MONTANA STATE UNIVERSITY

Effects of heteroatoms in heterocyclic molecules
by Kauo-rong Sun

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:
By utilizing data obtained from chemical and spectroscopic studies, the ground state conformation of an oxygen-containing heterocyclic compound, cis-8-oxabicyclo [4.3. 0]non-3-ene, has been established. A long-range electronic participation from the π-system of the double bond to the nonbonded electrons of the oxygen was proposed from the spectroscopic study.

Cis-7,7,9,9-tetramethyl-8-oxabicyclo [4.3.0]non-3-ene was prepared, and the conformation of this molecule was proposed by utilizing chemical and spectroscopic data. Furthermore, the spectroscopic study indicated the blockage of the electronic participation between the 77-system of the alkene and the nonbonded electrons of the oxygen atom due to the steric factor of the four methyl groups.

A similar spectroscopic study was extended to the nitrogen analogs, the cis-N-substituted-8-azabicyclo [4. 3. 0]non-3-ene systems. The primary data led to the proposal of the nitrogen inversion and the similar electronic participation was obtained.

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Date June 16, 1972

EFFECTS OF HETEROATOMS IN HETEROCYCLIC MOLECULES

by

KAUO - RONG SUN

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

of

MASTER OF SCIENCE

in

Chemistry

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Bozeman, Montana

August, 1972

To

My Parents, Wife, and Daughter

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TABLE OF CONTENTS

		Page
VITA		ii
ACKNOWLEDGEMENT		iv
LIST OF TABLES		vii
LIST OF FIGURES		ix
ABSTRACT		xii
PART I.	The Conformation of Cis-8-oxabicyclo [4.3.0] non-3-ene	
I.1	Introduction	1
I.2	Synthesis	6
I.3	nmr Spectroscopic Data	9
I.4	Hydroboration	16
I.5	Cis-8-oxabicyclo [4.3.0] nonan-3-one	19
PART II.	Synthesis and Reactivity of Cis-7,7,9,9-tetra-methyl-8-oxabicyclo [4.3.0]non-3-ene	
II.1	Introduction	23
II.2	Molecular Model	23
II.3	Synthesis	24
II.4	nmr Spectroscopic Data	26
II.5	Oxymercuration	27
II.6	nmr Study for the Electronic Participation	30
PART III.	Cis-N-substituted-8-azabicyclo [4.3.0] non-3-ene Systems	
III.1	Introduction	36
III.2	Synthesis	37
III.3	nmr study for the Electronic Participation	38

TABLE OF CONTENTS (CONTINUED)

III. 4	Relation to the Corresponding Oxygen Systems	50
EXPERIMENTAL		
General Information		51
Part I		51
Part II		59
Part III		64
APPENDIX		
I.	The Analysis of Gas Liquid Chromatography	67
II.	The Commonly Used Gas Liquid Chromatography Columns	68
III.	The Commonly Used Names of Some of the Heterocyclic Compounds	69
IV.	The nmr Spectra of Some of the Heterocyclic Compounds	70
REFERENCES		89

LIST OF TABLES

Table		Page
1.	Competition Results of Oxymercuration Reaction	2
2.	Tentative Coupling Constants From Conformations of Cis-8-oxabicyclo [4.3.0]non-3-ene	15
3.	Results From Reduction of Cis-8-oxabicyclo [4.3.0] nonan-3-one	19
4.	Report of Elemental Analysis of 3,5-dinitrobenzoate Derivative of Cis-7,7,9,9-tetramethyl-8-oxabicyclo [4.3.0] nonan-3-ol	30
5.	The Observed Chemical Shifts of Protons in Cis-8-oxabicyclo [4.3.0]non-3-ene From nmr Studies	32
6.	The Observed Chemical Shifts of Hydrogens in Cis-7,7,9,9-tetramethyl-8-oxabicyclo [4.3.0] non-3-ene From nmr Studies	32
7.	The Observed Chemical Shifts of Hydrogens in Cis-8-oxabicyclo [4.3.0]nonane From nmr Studies	34
8.	The Observed Chemical Shifts of Hydrogens in Cis-7,7,9,9-tetramethyl-8-oxabicyclo [4.3.0] non-3-ene at Different Concentrations in Acidic Solvent	35
9.	The Observed Chemical Shifts of Hydrogens in Cis-8-phenyl-8-azabicyclo [4.3.0]non-3-ene From nmr Studies	39
10.	The Observed Chemical Shifts of Hydrogens in Cis-8-phenyl-8-azabicyclo [4.3.0] nonane From nmr Studies	40
11.	The Comparison of Observed Chemical Shifts of Hydrogens in Cis-8-phenyl-8-azabicyclo [4.3.0] non-3-ene and its Quaternary Methiodide Salt	41
12.	The Comparison of Observed Chemical Shifts of Hydrogens in Cis-8-phenyl-8-azabicyclo [4.3.0] nonane and its Quaternary Methiodide Salt	41

LIST OF TABLES (CONTINUED)

13.	The Observed Chemical Shifts of Hydrogen in Cis-8-propyl-8-azabicyclo [4.3.0]non-3-ene From nmr Studies	42
14.	The Comparison of Observed Chemical Shifts of Hydrogens in Cis-8-propyl-8-azabicyclo [4.3.0] non-3-ene and its Quaternary Methiodide Salt	43
15.	The Observed Chemical Shifts of Hydrogens in Cis-7,7,9,9-tetradeutero-8-propyl-8-azabicyclo [4.3.0] non-3-ene From nmr Studies	47
16.	The Comparison of Observed Chemical Shifts of Hydrogens in Cis-7,7,9,9-tetradeutero-8-propyl-8-azabicyclo [4.3.0]non-3-ene and its Quaternary Methiodide Salt	48
17.	The Observed Chemical Shifts of Hydrogens in Cis-8-phenyl-8-azabicyclo [4.3.0] non-3-ene in Solvents of Different Acidities	49
18.	The Relative Retention Time of Compounds From Cis-8-oxabicyclo [4.3.0]non-3-ene System From Analytical Gas Chromatography	56
19.	The Observed Yield of Reactions From Cis-8-oxabicyclo [4.3.0]non-3-ene System When Analyzed by Gas Chromatography	56
20.	The Relative Retention Time of Compounds From Cis-7,7,9,9-tetramethyl-8-oxabicyclo [4.3.0] non-3-ene System From Analytical Gas Chromatography	63

LIST OF FIGURES

Figure		Page
1.	The Cis-8-hetero-bicyclo [4.3.0] non-3-ene Systems	1
2.	The Long-range Oxygen Participation	3
3.	The Products From Oxymercuration-demercuration Reaction of Cis-8-oxabicyclo [4.3.0]non-3-ene	3
4.	Suggested Possible Conformations of Cis-8-oxabicyclo [4.3.0]non-3-ene	4
5.	Suggested Possible Conformations of Cis-bicyclo [4.3.0] non-3-ene and Cis-bicyclo [4.2.0]oct-3-ene	4
6.	Preparation of Cis-8-oxabicyclo [4.3.0]non-3-ene	6
7.	The Main- and By-product of Lithium Aluminum Hydride Reduction of Cis-1,2,3,6-tetrahydrophthalic Anhydride	6
8.	Mechanism of Cyclization to the Bicyclic System	7
9.	Preparation of Cis-7,7-dideutero-8-oxabicyclo [4.3.0] non-3-ene	7
10.	The Protons Adjacent to the Ether Oxygen in Cis-8-oxa-bicyclo [4.3.0] non-3-ene and Cis-7,7-dideutero-8-oxa-bicyclo [4.3.0] non-3-ene	9
11.	Possible Conformations of Cis-8-oxabicyclo [4.3.0]non-3-ene	10
12.	The Observed Dihedral Angles in Models of Conformation 2-I	11
13.	Partial nmr Spectrum of Hydrogens Adjacent to the Ether Oxygen of Cis-8-oxabicyclo [4.3.0]non-3-ene	12
14.	The Angular Dependence of the Geminal and Vicinal Proton-proton Coupling Constants	13
15.	The Observed Dihedral Angles in Conformation 2-II and 2-III, From Space-filling Molecular Models	14
16.	Possible Conformations of Thujopsene	16

LIST OF FIGURES (CONTINUED)

17.	The Transition States of Hydroboration of Cis-8-oxabicyclo [4.3.0] non-3-ene	17
18.	The Products From Hydroboration of Cis-8-oxabicyclo [4.3.0] non-3-ene	18
19.	Steric Approach Control vs. Product Development Control	20
20.	Torsional Strain vs. Steric Strain	21
21.	Possible Conformations of 23, and the Possible Approach of the Metal Hydrides to the Carbonyl Function	22
22.	Possible Conformations of Cis-7,7,9,9-tetramethyl-8-oxabicyclo [4.3.0]non-3-ene	23
23.	Preparation of Cis-7,7,9,9-tetramethyl-8-oxabicyclo [4.3.0] non-3-ene	24
24.	The Grignard Reaction of Dimethyl-cis-4-cyclohexene-1,2-dicarboxylate	25
25.	Cis- and Trans-7,7,9,9-tetramethyl-8-oxabicyclo [4.3.0] non-3-ene	26
26.	Possible Product or Product Mixture From Hydration of Conformation 3-II and 3-III	28
27.	The Observation of the Product Mixture From the Oxymercuration of Cis-7,7,9,9-tetramethyl-8-oxabicyclo [4.3.0] non-3-ene by an Analytical Gas Chromatography	29
28.	The Long-range Electronic Participation Between the π-system of the Double Bond and the Nonbonded Electrons of the Oxygen Atom in Cis-8-oxabicyclo [4.3.0]non-3-ene	31
29.	Cis-8-oxabicyclo [4.3.0]nonane	33
30.	The Cis-N-substituted-8-azabicyclo [4.3.0]non-3-ene Systems	36
31.	Preparation of Cis-N-substituted-8-azabicyclo [4.3.0] non-3-ene Systems	37

LIST OF FIGURES (CONTINUED)

32.	Preparation of the Quaternary Methiodide Salt of the Cis-N-substituted-8-azabicyclo [4.3.0] non-3-ene Systems	37
33.	Cis-8-phenyl-8-azabicyclo [4.3.0] nonane and its Quaternary Methiodide Salt	38
34.	Possible Conformations of Nitrogen Inversion of Cis-8-propyl-8-azabicyclo [4.3.0] non-3-ene	44
35.	The Quinolizidine Ring System	44
36.	The Aziridine System	45
37.	The N-substituted-2,2-dimethyl Aziridine Systems	45
38.	The Cis-7-chloro-7-azabicyclo [4.3.0] heptane System	46
39.	Stereospecific Synthesis of Cis-8-oxabicyclo [4.3.0] nonan-3-ol-endo	54
40.	The Observation of Compounds in Table 18 From an Analytical Gas Chromatography	56
41.	The Observation of the Product Mixture From Dehydration of Cis-$\alpha,\alpha,\alpha',\alpha'$-tetramethyl-4-cyclohexene-1,2-dimethanol From an Analytical Gas Chromatography	60
42.	The Observation of Compounds in Table 20 From an Analytical Gas Chromatography	63

ABSTRACT

By utilizing data obtained from chemical and spectroscopic studies, the ground state conformation of an oxygen-containing heterocyclic compound, cis-8-oxabicyclo [4.3.0]non-3-ene, has been established. A long-range electronic participation from the π-system of the double bond to the nonbonded electrons of the oxygen was proposed from the spectroscopic study.

Cis-7,7,9,9-tetramethyl-8-oxabicyclo [4.3.0]non-3-ene was prepared, and the conformation of this molecule was proposed by utilizing chemical and spectroscopic data. Furthermore, the spectroscopic study indicated the blockage of the electronic participation between the π-system of the alkene and the nonbonded electrons of the oxygen atom due to the steric factor of the four methyl groups.

A similar spectroscopic study was extended to the nitrogen analogs, the cis-N-substituted-8-azabicyclo [4.3.0]non-3-ene systems. The primary data led to the proposal of the nitrogen inversion and the similar electronic participation was obtained.

PART I

THE CONFORMATION OF CIS-8-OXABICYCLO[4.3.0]NON-3-ENE

INTRODUCTION

Compounds containing a ring made up of more than one kind of atom are called heterocyclic compounds, and are often found in drugs, natural products, and many biologically important molecules. The role of the heteroatoms in the molecule is important, and is different from that of a carbon atom. Yet, the influence of the heteroatom to the conformation, stereochemistry, and reactivity of the whole molecule is still unknown in many heterocyclic systems.

In this laboratory, some simple heterocyclic systems, as shown in figure 1, have been studied. The main interest of the investigation concerns the influence between the heteroatoms and the alkene bond.

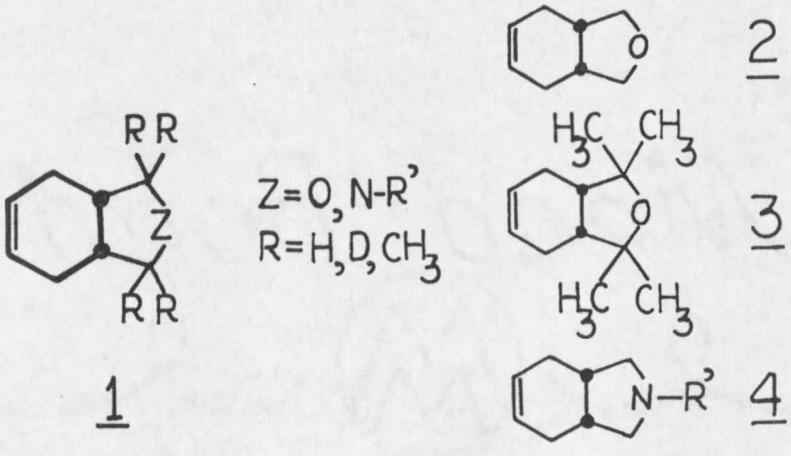


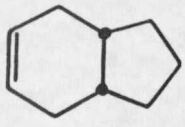
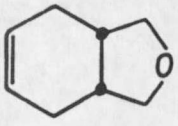
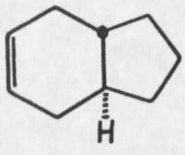
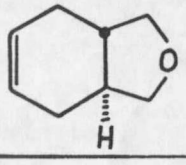
Figure 1: The Structure of Cis-8-hetero-bicyclo[4.3.0]non-3-ene Systems.

Cis-8-oxa-bicyclo[4.3.0]non-3-ene, (2), has been used as a model for the corresponding carbocyclic compound[1]. It has been assumed that this oxygen-containing heterocycle will exhibit steric and conformational characteristics similar to the corresponding carbocycle, especially in reactions on the cyclo-

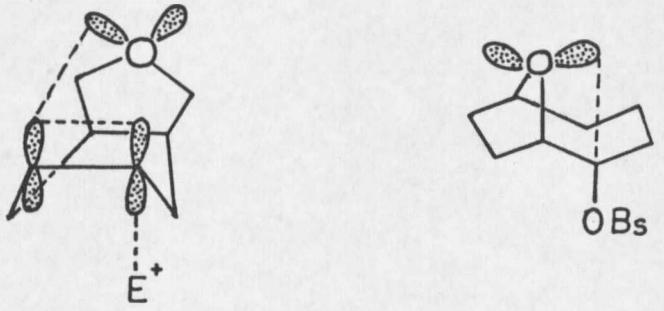
hexene moiety. However, in recent investigations of other oxygen-containing heterocycles, the influence of the heteroatom on the reactivity of the whole molecule has been noted. These changes in reactivity, relative to the corresponding carbocyclic systems, can be rationalized by resonance[2], inductive effects[3], dipole effects[4], directive and electronic effects[5,6], and conformational effects[7] due to the presence of the heteroatoms.

From this laboratory, Mundy and Otzenberger[8,9] reported the competition results of oxymercuration-demercuration reaction, (shown in Table 1) and proposed the contribution of the oxygen in 2 to the chemistry of the alkene bond[5].

Table 1: Competition Results of Oxymercuration

Compound	Compound No.	Relative Rate
	5	1.00
	6	0.11
	2	0.93
	7	0.15
	8	0.40

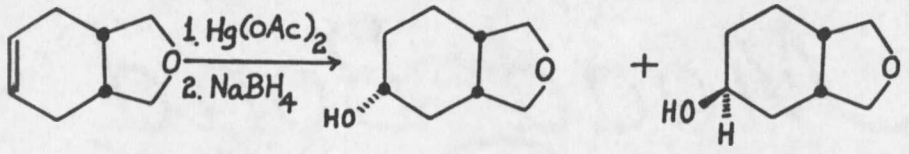
The eightfold increase of reactivity of 2 as compared to 6 demonstrated that the alkene bond in 2 was more reactive. They suggested that the non-bonded electrons of the oxygen stabilized any incipient charge which might result from electrophilic attack on the π-system of the alkene. This interaction, as indicated by 9, might be similar to the long-range oxygen participation reported by Paquette for 10[3].



9 10

Figure 2: The Long-range Oxygen Participation

The products of the oxymercuration from cis-8-oxabicyclo [4.3.0] non-3-ene, (2), were cis-8-oxabicyclo [4.3.0] nonan-3-ol-endo, (11), and cis-8-oxabicyclo [4.3.0] nonan-3-ol-exo, (12), as shown in Figure 3.



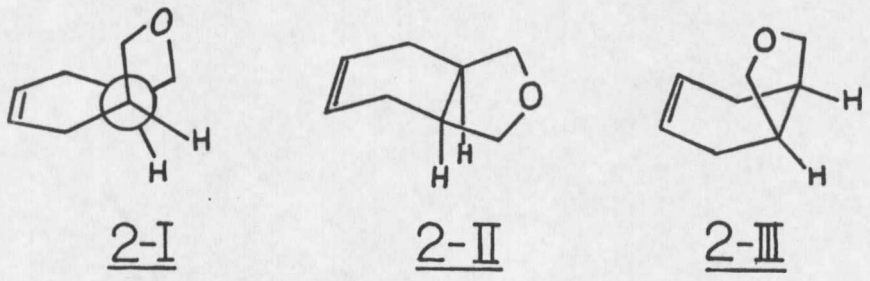
2 11 12

Ratio* 3 : 1

(*Reaction repeated by this worker)

Figure 3: Oxymercuration-Demercuration Products From Cis-8-oxabicyclo [4.3.0]non-3-ene.

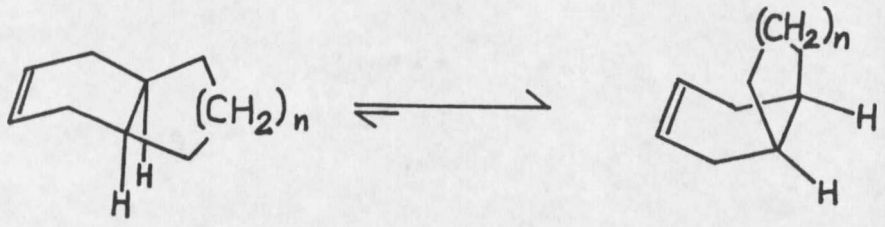
Otzenberger[9] also proposed that the ground-state conformation of 2, among all the possible conformations, was 2-II (figure 4). 2-I was the distorted pseudo-chair conformation; 2-II and 2-III were the two possible boat conformations.



2-I 2-II 2-III

Figure 4: Possible Conformations of Cis-8-oxabicyclo [4.3.0] non-3-ene.

Casadevall[10] proposed that the ground state conformation of cis-bicyclo [4.3.0] non-3-ene, (6), was 6-III (figure 5), based on the result of epoxidation reaction.



II III

Figure 5: Suggested Conformations of Cis-bicyclo [4.3.0] non-3-ene and Cis-bicyclo [4.2.0] oct-3-ene.

The rationalization was that if 6-II were the preferred conformation, epoxidation should have yielded approximately a 50:50 mixture of the endo and exo epoxides. But if 6-III were preferred, one expected to find that the top side of the molecule was more hindered than the bottom side (figure 5), therefore, the exo-epoxide

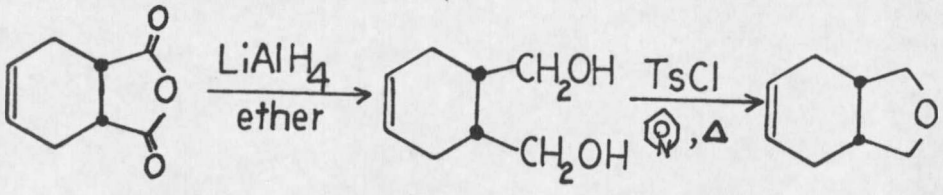
should have predominated. The results were that the endo:exo ratio was 14:86 which indicated that the 6-III was preferred.

Cope[11] also reported similar ratio (13:87) for the endo:exo epoxides from epoxidation of cis-bicyclo[4.2.0]oct-3-ene, (13), and proposed that the conformation was 13-III, based on the same argument. Cope[11] and Casadevall[10] concluded that the cis-fused cyclohexene compounds 13 and 6 existed respectively in the pseudo-boat form.

Otzenberger[9] suggested that 2-I was not the conformation. However, because of limiting data, there was little concrete support for this suggestion. This need for supporting data led this researcher to the investigation of the first part of this report[12].

SYNTHESIS

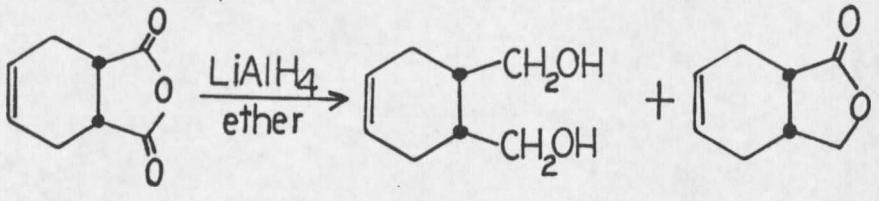
Cis-8-oxabicyclo[4.3.0]non-3-ene, (2), was prepared according to figure 6.



14 15 2

Figure 6: Preparation of Cis-8-oxabicyclo[4.3.0]non-3-ene.

The commercially available anhydride 14 was reduced to the cis-diol 15 by lithium aluminum hydride. The interesting by-product obtained from this reaction was the lactone (16) (figure 7), as evidenced by infrared spectroscopy.



14 15 16

Figure 7: The Main and By-products of $LiAlH_4$-reduction of Cis-1, 2,3,6-tetrahydrophthalic Anhydride.

It was noted that further reduction of the lactone (16) with lithium aluminum hydride gave a quantitative yield of the diol (15).

The diol was then converted to the tetrahydrofuranyl system, presumably by way of a monotosylate under conditions for which it was known that systems of this type readily underwent cyclization to the bicyclic systems (figure 8). The

product 2 was identified by infrared spectroscopy and nmr.

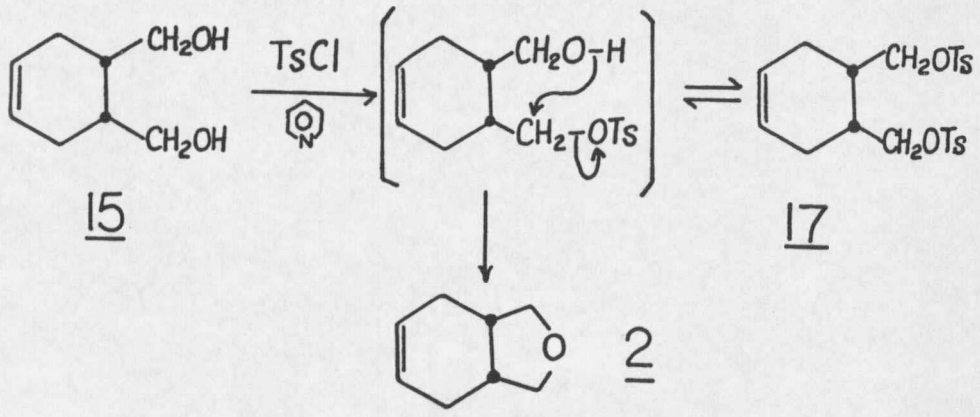


Figure 8: Mechanism of Cyclization to the Bicyclic Systems

For the investigation of nmr spectroscopic data to confirm that the conformation 2-I was not the ground-state conformer, it was necessary to prepare cis-8-oxa-bicyclo [4.3.0] -7,7-dideutero-non-3-ene[13], (19), (figure 9).

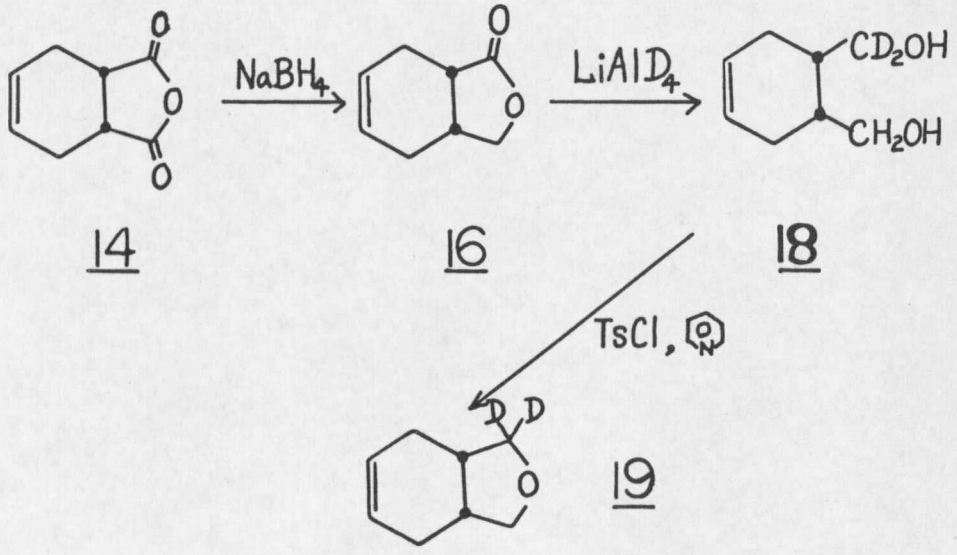


Figure 9: Preparation of Cis-8-oxabicyclo [4.3.0] -7,7-dideutero-non-3-ene.

Following the method of Bailey[14], the anhydride (14) was first reduced to the lactone (16) by sodium borohydride, then further reduced to the 1,6-diol (18) by lithium aluminum deuteride, and then cyclized to 19 by p-toluensulfonyl chloride in pyridine. The bicyclic compound (19) was verified by infrared spectroscopy, and used for nmr investigation.

NMR SPECTROSCOPIC DATA

The nmr spectrum of 2 exhibited a multiplet for the protons adjacent to the ether oxygen, and the spectrum of 19 exhibited the same multiplet, but with only half the "intensity". (The full nmr spectrum of 2 is attached in Appendix IV; the partial nmr spectrum of the protons adjacent to the ether oxygen of 2 is shown in figure 13). This required that H_a and $H_{a'}$ share equivalent magnetic environments, as must H_b and $H_{b'}$ (figure 10).



2 19

Figure 10: The Protons Adjacent to the Ether Oxygen in Compounds 2 and 19.

By examining space-filling molecular models of 2, one could observe three different conformations - 2-I, 2-II, and 2-III (figure 11); and in each conformation, there were three possibilities, A, B, and C. In B, the tetrahydrofuran moiety was flat.

One could observe that H_b and $H_{b'}$ were in entirely different environments in conformation 2-I; the $H_{b'}$ was close to the π-system of the double bond, while H_b was far away from the double bond. One also would observe further information supporting that H_b and $H_{b'}$ were in different environments from the dihedral angles. Since the tetrahydrofuran moiety was distorted in conformation 2-I, it was impossible to keep this five-membered ring flat. Therefore, only conformers 2-I-A and 2-I-C were discussed here. The dihedral angle between the H_c'-$C_3'o$-C_α' and $C_3'o$-C_α'-H_b' planes was 150 ± 10^o, and that between the

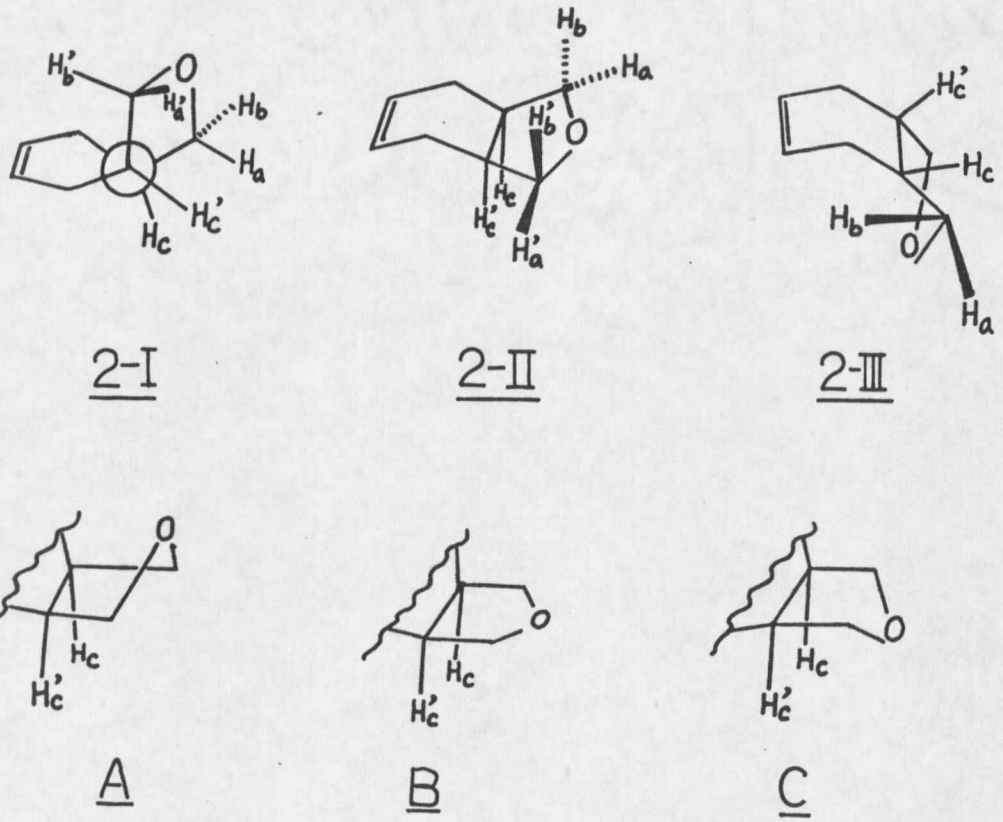


Figure 11: Possible Conformations of 2.

H_c-C_3o-C_α and C_3o-C_α-H_b planes was 120 ± 10^o in 2-I-A. In 2-I-C, the corresponding dihedral angles were 165 ± 10^o and 135 ± 10^o, respectively (figure 12). All this information clearly indicated that the ground state conformation was not 2-I.

In both conformation 2-II and 2-III, one would observe that H_a and $H_{a'}$, and H_b and $H_{b'}$ were in the same environments respectively.

For the three nonequivalent protons H_a ($H_{a'}$), H_b ($H_{b'}$), H_c ($H_{c'}$), an ABX system was designated by following Silverstein[15] and Pople[16]. From the analysis of the nmr spectrum of 2 (figure 13), H_a ($H_{a'}$) differed in chemical shift from H_b ($H_{b'}$) by 22.2 cycles per second (cps). H_a ($H_{a'}$) coupled with

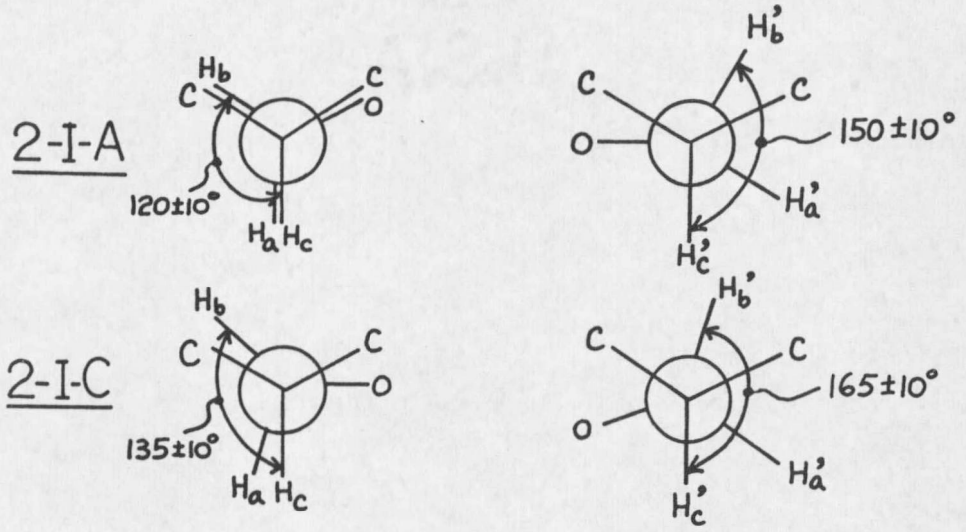


Figure 12: The Observed Dihedral Angles in Models of Conformation 2-I.

H_b ($H_{b'}$) respectively with a coupling constant, J_{ab} ($J_{a'b'}$), of 7.8 cps. (The only other coupling available now was between H_a and H_c, and H_b and H_c). The interpretative problem was faced because coupling constant - dihedral angle relationships have not been well studied for heterocyclic systems. However the reported dihedral angle-coupling constant relationships for carbon systems would be used tentatively.

(Karplus[17(a), (b)] has pointed out the dependence of coupling constant, J, on bond angles for both the coupling between the geminal protons and the coupling between protons on vicinal carbons in carbon systems) (figure 14).

The conformation 2-III-A clearly indicated the repulsion between the nonbonded electrons of the oxygen atom and the π-system of the double bond, by their close proximity.

The dihedral angle between H_c-C_3o-C_α and C_3o-C_α-H_b planes and also that between H_c-C_3o-C_α and C_3o-C_α-H_a planes in conformations 2-II, 2-III-B,

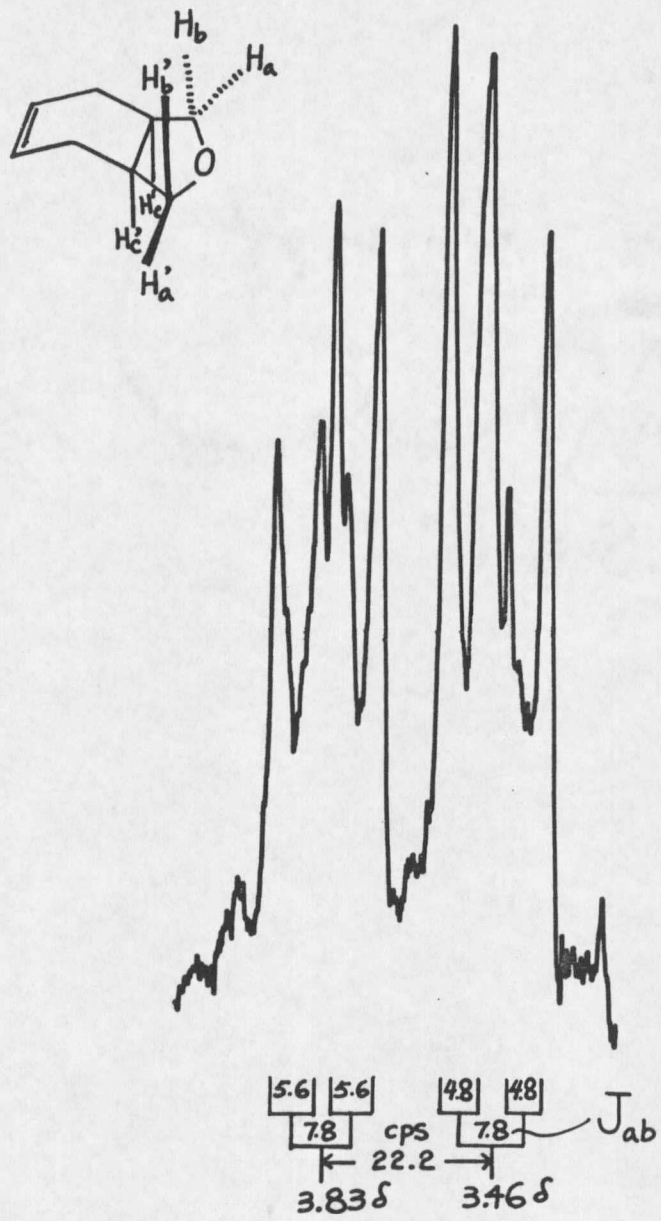


Figure 13: Partial NMR Spectrum of Hydrogens Adjacent to the Ether-oxygen of Cis-8-oxabicyclo [4.3.0] non-3-ene.

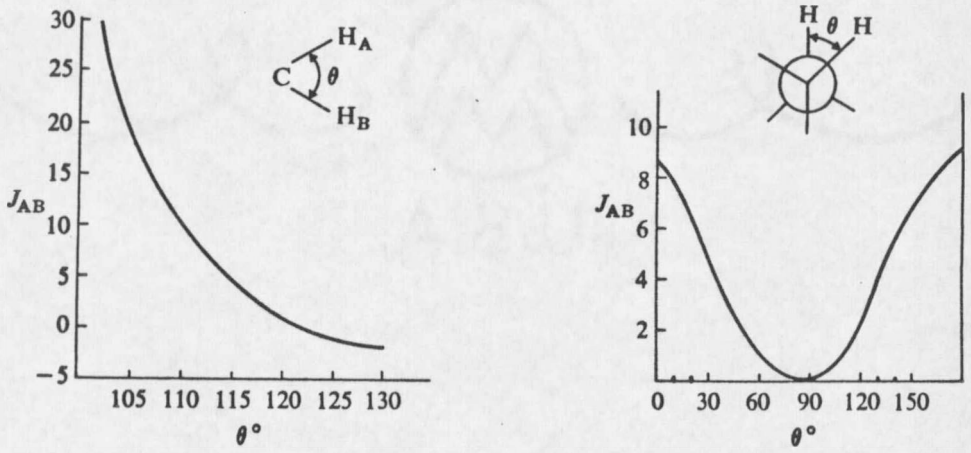


Figure 14: The Angular Dependence of the Geminal and Vicinal Proton-Proton Coupling Constants[17].

and 2-III-C were carefully investigated and shown in figure 15.

The corresponding tentative coupling constants were found by using Karplus[17] diagram from carbon systems, and were tabulated in table 2. From these approximate figures, no conclusion could be obtained.

However, if the simplified observation - trans coupling is usually more effective than cis coupling - was used, the larger coupling constant 5.6 cps would be assigned to the J_{cb}, and the smaller one, 4.8 cps, to the J_{ca}. Therefore, the chemical shift for H_b would be the less shielded one, i.e., 3.83δ, and that for H_a would be the 3.46δ. These indicated that 2-II was the ground state conformation. If 2-III were the ground state conformation, proton H_b would be expected to be more upfield because it would be influenced by the magnetic shielding cone of the alkene system.

All in all, as it was already noted, nmr evidence was consistent with, but did not prove, that 2-II was the ground state conformation. Therefore, chemical evidence to substantiate this assignment was required.

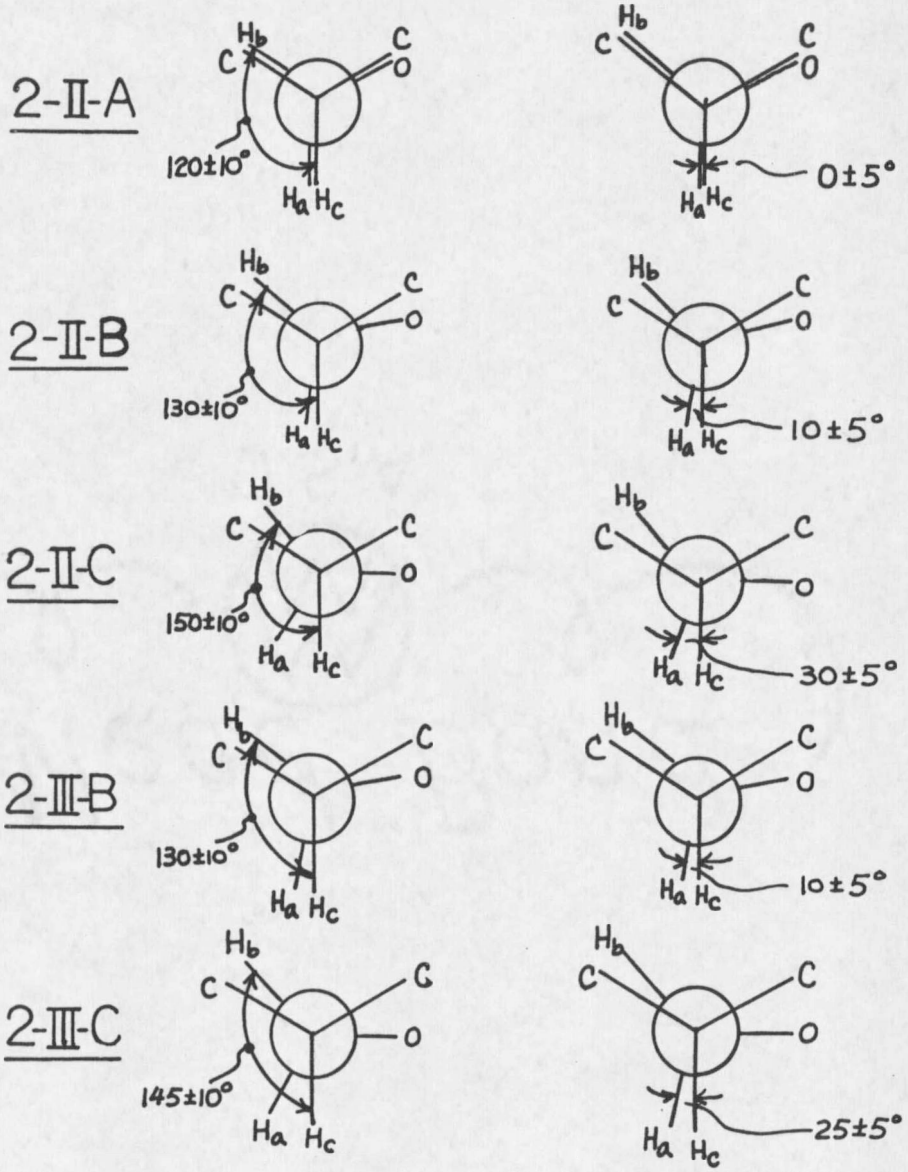


Figure 15: The Observed Dihedral Angles in Conformation 2-II, 2-III-B, and 2-III-C, From Space-filling Molecular Models.

Table 2: Tentative Coupling Constants.

Conformation	J_{cb}	J_{ca}	Larger Coupling	
2-II-A	2.5	8.2	J_{ca}	(cis)
2-II-B	4.2	7.4	"	"
2-II-C	7.0	4.9	J_{cb}	(trans)
2-III-B	4.2	7.4	J_{ca}	(cis)
2-III-C	6.3	5.3	J_{cb}	(trans)

HYDROBORATION

The hydroboration-oxidation of olefins has been reported to be a convenient procedure for achieving the anti-Markovnikov hydration of carbon-carbon double bonds[18,19], and to be highly sensitive to the steric environment of the double bond and generally takes place from the less hindered side[20,21]. This reaction has been also reported to be highly exothermic, but is remarkably free of skeletal rearrangement[18]. Brown proposed that the transition state for such a reaction should resemble the reactants[22]. In other words, the stereochemistry of the reaction products can be correlated with the ground state of the reactants[23,24]. Since the reaction of diborane with olefins in ether solvent is very fast, Brown[22] strongly suggested that the activation energy for the hydroboration step may be less than that for the interconversion stage of the flexible cyclic thujopsene (figure 16). By comparing the possible conformations of thujopsene and that of the system 2, it is reasonable to suggest that the conformational interconversions in the fused ring system 2 might be also expected to be higher than the activation energy for diborane addition.

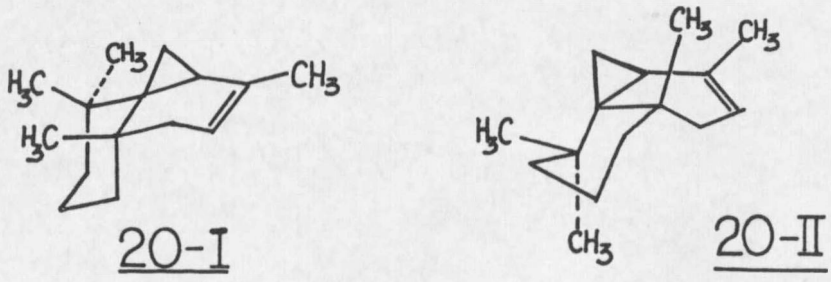


Figure 16: Possible Conformations of Thujopsene

With this assumption, the transition states 21 and 22, resembling 2-II and 2-III respectively, were considered (figure 17).

Since the addition of diborane to the double bond is cis and the replacement of boron by hydroxyl in the oxidation proceeds with the retention of con-

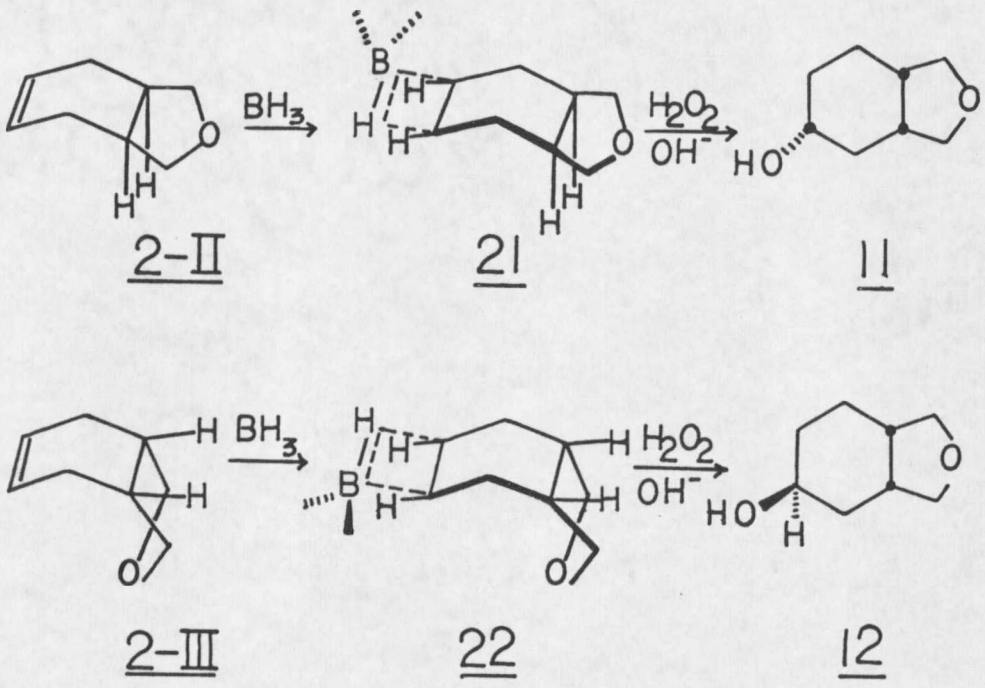
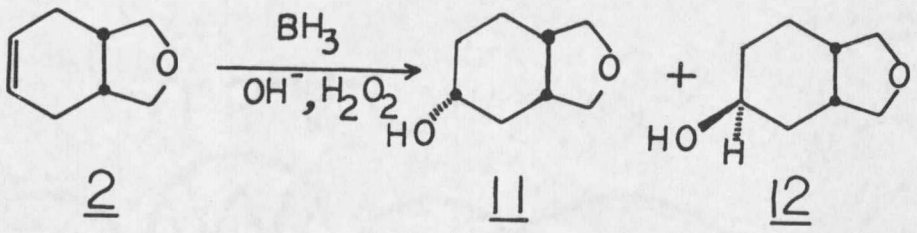


Figure 17: The Transition State

figuration[25-27], the major alcohol product resulting from 21 would be 11, and from 22 would be 12. The space-filling molecular models clearly indicate that in conformation 2-II, the bottom side of the molecule (figure 17) is more hindered due to the interference of the protons at the ring juncture, and also that in conformation 2-III there is much less possibility of attack from the other side of the π-system since that side of the double bond is hindered by the oxygen atom and its neighboring atoms. The product of this reaction was found a mixture of exo alcohol 12 and endo alcohol 11 in the ratio of 28:72 (figure 18). This supports our suggestion that 2-II is the ground state conformation.



2 11 12

Ratio: 28 : 72

Figure 18: The Products From Hydroboration of 2.

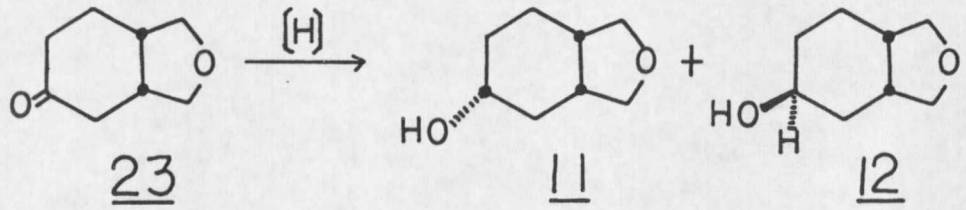
CIS-8-OXABICYCLO[4.3.0]NONAN-3-ONE

Oxidation of the alcohols 11 and 12 by Jone's procedure gave a single ketone cis-8-oxabicyclo[4.3.0]nonan-3-one, (23), in almost quantitative yield.

When oxidizing the alcohols 11 and 12, two methods had been attempted. Brown's chromic acid-ether procedure[18,28] was tried and lead to a decomposed product. This type of oxidation was apparently too strong for alcohols from 2. Jone's oxidation[29] was found very satisfactory - simple to run, and gave high yields.

The ketone 23 on reduction with sodium borohydride afforded the exo and endo alcohols 12 and 11 in the ratio of 17:83, and with lithium aluminum hydride in the ratio of 20:80 (table 3).

Table 3: Results From Reduction of Cis-8-oxabicyclo[4.3.0] nonan-3-one.

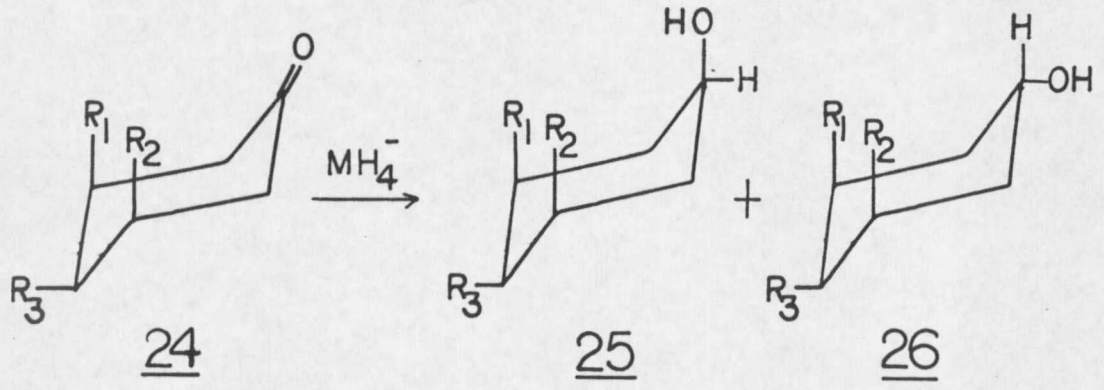


23 11 12

Method of reduction	Product ratio 11 : 12
(1) $NaBH_4$	83 : 17
(2) $LiAlH_4$	80 : 20

It was first proposed[30-34] that the reactions of cyclic ketones with metal hydrides was governed by two opposing factors: (1) Steric Approach Control, the steric hindrance to approach of the reagent to the carbonyl function. (2) Product Development Control, the stability of the final product. In terms of these two factors, it was proposed that the steric approach control predominated in the reaction of hindered cyclic ketones[34], e.g., 24(a)[33], (figure 19); and that

the product development control predominated in the reduction of unhindered cyclic ketones, e.g., 24(b)[31,33] (figure 19). Unless approach to one side of the carbonyl group in a cyclic ketone was clearly much more hindered than approach to the other side, the usual result of a metal hydride reduction was the formation of a mixture of alcohols in which the more stable alcohol predominated[35].



24 25 26

(a): R_1 = alkyl, R_2 = alkyl $\quad \frac{25(a)}{26(a)} > 1$ (Steric Approach Control predominated)

(b): $R_1 = R_2 = H$

R_3 = -H, $-CH_3$, $-C(CH_3)_3$,  $\quad \frac{25(b)}{26(b)} < 1$ (Product Development Control predominated)

Figure 19: Steric Approach Control vs Product Development Control

It was proposed later[36-38] that the reaction between cyclic ketones and nucleophilic reagents such as metal hydrides, were governed by the relative magnitude of steric strain[36] and torsional strain[37] in the eclipsed reactant-like transition state, as shown in Figure 20. When the substituents on C_3 and C_5 of the cyclohexanone ring were small, e.g. R_1 = H, R_2 = H, the steric strain in transition state 27 was expected to be small, smaller than the torsional strain

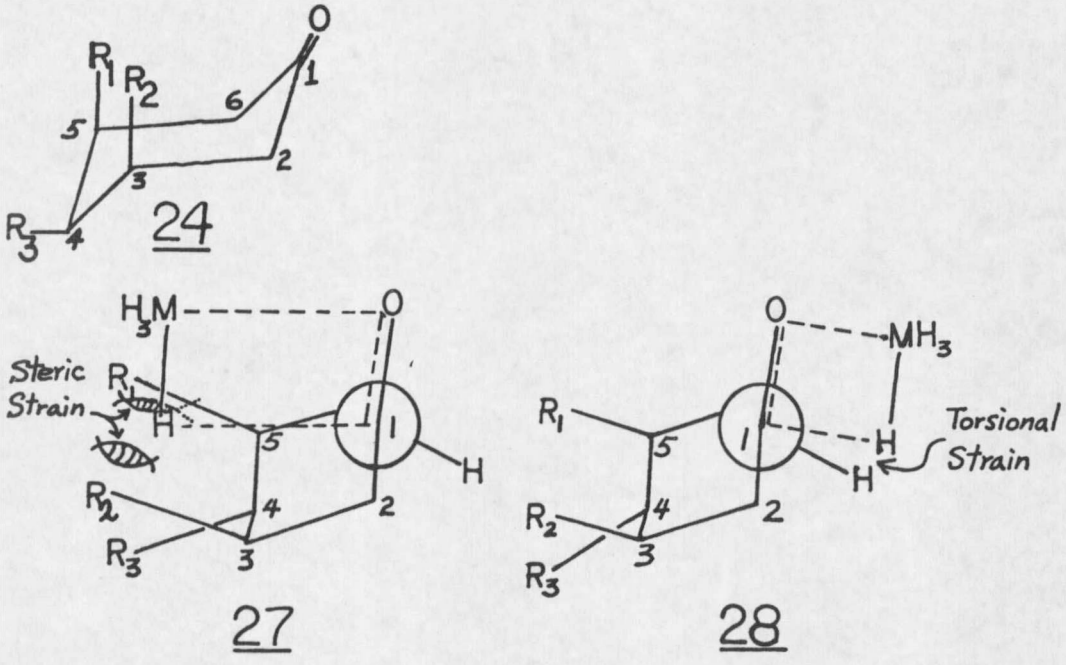


Figure 20: Torsional Strain vs Steric Strain in the Transition State

in transition state 28. This resulted in the predominant formation of the equatorial alcohol 26 (figure 19). When the size of the substituents of C_3 and C_5 increased, the steric strain in 27 increased, and the torsional strain in 28 was remaining unchanged. This led to the increasing proportion of axial alcohol 25 in the product mixture.

In the case of cis-8-oxabicyclo [4.3.0]nonan-3-one, (23), the two possible chair conformations 23-I and 23-II (figure 21) both indicated the predominant formation of endo alcohol 11, in terms of relative magnitude of steric strain and torsional strain in transition states. In conformation 23-I, the Newman projection clearly indicated that the cis-substituents on C_3 and C_5 in the cyclohexanone moiety were hydrogens. The steric strain is expected to be

smaller than the torsional strain. In conformation 23-II, the substituents on C_3 and C_4 in the cyclohexanone moiety are bulky. Therefore, the steric strain is expected to be larger than the torsional strain. In both cases, the attack of metal hydride is favored from the less strained side and affords the predominant endo-alcohol 11. This theoretical prediction agrees with the observed data shown in table 3.

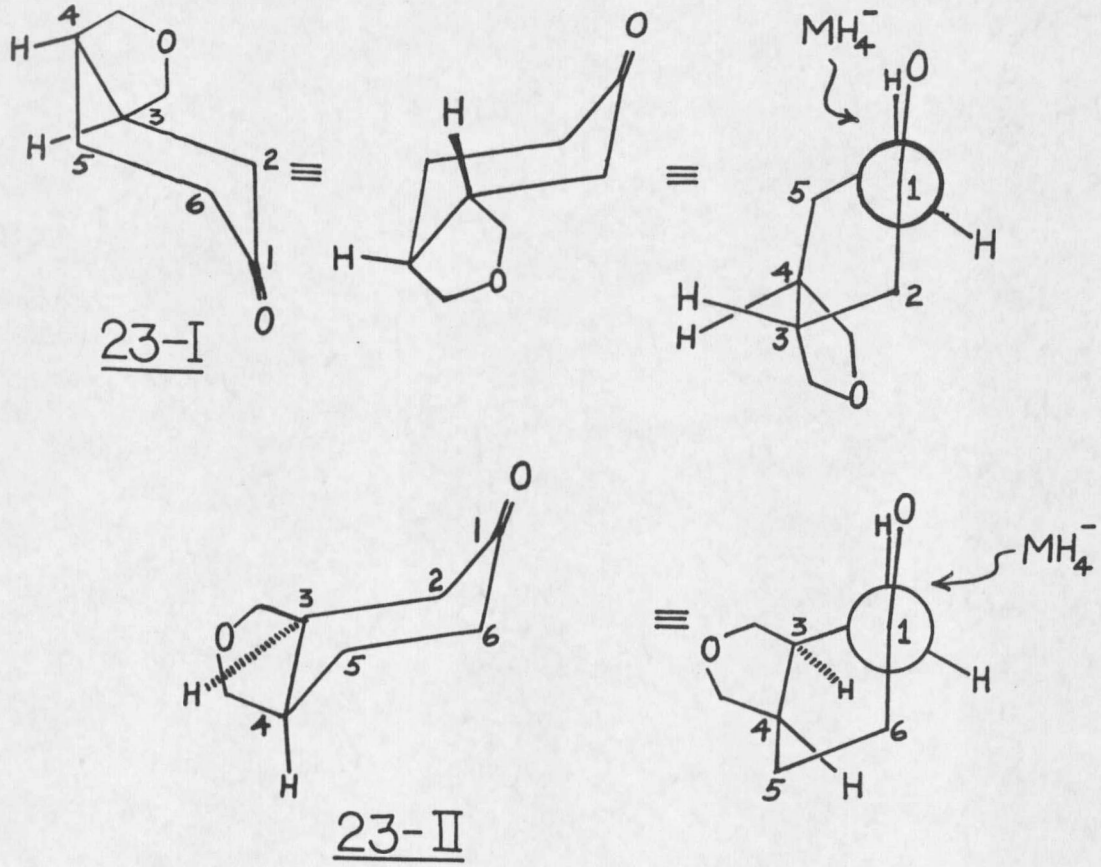


Figure 21: Possible Conformations of 23, and the Possible Approach of the Metal Hydrides to the Carbonyl Function.

PART II

SYNTHESIS AND REACTIVITY OF CIS-7,7,9,9-TETRAMETHYL-8-OXABICYCLO[4.3.0]NON-3-ENE

INTRODUCTION

While investigating the conformation of cis-8-oxabicyclo[4.3.0]non-3-ene, (2), one of the similar systems was found to be very interesting. The backbone structure of 8-oxabicyclo[4.3.0]non-3-ene with four methyl groups added to the α and α' carbons of the ether oxygen constructed the molecule of cis-7,7,9,9-tetramethyl-8-oxabicyclo[4.3.0]non-3-ene (3). These four methyl groups were expected to contribute to the conformation and the chemistry of the whole molecule.

MOLECULAR MODEL

By examining the space-filling molecular models of 3, one would observe three possible conformations corresponding to that of 2 (2-I, 2-II, and 2-III) (figure 22).

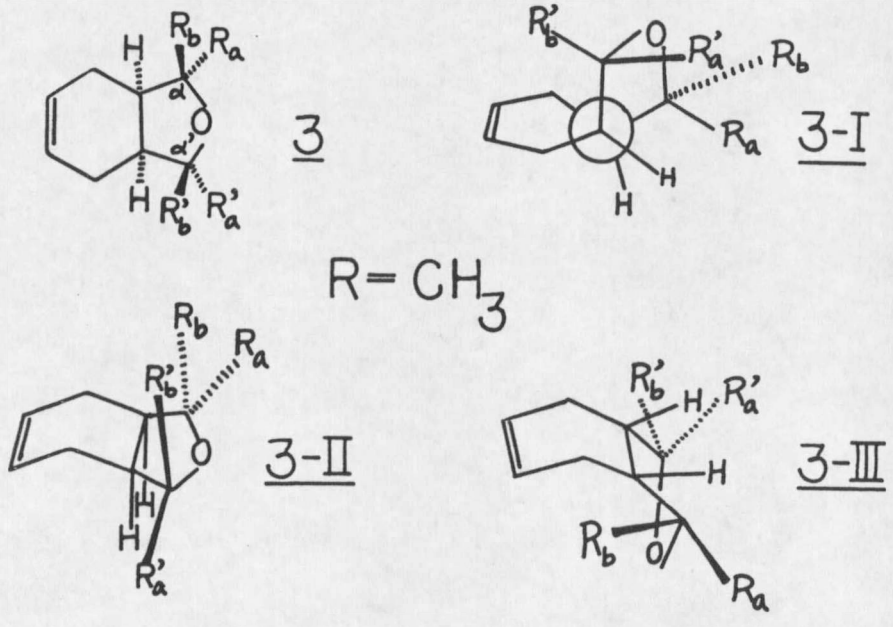


Figure 22: Possible Conformations of Cis-7,7,9,9-tetramethyl-8-oxabicyclo[4.3.0]non-3-ene.

3-I was the distorted pseudo-chair form, and 3-II and 3-III were the two possible boat forms. One finds that the π-electrons of the double bond at one side of the molecule are blocked and shielded by the methyl group(s) in both conformation 3-I and 3-III. Yet in conformation 3-II the π-electrons of the double bond are freely open at both sides of the molecule.

SYNTHESIS

Cis-7,7,9,9-tetramethyl-8-oxabicyclo[4.3.0]non-3-ene, (3), was prepared according to figure 23.

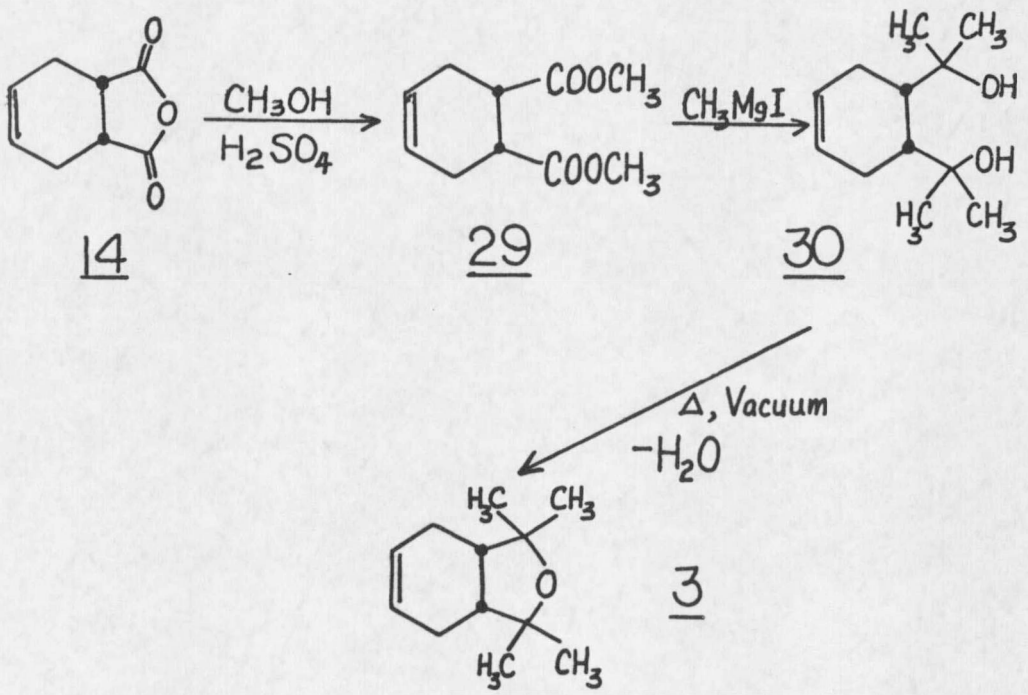


Figure 23: Preparation of Cis-7,7,9,9-tetramethyl-8-oxabicyclo [4.3.0]non-3-ene.

The commercially available anhydride 14 was converted into the diester 29 by methanol and acid. Then, 29 was reacted with a large excess (7.5 equiv.)

of methylmagnesium iodide, the Grignard reagent, to give the cis-diol 30. The interesting product, lactone 31, as evidenced by infrared spectroscopy, could be obtained if only 2.5 equiv. of methylmagnesium iodide was used for diester 29 (figure 24).

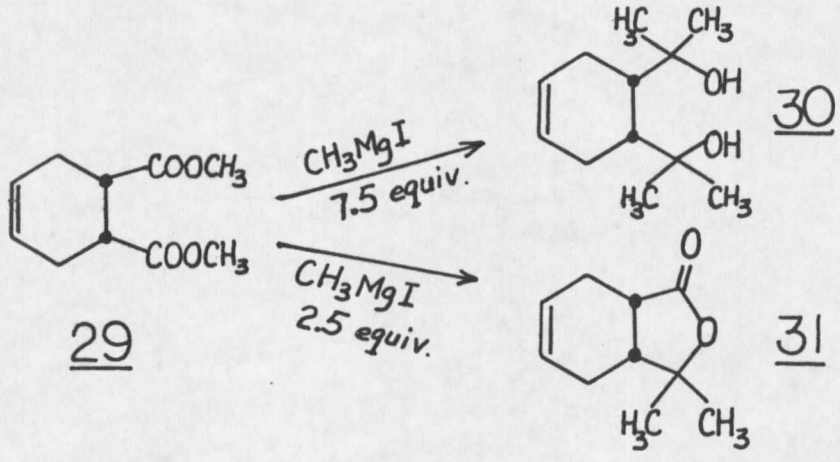
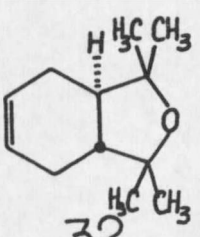


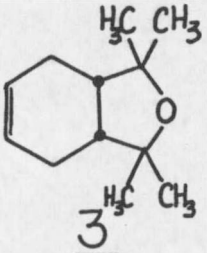
Figure 24: The Grignard Reaction of Dimethyl-cis-4-cyclohexene-1,2-dicarboxylate.

The diol 30 readily dehydrated on distillation, in vacuo, and afforded the bicyclic ether 3 (figure 23). Sometimes a mixture of two compounds with the ratio of 30:70, as analyzed by glc, was obtained when diol 30 was dehydrated. The major product was 3; the minor one, as analyzed by nmr, was suspected to be the trans isomer, 32 (figure 25).

Further verification for this unreported trans isomer was not possible due to the difficulties of separation encountered.



32



3

Figure 25: Cis- and Trans-7,7,9,9-tetramethyl-8-oxabicyclo [4.3.0] non-3-ene.

NMR SPECTROSCOPIC DATA

The nmr spectrum of cis-7,7,9,9-tetramethyl-8-oxabicyclo [4.3.0] non-3-ene, (3), exhibits two singlets with equal intensity for the methyl groups adjacent to the ether oxygen. (The full nmr spectrum of 3 is attached in Appendix IV). This requires that R_a and $R_{a'}$ share equivalent magnetic environments, as must R_b and $R_{b'}$ (figure 22).

One expects to observe the spectrum exhibiting four singlets for the four methyl groups if 3-I were the ground state conformation, since the four methyl groups are all in different environments in 3-I. This is not the case; therefore, 3-I is not the ground state conformation.

Though R_a and $R_{a'}$, also R_b and $R_{b'}$, share equivalent environments in 3-II and 3-III, the stereochemistry of 3-II and 3-III are very much different from each other. Therefore, the conformation should be able to be rationalized with the assistance of chemical data.

OXYMERCURATION

The oxymercuration-demercuration of olefins has been reported to be a convenient procedure for the Markovnikov hydration of carbon-carbon double bonds[39,40], and also to be free from skeletal rearrangement[39,41]. The mechanism of mercuration of olefins has been proposed to be via a mercurinium ion[42-44], and the hydration stage of the initial mercury intermediate to be occuring predominantly from the less hindered side of the molecule[41,45] by a trans-addition.

This hydration of double bond of 3-II and 3-III will lead to different product or product mixtures, assuming that the mechanism of trans-addition is not changed. From the space-filling molecular models of 3-III, one will observe, very clearly, that the double bond is hindered from one side of the molecule. Therefore, only the other side of the double bond will form the mercurinium ion intermediate, then trans addition of entering water molecule will lead to the only product, the endo-alcohol 34, (figure 26).

Yet the space-filling model of 3-II indicates that the double bond is freely open for addition reaction from either side of the molecule, with the bottom side (figure 26) less free because of the presence of the two ring - juncture hydrogens. The mercurinium ion intermediate can form at either side of the double bond, and then the hydration of the mercurinium intermediate. In this case, one might expect to observe a product mixture of exo and endo alcohols 33 and 34.

The product mixture from the oxymercuration-demercuration of 3 was analyzed by analytical glc, and the chromatogram exhibited a single broad unsymmetrical peak, with the smaller slope present at the left side of the peak (figure 27).

Usually a single sharp peak will be detected when a pure compound is

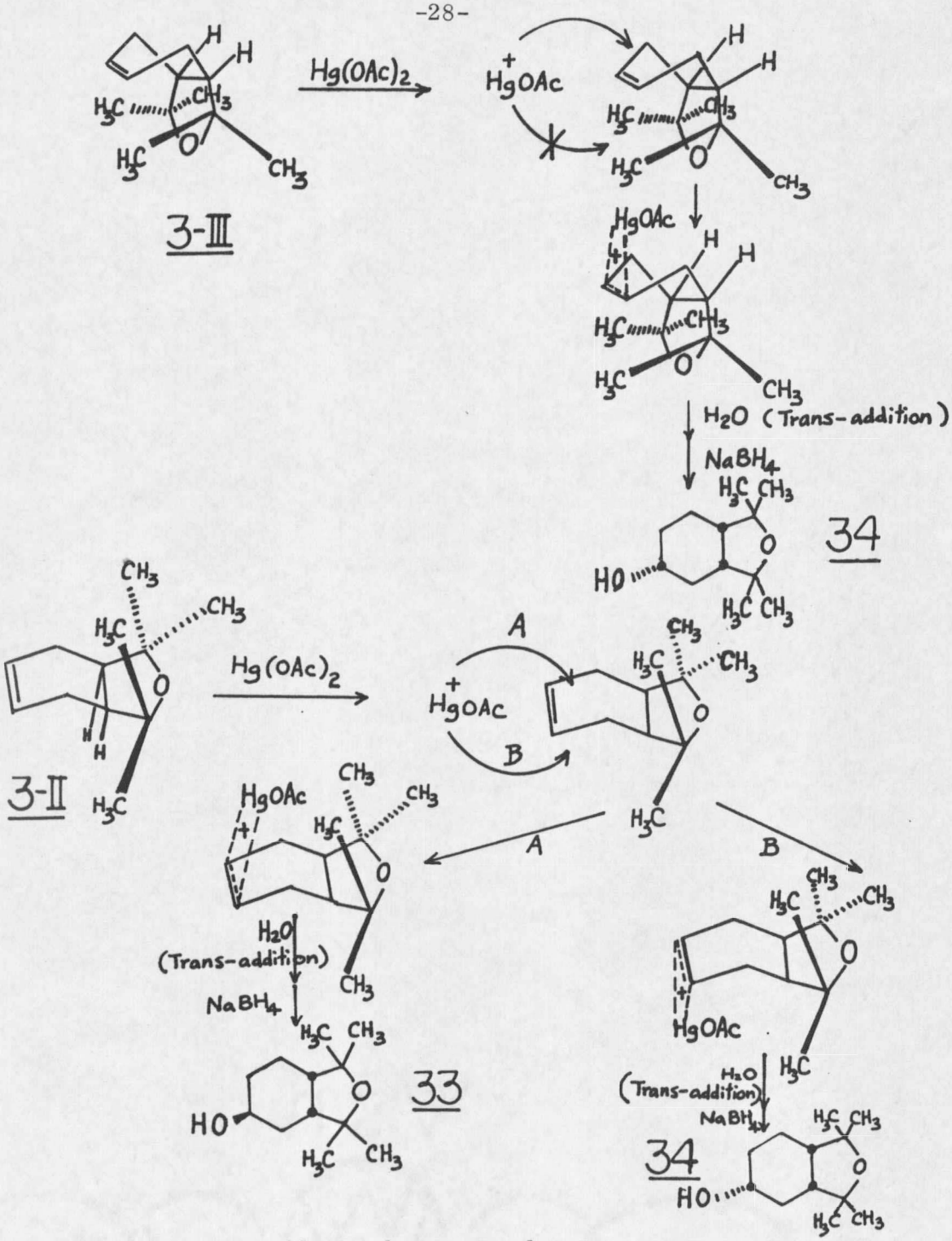


Figure 26: Possible Product or Product Mixture From Oxymercuration-demercuration of 3-II and 3-III.

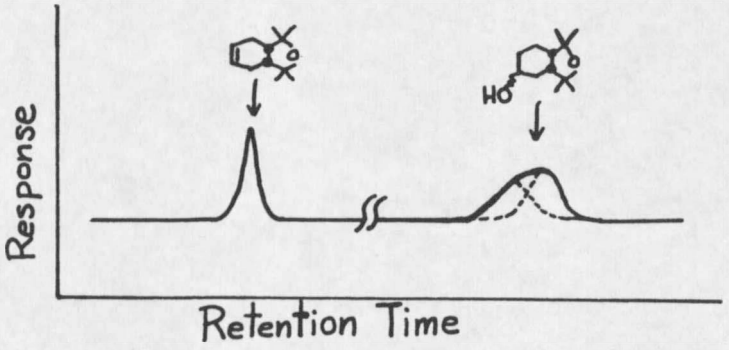


Figure 27: The Observation of the Product Mixture From Oxymercuration-demercuration of 3.

analyzed by analytical glc with the right column chosen. It is also observed that a single broad peak will be detected when a mixture of two compounds with very close retention time is analyzed by glc. When this mixture has a 50:50 ratio, this broad peak usually is symmetrical; when the ratio is not 50:50, this broad peak will be unsymmetrical.

The ratio of the two isomeric alcohols 33 and 34 was found (30-40):(60-70), when the chromatogram was analyzed by the method of triangulation (figure 27). Though these two isomers were not further purified, due to the experimental difficulties encountered, infrared spectroscopy of the product mixture supported the alcohol functionality. Oxidizing this product mixture by Jone's reagent (CrO_3 in H_2SO_4) showed the complete disappearance of the alcohol functionality and the presence of a single ketone, as evidenced by analytical glc and infrared spectroscopy. Also, the result of the elemental analysis of the derivative of the product mixture showed the correct composition (table 4). The sharp melting point of the derivative is not consistant with a product mixture. However, the repeated purifications may have effectively removed one of the isomers.

Table 4: Report of Elemental Analysis of the 3,5-dinitrobenzoate Derivative[46] of the Product Mixture From Oxymercuration of Cis-7,7,9,9-tetramethyl-8-oxabicyclo[4.3.0] non-3-ene[a,b,c]

Composition	%C	%H	%N	%O
Calculated	58.16	6.17	7.14	28.54
Found	57.88	5.93	-	-

a. Empirical formula: $C_{19}H_{24}N_2O_7$

b. Color of this crystal is silvery white

c. Recrystallized from ethanol-water. Melting point is 143-144.5°C, measured by Fisher-Johns melting point apparatus.

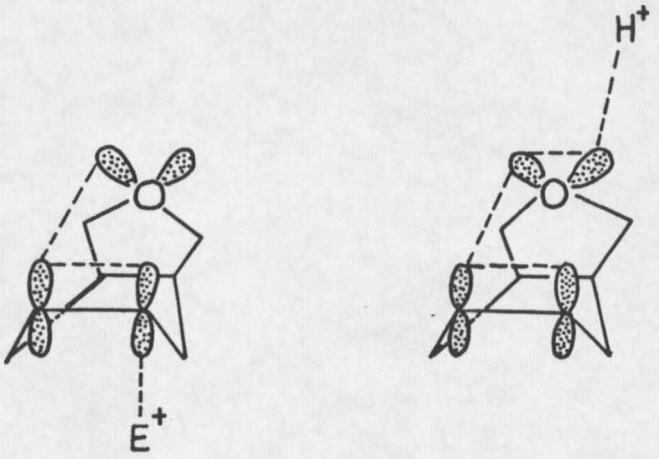
Based on the information from the molecular models, the glc analysis, the oxidation of the alcohol mixture, and the report of elemental analysis of the alcohol derivative, this researcher proposed that the conformer 3-II is the ground state conformation.

It is of interest to mention a qualitative result: Whereas we note almost immediate reaction of 2 under conditions of oxymercuration, 3 appeared to react quite slowly. This may have some significance and is consistent with nmr data to be presented later.

NMR STUDY FOR THE LONG-RANGE ELECTRONIC PARTICIPATION

After Mundy and Otzenberger[8,9] reported the effect of long-range electronic participation from the nonbonded electrons of the ether oxygen to the π-electrons of the double bond in system 2, this researcher found that it was equally interesting to investigate the effect of the long-range electronic

participation from the π-system of the double bond to the non-bonded electrons of the ether oxygen in the systems 2 and 3 (figure 28).



9 35

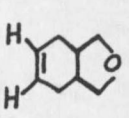
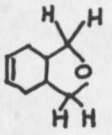
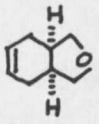
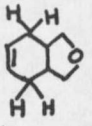
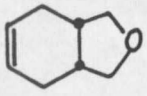
Figure 28: The Long-range Electronic Participation Between the π-system of the Double Bond and the Nonbonded Electrons of the Oxygen in 2.

The nmr study was chosen for this research and was started by comparing the nmr spectra of systems 2 in two different solvents; deuterochloroform, and a mixture of deuterochloroform and deuterotrifluoroacetic acid with a 50:50 ratio. A deshielding effect was observed for the protons adjacent to the oxygen atom, and also for the other protons in this molecule. Then, the same experiment was carried on to the system 3. The deshielding effect to the protons of the double bond in 3 was found to be smaller than that in system 2 (tables 5 and 6).

This observation was rationalized by the difference of the long-range electronic participation between systems 2 and 3.

Conformer 2-II (figure 10) could convert to conformer 2-III to allow the π-electrons of the double bond to stabilize any influence from the approaching

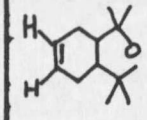
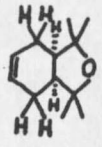
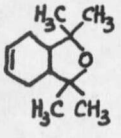
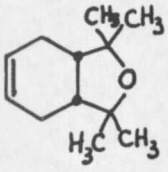
Table 5: The Observed Chemical Shifts of Protons in 2.

Compound	Solvent	Chemical Shift (δ)			
					
 2	$CDCl_3$	5.59	3.67	2.35	2.12
	$\frac{CDCl_3}{CF_3COOD}=1$	5.67	3.88	2.47	2.15
Change of Chemical shift[a] (Δδ)		+0.08	+0.21	+0.12	+0.03

a. (+) sign represents the increase in δ value; downfield δ value.

(−) sign represents the decrease in δ value; upfield δ value.

Table 6: The Observed Chemical Shifts of Hydrogens in 3.

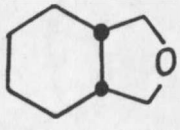
Compound	Solvent	Chemical Shift (δ)			
					
 3	$CDCl_3$	5.69	2.13	1.27	1.14
	$\frac{CDCl_3}{CF_3COOD}=1$	5.72	2.20	1.38	1.26
Change of Chemical shift (Δδ)		+0.03	+0.07	+0.11	+0.12

positive charge to the non-bonded electrons of the oxygen. Therefore, the deshielding effect due to the presence of the positive charge influenced the protons of the double bond more than that without the long-range electronic participation. The larger deshielding effect to the protons of the alkene than that to the other protons on the cyclohexene moiety in 2 supported this postulation clearly (table 5).

On the other hand, though the conformation 3-II (figure 22) could also convert to conformer 3-III; the methyl groups adjacent to the oxygen blocked the long-range electronic participation. Examination of molecular models support this.

In this case, the deshielding effect to the hydrogens of the double bond would be the smallest among all the hydrogens in system 3, since they were the farthest hydrogens to the oxygen. The observation (table 6) again supported this proposal.

To further verify this suggestion, the same experiment was carried on to the corresponding saturated system, cis-8-oxabicyclo [4.3.0] nonane[47], (36), (figure 29). It was again noted that the farthest hydrogens to the oxygen was



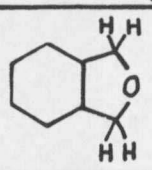
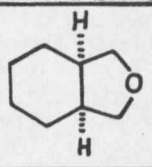
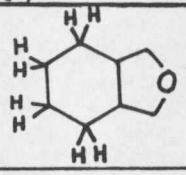
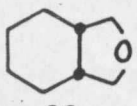
36

Figure 29: The Structure of Cis-8-oxabicyclo [4.3.0] nonane.

influenced the least when 36 was in an acidic solvent (table 7).

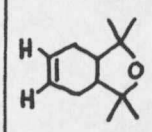
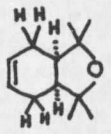
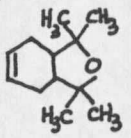
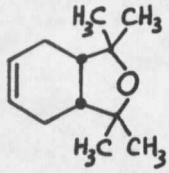
While carrying on these experiments, the effect of the concentration of the sample in the solvent mixture was investigated and found independent to the deshielding effect. Compound 3 was used for the investigation. The ratio of deuterochloroform and deuterotrifluoroacetic acid was carefully kept

Table 7: The Observed Chemical Shifts of Hydrogens in 36.

Compound	Solvent	Chemical Shift (δ)		
				
 36	$CDCl_3$	3.69	2.21	1.48
	$\frac{CDCl_3}{CF_3COOD}$=1	3.90	2.36	1.51
Change of Chemical shift (Δδ)		+0.21	+0.15	+0.03

the same, i.e. one to one, during all the investigation. The results were shown in table 8.

Table 8: The Observed Independence of Deshielding Effect to the Concentration of the Sample in Acidic Solvent.

Compound	Concentration[a,b]	Chemical Shifts (δ)			
					
 3	1	5.72	2.20	1.38	1.26
	1/2	5.72	2.20	1.38	1.26
	1/8	5.72	2.20	1.38	1.26

a. The solvent is a mixture of $CDCl_3$ and CF_3COOD, with a 50:50 ratio.

b. The actual concentration of 3 in the solvent was not calculated and was tentatively assigned as 1, then diluted to half, and then one-eighth of this concentration.

PART III

CIS-N-SUBSTITUTED-8-AZABICYCLO [4.3.0] NON-3-ENE SYSTEMS

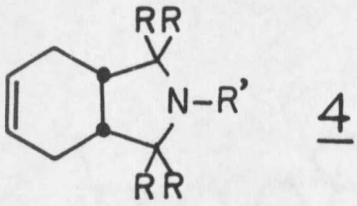
INTRODUCTION

"The use of analogies -- or guessed-about analogies -- is probably still one of the main characteristics of organic chemistry. Hopefully, this method offers the advantage that we may proceed from a group of 'simple', well-established data toward slightly different or more complex situations. In fact, this is done not only in preparative organic chemistry, but also in the application of quantum mechanics. In such an approach-by-analogy, we have to use intuitive corrections and extrapolations, the main difficulty being to predict or assess the differences between our analogs and the new systems to be considered."

-- E. C. Kooyman[48]

From the same attitude and philosophy as the above quotation, this part was carried on to the nitrogen-containing heterocyclic compounds.

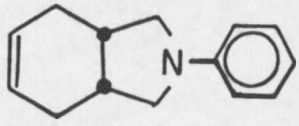
Several cis-N-substituted-8-azabicyclo [4.3.0] non-3-ene systems, 4, were studied (figure 30).



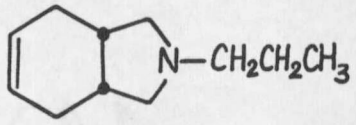
4

R' = ⬭, $-CH_2CH_2CH_3$
R = H, D

37



38



39

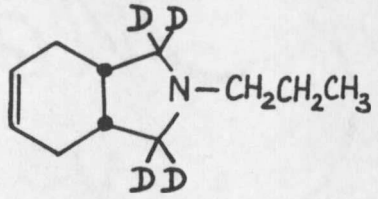
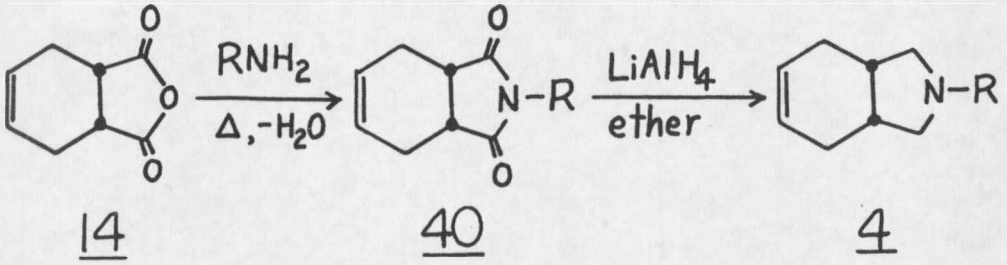


Figure 30: The Structures of Cis-N-substituted-8-azabicyclo [4.3.0] non-3-ene Systems.

SYNTHESIS

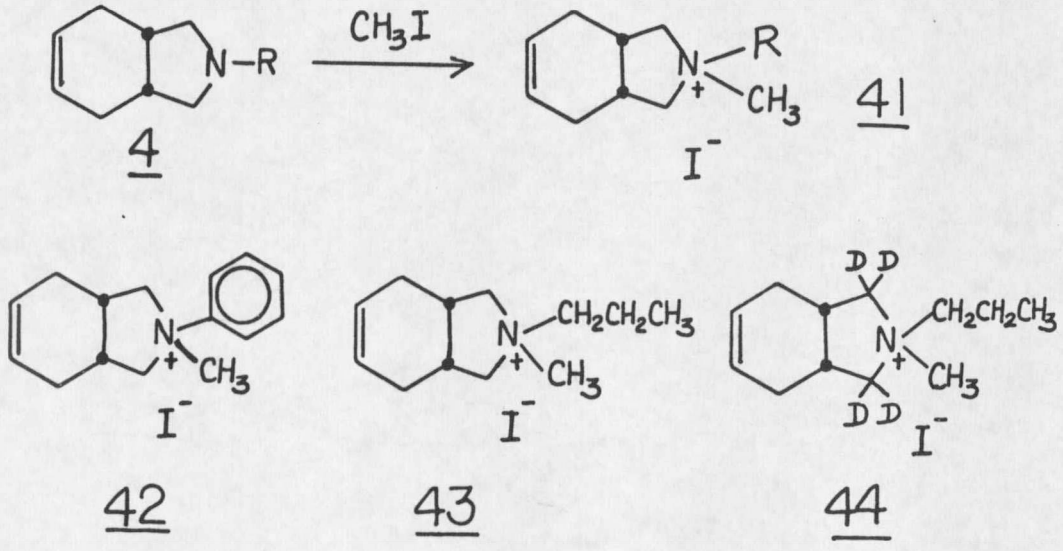
The general synthesis of the cis-N-substituted-8-azabicyclo [4.3.0] non-3-ene systems were outlined in figure 31.



14 40 4

Figure 31: The Preparation of Cis-N-substituted-8-azabicyclo [4.3.0]non-3-ene Systems.

The quaternary methiodide salts of the cyclic tertiary amines were prepared according to figure 32.



4 41 42 43 44

Figure 32: The Preparation of the Quaternary Methiodide Salt of the Cyclic Tertiary Amines.

NMR STUDY FOR THE LONG-RANGE ELECTRONIC PARTICIPATION

The nmr study of the effect of long-range electronic participation was carried out in the same method as that used for the oxygen-containing heterocyclic analogues.

After the comparison of the nmr spectra of 37 in deuterochloroform, and the solvent mixture of deuterochloroform and deuterotrifluoroacetic acid in the ratio of 50:50, the deshielding effects to the protons in 37 were observed as tabulated in table 9.

Similar experiments were carried out on the saturated analogy of 37, cis-N-phenyl-8-azabicyclo[4.3.0]nonane, (45), (figure 33). The deshielding effects to the hydrogens in 45 are tabulated in table 10.



45 46

Figure 33: The Cis-8-phenyl-8-azabicyclo[4.3.0]nonane and its Quaternary Methiodide Salt.

For further investigation of the influence from the π-electrons of the double bond to the nitrogen, the quaternary methiodide salts of 37 and 45 were prepared for the same nmr experiments. The results are shown in table 11 and table 12 respectively. One observes the deshielding effect on the hydrogens of the double bond from the positive charge of the nitrogen in 42, while in 46, the hydrogens on the cyclohexene moiety were not deshielded at all.

Table 9: The Observed Chemical Shifts of Protons in 37.

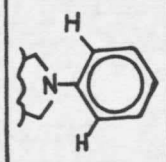
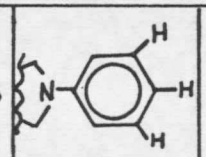
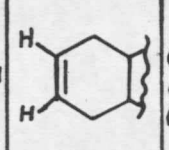
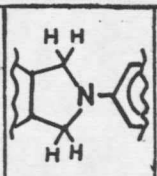
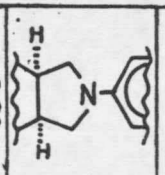
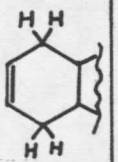
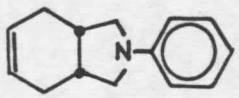
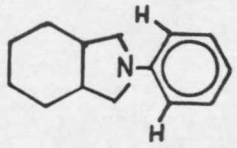
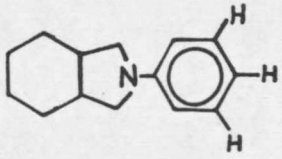
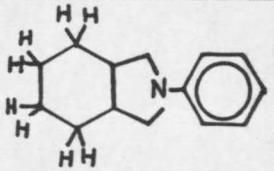
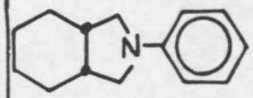
Compound	Solvent	Chemical Shift (δ)					
							
 37	$CDCl_3$	7.16 (6.84)	6.52	5.62	3.20	2.40	2.12
	$\frac{CDCl_3}{CF_3COOD}=1$	7.54		5.88	3.98	2.99	2.29
Change of Chemical Shift (Δδ)		+0.38 (+0.70)	+1.02	+0.26	+0.78	+0.59	+0.17

Table 10: The Observed Chemical Shifts of Some of the Protons in 45.

Compound	Solvent	Chemical Shift[a] (δ)		
				
 45	$CDCl_3$	7.15 (6.88)	6.61	1.48
	$\frac{CDCl_3}{CF_3COOD}=1$	7.50		1.57
Change of Chemical Shift (Δδ)		+0.35 (+0.62)	+0.89	+0.09

a. The chemical shifts of the other hydrogens in 45 were not completely identified due to its complexity of overlapping peaks.

Table 11: The Observed Chemical Shifts of Some of the Hydrogens in 37 and 42.

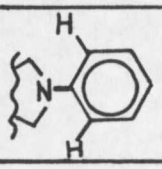
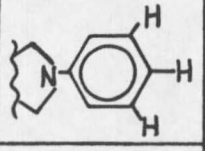
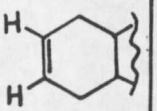
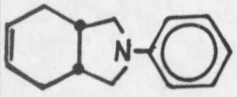
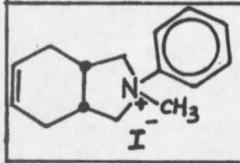
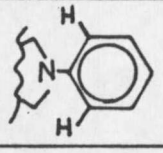
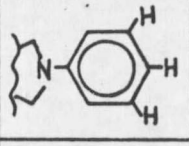
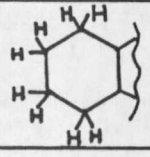
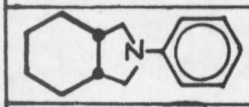
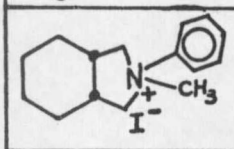
Compound	Solvent	Chemical Shift[a] (δ)		
				
 37	$CDCl_3$	7.16	6.52	5.62
 42		7.97	7.60	5.98
Change of Chemical Shift (Δδ)		+0.81	+1.08	+0.36

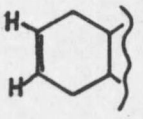
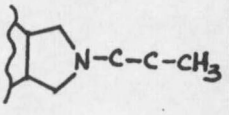
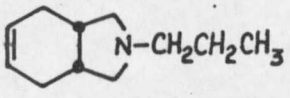
Table 12: The Observed Chemical Shifts of Some of the Protons in 45 and 46.

Compound	Solvent	Chemical Shift[a] (δ)		
				
 45	$CDCl_3$	7.15	6.61	1.48
 46		7.88	7.56	1.46
Change of Chemical Shift (Δδ)		+0.73	+0.95	-0.02

a. The other parts of the nmr spectra were not clearly designated due to the complexity of the peaks.

Another interesting nitrogen-containing heterocyclic system, 38, was also investigated by the same nmr experiments. The observations are tabulated in table 13.

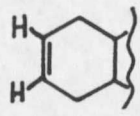
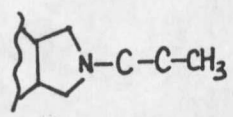
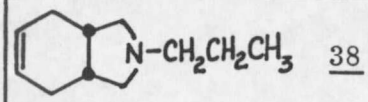
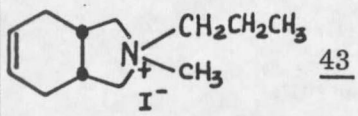
Table 13: The Observed Chemical Shifts of Some of the Hydrogens in 38.

Compound	Solvent	Chemical Shift[a] (δ)	
			
 38	$CDCl_3$	5.74	0.87
	$\frac{CDCl_3}{CF_3COOD}$ =1	5.73	0.97
Change of Chemical Shift (Δδ)		-0.01	+0.10

a. The chemical shifts of the other hydrogens in system 38 were not completely identified due to the complexity of the overlapping of the peaks.

The deshielding effect was observed for all but the hydrogens of the double bond in system 38. For further understanding, the nmr spectra of 38 and its quarternary methodide salt 43, were compared (table 14).

Table 14: The Observed Chemical Shifts of Some of the Protons in 38 and 43.

Compound	Solvent	Chemical Shift[a] (δ)	
			
 38	$CDCl_3$	5.74	0.87
 43		5.95	1.05
Change of Chemical Shift (Δδ)		+0.21	+0.18

a. Same as that of Table 13.

The hydrogens of the double bond in quaternary salt 43 were found also to be deshielded, as were the other hydrogens.

These phenomena would be explained by the preferential nitrogen inversion of 38-II (figure 34).

Some techniques and observations had been reported for investigating the conformation of the non-bonded electrons of the nitrogen atom.

Bohlman[49] and Hamlow[50] reported the study of the conformation of the non-bonded electrons of nitrogen in the quinolizidine ring system (figure 35). Because of the stereochemistry of the ring fusion, H_C is trans to the non-bonded electrons on the nitrogen atom. The nmr spectrum of 47 shows that the chemical shift between H_A and H_B is 0.93 ppm. The proton (H_A) which is

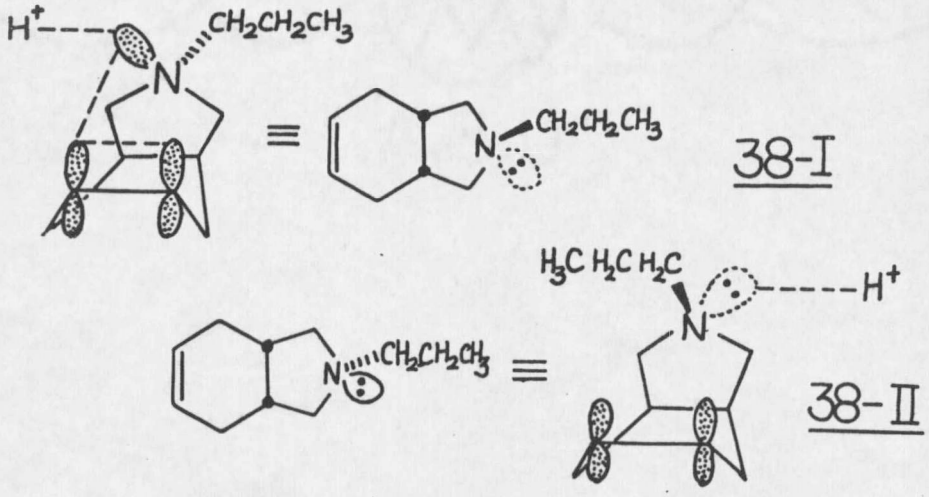


Figure 34: Possible Conformations of the Nitrogen Inversion of System 38.

anti-coplanar to the non-bonded electrons of nitrogen atom appears upfield from H_B. When 47 was protonated to 48, the chemical shift between H_A and H_B decreases to 0.4-0.5 ppm, a difference that is typical for "normal" axial vs equatorial protons.

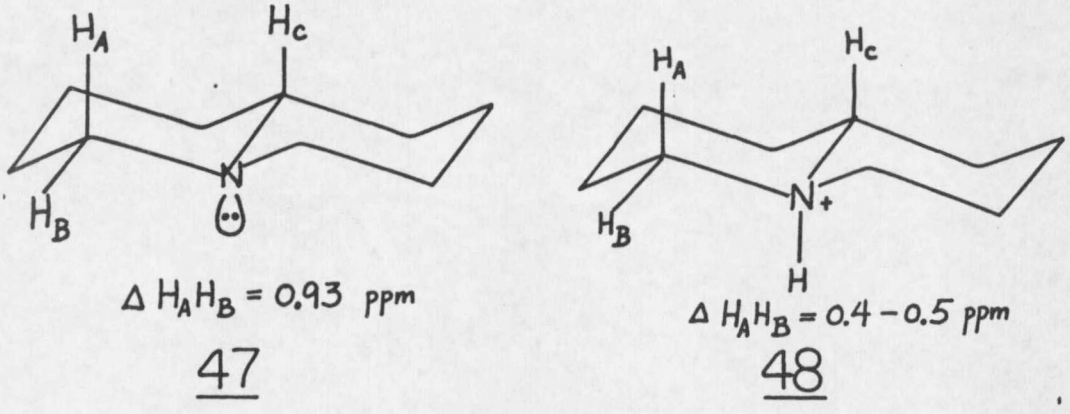
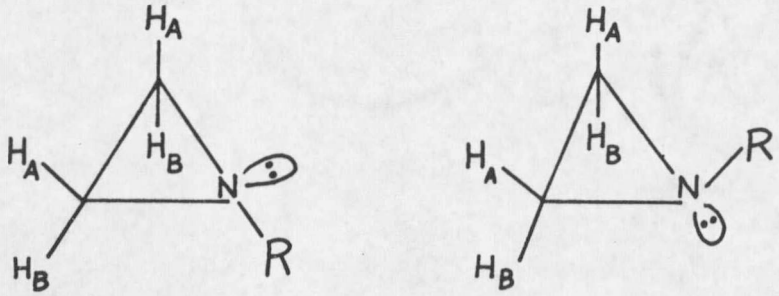


Figure 35: The Quinolizidine Ring System

Brois[51] and Roberts[52] have reported the behavior of the nitrogen atom in the aziridine ring system (figure 36). When the inversion between 49-I and

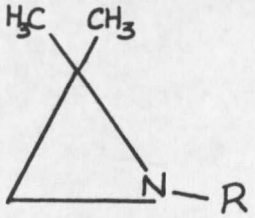


49-I 49-II

Figure 36: The Aziridine System

49-II is rapid, then all four of the ring protons are expected to be magnetically equivalent. On the other hand, if the inversion process is slow enough, the ring proton will appear as an A_2B_2 system. It has been found that the barrier to nitrogen inversion in the series N-methyl, N-ethyl, N-isopropyl, and N-tert-butyl aziridine decreases with increasing size of substituents on nitrogen atom.

Rauk[53] reported the inversion barriers of N-substituted-2, 2-dimethyl-aziridine systems (figure 37). When the substituents was methyl group, the



50

	Inversion barrier
$R = CH_3$	18-20.5 kcal/mole
$R = C_6H_5$	11.2 kcal/mole

Figure 37: The N-substituted-2, 2-dimethylaziridine Systems

energy for inversion was larger than that for the phenyl group.

Felix[53,54] reported that the conversion of a bicyclic system 51 (figure 38). Due to the steric crowding in the cis conformation, this molecule preferred to convert form cis- to trans- conformation.

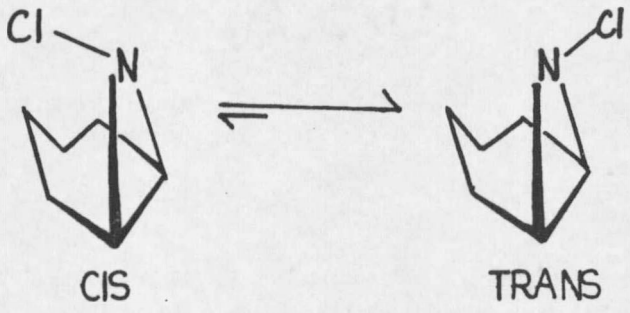


Figure 38: The Cis-7-chloro-7-azabicyclo [4.1.0] heptane System

Based on the above information and the factors that affect the magnitude of inversion barrier[53], one expects to predict that, besides the steric factor, the repulsion between the nonbonded electrons of nitrogen atom and the π-system of the alkene also contribute to the preferential conformation of the nonbonded electrons on nitrogen atom in 38-II (figure 34).

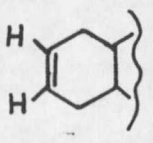
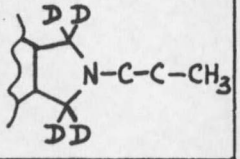
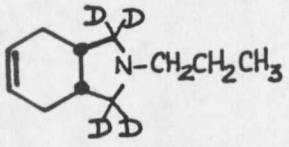
In 38-I, one expects to observe the long-range electronic participation from the π-system of the alkene to the nonbonded electrons of nitrogen atom. This electronic participation will cause the deshielding effect to the hydrogens on the double bond, which is not observed. In 38-II, the possibility of this long-range electronic participation will be totally blocked. In this case, the hydrogens on the double bond will not be deshielded, as was observed.

When 38 was converted to its quarternary salt, 43, the nitrogen atom carried positive charge, which influenced all the hydrogens in the molecule.

This rationalized the existence of the deshielding effect to the hydrogens of the double bond in 43, and the non-existence of the deshielding effect to the corresponding hydrogens in 38, (tables 13 and 14).

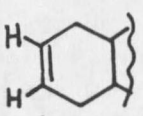
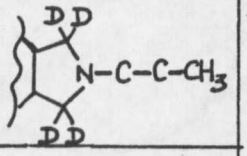
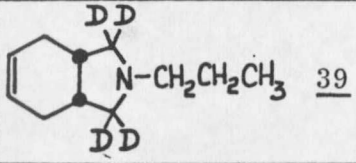
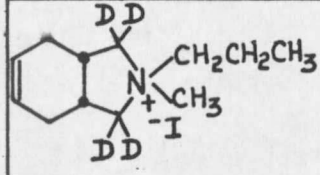
For simplifying the nmr spectrum of 38, the deuterated analogy 39 was prepared and studied similarly. Yet the nmr spectrum of 39 still exhibited the complex of overlapping peaks (tables 15 and 16).

Table 15: The Chemical Shifts of Some of the Protons in 39.

Compound	Solvent	Chemical Shift[a] (δ)	
			
 39	$CDCl_3$	5.77	0.87
	$\frac{CDCl_3}{CF_3COOD}=1$	5.76	0.99
Change of Chemical Shift (Δδ)		-0.01	+0.12

a. The chemical shift of the other hydrogens were not completely identified due to the complicated overlapping of peaks

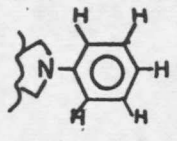
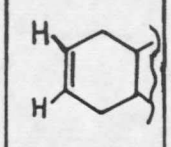
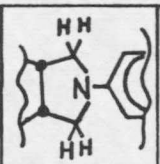
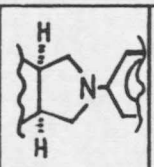
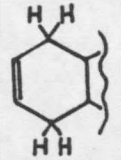
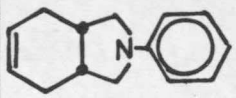
Table 16: The Observed Chemical Shifts of Some of the Protons in 39 and 44.

Compound	Solvent	Chemical Shift[a] (δ)	
			
 39	$CDCl_3$	5.77	0.87
 44		5.94	1.05
Change of Chemical Shift (Δδ)		+0.17	+0.18

a. The chemical shift of the other hydrogens were not completely identified due to the complicated overlapping of peaks.

Since all the above nmr studies are carried out in deuterochloroform, and the mixture of deuterochloroform and deuterotrifluoroacetic acid, one might expect to investigate the effect of the ratio of the solvent mixture. The experiment of the effect of the solvent ratio clearly indicates that the deshielding effect increases with the increasing acidity of the solvent (table 17).

Table 17: The nmr Study of the Dependence of the Deshielding Effect to the Acidity of the Solvent.

Sample	Solvent[a]	Concentration[b] of Sample	Chemical Shift (δ)				
							
 37	$\frac{CDCl_3}{CF_3COOD}=1$	1	7.54	5.88	3.98	2.99	2.29
	$\frac{CDCl_3}{CF_3COOD}=\frac{1}{4}$	2/5	7.54	5.89	4.00	3.00	2.31
Change of Chemical Shift (Δδ)			±0.00	+0.01	+0.02	+0.01	+0.02

a. The solvent mixture of $CDCl_3$ and CF_3COOD in the ratio of 1:4 was prepared by diluting the solvent mixture in the ratio of 1:1 by three more equivalents of CF_3COOD.

b. The actual concentration of the sample in the solvent is not calculated, and was tentatively assigned as 1, and then was diluted to 2/5.

RELATION TO THE CORRESPONDING OXYGEN SYSTEM

From the nmr study of the deshielding effect from the oxygen- and nitrogen-containing heterocyclic systems similar to 1 when present in an acidic solvent, one resemblance between these two systems was noticed. The enhancement of the deshielding effect to the hydrogens of the double bond was detected in both systems when the long-range electronic participation from the π-system of the double bond to the non-bonded electrons of the heteroatom existed. When this electronic participation was blocked, the deshielding effect to the hydrogens of the double bond was the smallest among that to all the hydrogens in the molecule, due to the factor that the hydrogens of the double bond were the farthest to the heteroatom in oxygen-containing systems. In nitrogen-containing systems, sometimes the hydrogens of the double bond were not even deshielded when the long-range electronic participation was blocked. It is probably due to the difference of the nonbonded electrons in these two systems.

When nitrogen compounds were studied, the nitrogen inversion must be also investigated, since the conformation of the nonbonded electrons on nitrogen atom would influence the chemistry of the whole molecule, as demonstrated by 38 and 37.

In summary, this type of research can offer much valuable information, though much of it is still not well understood at this point. Further research and investigation toward this end is recommended, not only for the nitrogen- and oxygen-containing systems, but also for the other heterocyclic systems with nonbonded electrons on the heteroatom. Further research should include low-temperature nmr studies, and possible molecular orbital calculations.

EXPERIMENTAL

GENERAL INFORMATION

(1) The analytical data available in this report were analyzed by the following instruments or company:

Elemental Analysis: By Chemalytics, Inc., Tempe, Arizona

Gas Liquid Chromatographic analysis:

(a) F&M Biomedical Gas Chromatograph Model 400

(b) Aerograph Autoprep Model A-700

The columns used are described in Appendix II.

Infrared Spectra (IR): Beckman IR-5A Infrared Spectrophotometer, using polystyrene as the standard.

Nuclear Magnetic Resonance Spectra (NMR):

Varian A-60 Analytical NMR Spectrometer, using tetramethylsilane (TMS) as an internal standard, and the deuterochloroform as the solvent unless otherwise indicated.

(2) The melting points (mp) and boiling points (bp) are uncorrected and are in degrees centigrade.

(3) Pressures are reported in mm of mercury (e.g. bp_7 85°C indicates the boiling point is 85°C at the pressure of 7 mm of mercury).

PART I

PREPARATION OF CIS-1,2,3,6-TETRAHYDROPHTHALYL ALCOHOL[55], (15):

A solution of cis-1,2,3,6-tetrahydrophthalic anhydride, 14, (15.2 g, 0.1 mole), in approximately 100 ml of anhydrous tetrahydrofuran[a] was added over a period of two hours to a mixture of lithium aluminum hydride[b] (4.18 g, 0.11 mole) in 350 ml of anhydrous ether. The reaction was carried out in a 5 liter, 3 necked flask equipped with a reflux condenser, mechanical stirrer, addition funnel and a mercury bubbler for isolation from the atmosphere. After

the reaction was complete, the mixture was refluxed for two hours. A saturated solution of Rochelle Salts was added dropwise for work up until no further reaction was noted. The reaction mixture was allowed to settle, and the liquid was decanted and concentrated. Methanol was added to the salts and this mixture was refluxed. Then the methanol solution was separated and added to the first crude product mixture. This oil was distilled to give a viscous colorless cis diol 15 (9.95 g, 70% yield).

$bp_{0.5}$ 126-129°C (Literature[55]: bp_{12} 165-170°C)

Infrared - 3200, 3000, 2850, 1650, 1430, 1320, 1170, 1095, 1025, 975, 955, and 925 cm^{-1}

nmr - 2.01δ (broad peak, 6H), 3.5δ (multiplet, 4H), 4.06δ (sharp singlet, 2H), 5.5δ (2H).

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a. Anhydrous ether could be also used as the solvent for anhydride 14. But the solubility of 14 in ether was much lower than that in tetrahydrofuran. Also due to the increase solubility of anhydride 14 in tetrahydrofuran, this reaction can be run on a 0.5 mole scale by using only 250 ml of tetrahydrofuran for the anhydride solution.

b. When the lithium aluminum hydride was not used in excess or was impure, the lactone 16 would be obtained. Further reduction of lactone 16 with lithium aluminum hydride would give cis diol 15 with quantitative yield. The boiling point of lactone 16 was 129-132°C at 10 mm Hg.

PREPARATION OF CIS-8-OXABICYCLO[4.3.0]NON-3-ENE, (2)[1]

A solution of cis-1,2,3,6-tetrahydrophthalyl alcohol, 15, (7.1 g, 0.05 mole) in pyridine (10 ml) was heated to reflux. A solution of p-toluenesulfonyl chloride (14 g, 0.07 mole) in pyridine (10 ml) was then added dropwise with stirring. The reaction mixture was further refluxed for one hour, after the addition was complete. The solution was cooled and poured into an ice-sulfuric acid bath to neutralize the pyridine. This aqueous mixture was extracted with

ether, and the ether extracts were dried over anhydrous magnesium sulfate. Distillation yielded 5.21 g of the colorless liquid product 2 (84% yield).

bp_{10} 54-56°C (Literature[1]: bp_{13} 63-64°C)

Infrared - 3000, 2910, 2840, 1650, 1490, 1455, 1088, 1053, 1018, 956, 940, 899, 882, 717, and 653 cm^{-1}

nmr (attached in Appendix IV) - 2.12δ (4H), 2.36δ (2H), 3.67δ (4H), 5.60δ (2H)

glc data - see table 18

OXYMERCURATION-DEMERCURATION[39,40] OF ALKENES

The alkene (0.01 mole) was added to a stirred mixture of mercuric acetate (3.2 g, 0.01 mole) in aqueous tetrahydrofuran (20 ml, in the ratio of 50:50) at room temperature. The reaction mixture was stirred for 15 minutes after the yellow color had disappeared. Potassium hydroxide solution (10 ml, 3M) was then added, followed by a sodium borohydride solution (0.19 g of $NaBH_4$ in 10 ml of 3M KOH). The mercury was allowed to precipitate, and then 10 ml of saturated sodium chloride solution was added. This mixture was extracted with methylene chloride, and the extracts were dried over anhydrous magnesium sulfate, and then concentrated for further purification.

OXYMERCURATION-DEMERCURATION OF CIS-8-OXABICYCLO[4.3.0]NON-3-ENE, (2)[a]

The usual procedure was carried out with the following quantities of reactants; 2 (1.24 g, 0.01 mole), mercuric acetate (3.2 g, 0.01 mole), THF (10 ml), water (10 ml), 3M potassium hydroxide (10 ml), sodium borohydride solution (0.19 g of $NaBH_4$ in 10 ml of 3M potassium hydroxide), and saturated salt solution (10 ml).

Distillation afforded a colorless liquid with boiling point 149-152°C at 18 mm Hg (1.2 g, 84.4% yield). This mixture of the exo and endo alcohols 12

and 11, in the ratio of 24:76[b,c], was separated by the preparative gas chromatography with a carbowax 20M column. The gas chromatographic data were tabulated in table 18.

The infrared and nmr spectroscopic data of the major alcohol, cis-8-oxabicyclo[4.3.0]nonan-3-ol-endo[d], (11), was shown in the following:

Infrared - 3320, 2900, 2840, 1485, 1450, 1365, 1197, 1070, 1047, 1020, 1000, 940, 925, 885, and 715 cm^{-1}

nmr - 1.2-1.9δ (6H), 1.9-2.5δ (2H), 2.73δ (sharp singlet, 1H), 3.3-4.0δ (multiplet, 5H)

glc data - see table 18 and table 19

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a. This reaction was repeated by this researcher

b. Average of three runs

c. R. D. Otzenberger reported the ratio as 1:3 (References 8 and 9)

d. This alcohol can also be prepared by the stereospecific synthesis[13] outlined in figure 39.

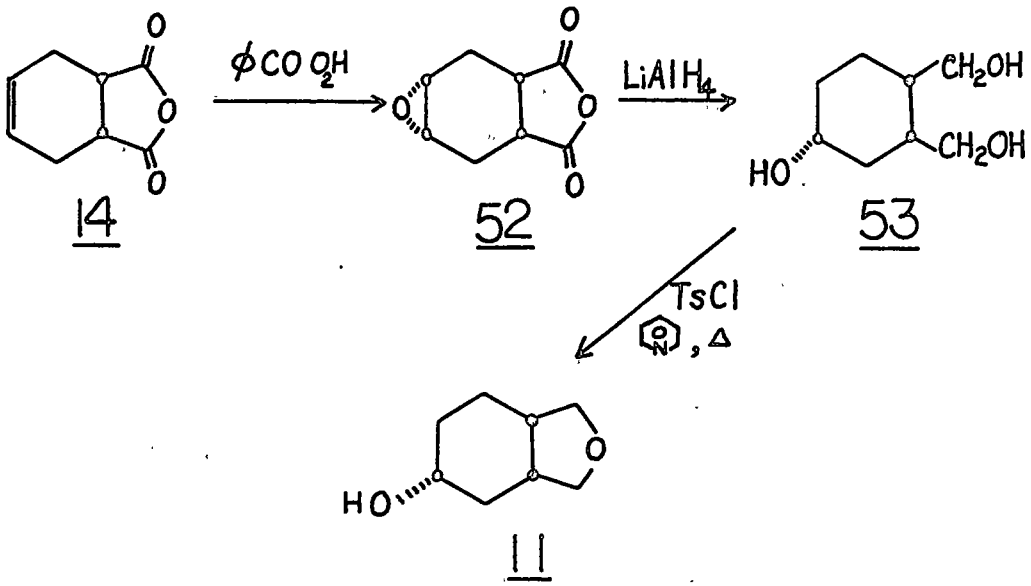


Figure 39: Stereospecific Synthesis of cis-8-oxabicyclo[4.3.0]nonan-3-ol-endo.

HYDROBORATION[57,58] OF CIS-8-OXA-BICYCLO[4.3.0]NON-3-ENE, (2)

The alkene 2 (3.6 g, 0.029 mole) was dissolved in 17 ml of dry diglyme, to which sodium borohydride (1.51 g, 0.04 mole) was added. The reaction mixture was stirred under nitrogen atmosphere at 20°C. Borontrifluoride etherate (3 ml, 99% pure) was added dropwise. The reaction mixture was stirred for 30 min. A solution of 2N NaOH (3.5 ml) was added dropwise followed by 3.5 ml of 30% hydrogen peroxide at 20-25°C. The reaction mixture was stirred for another hour, then extracted by ether and washed by distilled water. The resulting crude alcohol mixture was compared with the known products[9] by analytical glc with the carbowax 20M column. The ratio of the exo and endo alcohols 12 and 11 in the mixture was found 28 to 72*.

glc data - see table 18 and table 19

JONE'S OXIDATION[29] OF THE CIS-8-OXABICYCLO[4.3.0]NONAN-3-OLS, (11) AND (12)

The alcohol mixture of 11 and 12, (0.02 mole, 2.84 g) was dissolved in acetone (20 ml) in an Erlenmeyer flask which was placed in a water bath so as to maintain the reaction mixture at 25°C. To this was added dropwise the Jones reagent (13.36 g CrO_3 in 12 ml concentrated H_2SO_4, then diluted to 50 ml with H_2O) until an orange-brown color remained. The reaction mixture was extracted with methylene chloride, and the extracts were dried over anhydrous magnesium sulfate, and then concentrated. Distillation afforded the colorless liquid ketone (99% yield).

bp_{17} 134-137°C

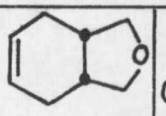
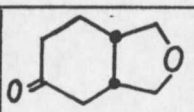
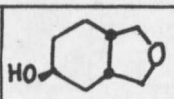
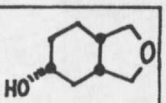
Infrared** - 2910(V.S.), 2840(V.S.), 1720(V.S.), 1645, 1480, 1455,

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*The average of three runs

**(V.S.-very strong; S-strong)

Table 18: The Relative Retention Time of Compounds in System 2.

Compound	 2	 23	 12	 11
Retention time[a,b] (min)	3.5	23.1	32.9	35.8

a. The average of five injections.

b. Data obtained from Aerograph Autoprep Model A-700 gas chromatograph, with carbowax 20M column at 170°C, and with flow rate of 120 ml/min.

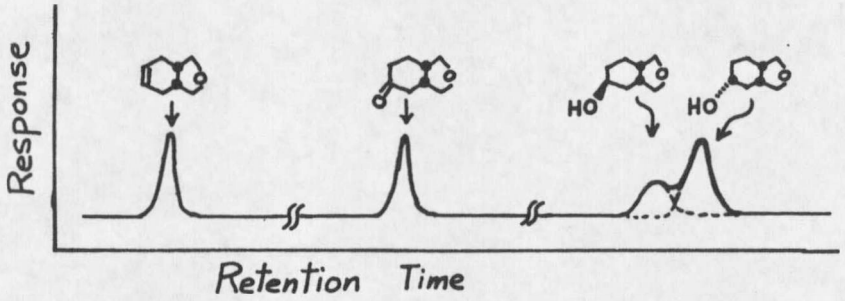


Figure 40: The Observation From the glc Analysis of Compounds in Table 18.

Table 19: The Observed Yield of Reactions From Compounds in Table 18.

Reaction	Oxymercuration of 2	Hydroboration of 2	Jone's Oxidation of 12 and 11	$NaBH_4$ Reduction of 23	$LiAlH_4$ Reduction of 23
Yield[a,b]	94.5%	95.8%	100%	99.0%	100%

a. Analyzed by F&M Model 400 Biomedical Gas Chromatography, with a disc integrator.

b. Average of two to three runs.

1420, 1360, 1350, 1325, 1300, 1240, 1200, 1115, 1095, 1080(S), 1070(S), 1045(S), 1025(S), 975, 950, 927(S), 893, 885, 741, 717, 692, 660 cm^{-1}

glc data - see table 18 and table 19

SODIUM BOROHYDRIDE REDUCTION OF CIS-8-OXABICYCLO[4.3.0]NONAN-3-ONE, (23)

The solution of ketone 23 (1.4 g, 0.01 mole) in absolute methanol (10 ml) was added dropwise to a stirring solution of $NaBH_4$ (0.28 g, 0.0074 mole) in absolute methanol (10 ml). After $NaBH_4$ disappeared, another 0.1 g (0.0026 mole) of $NaBH_4$ was added, stirred for 15 min., then the methanol was removed, and 3 ml of H_2O was added. The reaction mixture was extracted with methylene chloride, and the extracts were dried over anhydrous magnesium sulfate and concentrated.

The resulting crude alcohol mixture was compared with the known products (prepared according to either p. 53 or p. 55) by analytical glc. The ratio of the exo and endo alcohol, 12 and 11, was found 17:83*. The yield was shown in table 19.

LITHIUM ALUMINUM HYDRIDE REDUCTION OF CIS-8-OXABICYCLO[4.3.0]NONAN-3-ONE, (23)

A solution of ketone 23 (1.4 g, 0.01 mole) in approximately 20 ml of anhydrous ether was added over a period of two hours to a mixture of lithium aluminum hydride (0.38 g, 0.01 mole) in 15 ml of anhydrous ether. The reaction was carried out in a round bottom flask fitted with a magnetic stirring bar, a reflux condenser, an addition funnel and a mercury bubbler for isolation from the atmosphere. After the reaction was complete, the mixture was refluxed for one hour. A saturated solution of Rochelle Salts was added dropwise for work up until no further reaction was noted. The liquid was separated from

*The average of two runs.

the solid salts by filtration, and washed by distilled water, then dried over anhydrous magnesium sulfate, and then concentrated by using a rotary evaporator. The resulting crude alcohol mixture was compared with the known products (prepared according to either p. 53 or p. 55) by analytical glc. The ratio of the exo and endo alcohols; 12 and 11, was found 20:80*. The yield was shown in table 19.

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*The average of two runs

PART II

PREPARATION OF DIMETHYL CIS-Δ^4-TETRAHYDROPHTHALATE[10,59], (29)

Concentrated sulfuric acid (4.9 g, 0.05 M) was first carefully added to anhydrous methanol (256 g, 8 M), and cis-1,2,3,6-tetrahydrophthalic anhydride, 14 (152 g, 1M), was then added, and the mixture was refluxed for 18 hours. After cooling, 5.3 g of anhydrous Na_2CO_3 is added to neutralize the sulfuric acid. The methanol solution was separated by filtration, and then distilled. The distilled cis diester, 29, is a clear colorless liquid (178.2 g, 90% yield).

bp_{14-15} 135-138°C (Literature[58]: bp_{20} 141.5-142°C)

PREPARATION OF CIS-$\alpha, \alpha, \alpha', \alpha'$-TETRAMETHYL-4-CYCLOHEXENE-1,2-DIMETHANOL[59,60], (30)

The methyl iodide (71.0 g, 0.5 mole) was added dropwise to a stirring anhydrous ether solution of magnesium (12.2 g, 0.50 g-atom) to prepare the Grignard reagent, methylmagnesium iodide[a,b]. To this was added dropwise an anhydrous ether solution of 13.2 g (0.0666 mole) of dimethyl cis-4-cyclohexene-1,2-dicarboxylate, 29, and the mixture was stirred at room temperature for 19 hours. Saturated ammonium chloride solution (125 ml) was added dropwise, and the mixture was filtered. The aqueous layer was extracted with ether, and the combined ether layers were dried over anhydrous magnesium sulfate. The ether was removed by using a rotary evaporator to leave a slightly brown solid. Recrystallization from methanol-water afforded 10.2 g of white crystals (77.2% yield).

---

a. Sometimes heating this mixture gently was required to initiate the reaction

b. If the methyl magnesium iodide was not used in excess, the lactone 31 would be obtained. The melting point of lactone 31 was 67-68°C. nmr - 1.38δ and 1.42δ ($2CH_3$), 1.90-2.57δ, and 5.75-5.80δ (CH=CH)

mp = 120-121°C (Literature[59]: mp = 119.5-120.5°C)
(Literature[60]: mp = 122-123°C)

nmr - 1.30δ and 1.36δ ($4CH_3$), 2.19δ ($-CH_2$), 4.07δ (-OH), and 5.67δ (CH=CH)

PREPARATION OF CIS-7,7,9,9-TETRAMETHYL-8-OXABICYCLO[4.3.0] NON-3-ENE[59,60], (3)

Distillation of diol 30 at 20 mm using a bath temperature of 150-160°C gave the cis-7,7,9,9-tetramethyl-8-oxabicyclo[4.3.0]non-3-ene, (3)[a].

bp_{20} 94-96°C (Literature[59]: bp_{20} 97.5-98.5°C)
(Literature[60]: bp_{10} 74-75°C)

Infrared* - 2950(S), 2900(S), 1665, 1465, 1445, 1380(S), 1365(S), 1300, 1270(S), 1230, 1210(S), 1190, 1160, 1136(S), 1107, 1075, 1002, 986(S), 970(S), 952, 937, 888(S), 870, 820(S), 751, 712(S), 660(S), and 642 cm^{-1}

nmr (attached in Appendix IV) - 1.14δ and 1.27δ ($4CH_3$), 2.13δ (6H) and 5.69δ (CH=CH)

glc data - see table 20 and figure 42

---

a. Sometimes, a mixture of two compounds with the ratio of 30:70, as analyzed by glc, was obtained (figure 39). The major component of this mixture was cyclic alkene 3, the minor component was suspected the trans-isomer 32.

*(S = strong peak)

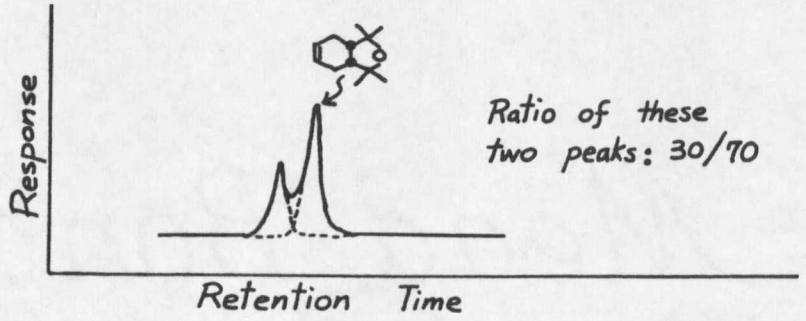


Figure 41: The Observation of the Product Mixture from Dehydration of 30.

OXYMERCURATION OF CIS-7,7,9,9-TETRAMETHYL-8-OXA-BICYCLO [4.3.0]NON-3-ENE, (3)

The usual procedure was carried out with the following quantities of reactants: 3 (1.80 g, 0.01 mole), mercuric acetate (3.2 g, 0.01 mole), THF (10 ml), water (10 ml), 3M potassium hydroxide (10 ml), sodium borohydride solution (0.19 g of $NaBH_4$ in 10 ml of 3M KOH), and saturated salt solution (10 ml).

It was noted that cyclic alkene 3 took much longer time to react with mercuric acetate than 2. This was indicated by the much longer time for the disappearing of the yellow color, which was from mercuric acetate in aqueous solution.

Distillation afforded a viscous colorless liquid with boiling point 140-143°C at 19-20 mm Hg.

Infrared* - 3400(S), 2950(S), 2900(S), 1470, 1450, 1440, 1380(S), 1368(S), 1325, 1290, 1270, 1255, 1235, 1210, 1177, 1150(S), 1120, 1110, 1080(S), 1055(S), 988(S), 971(S), 960, 949, 894, 846, 816, 793, and 741 cm^{-1}

glc data - see table 20 and figure 42

The resulting alcohol mixture shows a broad unsymmetrical peak (figure 42). The glc analysis of the ratio of exo alcohol 33 and endo alcohol 34, by the method of triangulation, shows (30-40):(60-70).

JONE'S OXIDATION OF THE CIS-7,7,9,9-TETRAMETHYL-8-OXABICYCLO [4.3.0]NONAN-3-OLS, (33) AND (34)

The usual procedure was carried out with the following quantities of reactants: alcohol mixture of 33 and 34, (0.0025 mole, 0.45 g), acetone (3 ml), Jone's reagent (1.5 ml).

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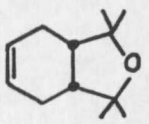
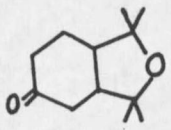
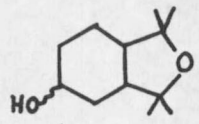
*(S = strong peak)

The reaction mixture was extracted with methylene chloride, and the extracts were washed with distilled water, dried over magnesium sulfate, and then concentrated.

The infrared spectroscopy of the crude product shows a strong ketone functionality, and also shows the loss of hydroxyl functionality. The glc analysis shows a sharp single peak for the crude ketone, and also shows the disappearance of the alcohol peaks. The yield of this oxidation was 100% as analyzed by glc.

glc data - see table 20 and figure 42

Table 20: The Relative Retention Time of Compounds in System 3.

Compound	 3	 54	 33/34 (exo/endo)
Retention time[a,b] (min.)	4.8	31.2	52.8/54.7

a. The average of three injections.

b. Data obtained from Aerograph Autoprep Model A-700 gas chromatography, with carbowax 20M column at 170°C, and with flow rate 110 ml/min.

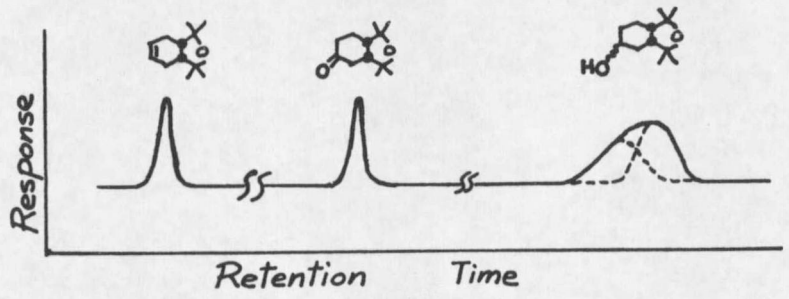


Figure 42: The Observation From the glc Analysis of Compounds in Table 20.

PART III

PREPARATION OF CIS-8-PHENYL-8-AZABICYCLO[4.3.0]NON-3-ENE[61], (37)

N-phenyl-1,2,3,6-tetrahydrophthalimide[13], (53), (11.35 g, 0.05 mole) was refluxed 36 hours with LAH (7.6 g, 0.2 mole) in 200 ml of anhydrous ether. After the reaction mixture was worked up in the usual way for LAH reduction, the solvent was stripped by the rotary evaporator. The crude product was slightly yellow solid. Recrystallization from EtOH-H_2O afforded 6.7 g (67.3% yield) of the white solid product 37.

mp = 47-48°C (Literature[61]: mp = 48°C)

PREPARATION OF CIS-2-METHYL-2-PHENYL-3a,4,7,7a-TETRAHYDROISOINDOLINIUM IODIDE, (42)

Cis-8-phenyl-8-azabicyclo[4.3.0]non-3-ene, (37), (1.99 g, 0.01 mole) was refluxed 12 hours with excess CH_3I in approximately 50 ml of CH_3NO_2. The solvent was stripped by rotary evaporation and left the crude product, the greenish yellow gum. Recrystallization from EtOH-Et_2O afforded the solid salt 42.

PREPARATION OF CIS-N-METHYL-N-PHENYL-HEXAHYDROISOINDOLINIUM IODIDE[61], (46)

Cis-8-phenyl-8-azabicyclo[4.3.0]nonane[13], (45), (2.01 g, 0.01 mole) was refluxed 12 hours with excess CH_3I in approximately 50 ml of CH_3NO_2. The solvent was stripped by rotary evaporation, and left the crude product, the yellowish brown gum. Recrystallization from EtOH-Et_2O afforded the solid salt 46, with melting point 215-216°C. (Literature[61]: mp = 217°C).

PREPARATION OF CIS-2-METHYL-2-PROPYL-3a,4,7,7a-TETRAHYDROISOINDOLINIUM IODIDE[62], (43)

Cis-8-propyl-8-azabicyclo[4.3.0]non-3-ene[13], (38), (1.65 g, 0.01 mole) was dissolved in ether. To this, was slowly added 1.5 ml of methyl iodide. A slightly yellow solid was formed quantitatively. Recrystallization from ethanol-

ether gave the methiodide as colorless crystals, mp 183-185°C. (Literature[62]: mp = 173-175°C).

PREPARATION OF CIS-1,1,3,3-TETRADEUTERO-2-METHYL-2-PROPYL-3a, 4,7,7a-TETRAHYDROISOINDOLINIUM IODIDE, (44)

Cis-7,7,9,9-tetradeutero-8-propyl-8-azabicyclo [4.3.0]non-3-ene[13], (39), (1.69 g, 0.01 mole), was dissolved in ether. To this was slowly added 1.5 ml of methyl iodide. A slightly yellow solid was formed quantitatively. Recrystallization from ethanol-ether gave the methiodide as white crystals, mp 179.5-181°C.

APPENDIX

APPENDIX I

THE ANALYSIS OF GAS-LIQUID CHROMATOGRAPHY (GLC)

(1) The analysis of peak area:

The following methods were generally used for analyzing the peak area:

(a) Disc integrator

(b) The method of triangulation

(c) The method of weighing the recording paper cut according to the shape of the peak

When the Disc integrator is not available, the method of triangulation and weighing are, usually, used simultaneously.

(2) The analysis of yield:

(a) An outer standard with the same number (or half the number) of moles as the reactant was carefully weighed, and then mixed with the to-be-analyzing product, and injected into the GLC immediately. By comparing the peak area of the outer standard and the product, the yield can be found easily and consistently.

(b) Another method, sometimes used by some chemists, is simply comparing the peak area of the reactant and the product, to calculate the yield of the reaction.

APPENDIX II

THE COMMON COLUMNS USED FOR GLC ANALYSIS

F & M Model 400 Biomedical Gas Chromatograph:

(1) 6 ft. 6 mm OD glass; 20% carbowax 20M on 30-60 mesh Firebrick

(2) 6 ft. 6 mm OD glass; 5% SE 30 on 100-120 mesh Gas Chrom Z

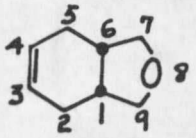
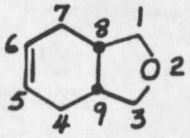
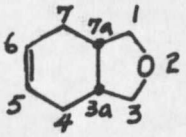
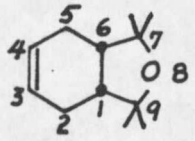
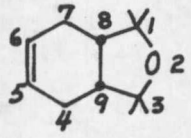
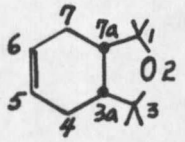
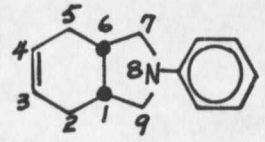
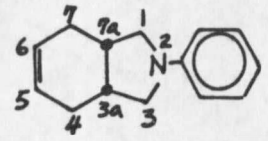
Aerograph Autoprep Model A-700 Gas Chromatograph:

(1) 10 ft. $\frac{1}{4}$ in. OD aluminum; 10% SE 30 on Chromosorb W

(2) 10 ft. 3/8 in. OD aluminum; 20% carbowax 20M on 30-60 mesh Firebrick

APPENDIX III

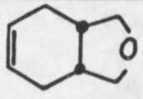
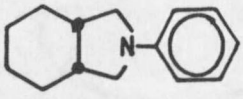
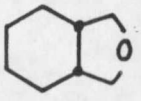
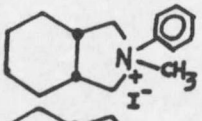
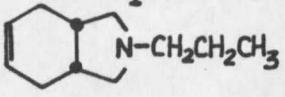
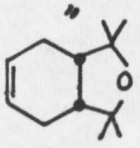
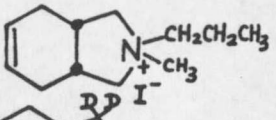
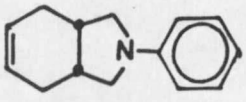
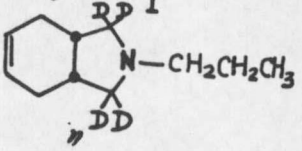
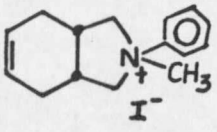
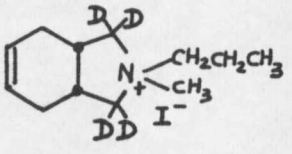
THE COMMONLY USED NAMES OF SOME OF THE HETEROCYCLIC COMPOUNDS

Empirical formula	Structure	Commonly Used Names
$C_8H_{12}O$	(1) 	(1) cis-8-oxabicyclo [4.3.0]non-3-ene
	(2) 	(2-a) cis-4,7,8,9-tetrahydrophthalan (2-b) cis- Δ^5-tetrahydrophthalan
	(3) 	(3) cis-2-oxa-3a,4,7,7a-tetrahydroindane
$C_{12}H_{20}O$	(1) 	(1) cis-7,7,9,9-tetramethyl-8-oxabicyclo [4.3.0] non-3-ene
	(2) 	(2) cis-1,1,3,3-tetramethyl- Δ^5-tetrahydrophthalan
	(3) 	(3) cis- $\alpha,\alpha,\alpha',\alpha'$, -tetramethyl-2-oxa-3a,4,7,7a-tetrahydroindane
$C_{14}H_{17}N$	(1) 	(1) cis-8-phenyl-8-azabicyclo-[4.3.0]non-3-ene
	(2) 	(2) cis-2-phenyl-3a,4,7,7a-tetrahydroisoindoline

APPENDIX IV

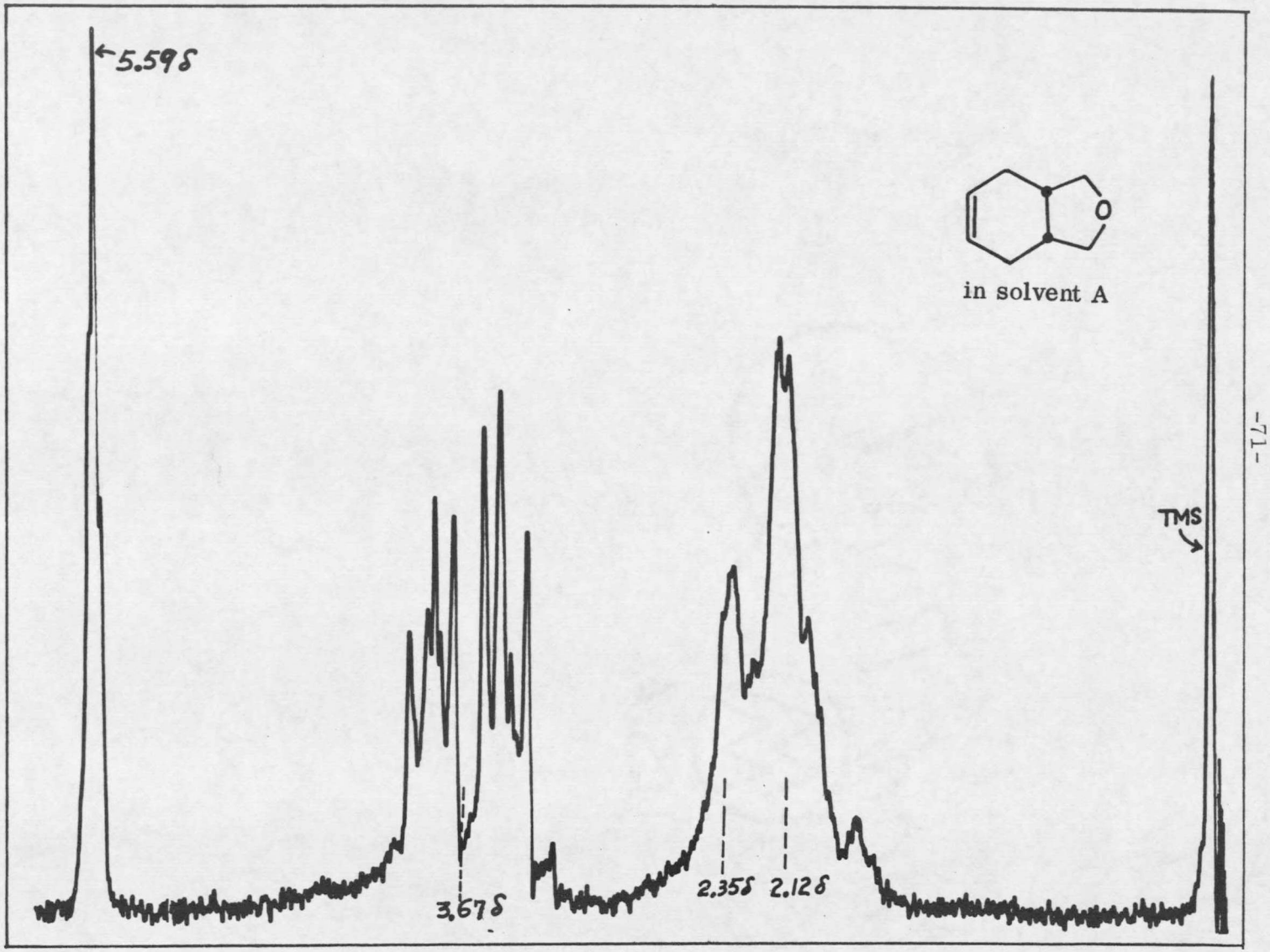
NMR SPECTRA

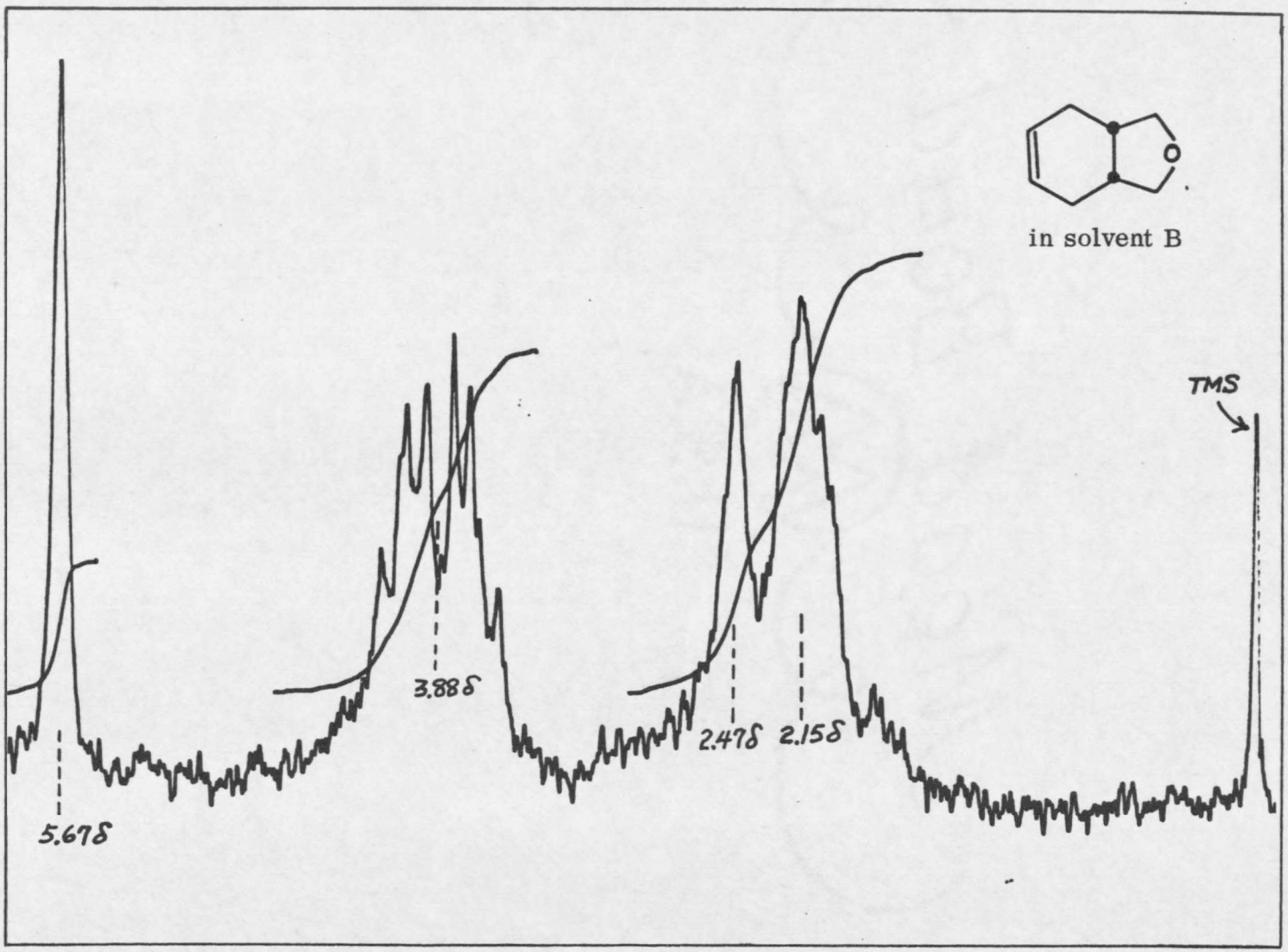
The nmr spectra of the following compounds were attached in this thesis.

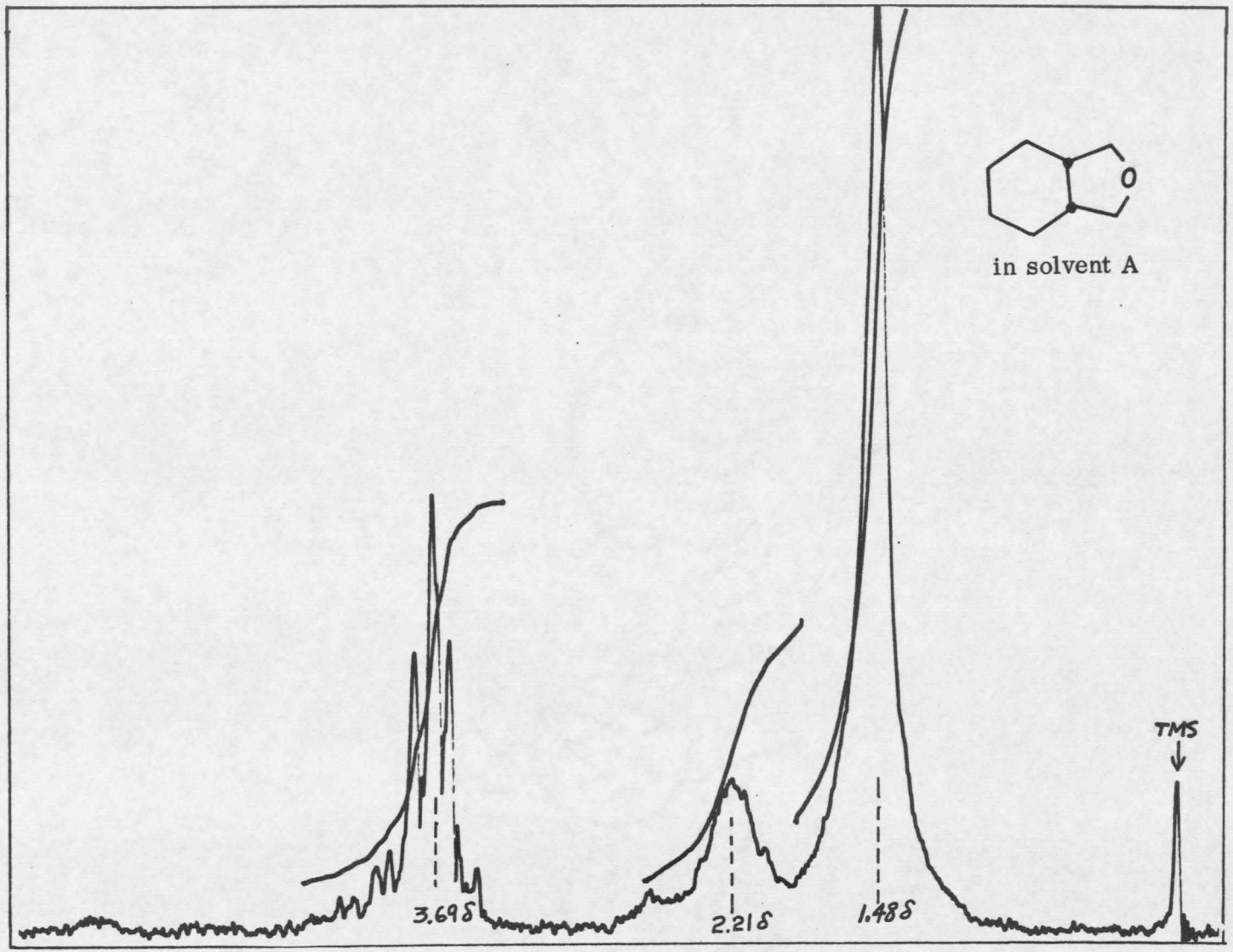
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2	〃	B	11	〃	B
3		A	12		A
4	〃	B	13		A
5		A	14	〃	B
6	〃	B	15		A
7		A	16		A
8	〃	B	17	〃	B
9		A	18		A

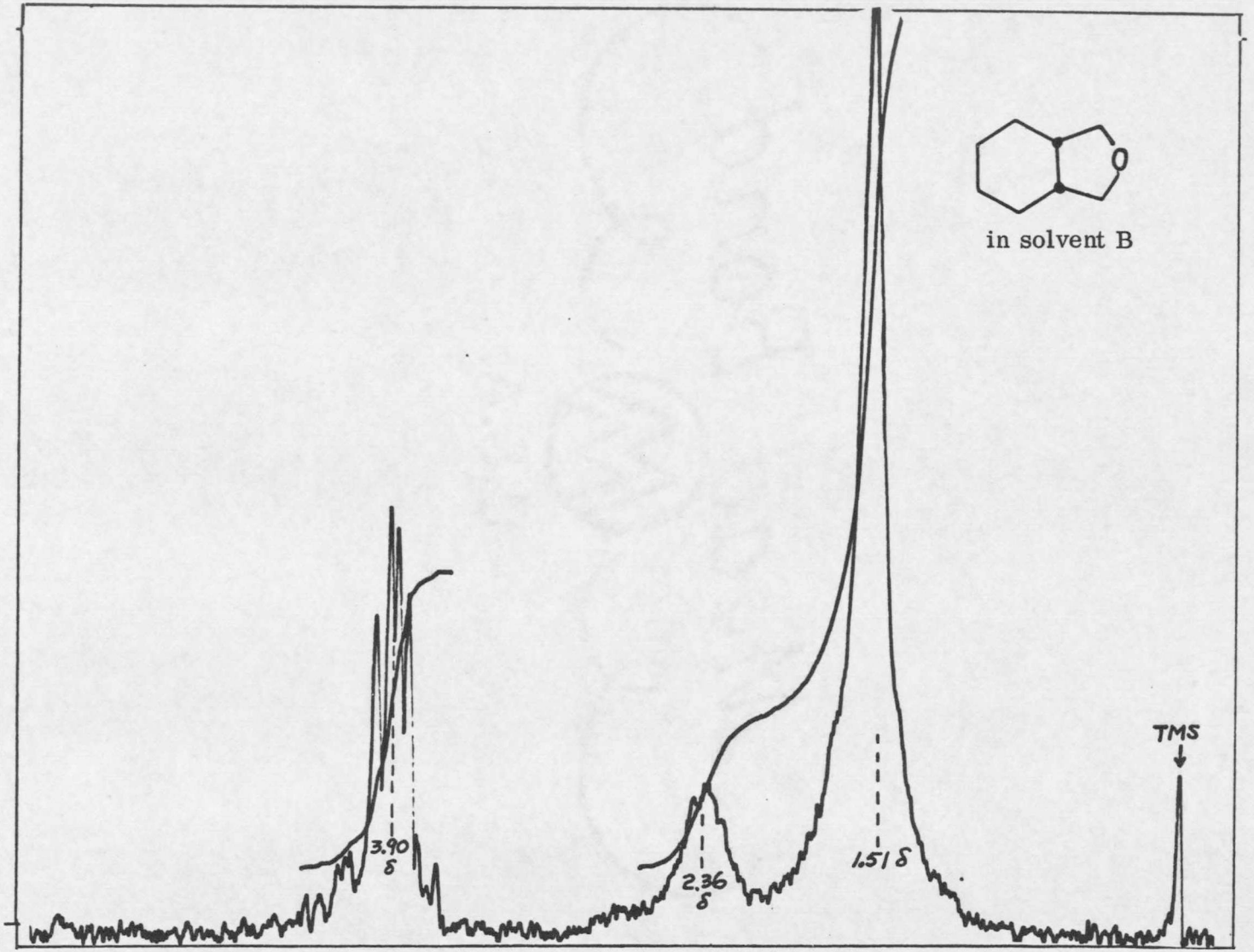
a. Solvent A: deuterochloroform

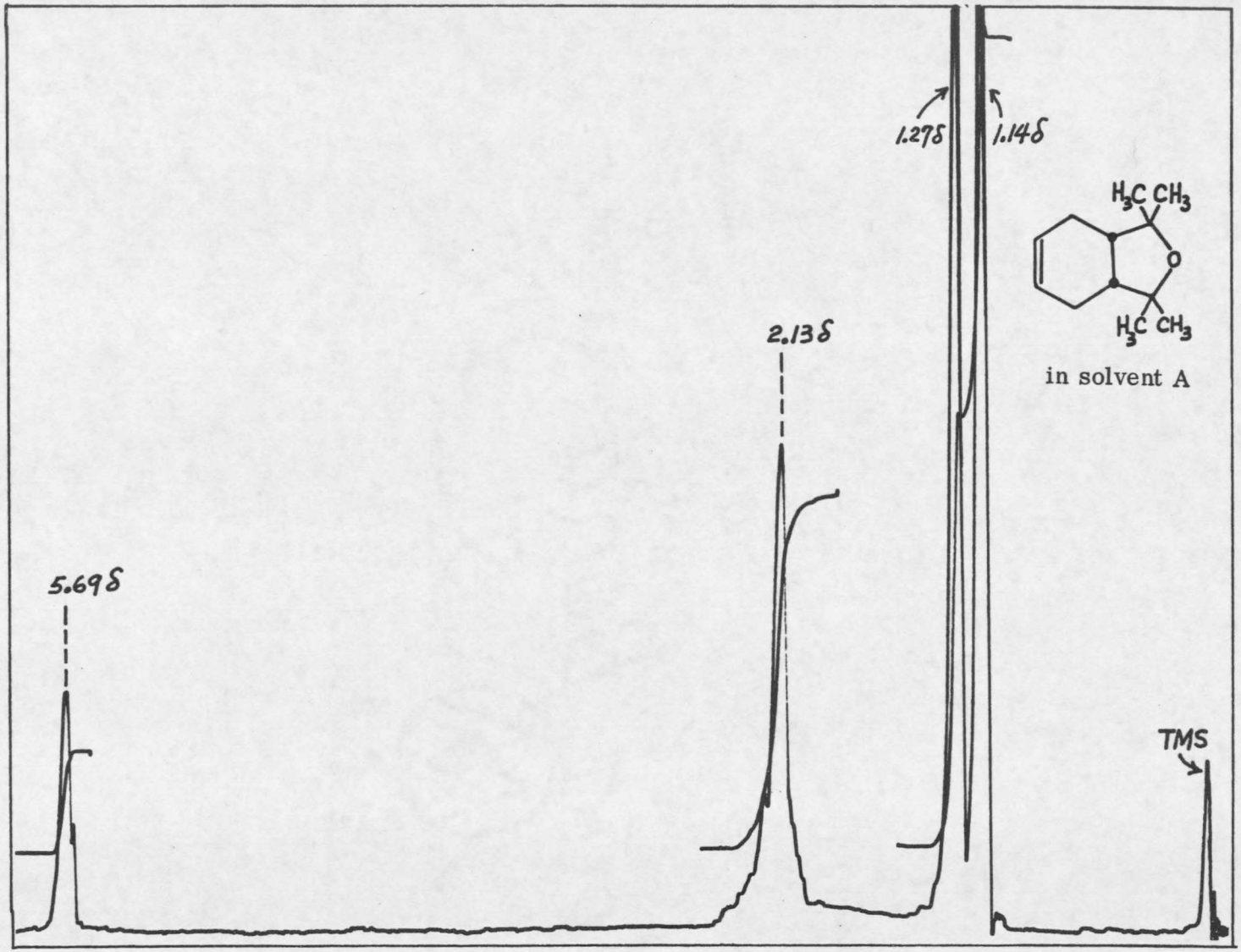
Solvent B: a mixture of deuterochloroform and deuterotrifluoroacetic acid, with a 50:50 ratio.


←5.59δ
O
in solvent A
TMS
3.67δ
2.35δ
2.12δ

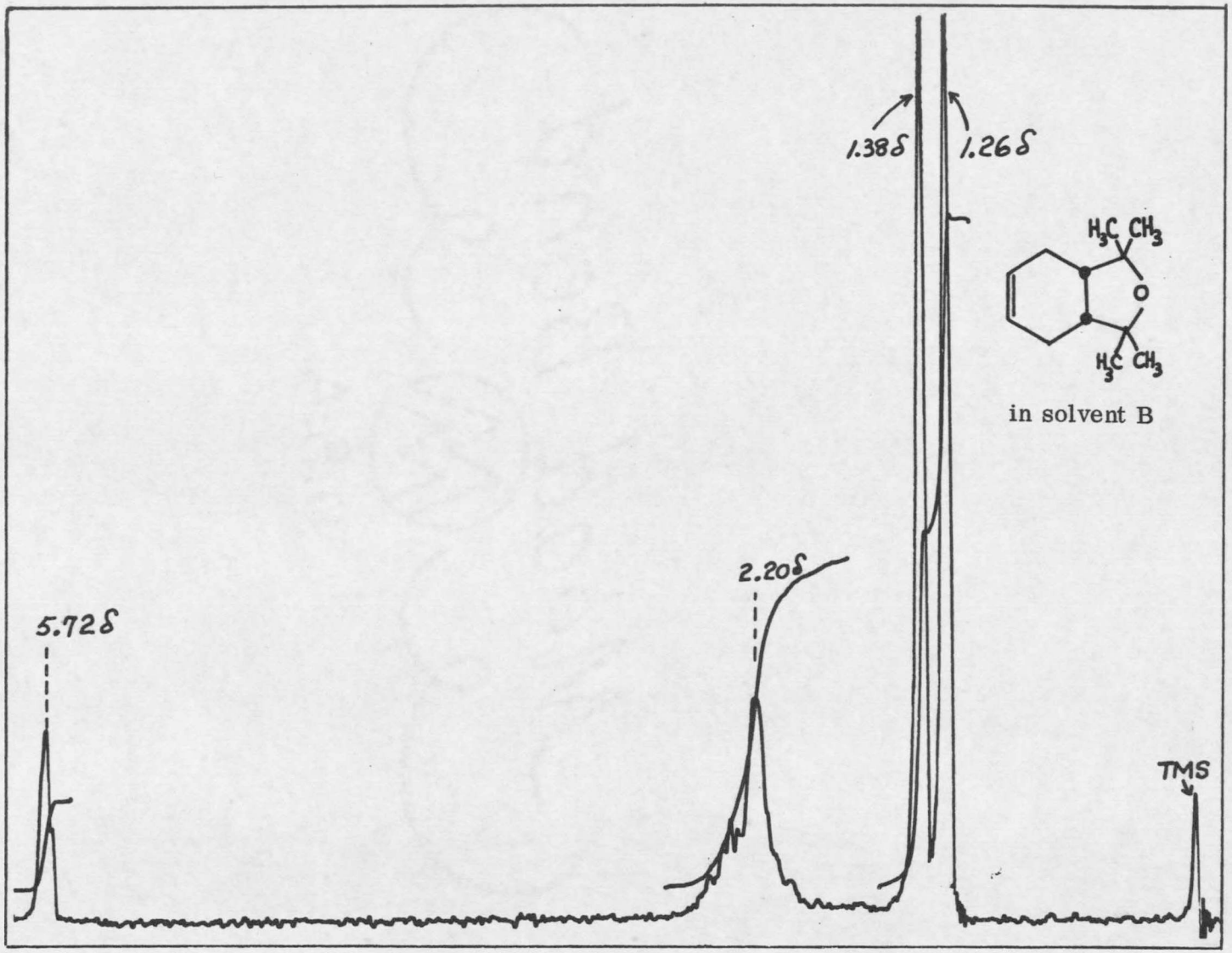

in solvent B
TMS
5.67δ
3.88δ
2.47δ
2.15δ


O
in solvent A
TMS
3.69δ
2.21δ
1.48δ

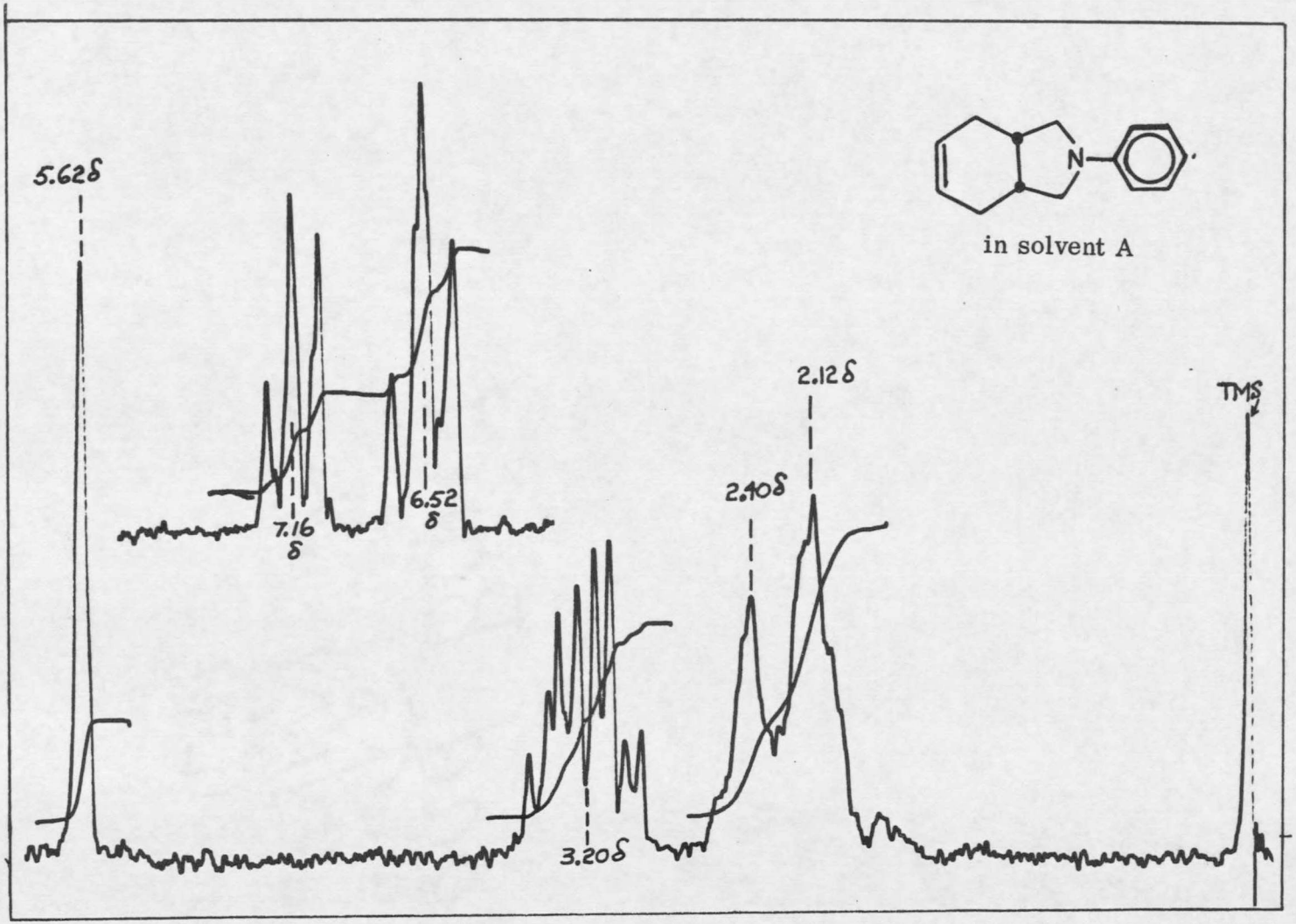

in solvent B
TMS
3.90 δ
2.36 δ
1.51 δ



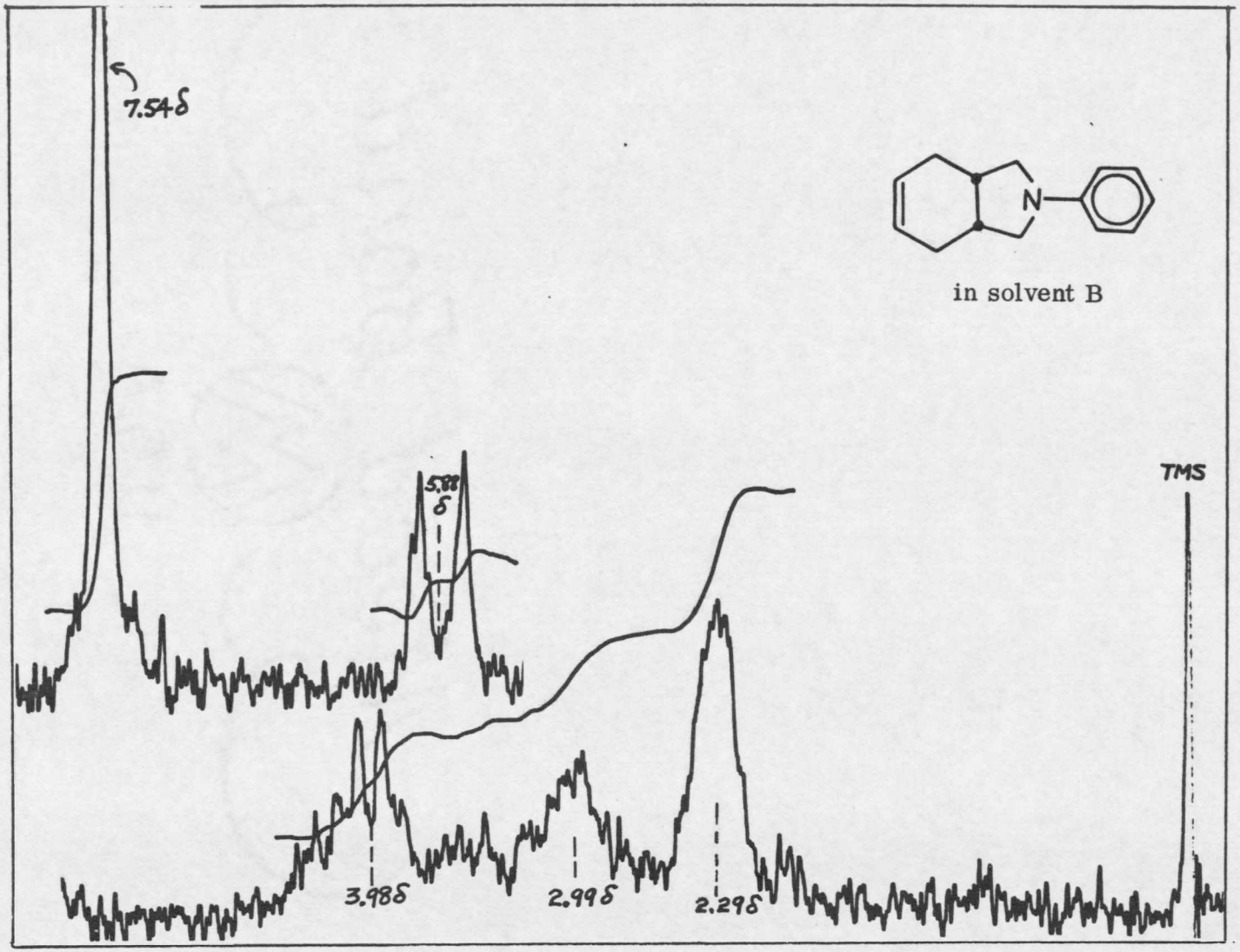
in solvent A



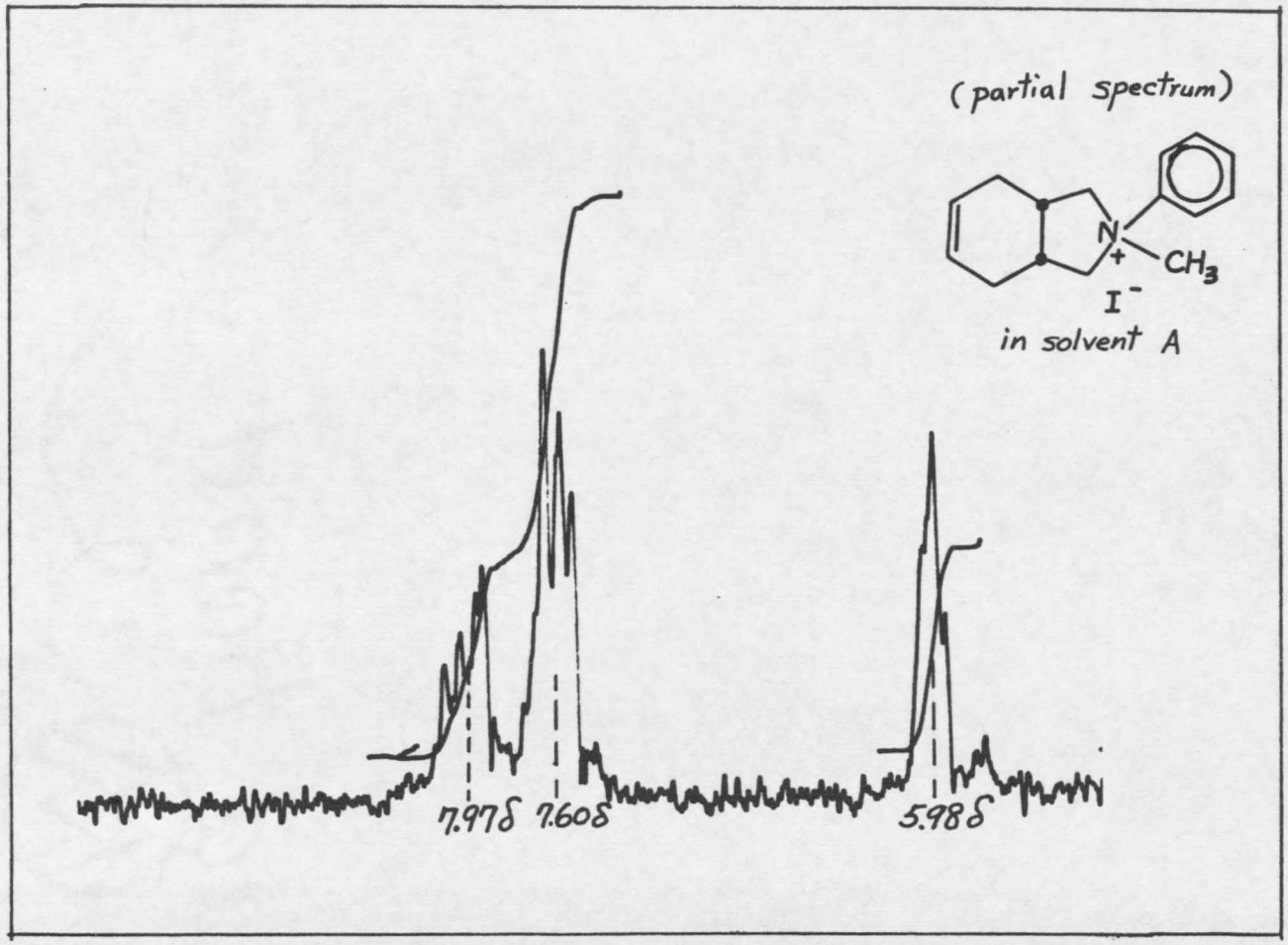
in solvent B

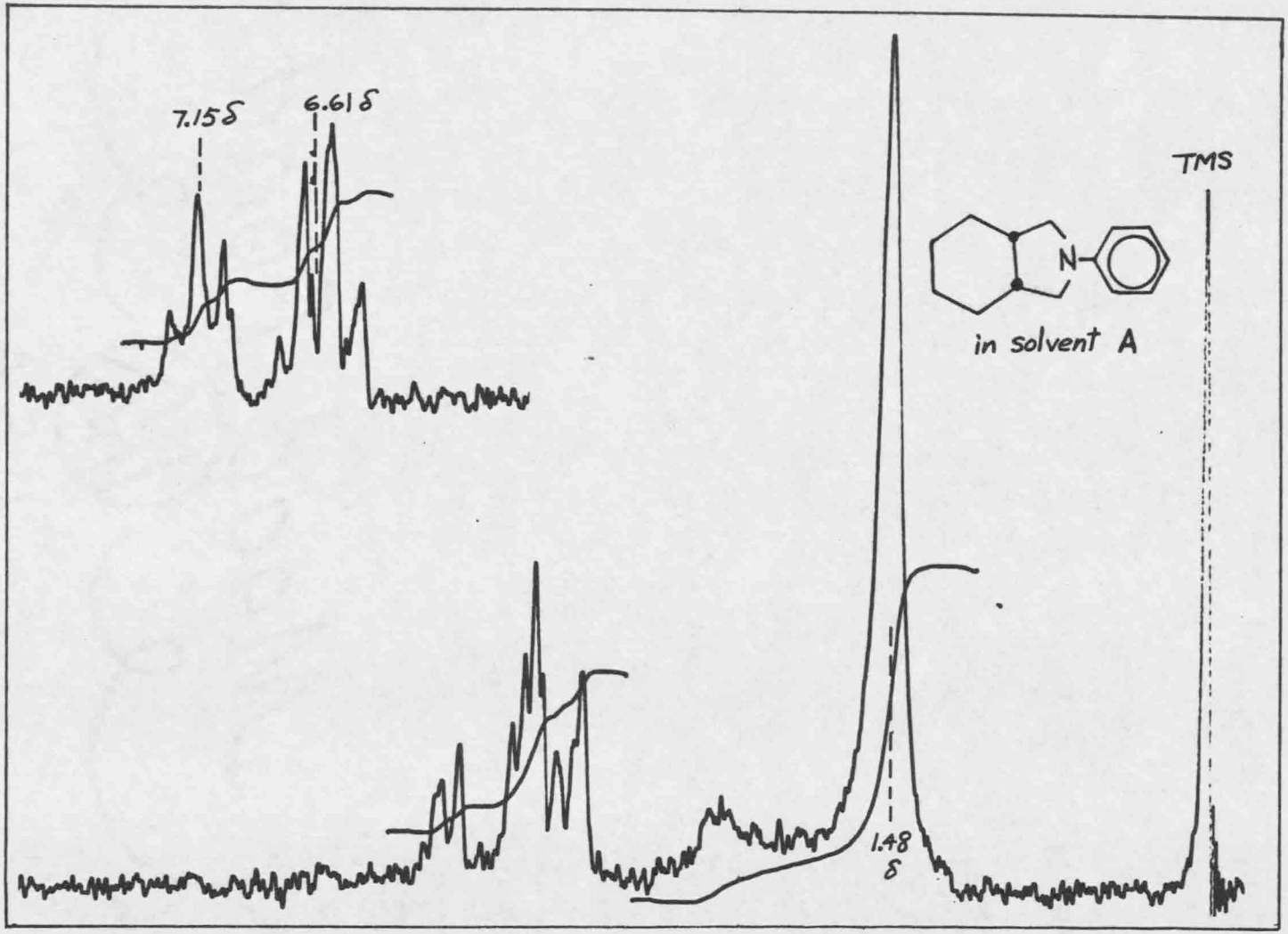


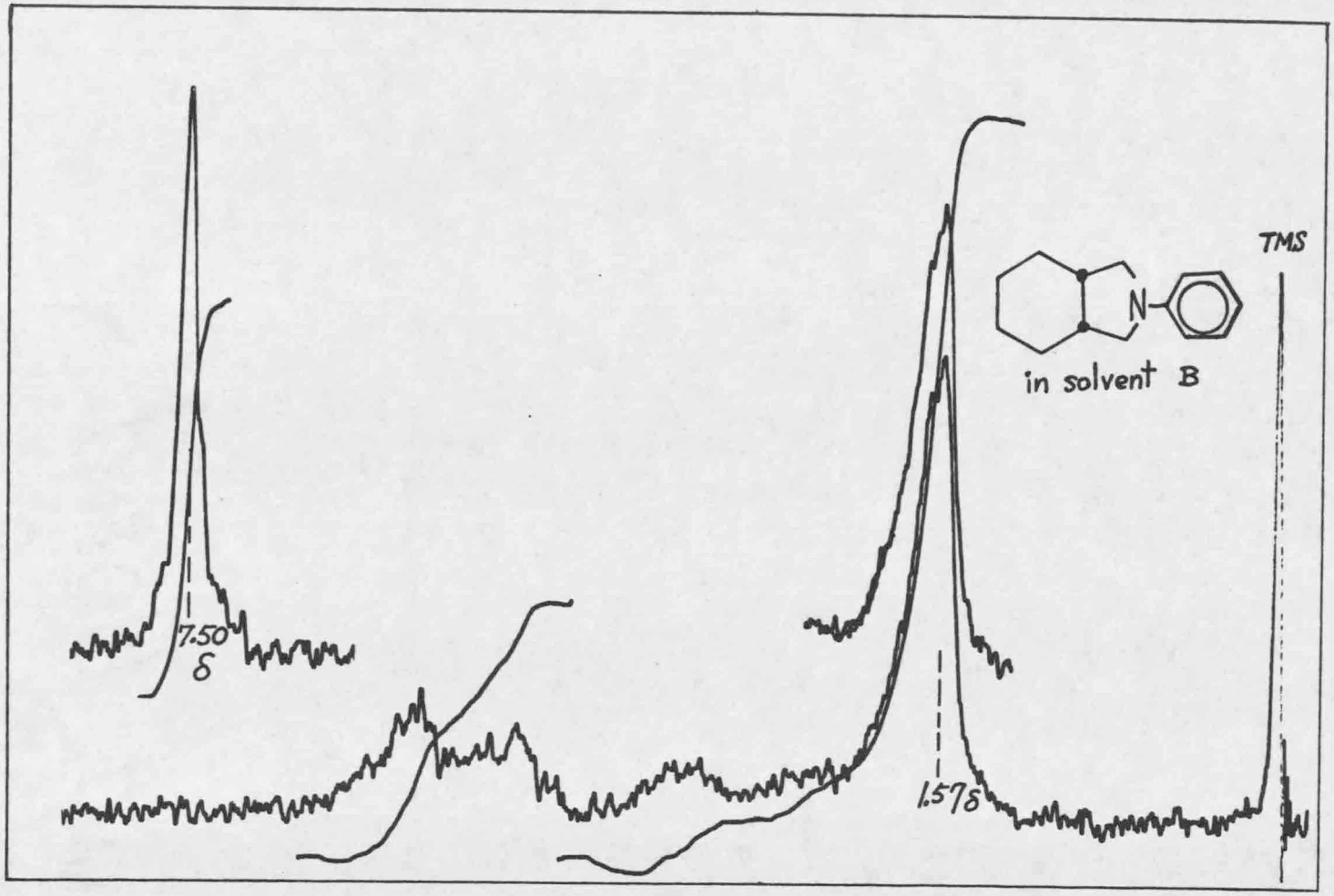
in solvent A

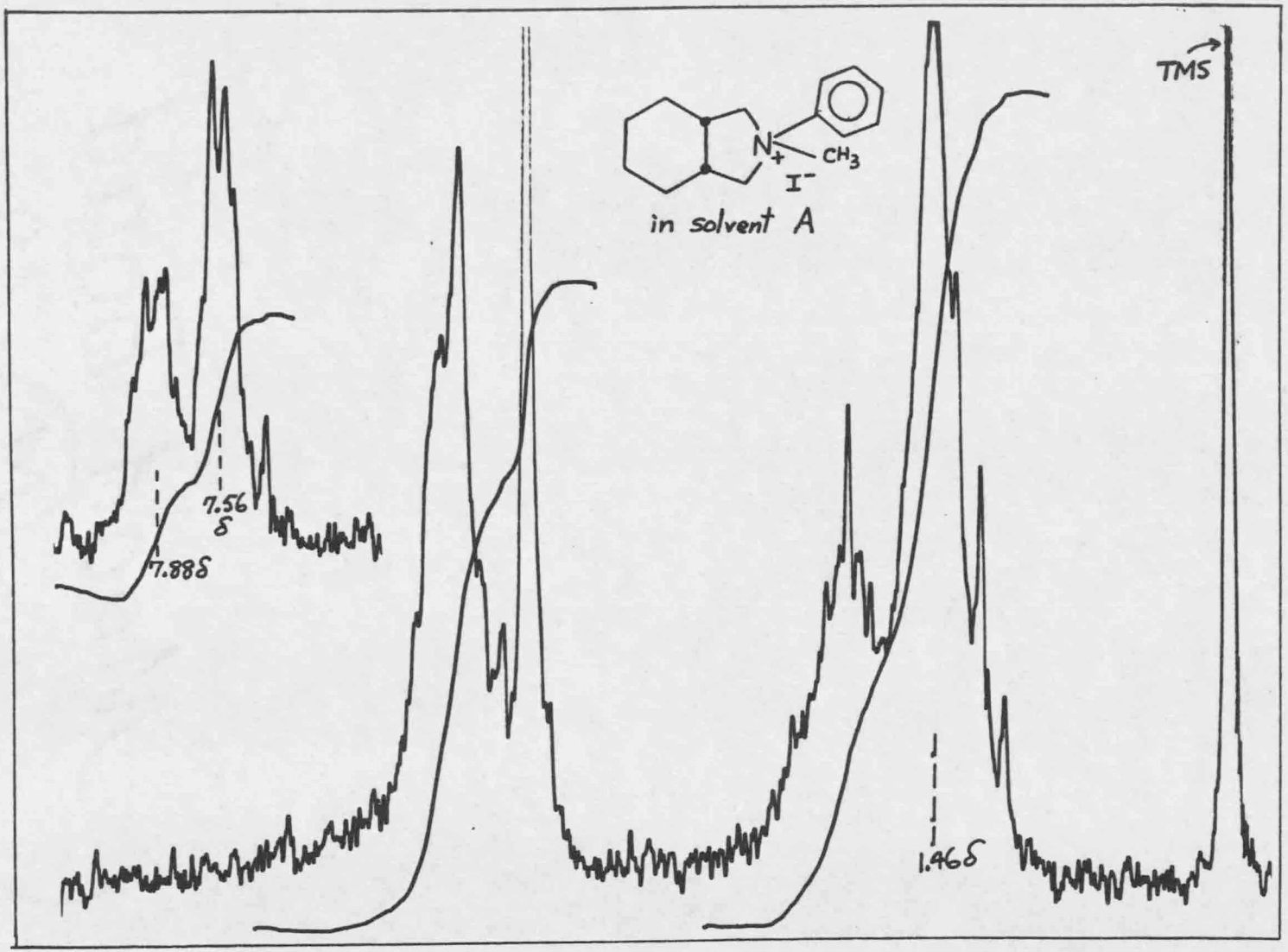


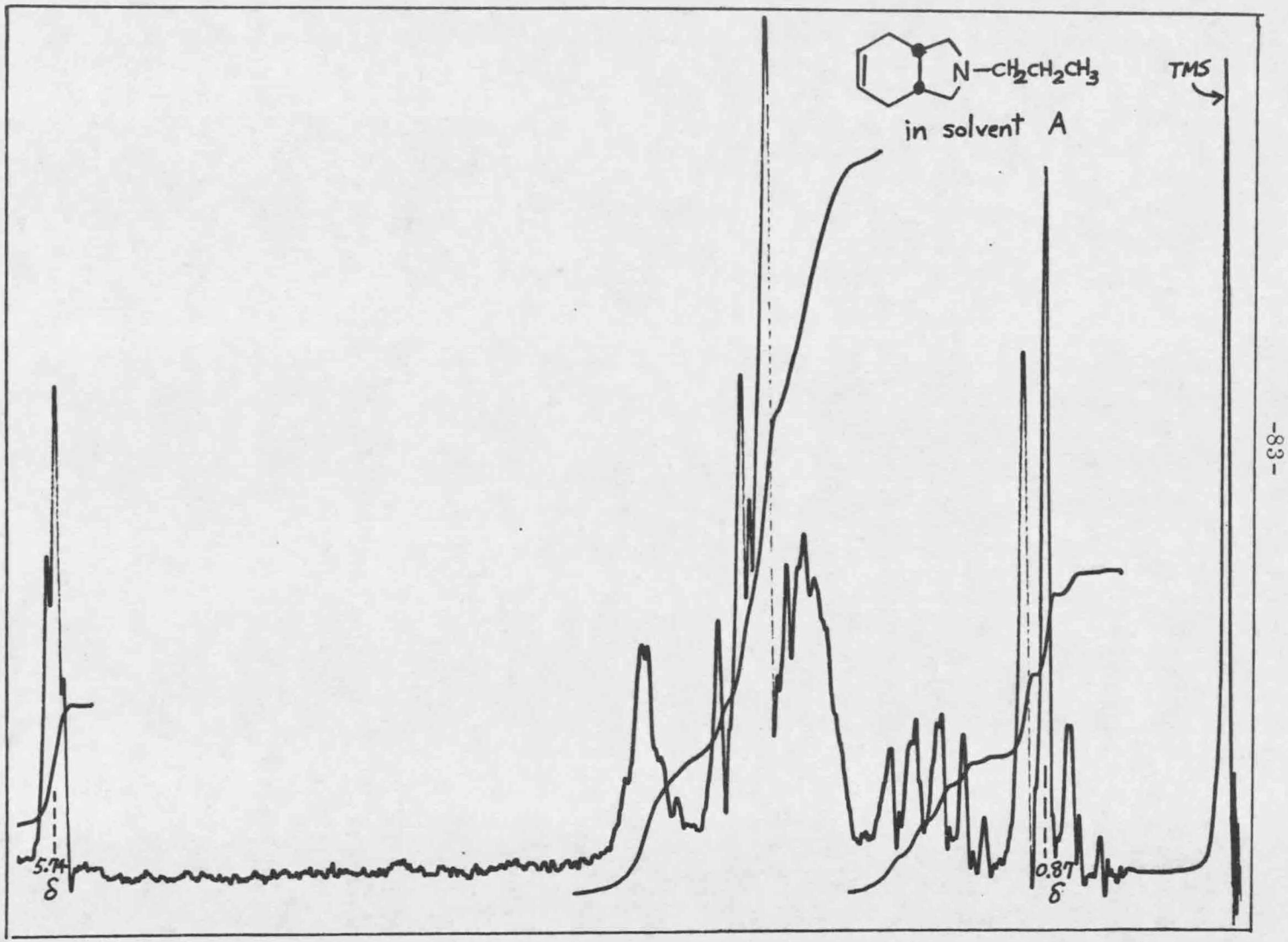
in solvent B

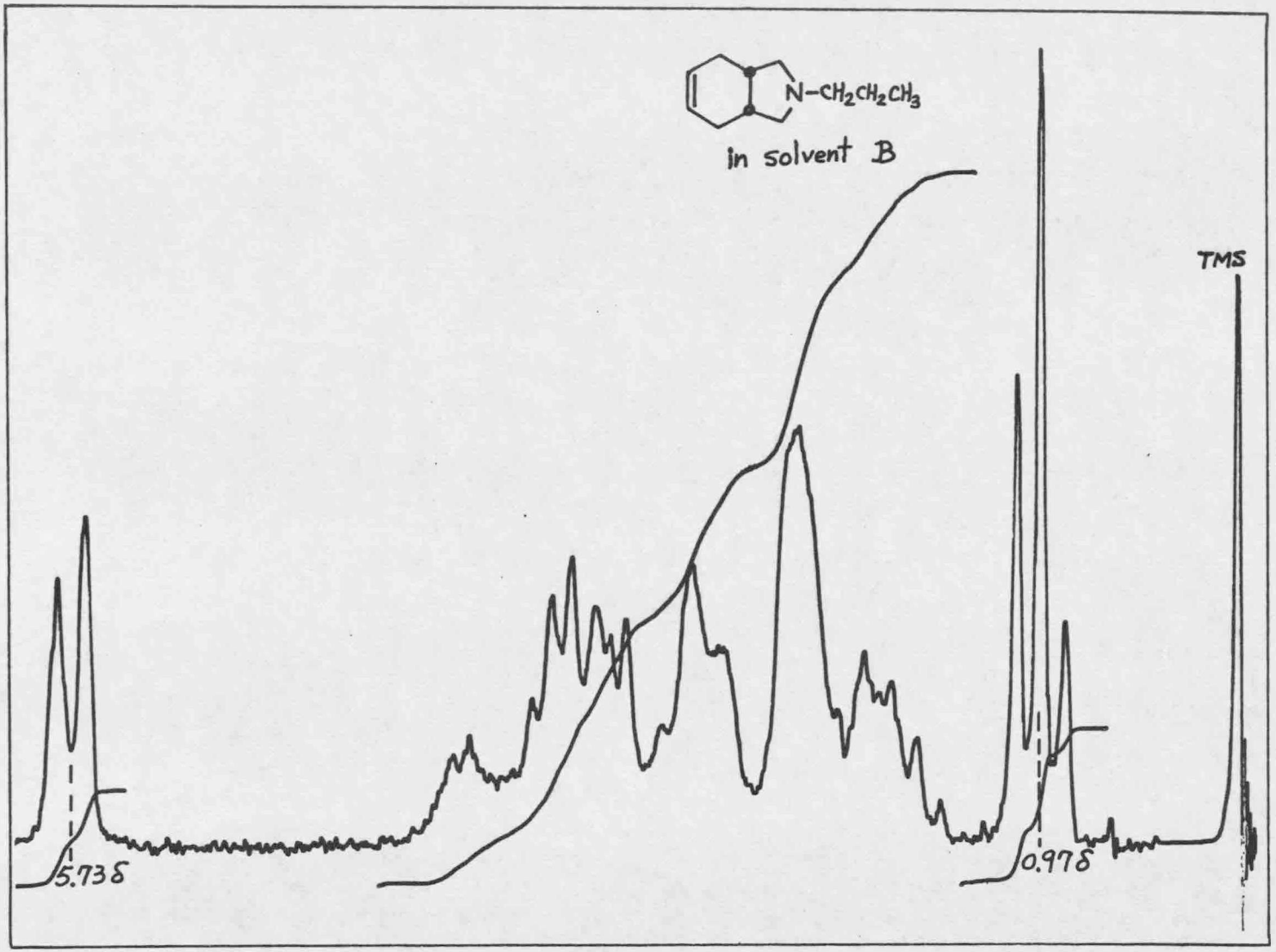

(partial spectrum)
N
+
CH3
I-
in solvent A
7.97δ
7.60δ
5.98δ

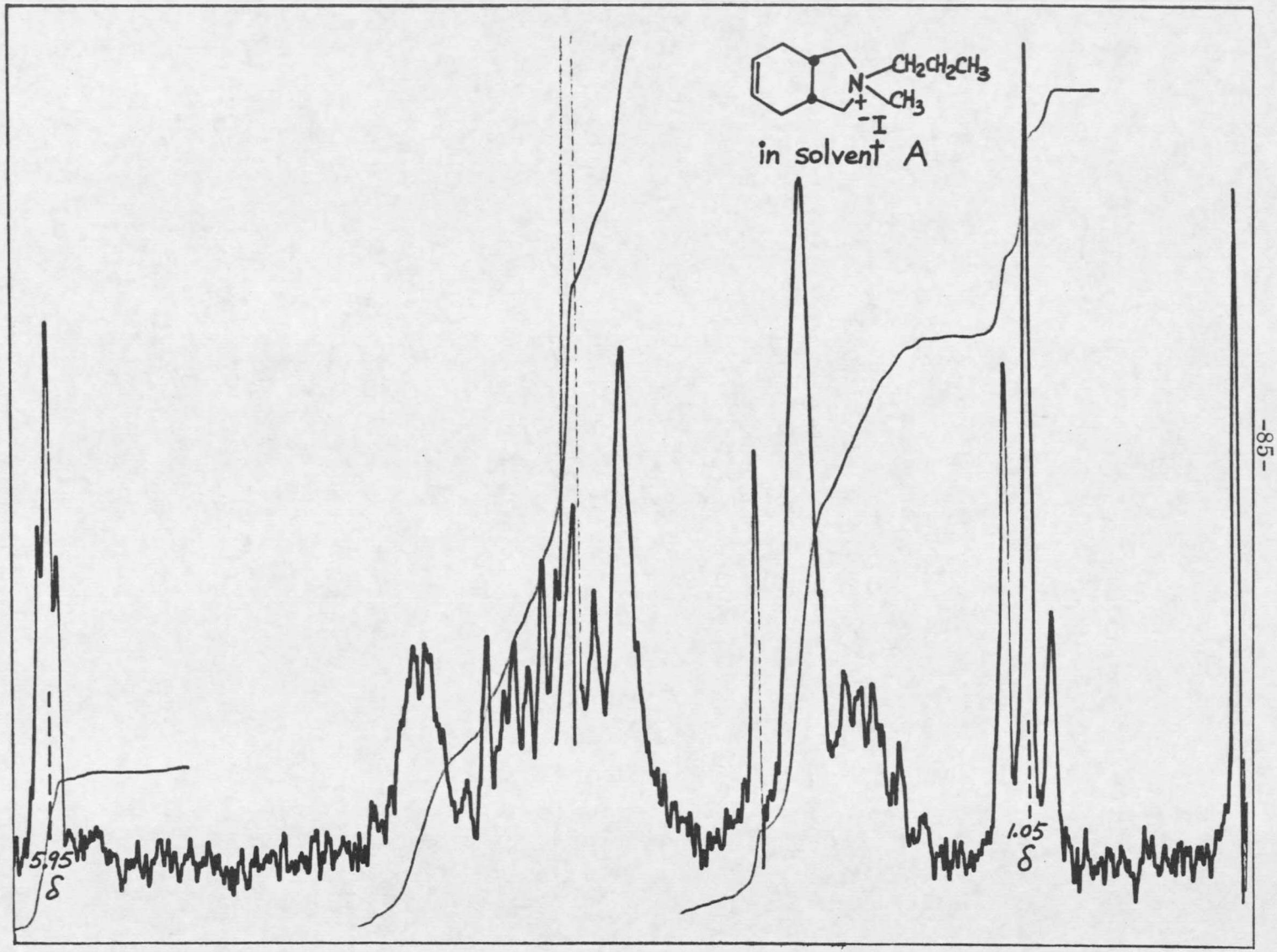

7.15δ
6.61δ
TMS
N
in solvent A
1.48
δ

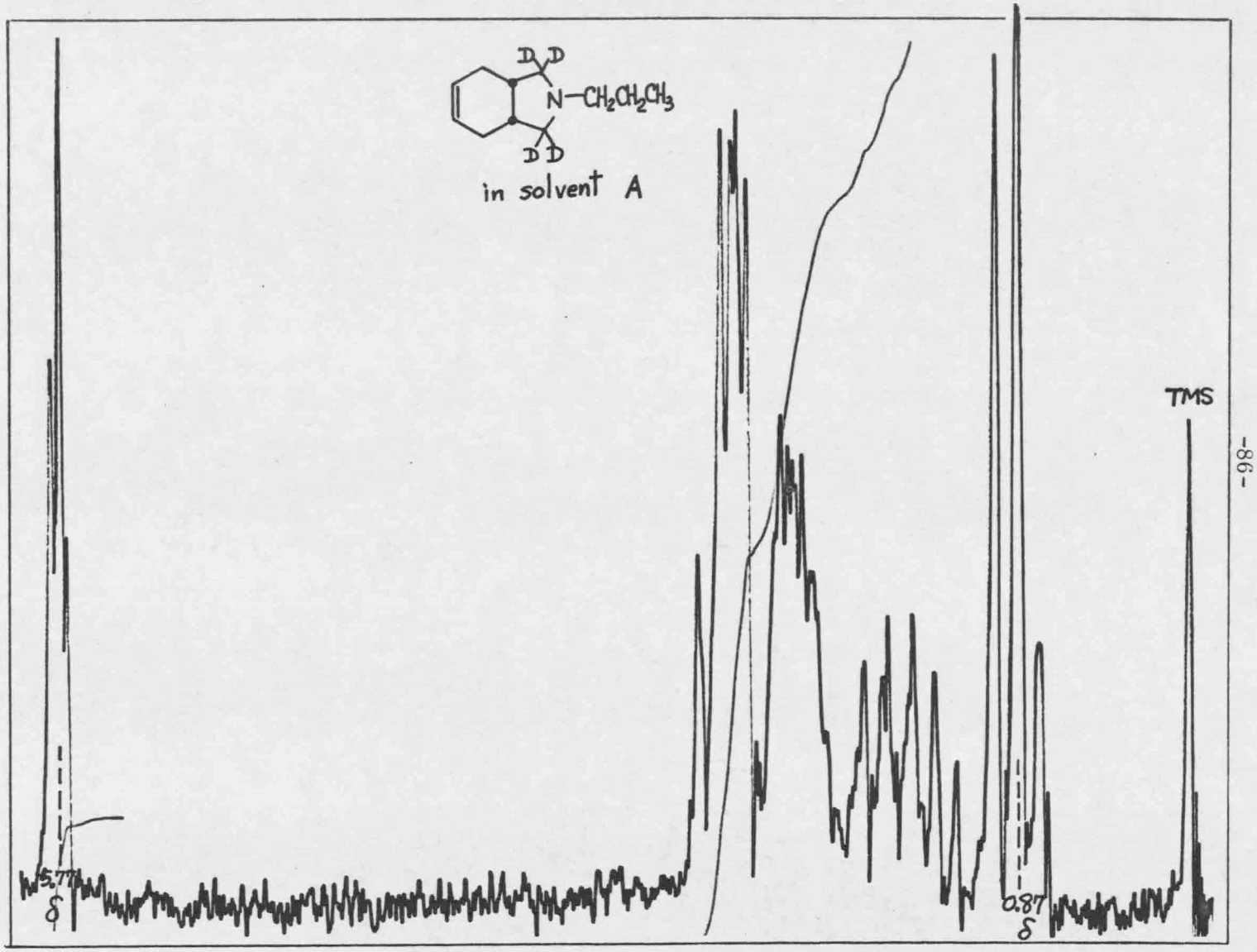

TMS
N
in solvent B
7.50
δ
1.57δ

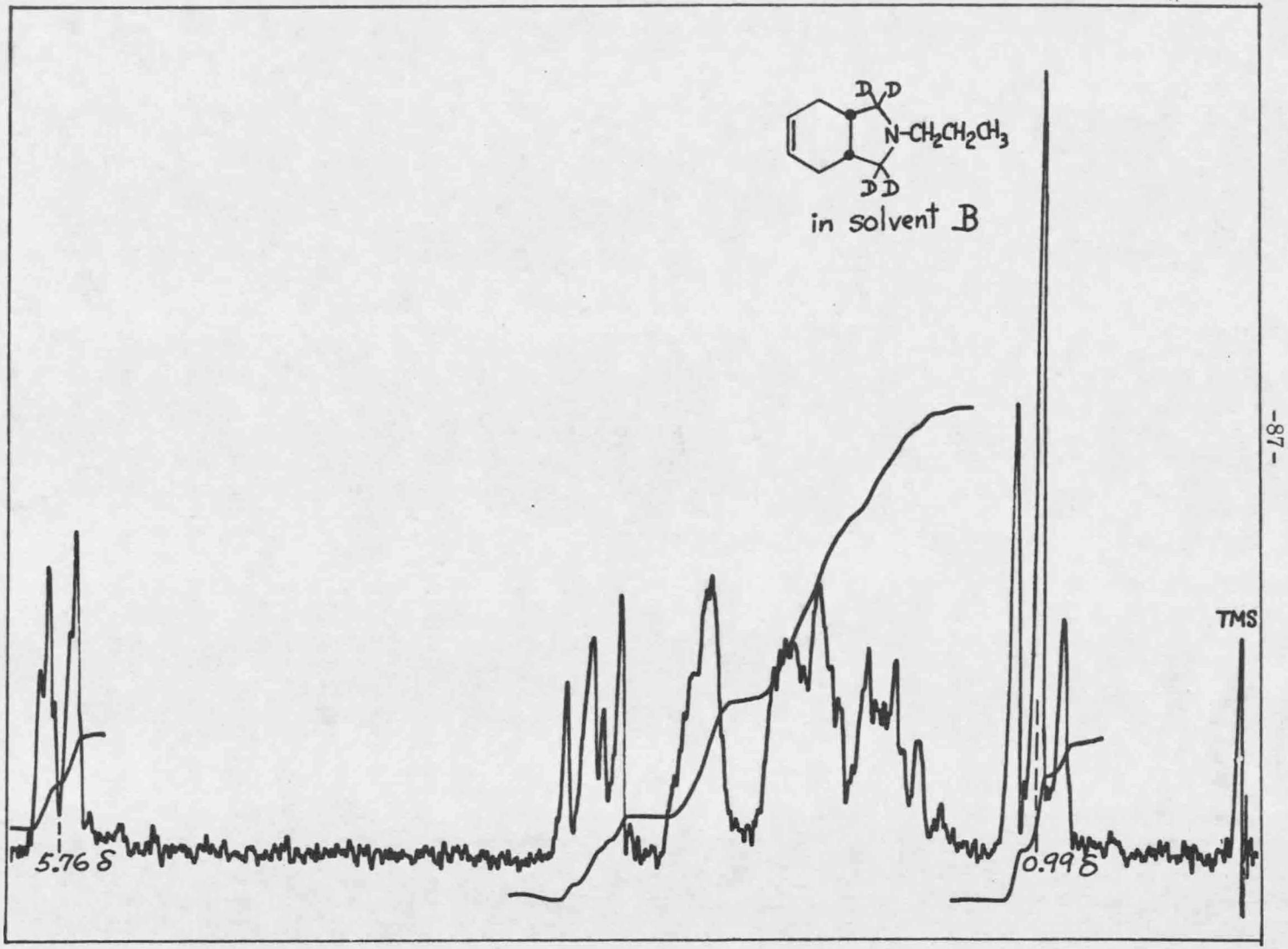

TMS
in solvent A
7.56 δ
7.88δ
1.46δ

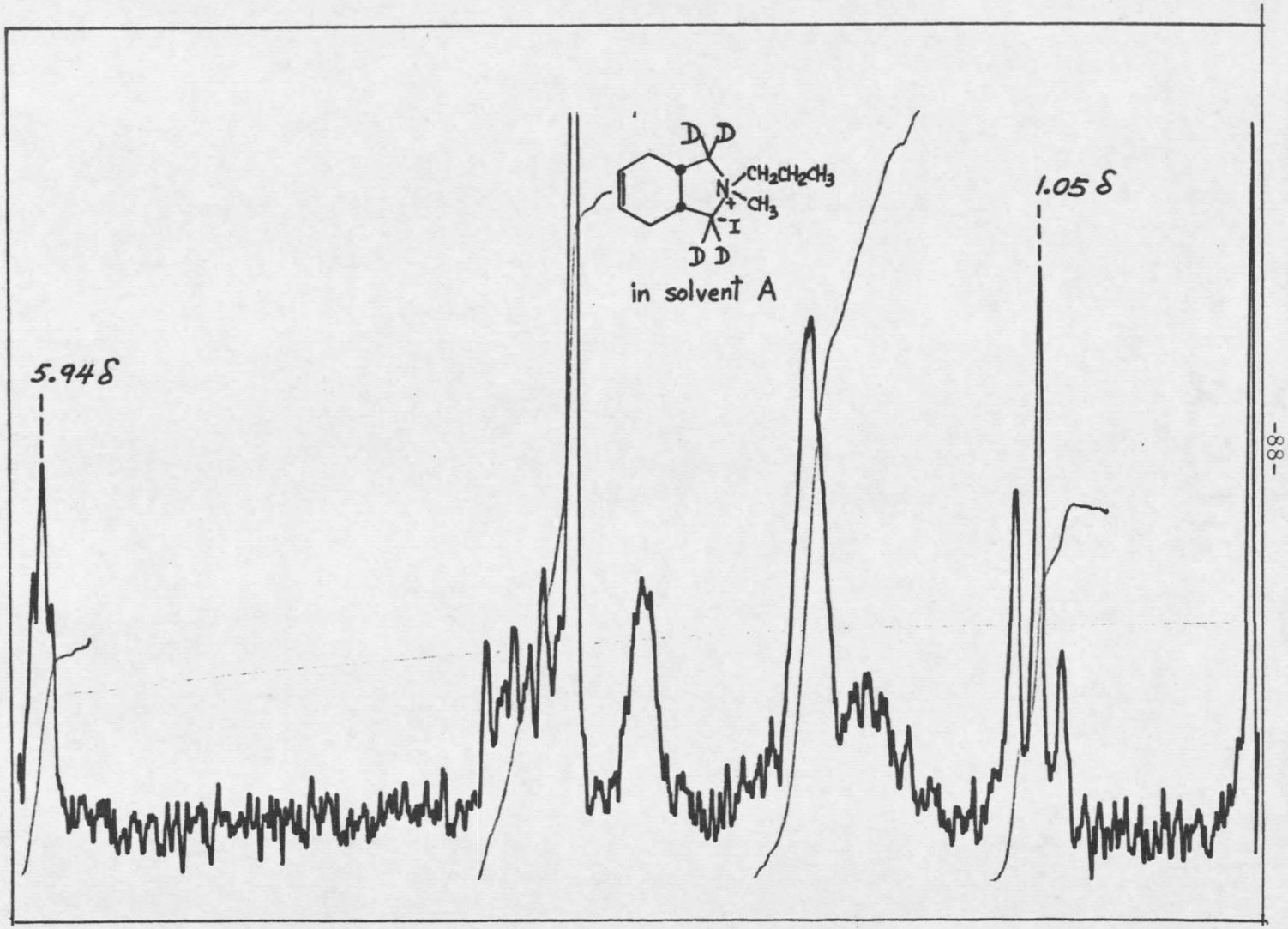

N—CH2CH2CH3
TMS
in solvent A
5.74
δ
0.87
δ


N-CH2CH2CH3
in solvent B
TMS
5.73δ
0.97δ


CH2CH2CH3
N
+
CH3
-I
in solvent A
5.95
δ
1.05
δ


D D
N—CH2CH2CH3
D D
in solvent A
TMS
5.77
δ
0.87
δ


D D
N-CH2CH2CH3
D D
in solvent B
TMS
5.76 δ
0.99 δ


D D
CH2CH2CH3
N+
CH3
-I
D D
in solvent A
5.94 δ
1.05 δ

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