ATTEMPTED SYNTHESIS OF BICYCLO [2.2.0] HEXAN-1-OL
AND
OTHER BICYCLO [2.2.0] HEXANE DERIVATIVES

by

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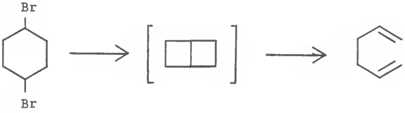
INTRODUCTION

Research on the chemistry of the bicyclo[2.2.0]hexane system has been rapidly expanding and a number of reviews either totally or partially concerned with it are now in print on the subject. Reineke[36] and Davis[17] have reviewed the literature prior to mid-1967. A large, excellent review on the bicyclo[2.2.0]hexa-2,5-diene system (Dewar Benzene) appeared in 1967 by Schäfer and Hellman.[41] The modes of synthesis and reactions of the system were discussed from a historical viewpoint. Another review, concerned with a complete compilation of all the intramolecular photochemical cycloaddition reactions of nonconjugated dienes through 1964 and most of 1965, was written by Dilling[20] and included a number of reactions producing the bicyclo[2.2.0]hexane system. Finally another short review on derivatives of the bicyclo-[2.2.0]hexane system by Criegee[14] appeared in 1965.

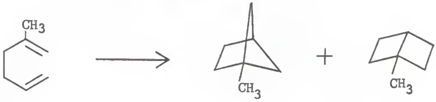
The present review updates those by Reineke and Davis covering the literature through February, 1968. Bicyclo[2.2.0]hexane (2), which was first erroneously reported by Zelinski and Nametkin[55] as the product of the Wurtz reaction between *cis*-1,4-dibromocyclohexane (1) and sodium, was the subject of a new attempt which was almost identical. Connor and Wilson[12] attempted to synthesize 2 using 1,4-dibromocyclobutane with lithium amalgam in ether. The intermediate, 2, was postulated as a route to 1,5-hexadiene (3), which



1 2 3

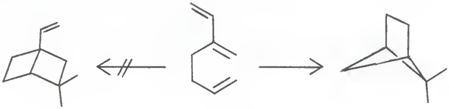
was the only product obtained. However, they did not rule out the possibility that 3 might arise by direct fragmentation of 1.

Srinivasan and Carlough[47] produced 1-methylbicyclo[2.2.0]hexane (5) as the minor product in the mercury sensitized dimerization of 2-methyl-1,5-hexadiene (4).



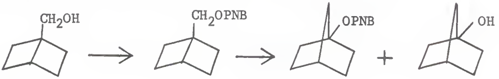
4 5

A structure of the following type (7) was considered, but was ruled out in the following photosensitized internal addition of myrcene (6) by Liu and Hammond.[29]



7 6

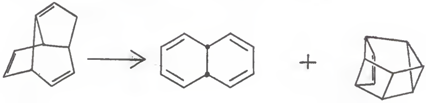
The preparation of bicyclo[2.2.0]hexane-1-methanol (8) and solvolysis of its *p*-nitrobenzoate (9) was discussed in a very recent paper by Dauben, Chitwood, and Scherer.[16] The same independently discovered mode of preparation as was utilized is described in the present work.



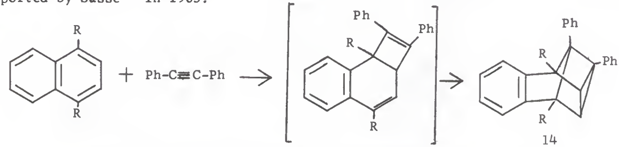
8 9 10 11

Solvolysis of the *p*-nitrobenzoate 9 in 60% aqueous acetone yielded 10 in an 81% yield and 11 in a 19% yield. The first order rate constant was 0.43×10^{-5} sec.$^{-1}$ at 99.5° and was compared to a number of *cis*-fused bicyclic neopentyl systems in an excellent discussion. Several attempts were made by these authors to synthesize the tosylate ester, but were unsuccessful.

A photolysis reaction on 12 was reported by Jones.[25] Small amounts of a pentacyclic compound of structure 13 were isolated, the n.m.r. spectrum of which agreed with this structural formulation.

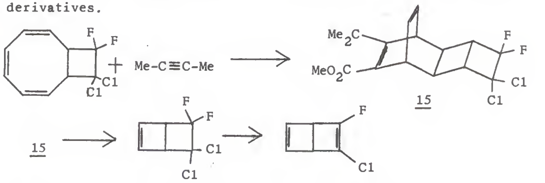

12
13

A series of derivatives 14 were prepared in a photolysis reaction reported by Sasse[39] in 1965.



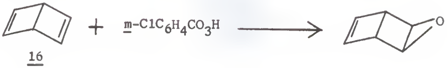
14

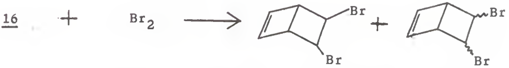
3-Chloro-2-fluorobicyclo[2.2.0]hexa-2,5-diene (15) was prepared by Schröder and Martini[49] in a Diels-Alder reaction and was the precursor to several derivatives.



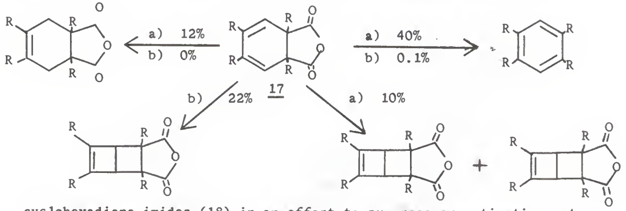
Van Tamelin and Carty[48] have studied the chemical behavior of bicyclo-[2.2.0]hexa-2,5-diene (16) by allowing it to react with various electrophilic species. They found that the reactions do not involve aromatization, but characteristically provide nonbenzenoid transformation products.

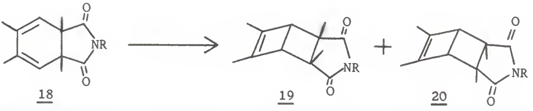
The following reactions illustrate a part of their work.



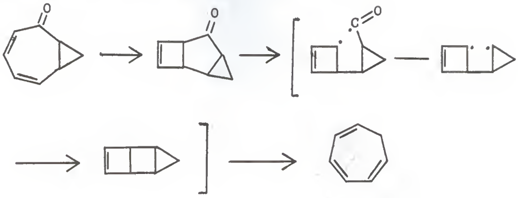


The photolysis of 17 with a, R=methyl, and b,R=H, was done by Warrener and Bremner[51]. The products were analyzed and mechanistic pathways were discussed. They[7] also studied the photolysis of a number of cyclohexadiene imides (18) in an effort to suppress aromatization yet retain the potential functionality of an anhydride group. When R was H, the corresponding benzene derivative was produced. However, when R was cyclohexyl or n-butyl, 19 and 20 were produced.

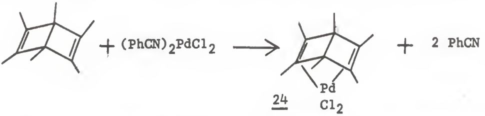




Paquette and Cox,[33] in studing the photochemistry of 2,3-homotropone, rationalized the following interconversion through 22 to explain the formation of one of the products 23. However, when 21 was subjected to the reaction conditions only a polymeric solid formed.



A small body of work on complexes of the bicyclo[2.2.0]hexa-2,5-diene system has appeared in the literature since the last review.[17] A paper by Dietl and Maitles[18] reported the first preparation of such a complex and its role in the isomerization of the ligand. Dewar hexamethylbenzene (hexamethylbicyclo[2.2.0]hexa-2,5-diene), when allowed to react with dichlorobis(benzonitrile)palladium in benzene, gives yellow platelets of the complex 24, dichloro(hexamethylbicyclo[2.2.0]hexa-2,5-diene)palladium.



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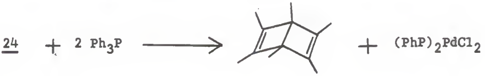
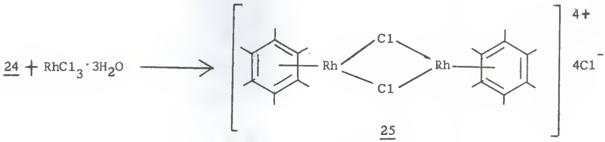
Reaction of triphenyl phosphine with 24 will regenerate the Dewar benzene.

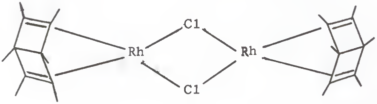


Booth, et al.,[5] in studying the reaction of 24 with rhodium chloride trihydrate in aqueous methanol at 60°, found 25 as a novel product.


24
$RhCl_3 \cdot 3H_2O$
Rh
Cl
Cl
Rh
4+
4Cl⁻

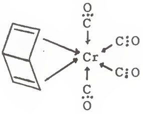
25

Volger and Hogeveen[50] reported the study of the thermal isomerization of μ-dichlorodi(hexamethyl-Dewar-benzene) dirhodium (26) and compared it to the thermal isomerization of hexamethyl-Dewar-benzene, which they also investigated.



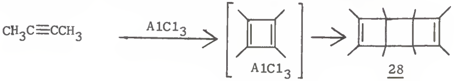
26

Fischer, et al.,[22] reported the synthesis of the following chromium complex (27), tetracarbonyl(hexamethylbicyclo[2.2.0]hexa-2,5-diene) chromium (0), in a 5% yield.

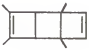

O
C
C:O
Cr
C:O
C
O

27

More papers have appeared on larger ring systems incorporating the bicyclo[2.2.0]hexane framework. Rosenberg and Eimutis[37] reported the facile synthesis of octamethyl-*syn*-tricyclo[4.4.0.$0^{2,5}$]octa-3,7-diene (28) from anhydrous aluminum chloride and 2-butyne in cyclohexane, which very closely resembles the former work by Schäfer.[40]


$CH_3C{\equiv}CCH_3$
$AlCl_3$
$AlCl_3$
28

Criegee,[15] who has done much work on the bicyclo[2.2.0]hexane system, reported the synthesis and identification of the following isomers 29, 30, and 31 in the dechlorination with lithium or sodium amalgam of 3,4-dichloro-3,4-dimethylcyclobutene.



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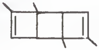

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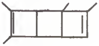
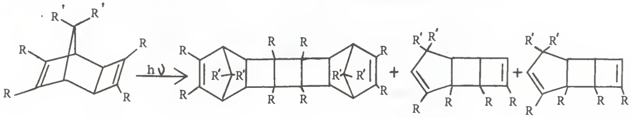


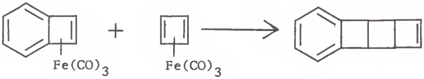
31

Eberback and Prinzbach,[21] who have also done much work on the bicyclo-[2.2.0]hexane system, have reported yet another synthesis including three derivatives (32, 33, and 34) in the following photolysis reaction.



32 33 34

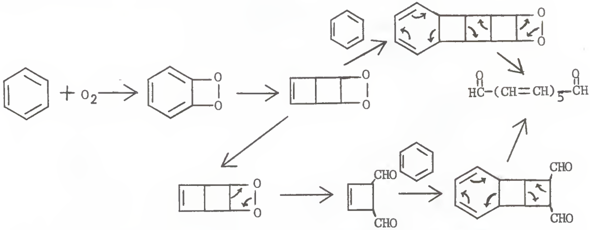
A question of whether or not free benzocyclobutadiene was liberated from (benzocyclobutadiene)irontricarbonyl (35) under oxidative decomposition and the role of the silver ion in such decompositions prompted two papers by Pettit.[31,32] Pettit found that free benzocyclobutadiene was released when



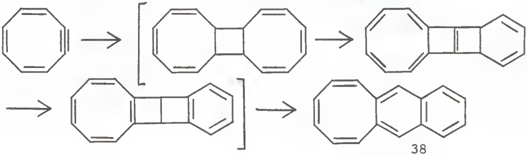
35 36 37

the proper oxidant was chosen and gave 37 when 35 and 36 were combined in the presence of lead tetraacetate. He also learned that the silver ion in the silver ion oxidation was implicated to be involved in other than mere oxidation.

The bicyclo[2.2.0]hexane system has also been utilized to explain routes to various products. K. Wei, et al.,[52] observed long chain conjugated dialdehydes in the photooxidation of pure liquid benzene and proposed the following mechanisms to explain their products.



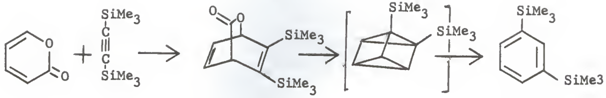
Krebs and Byrd[28] postulated bicyclic intermediates to explain the dimerization product 38 from 1,2-dehydrocyclooctatetrene.



38

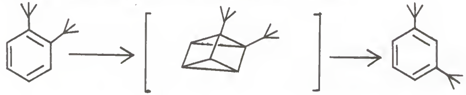
Raciszewski[35] also discussed the theoretical mechanistic pathways and excited states involved in the γ-irradiation of maleic anhydride in benzene and included the bicyclo[2.2.0]hexane system in his discussion.

A small amount of work including the prismane structure as a proposed intermediate is reported. Seyferth, et al.,[45] observed a novel isomerization in the Diels-Alder reaction of α-pyrone and bis(trimethylsilyl)acetylene yielding the meta isomer 39 in a 53% yield instead of the expected ortho isomer, which was found along with the para isomer in only a trace amount. The following mechanism was one of four proposed.

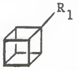

O
O
SiMe3
C
C
SiMe3
O
O
SiMe3
SiMe3
SiMe3
SiMe3
SiMe3
SiMe3

39

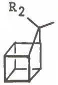
Much the same type of intermediate was proposed by Burgstahler, et al.,[10] in the following photochemical isomerization.



A number of cage type derivatives containing the bicyclo[2.2.0]hexane structure have been synthesized. Smith, Kline, and French Labs.[46] have produced a number of derivatives (40 and 41) where $R_1 = NH_2$ and $R_2 = COOH$ or NH_2.

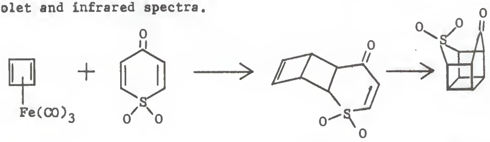


40



41

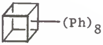
Paquette and Wise[34] synthesized 42 following the method of Pettit. Irradiation of 42 gave 43, which was then compared to other compounds having $S\text{-}C_{co}$ transannular interactions by studying the dipole moment and ultraviolet and infrared spectra.


Fe(CO)3
O
S
O
O
O
S
O
O
O
S
O
O

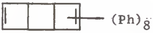
42

43

Octaphenyl cubane (44) was prepared by Throndsen and Zeiss[49] and another derivative 45 explaining the n.m.r. spectral data was proposed.

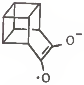


44



45

Finally Russell et al.,[38] have prepared the semidione 46 and studied its e.s.r. spectrum.



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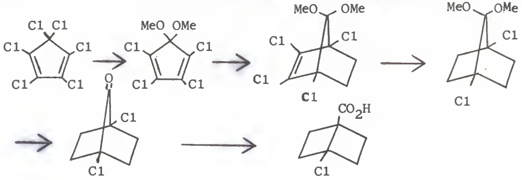
OBJECTIVES OF THIS INVESTIGATION

The objectives of this investigation were to synthesize bicyclo[2.2.0]-hexan-1-ol and certain of its precursors.

DISCUSSION OF EXPERIMENTAL RESULTS

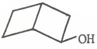
Several highly successful techniques for generating compounds of bicyclo [2.2.0]hexane parentage had been developed by the time this work was undertaken. One of the most intriguing appeared in a paper by Scherer.[42]



47

Using hexachlorocyclopentadiene as the readily available starting material, he was able to prepare the 4-chlorobicyclo [2.2.0]hexane-1-carboxylic acid (47) in a high overall yield. Acid 47 was felt to be an elegant precursor to many other derivatives by applying carefully thought out conversions.

As Reineke[36] and Davis[17] had prepared the exo- (48) and endo-bicyclo [2.2.0] hexan-2-ols (49), respectively, bicyclo [2.2.0]hexan-1-ol (50) was the first derivative desired. The preparation of it would complete the series



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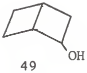
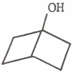
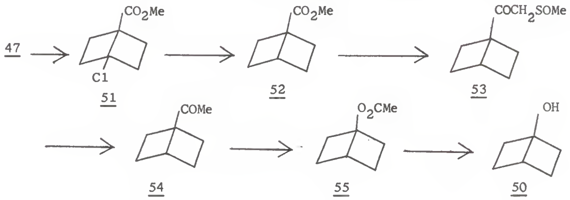


49



50

and provide valuable information on the stability and the nature of the products of the bridgehead carbonium ion generated through solvolysis of the tosylate ester. The solvolysis of the exo-bicyclo [2.2.0]hexan-2-ol had been completed by Reineke,[36] and the preparation for the solvolysis of the endo isomer was already in progress by Davis.[17] The following reaction sequence was proposed as the most plausible for entry into the bicyclo[2.2.0]hexan-1-ol (50). One of the strongest arguments for the sequence



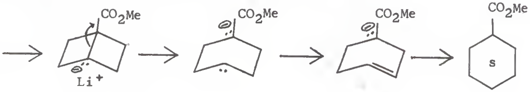
was the fact that it was the same used successfully by Davis[17] for entry into a mixture of alcohols 48 and 49.

Many difficulties were encountered in this synthesis. The first arose on the dechlorination of the ester 51. Even though mild conditions were used (i.e., reaction temperature of 73° for one hour, using lithium and tert-butyl alcohol), the major product from the reaction was the ester of cyclohexane carboxylic acid. To complicate things even further the methyl ester has partly transesterified to the tert-butyl ester giving a mixture of the two.

In an effort to clear this up, the dechlorination was run under milder conditions (i.e., 35-40° for eight hours) on the acid 47. The acid was not used initially as it was felt that a greater solubility problem would be encountered in the reaction mixture over that of the methyl ester. After the reaction was felt to be complete, the methyl ester of the products was made using diazomethane in ether. Work-up gave methyl cyclohexanecarboxylate as the major product in a 41.3% yield of the product mixture. Rearranged chloroesters made up 32.3% of the product, while 26.4% was dechlorinated, but contained double bonds. The g.c. analysis of the product mixture was done using a 6' x ¼", 20% Carbowax column on 60/80 Chromosorb W under the same conditions as employed be Davis[17] for the purification of his methyl bicyclo [2.2.0]hexa-2,5-diene-2-carboxylate. It was felt at the time that the product would be stable under those conditions (detector temperature 300°, injection port temperature 305°, column temperature 100°, and helium gas flow rate of 60 ml./minute). Later analysis proved that it was not. Therefore, the unsaturated, dechlorinated product may have been the desired one. Comparison of its n.m.r. spectrum with that of the actual rearranged product was somewhat difficult, because it had been collected as a mixture of two products with the other product dominating the mixture.

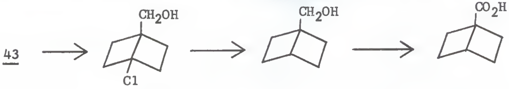
Since the methyl cyclohexanecarboxylate was the major product, rearrangement during the reaction occurred. It was felt that the carboxyl group might be increasing the lability of the zero bridge to rupture under the reaction conditions. The following mechanism was postulated.

51



It was felt that the lithium had bonded to the organic substrate followed, then, by anchimerically assisted zero bridge rupture. The assistance was provided by the carbonyl group in the 1-position. Later work showed that whenever a carbonyl group was in the 1-position, be it acid, ester, or ketone, the compound was not likely to be stable to thermal conditions above 100°. Davis[17] had no trouble with thermal stability when the carbonyl group was in the 2-position. Whenever a saturated function was in the 1-position, such as in the bicyclo [2.2.0]hexane-1-methanol (57), the compound was found to be thermally stable.

Since the dechlorination of the chloroacid failed a new sequence was proposed to synthesize the alcohol 50. This is outlined below.



56 8 57

$$\longrightarrow 52 \longrightarrow 53 \longrightarrow 54 \longrightarrow 55 \longrightarrow 50$$

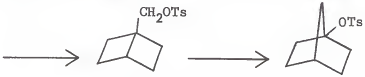
Initially lithium aluminum hydride was used to reduce the ester, 51; however, a mixture of products was obtained. Scherer[43] had suggested the use of diborane reduction on the acid after having the same problem. This reduction gave only one product, 56. A mass spectrum was run at both high and low ionization energy (70 and 14 ev.). M/e 93 was the base peak for the low ionization energy and 95% of the base for the high ionization energy. This was easily explained by loss of water and chlorine from the parent. The parent was not present under high ionization energy, but did show up under the low energy.

Lithium and *tert*-butyl alcohol were used in one attempt to dechlorinate the chloromethanol 56 without success. The lithium seemed to be too reactive. Gassman[23] found the same difficulty when he reduced 1,2,3,4-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-2-ene to 7,7-dimethoxybicyclo-[2.2.1]hept-2-ene. Using lithium he found partial reduction of the double bond to the completely saturated compound. Sodium gave him the desired product only with no reduction of the double bond.

Many difficulties were encountered by this author using sodium. On small reactions using 3 g. (23 mmoles) or less of the chloromethanol 56, the product was relatively pure, but the yields were low (24%). On large reactions using 7 g. (48 mmoles) or more, the sodium balled together reacting slowly, causing the reaction length to run in some cases over a week. The yields were higher (50%); however, there were a larger number of impurities which could be separated by g.c. only. Of the columns tried, a 6' x $\frac{1}{4}$", 4% Carbowax on 60/80 Chromosorb G column worked best and gave some separation of a minor shoulder component (12.3%) from the major product. A mass spectrum was run at both high and low ionization energy (70 and 14 ev.). The base peak on both was at m/e 83. This was readily explainable by loss of the hydroxyl hydrogen and ethylene from the parent compound. Another large peak at m/e 85 might be explained by a rearrangement of the parent to hexa-2,5-diene-2-methanol, followed by loss of two carbons and three hydrogens by breaking the bond between carbons four and five. No parent ion, m/e 112, was observed at high energy, but it was present at low ionization energy as expected for alcohols.

An attempt was made at this point to prepare the tosylate ester 58 following a procedure given by Reineke.[36] A 93% yield was obtained of fairly pure product as indicated from its n.m.r. spectrum. An attempt to purify it on an alumina column of activity three resulted in complete conversion to 1-norbornyl tosylate (59). Dauben, Chitwood, and Scherer[16]

8

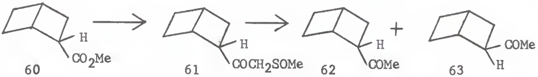


58 59

independently had attempted to synthesize the same tosylate ester 58 by several methods without success. They were able to make the p-nitrobenzoate and study the solvolysis of this ester in 60% aqueous acetone. They attributed their fast rate constant of 0.43×10^{-5} sec.$^{-1}$ at 99.5° to relief of ring strain in going to 1-norbornyl p-nitrobenzoate.

As the synthesis of the bicyclo[2.2.0]hexan-1-ol was still the major object, further study on the methanol 8 was tabled. Oxidation of 8 to the acid 57 was then tried with Jones' reagent resulting in a 32% yield of product. Better yields, as high as 63%, were obtained by basic permanganate oxidation using a method of Kenyon and Platt.[26] The methyl ester 52 was then synthesized by reaction with diazomethane and brought the work back to the point where an attempt could be made to make the ketone 54.

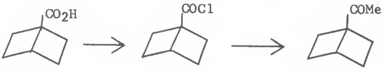
Reaction of methyl ester 52 with methylsulfinyl carbanion was chosen, as Davis[17] had previously found success with it except for isomerization problems. His *endo*-ketone 62 isomerized under the reaction conditions to the *exo*-isomer 63. No such problem was involved in the present work.



60 61 62 63

The n.m.r. spectrum run on the adduct 49 suggested the presence of several compounds. The adduct was reduced with aluminum amalgam, and upon work-up the n.m.r. spectrum showed the possibility of several ketones, none of which appeared to be the desired product, as the bulk of the n.m.r. spectral absorption was too high, from τ7.7 to 9.35. G.c. separation and collection of products only gave ketones with the wrong structure.

This method was dropped in favor of the dimethyl cadmium reaction

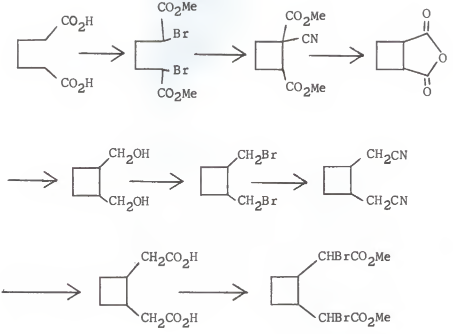


57 64 54

outlined above. Again the n.m.r. spectrum of the product indicated a mixture of several compounds. A noticeable amount of decomposition occurred as early as in the preparation of the acyl halide. Attempts were made to decrease this by altering reaction conditions. An indication of optimum conditions was gained. Nothing could be done to improve the yield of the acyl halide, but a trap-to-trap distillation of it at 35° and 0.10 mm. did improve the purity

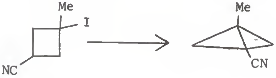
To optimize the yield, the dimethyl cadmium for the next step must be made under a deoxygenated nitrogen atmosphere to minimize the amount of the unidentified ester formed. An injection of the product mixture from reaction of acid chloride 64 and dimethyl cadmium on the g.c. resulted in rearrangement of some of the product mixture. It was felt that the best method of separation and identification of the product would be to proceed to the Baeyer-Villiger reaction with the mixture as it was. This, if successful, would give the acetate, which was anticipated to be stable to g.c. conditions. The oxidation was performed and four products were obtained by g.c. collection, two of which were acetates. The n.m.r. spectrum of one of the acetates gave precisely what one would expect for the product, bicyclo-[2.2.0]hex-1-yl acetate. The amount of product varied from 59% to 17% of the mixture for the two runs made as analyzed by g.c. integration. A singlet absorption at τ8.06 and a relatively large multiplet at τ7.52-7.64 and a small continuous absorption at τ7.25-8.98 was found in the n.m.r. spectrum. No further work was done.

Before the above work was undertaken, an attempt to couple the α-carbons in dimethyl cyclobutane-*cis*-1,2-di-α-bromoacetate (65) was tried. The precursor was prepared according to the following sequence.

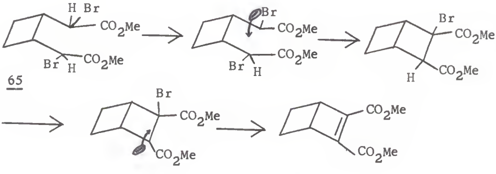


65

Blanchard and Cairncross[3] found the following coupling reaction with sodium hydride to give a 92% yield of bicyclo[1.1.0]but-1-yl nitrile.



It was felt that the reaction outlined below might afford a cheap, relatively high yield method of attaining a bicyclo[2.2.0]hexene derivative.



65

Upon reaction of 65 with sodium hydride in tetrahydrofuran, employing the method of Blanchard and Cairncross, a tar was recovered which did not chromatograph on an alumina column. The project was subsequently dropped.

SUMMARY

The synthesis of 4-chlorobicyclo[2.2.0]hexane-1-carboxylic acid (47) has been reported,[42] and it was felt that 47 should be a practical precursor to the desired bicyclo[2.2.0]hexan-1-ol (50). The acid 47 was converted to the methyl ester. Dechlorination of the ester with lithium and tert-butyl alcohol gave tert-butyl cyclohexanecarboxylate as the major product. Sixteen other products were obtained and were a mixture of methyl and tert-butyl esters. Some were attributed to starting material; others were dechlorinated, but contained double bonds. This was cleared up by dechlorinating the acid 47 and then analyzing the products after conversion to the methyl esters. Methyl cyclohexanecarboxylate was recovered in a 41.3% yield. Rearranged chloroesters made up 32.3% of the product; while 26.4% was dechlorinated, but contained double bonds. The chloro acid 47 was then reduced with diborane to give 4-chlorobicyclo[2.2.0]hexane-1-methanol (52), which was then successfully dechlorinated to give bicyclo[2.2.0]hexane-1-methanol (8) in a 50% yield. A successful preparation of the bicyclo[2.2.0]hexane-1-methyl tosylate was carried out and total rearrangement to 1-norbornyl tosylate was effected in an attempt to purify it by chromatography on an activity three alumina column. Oxidation of the alcohol 8 with Jones' reagent gave a 32% yield of bicyclo[2.2.0]hexane-1-carboxylic acid (53). Better yields, as high as 63%, were obtained with basic permanganate.

The corresponding ester, methyl bicyclo[2.2.0]hexane-1-carboxylate (48), was synthesized and an unsuccessful attempt was made to make the ketone, methyl bicyclo[2.2.0]hexyl ketone (54), in a reaction with methylsulfinyl carbanion in tetrahydrofuran. None of the desired ketone was

obtained. The dimethyl cadmium reaction was then carried out on bicyclo-[2.2.0]hexane-1-carbonyl chloride (60), prepared by reaction of the acid 48 with thionyl chloride. A more promising mixture of ketones was obtained. A Baeyer-Villiger reaction was run and the products were isolated by g.c. collection. Two acetates were isolated. One is believed to be the desired bicyclo[2.2.0]hex-1-yl acetate produced in a low yield.

One of the major accomplishments of this work was the discovery of anchimerically assisted decomposition of the bridge bond under thermal conditions whenever a carbonyl group was in the 1-position. Decomposition was followed by n.m.r. analysis of products before and after g.c. collection. The bicyclo[2.2.0]hexane system was found to be fairly stable whenever a saturated function was in the 1-position. This observation included the acetate, which was found to be stable to the conditions used for g.c. purification.

Before the above work was done, research was done on a coupling reaction involving sodium hydride and dimethyl cyclobutane-cis-1,2-di-α-bromoacetate (65) in an attempt to synthesize 1,2-dicarbomethoxybicyclo[2.2.0]hex-2-ene. The method of Blanchard and Cairncross[3] was employed without success. An intractable tar was the only product.

INFRARED SPECTRA

4-Chlorobicyclo[2.2.0]hexane-1-carboxylic Acid

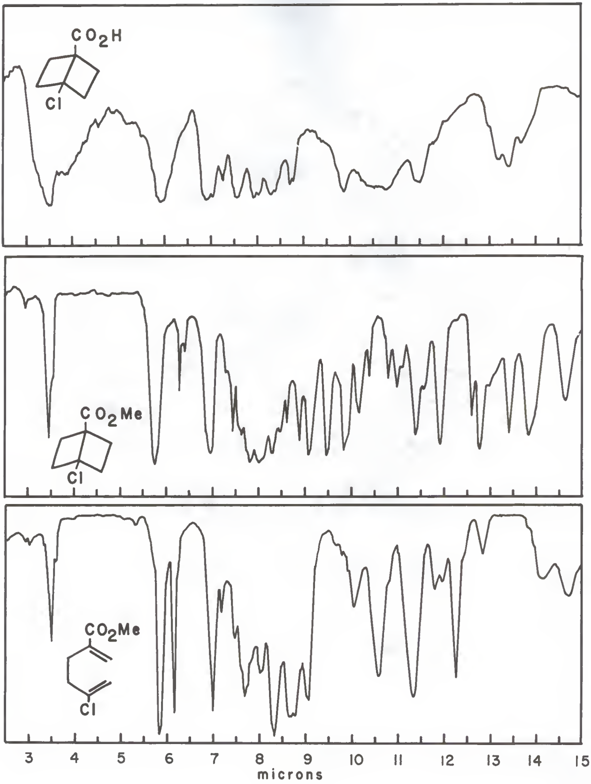
(in Nujol mull)

Methyl 4-Chlorobicyclo[2.2.0]hexane-1-carboxylate

(neat)

Methyl 5-Chlorohexa-1,5-diene-2-carboxylate

(neat)


CO2H
Cl
CO2Me
Cl
CO2Me
Cl
3
4
5
6
7
8
9
10
11
12
13
14
15
microns

INFRARED SPECTRA

4-Chlorobicyclo[2.2.0]hexane-1-methanol

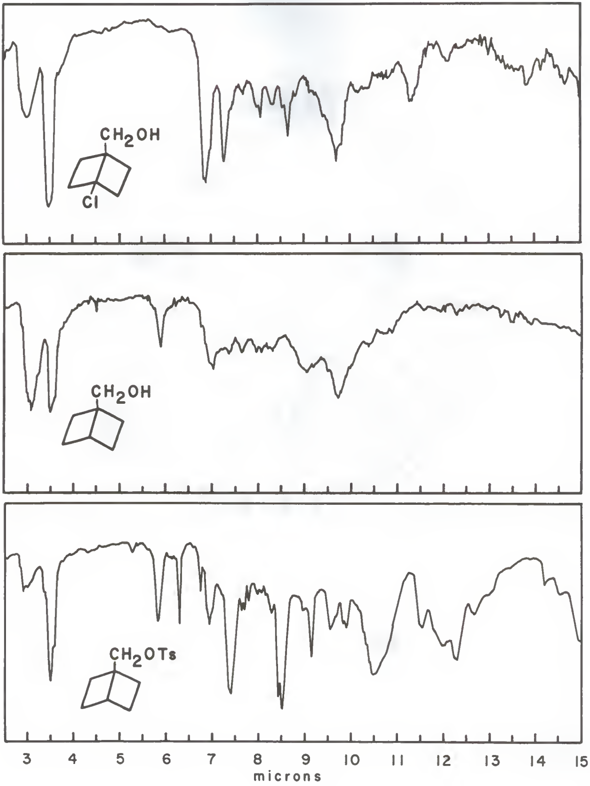
(in Nujol mull)

Bicyclo[2.2.0]hexane-1-methanol

(neat)

Bicyclo[2.2.0]hexane-1-methyl Tosylate

(neat)


CH₂OH
Cl
CH₂OH
CH₂OTs
3
4
5
6
7
8
9
10
11
12
13
14
15
microns

INFRARED SPECTRA

1-Norbornyl Tosylate

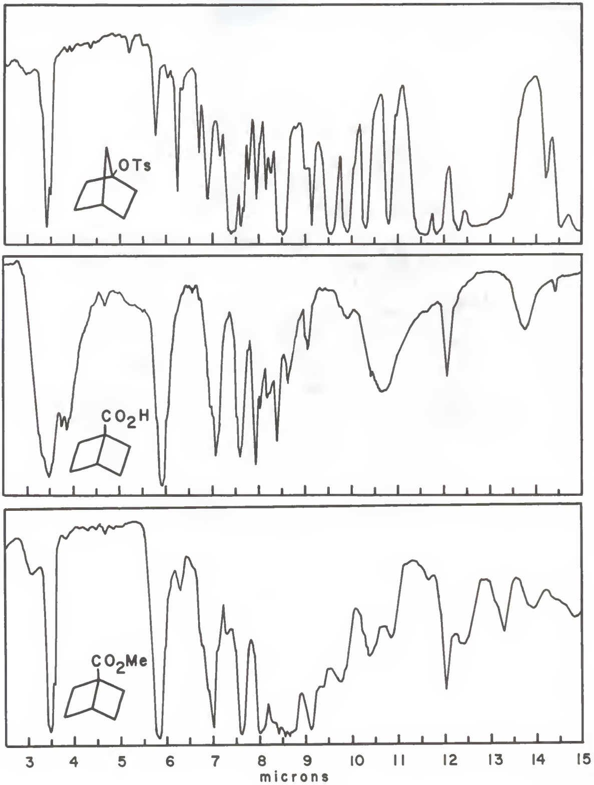
(neat)

Bicyclo [2.2.0] hexane-1-carboxylic Acid

(neat)

Methyl Bicyclo [2.2.0] hexane-1-carboxylate

(neat)


OTs
CO2H
CO2Me
3
4
5
6
7
8
9
10
11
12
13
14
15
microns

N.M.R. SPECTRA

4-Chlorobicyclo[2.2.0]hexane-1-carboxylic Acid

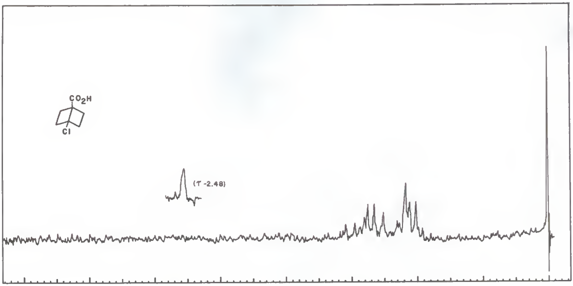
(in $CCl_2{=}CCl_2$ with TMS internal standard)

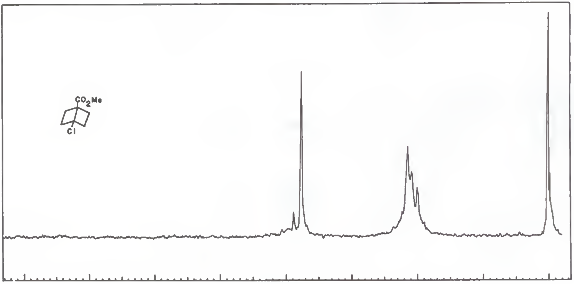
Methyl 4-Chlorobicyclo[2.2.0]hexane-1-carboxylate

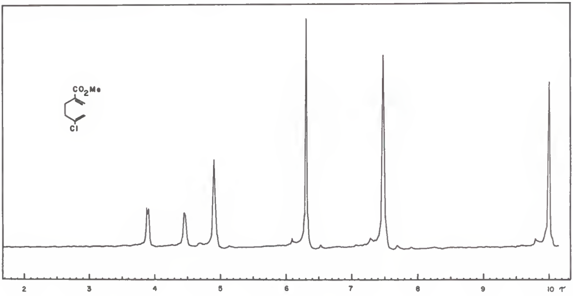
(in CCl_4 with TMS internal standard)

Methyl 5-chlorohexa-1,5-diene-2-carboxylate

(in CCl_4 with TMS internal standard)


CO2H
Cl
(τ -2.48)


CO2Me
Cl


CO2Me
Cl
2
3
4
5
6
7
8
9
10 τ

N.M.R. SPECTRA

4-Chlorobicyclo[2.2.0]hexane-1-methanol

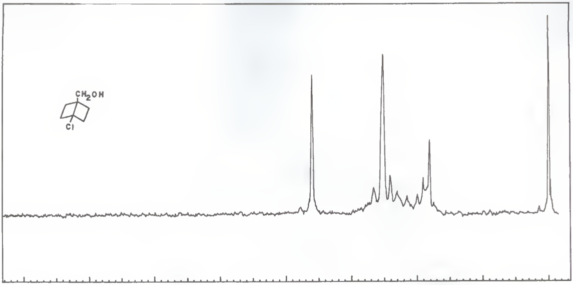
(in CCl_4 with TMS internal standard)

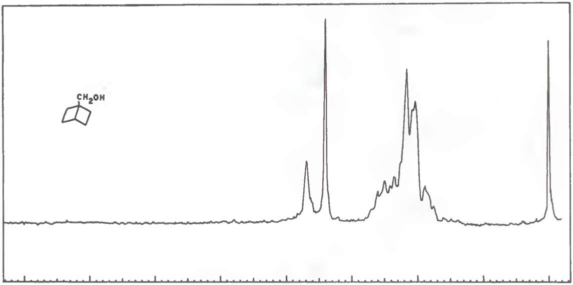
Bicyclo[2.2.0]hexane-1-methanol

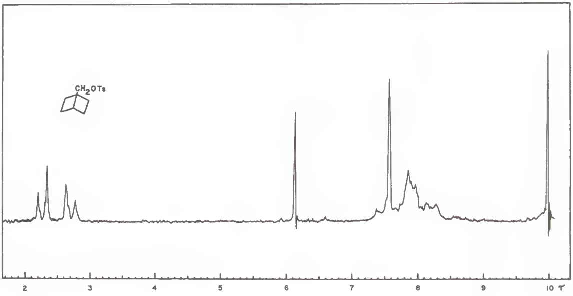
(in CCl_4 with TMS internal standard)

Bicyclo[2.2.0]hexane-1-methyl Tosylate

(in CCl_4 with TMS internal standard)


CH₂OH
Cl


CH₂OH


CH₂OTs
2
3
4
5
6
7
8
9
10 τ

N.M.R. SPECTRA

1-Norbornyl Tosylate

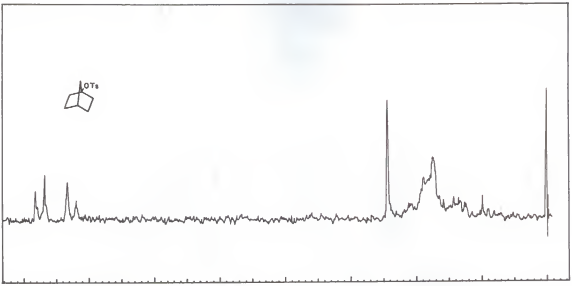
(in CCl_4 with TMS internal standard)

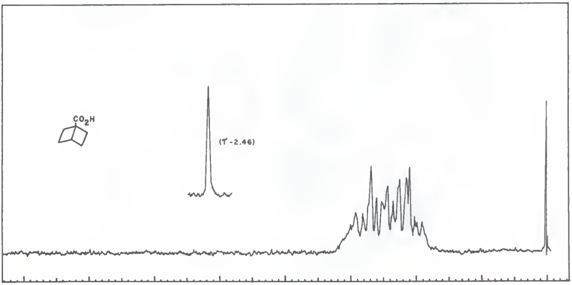
Bicyclo[2.2.0]hexane-1-carboxylic Acid

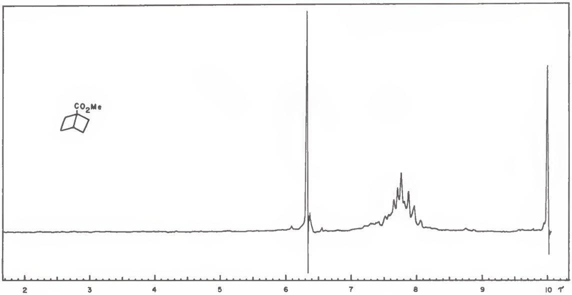
(in CCl_4 with TMS internal standard)

Methyl Bicyclo[2.2.0]hexane-1-carboxylate

(in CCl_4 with TMS internal standard)


OTs


CO₂H
(τ -2.46)


CO₂Me
2
3
4
5
6
7
8
9
10 τ

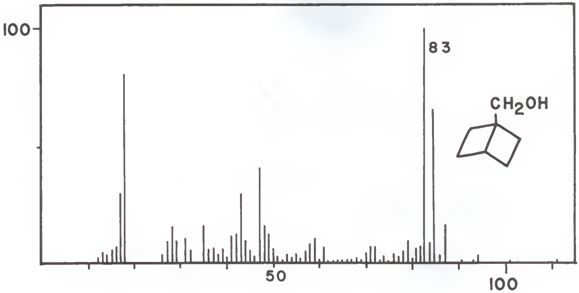
MASS SPECTRA

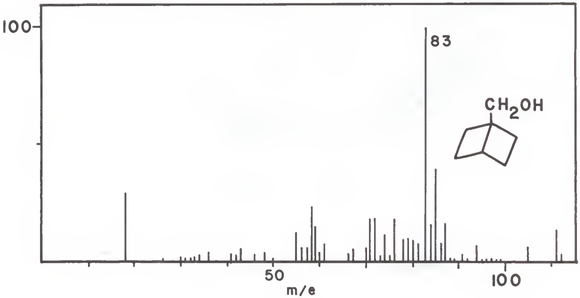
Bicyclo[2.2.0]hexane-1-methanol

(70 ev.)

Bicyclo[2.2.0]hexane-1-methanol

(14 ev.)


100
83
CH$_2$OH
50
100


100
83
CH$_2$OH
50
100
m/e

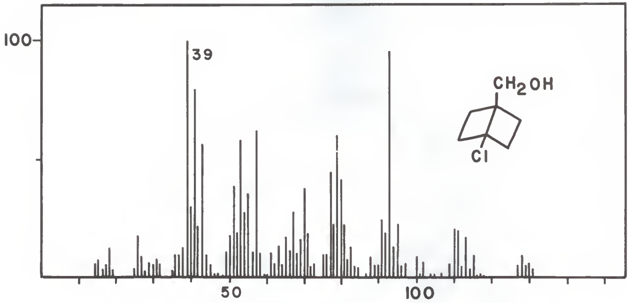
MASS SPECTRA

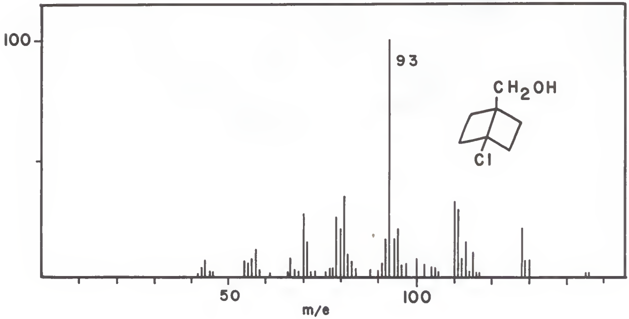
4-Chlorobicyclo[2.2.0]hexane-1-methanol

(70 ev.)

4-Chlorobicyclo[2.2.0]hexane-1-methanol

(14 ev.)


100
39
CH2OH
Cl
50
100


100
93
CH2OH
Cl
50
100
m/e

EXPERIMENTAL[56]

5,5-Dimethoxytetrachlorocyclopentiadiene. The method of McBee, et al.[30] was used to synthesize the title compound in a 90% yield, b.p. 64°/0. 6 mm., $n_D^{26.3}$=1.5385. (lit.[30] 62% yield, b.p. 82-84°/2 mm., n_D^{20}=1.5250). The infrared and n.m.r. spectral data were consistent with the product expected. The infrared spectrum displayed absorptions at 3.32 (m), 3.42 (m), 5.65 (m), 6.16 (s), 6.90 (w), 8.35 (w), 9.05 (w), 9.25 (w), 9.55 (w), 10.37 (s), 11.94 (s), 13.05 (s), and 13.36 (m)μ. The n.m.r. spectrum displayed a sharp singlet at τ 6.64.

7,7-Dimethoxy-1,2,3,4-tetrachlorobicylo [2.2.1] hept-2-ene. The method of Gassman and Pape[23] was used for the preparation of the title compound in a 70.3% yield, b.p. 68°/0.15 mm., $n_D^{26.5}$=1.5265 (lit.[23] 78.5% yield, b.p. 72-81°/0.10 mm.). The infrared and n.m.r. spectra were consistent with the expected product. The infrared spectrum exhibited absorptions at 3.46 (s), 3.58 (m), 6.22 (s), 6.89 (s), 7.80 (s), 7.91 (s), 8.22 (w), 8.48 (w), 9.20 (w), 9.50 (s), 9.90 (s), 10.12 (s), 10.91 (s), 11.50 (s), 11.98 (s), 12.69 (s), and 13.83 (m)μ. The n.m.r. spectrum gave a doublet centering at τ 6.45(6H) and a symmetric multiplet centering at τ 7.95 (4H).

1,4-Dichloro-7,7-dimethoxybicyclo [2.2.1] heptane. The title compound was prepared by a modification of the procedure given by Scherer[42]. To 25 g. (86 mmoles) of 7,7-dimethoxy-1,2,3,4-tetrachlorobicyclo-[2.2.1] hept-2-ene, placed in a 150 ml. capacity Magna Dash autoclave was added 50 ml. of triethylamine (over threefold excess) two spatula tips full of 5% palladium on carbon, and enough ethanol (90%)

to bring the volume to 100 ml. Hydrogen was pressured into the autoclave from 1000 to 2000 lbs./ in.^{2} and heated at 82^o for 24 hours. After removal from the autoclave, methanol was added to dissolve the triethylamine hydrochloride formed and the mixture was suction filtered through a layer of filter-cell to remove the catalyst. Water was then added to the mixture, which was then continuously extracted with ether for 24 hours. The solvents were distilled off to give a crude solid product which was recrystallized from methanol to give an 87.4% yield, sealed ampoule m.p. 95.0-96.0^o (lit.[42] 93% yield, m.p. 95.0-96.5^o).

The infrared spectrum was in agreement with the expected product and the n.m.r. spectrum was consistant with that reported.[42] The infrared spectrum gave absorptions at 3.55 (s), 6.92 (m), 7.30 (m), 7.78 (s), 8.08 (s), 8.18 (s), 8.48 (w), 8.50 (m), 8.58 (s), 8.60 (w), 9.12 (s), 9.36 (s), 9.66 (s), 9.98 (s), 12.00 (s), 12.48 (m), and 12.65 (m)μ. The n.m.r. had a sharp singlet at τ6.46 (6H) and a symmetric multiplet centering at τ7.98 (8H).

The original work by Scherer utilized a Parr shaker hydrogenation apparatus and a catalyst of 5% palladium on carbon.[42] In a more recent paper[16] the conditions used were 50 psi. of hydrogen, and hydrogen uptake ceased after 12 hours. A Parr shaker utilizing 50 psi. and palladium-carbon catalyst was used by this author for 24 hours with no hydrogen uptake in several attempts.

1,4-Dichlorobicyclo[2.2.1]heptan-7-one. A modification of the method given by Scherer[42] was utilized for the preparation of the title compound. To 49 g. (0.23 moles) of 1,4-dichloro-7,7-dimethoxybicyclo[2.2.1]-heptane in 250 ml. of dichloromethane was added 150 ml. of 79% sulfuric acid (prepared by diluting 100 ml. of concentrated sulfuric acid with 50 ml.

water and cooling to room temperature). The reaction mixture was magnetically stirred at room temperature for 22 hours. The dichloromethane was then separated from the acid layer and washed quickly with sodium carbonate solution and then dried with anhydrous magnesium sulfate. With the acid layer still acidic after combination with the sodium carbonate wash solution, continuous extraction was carried out with petroleum ether for 24 hours. The petroleum ether layer was then separated and dried with anhydrous magnesium sulfate. Distillation of the dichloromethane and petroleum ether solutions gave an 89% yield, m.p. 94-96^o.

The infrared spectrum exhibited absorptions at 3.50 (s), 5.55 (m), 6.89 (s), 7.26 (s), 7.57 (m), 7.72 (m), 8.03 (m), 8.57 (m), 8.68 (m), 8.82 (m), 8.99 (m), 9.12 (m), 9.61 (m), 12.50 (m), 12.89 (s), 13.37 (m), 13.60 (m) and 13.85 (m)μ. The n.m.r. spectrum exhibited a sharp singlet at τ7.71.

On exposure to moisture the product changes composition. Dauben, et. al.,[16] mention the fact that the ketone readily forms a hydrate. The original work by Scherer[42] mentioned only that 96% sulfuric acid was used for the hydrolysis of the compound at room temperature in dichloromethane solution. No mention was made of the length of reaction time or work up conditions. In the paper by Dauben, et al.,[16] full conditions were given. The method of this author gives more hydrated product than the method of Scherer, but it was felt that the hydrated product proceeds through the next sequence with no difficulty as the yields for the next reaction ran very high.

4-Chlorobicyclo [2.2.0] hexane-1-carboxylic Acid. This compound was prepared according to the method given by Scherer.[42] To 81 g. (0.409 moles) of 1,4-dichlorobicyclo [2.2.1] heptan-7-one dissolved in

750 ml. of tetrahydrofuran (previously dried and distilled from lithium aluminium hydride) was added 36.7 g (0.918 moles) of sodium hydroxide (previously ground to a powder under a nitrogen atmosphere). The reaction was stirred under a nitrogen atmosphere for 6.5 hours. A heavy precipitate had formed by the end of the reaction time which prevented further stirring. The reaction mixture was then poured (with the aid of rinsing water) into a 600 ml. beaker half filled with ice and water. Ether was added and the mixture was extracted. This ether layer, containing possible starting material, was washed with water, dried with anydrous magnesium sulfate, and distilled.

The combined water layers were cooled in an ice bath and ice was added. Hydrochloric acid (6 N) was then added until the water layer tested acidic. Ether was used to extract the acid product. The ether extracts were combined, washed with water, dried with anydrous magnesium sulfate, and evaporated under reduced pressure 15° to give 62.3 g. (95.5%) crude product. Sublimation five times gave a product with a m.p. of 145-146° (lit.[42] 143.0-143.9°). The infrared spectrum, page 23, and the n.m.r. spectrum, page 29, were consistant with that expected for the product.

Methyl 4-Chlorobicyclo[2.2.0]hexane-1-carboxylate. To 3.0 g. (18.7 mmoles) of 4-chlorobicyclo[2.2.0]hexane-1-carboxylic acid, dissolved in 20 ml. of ether, was added 20 mmoles of freshly prepared diazomethane in 100 ml. of ether. (The diazomethane solution was prepared by slowly adding 2 g. (20 mmoles) of N-methyl-N-nitrosourea to 100 ml. of cold ether over a cold solution of 80 g. of potassium hydroxide in 120 ml. of water. The 40% potassium hydroxide solution was separated after preparation of the diazomethane and discarded. The diazomethane solution was dried with potassium hydroxide pellets and then used directly in the ester preparation). Distillation of the ether after preparation of the ester gave the desired ester in an 80% yield after distillation on a modified Hickman still at 0.10 mm. The infrared spectrum is shown on page 23. The n.m.r. spectrum in benzene (internal TMS) agreed with that in the literature[42] and exhibited absorptions at τ6.46 (6H, singlet) and τ7.98 (8H, symmetric multiplet). The n.m.r. spectrum in carbon tetrachloride is shown on page 29.

Attempted Dechlorination of 4-Chlorobicyclo[2.2.0]hexane-1-carboxylic Acid. Using a procedure given by Gassman,[23] 2.83 g. (38 mmoles) of *tert*-butyl alcohol was added to 1.9 g. (11 mmoles) of the acid dissolved in 30 ml. of tetrahydrofuran, dried and distilled from lithium aluminum hydride. The mixture, under a nitrogen atmosphere at all times, was cooled over an ice bath and 0.51 g. (72 mmoles) of finely chopped lithium wire was added. The reaction mixture was allowed to warm to room temperature and then heated to 35-40° for eight hours while stirring magnetically. A precipitate formed after about two hours of heating. The reaction mixture was cooled to room temperature, poured over ice, acidified with hydrochloric acid, and extracted three times with ether. The ether layer was dried over anhydrous magnesium sulfate and, after concentrating slightly by distillation, the product was esterified with freshly prepared ethereal diazomethane. The ether was then distilled and the products were trap-to-trap distilled at 40° and 0.10 mm. The product mixture was analyzed by g.c. on a $7\frac{1}{2}$' x $\frac{1}{4}$", 20% Carbowax 20M on 60/80 Chromosorb W column at 100° with a helium flow rate of 60 ml./minute, a detector temperature of 300°, and an injection port temperature of 305°. Four peaks with the following retention times were collected: 1), 7.9 minutes (26.4%; 2), 10.8 minutes

(18.3%); 3), 12.1 minutes (41.3%); and 4), 16.4 minutes (14%). The fourth peak was rearranged methyl ester of starting acid (methyl 5-chlorohexa-1,5-diene-2-carboxylate) and was compared to an authentic sample. The third was methyl cyclohexanecarboxylate as compared to a sample synthesized independently. The second peak contained chlorine (by Beilstein test) and the first peak had no chlorine, but was unsaturated. As the dechlorinated products were either rearranged, containing double bonds, or completely reduced, the identity of them was not analyzed further.

At the time this work was done the expected product, bicyclo [2.2.0]-hexane-1-carboxylic acid (methyl ester), was felt to be stable to the conditions employed for the g.c. analysis. Davis,[17] using slightly stronger conditions on the same column, was able to isolate his methyl endo-bicyclo-[2.2.0] hex-5-ene carboxylate.

The methyl bicyclo [2.2.0] hexane-1-carboxylate made by another method was also found to be unstable to the g.c. conditions employed for this reaction work up. Therefore, the minor dechlorinated product, which contained double bonds after g.c. collection may have been the desired ester. The n.m.r. spectrum of it was difficult to compare with that of the decomposed methyl bicyclo [2.2.0] hexane-1-carboxylate as it was only a minor component and was isolated as a mixture of two compounds.

Attempted Dechlorination of Methyl 4-Chlorobicyclo [2.2.0] hexane-1-carboxylate. Using the same procedure as for the above dechlorination of the acid, 9 g. of the ester were allowed to react with lithium and tert-butyl alcohol in tetrahydrofuran. In this reaction the pot temperature was heated higher (73°). A g.c. analysis on the same column as above (conditions: 60 ml./minute helium gas flow, injection port temperature 304°, detector block temperature 310°, and column temperature of 80° from 0 to 5.4 minutes, 90° from 5.4 to 12.4 minutes, 100° from 12.4 to 15.75 minutes, 140° from 15.75 to 24.9 minutes, and 225° from 24.9 minutes to the end) gave 17 peaks beside those of tetrahydrofuran and tert-butyl alcohol. Of these 17 peaks only 14 were of any consequence (above 1% of the total). Tert-butyl cyclohexanecarboxylate was the major product (37%) and was compared directly to a sample independently synthesized. The other products were difficult to analyze due to partial transesterification of the methyl esters to the tert-butyl esters. Three products totalling 20% of the product distribution were due to rearrangement of the starting material. A sample of methyl 4-chlorobicyclo[2.2.0]hexane-1-carboxylate was injected to determine which peaks were due to it. Another product amounting to 16% of the total was tert-butyl 5-chlorohexa-1,5-diene-2-carboxylate. The remaining products were not analyzed. As this reaction had been run before the attempted dechlorination of the acid, it was felt that the analysis of products would be much easier if the switch from ester to acid was made.

Thermal Decomposition of Methyl 4-Chlorobicyclo[2.2.0]hexane-1-carboxylate. In an attempt to correlate some of the products from the dechlorination reactions with decomposition products from the starting material, the thermolysis by Scherer was followed.[42] One gram of the acid was converted to the corresponding methyl ester with diazomethane in ether. The product, upon purification by removal of the ether, was dissolved in 8 ml. of benzene (purified by distillation-middle fraction). It was then placed in a sealed pyrex tube and heated in a steam bath for 12.5 hours. Of the two compounds recovered 27.8% was starting material and 72.2% was rearranged product. The n.m.r. spectrum of the rearranged product in benzene corresponded to methyl 5-chlorohexa-1,5-diene-2-carboxylate obtained by Scherer.[42] It showed absorptions at τ 3.90 (1H,doublet, 1.4 cps), 4.70 (1H, multiplet), 4.97 (1H, doublet, 1.2 cps), 5.12 (1H, multiplet), 6.56 (3H, singlet), and 7.55 (4H, broad singlet). The n.m.r. spectrum in carbon tetrachloride, page 29, differed slightly. An infrared spectrum, page 23, was also obtained.

4-Chlorobicyclo [2.2.0] hexane-1-methanol. The procedure for this reaction was patterned after that of Brown.[8] To a solution of 67.6 g. (0.415 moles) of 4-chlorobicyclo [2.2.0] hexane-1-carboxylic acid in 240 ml. of dry tetrahydrofuran in a flame dried 1000 ml. three-neck round bottom flask fitted with a reflux condenser, a selfequilibrating addition funnel (fitted with a nitrogen gas inlet adapter), and a stopper was added, dropwise, through the addition funnel, 500 ml. of an approximately 0.7 M. solution of diborane (0.35 moles) in tetrahydrofuran. The reaction mixture, under a nitrogen atmosphere, was cooled in ice and stirred magnetically. The amount of diborane added was in excess of that required (0.312 moles). The reaction mixture was allowed to warm to room temperature after the addition was complete and stirred for four hours. It was then cooled in ice and water was added dropwise to destroy the excess diborane. The mixture was then ether extracted after additional water had been added to dissolve the inorganic salts. The ether layers were combined, washed with sodium bicarbonate solution followed by water, and dried over anhydrous magnesium sulfate. The organic solution was carefully distilled through a Vigreux column until the ether had been stripped. The distillation was then continued at reduced pressure such that the tetrahydrofuran boiled off at 40° followed by trap-to-trap distillation at 0.10 mm. and gave 73.44 g. of crude product in tetrahydrofuran. The overall yield of pure product was 83.5% by n.m.r. integration. An analytical sample was prepared by subliming three times to give material with m.p. 77-78°. The n.m.r. spectrum, page 31, infrared spectrum, page 25, and mass spectrum, page 37 were in agreement with the data expected for the product.

In subsequent runs the ether and tetrahydrofuran were distilled from the alcohol on a spinning band column at atmospheric pressure with a decrease in product yield. It was found that the alcohol decomposed at room temperature even in the pure crystalline form. This decomposition was cut to a minimum by keeping the sample in a freezer.

An initial attempt had been made to reduce the corresponding methyl ester of the acid using lithium aluminum hydride by a general method. However, a mixture of products were obtained. This was the same difficulty mentioned by Scherer.[43] He recommended switching to diborane. The diborane reduction gave only one product.

Dechlorination of 4-Chlorobicyclo [2.2.0] hexane-1-methanol. Initially a procedure by Gassman[23] was followed in an attempt to reductively dechlorinate the molecule. It was found insufficient for amounts of alcohol weighing over 3.0 g. and a variation was devised. A mixture of 17.2 g. (0.116 moles) of 4-chlorobicyclo [2.2.0] hexane-1-methanol, 120 g. of *tert*-butyl alcohol, and 60 g. of sodium, finely chopped, were combined in that order under a nitrogen atmosphere in 600 ml. of tetrahydrofuran (dried and distilled from calcium hydride). The reaction was set up in a three-neck round bottom flask fitted with a reflux condenser, thermometer, heating mantle, and power stirrer. Since problems were encountered in that the sodium in the reaction pot stuck together in a ball, the sodium and the *tert*-butyl alcohol were introduced to the reaction mixture in four-15 g. and four-30 g. quantities, respectively (i.e., after the first-15 g. of sodium had reacted with the first-30 g. of tert-butyl alcohol, 15 g. more sodium was added followed by 30 g. more tert-butyl alcohol). This procedure was followed until all the sodium had reacted. The temperature of the reaction was kept at a very mild reflux (65°). The duration of the reactions varied from five days to over a week. After the reaction of the sodium was complete the reaction mixture was poured into 200 ml., ice and/or water was added until the precipitate of sodium tert-butoxide had dissolved. The mixture was separated at this point. The organic layer was washed with 3 N. hydrochloric acid until just basic to indicator paper, then washed further with water until neutral. Sodium chloride had to be added to cause separation of the organic and water layers. Anhydrous magnesium sulfate was used to dry the organic solution. The combined aqueous solutions were cooled in ice, neutralized with hydrochloric acid (conc.) (this was done conveniently by adding conc. hydrochloric acid and following the color change from brown to yellow as the solution became neutral), and saturated with sodium chloride. Ether or petroleum ether was then used to extract (petroleum ether was found to work best) and this extract was combined with the previous organic solution and dried. Continuous extraction of the saturated water solution yielded no further product. A 90 cm. spinning band was used to remove the ether and most of the tetrahydrofuran from the organic layer. Trap-to-trap distillation at room temperature and 0.10 mm. further concentrated the mixture and the product was then trap-to-trap distilled at 40° and 0.10 mm. in order to prepare it for g.c. separation. (An attempt was made to distill the mixture on a semi-micro spinning band column at a pressure such that the mixture distilled around 45° with little effective separation.)

The reaction run under the above conditions gave a mixture of products. Several g.c. columns were tried to achieve separation since the product peak had a shoulder impurity amounting to 12.3% of the total of the two components. The columns tried were a 12' x $\frac{1}{4}$" silicon gum rubber on Chromosorb, a 6' x $\frac{1}{4}$", 10% diisodecylphthalate on Chromosorb W, a 6' x $\frac{1}{4}$", 10% β,β'-oxydipropionitrile on 60/80 Chromosorb W, and several Carbowax columns at various conditions. Of the columns tried a 6' x $\frac{1}{4}$", 4% Carbowax 20M on 60/80 Chromosorb G worked best giving some separation on 3 μl. or less injections (conditions: detector block temperature 234°, injection port temperature 214°, column temperature 125°, and a helium gas flow of 90 ml./minute). The yield on this reaction was 50% by g.c. integration.

On dechlorination reactions run using the method of Gassman[23] on 3 g. or less concentrations of the chloro alcohol, only two products without impurities were isolated. Separation of them was effected by using the 6' x $\frac{1}{4}$", 10% β,β'-oxydipropionitrile on 60/80 Chromosorb W column with injections as large as 40 μl. (conditions: injection port temperature 112°, detector block temperature 120°, column temperature 100°, and a nitrogen gas flow of 60 ml./minute). Analytical samples were purified in this manner and a yield of 24% pure product was obtained. The n.m.r., page 31, infrared, page 25, and mass spectra, page 35, were recorded.

Anal. Calcd. for $C_7H_{12}O$: C, 74.95; H, 10.74; O, 14.26

Found: C, 74.83; H, 10.64

The other major product from the reaction, according to Dauben, Chitwood, and Scherer[16]. was spiro[2.3]hexane-4-methanol but was not isolated in the present work.

Bicyclo[2.2.0]hexane-1-methyl Tosylate. The method of Reineke,[36] which was a modification of that by Wiberg, Lowery, and Colby,[54] was followed precisely for the preparation of the title compound. To 40 mg. (0.328 mmoles) of the alcohol (purified by g.c. on the 10% β,β'-oxydipropionitrile column as above) dissolved in 1.5 ml. ether (distilled from lithium aluminum hydride) cooled in an ice bath was added 63 mg. (0.328 mmoles) of p-toluenesulfonyl chloride and 56 mg. (1.0 mmoles) of powdered potassium hydroxide. The ice bath was removed and the reaction mixture was allowed to warm to room temperature while being stirred magnetically. Stirring continued for four hours. One more milliter of ether was added after one and one half hours to more fully suspend the precipitate which had started to form. At the end of the four hours, the reaction mixture was added to 20 ml. of ice water and extracted four times with ether. The ether layer was washed with water and dried with anhydrous sodium sulfate. A trap-to-trap distillation was done at 20° and 0.10 mm. to strip off the solvent giving a 92% yield of product. An infrared spectrum, page 25, and an n.m.r. spectrum, page 31, was run at this point and relatively pure product was indicated. An attempt to purify the product further on activity three alumina (prepared by shaking 150 g. of alumina suspended in distilled petroleum ether with 4.5 ml., 10% acetic acid for 40 minutes) resulted in total rearrangement to 1-norbornyl tosylate.

The n.m.r. spectrum, page 33, of this rearranged tosylate was run and compared with the n.m.r. spectrum of a sample of 1-norbornyl chloride kindly provided by Prof. K. B. Wiberg. The n.m.r. spectrum (neat, external TMS) exhibited absorption at τ6.90-9.15 (multiplet) with singlets τ7.70 and τ7.83. The n.m.r. spectrum (CCl_4, internal TMS) exhibited absorption at τ7.70-9.40 (multiplet) with singlets at τ8.25 and τ8.40. An infrared spectrum (page 27) was also run on the 1-norbornyl tosylate.

Oxidation of Bicyclo [2.2.0] hexane-1-methanol. Two methods of oxidation were successful, but higher yields were obtained using method B.

A) Jones Reagent Oxidation. The method given by Gibson and Erman[24] was used to oxidize 1.95 g. (17 mmoles) of the alcohol with 10 ml. (80 mequiv.) of Jones' Reagent prepared by the procedure of Bowers, Halsall, Jones, and Lemin.[6] The yield was 0.70 g. (32%) of pure acid. Purity was determined by the n.m.r. spectral integration.

B) Basic Potassium Permanganate Oxidation. Using a procedure by Kenyon and Platt,[26] 7.1 g. (64 mmoles) pure bicyclo [2.2.0] hexane-1-methanol were added to 3 g. (75 mmoles) of sodium hydroxide dissolved in 25 ml. of water. To this, with magnetic stirring, was added 31.6 g. (0.20 moles) of potassium permanganate dissolved in 300 ml. of water. The mixture was stirred at room temperature for seven hours. A slight excess over the calculated amount of sulfuric acid (conc.) was added dropwise until the mixture was acidic. Sodium bisulfite was then added until the excess permanganate was expended. The mixture was then extracted twice with ether. Sodium chloride was added to the water layer until a saturated solution was obtained and the mixture was extracted twice more with ether. The ether extracts were combined, dried with anhydrous magnesium sulfate, and concentrated by distillation to give an oily residue. This was then vacuum distilled in a modified Hickman still at room temperature and 0.10 mm. to give 4.93 g. (62.5%) yield. The n.m.r. and infrared spectra, pages 33 and 27, respectively, were consistent with the assigned structure. Continuous extraction with ether of the aqueous layer gave no additional desired product.

Oxidation to the acid proved to be a very good method of purifying the alcohol. All non-acidic compounds were removed by extraction of the sodium salt of the acid. Some of the acids were solids and were removed in the distillation step.

The analytical sample of the acid was purified by distilling three times as above on the Hickman still with no change in the n.m.r. spectrum. The refractive index was $n_D^{25.8} = 1.4730$.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.645; H, 7.990; O, 25.365

Found: C, 67.01; H, 8.11

Methyl Bicyclo[2.2.0]hexane-1-carboxylate. The acid (0.70 g., 56 mmoles) in 20 ml. of ether was methylated with a diazomethane-ether solution made from 1.13 g. of N-methyl-N-nitrosourea decomposed in 100 ml. of a 40% potassium hydroxide in water solution and 100 ml. of ether. A careful trap-to-trap distillation was done at 15° and 0.15 mm. after distillation of the ether at atmospheric pressure. An infrared spectrum, page 27, was obtained. An n.m.r. spectrum was determined, page 33, and the product was indicated to be reasonably pure. The yield was 0.580 g. (74.1%). G.c. analysis was done on a 6' x ¼", 10% β,β'-oxydipropionitrile on 60/80 Chromosorb W column set on the following conditions; injection port 213°, detector block 231°, column 100°, and helium gas flow of 60 ml./minute. Collection of all eluate and determination of its n.m.r. spectrum established that considerable rearrangement had occurred on the g.c.

Methyl Cyclohexyl Ketone via the Methylsulfinyl Carbanion. The method of Davis,[17] which was a slight modification of that by Corey,[13] was followed to synthesize the title compound. A 74.5% overall yield of product was obtained. The n.m.r. and infrared spectra of the ketone were compared to those of a sample previously prepared by Davis.[17]

Attempted Synthesis of Methyl Bicyclo[2.2.0]hexyl-1 Ketone via the Methylsulfinyl Carbanion. The procedure above for the preparation of methyl cyclohexyl ketone was followed exactly for the attempted preparation of the title compound. To a 25 ml. three-neck flask (fitted with a reflux condenser, a self-equilibrating addition funnel, a magnetic stirrer, and a stopper) was added 0.556 g. 44% (0.01 moles) sodium hydride in oil dispersion. The equipment had previously been flame dried and a nitrogen flow had been set up through a three-way stopcock fitted to the top of the condenser. Also fitted to the three-way stopcock was a water aspirator with a potassium hydroxide drying tower in between. The sodium hydride was washed five times by magnetic stirring with dry petroleum ether, which was removed with an eye dropper after each washing. After the final washing, the sodium hydride was dried by reducing the pressure slowly with the aspirator. A nitrogen atmosphere was regained by alternate bleeding in nitrogen and vacuuming out the system via the aspirator. After doing this three times the aspirator line was disconnected and a mercury bubbler was added in its place. Dimethyl sulfoxide (1.3 ml.) (an excess) was added dropwise slowly, and the mixture was heated over a magnetically stirred oil bath to 70^{o} for one hour. The reaction mixture was then cooled over ice and 1.3 ml. of tetrahydrofuran (distilled from lithium aluminum hydride) was added slowly. The ester (0.580 g. (4.15 mmoles) of methyl bicyclo[2.2.0]-hexane-1-carboxylate) was then added neat very slowly and the reaction mixture was allowed to come to room temperature and was stirred for one hour. It was then cooled over ice and 10 to 15 ml. of water was added. Hydrochloric acid (6 N.) was then added until the pH dropped to five. Chloroform was added to extract three times. The organic extracts were dried over anhydrous magnesium sulfate and roto-vacuumed at water aspirator pressure and room temperature to give a brownish oil which was the adduct. A bright orange color accompanied the addition of the methyl ester to the methylsulfinyl carbanion the first time the reaction was run. On the second attempt no noticeable change followed the addition of the ester. Other than that the two runs were identical. The yield of the adduct mixture was 83.5% for the first run and 57% for the second. The n.m.r. spectrum of the adducts from both runs were virtually identical and gave absorptions at τ4.38 (multiplet), 5.92-6.17 (multiplet), and 6.73-8.90 (continuous absorption) with singlets at τ7.24, 7.28 and 8.74. The adduct was reduced with aluminum amalgam prepared by soaking strips of aluminum (0.84 g., 31 mmoles) one centimeter wide in a saturated aqueous solution of mercuric chloride for 45 seconds. The strips were then cut in one centimeter squares after dipping into a 95% ethyl alcohol solution. The adduct and the aluminum amalgam were combined in 36 ml. of a 10% aqueous solution (3.6 ml. water to 33 ml. tetrahydrofuran) and stirred magnetically for two hours at 60°. The reaction mixture was then filtered and the filtered solids were washed with tetrahydrofuran. The filtrate was concentrated by distillation to remove most of the tetrahydrofuran. Ether and water were added and the mixture was ether extracted three times. The organic layer was dried over anhydrous magnesium sulfate and distilled to give the ketone. Similar n.m.r. spectra were obtained on the ketone products of the two runs. The first run ketone mixture gave an n.m.r. spectrum having absorption at τ4.4-4.9 (multiplet), 7.35-91 (multiplet), and 9.4-9.6 (mu;tiplet) with singlets at τ7.82, 7.90, 8.40, and 8.62. G.c. analysis on a 6' x $\frac{1}{4}$", 20% Carbowax 20M on 60/80 Chromosorb column (conditions: injection port temperature 227°, detector block temperature 233°, column temperature 125°, and helium gas flow of 60 ml./minute) gave three peaks after solvent. See the table below for the retention times and percentages. The product with a retention time of 2.95 minutes gave an n.m.r. spectrum exhibiting absorption at τ6.6-7.05 (multiplet), 7.5-8.4 (multiplet), and 9.25-9.83 (multiplet), with singlets at τ7.90, 8.06, and 9.46. The product with a retention time of 2.35 minutes gave an n.m.r. spectrum with absorption at τ4.10 (multiplet), 4.32 (multiplet), 4.86-5.10 (multiplet), 5.12-5.31 (multiplet), 7.52-8.10 (multiplet), and 7.74 (singlet). The final peak with a retention time of 3.70 minutes gave a compound with the following n.m.r. spectral absorptions: τ3.30-3.63 (multiplet), 6.40 (sharp multiplet), and 7.20-9.25 (multiplet), with singlets at τ2.92, 7.98, 8.70, and 8.80. The second run gave the same products, but in a different ratio. The following table corresponds the two runs.

TABLE 1

COMPARISON OF REACTION RUNS ON THE ATTEMPTED SYNTHESIS OF METHYL BICYCLO[2.2.0]HEXYL-1 KETONE FROM METHYLSULFINYL CARBANION

Peak	Retention Time	Reaction Run	Percent
1	2.35 minutes	1	20
"	" "	2	48
2	2.95 "	1	53.4
"	" "	2	4
3	3.70 "	1	26.6
"	" "	2	45

In both runs there were other smaller peaks in the g.c. amounting to three percent or less of the total composition. As no desired product was obtained, the reaction was abandoned.

Synthesis of Methyl Cyclohexyl Ketone via the Dimethyl Cadmium Reaction.

The acyl halide was made by the general method. Methyl magnesium bromide was made in the usual manner, and the dimethyl cadmium was made by the method of Cason.[11] The ketone was synthesized by the method given by Wiberg, Lowry and Colby[54] to make methyl bicyclo[2.1.1]hexyl-5 ketone. To 1.0 g. (7.8 mmoles) of cyclohexanecarboxylic acid was added 1.3 ml. distilled thionyl chloride and one drop of dimethylformamide (dry). The mixture was stirred at room temperature for six hours. The acyl halide produced was isolated by distilling the thionyl chloride under a vacuum. The acyl halide was set aside.

Methyl bromide (3.5 g. 37 mmoles) was dissolved in 20 ml. of dry ether by bubbling it into the ether which was cooled in an ice-salt bath placed on a balance to weigh the methyl bromide added. This was transferred in 5 ml. portions to a pressure equalizing addition funnel and then added dropwise under the surface of a suspension of 0.67 g. (28 mmoles) magnesium turnings in 20 ml. of dry ether and one crystal of iodine. The flask was previously flame dried and had a static nitrogen (dried and deoxygenated) atmosphere. The reaction mixture was stirred magnetically and the reflux was cooled by a Dry Ice condenser. The addition of the ether-methyl bromide solution was kept fast enough to cause a steady reflux and was heated under reflux for 20 minutes after the addition was complete. To the methyl magnesium bromide (cooled in ice) was added, in one charge, 2.73 g. (15 mmoles) of cadmium chloride (dried for two days at 110°). The mixture was heated under reflux for 45 minutes. The ether was removed by distillation until almost dry. Twenty milliters of dry benzene was then added and distilled until the boiling point reached 78°. More benzene (10 ml.) was then added and approximately five ml. were distilled off. The acyl halide (after the addition of 20 ml. dry benzene to it) was then added and the reaction mixture was allowed to stir overnight. Work up of the product was afforded by adding 20 ml. of petroleum ether, 20 ml. of water, and enough 6 N. hydrochloric acid to dissolve the salts. It was extracted several times with petroleum ether. The organic layers were combined, washed with sodium carbonate, and water solutions in order. Distillations gave 0.81 g. (83%) pure product. N.m.r. and infrared spectra were compared with those of an authentic sample made by Davis.[17] The n.m.r. spectrum exhibited a sharp singlet at τ 7.98 and a multiplet at τ7.90-9.0. The infrared spectrum exhibited absorptions at 3.50 (s), 3.59 (m), 5.89 (s), 6.93 (s), 7.33 (m), 7.42 (m), 7.98 (m), 8.09 (m), 8.60 (m), 9.20 (w), 9.70 (w), 10.40 (sh), 11.30 (sh), 12.45 (w), and 14.85 (s)μ.

A second run was made to check out the effect of trap-to-trap distillation of the dimethyl cadmium at room temperature and 0.10 mm. after the ether was distilled to near dryness. It worked very well and the remaining ether was distilled from the dimethyl cadmium after the addition of 20 ml. of (dry) benzene as before. A slight reduction in yield was encountered, but this was attributed to a poorer yield of the acyl halide than on the first run.

Synthesis of Methyl Bicyclo [2.2.0] hex-1-yl Ketone via the Dimethyl Cadmium Reagent. Three runs were made on this reaction following the method outlined above for the synthesis of methyl cyclohexyl ketone. Minor modifications were made for each run and are itemized below. In all runs 1 g. (79.5 mmoles) of thionyl chloride, 3.5 g. (37 mmoles) of methyl bromide,).67 g. (28 mmoles) of magnesium, one crystal of iodine, and 2.73 g. (15 mmoles) of cadmium chloride were used.

Run 1) For the preparation of the acyl halide, 1.3 ml. of thionyl chloride was added to 1 g. of the acid and was stirred overnight under nitrogen. It was noticed that a vigorous endothermic reaction accompanied by the bubbling off of a gas followed the addition of the thionyl chloride to the acid and continued for about 1 minute before ceasing. This was the case for all three runs. The acyl halide was isolated by trap-to-trap distilling the thionyl chloride to leave the crude acyl halide for use in the reaction with the dimethyl cadmium. The n.m.r. spectrum of the acyl halide exhibited a strong multiplet at τ7.15-8.16. A small sample was successfully hydrolyzed back with water to the acid and compared spectrally.

The dimethyl cadmium was made as outlined above (i.e., the dimethyl cadmium was trap-to-trap distilled and deoxygenated nitrogen was used). A mixture of products were obtained after the workup as above. The infrared spectrum exhibited the following absorptions: 3.46 (s), 5.80 (s), 6.92 (m), 7.28 (m), 7.60 (s), 7.98 (s), 8.70 (w), 9.10 (s), 10.00 (m), 10.78 (m), 11.30 (w), 11.70 (w), 12.60 (w), 13.20 (m), and 14.37μ. The n.m.r. spectrum exhibited absorption at τ6.40 (singlet), 6.75-9.15 (multiplet), with singlets at τ8.00, 8.22, and 8.55. The peak at τ6.40 indicated that a very small amount of an ester was present. As no double bond absorption was found and since some absorption was found where one would anticipate the bicyclo[2.2.0]hexane structure, it was felt that some of the desired product might be present. G.c. analysis with collection of all peaks showed a large amount of rearrangement due to the conditions employed: 6' x $\frac{1}{4}$", 20% Carbowax 20M 60/80 Chromosorb W with a detector block temperature of 230°, and injection port temperature of 226°, a column temperature of 226°, and a helium gas flow of 60 ml./minute.

Run 2) The synthesis of the acyl halide was done differently than in the first run. An attempt was made to follow the Wiberg and Hess procedure[53] for making endo-bicyclo[3.1.1]heptane-6-carbonyl chloride. To one gram of the acid was added one drop of dry dimethylformamide and 1.3 ml. of thionyl chloride distilled under a nitrogen atmosphere. Vigorous bubbling for about one minute was again noted. The mixture was stirred at room temperature for one hour then heated to reflux. Immediately before attaining reflux the reaction mixture started to turn dark brown. Therefore, it was immediately cooled back to room temperature and stirred at that temperature for four hours before work-up as above. The acyl halide was trap-to-trap distilled at 35° and 0.10 mm. in attempt to purify it somewhat. The dimethyl cadmium was synthesized in the same manner as in the first run except that the deoxygenator was not used. It was thought that possible rearrangement might have been caused in the first reaction by impurities bleeding off of the hot copper column. Diborane had backed up on the column in a previous synthesis of that molecule. The n.m.r. spectrum of the second run showed the same general appearance with a greatly enhanced large singlet at τ6.40, an ester.

Run 3) The acyl halide was made by the same method as in the first run (i.e., a nitrogen flow and at room temperature overnight (fifteen hours)). The acyl halide was purified as in run number two by trap-to-trap distilling at reduced pressure (0.08 mm.) and 30°. Some additional precautions were taken in the synthesis of the dimethyl cadmium. Thiophene free benzene was used. Sodium was added to the ether in an attempt to destroy any methanol possibly present. However, the deoxygenator was not used. This must be used in order to cut down the amount of ester formed. Again the product distribution was essentially the same as in the first run. The amount of ester was cut down over the amount of ester in the second reaction by over half. The n.m.r. spectrum of this product mixture looked the most promising of the three runs. A sharp singlet at τ 8.00 dominated the large multiplet from τ6.75-9.3. A sharp multiplet at at τ7.37 also appeared much larger (with respect to the other peaks) than in the previous runs.

As the products from the reaction were unstable to g.c. separation and there were several possible ketones present, it was felt that the best means of separation might be effected by converting to the acetate and then separating by g.c. Therefore, the products from reaction runs one and three were carried forward to the Baeyer-Villiger reaction.

Baeyer-Villiger Oxidation of the Ketone Mixture. The method given by Wiberg and Hess[53] was followed for this reaction. Two runs were made.

Run 1) The first reaction was done on the product mixture from the third ketone synthesis as the possibility of the presence of methyl bicyclo[2.2.0]hex-1-yl ketone was most promising in the mixture. The entire 0.35 g. of mixture was combined with 1 g. *m*-chloroperbenzoic acid (80% pure) in 2.8 ml. dichloromethane and magnetically stirred for three days. The reaction mixture was diluted with 10 ml. of dichloromethane, washed twice with 5 ml. portions of a 10% sodium hydroxide solution, two 5 ml. portions of water, two 5 ml. portions of 10% sodium bisulfite, and 3 ml. of water. The organic layer was dried over anhydrous magnesium sulfate, concentrated under trap-to-trap conditions (i.e., room temperature, and reduced pressure), and the residue was then distilled at 35° and 0.10 mm.

An infrared and n.m.r. spectra were run at this point. The n.m.r. spectrum exhibited absorptions at τ8.06 (sharp singlet, acetate), 6.33-6.48 (multiplet), 7.52-7.64 (multiplet), and 7.25-8.98 (weak, continuous multiplet). The infrared spectrum exhibited absorptions at 3.42 (s), 5.78 (s), 6.90 (m), 7.35 (m), 7.56 (m), 7.93 (s), 8.73 (w), 9.17 (w), 9.75 (w), 10.56 (w), 10.70 (sh), 12.50 (w), 13.50 (w), 14.30 (m), and 14.80 (m)μ. The product mixture was then combined with that of the second run for g.c. separation after an initial check by g.c. for product distribution by integration.

Run 2) The second run was carried out exactly like the first on the reaction mixture from the first ketone synthesis. The n.m.r. spectrum was much the same as that from the first run but with increased absorption from τ7.90-8.90. A sharp multiplet at τ8.54 dominated this spectrum.

Analysis of Products. Four products were isolated by g.c. collection of three peaks obtained on a 6' x $\frac{1}{4}$", 20% Carbowax 20M on 60/80 Chromosorb W column (conditions: injection port temperature 205°, detector block temperature 235°, column temperature 100°, and a helium gas flow of 120 ml./minute). The following table gives the retention time and percent composition per run.

TABLE 2

COMPARISON OF REACTION RUNS ON THE BAEYER-VILLIGER OXIDATION OF THE KETONE MIXTURE

Peak	Retention Time	Reaction Run	Percent
1	4.55 minutes	1	59
"	" "	2	17
2	5.60 "	1	5
"	" "	2	46
3	6.50 "	1	36
"	" "	2	37

The third peak gave a compound with an n.m.r. spectrum having absorptions at τ6.40 and continuously from τ7.80-9.20. The second peak was an acetate exhibiting the following n.m.r. spectral absorptions at τ3.90 (multiplet), 4.30 (multiplet), 4.50 (multiplet), 5.10-5.50 (multiplet), 6.28 (singlet), 6.35 (singlet), 6.41 (singlet), 7.28-9.20 (multiplet), and 9.42 (singlet). The first peak was a 70/30 mixture of two components. The larger component was felt to be the desired bicyclo[2.2.0]hex-1-yl acetate. The n.m.r. spectrum was changed little from that mentioned above for the product mixture from the first run. Absorptions appeared at τ3.98 (multiplet), 4.55 (multiplet), 4.92 (multiplet), 6.28 (singlet), 7.52-7.64 (multiplet), 7.66-7.74 (multiplet), 8.06 (sharp singlet), and 8.72-8.83 (multiplet). The minor component had rearranged, clearly defining the n.m.r. spectral peaks due to the desired acetate, which included absorptions at τ7.52-7.64 (multiplet), 8.06 (singlet), and possible some of the weak absorptions from 7.25-8.98. Only enough product to obtain an n.m.r. spectrum was obtained and the project was stopped.

Synthesis of Tert-Butyl Cyclohexanecarboxylate. To 6 ml. (0.83 moles) of thionyl chloride (distilled) was added 5.12 g. (0.04 moles) of cyclohexanecarboxylic acid and heated under reflux for three hours while being stirred magnetically. *Tert*-butyl alochol (6 g.) was added dropwise at reflux temperature and the reaction mixture was allowed to heat one more hour. A trap-to-trap distillation was done to remove the excess reactants leaving behind relatively pure *tert*-butyl ester. An n.m.r. spectrum was run at this point to check purity and exhibited a sharp singlet at τ8.61 (9H) and a broad multiplet from τ7.65-8.95 (11H).

Synthesis of Methyl Cyclohexanecarboxylate. The same procedure was followed as given above for the preparation of *tert*-butyl cyclohexanecarboxylate (above). An n.m.r. spectrum was run to check the purity of the product ester and exhibited a sharp singlet at τ6.42 (3H) and a broad multiplet from τ7.60-8.90 (11H).

cis-Cyclobutane-1,2-dicarboxylic Anhydride. The procedure of Buchman, Reims, Skei, and Schlatter[9] was used in the preparation of this compound from 1-cyano-1,2-bis(carbomethoxy)cyclobutane to give a yield of 52%, b.p. 115°/0.3 mm. (lit.[9] 78% yield, b.p. 129-131°/2.5 mm.).

cis-1,2-Bis(hydroxymethyl)cyclobutane. The method of Reineke[36] which was a modification of that given by Bailey, Cunov, and Nicholas[2] to give the desired product in 89% yield, b.p. 91°/0.5 mm. (lit.[2] 80% yield, b.p. 64-67°/0.03 mm.).

cis-1,2-Bis(bromomethyl)cyclobutane. The method of Blomquist and Verdol[4] was used to prepare the above compound in an 88% yield, b.p. 74-75°/1.0 mm. (lit.[4] 62.5% yield, b.p. 71-73°/1.8 mm.). The infrared spectrum was in agreement with that obtained by Reineke in his previous sysntheis.[36]

cis-1,2-Bis(cyanomethyl)cyclobutane. The method of Allinger, Nakazaki, and Zalkow[1] was used to prepare the title compound in a 51% yield, b.p. 144°/1.4 mm. (lit.[1] gave no yield or physical data other that the infrared spectrum, which was in good agreement with the one obtained in this preparation).

cis-1,2-Cyclobutanediacetic Acid. The method of Kleiman[27] was used to prepare the title compound in a 51% yield, m.p. 169-173°.(lit.[27] 78% yield, m.p. 178-179°). The infrared spectrum was in agreement with that previously published.[27]

Dimethyl Cyclobutane-cis-1,2-di-α-bromoacetate. The method of Kleiman[27] was again followed to prepare the title compound in a 19.0% yield, m.p. 78-81° (lit.[27] 18% yield, m.p. 81-82°). The infrared spectrum was in agreement with that previously published.

Reaction of Dimethyl Cyclobutane-cis-1,2-di-α-bromoacetate with Sodium Hydride. The Method of Blanchard and Cairncross[3] was modified for this reaction. To 0.432 g. (9 mmoles) of sodium hydride dispersed in 8 ml. tetrahydrofuran was added dropwise, with magnetic stirring at room temperature, 1.5 g. (4.2 mmoles) of dimethyl cyclobutane-cis-1,2-di-α-bromoacetate dissolved in 12 ml. tetrahydrofuran. The tetrahydrofuran used had been previously distilled from calcium hydride. The addition of the compound was complete after thirty minutes. It was allowed to stir at room temperature for 18 hours. Since no noticeable signs of reaction were observed, the reaction mixture was heated under reflux for 7 hours. The reaction mixture was then allowed to stir at room temperature again for another 16 hours. Methanol was used to kill off the excess sodium hydride, 15 ml. water was added, and the mixture was extracted three times with ether. Evaporation of the ether layer, after drying over anhydrous magnesium sulfate, gave a very small amount of yellow oil which was unidentifiable. The aqueous layer yielded an intractable brown solid which would not chromatograph. An attempt was made to methyl esterify the brown solid with diazomethane in ether in the event that the ester had saponified during the reaction. No change in the compound was noted and it was not identified. After two further attempts, the problem was deemed a failure and the work on it was stopped.

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VITA

Ronald T. Sleeter was born in Decatur, Illinois on August 29,1942. He graduated from MacArthur High School in 1960. He attended Illinois College for one year (1960-1961) and, then, Millikin University for four, receiving his Bachelor of Arts Degree in Chemistry in June, 1965. While he attended Millikin, he worked on Mannich base condensation reactions involving 2-naphthalenethiol, formaldehyde, and various primary amines under Dr. Carl Weatherbee, Head of the Chenistry Department at Millikin. This work culminated in a paper, Tetrahedron Letters, 4069 (1965).

In September, 1965 he entered Kansas State University in Manhattan, Kansas to pursue study toward the M. S. Degree in organic chemistry. He began the present work under Dr. Richard N. McDonald in the summer of 1966.

In June of 1962 he married the former Mary Whitmore of Decatur, Illinois. They have two sons: Anthony L., born June 13, 1963; and Scott M., born October 23, 1967.

He survives his father, who died March 29, 1957, and his mother, who died February 1, 1962.

ATTEMPTED SYNTHESIS OF BICYCLO[2.2.0]HEXAN-1-OL
AND
OTHER BICYCLO[2.2.0]HEXANE DERIVATIVES

by

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AN ABSTRACT OF A MASTER'S THESIS

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ABSTRACT

The attempted synthesis of bicyclo [2.2.0] hexan-1-ol is described. Starting with 4-chlorobicyclo [2.2.0] hexane-1-carboxylic acid and its methyl ester, several attempted dechlorination reactions with lithium and tert-butyl alcohol were run, resulting in a 41.3% yield of methyl cyclohexanecarboxylate. Rearranged chloroesters accounted for 32.3% of this material, and the remaining 26.4% was dechlorinated but contained double bonds. Reduction of the 4-chlorobicyclo[2.2.0] hexane-1-carboxylic acid with diborane was followed by a successful dechlorination with sodium and tert-butyl alcohol and gave bicyclo [2.2.0] hexane-1-methanol in a 50% yield. Oxidation of this with basic permanganate gave a 63% yield of the bicyclo [2.2.0] hexane-1-carboxylic acid (57). An attempt to make the methyl ketone by reaction of the methyl ester of 57 with methylsulfinyl carbanion failed. Attempted preparation of bicyclo [2.2.0]-hexan-1-ol, by reaction of the acid chloride of 57 with dimethyl cadmium followed by a Baeyer-Villiger oxidation with m-chloroperbenzoic acid, gave an acetate, the n.m.r. spectrum of which resembled that expected for bicyclo [2.2.0] hex-1-yl acetate.

During the course of work, bicyclo [2.2.0] hexane-1-methyl tosylate was made and found to rearrange to 1-norbornyl tosylate. Also, the bicyclo [2.2.0] hexane ring system was found to be thermally unstable whenever a carbonyl group was present in the 1-position.