



Synthetic routes to perhydroazulenes; studies with oxygenated models
by Amo Richard DeBernardis

A thesis submitted to the Graduate Faculty in partial fulfillment of the requirements for the degree of
MASTER OF SCIENCE in Chemistry

Montana State University

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Abstract:

The research program was initiated to learn whether diazomethane ring expansion might prove a reasonable method of arriving at perhydroazulenes that are related to some sesquiterpenes. In the course of the investigation, which involved 4-methyl-cis 3a,4,7,7a-tetrahydrophthalan as a model, it was concluded that a methyl group can have powerful directive effects; possibly more electronic in nature than steric. Also, the choice of an oxygen heterocyclic system as a model for the carbocyclic systems resulted in an analysis of the long range directive effects of oxygen. Additional studies using a sulfur hetero-atom confirmed the long range hetero-interactions. As part of the study using oxygenated systems, the sex attractant of the bark beetle, *Dendroctonus brevicomis*, was prepared by an unambiguous synthesis. The initial question of the program, that of investigating the use of diazomethane ring expansion, was answered and evidence shows that the desired product is that obtained in greater quantity. Overall yields, however, appear to be prohibitive in using this as a synthetic route. The poor ring expansion may result from electronic and/or steric effects.

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Date August 6, 1971

SYNTHETIC ROUTES TO PERHYDROAZULENES

STUDIES WITH OXYGENATED MODELS

by

A.^{MD} Richard DeBernardis

A thesis submitted to the Graduate Faculty in partial
fulfillment of the requirements for the degree

of

MASTER OF SCIENCE

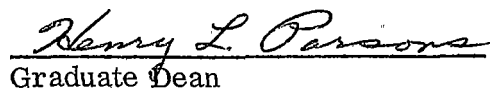
in

Chemistry

Approved:


Head, Major Department


Chairman, Examining Committee


Graduate Dean

MONTANA STATE UNIVERSITY

Bozeman, Montana

August, 1971

to

Beau

who has suffered many lonely hours

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I would especially like to thank my parents without whose help the completion of this thesis would not have been possible. I would like to acknowledge the Chemistry Department of Montana State University for its support in the way of teaching assistantships; and for making it possible for me to participate in the Northwest regional meeting of the American Chemical Society (Utah, summer 1969) and to attend the National Organic Symposium (Utah, 1969). For its generosity in the way of partial summer support in the summer of 1968 and complete support during the summer of 1970, I would like to thank Dr. Roy Huffman, vice president of research, and the Endowment and Research Foundation of Montana State University. I would like to thank Dr. A. P. Krapcho, University of Vermont, for his helpful information. I also thank my fellow researcher, Mr. R. D. Otzenberger, for his time involved in discussions and in helping to build laboratory apparatus.

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TABLE OF CONTENTS

	PAGE
Abstract	vii
List of Tables.....	viii
List of Figures.....	ix
CHAPTER	
I Introduction.....	1
II Synthesis of Alkene System	10
III Ring expansion of Alkene	37
IV Analysis of sulfur-heteroatom.	46
V Synthesis of the sex attractant Brevicomin	50
VI Experimental	58
VII Appendix	77
VIII References	94

ABSTRACT

The research program was initiated to learn whether diazomethane ring expansion might prove a reasonable method of arriving at perhydroazulenes that are related to some sesquiterpenes. In the course of the investigation, which involved 4-methyl-cis 3a,4,7,7a-tetrahydrophthalan as a model, it was concluded that a methyl group can have powerful directive effects; possibly more electronic in nature than steric. Also, the choice of an oxygen heterocyclic system as a model for the carbocyclic systems resulted in an analysis of the long range directive effects of oxygen. Additional studies using a sulfur heteroatom confirmed the long range hetero-interactions. As part of the study using oxygenated systems, the sex attractant of the bark beetle, Dendroctonus brevicomis, was prepared by an unambiguous synthesis. The initial question of the program, that of investigating the use of diazomethane ring expansion, was answered and evidence shows that the desired product is that obtained in greater quantity. Overall yields, however, appear to be prohibitive in using this as a synthetic route. The poor ring expansion may result from electronic and/or steric effects.

LIST OF TABLES

TABLE	PAGE
1. Diborane hydration of cyclic systems	13
2. Analysis of the pinacol rearrangement	23
3. Hydration of 3-methylcyclohexene	31
4. Hydration of 4 - Methyl-cis-3a, 4, 7a, 7 -tetrahydrophthalan	34
5. Ring expansion of the model cyclohexanone	41
6. Diels-Alder reaction for formation of 2-carboxaldehyde-6-methyl-3, 4-dehydro-2H-pyran	56

LIST OF FIGURES

FIGURE	PAGE
1. Examples of perhydroazulene compounds	1
2. The correct structure for β - vetivone.....	2
3. Synthesis of Aromadendrene	3
4. Synthesis of β -vetivone by Krapcho and Mundy	4
5. Synthesis of β -vetivone by Marshall	5
6. Approach to all carbon system	7
7. Attempted cyanide displacement	7
8. Proposed system that might be of interest to look into	8
9. Preparation of phthalan (3)	10
10. Mechanism of cyclization to the furan derivative	12
11. The hydration of <u>3</u> with diborane	15
12. Gas chromatogram of hydroboration products	15
13. Deuterium exchange of 2-methycyclohexanone ,.....	18
14. Nmr study of dueterated system <u>9</u> and <u>10</u>	19
15. The Use of Disiamylborane for Hydroboration	21
16. Proposed mechanism for the pinacol rearrangement	24
17. Carbonium ion stability	24
18. Model of 4-Methyl-cis-3a,4,7,7a-tetrahydrophthalan	26

FIGURE	PAGE
19. The process of oxymercuration -- demercuration	27
20. Oxymercuration of 3-methylcyclohexene	28
21. Oxymercuration of the alkene (<u>3</u>).....	28
22. Pasto's work on Hydration of alkenes	29
23. Conformational isomers of 3-methylcyclohexene	32
24. Methyl group interactions in 3,3-dimethylcyclohexene	32
25. Effect of oxygen atom on alkene (<u>3</u>) system	35
26. Ring expansion of methyl-cyclohexanone	37
27. Ring expansion of the ketone (<u>10</u>)	38
28. Unambiguous synthesis of the expansion product (<u>25</u>)	40
29. Comparison of gas chromatograms of expansion products	42
30. Gas chromatogram of product obtained from ring expansion	44
31. Synthesis of sulfur system alcohols (<u>29</u>).....	46
32. Comparison of alcohol retention times	47
33. Nmr comparison of compounds in cps.....	49
34. Internal cyclization with mercuric acetate	50
35. The sex attractant brevicomin	50
36. Silverstein's synthesis of brevicomin	53
37. Wasserman's synthesis of brevicomin	54

FIGURE	PAGE
38. Synthesis of brevicomin	55
39. Possible products from the Diels-Alder reaction	57

PART I

INTRODUCTION

Although terpenes have, in general, occupied a position of interest to organic chemists based almost entirely on interesting skeletal features, and ability to undergo complex skeletal reorganization, in the past their pharmacological use has been of little concern. The synthesis of perhydroazulenes has recently become of considerable interest, due to their pharmacological activity. Members of this unique class of sesquiterpenes bear in common the characteristic ring system composed of mutually fused five and seven ring (figure 1). The positioning of additional moieties are, as a rule, predictable on simple biogenetic reasoning. However, non-isoprenoid structures are known, and are particularly common in the perhydroazulene terpenes.

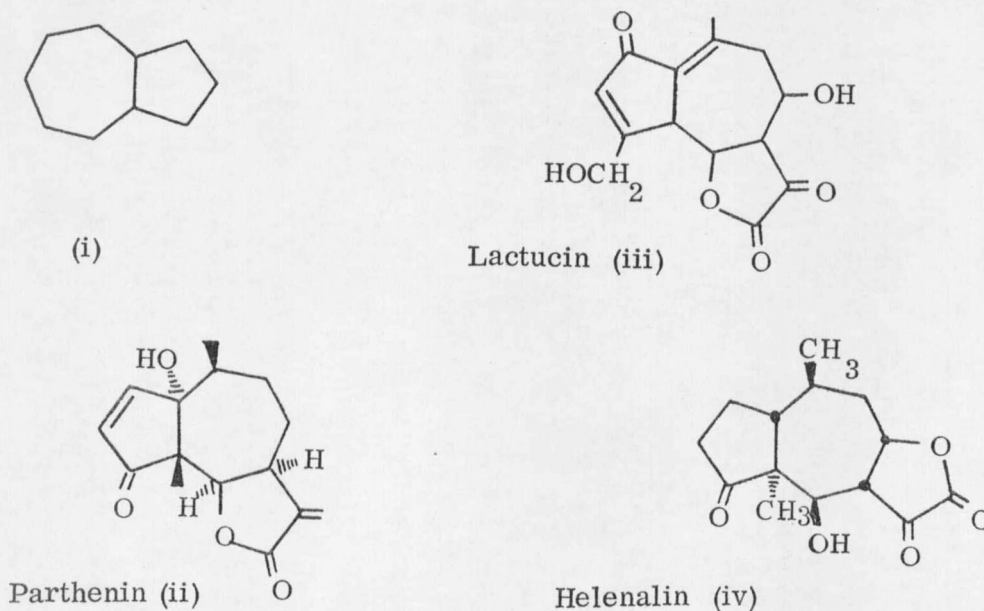


Figure 1: Examples of perhydroazulene compounds.

Examples of several perhydroazulene sesquiterpenes are shown in figure 1. The extent of pharmacological and other physiological activities are well represented in the sesquiterpene parthenin (ii)¹ in which both effects have been exhibited. Lactucin (iii)² and helenalin (iv)³ have also been shown to be active pharmacologically.

The potential of these interesting compounds has not been reflected in abundant synthesis. Research in this synthetic area is exemplified by the notable synthesis of Aromadendrene by Buchi⁴ (figure 3), and β -vetivone by A. P. Krapcho and B. P. Mundy⁵ (figure 4) and also the independent synthesis of β -vetivone by J. A. Marshall⁶ (figure 5) with these examples, the complexities of the synthesis can be noted. In the case of the Aromadendrene synthesis the assigned structure (vii) was shown not to agree with the synthetic product (vi). The two independent syntheses of β -vetivone gave products which were not consistent with the isolated natural product and led to eventual structure reassignment. The correct structure, as was finally determined by Marshall⁷, is shown in figure 2. Thus, in both cases it was only because of the attempted syntheses that the assigned structures were found to be incorrect.

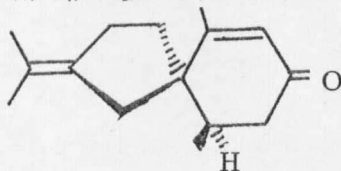
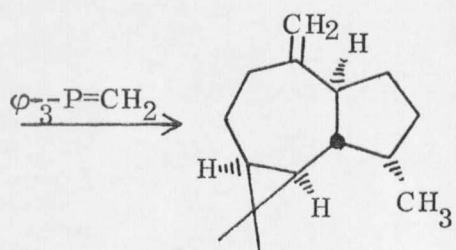
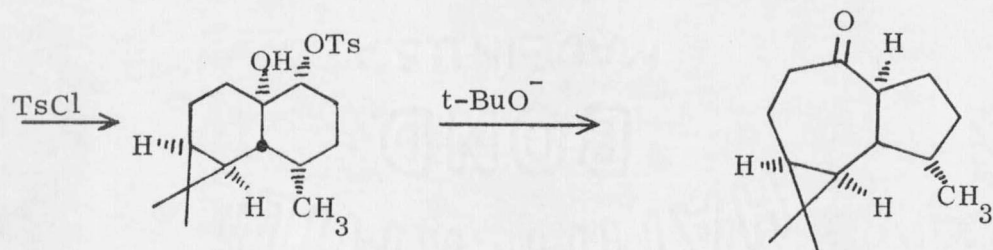
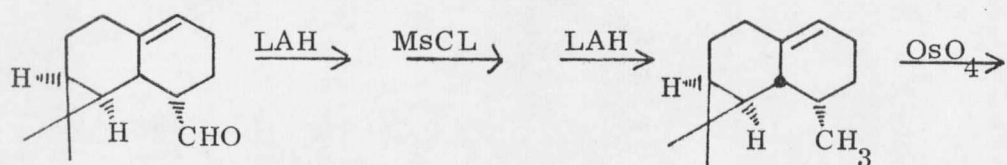
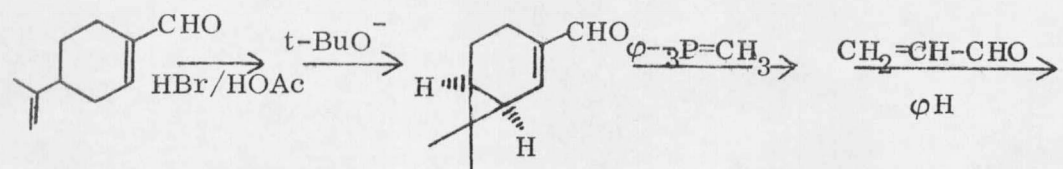
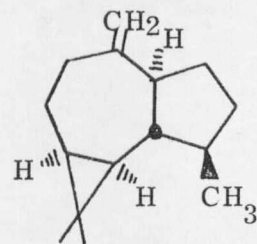


Figure 2 : The correct structure for β - vetivone.

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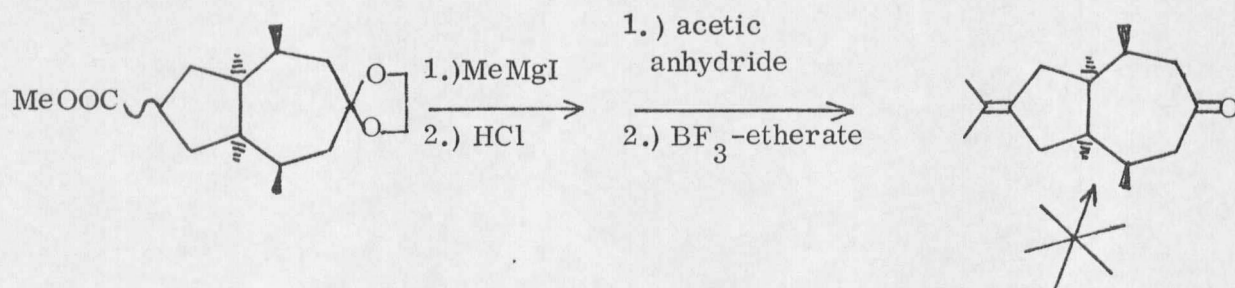
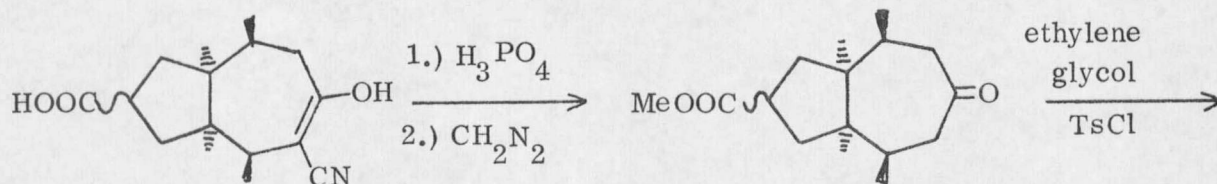
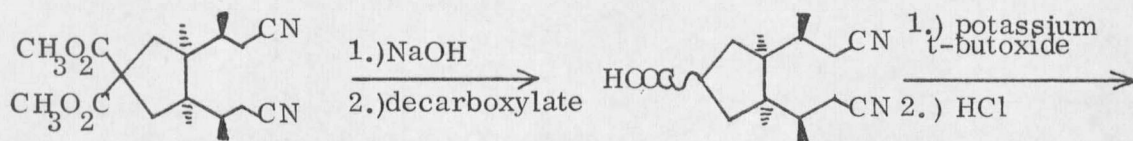
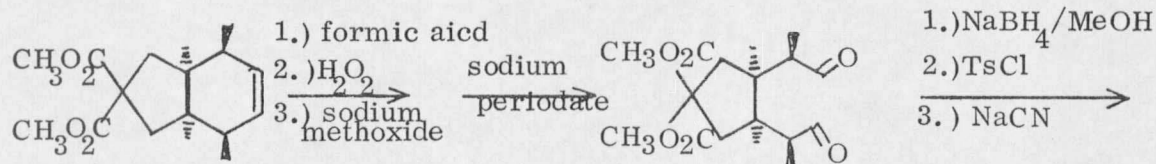
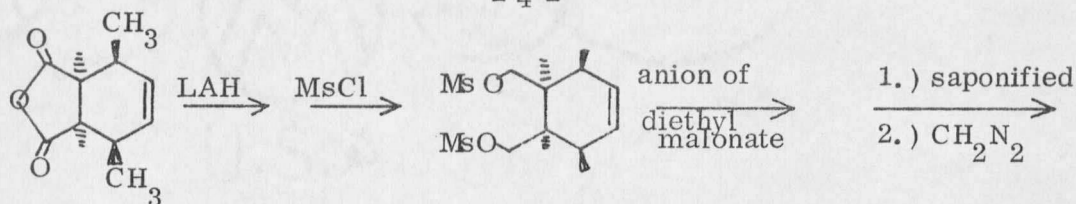
(-) Aromadendrene
(VI)



(VII)

Figure 3: Synthesis of Aromadendrene.

- 4 -



β -vetivone $\xrightarrow{\text{reduction}}$ $\longrightarrow$ Derivative

Figure 4: Synthesis of β -vetivone by Krapcho and Mundy.

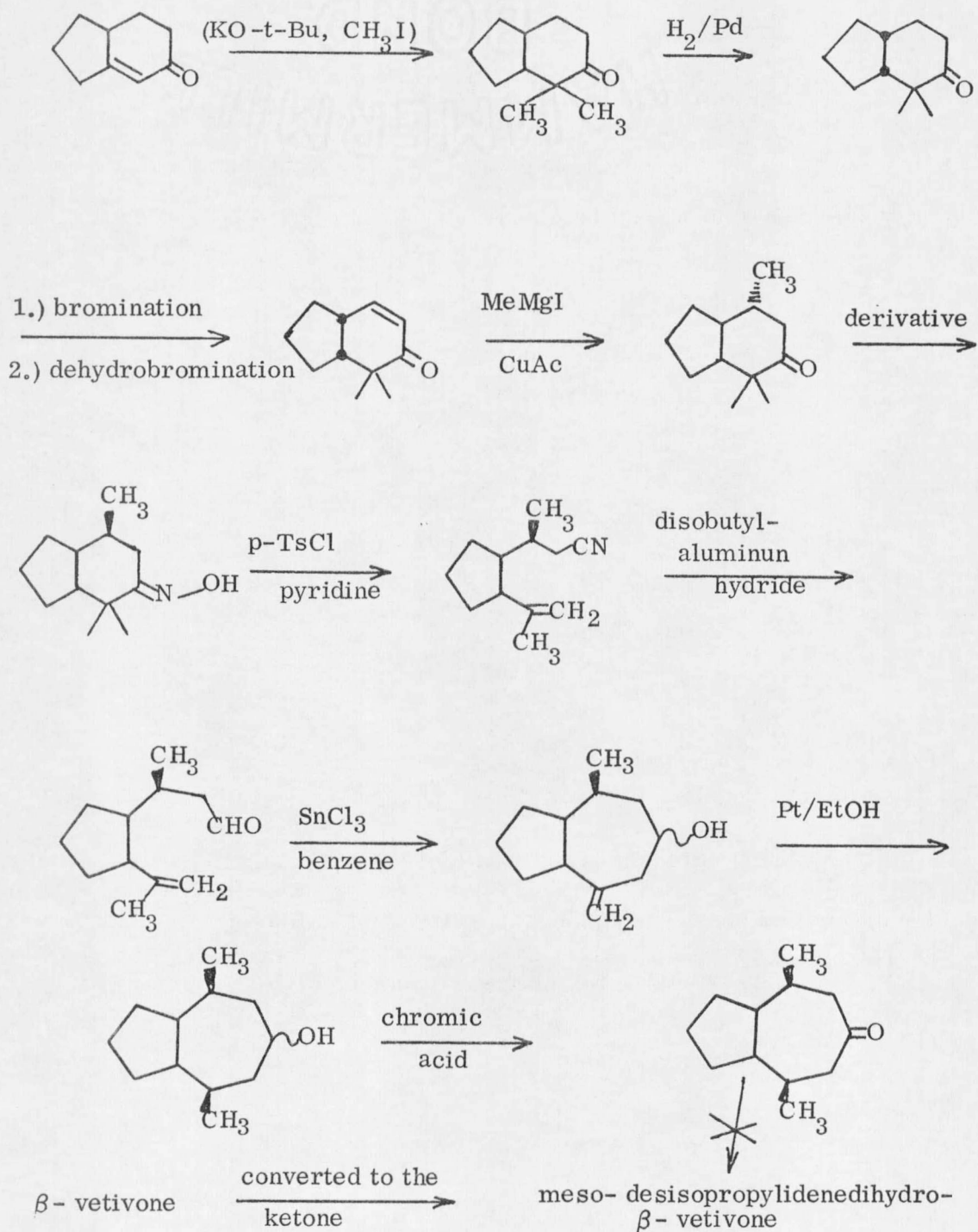
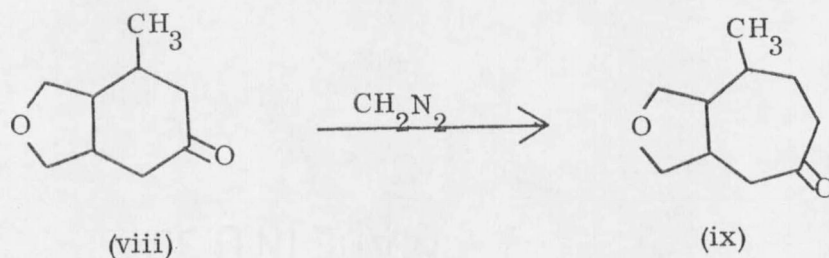


Figure 5: Synthesis of β -vetivone by Marshall.

In the synthesis of " β -vetivone" by Krapcho and Mundy, many of the reactions were tested on oxygenated model systems. Eliel⁸ has used an oxygen containing system as a model for the less available carbocyclic system. Oxygenated models have also been used by Rickborn⁹. The noted success with oxygenated models would indicate they can lend insight into problems that might be encountered in the carbocyclic analogs.

The objective of this research was to design an efficient preparation of (viii) and investigate the possible ring expansion to the perhydroazulene model (ix). This model system would be easily prepared and problems worked out



with it would make the subsequent preparation of the carbon system much easier, and hopefully provide an easier route to some of the perhydroazulenes.

The logical way to approach the all carbon compound would be through a dicyanide as is shown in figure 6. However, it is not possible to obtain the dicyanide directly from the ditosylate or dimesylate (xiii).

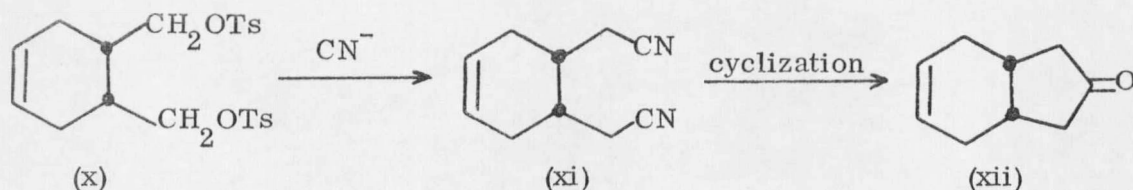


Figure 6: Approach to all carbon system.

This can be explained on the basis of the sterically hindered ditosylate system (figure 7). A possible route to the perhydroazulene skeleton from the oxygenated system is delineated in figure 8. Although there are no direct literature analogies, there are isolated examples to suggest that once this basic ring skeleton (ix) is prepared it would be feasible to convert it to some of the analogous sesquiterpene like systems (figure 8).

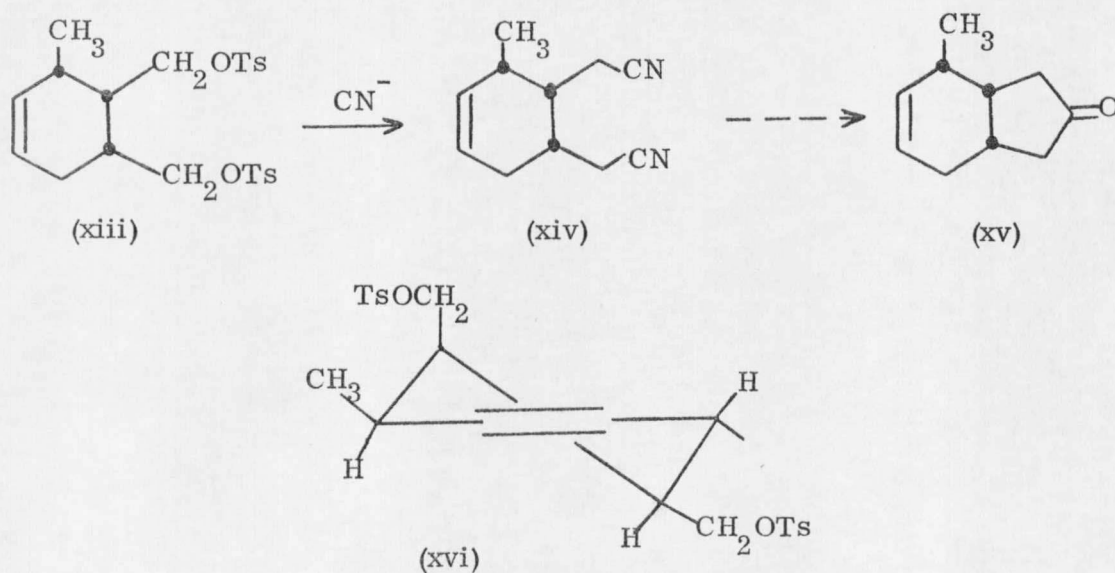


Figure 7: Attempted cyanide displacement.

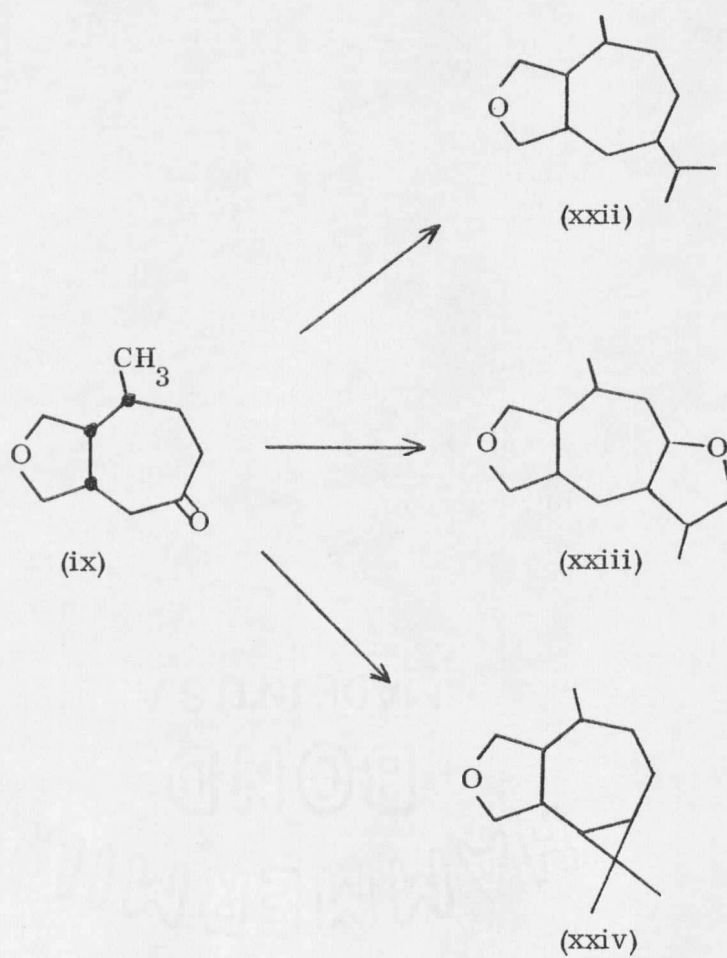


Figure 8 : Proposed system that might be of interest.

PROPOSED RESEARCH

To establish whether diazomethane ring expansion of 4-methyl-6-oxo-cis-3a, 4, 7, 7a-hexahydrophthalan to 4-methyl-cis-2-oxa-7-ketodexahydroazulene, the oxo-model of a perhydroazulene, would be an efficient method of preparing perhydroazulenes related to the sesquiterpenes. The steric and electronic effects of a suitable positioned methyl group in directing the course of the reaction would also be investigated.

PART II

SYNTHESIS OF ALKENE SYSTEM

In order to synthesize the required ketone (9) it was first necessary to prepare the alkene (3). The subsequent hydration and oxidation of 3 would then give the desired ketone (9). Following procedures used previously by Mundy¹², the phthalan (3) was prepared according to figure 9.

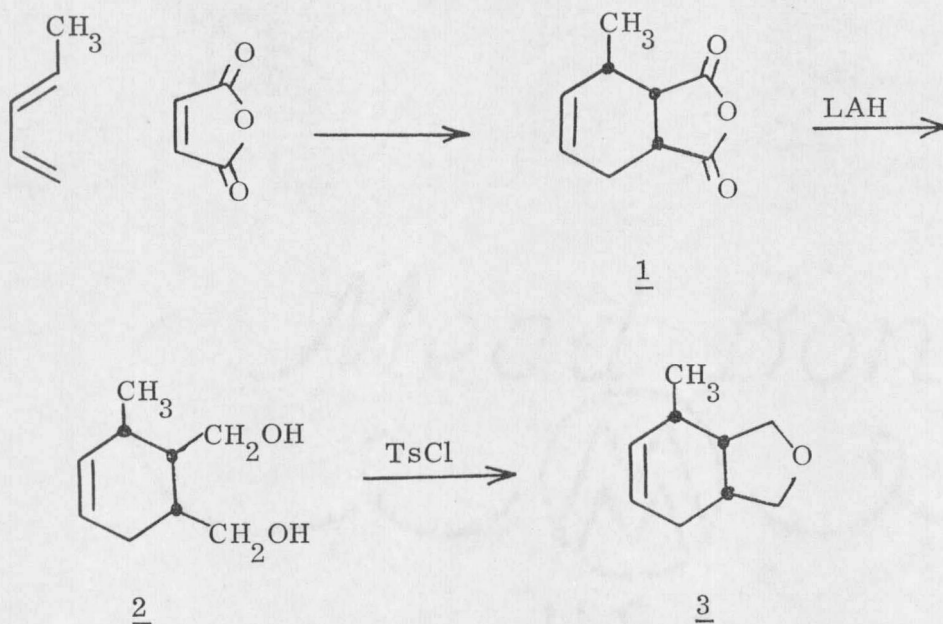
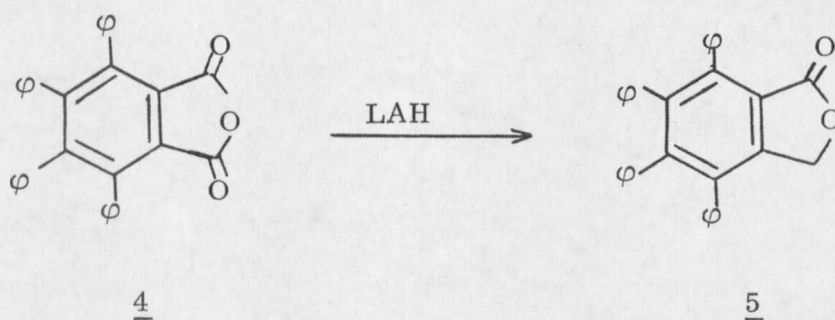


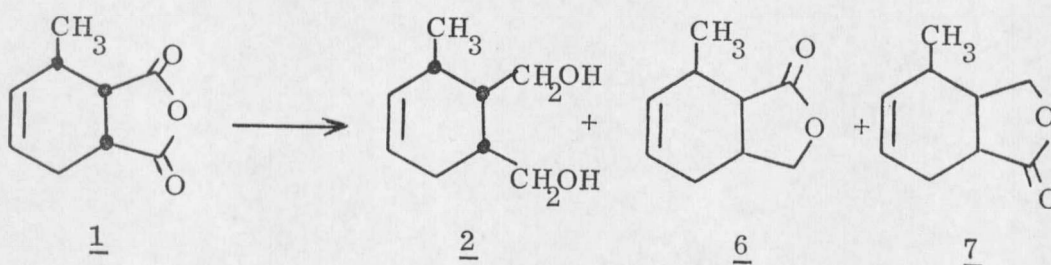
Figure 9: Preparation of phthalan (3).

Piperylene and maleic anhydride were refluxed in benzene which contained a trace of iodine¹³. The crystalline anhydride (1) was then reduced to 2 with lithium aluminum hydride. There were interesting by-products formed in this reduction that consisted of one or both of two isomeric lactones (6) and (7), as evidenced by infrared spectroscopy.

The formation of lactones during reduction of anhydrides with lithium aluminum hydride has been well established¹⁴. It has been observed that when the anhydride 4 was reduced with lithium aluminum hydride, the only product obtained was the lactone 5. It was also noted that further reduction of the



lactones (6) and (7) with lithium aluminum hydride gave a quantitative yield of the diol (2). The mechanism of this anomalous reaction has recently been reported¹⁵.



The diol was then converted to the monotosylate under conditions for which it is known that systems of this type readily undergo cyclization to the furan derivative (figure 10). The infrared and nuclear magnetic spectra

(appendix, page 78) were consistent with the assigned structure for the phthalan.

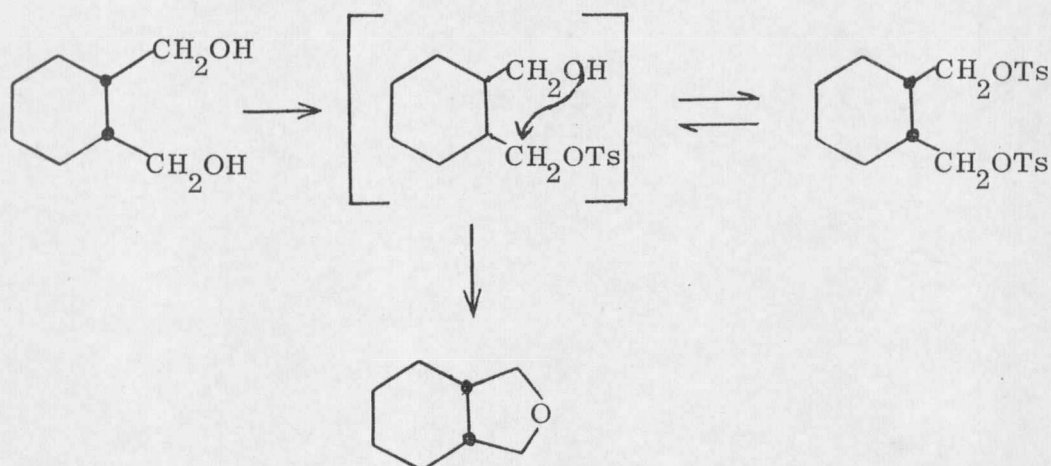


Figure 10: Mechanism of cyclization to the furan derivative.

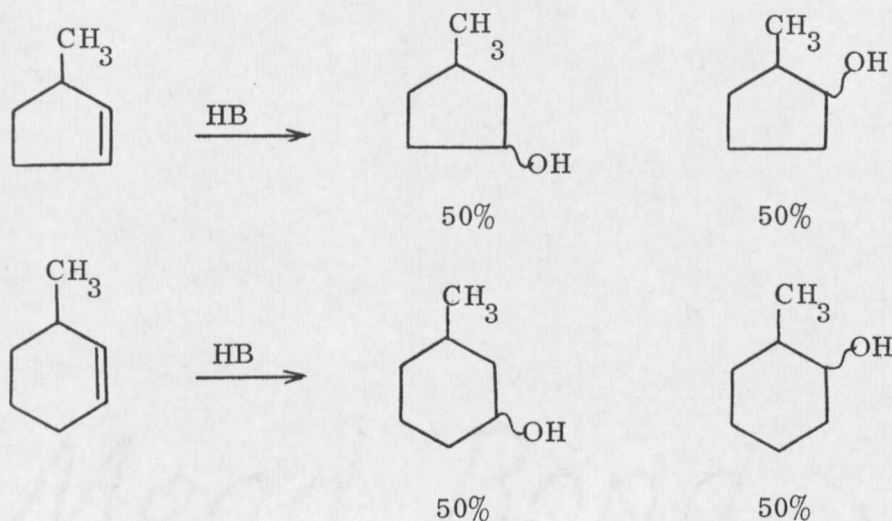
Having successfully prepared 3 in reasonable quantity, it was necessary to find a good method for the preparation of the ketone (9). There were several methods available for hydration, the results of which are described below. The chemistry of 3 had not been previously studied, thus it was unimportant where one started. The first method tried was that of hydroboration. The literature has evidence of considerable work done in this area by H. C. Brown¹⁶ and D. J. Pasto¹⁷. The results of some of this work are shown in Table 1.

Pasto's work with 3-methylcyclohexene agreed very well with that of Brown¹⁸. All of these systems tried were conformationally inhomogeneous,

whereas the alkene (3) system was of a rigid nature. One of our interests in this research was to analyze the effects of the methyl group upon the development of a basic perhydroazulene system. This method of hydration will then give insight into some of its effects.

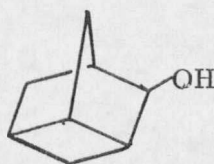
TABLE 1

Diborane hydration of cyclic systems



The hydroboration was carried out in a similar manner as that of Brown¹⁹. Infrared analysis at this point indicated the products to be the expected alcohols. However, when oxidation was attempted with sulfuric acid and potassium dichromate all that was recovered was a decomposition product²⁰. This type of oxidation was apparently too strong and a less drastic method was needed. A

very good method was found in the Jones oxidation²¹. It is known that even such unstable compounds as 8 can be oxidized without destruction of other skeletal features²². This oxidation was carried out at 25°C, was very simple to run, and gave high yields; thus, making it a very acceptable method for oxidation. When it was carried out on the alcohols there was an almost quantitative yield of ketone product. This was indicated in the strong absorbtion at 1720 cm⁻¹ in the infrared spectrum and the almost complete loss of the -OH absorbtion.



8

The problem of separation and identification turned out to be somewhat more difficult. However, it was possible to separate the ketones by gas chromatographic methods. A column 6 feet long and 4 mm inside diameter packed with 20% Carbowax on 40/60 firebrick provided good separation. The ratio of the ketones was 60/40. As can be seen in figure 12, one of the peaks has a rather large shoulder. This, it was felt, might be attributed to the possible epimer that would result in ketone (9). This epimerization would result in a third ketone which would explain the shoulder.

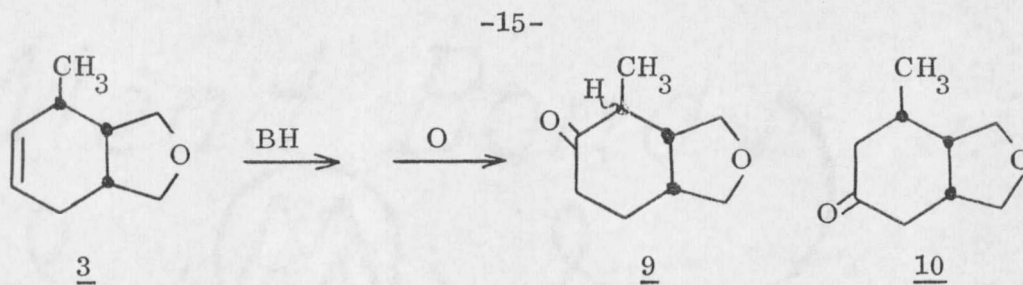


Figure 11 : The hydration of 3 with diborane.

Column : 20% Carbowax on firebrick
 Length : Six feet
 Temperature : 180° C

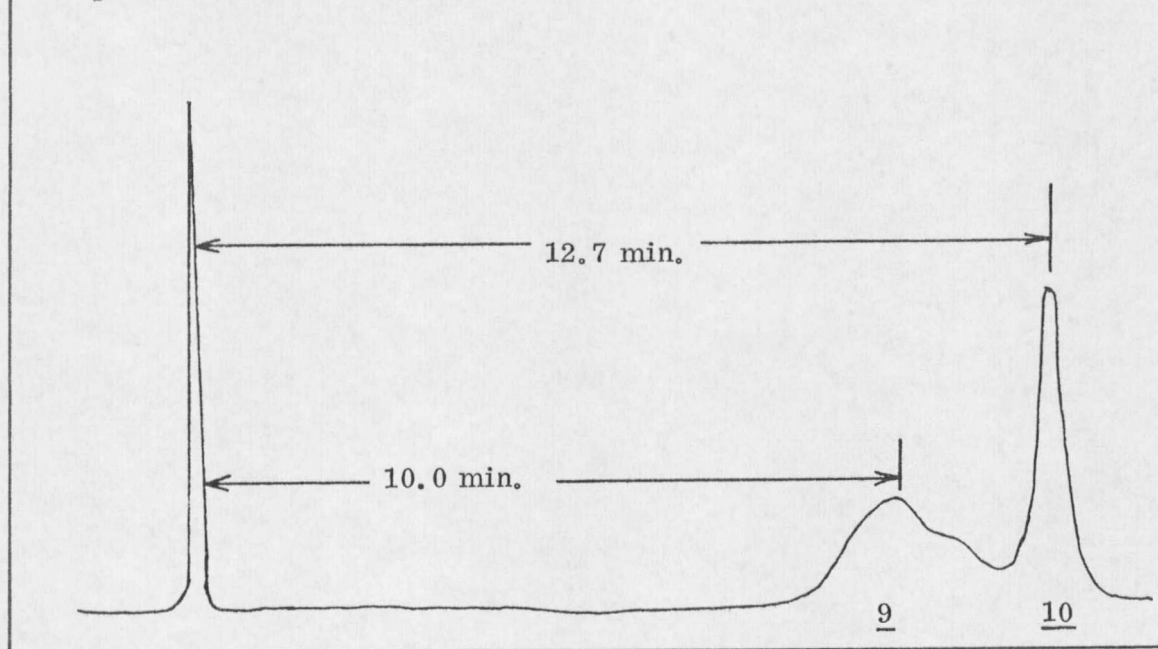


Figure 12 : Gas chromatogram of hydroboration products.

In order to positively identify the two ketones and also verify this epimerization of the hydrogen it was necessary to obtain pure samples of each ketone. The logical approach would be with preparative gas chromatography. A glass column twelve feet long with an inside diameter of 4 mm was made in our laboratory. Separation and collection of a sample of the two ketones was attempted by this method. Separation was achieved; however, since the recovery was low (50%) and the time required for obtaining milligram samples was so long, this method was felt to be impractical. Also, since large amounts of ketone (10) were necessary for the ring expansion a more efficient separation process was required.

The other method available was that of column chromatography, but it was first necessary to find a means for separation with thin layer chromatography. The support selected was silica as opposed to alumina due to possible reactions and rearrangements of the keto group. With some experimentation the conditions and solvents for separation were found.

The separation on thin layer indicated that it would be necessary to increase the length of the solid phase to achieve a clean separation. Since a commercial column was not available, with the help of Mr. Otzenberger²³ it was possible to fashion a suitable one out of glass. The column was 60 cm long and had a 30 mm inside diameter and was water jacketed. The high volatility of the

elutant solvents used made it necessary to cool the column to remove the heat generated by absorption and deabsorption of the solvents on the solid phase.

With this column it was possible to separate one gram samples of the ketone mixture. The gas chromatogram of the collected fractions indicated each ketone to be uncontaminated with the other.

Each fraction gave a 2,4-dinitrohydrazone derivative and the melting ranges were considerably different (fraction 10: m.p. 164-5, and fraction 9: m.p. 176-7).

Infrared analysis of fractions 9 and 10 showed each to contain a strong absorption for a ketone with the carbonyl frequency for each ketone being the same (see appendix, page 79).

The nuclear magnetic resonance spectrum of each ketone was considerably different; however, conclusive assignment of structure could not be accomplished at this point (see appendix, pages 83 and 84).

It was felt that if an epimerization was taking place and if one ketone did have the structure of ketone (9) then it should be possible to employ deuterium exchange as an analytic method. This exchange would be evident in the nuclear magnetic resonance as a loss in the splitting of the methyl signal for the compound having the secondary methyl group α to the carbonyl function.

Experiments on a model compound were first attempted in order to

establish the experimental technique. A gas chromatographically pure sample of 2-methylcyclohexanone was selected as the model. The nuclear magnetic resonance spectrum of the deuterated compound did show a loss of the splitting of the methyl group at 1.1δ as was expected (figure 13).

The ketones (9) and (10) were then subjected to the same condition for deuterium exchange and the nuclear magnetic resonance spectrum of each was taken (figure 14). As was expected there was a loss in the splitting of the methyl group in one of the ketones (11). The doublet for the methyl group was retained in the other ketone (12).

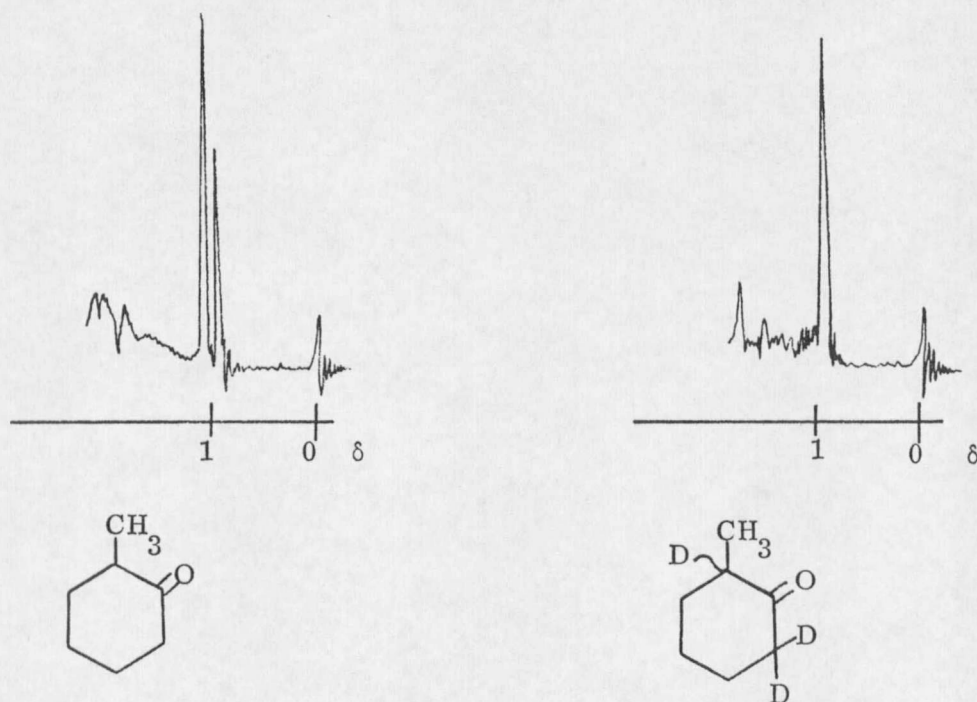
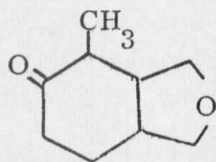
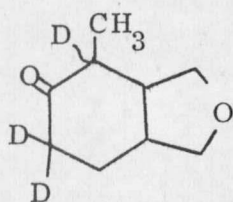
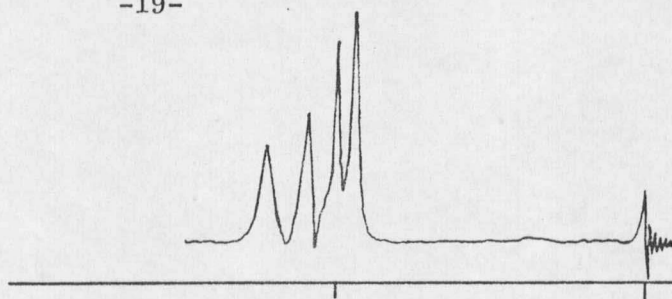


Figure 13: Deuterium exchange of 2-methylcyclohexanone.

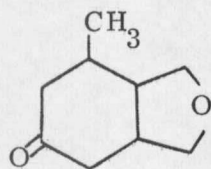
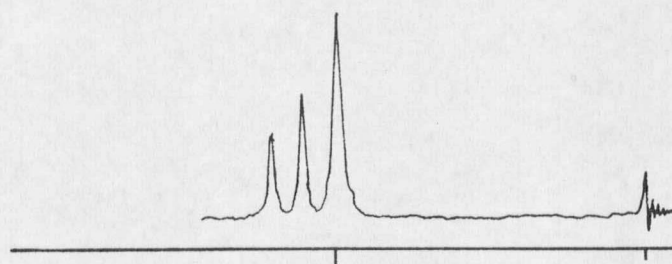
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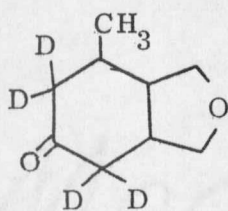
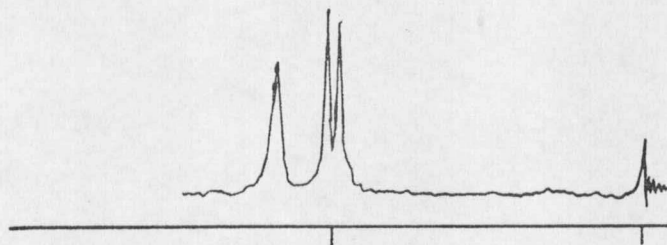
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11



10



12

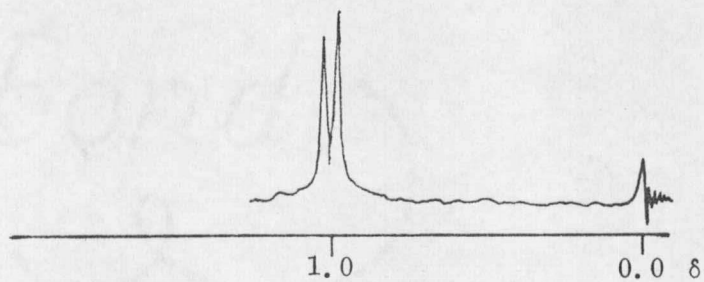


Figure 14 : Nmr study of dueterated system 9 and 10 .

On the basis of the information and subsequent further evaluation of the nuclear magnetic spectra the given structures were assigned to ketones (10) and (9).

Returning now to the quantitative results obtained from gas chromatography it was possible to evaluate hydroboration as a method for hydration. The desired ketone (10) was not the major product and at this point it was not possible to further consider hydroboration as a method of hydration.

The use of a more hindered hydroborating group provided a second method for hydration. This method of hydration using disiamylborane (bis-3-methyl-2-butylborane) has been reported in the literature by Brown²⁴. With a much larger group on the borane it was felt that this would hinder attack at the C-5 carbon.

Information provided in the literature shows that disiamylborane directs predominantly to the less hindered carbon atom. In two examples this is shown to be true²⁵ (see figure 15). Some work on simple cyclic systems have given contradictory results and will be further discussed at a later time.

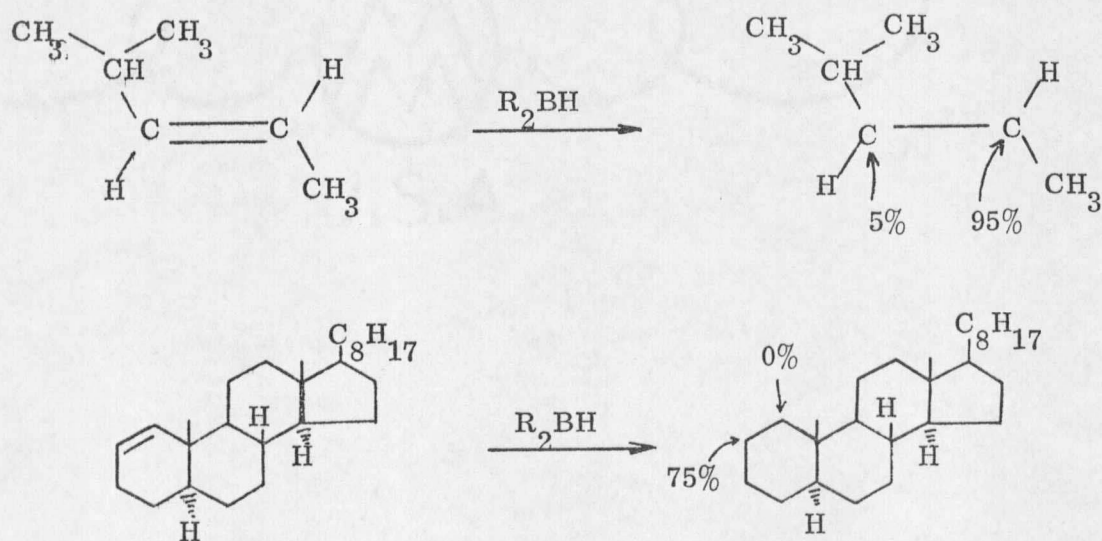


Figure 15: The Use of Disiamylborane for Hydroboration.

The disiamylborane was prepared in the same way as by Brown²⁶. The alkene was then subjected to hydroboration with disiamylborane under the same

conditions as were used in the literature²⁷.

Indeed, the results were in good agreement with those obtained by Brown and co-workers. The use of disiamylborane did shift the ketone product ratio towards the expected ketone (10). However, 10 was still not the predominate product as was desired. The methyl group did seem to play some role in the direction of attack but further study was still needed to determine how strong or important it was.

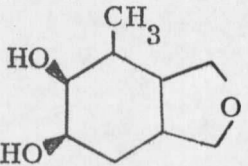
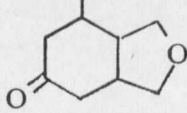
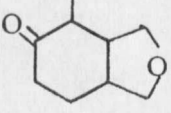
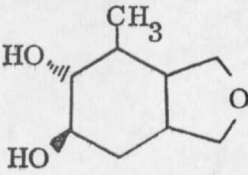
There is yet a third method for hydration of the alkene (3), the pinacol rearrangement. This method was selected largely because of a concurrent study being done on the pinacol rearrangement in our laboratory. The pinacol rearrangement does, however, provide a potentially easy and quick method for obtaining ketone products from the system being studied. The alkene (3) was readily converted to the alcohols needed for the pinacol rearrangement. Since it was easy to prepare both the cis and trans diols from the alkene it was felt both systems should be attempted in the rearrangement. The cis diol (13) was prepared by potassium permanganate oxidation of 3 in good yields. Preparation of the trans diol (14) system was achieved using the performic acid hydroxylation procedure.

The conditions under which the pinacol rearrangement should be carried out were not well established. Some recent work in this area in our laboratory

indicated variations in reaction conditions would change the product ratios. Qualitative analysis of ketone formation under various acid concentrations, using both the cis and trans isomers of cyclohexane diol, indicated that the optimum conditions involved acid concentrations of 80% or greater. Table 2 shows the results of the pinacol rearrangement under various conditions.

TABLE 2

Analysis of the pinacol rearrangement.

 <u>13</u>	Reflux $20\% \text{ H}_2\text{SO}_4$	 11%	 89%	Over- all Yield
	Room Temp. $\text{Con. H}_2\text{SO}_4$	None	None	40%
	Reflux $20\% \text{ H}_2\text{SO}_4$	None	Trace	
	Room Temp. $\text{Con. H}_2\text{SO}_4$	15%	85%	59%

It is easily seen from Table 2. that the results from the pinacol rearrangement were not very desirable. There were also many side products and in some reactions the starting materials were so decomposed that this method was discontinued.

The results up to this point were not very encouraging and an evaluation of the data at this time helped to decide the direction of ketone research pursuits.

The effect of the methyl group upon the formation of 3 is not a very strong one. In all three²⁹ of the hydrations tried there were nearly equal amounts of both ketones or in the case of the pinacol a larger percentage of 9. It would appear that the rigidity of the system is of little importance. The hydroboration experiments seemed to agree very well with what was reported in the literature.

Analysis of the pinacol rearrangement results; even though, they were not satisfactory as a synthetic method were very interesting. Considering the mechanism of the pinacol rearrangement and the major product from the reactions of the diols (13) and (14), it is possible to determine which carbonium ion would be the more favorable. Figure 16 suggests the mechanism to explain the predominate formation of 10. This mechanism would indicate that the more stable of the two possible carbonium ions is 15. Experimental results would

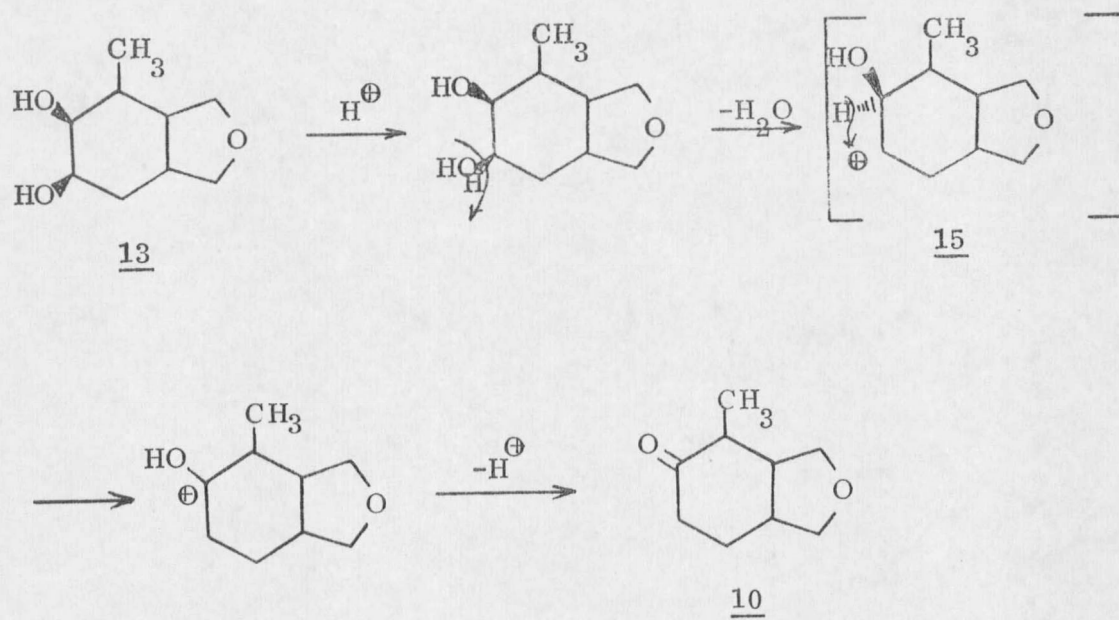


Figure 16 : Proposed mechanism for the pinacol rearrangement

also indicate that a carbonium ion at C-6 is more stable than at C-5 (figure 17).

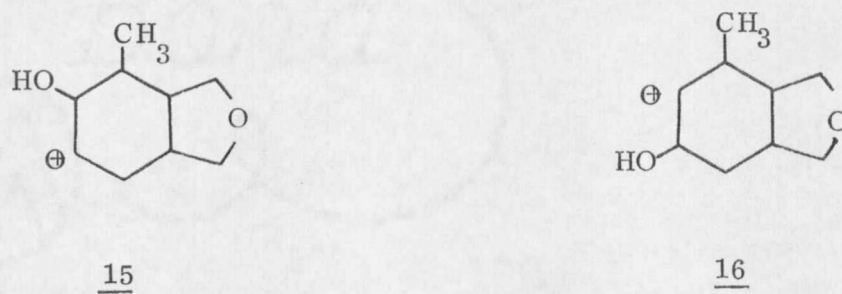


Figure 17: Carbonium ion stability.

A plausible explanation of these results would be that the oxygen of the furan ring is participating to produce an electronic effect that would stabilize this carbonium ion (figure 18). Further investigation of the system was necessary in order to determine the possible effects of the oxygen, and other research

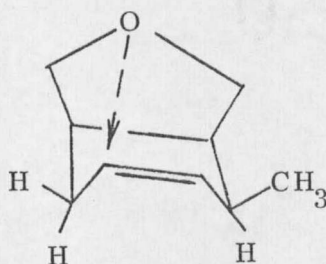


Figure 18: Model of 4-Methyl-cis-3a,4,7,7a-tetrahydrophthalan.

in our laboratory is trying to evaluate the effects of heteroatoms.

Oxymercuration provides another route for alkene hydration. This method has been shown to be an effective Markownikoff hydration technique. Oxymercuration is also a very desirable method of hydration because of the mild experimental conditions involved. It is very selective in its reactivity and will not interfere or react with any other functional groups³⁰.

The mechanism for oxymercuration has been under investigation for some time (figure 19). There has been some discussion as to whether the mercuric acetate complexes with the pi system of the double bond in the first step

or if there is a displacement of an acetate ion by one of the carbon centers of the double bond. However, at this point the mechanistic details of the oxymercuration reaction are not the focus of the research.

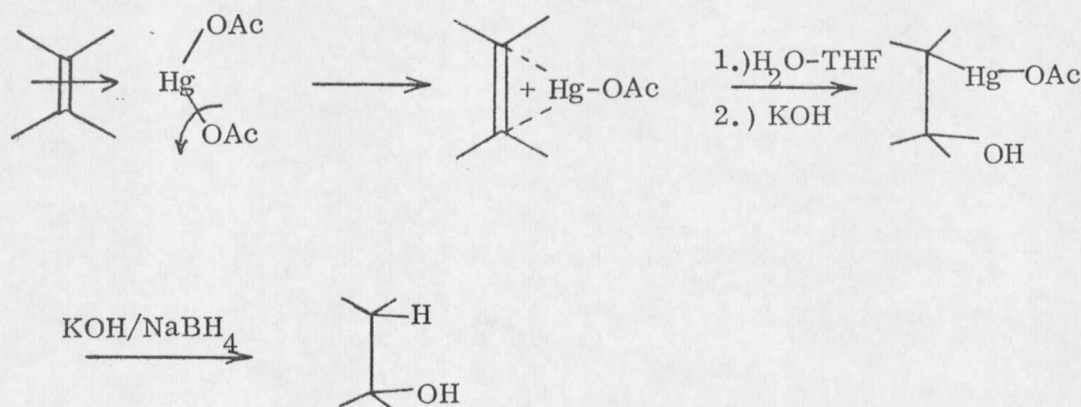


Figure 19: The process of oxymercuration — demercuration.

If there is a steric effect to displacement taking place in oxymercuration then this should be easily seen in a model system. The model of choice was 3-methylcyclohexene. Evidence from disiamylborane reactions would suggest that the center of higher electron density would be at C-2. Therefore, it would be predicted that for oxymercuration 3-methylcyclohexanone would be the major product.

The oxymercuration of 3-methylcyclohexene was carried out and the products were analyzed by gas chromatography. With both possible ketones available, determination of the products was very easy. As expected, the major

product was 3-methylcyclohexanone (figure 20). This method of hydration was

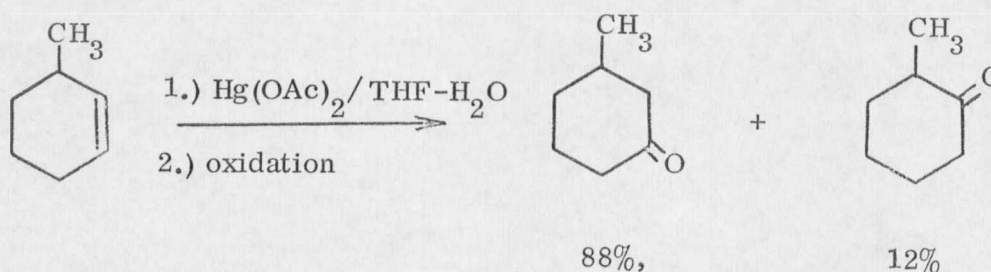


Figure 20: Oxymercuration of 3-methylcyclohexene.

next applied to 3. If the idea is correct that the bond is polarized towards C-5, it would be predicted that the major product of oxymercuration would be ketone (10). When 3 was subjected to hydration by oxymercuration the major product was the ketone (10) as predicted (figure 21). This method of hydration,

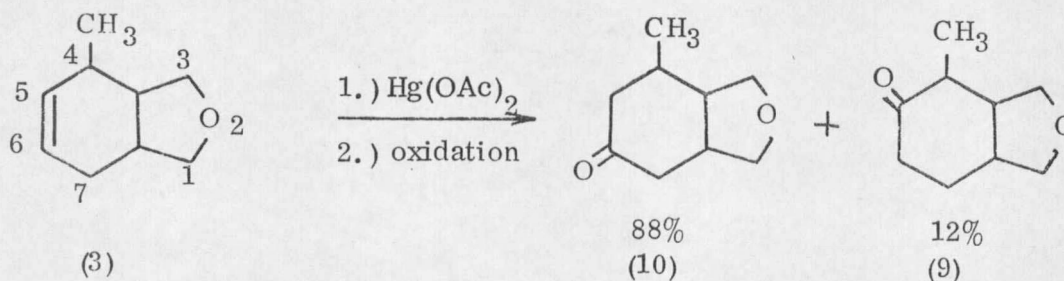


Figure 21: Oxymercuration of the alkene (3).

oxymercuration, then provides a reasonable means of obtaining large quantities of the needed ketone (10) and makes its purification by column chromatography relatively easy.

Before proceeding on to the question of ring expansion there was a desire to look further into the chemistry of the compound used as a model. This helped to clarify some of the results obtained in the other methods used for hydration.

Investigation of the hydroboration of 3-methylcyclohexene has been mentioned before as being studied by Brown, who found essentially equal addition of boron to C-1 and C-2³¹. Pasto in a more detailed analysis found that the addition trans to the methyl group was favored with the overall addition again being equal³² (figure 22). When the compound was subjected to hydroboration with disiamylborane there was no extreme difference between addition at C-1 and C-2; a considerable departure from examples in the acyclic systems³³. However,

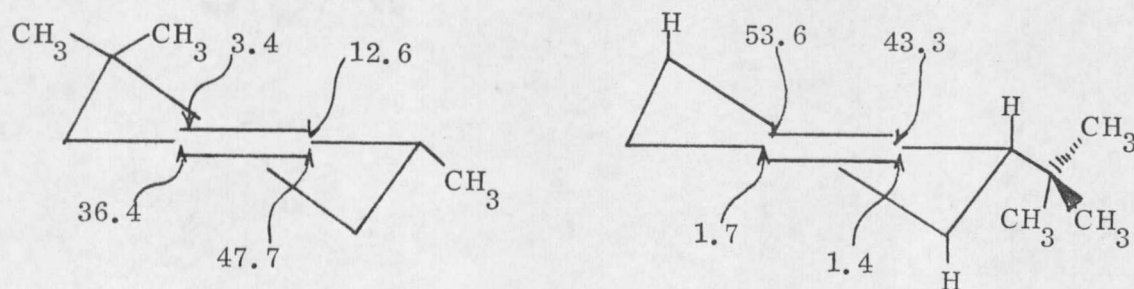


Figure 22: Pasto's work on Hydration of alkenes.

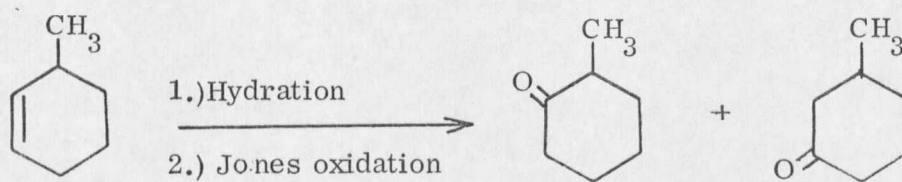
when Brown reacted 3,3-dimethylcyclohexene there was a steric interaction noted in the product ratio³⁴.

Since evidence gained from this model compound has a strong bearing on this research, re-evaluation of these reactions was undertaken. The pinacol rearrangement was not used due to the large number of side products which made the analysis of the ketones difficult and unreliable. Results are shown in Table 3. Good agreement was found in experiment 1 with both Brown³⁵ and Pasto's³⁶ results. However, the results of experiment 2 were not in agreement with those of Brown but can be well rationalized by a mechanism to be proposed later.

In all of the cases examined the methyl group has maintained its ability to direct addition both in the electronic and steric cases. This is particularly evident in the case of oxymercuration where it is evident that C-2 is much more capable of displacing the acetate group from mercuric acetate than C-1. This electronic effect, in combination with a seemingly small steric effect, can be rationalized by the concept of allylic strain³⁷, in which 3-methylcyclohexene takes the preferred conformation that has the methyl group in the axial position. In this A^(1,2) conformation the methyl group allows for bottom-side attack while also reducing steric interaction as is possible in A (figure 23).

TABLE 3

Hydration of 3-methylcyclohexene.



METHODS OF HYDRATION	PRODUCT RATIOS	
1) B_2H_6	54	46
2) Disiamylborane	67	33
3) Oxymercuration	12	88
4) Pinacol Rearrangement	No observed ketone products	

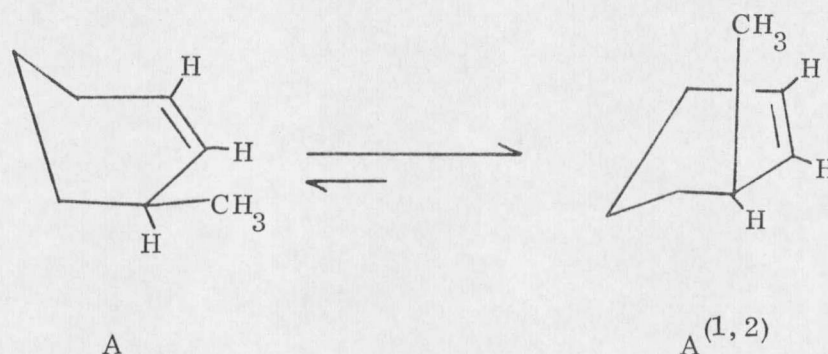


Figure 23: Conformational isomers of 3-methylcyclohexene.

Still, the methyl group can participate in its inductive effect making C-2 electronically the more favorable of the two addition sites. This argument is consistent with Brown's observation that 3,3-dimethylcyclohexene directs addition in predominantly one direction, because in the A^(1,2) conformation, one methyl group still creates a steric interaction (figure 24).

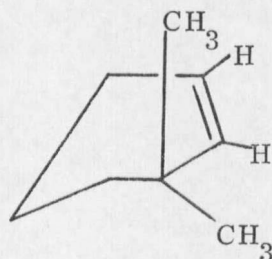


Figure 24: Methyl group interactions in 3,3-dimethylcyclohexene.

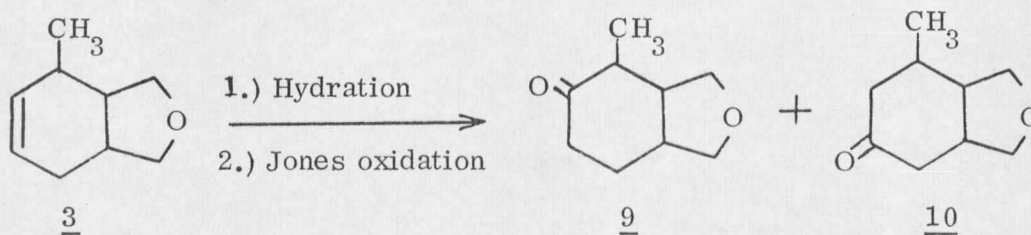
Returning now to the alkene (3) system, for which the combined results are listed in Table 4, it is interesting to note that in two out of the three cases the results were not in agreement with those of the simple 3-methylcyclohexene system. The model would suggest that the hydroboration reaction 2 should go predominantly in the direction of C-5 because there would still be the possibility of attack from the bottom side. In the case of oxymercuration since the higher electron center should be at the C-6 center because of the induction of electrons from the methyl group. However, results show that in neither case is this true. Why then are the results in such disagreement with the model system?

The only possible element that could influence this reaction would be an interaction caused by the oxygen atom. This effect has been referred to as a "supra-annular" interaction³⁸. If one analyzes the space filling model a diagram may be drawn as shown in figure 25. This supra-annular effect of the oxygen causes a shift in the electron density about the pi bond. Therefore the higher concentration of electron charge is at C-5 and this would cause the discrepancy between the model and the alkene (3).

The 50:50 mixture resulting from the reaction of 3 with diborane can be rationalized by a combination of: 1, little steric effect; 2, oxygen participation which might compensate for any small steric effect; and 3, the non-discrimination

TABLE 4.

Hydration of 4-Methyl-cis-3a,4,7a,7, tetrahydrophthalan.



METHODS OF HYDRATION		PRODUCT RATIOS	
1)	Diborane	60	40
2)	Disiamylborane	38	62
3)	Oxymercuration	18	82
4)	Pinacol Rearrangement	85	15

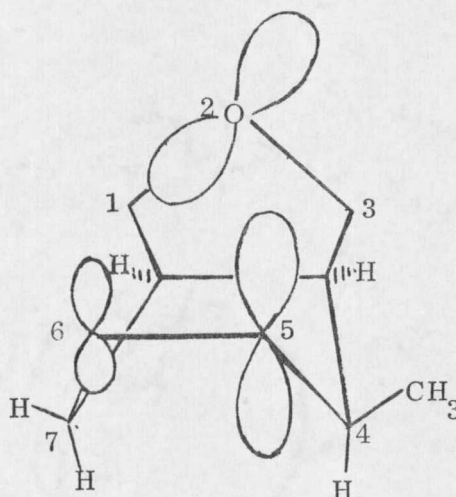


Figure 25: Effect of oxygen atom on alkene (3) system.

of the sterically small diborane and its relatively high reactivity. Considering only the steric effects, one would expect a slight favor of boron attack at C-6 with disiamylborane. However, the oxygen participation complexed with a "twist conformation" results in a slight preference of addition at C-5. In the reaction of mercuric acetate the mechanism would suggest that the carbon with the highest electron density would be the one that would displace the acetate ion. The supra-annular interaction of the ether oxygen, as already indicated has

shifted the electron density towards C-5. Thus, displacement would be by C-5 and the predominate ketone would be at C-6, which was the case. Finally, it is also possible to rationalize the results of the pinacol rearrangement. This reaction proceeds via a carbonium ion mechanism and the model would suggest that the C-6 carbon would be the more stable of the two possible ions and the major product would then be the C-5 ketone (9).

PART III

RING EXPANSION OF ALKENE

The next question involved in the project was that encountered in ring expansion. The proposed method was that using diazomethane to ring enlarge the ketone obtained from hydration. A large amount of the work in the literature has shown that ring expansion results in several possible products depending on the conditions³⁹ (figure 26). The diazomethane reaction with the ketone

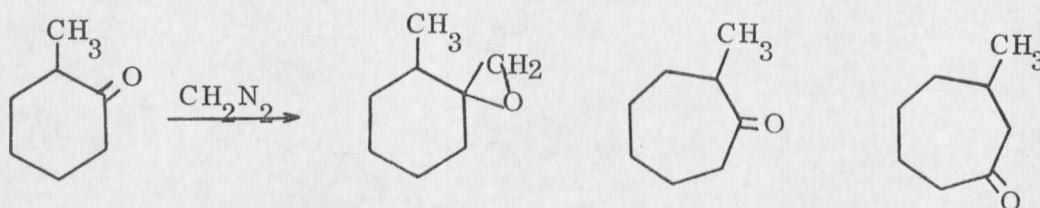


Figure 26: Ring expansion of methyl-cyclohexanone.

(10) would then result in two ketone products (figure 27). It was felt that if one of these ketones could be synthesized by an alternate method then the identification of the products would be easier. Ketone (19) was chosen because it was felt to be the easier of the two to synthesize. This feeling was in light of previous synthetic work by Mundy, and mentioned in the introduction. The only difference is in the two syntheses in the lack of one methyl group in the starting

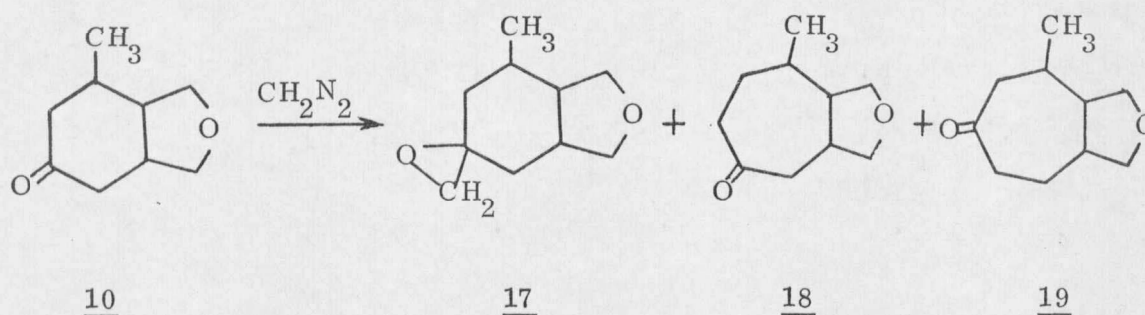


Figure 27: Ring expansion of the ketone (**10**).

materials. The approach to this synthesis is shown in figure 28, starting with the already available alkene (**3**).

The alkene (**3**) was treated with performic acid, followed by hydrolysis, to give the trans diol (**14**) in reasonably good yields. This diol was then cleaved with sodium bismuthate, according to the method of Rigby⁴⁰, to give an uncyclized aldehyde (**20**) that was immediately reduced with lithium aluminum hydride to the diol (**21**).

Infrared analysis of the crude aldehyde did indicate that the product was uncyclized, and further purification was not attempted due to the instability of this type of system.

The diol (**21**) was then converted to the ditosylate derivative (**22**). Purification of the uncyclized system was done at this point and the infrared analysis

proved it to be the expected ditosylate. Cyanide displacement of the tosylate in anhydrous dimethylsulfoxide resulted in the desired dicyanide (23) which was hydrolyzed to the diacid (24).

The pyrolysis of the diacid in the presence of barium hydroxide and powdered iron yielded the cycloheptanone ring system (25). Infrared analysis showed the loss of the acid function with the retention of the strong carbonyl peak (appendix, page 81). Gas chromatography showed the product to contain one major peak that had a retention time somewhat longer than the cyclohexanone systems. The mass spectrum of this system also showed it to have a mass weight of 168. It also formed a 2,4-dinitrophenylhydrazone derivative. The similarity in the fragmentation pattern of this compound (25) and the cyclohexanones (9) and (10) would suggest that indeed 25 is the cyclized compound.

Now having one of the ring expansion products it was possible to go ahead with the diazomethane ring expansion experiments. Previous work reported in the literature suggest that a catalyst is necessary to reduce the amount of epoxide formation and at the same time help in the ring expansion⁴⁰. Work was first done on a model system to insure that expansion was taking place. Reaction with methylcyclohexanone showed that when aluminum chloride was used in catalytic amounts and the diazomethane was generated in excess, ring expansion did take place (Table 5):

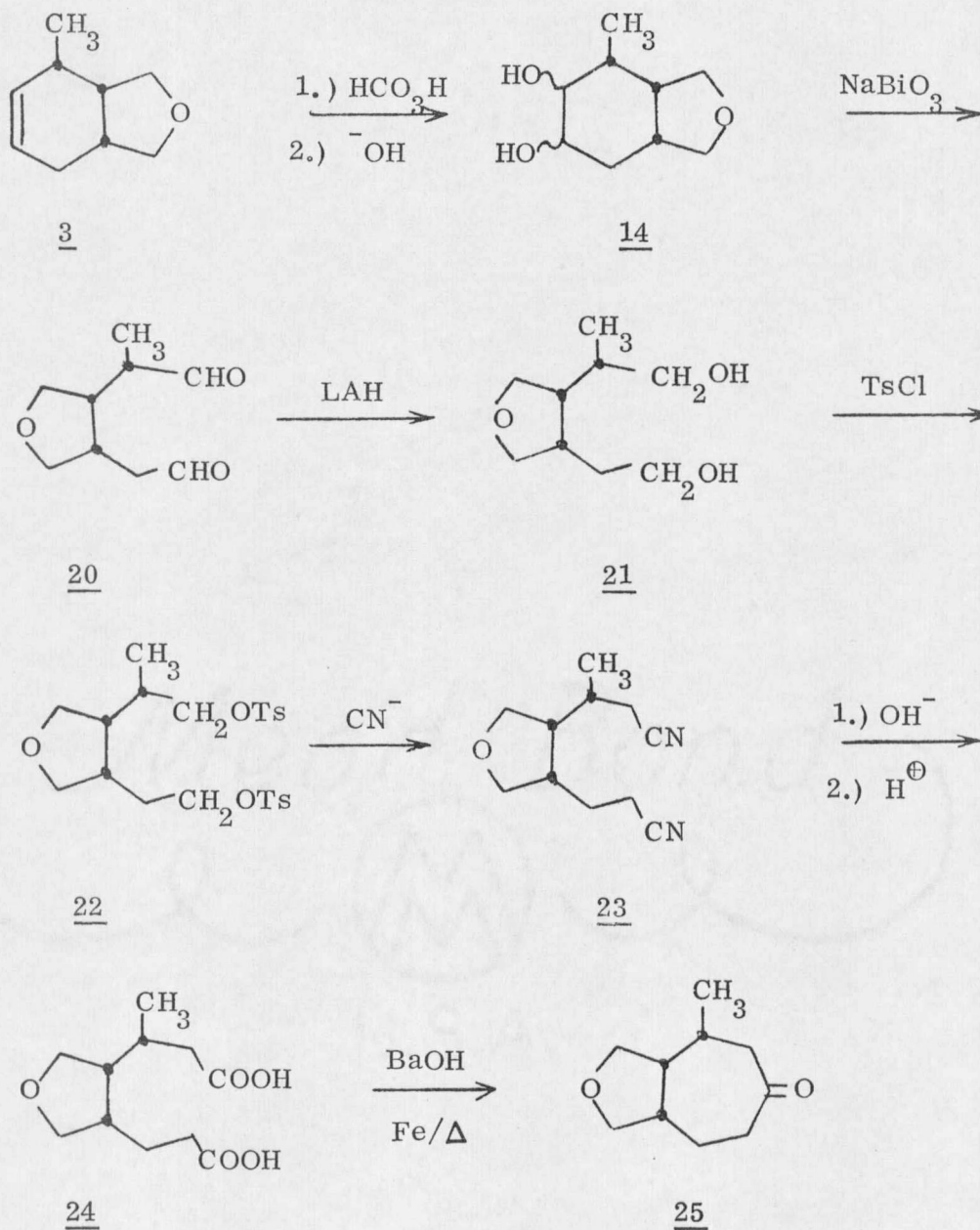


Figure 28 : Unambiguous synthesis of the expansion product (25).

TABLE 5.

Ring expansion of the model cyclohexanone.

<u>Catalyst</u>	<u>Diazomethane (mole/mole) CH₂N₂/C₆H₁₀</u>	<u>Type of CH₂N₂ addition</u>	<u>(hr.) Time before work-up</u>	<u>Solvent</u>	<u>Expansion Product</u>
BF ₃	1:1	indirect (a)	none	ether	none
BF ₃	1:10	indirect	none	ether	none
BF ₃	1:30	indirect	18	ether	none
BF ₃	1:30	direct (b)	18	ether	none
BF ₃	1:30	direct	18	ethanol	trace
AlCl ₃ (c)	1:30	direct	18	ethanol	20%
AlCl ₃ (d)	1:30	direct	18	ethanol	none
AlCl ₃ (e)	1:30	direct	18	ethanol	none

(a) Solution of diazomethane prepared and then a portion was added to the ketone.

(b) Diazomethane generated in situ with the ketone.

(c) Anhydrous AlCl₃ left open to the atmosphere for two days.(d) Anhydrous AlCl₃.(e) Unactivated AlCl₃.

Application of the ring expansion to 10 did indicate that there were indeed two expansion products. This was indicated by gas chromatographic analysis, which indicated that the synthesized ketone (25) and one of the expansion products (14) had exactly the same retention times. (Compounds 19 and 25 have now been established as the same.) The other peak was felt to be the other expansion product, and had a very similar retention time (figure 29). The mass

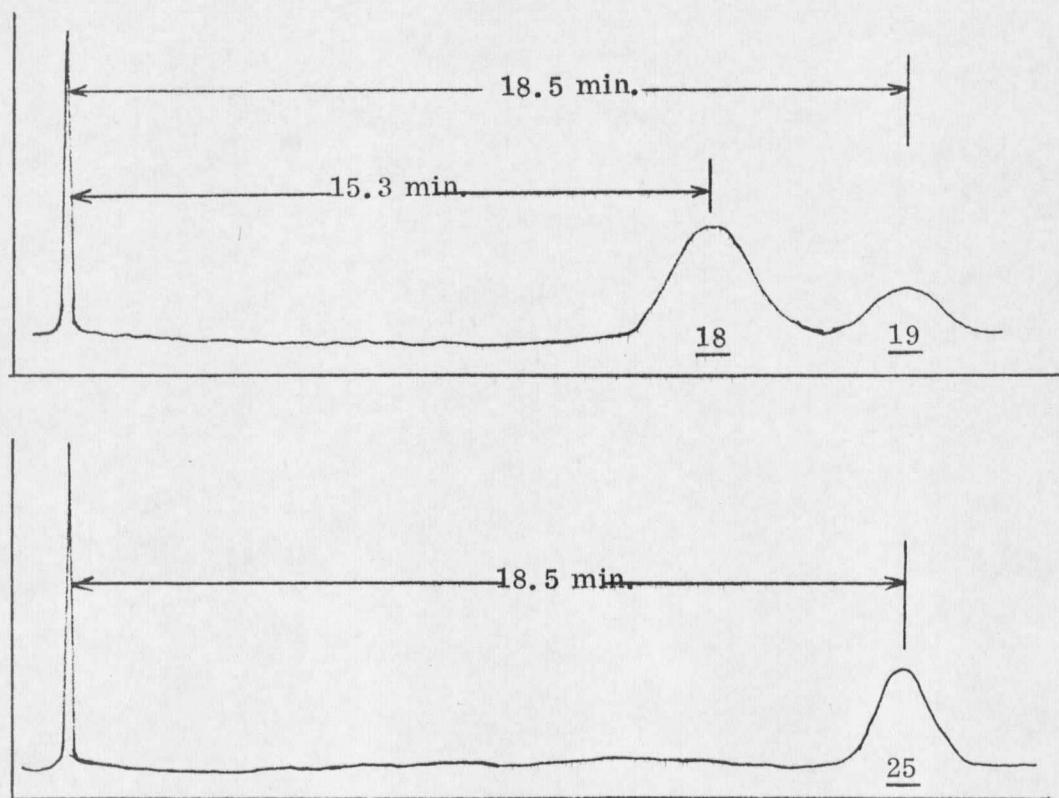
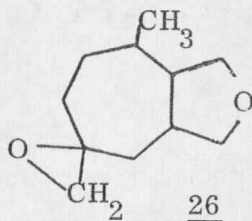


Figure 29: Comparison of gas chromatograms of expansion products.

of the expansion products showed both peaks to have exactly the same m/e

values; with the mass spectrum of the second peak having the same fragmentation pattern as that of the synthetic ketone (appendix, pages 90 and 91). Gas chromatographic collection of these ring expanded ketones and the subsequent infrared analysis showed both peaks to contain the strong carbonyl and retention of the tetrahydrofuran ring system. Nuclear magnetic resonance of the desired ketone showed the product to contain the correct spectrum for the assigned structure (appendix, page 85). It is also interesting to note that there was no epoxide formed that corresponded to the m/e of the proposed epoxide (17). The mass spectrum indicated a compound that had a mass ion of 182, however, there is some indication that this may be an epoxide of the structure (26). This



idea is a result of the gas chromatogram which shows this compound to have a much shorter retention time than the ketones (9) and (10) (figure 30). The possibility of the compound being an eight membered ketone system could be eliminated on the basis of a short retention time. A high molecular weight ketone such as this should be retained until after ketones (18) and (19) have come off the column. The mass spectrum (appendix, pages 90 and 91) is very similar to that of the expanded ketones. The infrared spectrum shows no carbonyl

absorption which helps to eliminate the idea of a ketone.

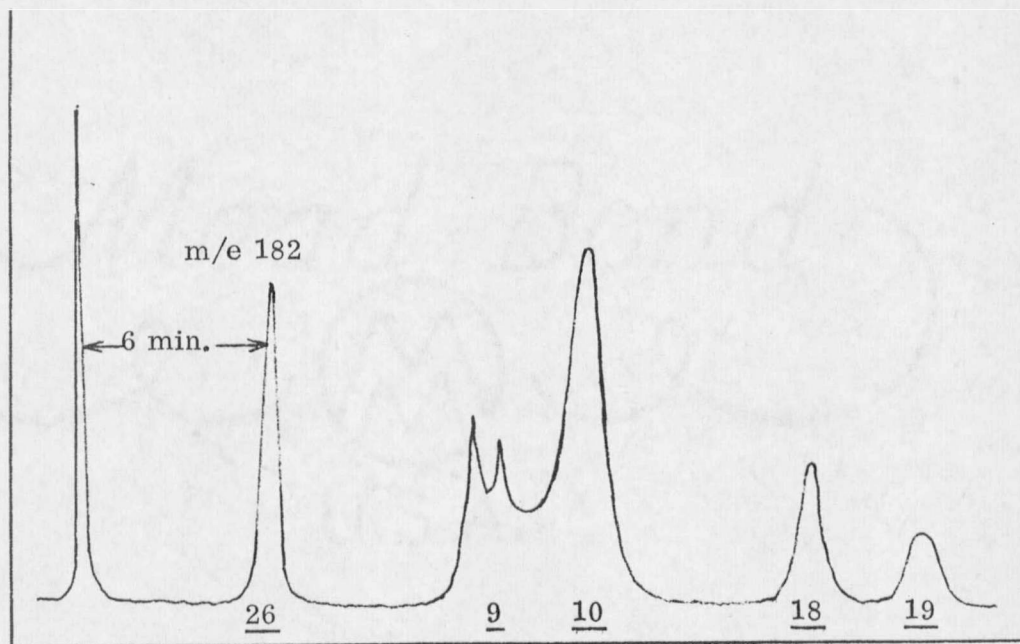


Figure 30: Gas chromatogram of product obtained from ring expansion.

Results would indicate that the possible ring expansion of ketone (10) would not provide a useful means for the preparation of the desired cycloheptanone system. The desired expansion product was the major isomeric product, but the overall yield of this ketone was not very high (less than 5%). Why doesn't the ring expansion work? One might suggest that it is due to the steric hinderance to attack at the carbonyl carbon, or to further supra-annular interaction. Also, it is not unreasonable to suggest that a

necessary 1,3 interaction (either $C \cdots C$, or $C \cdots O$) in the transition state might inhibit the reactivity. However, at this time there is not enough evidence to support either possibility.

PART IV

The effects of the oxygen heteroatom was of interest because of its directive effects. Another heteroatom that was of interest was the sulfur atom. Since the synthesis of (28) was relatively easy, we looked into its effect on oxymercuration. The hydration (figure 31) was carried only as far as the alcohols (29) because oxidation of the alcohols would have resulted in the destruction

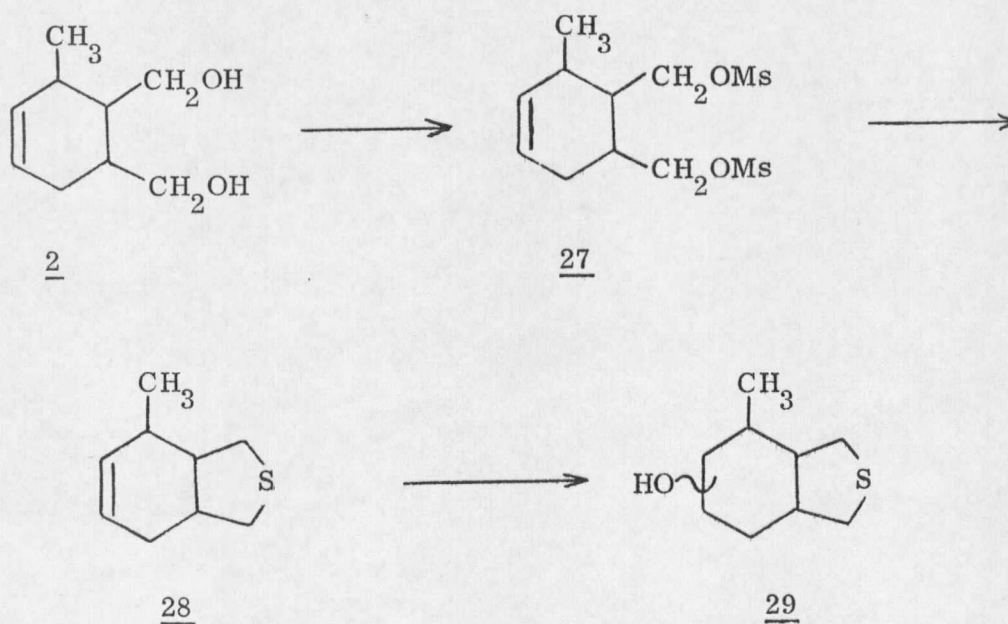


Figure 31: Synthesis of sulfur system alcohols (29).

of the tetrahydrothiophene ring. Therefore the directive effect was compared by using the alcohols of the oxygen system as standards. Gas chromatographic retention times of the alcohols of the sulfur system were similar to those of

the oxygen system. As it turned out the sulfur system alcohols were crystal so purification and then gas chromatographic analysis gave the unambiguous information on the alcohol ratios (figure 32).

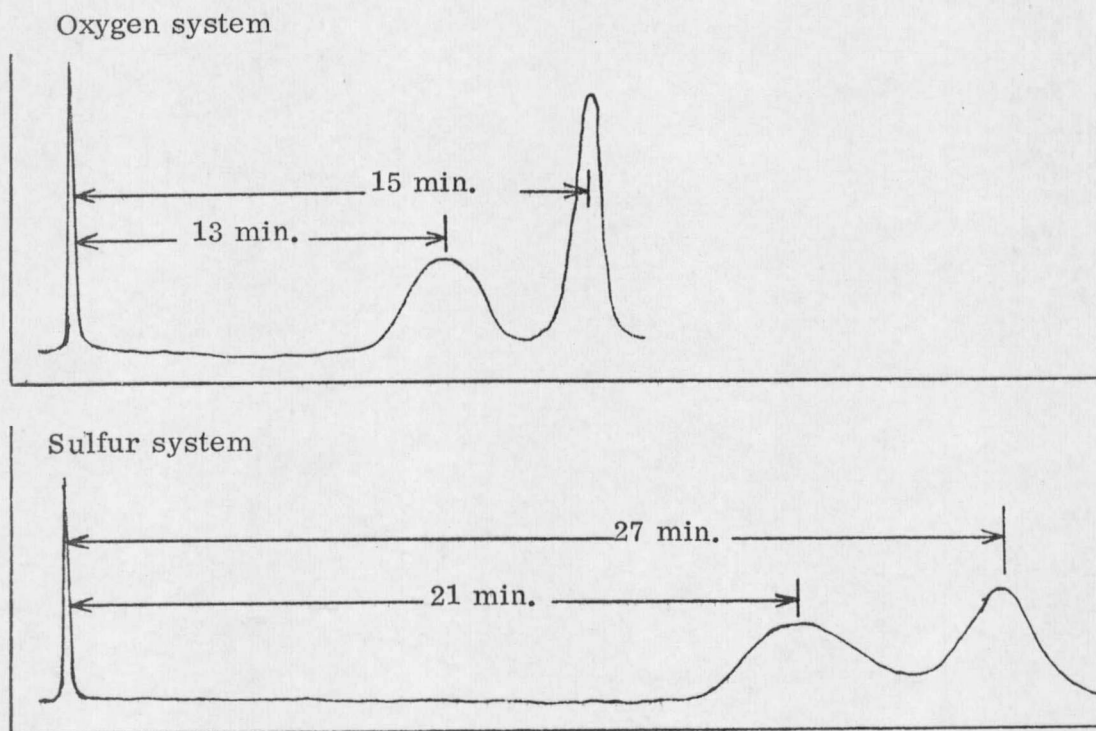
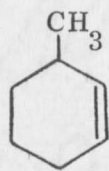


Figure 32: Comparison of alcohol retention times.

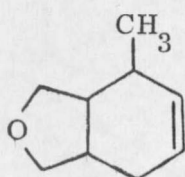
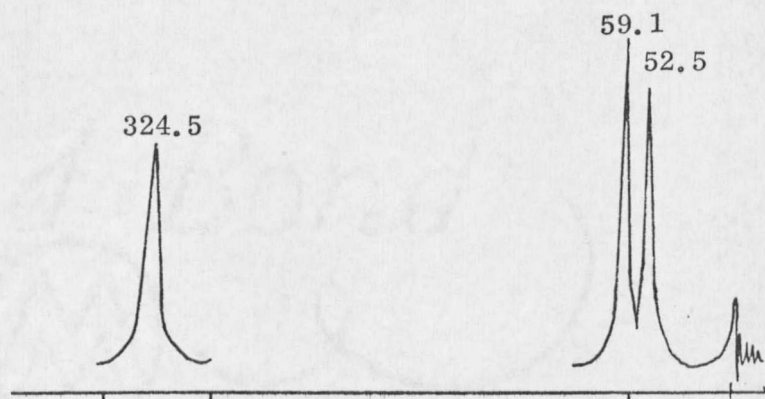
If one assumes that the isomer retention time in the gas chromatograph of the oxygen system can be compared with the sulfur compound, then the oxymercuration of the sulfur compound would give approximately an equal molar ratio of the alcohols.

The results of the sulfur system fit very well with the other information. If one extends the idea of the electrons of the oxygen system to that of the sulfur it is found that the d orbitals of the sulfur atom will be influencing the electrons of the double bond. Since these orbitals are a little larger and will encompass a wider area the directive effect will be decreased. At the same time it would be expected that the reactivity of the sulfur compound would be slower than any others. This was qualitatively observed in that the oxygen system was completed in several minutes while the sulfur system was completed in two hours. Other evidence supporting this idea was obtained through a nuclear magnetic study of methylcyclohexene (30), alkene (3), and the sulfur alkene (28). It was significantly noted that there was a shift in the alkene protons with the increasing size of the heteroatoms (figure 33). This would say that the heteroatom is shielding these protons and causing the shift upfield.

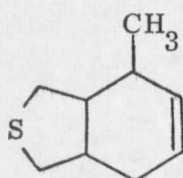
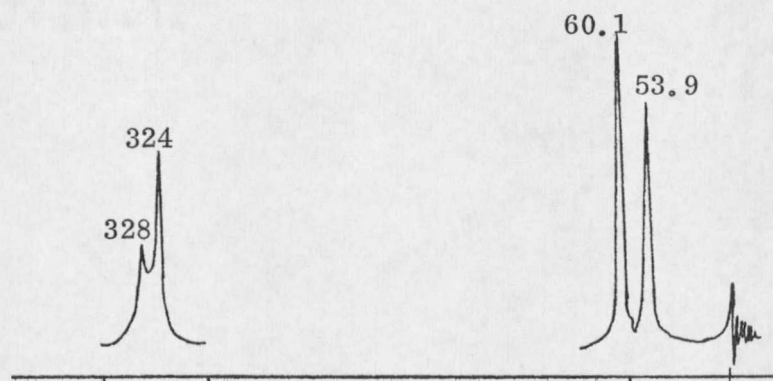
At this time we are not prepared to fully discuss the mechanism or the stereochemical consequences of the reaction. However, the known sulfur-mercury affinity as evidenced by denaturation of S-containing proteins, coupled with the reasonable yields of alcohol product obtained, leads to the interesting problem of what is the role of the heteroatom in influencing chemical reactivity.



30



3



28

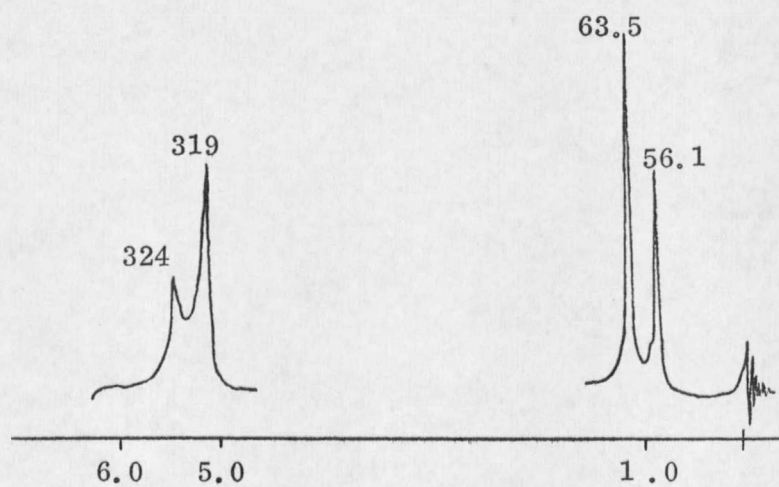


Figure 33 : Nmr comparison of compounds in cps.

PART V

SYNTHESIS OF THE SEX ATTRACTANT BREVICOMIN

As part of the program concerned with oxygenated systems, work in our laboratory showed that in the absence of water an internal hydroxyl group could participate in the oxymercuration reaction (figure 34).

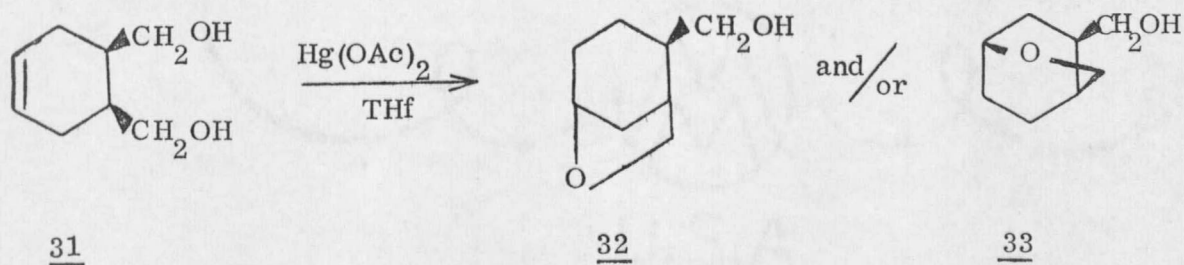


Figure 34: Internal cyclization with mercuric acetate.

Since 32 bears a similarity to the insect sex attractant, brevicomin (34), we undertook a simple synthesis of this important compound (figure 35).

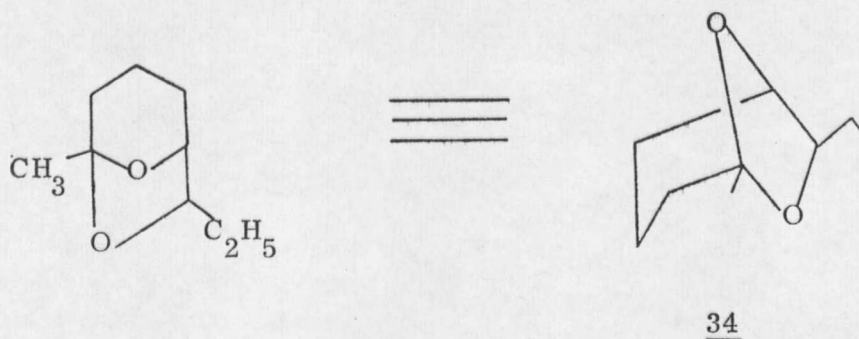


Figure 35: The sex attractant brevicomin.

This sex attractant, brevicomin, is released by the bark beetle, Dendroctonus brevicomis. There are many reasons for this interest; the major one being that this beetle alone is responsible for the destruction of the equivalent of five billion board feet of timber each year⁴². This figure represents about six times the amount caused by fire. At the present time there is no effective control of these beetles.

The process through which the destruction takes place begins with the attack of a few bark beetles upon the trees which is then followed by a large secondary invasion which eventually kills the tree. While the initial beetles are boring into the tree to construct a nuptial chamber, they excrete frass, a mixture of fecal pellets and wood fragments. Contained in the frass is an attractant which causes the secondary invasion. This attractant is produced by the female and it attracts the male.

A considerable amount of research was carried out to try and isolate the attractant and characterize its structure in hopes that it might be used in some way to control these beetles.

The identification of the attractant was accomplished by isolation of 2 mg of the active compound from 1.5 Kg of frass. It was identified by R. M. Silverstein in 1968⁴³.

Brevicomin has recently been synthesized by two independent methods.

Silverstein⁴⁴ (figure 36) was the first to make this compound and it was later synthesized by H. W. Wasserman⁴⁵ (figure 37). In both cases the syntheses are relatively long and involved with a few chemicals that cause the expense of these methods to be rather high.

It was felt that with the similarities between the cyclized compound (32) and brevicomin (34) that we might be able to approach the synthesis of brevicomin in a less expensive way with fewer steps. The synthesis involved the synthetic route shown in figure 38.

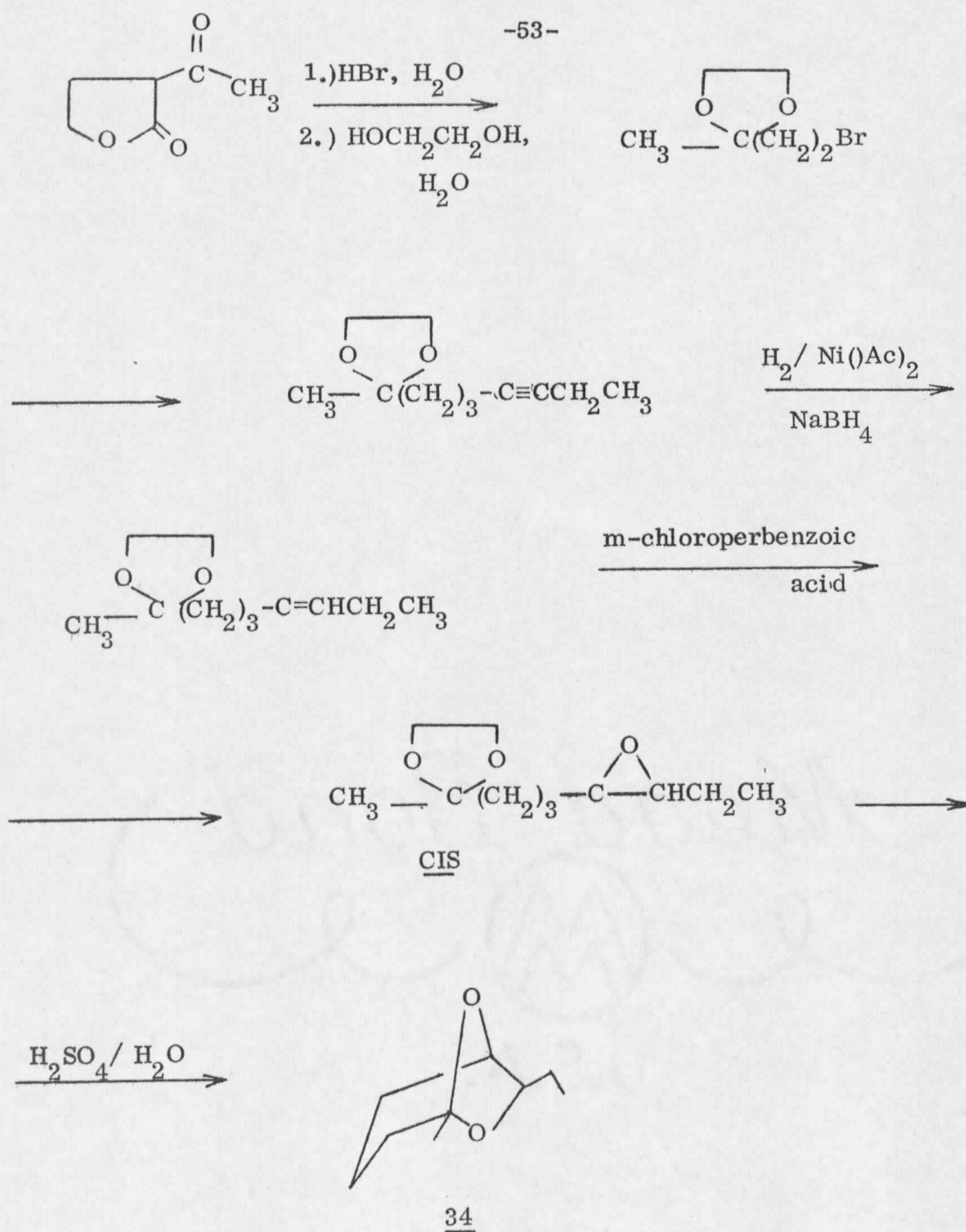


Figure 36: Silverstein's synthesis of brevicomin.

-54-

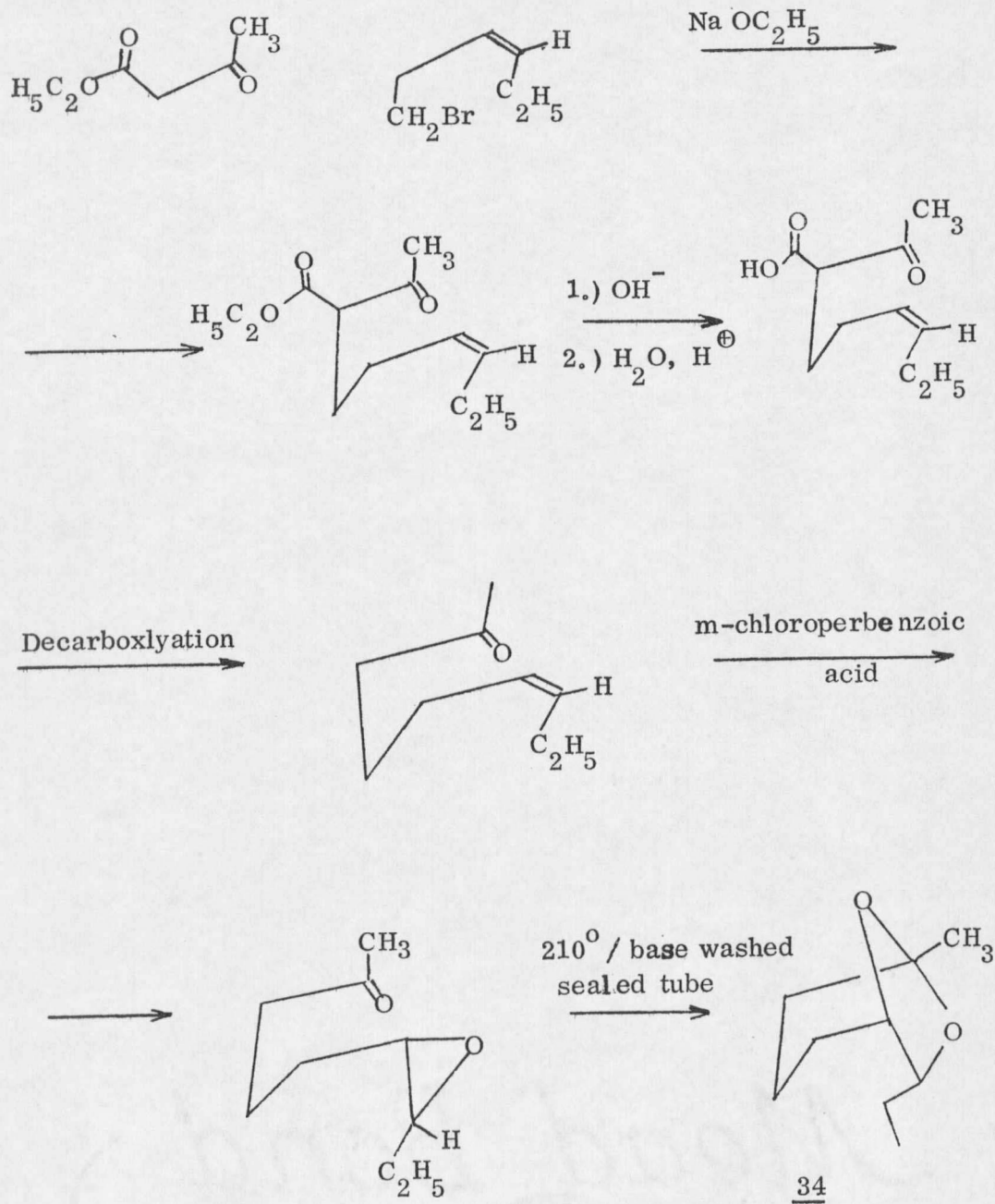


Figure 37 : Wasserman's synthesis of brevicomin

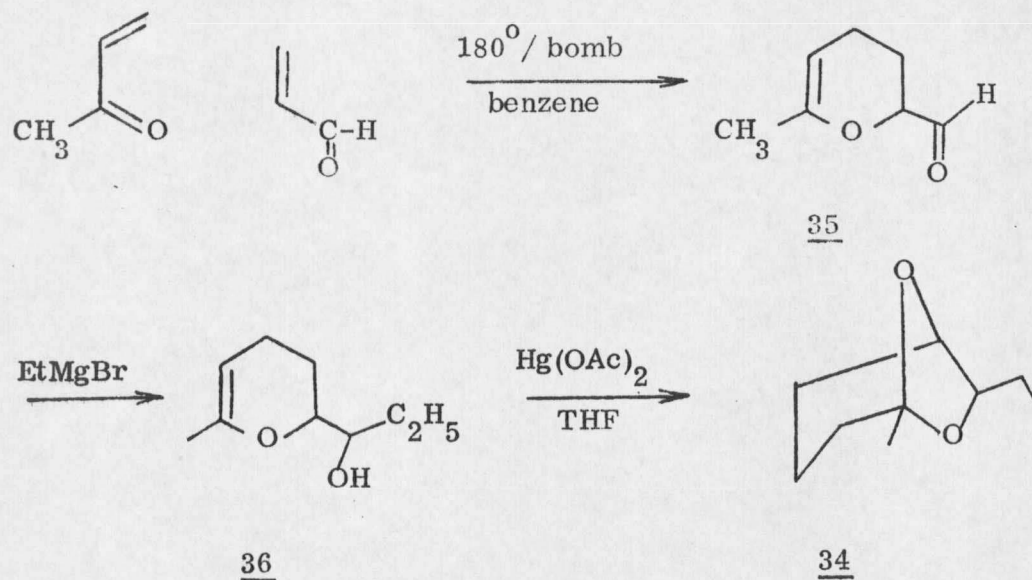


Figure 38. Synthesis of brevicomin

The two starting materials acrolin and methyl vinyl ketone, which are both relatively inexpensive, would through a Diels-Alder reaction lead to the pyran derivative (35). The conditions under which the Diels-Alder reaction would result in the desired product were established after some experimentation (Table 6). Systems very similar to these have been made by Buchi⁴⁶. Analysis of the product from this reaction by gas chromatography showed three strong peaks. These peaks might be attributed to the possible products shown in figure 39. This mixture of aldehydes and ketones

TABLE 6.

Diels-Alder reaction for formation of 2-carboxaldehyde-6-methyl-3,4-dihydro-2H-pyran.

Acrolein (g)	Methyl Vinyl Ketone (g)	Benzene Solvent (ml)	Time (hr.)	Temp. (°C)	Results
5	10	--	1	180	Alcohol present
5	10	--	2	180	Low yield (0.5 g)
5	10	25	2	180	yield (2 g)
10	15	25	2	180	yield (6 g)
30	5	80	1.5	180	yield (8 g)
30	15	80	2	180	yield (18 g)

was carried on to the next step without further attempt at separation.

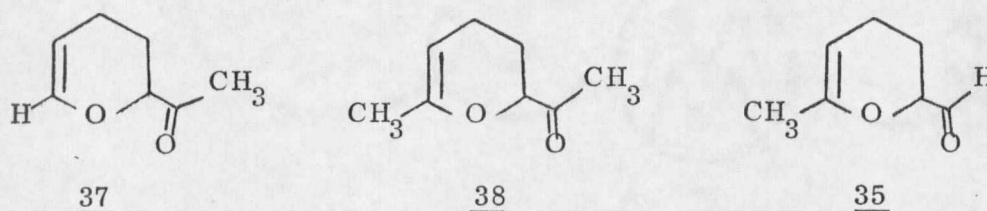


Figure 39: Possible products from the Diels-Alder reaction.

The Grignard addition to the carbonyls was carried out and the alcohol products were isolated without any complications. Again, gas chromatography of these alcohols showed there to be three components.

Oxymercuration in the absence of water nicely converted the alcohol product to a cyclic system. Gas chromatographic comparison of a known sample of brevicomin (obtained from Jim Lotan, U. S. Forest Service) showed the product to contain brevicomin. Separation of a sample and the instrumental analysis of it showed brevicomin to be identical with the synthesized compound (infrared, nuclear magnetic resonance, and mass spectrography; appendix, pages 82, 86, and, 92.

The overall yields at the present time are not considered to be at the optimum level but with a little further work it is felt it can be increased.

PART VII

EXPERIMENTAL SECTION

The infrared spectra were recorded on a Beckman IR-5, using polystyrene as the standard. NMR spectra were recorded on a Varian A-60 using TMS as an internal standard and deuteriochloroform as the solvent. The melting and boiling points are uncorrected and are in degrees centigrade. Gas chromatographic analysis were performed on an F & M Model 400 unit, using a hydrogen flame detector and Disc integrator. Analytical data followed by (*) were kindly obtained from Professor Krapcho, and have not been reported in the literature.

Cis-3-Methyl-4-Cyclohexane-Cis, Cis-1,2-Dicarboxylic Acid Anhydride (1):

In 50 ml of benzene, (52 g, 0.76 mole) of piperidine was dissolved. The mixture was stirred and heated to a gentle reflux. A few crystals of iodine were added until a slight red color remained. To the mixture was added maleic anhydride (52 g, 0.53 mole) dissolved in 200 ml of benzene, over a three hour period. After the addition had been completed the solution was allowed to reflux for an additional three hours. The excess benzene was then removed by reduced pressure distillation. The concentrated mixture was allowed to remain at room temperature overnight, after which a solid had formed. This crude material was then filtered and washed with cold ethanol, to remove the excess benzene and iodine. The resulting white crystals (51 g, 97%) had a melting

range of 61-62° (lit.⁴⁷, 61°).

Cis-3-Methyl-4-Cyclohexene-Cis, Cis-1,2-dimethanol (2):

The anhydride (60.0 g, 0.36 mole) was dissolved in 600 ml of anhydrous ether. The solution was added during a five hour period to a refluxing solution prepared from lithium aluminum hydride (15.2 g, 0.40 mole) in 600 ml of anhydrous ether. When the addition was completed, the mixture was refluxed for an additional 24 hours. After this time, the reaction mixture was then cooled, and sufficient wet ether was added to hydrolyze the aluminum salts. A 100 ml saturated aqueous solution of Rochelle salts was then added. The mixture was stirred for an additional hour and the salts were then filtered from the solution.

The ether filtrate was dried with magnesium sulfate and concentrated at reduced pressure (0.5 mm Hg), yield 33.0 g (59%).

Infrared analysis showed a strong broad peak for the -OH and also that no carbonyl remained in the product.

4-Methyl-cis-3a,4,7,7a-tetrahydrophthalan (3):

In 40 ml of dry pyridine was dissolved the diol (2), (21 g, 0.13 mole). This solution was heated to reflux while a solution of tosylchloride (38 g, 0.2 mole) in 40 ml of pyridine was slowly added. The reaction mixture was allowed to remain at reflux for about 12 hours, after which time it was cooled and poured over an ice-sulfuric acid slurry. The product was extracted with

pentane and was distilled to yield 14 g (73% yield) of a water-clear liquid having a boiling range of 44-48° at 0.2 mm Hg. The infrared spectrum (KBr plate) showed the characteristic ether linkage of tetrahydrofuran derivatives at 9.2μ (1087 cm^{-1}).

Anal.(*) Calcd. for $\text{C}_9\text{H}_{14}\text{O}$: C, 78.21; H, 10.21

Found: C, 78.00; H, 10.14

Hydration of (3) by Hydroboration:

The alkene (3.49 g, 0.24 mole) was dissolved in 15 ml of dry tetrahydrofuran to which sodium borohydride (1.43 g, 0.37 mole) was added. The reaction mixture was placed under nitrogen atmosphere after which borontrifluoride etherate (9.3 g, 0.065 mole) was slowly added. The reaction was performed at 0°. Hydrolysis of the boron complex was affected by adding 10 ml of water saturated ether, followed by 5 ml of water. A solution of 4M NaOH (10 ml), followed by 10 ml of 30% hydrogen peroxide completed the hydrolysis. The reaction mixture was allowed to warm to room temperature and stir for 12 hours. Extraction with ether yielded the crude alcohol mixture. The alcohols were placed in an Erlenmeyer flask with 20 ml of analytical grade acetone. This flask was placed in a water bath so as to maintain the solution at 25°. To this was added dropwise the Jones reagent; made up to 50 ml with water, until an orange-brown color remained. The mixture was then extracted three times

with methylene chloride and back extracted twice with water. The methylene chloride was then dried with magnesium sulfate and reduced in volume, yielding the ketones (9) and (10) in almost quantitative yield.

The ketones could be separated on a 6 foot x 6 mm glass column packed with 20M carbowax on 30/60 mesh firebrick or by column chromatography utilizing a 30 mm x 60 cm water cooled column packed with silica gel (14 g silica gel G, 30 ml of H₂O, activated for 45 minutes) and eluted with solvent (chloroform : ether : pentane : 55:28:17). The identity of 9 was established by deuterium exchange, resulting in the loss of the methyl doublet. No distinguishing features could be noted in the infrared spectrums. The NMR spectra of the ketones were consistent with the assigned structures.

The 2,4-dinitrophenylhydrazones of 9 and 10 were prepared:

10 ml. 164-5 and 9 mp. 176-7

Anal: Calcd. for $C_{15}H_{18}N_4O_5$: C, 53.89; H, 5.43

Found: 10 C, 53.91; H, 5.31

9 C, 53.92; H, 5.55

Deuteration of 2-methylcyclohexanone:

A gas chromatographically purified sample of 2-methyl-cyclohexanone (0.25 g) was stirred with 2 ml of deuterium oxide at room temperature, to which had been added 500 mg of sodium. This reaction mixture was stirred for

24 hours.

The aqueous solution was extracted three times with carbon tetrachloride and then dried over sodium sulfate. The extracts were then concentrated to the point at which resonance spectrum could be taken.

The above procedure was also used for deuterium exchange of the ketones (9) and (10). The amount of sodium, however, was reduced to 250 mg.

Preparation of Bis-3-methyl-2-butylborane (disiamylborane):

In a three neck 500 ml flask equipped with a condenser and dropping funnel, was placed 80 ml of dry monoglyme, 23.1 g (0.33 mole) of 2-methyl-2-butene in 20 ml of dry monoglyme and 4.7 g (0.125 mole) of sodium borohydride. The flask was placed in an ice-bath and the system purged and placed under nitrogen atmosphere. Then 23.5 g of boron-trifluoride etherate was added dropwise over a 30 minute period.

The semi-solid reaction mixture was permitted to remain an additional 15 hours at 0°.

The hydroboration with disiamylborane of the alkene was then carried out in the usual manner followed by Jones oxidation. The product was then subjected to gas chromatographic analysis showing the products to be 38% 9 and 62% 10.

4-methyl-cis-5,6-hydroxy-cis-3a,4,7a,-hexahydrophthalan (13):

The alkene (3) (4 g, 0.03 mole) in 42 ml of water was stirred vigorously and to this was added a solution of potassium permanganate (4.6 g in 100 ml of water) at a rate so as to maintain the temperature at 5°. After the addition was completed the mixture was stirred for 15 minutes and then left to stand at room temperature overnight.

The water solution was extracted three times with dichloromethane and the concentration of this solution yielded (2.5 g, 50%) of a crystalline compound with a melting range of 92-4°.

The crude product was recrystallized from chloroform and skelly B. to give a white crystalline product with a melting range of 99-100°. The infrared spectrum (potassium bromide pellet) exhibited a broad, strong -OH region.

Anal: Calcd. for C₉H₁₆O₃: C, 62.76; H, 9.37

Found: C, 63.17; H, 8.95

Mass spec. m/e: 172

4-methyl-trans-5,6-hydroxy-cis-3a,4,7a,-hexahydrophthalan (14):

The alkene (3) (11.1 g, 0.08 mole) was added dropwise to a stirred and cooled solution of performic acid (prepared from 13 g of 31% hydrogen peroxide and 55 ml of 90% formic acid). The temperature of the mixture was maintained at 40° during the addition. This mixture was then stirred for an additional 20

hours at room temperature.

The excess solvent was removed by vacuum distillation (water aspirator), with slight heating. A solution of sodium hydroxide was added to the remaining viscous solution until it was basic. The basic mixture was stirred overnight.

The entire mixture was continuously extracted with methylene chloride overnight. The solid was filtered from the solution and rotary evaporation of solution yielded some additional product.

The pure trans-glycol (weight 8 g, 70% yield) melted at 125-7°.

The infrared spectrum (potassium bromide pellet) showed a strong -OH stretch at 2.92 μ (3425 cm^{-1}).

Anal:(*) Calcd. for $\text{C}_9\text{H}_{16}\text{O}_3$: C, 62.73; H, 9.36

Found: C, 62.96; H, 9.58

Procedure for Pinacol Rearrangement

In a 250 ml flask with a reflux condenser was placed the glycol (13) (4.2 g, 0.02 mole) in 30 ml of 20% sulfuric acid. This mixture was then stirred at reflux temperature for two hours. The solution was cooled and diluted with 20 ml of water. The aqueous solution was extracted three times with dichloromethane and the combined extracts were dried over sodium carbonate. Rotary evaporation of the solvent yielded a dark brown oil.

The gas chromatographic analysis of the product showed it to contain no

significant amount of ketone products.

In a small flask was placed the glycol (13) (0.2 g, 0.001 mole) and to this was added 1 ml of concentrated sulfuric acid. To the mixture was then added 5 ml of water and then extracted three times with dichloromethane. The extracts were dried over sodium sulfate and concentrated. The gas chromatographic analysis of the product showed a 40% yield of ketones in an 98:11 ratio of 9 to 10.

The glycol (14) (0.1 g, 50 millimoles) was placed in a small flask and to it was added 1 ml of 20% sulfuric acid. This mixture was stirred at an oil bath temperature of 120°. The mixture was worked up in the same manner as the previous reaction of this type. The gas chromatograph showed only a small amount of the ketone (9) and several other unidentifiable compounds.

The glycol (14) was then subjected to the same procedure as that used for the glycol (13) in the presence of concentrated sulfuric acid at room temperature. Gas chromatographic analysis of the product obtained from (14) showed a yield of 59% in the ratio of 85:15 for the ketones (9) and (10) respectively.

Oxymercuration

The alkene (3) (13.8 g, 0.1 mole) was added to a stirred mixture of 31 g of mercuric acetate in 100 ml of water and 100 ml of tetrahydrofuran. The

reaction mixture was stirred until the yellow color had disappeared and then an additional five minutes. The flask was placed in an ice bath and 100 ml of 3M potassium hydroxide was added followed by a solution of 1.9 g of sodium borohydride in 100 ml of 3M potassium hydroxide. This mixture was stirred until a grey-colored solution was obtained and elemental mercury was observed. At this time 100 ml of a saturated solution of sodium chloride was added. The mixture was extracted three times with dichloromethane and the solution concentrated to yield the crude alcohols. Gas chromatographic analysis showed the ratios to be 18% (9) and 82% (10).

Hydration of 3-methylcyclohexane

The hydroboration of 3-methylcyclohexene (30) (0.5 g, 52 millimoles) was carried out in the same manner as that procedure for the hydroboration of the alkene (3). The gas chromatographic analysis of the products showed the ketones (a) and (b) to be in the ratio of 46 : 54.

The hydroboration, using disiamylborane, of 3-methyl-cyclohexene (30) (0.5 g, 52 millimoles) and using 60 ml of a 0.165 molar solution of disiamylborane, was accomplished in the same manner as that procedure used on the alkene (3). The gas chromatographic analysis of the ketone products showed a 33 : 67 ratio of a and b.

The oxymercuration of 3-methylcyclohexene was done in the same

manner as described for the alkene (3). Analysis by gas chromatograph showed the ketone ratio to be 88 : 12 for a and b respectively.

α -Methyl-4-Oxa-cyclopentane-cis-1,2-diacetaldehyde (20):

The glycol (2) (3 g, 0.0174 mole) was mixed with (6.3 g, 0.023 mole) of sodium bismuthate, 8 ml of water, 15 ml of 33% phosphoric acid and 25 ml of ether. This reaction was placed in a 100 ml one neck round bottom flask and stirred at room temperature for 16 hours. At this time, the bismuthate-phosphate salts had turned gray in color. The reaction mixture was subjected to vacuum filtration and rinsed twice with dichloromethane. The combined dichloromethane layers were dried over anhydrous sodium sulfate. Aspirator evaporation of the solvent yielded 2.5 grams of product. No further purification of the product was attempted due to the known thermal instability of this type of compound.

The infrared spectrum (sodium chloride plates, neat) showed the characteristic C-H stretch of the aldehyde group at 3.64 (2740 cm^{-1}) and the aldehyde group at 5.78 (1725 cm^{-1}), also a weak -OH stretch was present.

α -Methyl-Oxa-cyclopentane-cis-1,2-diethanol (21):

The crude aldehyde (20) (2.5 g) in 25 ml of anhydrous ether was added to a refluxing solution of lithium aluminum hydride (1.0 g) in 50 ml of anhydrous ether. When the addition of the aldehyde had been completed, another 100 ml

of ether was slowly added to the mixture. The mixture was then stirred for an additional 14 hours, at reflux temperature.

The solution was then cooled and a small amount of a saturated Rochelle salt solution was added. After the solution was stirred for an hour, the solution was filtered and the salts were washed with dichloromethane. The combined extracts were reduced in volume to yield 1.0 grams of a viscous oil.

The infrared spectrum of the crude product showed a strong -OH at 2.98μ (3360 cm^{-1}) also two carbonyl absorptions were present 5.82μ , 5.98μ (1710 , 1670 cm^{-1}).

α -methyl-4-oxa-cyclopentane-cis-1,2-diethanol-di-p-toluene sulfonate (22):

The crude diol (8.64 g, 0.057 mole), calculated on the basis of pure diol, was dissolved in 40 ml of pyridine and was added dropwise to a cooled, stirred solution of p-toluene sulfonylchloride (19.8 g, 0.104 mole) in 50 ml of pyridine. The addition was completed in one-half hour and the reaction mixture was stirred for two additional hours. At this time a precipitate had formed in the pyridine solution. The pyridine solution was then kept at 0° overnight.

The cold solution was then poured into ice-water resulting in a heavy oil. The water was decanted from the oil and crystallization was accomplished by dissolving the oil in ether followed by a small amount of petroleum ether. Upon addition of ethanol, crystals were produced. The product was then filtered and

washed with ether, yielding 6.1 g (70%) of white tosylate, with a melting range of 98-9^o.

The infrared spectrum (potassium bromide pellet) showed two strong peaks characteristic of SO₂ stretches at 7.43 (1348 cm⁻¹) and 8.55 (1170 cm⁻¹) and that of the furan ring at 9.12 (1098 cm⁻¹).

Anal. (*): Calcd. for C₂₃H₃₀O₇S₂: S, 13.29

Found: S, 13.47

α-Methyl-4-oxa-cyclopentane-cis-1,2-dipropionitrile (23):

The tosylate (3.0 g, 0.06 mole) was stirred with potassium cyanide (2.4 g, 0.043 mole) in 35 ml of dimethylsulfoxide at room temperature for 13 hours. The reaction was then heated to 85^o and was maintained at this temperature for 24 hours.

The dimethylsulfoxide was then removed by reduced pressure distillation. After removal of most of the solvent, the mixture was poured into an ice-water slurry. This water solution was then continuously extracted for 13 hours with dichloromethane. Rotary evaporation of the solvent yielded a yellow colored solution.

The crude product was then distilled in a high temperature high vacuum apparatus yielding 1.4 g (47%) product at 180-5^o at 0.3 mm Hg.

The infrared spectrum showed a strong absorption for C N at 4.48

(2240 cm^{-1}) and that for the tetrahydrofuran ring at 9.45 (1058 cm^{-1}).

Anal. (*): Calcd. for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}$: C, 68.81; H, 8.40; N, 14.59

Found: C, 68.91; H, 8.59; N, 14.51

β -Methyl-4-oxa-cyclopentane-cis-1,2-dipropionic Acid (24):

The dinitrile (1.4 g, 0.0074 mole) was refluxed for 48 hours with 17.8 ml of an aqueous solution of KOH (33% by weight). The evolution of ammonia was noted as an indication of the reaction occurring.

The solution was then cooled to room temperature and acidified with 50% phosphoric acid. After 12 hours, at room temperature, a white crystal precipitated out and 12 hours later a dark creamed colored crystal precipitated.

Recrystallization from hot water yielded white crystals 0.55 g (39%) with a melting range of 128-30°.

The infrared spectrum (potassium bromide pellet) showed the characteristic hydrogen-bonded -OH and a split carbonyl with the two peaks at 5.72 (1747 cm^{-1}) and 5.91 (1698 cm^{-1}).

Anal. (*): Calcd. for $\text{C}_{11}\text{H}_{18}\text{O}_5$: C, 57.37; H, 7.87

Found: C, 57.18; H, 7.86

4-Methyl-cis-2-oxa-6-ketodecahydroazulene (25):

An intimate mixture of the diacid (0.55 g, 0.0024 mole), 0.55 g of iron powder and 0.18 g of Barium hydroxide, were placed in a piece of glass tubing

with a side arm leading into a cooled collection tube. The mixture was then heated with a free flame in an air bath. Water distilled and then a dark oil distilled from the mixture. The dark oil was then redistilled at reduced pressure in a micro distillation apparatus to yield a yellow colored oil.

The infrared spectrum of the product showed a strong carbonyl peak at 5.88 (1700 cm^{-1}) and the tetrahydrofuran ring at 9.40 (1062 cm^{-1}). The mass spectrum of the product showed the m/e to be 168 and many similarities were found between it and the six member systems (10) spectrum (appendix, page 89 and 91).

General procedure for ring expansion

The generation of diazomethane was accomplished from commercially available N-Methyl-N-nitroso-p-toluenesulfonamide (Diazald, Aldrich). The apparatus was set up in a well ventilated hood and all glass edges were thoroughly fire-polished, due to the explosive nature of diazomethane. The system contained no ground glass joints, cork joints were used exclusively.

In a round bottom two neck distillation flask was placed 8.7 ml of 95% ethanol and 1.5 g of potassium hydroxide in 2 ml of water. This solution was heated to 70° with stirring and a solution of Diazald (5.3 g) in 40 ml of anhydrous ether was added dropwise. The resulting yellow colored distillate was added directly into an Erlenmeyer flask containing the reactants. This was

accomplished by fitting the condensor with an extension so that the diazomethane was introduced below the surface of the solution.

In the Erlenmeyer flask was placed 0.3 g of cyclohexanone in 100 ml of anhydrous ether to which had been added a small amount of anhydrous aluminum chloride. The aluminum chloride had been left open to the air approximately two days.

After the addition of the diazomethane had been completed the solution was dark yellow in color, and was left at room temperature overnight. At the end of this time the yellow color was no longer present. The ether solution was washed three times with water and then dried over magnesium sulfate. Concentration of the ether solution and gas chromatographic analysis of the product indicated a 25% yield of cycloheptanone.

This same procedure, was then applied to the ketone (10), using twice the amount of diazomethane. The gas chromatogram showed a 9 % yield of the desired ring expansion product (18) along with a 5 % yield of the ketone (19). Cis-3-methyl-4-cyclohexene-cis, cis-1, 2-dimethanol-dimethane-sulfonate (26)

The diol (2) (10 g, 0.06 mole) in 40 ml of pyridine was added dropwise to a cooled and stirred solution of 29 g (0.25 mole) methanesulfonyl chloride in 50 ml of pyridine. The addition was completed in one hour and the mixture was allowed to stir an additional 12 hours. The solution was kept at 0° overnight.

The cold pyridine solution was poured into ice water and an oil was obtained. Crystallization of the oil from methanol afforded a white crystalline product (16 g, 85%) with a melting range of 59-60°.

The infrared spectram (potassium bromide pellet) showed the characteristic -SO₂ stretches at 7.48 (1338 cm⁻¹) and 8.57 (1170 cm⁻¹).

Anal. (*): Calcd. for C₁₁H₂₀S₂O₆: C, 42.31; H, 6.46

Found: C, 42.50; H, 6.44

4-Methyl-cis-4, 4a, 7, 7a-tetrahydro-2-benzothiophene (27)

In 200 ml of anhydrous ethanol was placed 3 g of sodium. Hydrogen sulfide was then bubbled through this solution until a saturated solution was achieved. To the saturated solution was added 15 g (0.048 mole) of the mesylate (26) and the mixture was heated to reflux. In one half hour a heavy white precipitate appeared in the solution. Another 100 ml of ethanol was added at this time and the solution was stirred for 24 hours.

The excess ethanol was distilled and water was added to the residue. This aqueous solution was extracted three times with dichloromethane and the combined extracts dried with magnesium sulfate. Rotary evaporation of the solvent and distillation at reduced pressure yielded 7.3 g (96%) of product.

Mass spectral analysis showed the mass ion to be 154. Infrared analysis showed the characteristic sulfur-carbon stretching frequencies to be

present (appendix, page 78).

Anal: Calcd. for $C_9H_{14}S$: C, 70.11; H, 9.08; S, 20.81

Found: C, 70.09; H, 9.44; S, 20.91

(5 or 6-hydroxy)-4-methyl-cis-4, 4a, 7, 7a-tetrahydro-2-benzothiophene

The sulfur alkene (27) (0.22 g, 1.4 moles) was subjected to oxymercuration (same procedure as described for the alkene (3), page 65) and the crystalline alcohol (yield 0.19 g, 90%) were compared to those obtained from alkene (3) when subjected to oxymercuration. The gas chromatogram showed the alcohols to be in a 55 : 45 ratio.

Anal: Calcd. for $C_9H_{16}OS$: C, 62.73; H, 9.38

Found: C, 62.96; H, 9.35

2-carboxaldehyde-6-methyl-3, 4-Dihydro-2H-pyran (35):

In a bomb were placed 30 g (0.54 mole) of acrolin, 15 g (0.21 mole) of methyl vinyl ketone and 80 ml of benzene. The bomb was then sealed and heated to 180° and kept at this temperature for two hours with occasional mixing. The bomb was then slowly cooled to room temperature and the reaction mixture removed. The solution was concentrated by rotary evaporation and the product was distilled at 35-40° (2 mm Hg), yield 18 grams. Gas chromatographic analysis of the product showed it to be a mixture. Mass spectrographic analysis of each peak present showed the mixture to contain a compound of the correct m/e

126 for the desired pyran derivative. The infrared spectrum showed a strong carbonyl absorption with the absence of -OH. No attempt was made to isolate the desired product at this point.

2-hydroxy propyl-6-methyl-3, 4-Dihydro-2H-pyran (36)

The ethylmagnesium bromide was prepared by the addition of (5.45 g, 0.05 mole) ethylbromide to a mixture of (1.20 g, 0.05 mole) magnesium and 80 ml of anhydrous ether (containing a small trace of Iodine). The resulting mixture was stirred until no trace of magnesium could be detected. The aldehyde mixture (3 g, 0.023 mole) was slowly added to the prepared ethylmagnesium bromide (0.05 mole) and the solution was then hydrolyzed with water. The salts were then dissolved by acidification of the solution with dilute hydrochloric acid. The acidic solution was extracted with dichloromethane. Concentration of the extracts and distillation of the crude product yielded 4.0 grams of an alcohol mixture. The desired alcohol was not isolated but carried on to the next step.

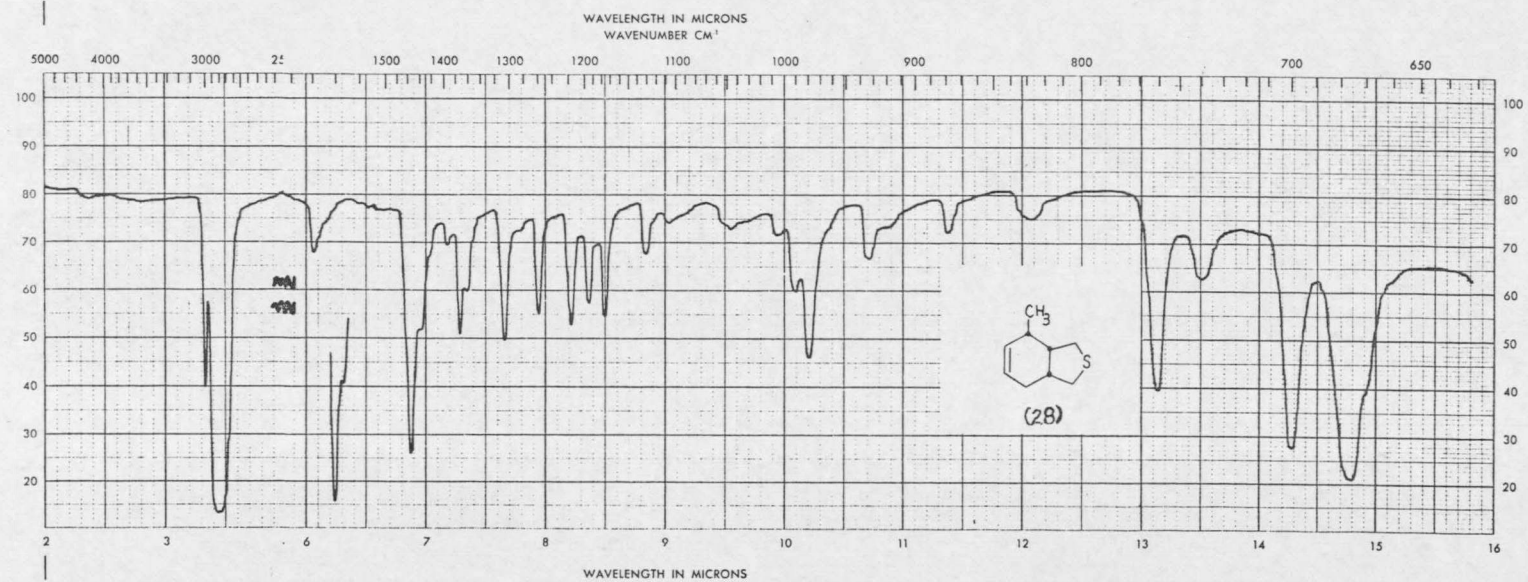
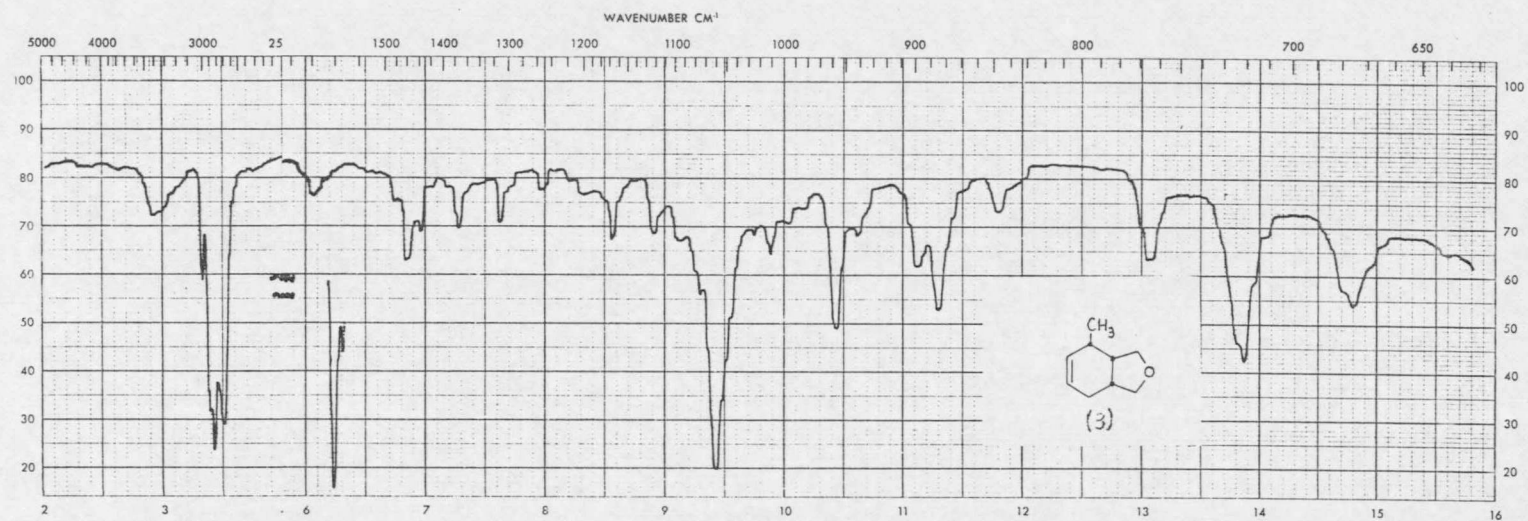
6,8-Dioxabicyclo [3.2.1.] octane-7-ethyl-5-methyl (34)

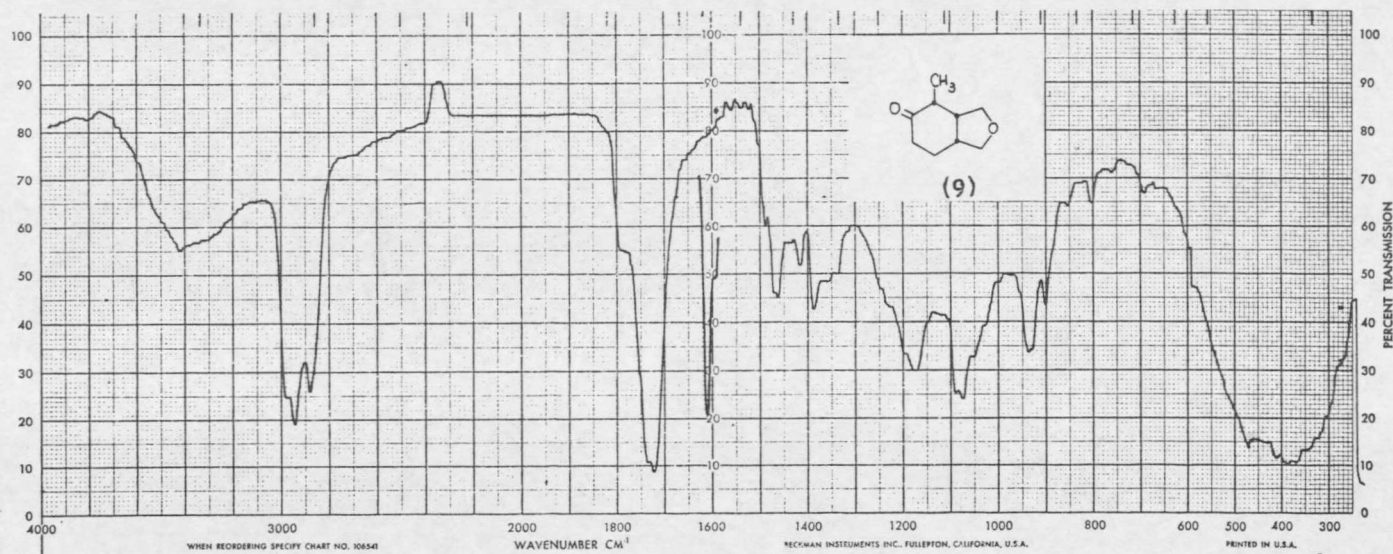
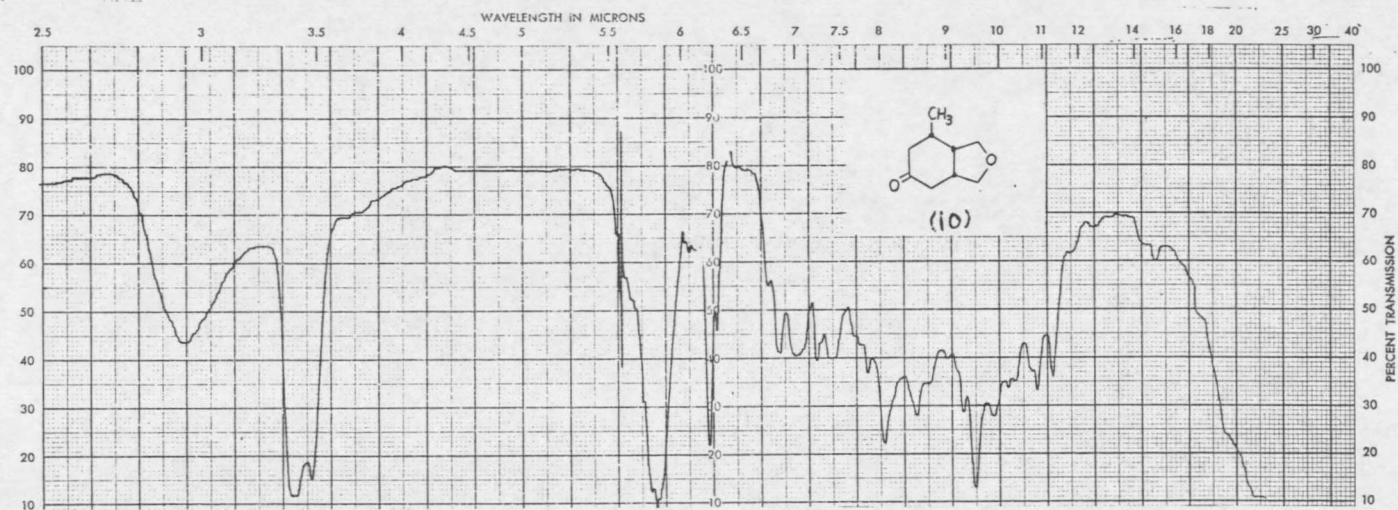
In 75 ml of dry tetrahydrofuran was placed (9.6 g, 0.03 mole) of mercuric acetate. This mixture was stirred with the addition of the alcohols (4.0 g, 0.03 mole) for three hours at room temperature. The addition of 30 ml of 3M potassium hydroxide imparted a yellow color to the solution. A solution of

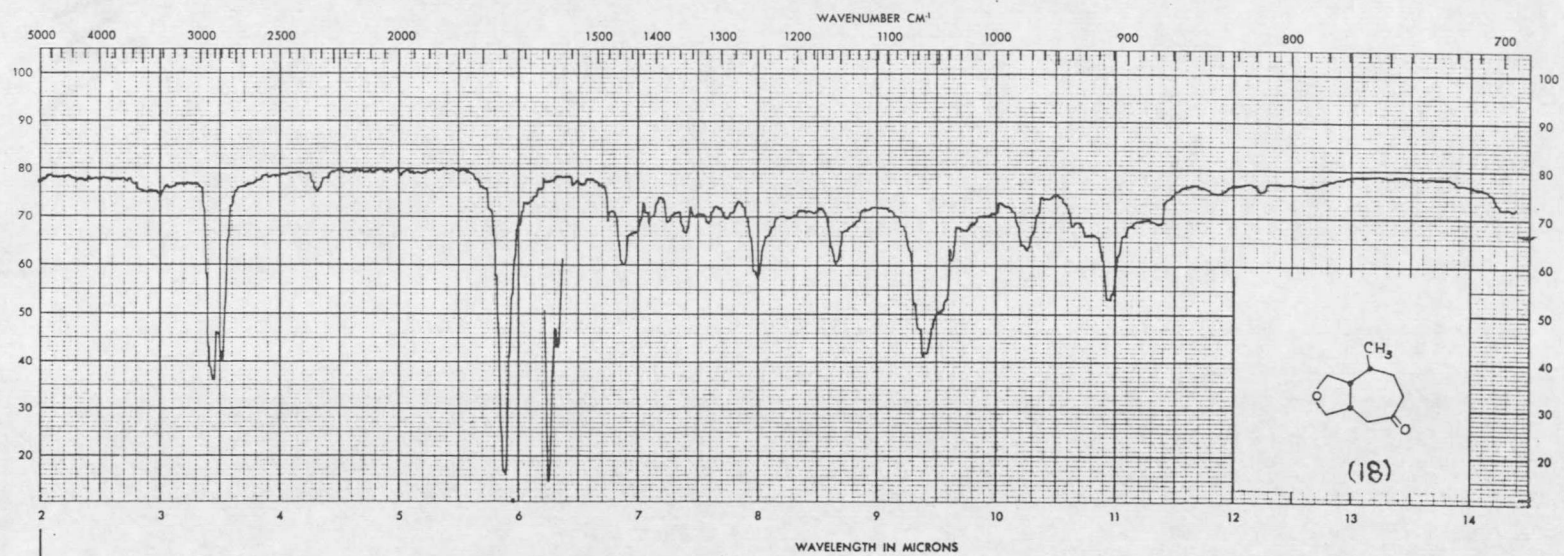
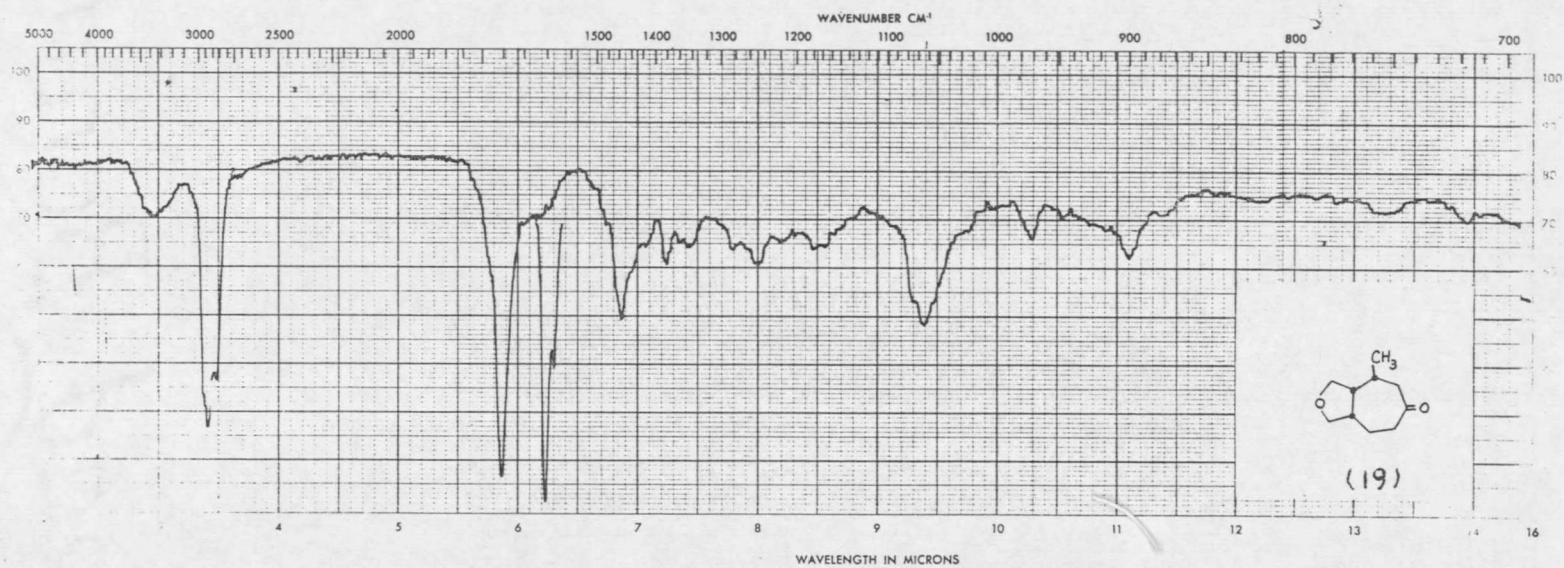
30 ml of 3M potassium hydroxide containing sodium borohydride (0.76 g/40 ml of 3M KOH) was then added to the cooled yellow reaction mixture resulting in a gray solution. A saturated sodium chloride solution (30 ml) was then added and the mixture was stirred for 10 minutes. The solution was filtered and then extracted with dichloromethane. The extracts were concentrated by rotary evaporation and the product was distilled at 63° (12 mm Hg) yielding 3.5 grams of a mixture. Gas chromatographic analysis on a 20% carbowax 20M column showed the yield of brevicomin to be 9%. Isolation of brevicomin was accomplished with the same type of column and was shown by infrared, nuclear magnetic resonance, mass spectrum and gas chromatographic retention time to be identical with brevicomin (appendix, page 92) (brevicomin sample obtained from Jim Lotan, U. S. Forest Service).

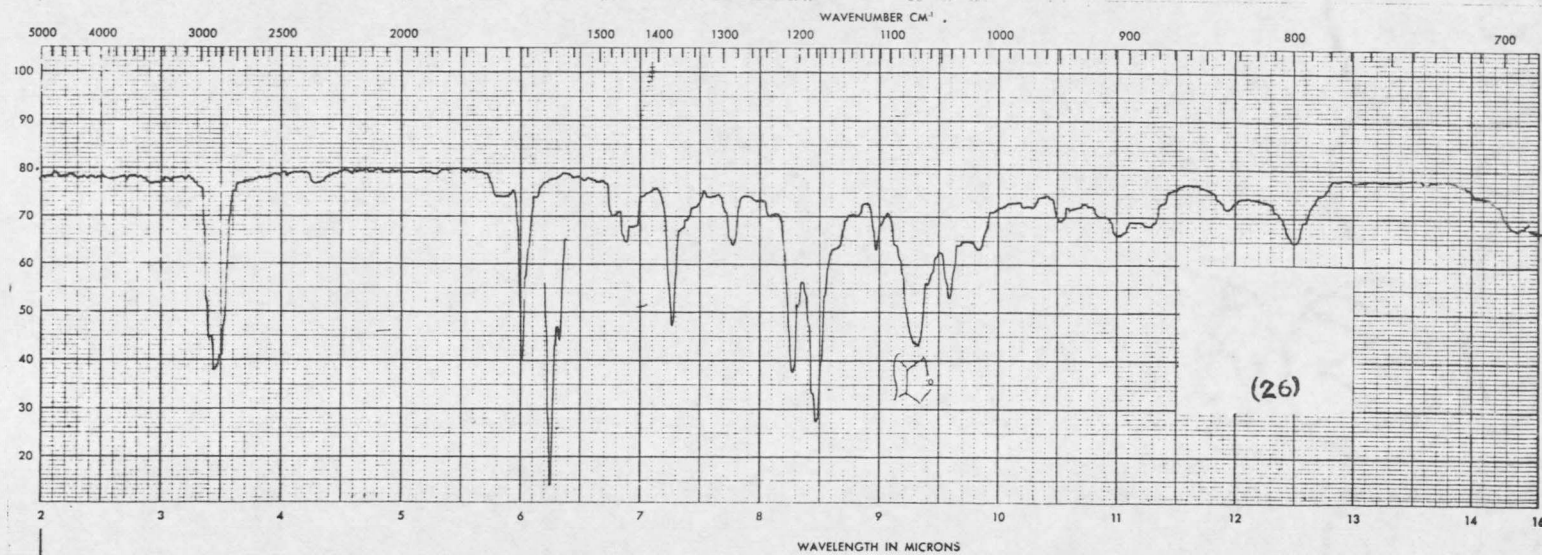
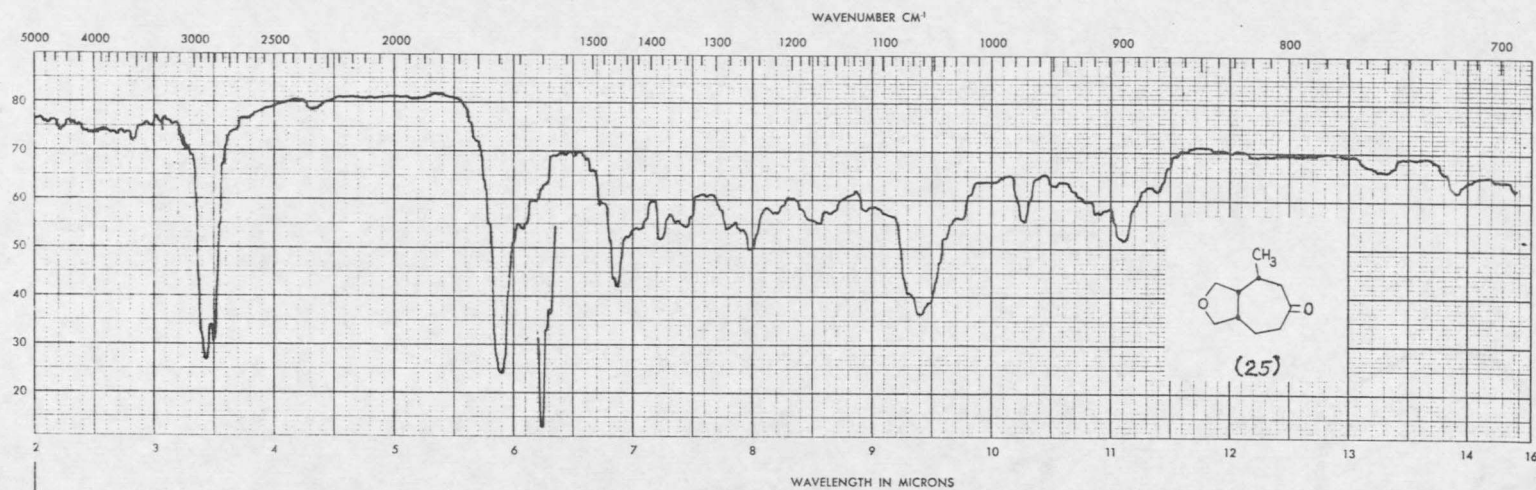
PART VIII

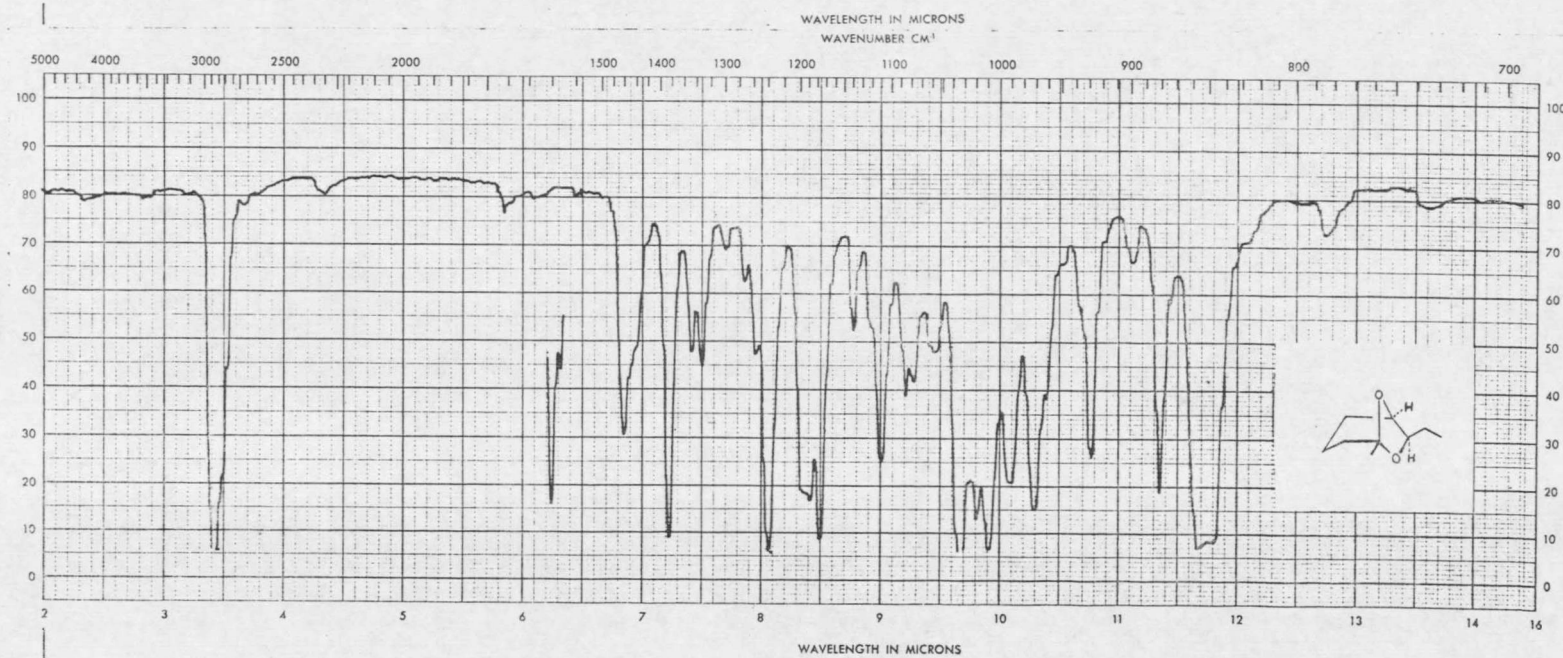
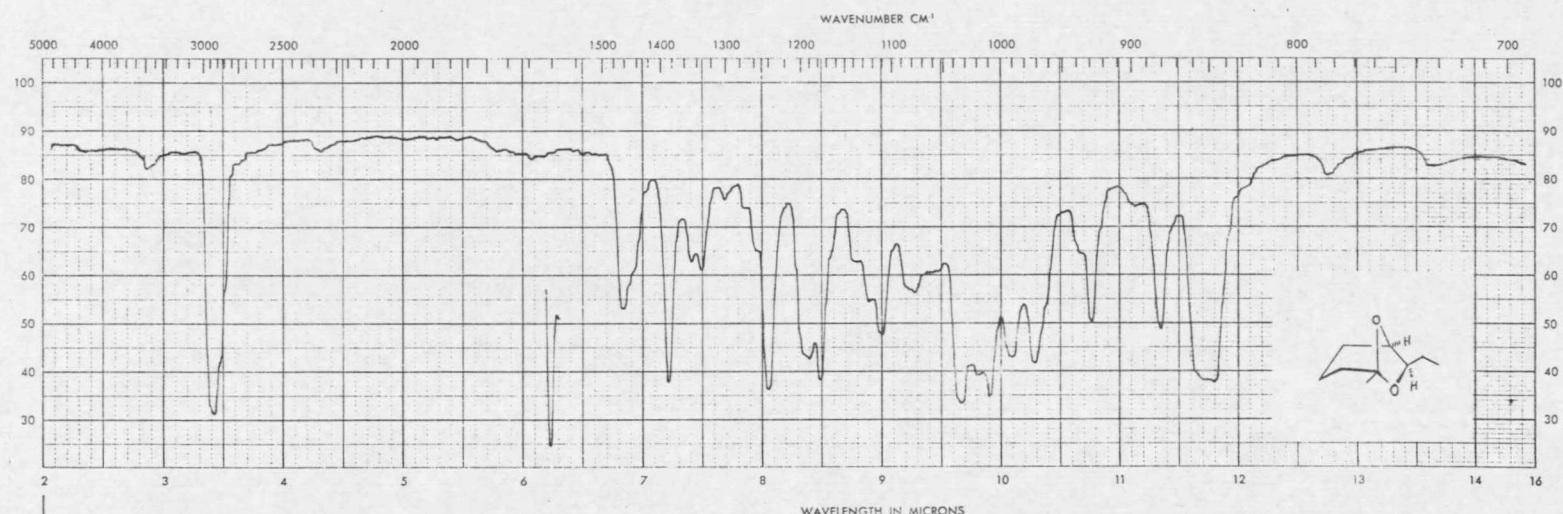
APPENDIX

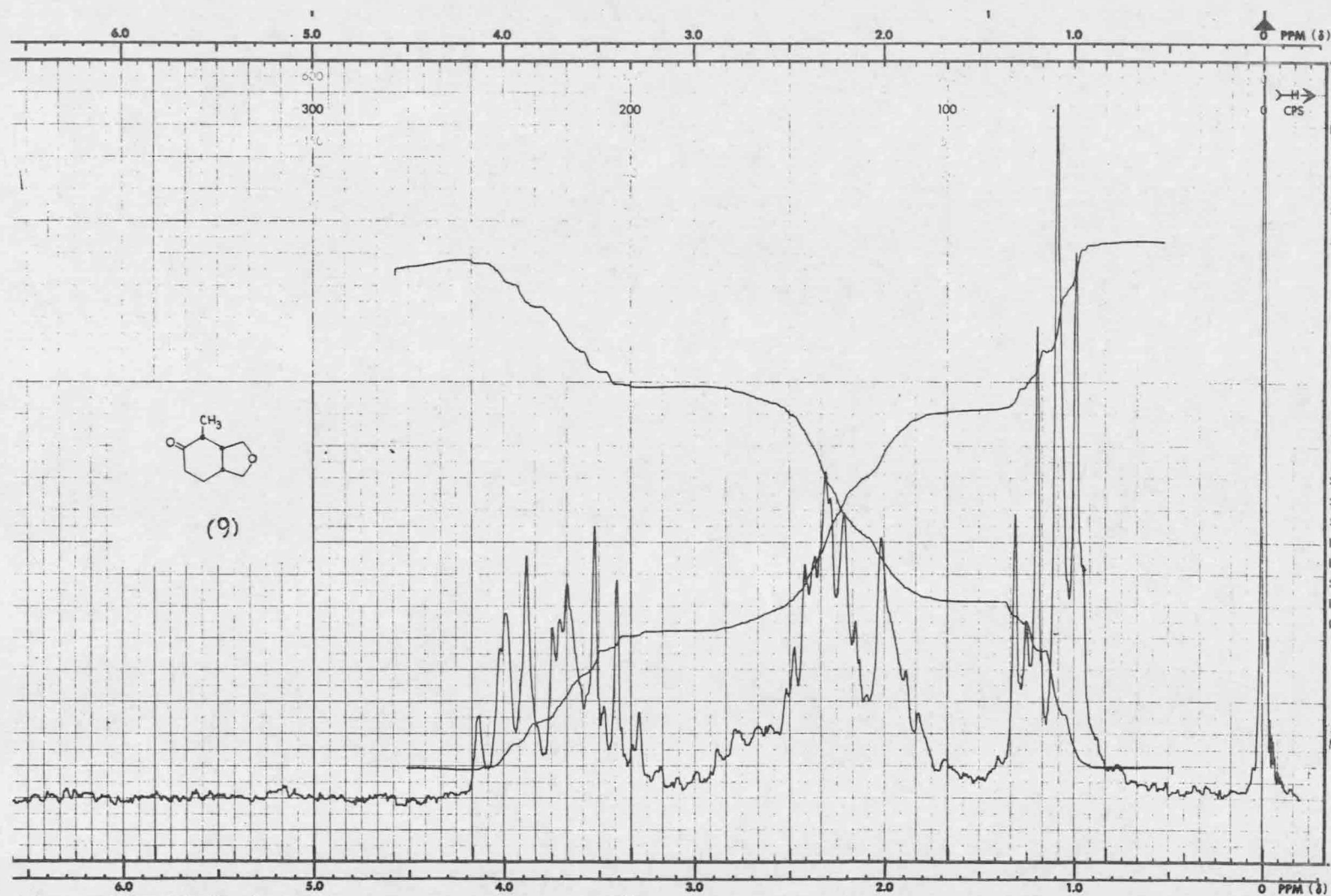


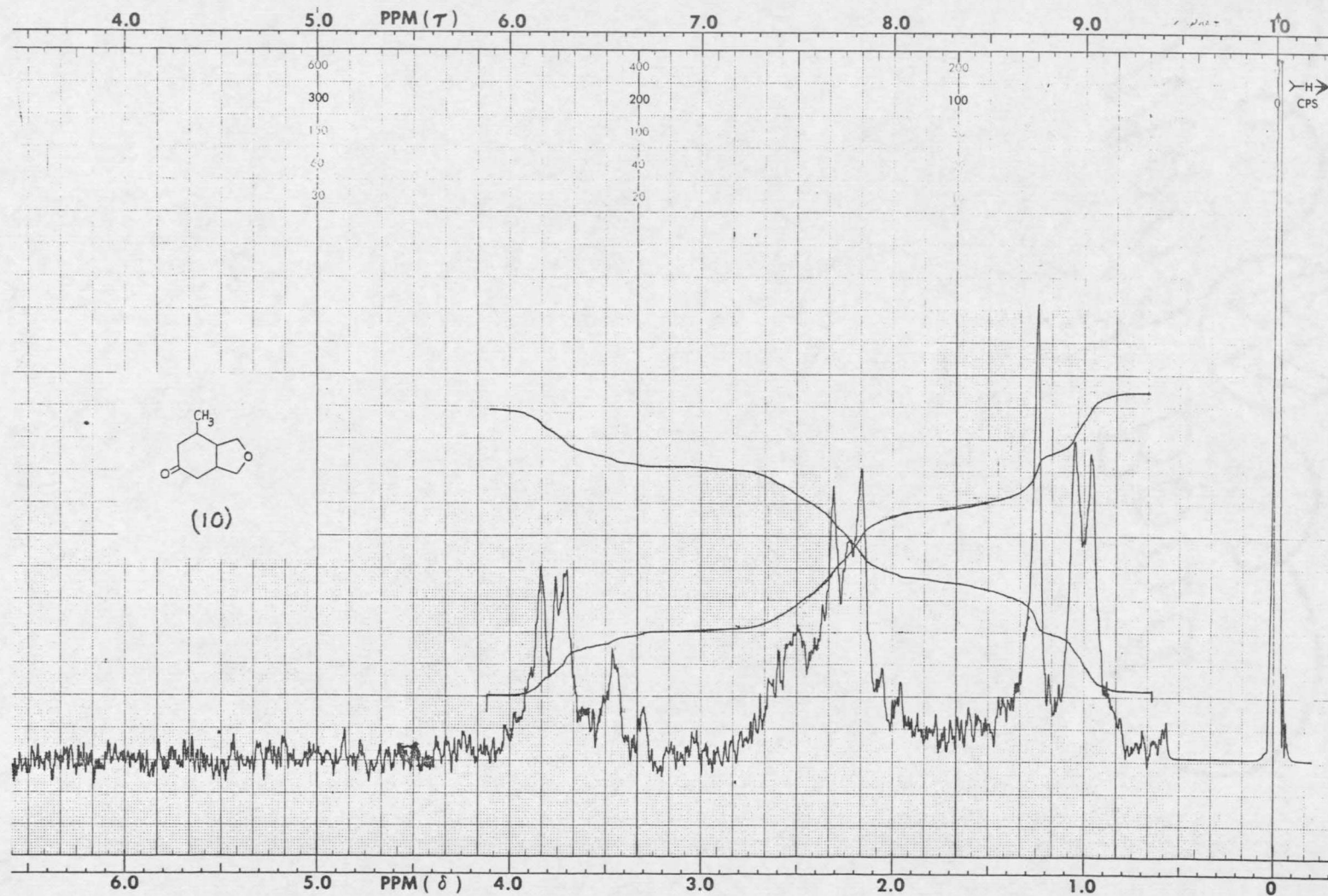


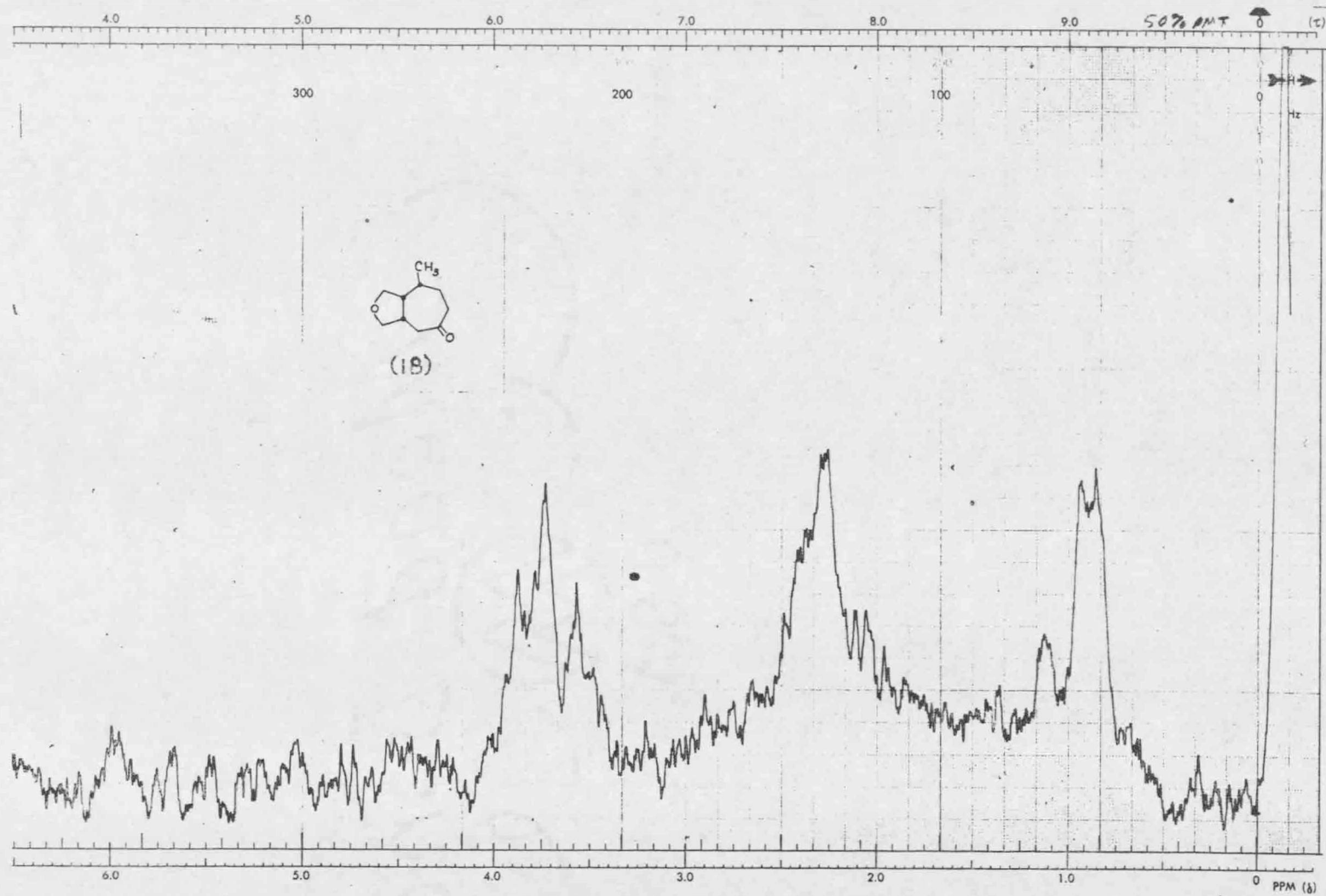


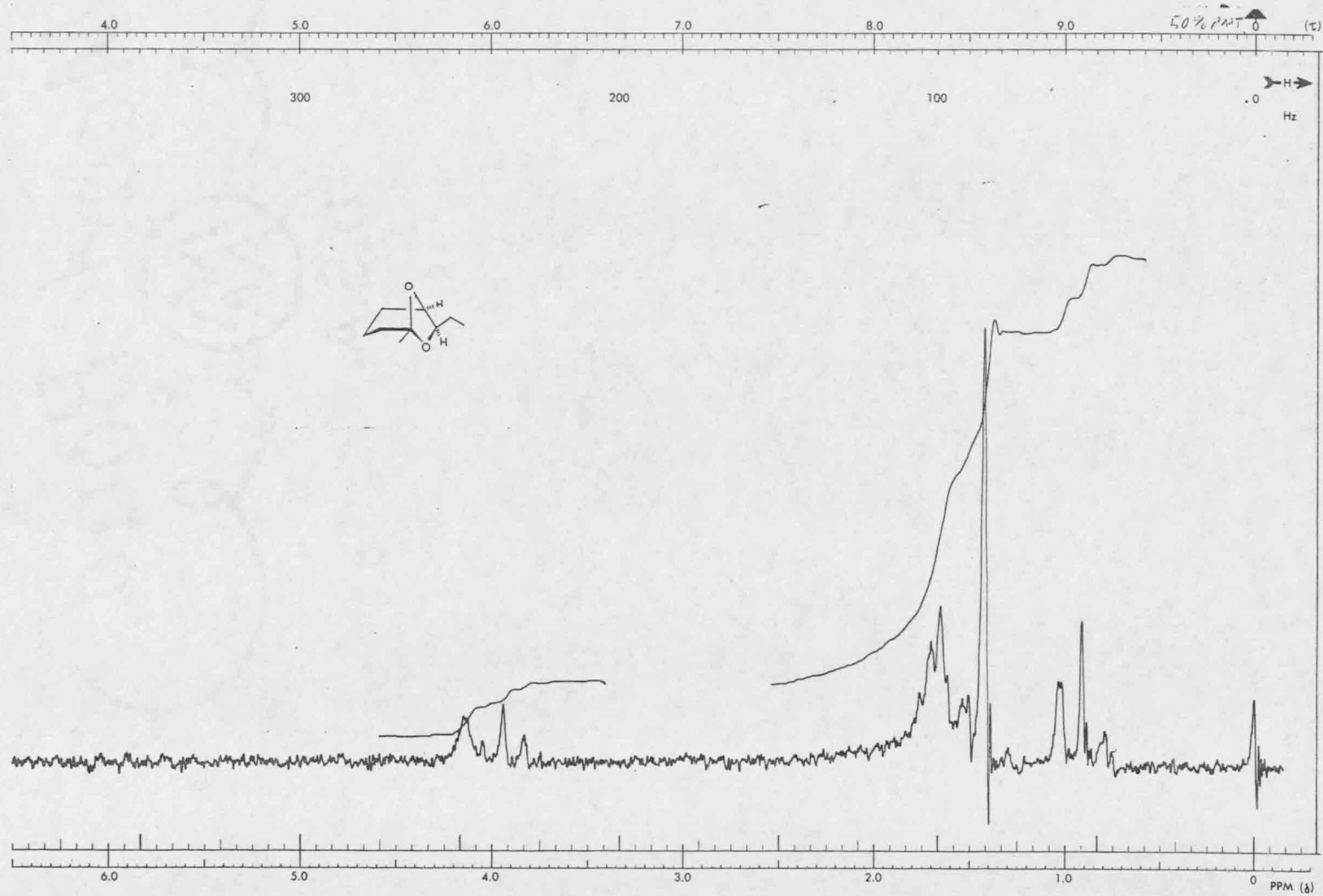


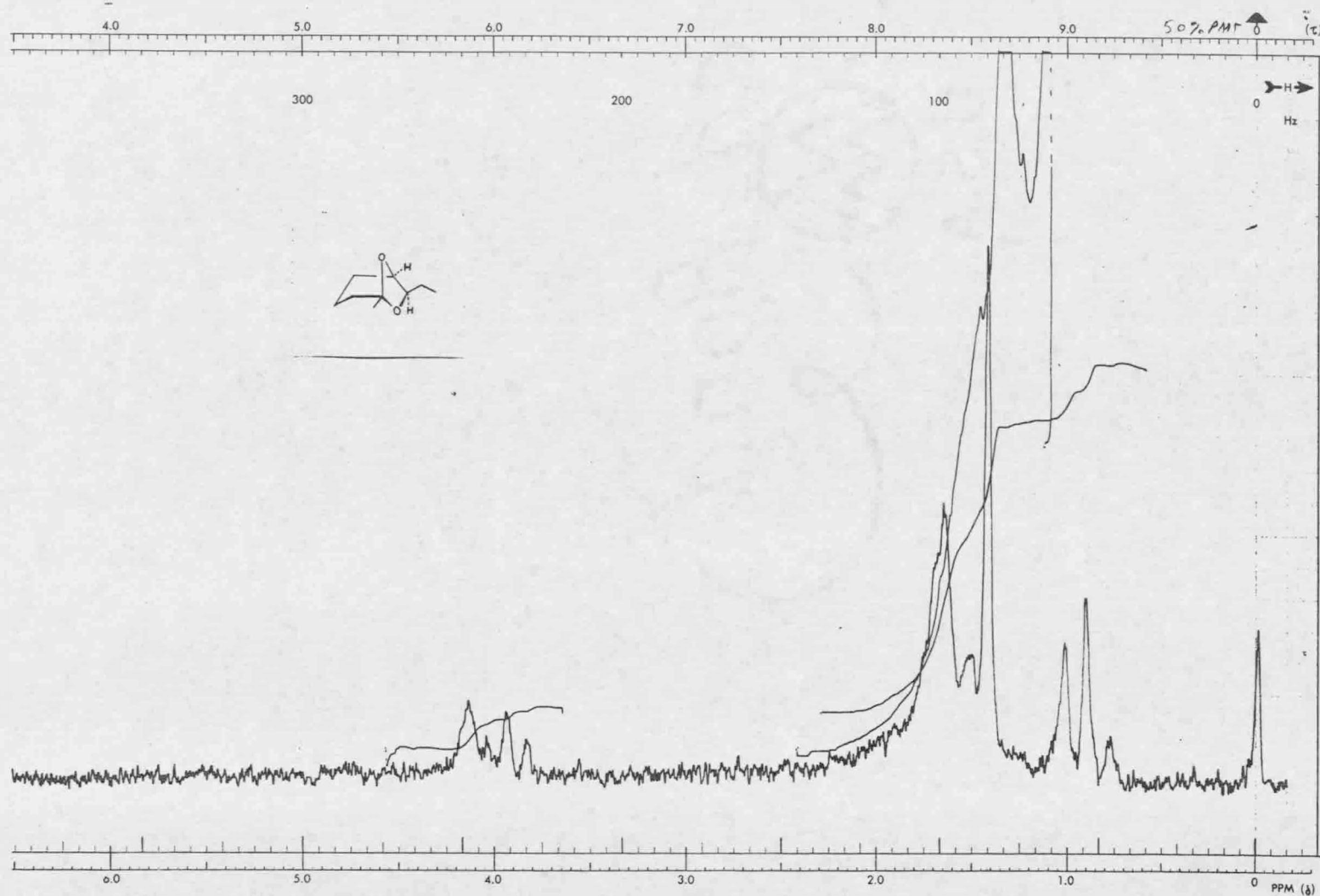


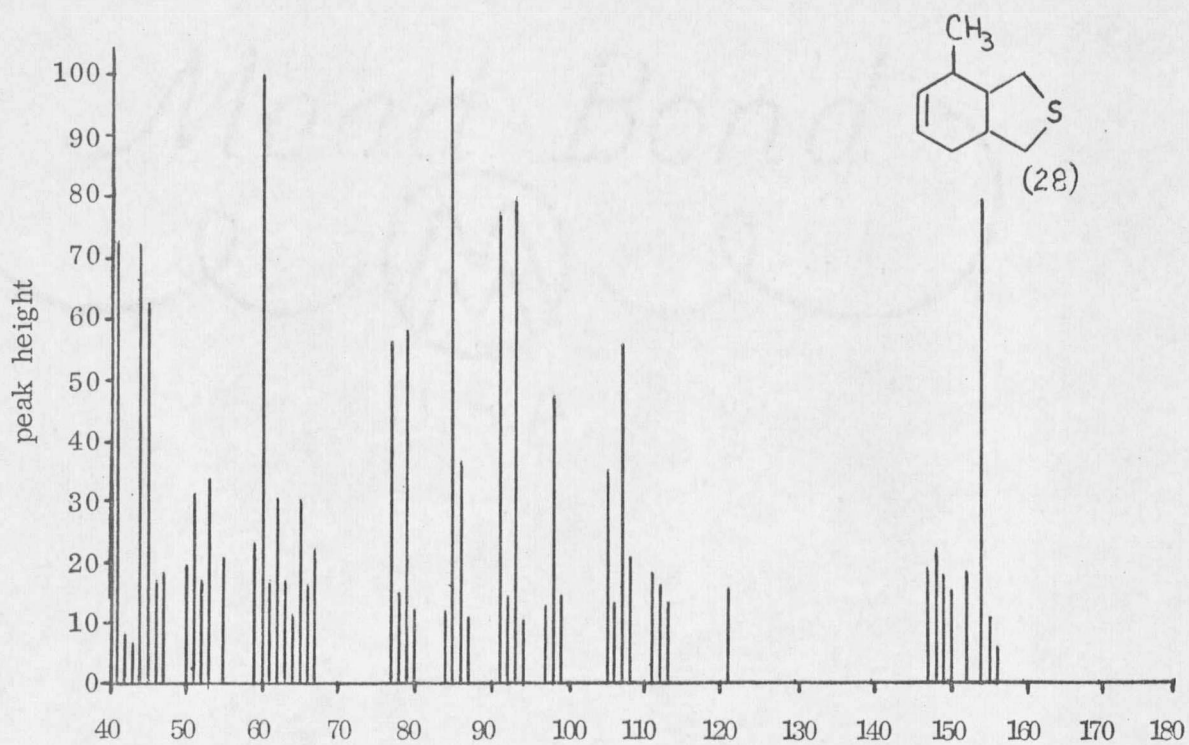
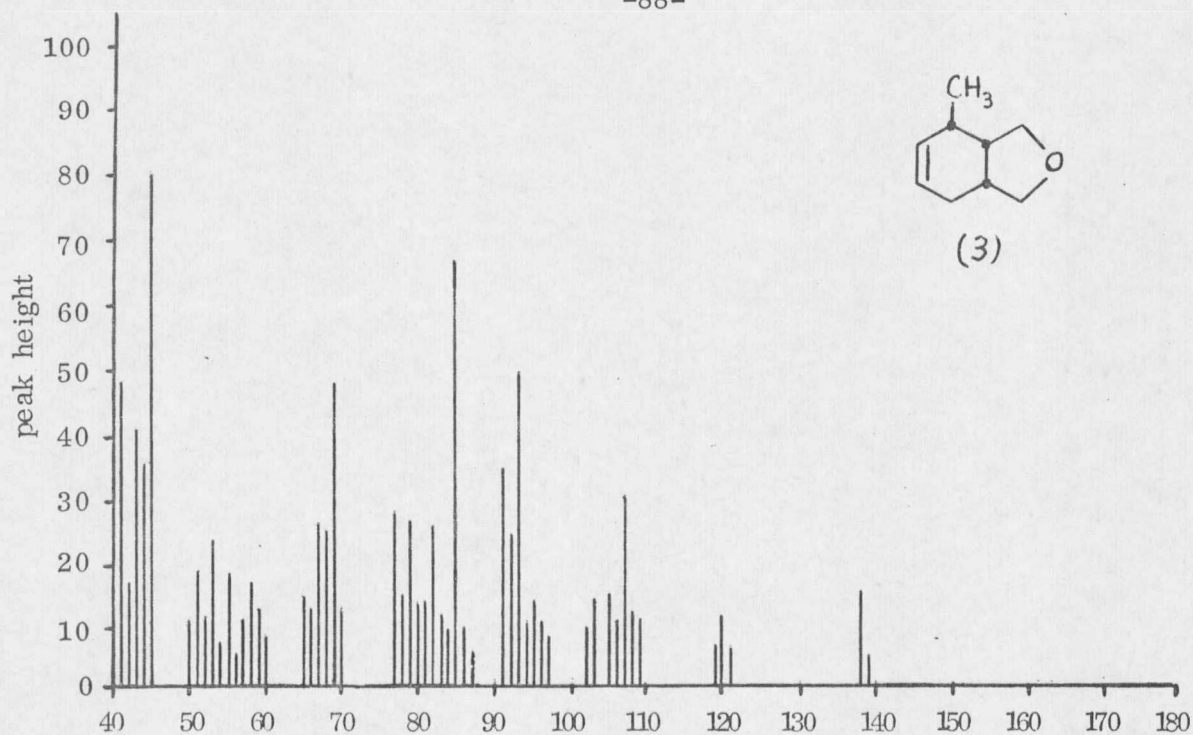


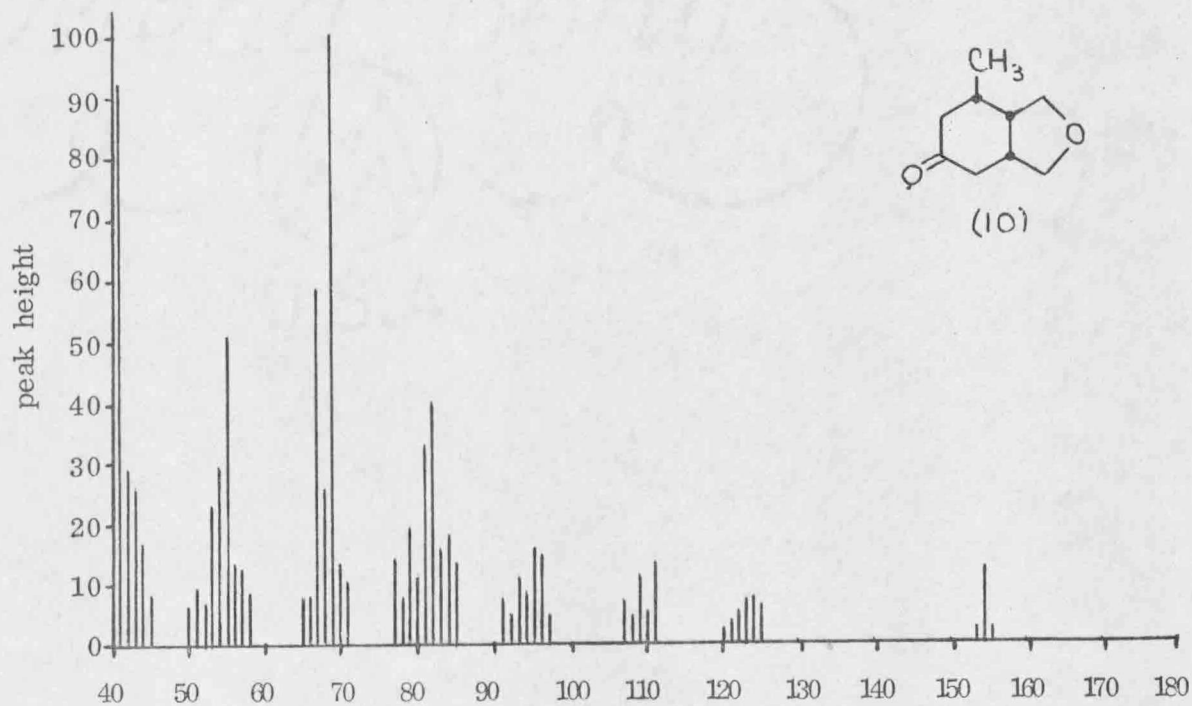
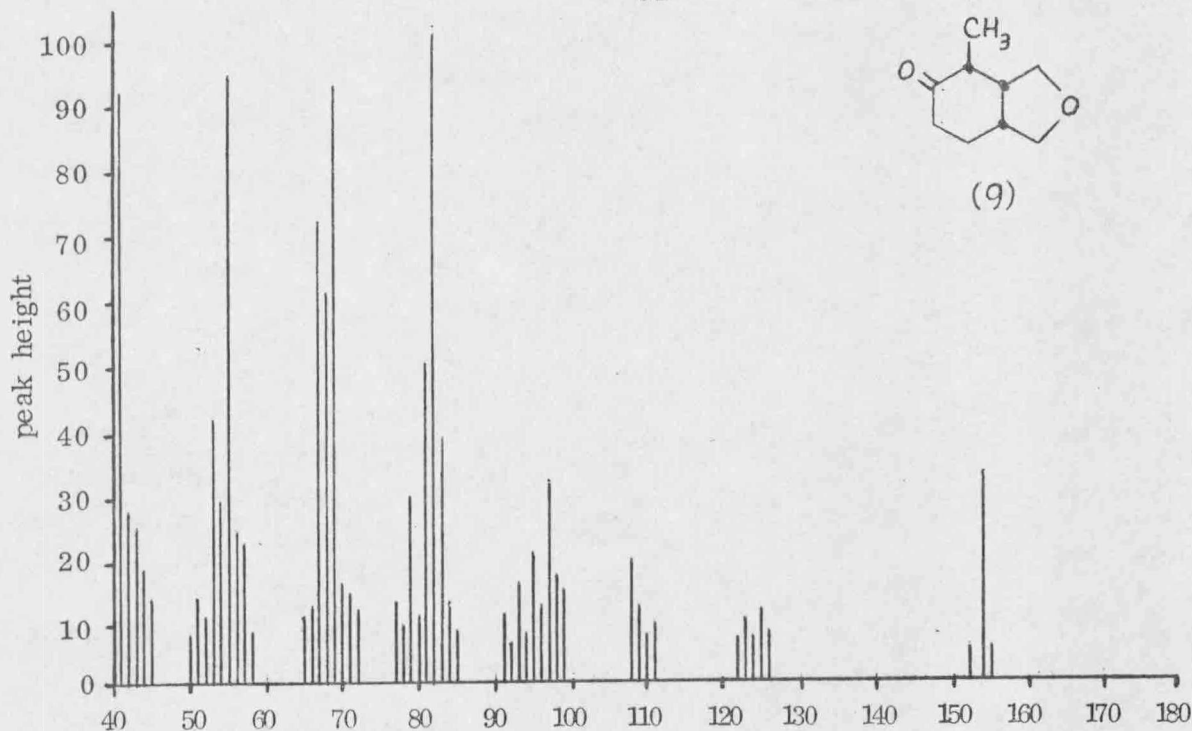


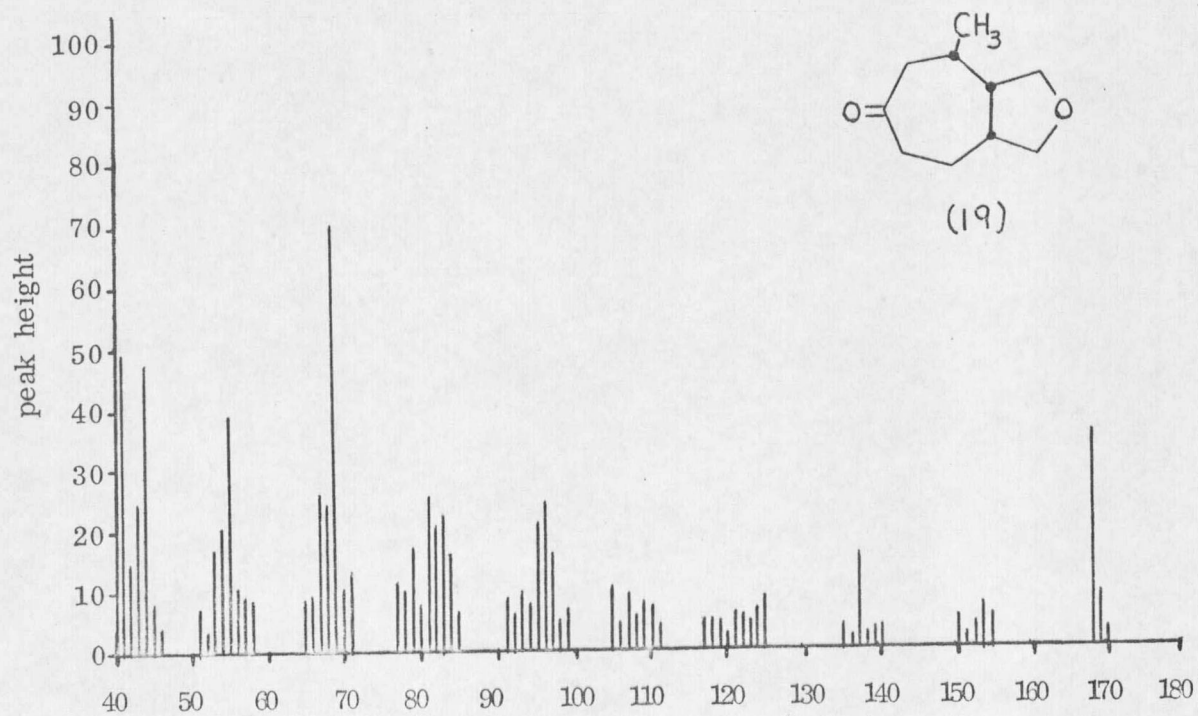
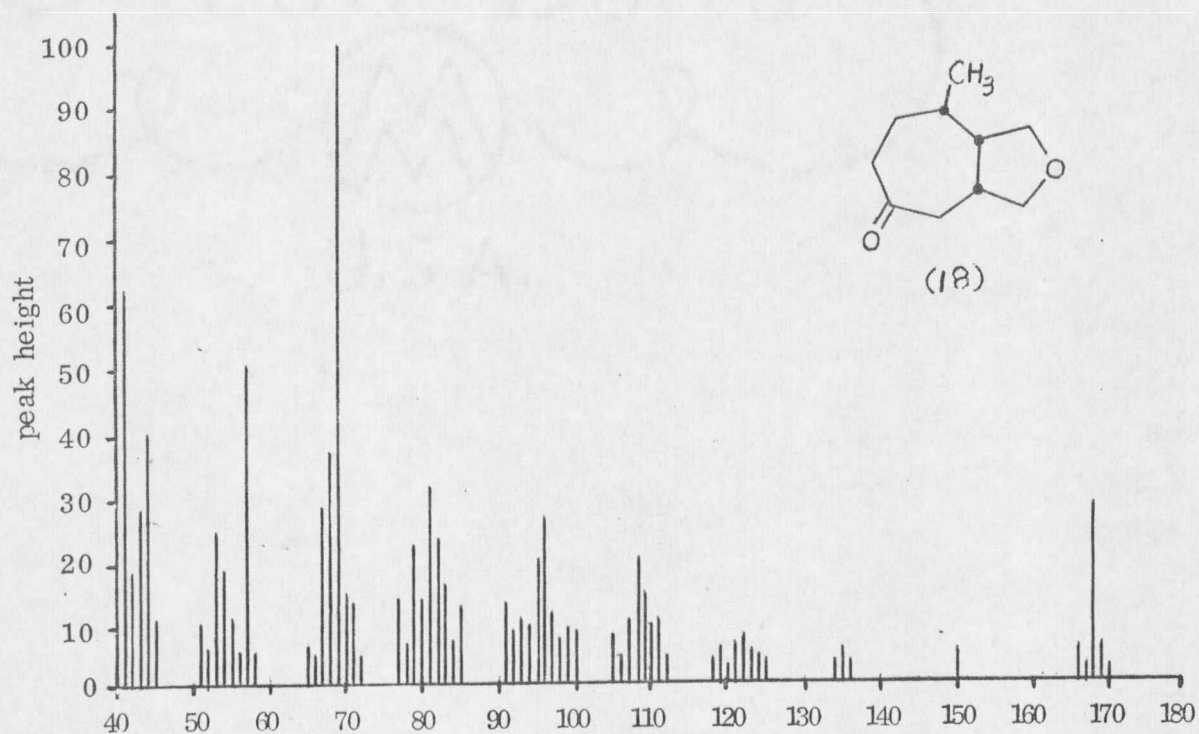


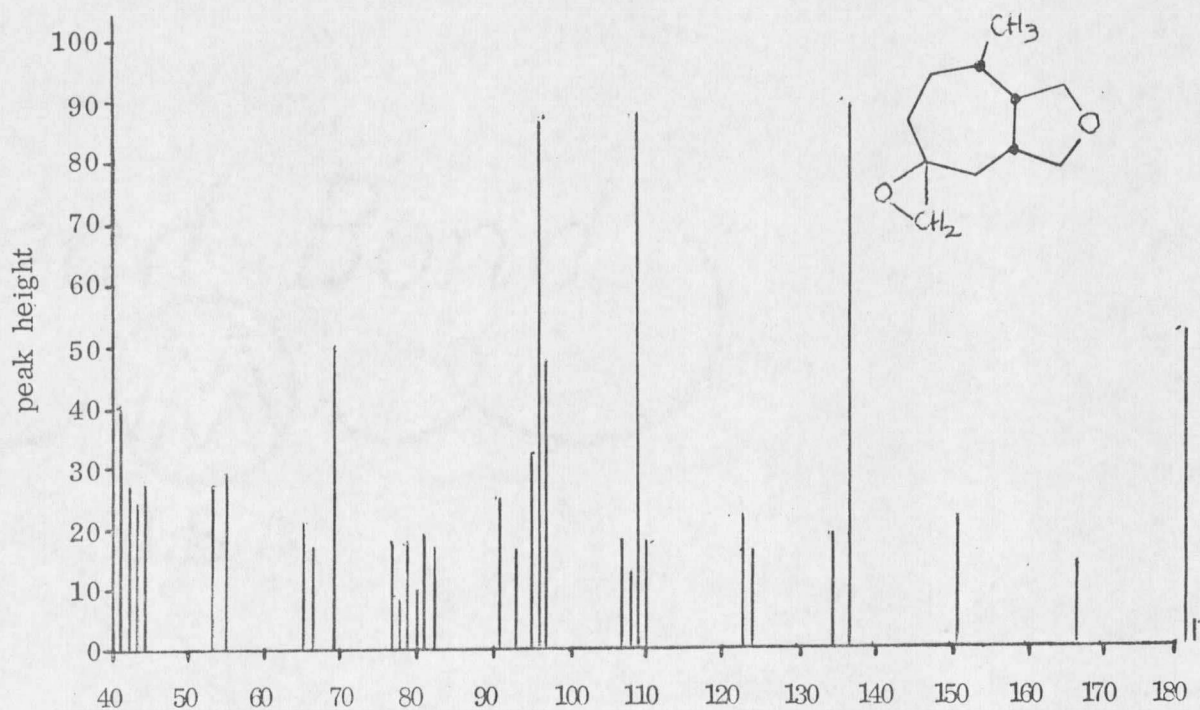
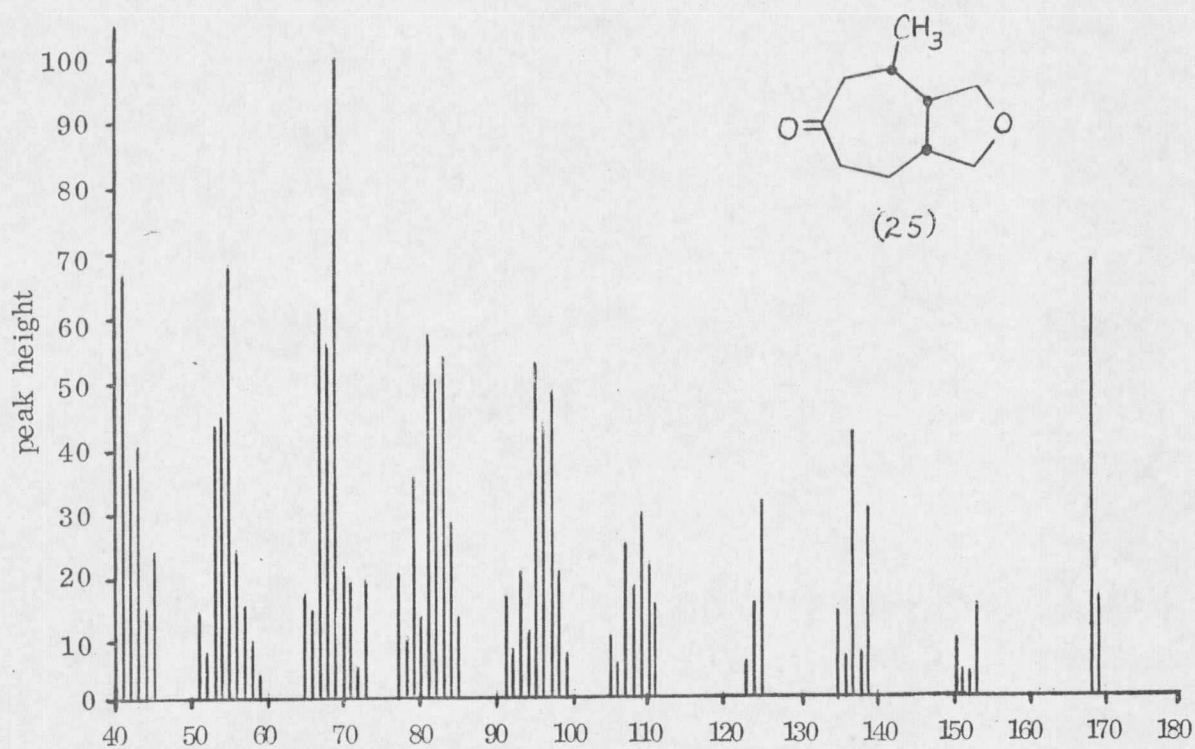




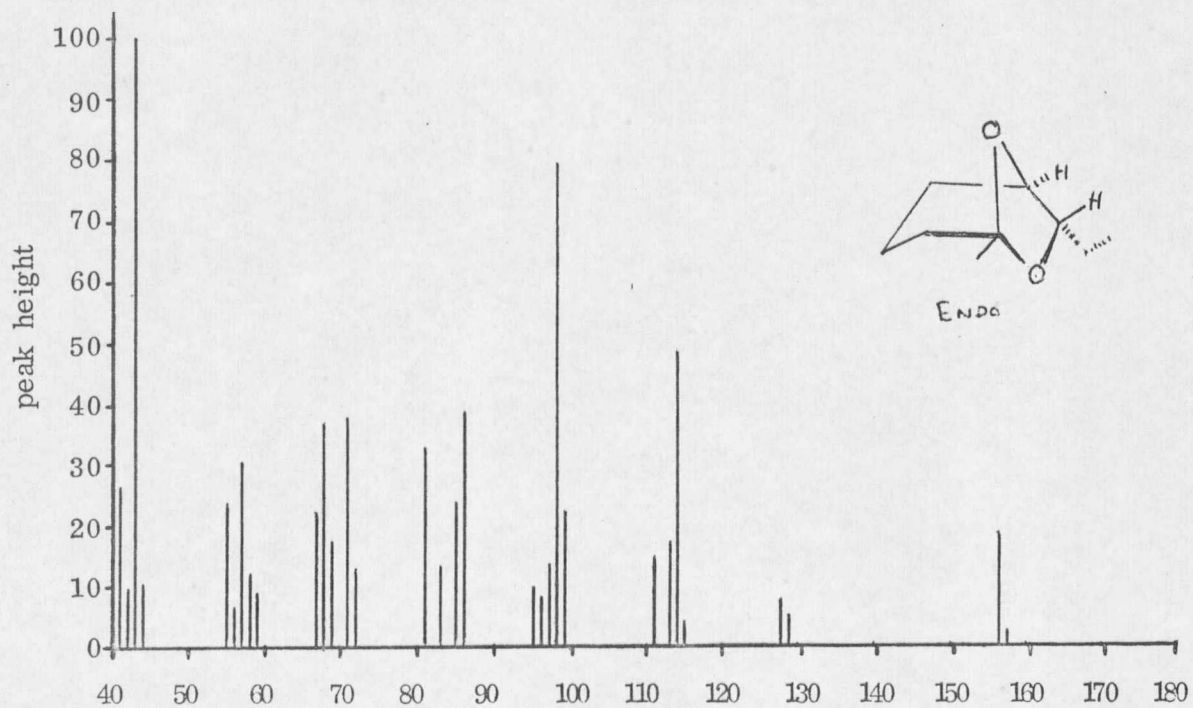
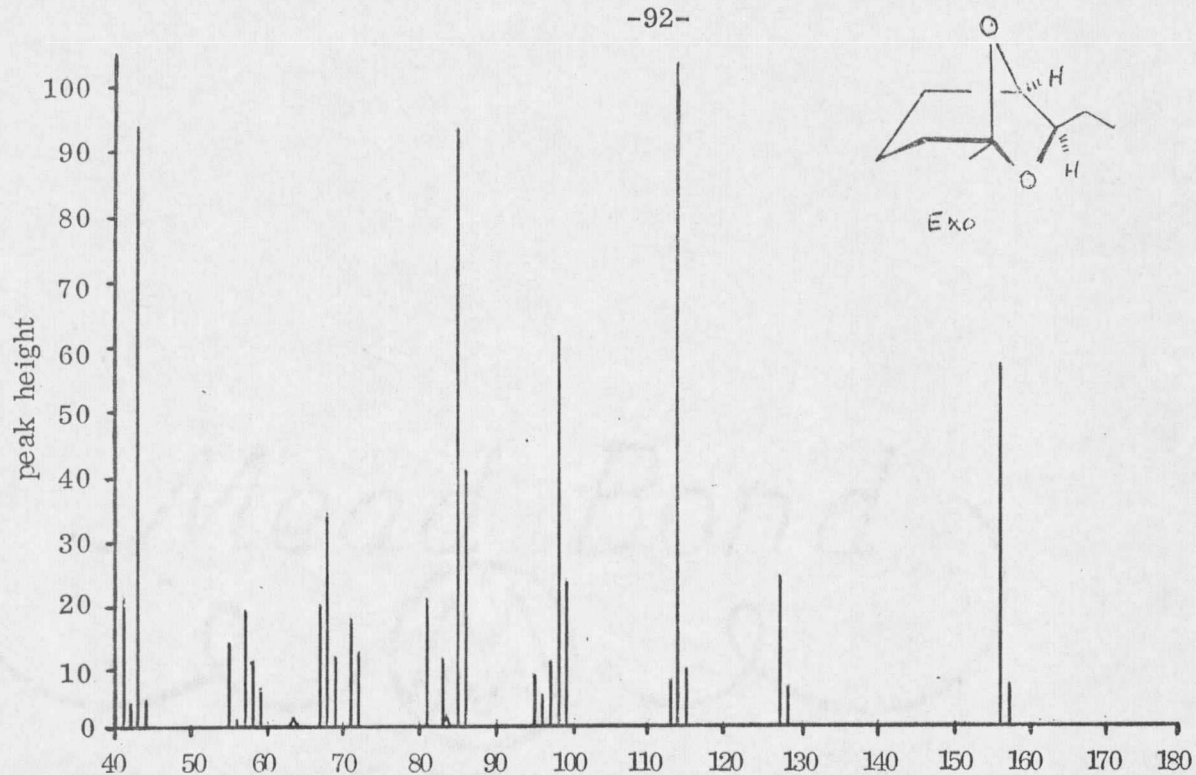


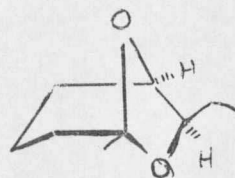
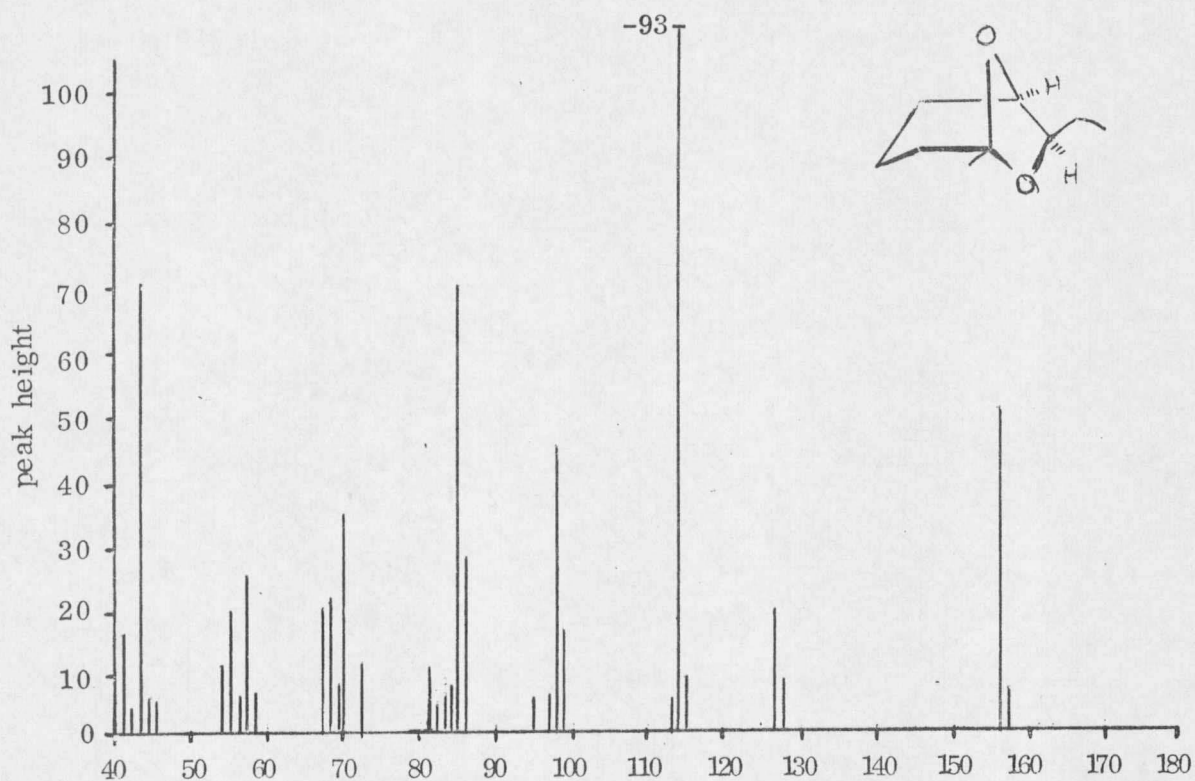






-92-





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