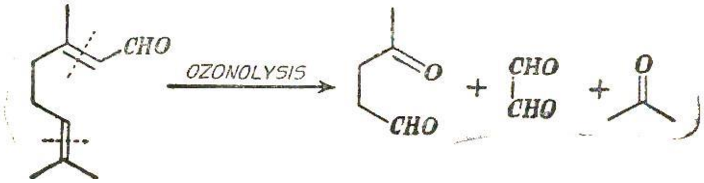
iii) Hydrolysis. When heated with potassium carbonate solution, citral undergoes hydrolysis and yields 6-methyl-5 hepten-2-one and acetaldehyde. During this reaction citral undergoes cleavage at the double bond. This cleavage by alkaline reagents is a general reaction of unsaturated carbonyl compounds.



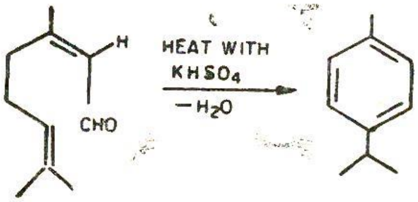
(iv) Oxidation with alkaline KMnO4 followed by chromic acid oxidation, gives acetone, oxalic acid and laevulic acid.



(v) Ozonolysis. On ozonolysis it gives acetone, laevula dehyde and glyxol.



(vi) Dehydration: One heating with $KHSO_4$ citral lose two molecules of water and gives p-cymene.



These reactions confirm the structure assigned to citral.

Use It is widely used as flavouring agent and in preparing synthetic perfumes e.g., and ionone. It is also employed for the manufacture of geraniol.

Constitution of Citral:

(a) Molecular formula of citral as deduced from its anyaltical data is $C_{10}H_{16}O$.

b) Presence of CHO group it gives the typical reaction of an aldehydic function e.g.,

i) It gives bisulphite compound and an oxime.

ii) On oxidation with silver oxide it gives geranic acid, an acid with same number of carbon atoms as citral.

c) Positions of methyl and isopropyl groups. On beating with potassium hydrogen sulphate, citral forms p-cymene (II), (p-methyl isopropylbenzene). It is concluded from this that citral molecule was acyclic and assigned it the structure (I), having two isoprene units joined head to tail.

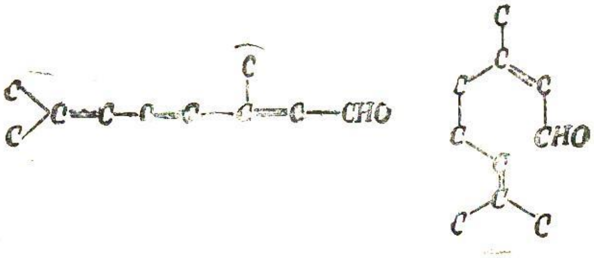
(d) Presence of two double bonds. On ozonolysis it gives accons, laevuladehyde and glyoxal, i.e., the chain breaks at two points. This suggests the presence of two double bonds.

(e) Location of two double bonds. The carbon atoms in the molecule are arranged as in the above three products and with CHO group at one end.

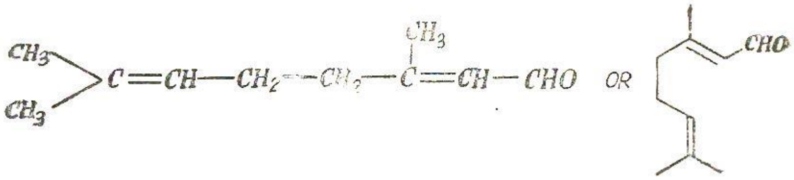
$$\begin{matrix}CH_3\\ CH_3\end{matrix}\!\!>C{=}O + OHC.CH_2.CH_2.\overset{CH_3}{C}{=}O + OHC.CHO$$

Acetone Laevulaldehyde Glyoxal

Hence the skeleton structure for citral is

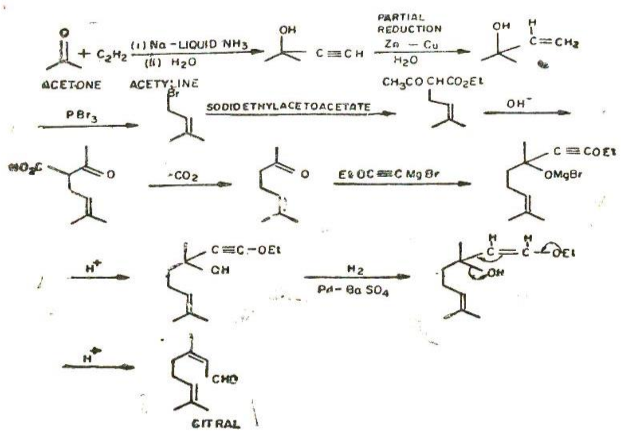


(f) Structural formula. From this we can write the structural formula of as



$$\begin{matrix}CH_3\\ CH_3\end{matrix}\!\!>C{=}CH{-}CH_2{-}CH_2{-}\overset{CH_3}{\overset{|}{C}}{=}CH{-}CHO \quad OR$$

g) Final confirmation. The structure of citral was finally confirmed by its synthesis from methytehptemone whose synthesis is given below:



13.5.3 ALKALOIDS:

Introduction: These are the basic nitrogenous compounds of vegetable usually having a marked physiological action and which may be regarded divided form parole, pyridine quinoline, isoquinoline or similar cyclic nitrogenous nuclei. Many of them possess curative properties and are of great value in medicine.

Occurrence: Generally they are usually found in plants in the form of their salts- in which they are either combined with organic acids such as lactic, citric, malic, oxalic commonly found plants or with certain characteristic acid such as quinic acid and meconic acid.

In some case they exist glycoside. Generally they accumulate in the first and seeds and some times in the break of the trees.

Isolation of Alkaloids Plants: Alkaloids are extracted form plarite the plant material is finally powdered and treated with water acidified with HCL, when alkaloids form salts with HCL dissolve in water. The water extract contains the hydrochlorides of the Alkaloids together with Carbohydrates and other products form the plant tissue and free alkaloids are obtained from the acidified water extract which when treated with alkali precipitate out the alkaloids (being sparingly soluble in water) in the case of volatile alkaloids, the acidulated water extract is treated with alkali and stream - distilled.

Purification of the crude product obtained above is carried out by special methods or frequently by crystallization of the freed compounds or their salts.

General Properties:

(i) State: Most of the alkaloids are crystalline solids which cannot be distilled. Only a few of them are liquids and can volatilize without decomposition, e.g., coniine and nicotine.

(ii)Physiological action: Most of them are bitter in taste and often exert a marked physiological action.

(iii)Solubility: Almost all of them are either insoluble or sparingly soluble in water. Liquids alkaloids (coniine and nicotine are notable exceptions (being readily soluble in water and appreciably volatile in steam.) Alkaloids are generally less soluble in chloroform, either and benzene but are readily soluble in alcohol.

(iv) Optical activity: Most of them are optically active and usually laevo- rotatory.

(v)Basic nature: In a number of cases their solutions give a strong alkaline reaction. All of them form salts with acids, among these salts the chlorides, sulphates and oxalates crystallize well, there chlorides give double salts with chlorides of gold, platinum and mercury.

(vi) Precipitation : Alkaloids are precipitated form their aqueous or acid solution by a number of substances such as picric acid, tannic acid, perchloric acid, potassium mercuric iodide, potassium bismuth iodide, potassium bismuth iodide, phosphomolybedic acid and phosphotungstic acid. Precipitation with these reagents is often employed for the isolation and purification of alkaloids. This procedure cannot, however, be used for quantitative analysis since the resulting compounds are not sufficiently insoluble and because the reagents precipitate some other organic substances as well.

Determination of the Chemical constitution of Alkaloids: Different steps involved in the determination of constitution of an alkaloid are:

(a) Determination of Molecular Formula: The sample is purified and subjected to qualitative analysis. Carbon, hydrogen and nitrogen are invariably present while oxygen is rarely is rarely absent. This is followed by quantitative analysis, determination of molecular weight and then calculation of empirical and molecular formula.

(b) Ditection of Groups: Knowing the presence of nitrogen and/or oxygen in the alkaloid, the functional nature of these elements is determined.

FUNCTIONAL NATURE OF OXYGEN

(1) Hydroxyl Group: The alkaloid is treated with acetic anhydride, acetyl chloride or benzoyl chloride to detect the presence of hydroxyl group.

The hydroxyl group present my be phenolic or alcoholic. It is phenolic if the alkaloid -

(i) Gives a colour with ferric chloride:

(ii) Is soluble in sodium 'hydroxide and is reprecipitated by carbon dioxide.

If the hydroxyl group is not phenolic, it must be alcoholic this is confirmed by treatment with dehydrating agents (eg. H_2SO_4 or O_4O_{10}) or by oxidation.

(2) Carboxyl group: Presence of a carboxyl group is indicated by the solubility of the alkaloid in aqueous sodium carbonate or formation of esters.

(3) Ester group: Identification of the products of hydrolysis of alkaloid indicates the presence or absence of an ester group.

(4) Methoxy group: The presence of methoxy groups and their number is determined by Zeisel method which is described under Estimation of groups.

FUNCTIONAL NATURE OF NITROGEN

(5) Amino Group.

(i) The reactions of the alkaloid with acetic anhydride, benzoyl chloride, nitrous acid and methyl iodide show whether the amino group is primary, secondary or tertiary.

(ii) Formation of methylamine, dimethylamine, trimethylamine (volatile products) on distillation with aqueous potassium hydroxide indicates the nature and number of methyl groups attached to nitrogen atom.

(6) Amide group: Products of hydrolysis (acid and ammonia) of the alkaloid will show the presence of an amide group.

(7) Presence of Unsaturation: It’s in an alkaloid sample is indicated by the treatment with bromine water or dilute alkaline permanganate.

(c) Estimation of Groups: The estimation of various groups, detected as above, is carried out as follows.

(1) Hydroxyl groups: The number of hydroxyl groups is determined by acetylating the alkaloid followed by hydrolysis of the acetyl derivative with a known volume of N-NaOH. The excess of the alkali left unused is estimated by back titration with a standard acid.

$$\underset{\substack{\text{Hydroxy}\\ \text{Compound}}}{\text{ROH}} \xrightarrow{\text{CH3COCl}} \underset{\substack{\text{Acetyl}\\ \text{derivative}}}{\text{RO.OCCH}_3} \xrightarrow{\text{NaOH}} \text{ROH} + \text{CH}_3\text{COONa}$$

From the volume of N-NaOH used, the number of acetyl groups or hydroxyl groups can be calculated.

(2) Carboxyl groups. The number of carboxyl groups in a given sample may be determined volumetrically by titration against standard barium hydroxide solution using phenolphthalein as an indicator or gravimetrically by the silver self method.

(3) Methoxy groups: The presence of methoxy groups and their number many are determined by the Zeisel's method. The alkaloid is treated with concentrated hydroiodic acid at 399 K (boiling point of HI). The methoxy groups present in the molecule are thereby changed into methyl iodide which is absorbed in alcoholic silver nitrate when silver iodide precipitated.

$$R(OCH_3)x + xHI \longrightarrow R(OH)x + xCH_3I$$

$$xCH_3I + xAgNO_3 \longrightarrow xAgI + xCH_3NO_3$$

The precipitate of AgI is boiled with HNO3, filtered, washed, dried and weighed.

From the weight of silver iodide, we calculate the number of methoxy groups as illustrated in the solved example given below:

Example: When treated according to Zeisel's method 0.226 gram of an alkoloid $C_{20}H_{21}O_4N$ yielded 0.626 gram of silver iodide. Calculate the number of methoxy groups present in the molecule of the alkaloid.

SOLUTION

Mol. mass of the alkaloid, $C_{20}H_{21}O_4N$ =240+21+64+14=339

Wt of alkaloid taken = 0.226 g

Wt of AgI obtained = 0.626 g

The wt of AgI that will be produced by I mole, i.e., 339g of alkaloid= $\frac{0626}{0.226} \times 339 = 939$ gm.

Mol. mass of AgI = 107.88+127=234.88

It is clear from the equations given above that corresponding to each methoxy group present, one melecule of AgI is obtained at the end. Hence the number of methoxy group in the molecule of the alkaloid = $\frac{939}{234.88} = 4$

(d) Degradation: The complex molecule is broken into relatively simple fragments whose nature gives useful information about the type of nuclei present in the molecule. Various methods employed for degradation of an alkaloid are:

(i) Hydrolysis: Molecules containing an ester or amide group break on hydrolysis into simpler products. For example, piperine on hydrolysis splits up to give piperic acid and piperidine.

From this we infer that piperine is a piperidinamide of piperic acid.

$$C_{11}H_9O_2CO\text{-}NC_5H_{10} + H_20 \longrightarrow C_{11}H_9O_2COOH + C_5H_{10}NH$$

Piperine Piperic Acid Piperidine

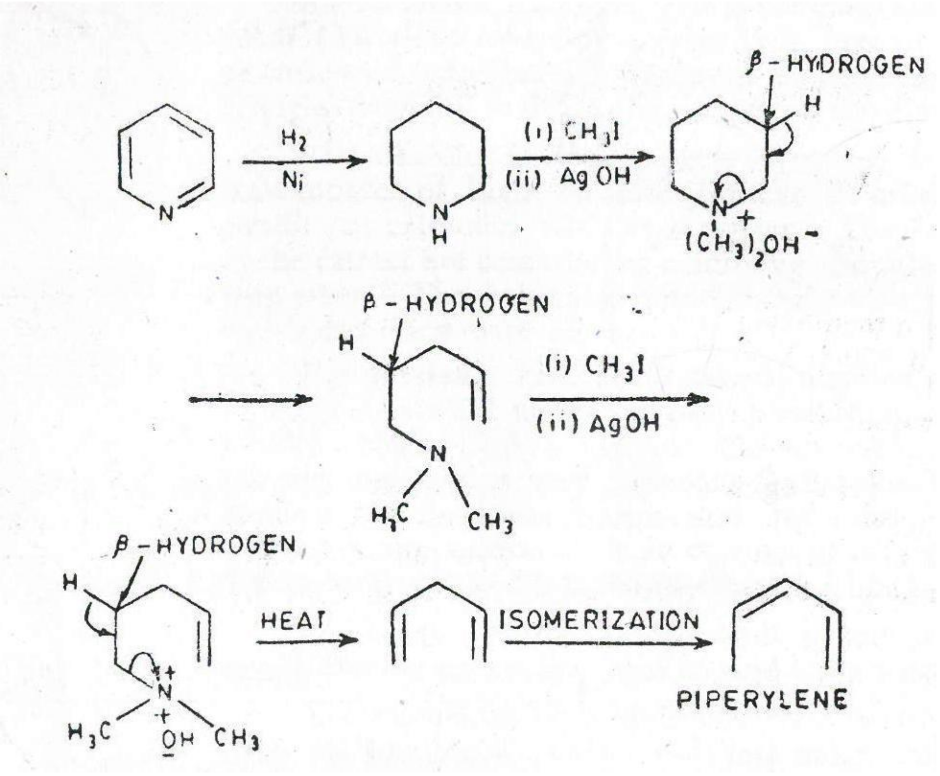
(ii)Oxidation: Alkaloids on oxidation give a variety of products depending the nature of oxidizing agents-mild (H_2O_2 or alkaline potassium ferricyanide), moderate (acid or alkaloid $KMnO_4$) or vigorous (K_2Cr_2O H_2SO_4; conc. HNO_3 or $MnO_2 + H_2SO_4$)

(iii) Distillation with Zinc dust: This brings about degradation or dehydrogenation of the alkaloid under study. When the alkaloid contains oxygen it is removed during distillation. For example, on distillation with zine dust morphine yields phenanthrene (parent compound) while coniine undergoes dehydrogenation to give conyrine.

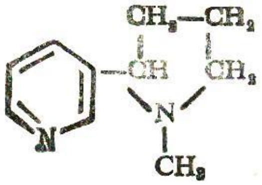
(iv) Hofmann Exhaustive Methytation: Heterocyclic rings containing nitrogenare opened with the elimination of nitrogen when subjected to exhaustive methylation. It thus helps us in knowing the nature of the carbon skeleton.

The heterocyclic, if unsaturated, is hydrogenated, and converted to the quaternary methylammonium hydroxide. This on heating loses a molecule of water by combination of -OH group with a hydrogen atom in B-position with respect to the nitrogen atom and the ring is opened at the nitrogen atom.

On repeating the process with the product, nitrogen atom is completely removed and an unsaturated hydrocarbon is left behind which generally isomerises to a conjugated diene. For example, starting with pyridine we have:



(e) Synthesis. The alkaloid under investigation is assigned a tentative structure on the basis of the foregoing analytical data. This is finally proved only if it could be synthesised by a suitable unambiguous method.



13.5.4 NICOTINE ($C_{10}H_{14}N_2$):

It is the chief alkaloid of the tobacco plant (Nicotiana tobacco) where in it is present as a salt of malic or citric acid. In leaves of tobacco its concentration is the highest. It varies from 0.6 to 8% depending upon the kind of tobacco.

The alkaloids are conveniently prepared from tobacco leaves. Raw tobacco of high nicotine is crushed and its soluble constituent extracted with cold water. The hydrocarbons present in the extract are removed by acidifying the solution and extracting with ether. The residual solution is made alkaline and nicotine sec free is extracted with other.

Properties: Freshly prepared nicotine is a colourless oily liquid. (b.p. 519.K under 730 mm pressure) readily soluble in water. Unlike tobacco, pure nicotine has an unpleasant smell. It has a burning taste and is very poisonous (lethal dose being 30 to 50 mg). In air it rapidly turns brown and resinifies and cab be distilled without decomposition only in vacuum or in a current of hydrogen. The natural alkaloid is laevo-rotatory and has [x] of - 169^o

In a mixture with soap solution it is one of the most effective exterminating agents for green fly and other insect pests.

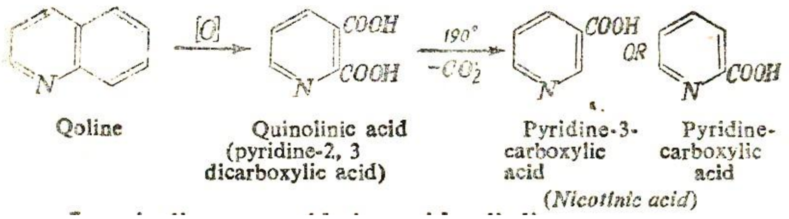
Constitution:

(1) Molecular formula of nicotine as deduced from its analytical data and molecular mass determination is $C_{13}H_{14}N_2$.

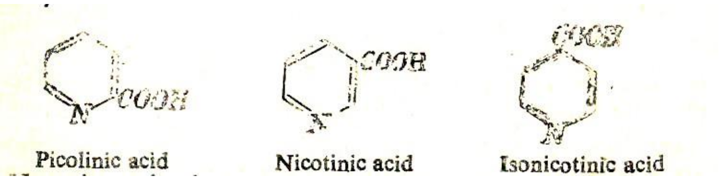
(2) Nicotine reacts with methyl iodide to form dimethiodide and two monomethiodidis but it does not form an acetyl or benzyl derivative. This show hat the two nitrogen atoms in nicotine are tertiary.

(3) Nicotine on oxidation with chromic acid or permanganate gives nicotinic acid ($C_6H_4N_2COOH$). Three pyridine carboxylic acids are known with COOH group in 2-,3- or 4-position. These are named picolinic acid, nicotinic acid. Their orlentation was proved as follows:

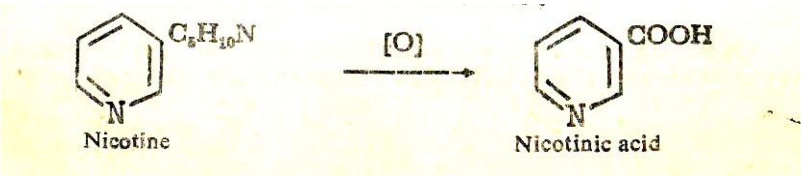
Quinoline on oxidation with alkaline permanganate gives quinolinic acid which must be pyridine-2, 3-dicarboxylic acid. Quinolinic acid on being heated to 360K loses one carboxyl group and gives nicotinic acid. Hence nicotinic acid must be either pyridine-2-carboxylic acid or pyridins-3-carboxylic acid.



By elimination, therefore, picolinic acid is pyridine 2-carboxylic acid.



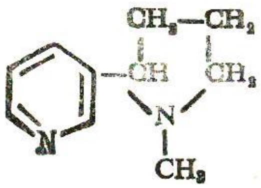
Now since nicotine on oxidation followed by heating at 460K yields nicotinic acid (pyridine-3-carboxylic acid), it suggests that nicotine contains a pyridine ring with some sort of group attached to it at the B- position. This group attached to pyridine ring is $C_5H_{10}N$ and the oxidation can be formulated as follows:



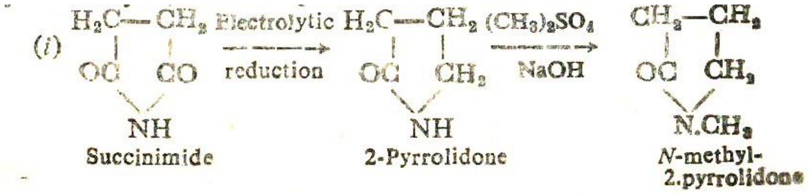
Nicotine hydriodide on treatment with methyl iodide gives a methiodide. This on oxidation yields hygrinic acid (N-methylpyr- rolidine-α -carboxylic acid.

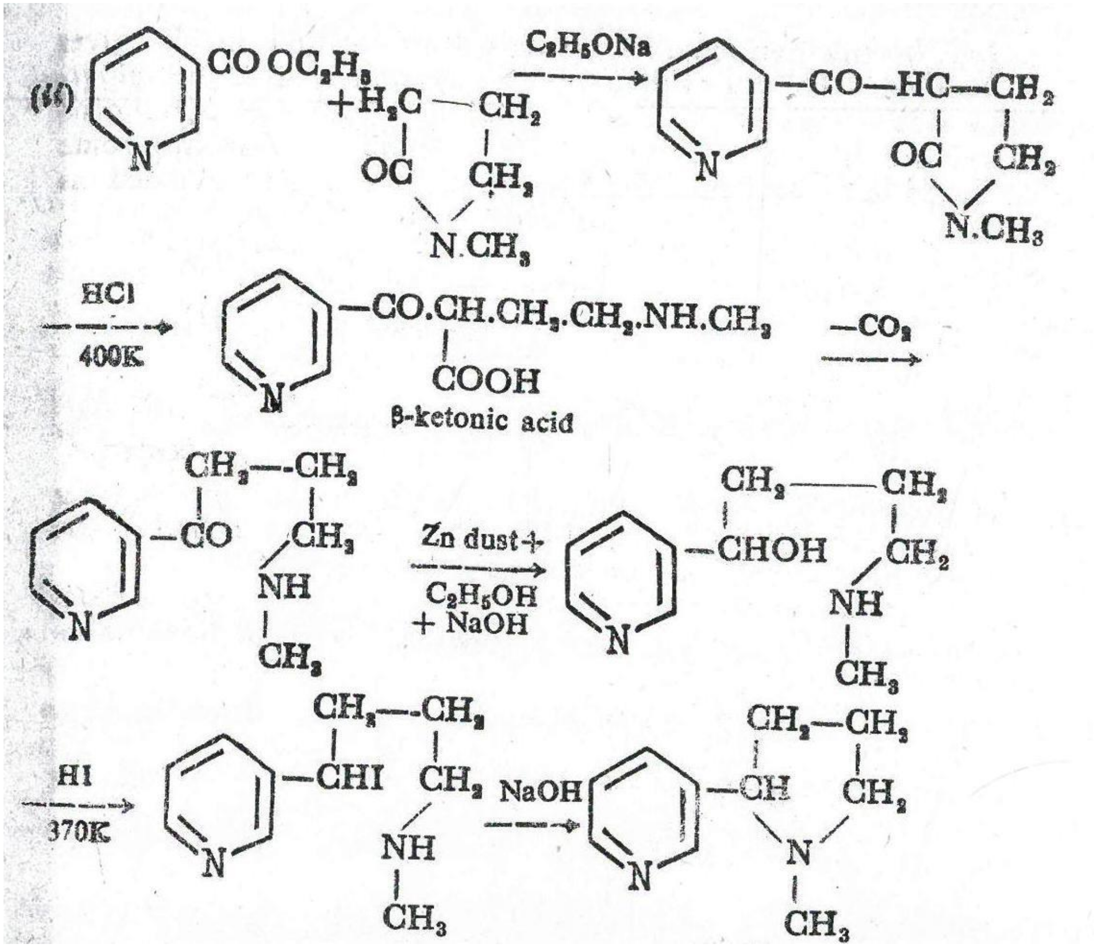
This indicates that pyridine ring has been destroyed during the above transformation and the group-$C_5H_{10}N$ attached to the pyridine ring in B-position is N-methylpyrrolidine.

Pyridine and pyrrolidine nuclei are joined through carbon atoms at B-position in pyridine and 2-position in pyrrolidine. This gives the structure of nicotine as:



This formula has been further confirmed by its synthesis by Spath and Bpetshneider (1928):

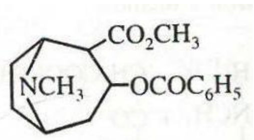




The (+/-) - mixture of nicotine obtained by the above synthesis was resolved by forming salts with (+/-) -tartaric acid and (-) - nicotine thus obtained was found to be identical with the natural product.

15.5.5 COCAINE:

It was first isolated in 1860 from the leaves of *Erythroxylon coca L.,* (Coca Plant) which is mainly grown in South America, particularly in Peru and Bolivin and now grown in java and Ceylon. However, the plant from which cocaine is obtained (*i.e.* coca plant) should not be confused with *Theobrama cocoa,* the beans of which are source of cocoa and chocolate.



(–)-Cocaine

Isolation: In order to obtain the crude cocaine, the Peruvian leaves are powdered and thoroughly digested with lime or sodium carbonate and a little water. The digested solution is then extracted with light petroleum when the alkaloids get dissolved in the light petroleum layer. From the organic layer, the alkaloids are removed by shaking with a controlled amount of dilute sulphuric acid (avoiding excess). This acid solution when evaporated yields a crystalline precipitate of a larger portion of the cocaine which can be further purified by crystallization of its hydrocholoride.

Cocaine can also be extracted directly from the leaves with high boiling petroleum.

Properties:

1. It forms colourless crystals (m.p. 98^0C). It is sparingly soluble in water, but its hydrochloride is quite soluble. It is a strong tertiary base (pk_a 8.7).

2. The hydrochloride of cocaine is used as a local anaesthetic in eye surgery and dentistry. Usually, cocaine is injected along with adrenaline.

3. Cocaine is the habit forming drug and is, therefore, used with great care. Taken internally, it increases physical and mental power but the after-effects is deep depression.

Constitution:

1. ***Molecular Formula.*** From analytical data and molecular weight determination, it follows that the empirical and molecular formula of cocaine i.e., $C_{17}H_{21}NO_4$.

2. ***Nature of the Nitrogen Atom.*** It is a strong tertiary base (pk_a 8.7) and adds on one molecule of methyl iodide to form a methiodide. It also reacts with cyanogens bromide to give methyl bromide and cyanonorcocaine and thus contains a N-methyl group.

$$C_{17}H_{21}NO_4 + CH_3l \longrightarrow C_{17}H_{21}NO_4 . CH_3l$$

1. ***Hydrolysis.*** When cocaine is heated with water, it is hydrolysed to methanol and benzoylecgonine.

$$\underset{\text{Cocaine}}{C_{17}H_{21}NO_4} + H_2O \longrightarrow \underset{\text{Benzoylecgonine}}{C_{16}H_{19}NO_4} + CH_3OH$$

But benzoylecgonine contains a carboxyl group. Therefore, cocaine is the methyl ester of benzoylecgonine which is also proved by the fact that benzoylecgonine when heated with methyl alcohol in presence of hydrochloric acid yields cocaine.

When benzoylegonine is boiled with barium hydroxide solution. It undergoes further hydrolysis, yielding benzoic acid and ecognine.

$$C_{16}H_{19}NO_4 + H_2O \xrightarrow{Ba(OH)_2} C_9H_{15}NO_3 + C_6H_5COOH$$

Benzoylecgonine (-)-Ecgonine Benzoic acid

From the above reactions, it is evident that the constitution of cocaine depends on the constitution of ecgonine.

4. ***Constitution of Ecgonine.*** It is established as follows:

a) Its molecular formula is $C_9H_{15}NO_3$.

b) It is a tertiary base because it gives the crystalline additive compound $C_9H_{15}NO_3.CH_3l$ with methyl iodide. This reaction shows that ecgonine contains tertiary nitrogen atom.

c) As ecognine forms ester and salt with alcohol and alkali respectively, it means that it contains one *carboxyl group.*

d) The presence of - OH group is indicated by the fact that it reacts with acid chloride and anhydride to form acyl derivatives. Since this acyl derivative can be further esterified, it shows that ecgonine is both an alcohol and an acid.

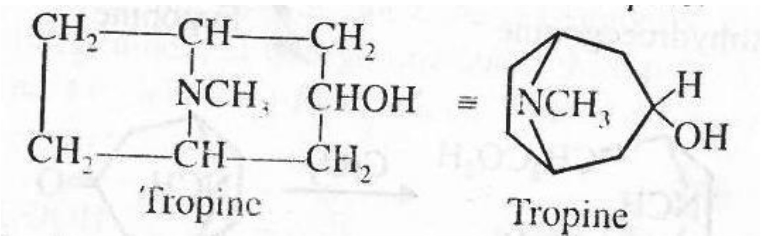
e) Ecgonine when oxidised with CrO_3 yields a ketone ecgoninone which soon loses a molecule of carbon dioxide to yield tropinone. The latter compound when further oxidised yields a mixture of tropinic acid and ecgoninic acid, former of which is also obtained from tropine.

$$C_9H_{15}NO_3 \xrightarrow{CrO_3} C_9H_{13}NO_3 \xrightarrow{-CO_2} C_8H_{13}NO \xrightarrow{CrO_3} C_8H_{13}NO_4 + C_7H_{11}NO_3$$

Ecgonine Ecgoninone Tropinone Tropinic acid Ecgoninic acid

From the nature of products obtained by oxidation of ecgonine, following conclusions are drawn :

(i) The reaction which involves the oxidation of ecgonine first to tropinone and then to tropinic acid reveals that ecgonine contains the tropane skeleton and furthermore position of the secondary alcoholic group in ecgonine remains the same as in tropine.

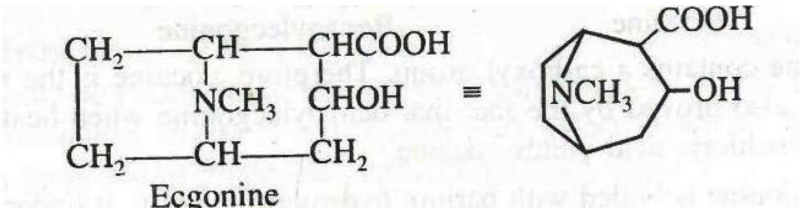


The close similarity between the structures of ecgonine and tropine is further proved by the fact that the dehydration of ecgonine yields anhydroecgonine which on decarboxylation yields tropidine. The latter compound is also formed by the dehydration of tropine.

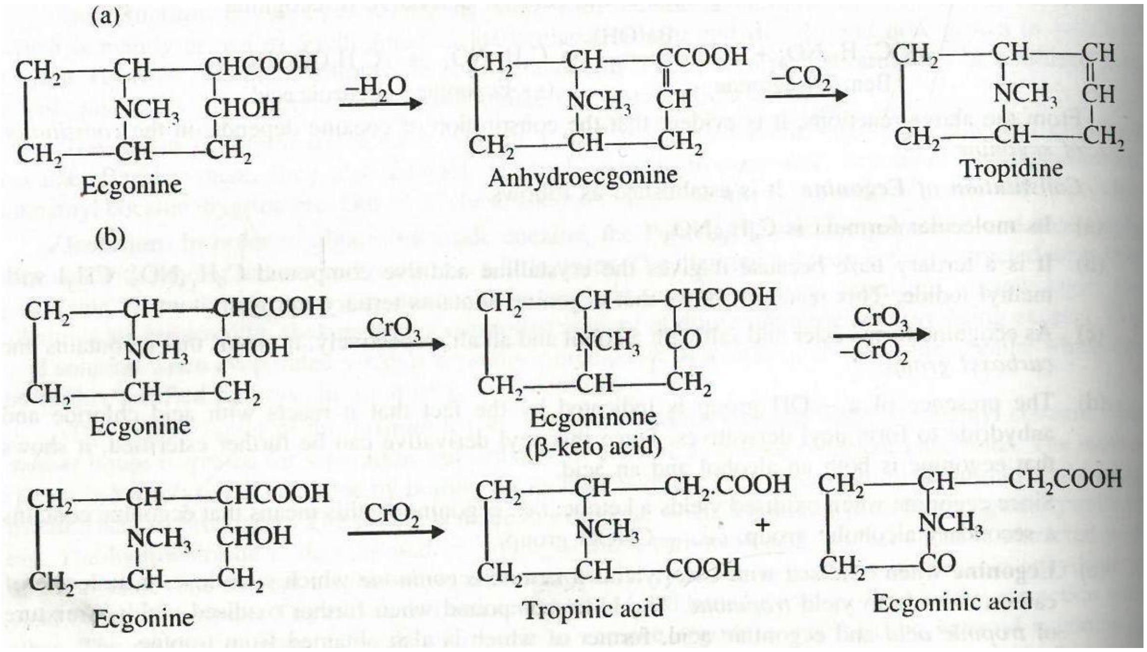
$$\text{Ecgonine} \xrightarrow{-H_2O} \text{Anhydroecgonine} \xrightarrow{-CO_2} \text{Tropidine}$$

$$\text{Tropine} \xrightarrow{-H_2O} \text{Tropidine}$$

(ii) The easy decarboxylation of the ecogonine reveals that it is a B-keto acid. This interpretation is confirmed by the fact that Willstatter actually observed the formation of an unstable ketonic acid which lost carbon dioxide to yield tropinone. Thus, ecgonine is :

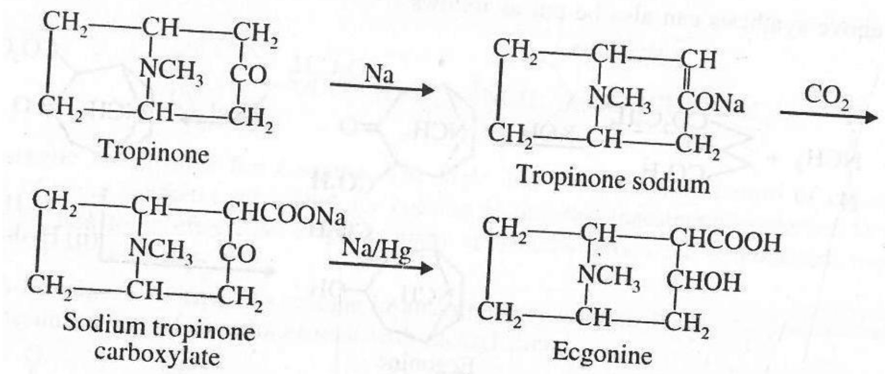


f)The above structure of ecgonine explains all its reactions :



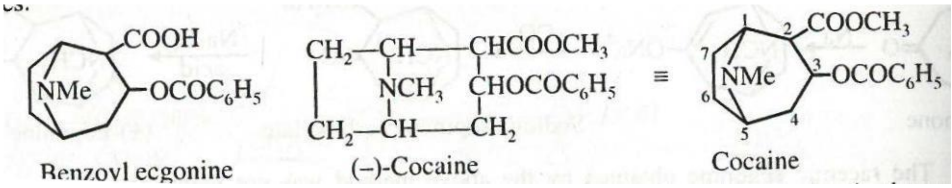
g) Finally the structure of ecgonine is proved by its synthesis:

The starting material is tropinone.

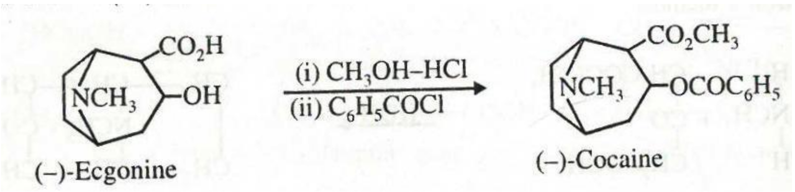


The racemic ecgonine obtained by the above method was not identical with (-) ecgonine obtained from (-). cocaine. However, its chemical properties were the same.

5. Constitution of Cocaine. Now since we know that cocaine is methyl ester of benzoyl ecgonine having a free carboxylic group; the benzoyl ecgonine and cocaine will be having the following structures.



The above structure of cocaine has been proved by its synthesis which consists in the resolution of the racemic ecgonine, esterification of (-). ecgonine followed by benzoylation to give cocaine identical to natural (-). form.



Similarly, (+) and (-) cocaines were obtained from the corresponding - ecgonines.

1.5 SUMMARY

In this unit we discuss natural product for i.e. Terpenoids and alkaloids. Natural products are usually found in plants in the form of their salts in which they are either combined with organic compounds. We studied their extraction from plant material in the form of crude and then their purification.

In Terpenoid we studied the limonene and citral with their physical and chemical properties, Also discuss their commercial value. as citral widely used as a flavoring agent and in preparing synthetic perfumes, eg. a and b-ionone.

Similarly limonene is principal terpene in lemon, orange, bergamot, caraway and celery oils. The inactive (+/-) mixtures, called dipentene, ocurs in lemon-grass oil and trupentene oil.

In alkaloid we will discuss isolation of alkaloid from plants and their purification, we also discuss general properties and therapeutic value of alkaloid like morphine, nicotine etc. physical and chemical properties of nicotine and cocaine are also explained.

We should studied natural product much wider ways.

13.6 TERMINAL QUESTION

Terpenoids:

1.What are terpenoids? How are they classified? How are these extracted? Write a short note on their chemical nature.

2. (a) What are terpenoids? How are they classified?

 (b) How is the structure of cital established?

3. (a) Describe the preparation, properties and uses of menthol as limonene.

 (b) Discuss the constitution, properties and uses of menthol as limonene.

2. Give the synthesis of methyl heptanone. Starting from methyl heptanone outline the synthesis of sitral using Reformatsky reaction.
3. How will you convert: 3 di-bromo -3-methyl butane into citral?
4. What sort of a terpene is limonene? Gives its structure.
5. What do you understand by the term terpenoids?
6. How terpenoids are classified.
7. How with you convert.

   (i) Limonene to corvoxime.
   (ii) L-terpineol to limonene.
8. What is isoprene rule? How is the structure of citral Established?

Alkaloids:

1. Define an alkaloid and outline methods for the extraction of alkaloids from plant materials. What are their uses?
2. Write an explanatory note on general characteristics of alkaloids.
3. What do you understand by the term alkaloid? Describe synthesis of Nicotine.
4. Describe the various steps involved in establishing the structure of Nicotine.
5. Discuss the constitution of Cocaine.
6. Suggest the heterocyclic units occurring in Nicotine. Outline the method for synthesis of dl. Nicotine.
7. What are alkaloids? How is cocaine isolated?
8. How could you prove that nicotine molecule has a pyrollidine nucleus? Write the structure of Nicotine. Is it optically active? If so, is it dextro rotatry or leavo - rotatry?

9. Discuss the degradation evidence for in structure of cocaine.
10. Explain natural products with special reference of alkaloids.

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