PART I. SYNTHESIS AND ANTIARRHYTHMIC PROPERTIES OF SUBSTITUTED 3,7-DIAZABICYCLO[3.3.1]NONANES AND 3-AZABICYCLO[3.3.1]NONANES, AND DERIVATIVES

PART II. ^{17}O NMR ANALYSIS OF SUBSTITUTED 1-HETERA-4-CYCLOHEXANONES

By

SATISH VASANT MULEKAR

Bachelor of Science
University of Bombay
Bombay, India
1979

Submitted to the Faculty of the Graduate College
of the Oklahoma State University
in partial fulfillment of the requirements
for the Degree of
DOCTOR OF PHILOSOPHY
May, 1989

PART I. SYNTHESIS AND ANTIARRHYTHMIC PROPERTIES OF SUBSTITUTED 3,7-DIAZABICYCLO[3.3.1]NONANES AND 3-AZABICYCLO[3.3.1]NONANES, AND DERIVATIVES

PART II. ^{17}O NMR ANALYSIS OF SUBSTITUTED 1-HETERA-4-CYCLOHEXANONES

Thesis Approved:

K D Berlin
Thesis Adviser

Warren T Ford

Ziad El Rassi

Richard C Essenberg

Norman N. Durham
Dean of the Graduate College

ACKNOWLEDGMENTS

Many people have assisted me during my graduate work. I would like to express my appreciation to them all. Dr. K. D. Berlin will always have my respect and appreciation for his patience and assistance (and his Macintosh). I would also like to say thank you to Drs. W. T. Ford, R. A. Bunce, R. C. Essenberg, Z. El Rassi, J. I. Gelder and G. J. Mains for their help during my graduate work.

I would also like to thank my fellow students and co-workers, Stan, Prasanna, Francis, Shankar, Marwan, Gary, Lyle, Shirish, Jonathan, Tim, and Vicki for their companionship. Special thanks are due Stan Sigle and Norman Perreira for technical assistance. I would also like to thank Dr. S. R. Otiv for carrying out preliminary experiments in Part I of this work. A thank you is also extended to the many researchers who prepared the compounds used in Part II of this work. Special gratitude is expressed to Sue for her help in the typing of the manuscript.

I would also like to thank my brother, Sanjay, sister, Sarojini, and her family for all the sweet memories. Words cannot express my appreciation for the undying love and support of my wife, Madhuri, who deserves special thanks. My parents deserve special mention for their love and support, without which this work would have been only a dream. This work is dedicated to my parents, Vasant and Shailaja Mulekar, and to Shri Ganesh, the supreme power of knowledge and intelligence.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF PLATES

INTRODUCTION

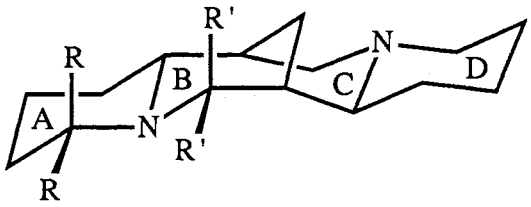
Owing to the differences in the primary objective of the two investigations recorded herein, this dissertation has been divided into two parts. Each is complete and independent of the other, containing its own Historical section, Results and Discussion, Experimental section and Bibliography.

PART I. SYNTHESIS AND ANTIARRHYTHMIC PROPERTIES OF SUBSTITUTED 3,7-DIAZABICYCLO[3.3.1]NONANES AND 3-AZABICYCLO[3.3.1]NONANES, AND DERIVATIVES

CHAPTER I

HISTORICAL

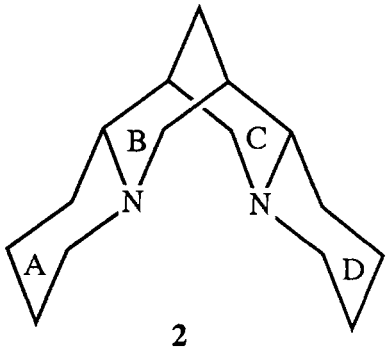
By 1949, sparteine (**1a**), one of the members of the lupine alkaloid family, was shown to have properties as a local anesthetic.[18] It was later found to have useful antiarrhythmic properties[13,24,33,37] and has actually been used in the management of various cardiac arrhythmias.[24] However, animals intoxicated with plants which produce sparteine showed signs of nervousness, difficulty in breathing, loss of muscular control and coma in extreme cases.[3] It is interesting to note that sparteine (**1a**), aphylline (**1b**) and α-isosparteine (**2**) are side products in the biosynthesis of lupanine (**1c**). This result is due to an excess of cadaverine, the metabolic precurser for these lupine alkaloids, as postulated by Wink and co-workers.[47]



1a R=R'=H

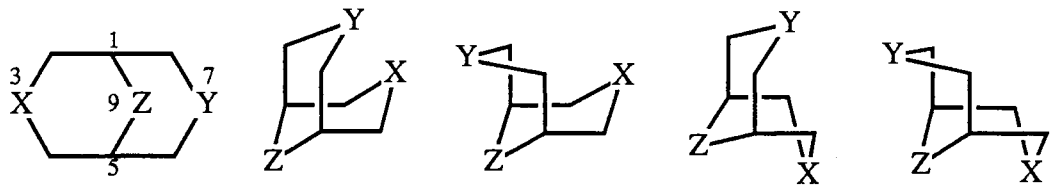
1b R=H, R'R'= =O

1c RR= =O, R'=H



2

The two central rings in these lupine alkaloids, namely rings B and C, form the skeleton of 3,7-diheterabicyclo[3.3.1]nonanes **3**.[38] Compounds containing the bicyclo[3.3.1]nonane ring system **3** have been of interest, mainly due to their conformational properties[19] and biological activity of certain derivatives.[4,33,34] This



3 **3-CC** **3-BC** **3-CB** **3-BB**

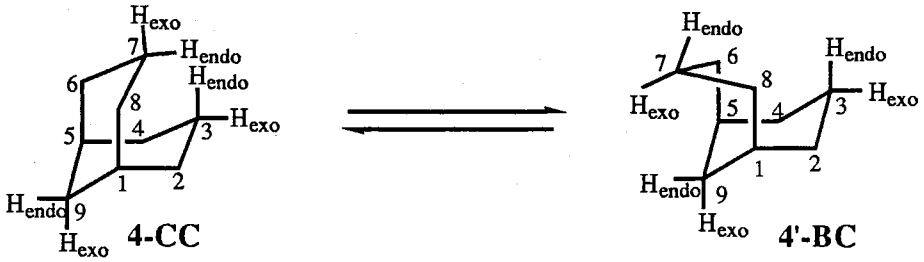
bicyclo[3.3.1]nonane ring system is interesting as it can exist in four conformations: chair-chair **3-CC**, boat-chair **3-BC**, chair-boat **3-CB** and boat-boat **3-BB**. The biological activity of this heterocyclic system is also not surprising, due to the structural similarity with B and C rings of a series of C-15 lupine alkaloids **1a-c** and **2**.

This discussion will focus on the 3,7-diheterabicyclo[3.3.1]nonanes **3** and related carbocyclic and heterocyclic analogues. First, there will be an evaluation of stereochemical and conformational aspects of such bicyclo[3.3.1]nonanes followed by a brief summary of synthetic routes that have been employed to arrive at such systems. This will be followed by a discussion on antiarrhythmic properties of certain derivatives of 3,7-diheterabicyclo[3.3.1]nonanes, including a short discussion on antiarrhythmic activity.

Conformational Aspects

As stated previously, compounds containing the bicyclo[3.3.1]nonane framework can exist in four possible conformations when X and Y are not identical. Although conformations **3-CC–3-BB** are supposedly free from angular strain, nevertheless none are likely free from strong destabilizing interactions between the non-bonded atoms.[19] One of the compounds studied in great detail is bicyclo[3.3.1]nonane (**4**). It has been shown to exist in a twin-chair conformation in the gas phase based on electron diffraction studies[9,21] at 65°C and at 400°C. However, a **C C⇌BC** equilibrium has been suggested, based on electron diffraction and molecular mechanics.[21] The amount of boat-chair conformation is only about 5 ± 4% at 65°C while it is 25 ± 3% at 400°C,[21] thus

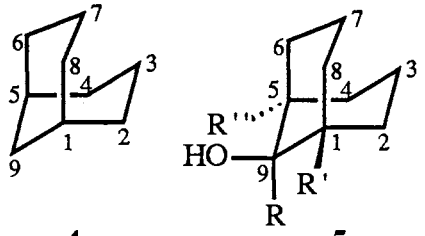
suggesting that at ambient temperatures the double chair conformation is the predominant one. The energy difference between the chair-chair and boat-chair conformers is 2.3



kcal/mol, as determined by molecular mechanics calculations.[12] This twin-chair conformation for **4** is further supported in certain examples by ^{13}C NMR[31] and IR data.[9] Conformations of several members of this family have been determined in the solid state by X-ray crystallography.[19] Selected data for 9-cyclohexylbicyclo[3.3.1]nonan-9-ol (**5a**)[36] and 1-*p*-bromobenzenesulfonyloxymethyl-5-methylbicyclo[3.3.1]nonan-9-ol (**5b**)[8] from X-ray analyses are listed in Table I along with the corresponding data for bicyclo[3.3.1]nonane (**4**–electron diffraction study and MM2 calculations[21]). Inspection of the data indicates that C(2)–C(3) and C(3)–C(4) bond lengths are shorter (0.014–0.061Å) in **5a** and **5b** as compared with the corresponding ones in **4**, while the bond lengths C(6)–C(7) and C(7)–C(8) are only slightly shorter (0.008–0.031 Å) in **5a** and **5b** as compared with **4**. The exception is bond length C(7)–C(8) in **5b** which is longer by 0.029 Å (compared to **4**). In contrast, the bond angles and torsion angles in **5a** indicate a flattening of the rings at both C(3) and C(7). To be specific, the torsion angles C(5)–C(6)-C(7)-C(8) [38.7°] and C(6)–C(7)-C(8)-C(9) [-38.1°] in the left ring with C(7) are smaller than the angles C(1)–C(2)-C(3)-C(4) [45.3°] and C(2)–C(3)-C(4)-C(5) [-45.3°] in the right ring with C(3), indicating that the left ring has been flattened to a greater extent than the right ring in **5a**. The C(3)–C(7) distance in **4** at 65°C is 3.06 Å[21] (based on the electron diffraction study) which is very close to the value of 3.13 Å observed for **5a** in the solid state.[36] The distance between the *endo*-hydrogen atoms in the 3- and 7-positions

TABLE I

SECTED BOND LENGTHS (Å), BOND ANGLES (°), TORSION ANGLES (°) AND NON-BONDED INTERATOMIC DISTANCES (Å) FOR **4**, **5a** AND **5b**



4 **5**

a R=cyclohexyl, R'=R''=H

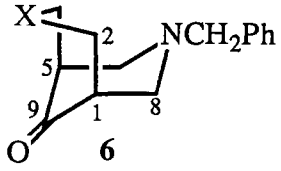
b R=H, R'=4-Br-$C_6H_4SO_3CH_2$, R''=CH_3

	4		**5a**[c]	**5b**[d]
	E.D.[a]	MM2[b]		
Bond lengths (Å)				
C(2)-C(3)	1.541	1.536	1.527	1.52
C(3)-C(4)	1.541	1.536	1.523	1.48
C(6)-C(7)	1.541	1.536	1.533	1.51
C(7)-C(8)	1.541	1.536	1.532	1.57
Bond angles (°)				
∠C(2)-C(3)-C(4)	113.2	112.9	111.9	116
∠C(6)-C(7)-C(8)	113.2	112.9	114.1	114
∠C(1)-C(9)-C(5)	110.1	108.1	106.6	111
Torsion angles (°)				
C(1)-C(2)-C(3)-C(4)	44.0	42.1	45.3	—
C(5)-C(6)-C(7)-C(8)	44.0	42.1	38.7	—
Non-bonded interatomic distances (Å)				
C(3)-C(7)	3.06	3.18	3.134	3.06
(C3)-C(9)	—	—	—	2.94
C(7)-C(9)	—	—	—	2.95
H(3a)-H(7a)	—	—	1.97	—

[a] Electron Diffraction: reference 21.
[b] MM2 Calculations: reference 21.
[c] X-ray Diffraction: reference 36.
[d] X-ray Diffraction: reference 8.

is 1.97 Å for **5a**.[36] Simple calculations using the normal angles and bond lengths show that the non-bonding interatomic distance between $H(3)_{endo}$ and $H(7)_{endo}$ should be only 0.81 Å.[19] This is smaller than the van der Waals radius of hydrogen (1.2 Å). This evidence further supports the view that non-bonded interactions between atoms or groups in the *endo*-orientation at C(3) and C(7) cause flattening of the ring and any *endo*-group bulkier than hydrogen will probably force the ring bearing the *endo*-group into a boat conformation. The destabilization of the boat conformation **4'** is believed mainly to be due to flagpole-flagpole repulsion between $H(7)_{exo}$ and $H(9)_{exo}$.

Several 3,7-diheterabicyclo[3.3.1]nonane derivatives have been studied via X-ray crystallography. Three members of this family, with a carbonyl group at the 9-position, were found to exist in **BC** form in solid state.[4,40] Thus **6a-6c** have the *N*-benzyl group in a chair while the other ring is in the boat form. The rings with S and Se in **6a** and **6b** have been flattened to some extent,[4] while in **6c** both rings are very near an ideal conformation.[40] However, when ketones **6a** and **6b** were reduced to the corresponding

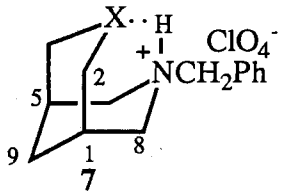


6

a X=S

b X=Se

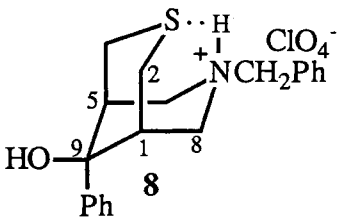
c X=NMe



7

a X=S

b X=Se

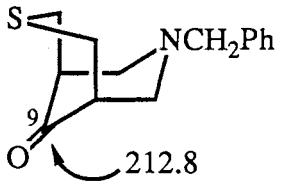


8

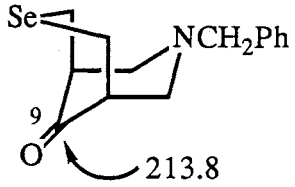
hydrocarbons, followed by salt formation, a twin-chair conformation resulted for **7a** and **7b**.[4] Both systems have rings with ends containing nitrogen and sulfur (or selenium) which are flattened as indicated by the torsion angles.[4] The 9-hydroxy-9-phenyl analogue of **7a**, namely **8**, was also found to exist in a chair-chair conformation.

However, greater flattening of the ring was observed in **8** (as compared with **7a**) at the sulfur end.[4]

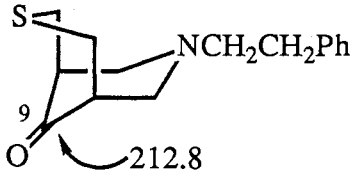
A ^{13}C NMR analysis of bicyclo[3.3.1]nonane and its derivatives has also proved helpful in stereochemical and conformational analysis. To illustrate, the ^{13}C signals for ^{13}C=O [C(9)] in certain ketones believed to be in CB form in solution are at higher field



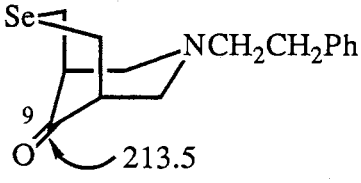
6a



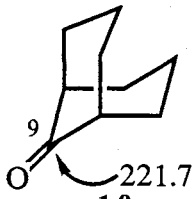
6b



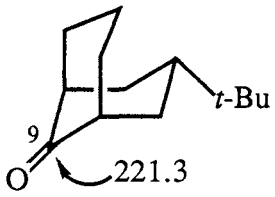
9a



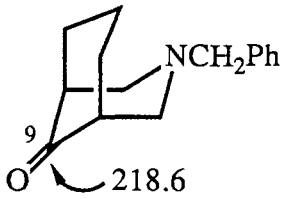
9b



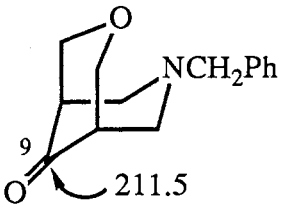
10



11



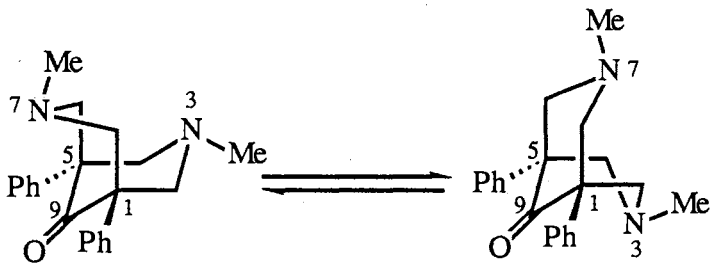
12



13

than in related systems considered to be in CC forms. For example, CB ketones **6a**, **6b**, **9a** and **9b** have a C(9) shift in the range of 212.8–213.8 ppm.[4,5] The CC ketones **10–12** have shifts for C(9) ranging from 218.6–221.7 ppm.[30] Based upon these observations, it

was concluded that in 3,7-diheterabicyclo[3.3.1]nonan-9-one systems a CB form can be diagnosed if the chemical shift for C(9) is at higher field than in corresponding 3-hetero analogues.[4] However, the shift for C(9) in **13** (postulated to be a CC form) occurs at 211.5 ppm[2] which is very similar to that of the sulfur analogue **6a** (212.8 ppm). Thus, the conclusion is open to question. These systems can, of course, exist in an equilibrium in solution. A boat-chair⇌chair-boat equilibrium has been observed for 1,5-diphenyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**14**) by variable-temperature ^{13}C NMR.[44] Thus, at ambient temperature only three aliphatic signals [C(1,5), C(2,4,6,8), and CH_3] were observed for **14**, with the signal for

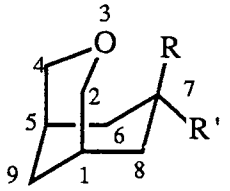


14 **14'**

C(2,4,6,8) at 67.9 ppm. As the temperature was lowered, the C(2,4,6,8) signal broadened, coalesced at -63°C, and finally split into two peaks of equal intensity, with the chemical shift difference being 6.0 ppm. This implies that **14⇌14'** equilibrium is operating or another equilibrium exists such as **CC⇌CB**. The **14⇌14'** system is favored.

A ^1H NMR study has been useful to a limited extent in the conformational analysis of such bicyclic systems, as high signal density usually exists in the aliphatic region from about 1–3 ppm. Thus, the spectra are often complex and do not allow a first-order interpretation.[26,27,29] Consequently, Peters and co-workers used lanthanide shift reagents (LSR) to study the conformations of various bicyclic systems.[25-30] For example, these authors examined conformations of 3-oxabicyclo[3.3.1]nonanes **15** and **16** by the combined use of ^{13}C and ^1H NMR spectroscopy, using LSR to obtain separation of

signals in the ^1H NMR spectrum.[26] They recorded ^1H NMR spectra of compounds **15** and **16** with increasing amounts of $Eu(dpm)_3$. The magnitudes of the H–H coupling



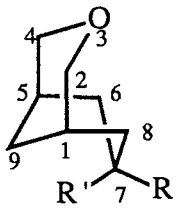
15

a R,R=H

b R=H, R'=CH_3

c R=H, R'=*i*-Pr

d R=H, R'=*t*-Bu



16

b R=CH_3, R'=H

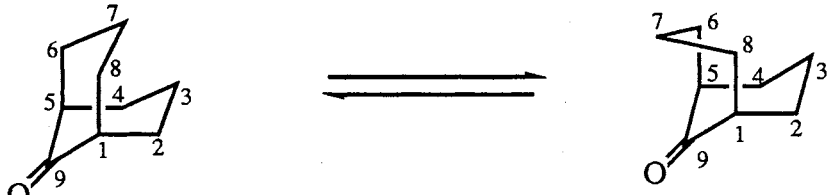
c R=*i*-Pr, R'=H

d R=*t*-Bu, R'=H

constants were found to be independent of the concentration of the shift reagent and the relative induced shifts were constant over the whole range of measurements. Therefore, it was assumed that the complexation had no significant influence on the conformation. A ^{13}C NMR analysis revealed that C(1) in **15** had an average shift of 30.4 while C(6), C(7) and C(9) had average shifts of 31.1, 22.0 and 33.7 ppm, respectively. The average shifts for C(1), C(6), C(7) and C(9) in **16** were 27.9, 26.9, 19.1 and 26.7 ppm, respectively. Thus, it can be seen that the ^{13}C shifts in **15** (believed to be in CC form) are at lower field than in **16** (believed to be in CB form). The ^1H NMR analysis revealed that $^3J_{1,8(a)}$ in **15** (CC form) is 3.3–4 Hz while in **16** (CB form) it is 10-11.5 Hz, which suggests that the cyclohexane ring in **15** is in chair form while in **16** it is in boat conformation. The corresponding coupling $^3J_{1,2(a)}$ in the tetrahydropyran ring is < 4 Hz in both **15** and **16**, indicating that the tetrahydropyran ring predominantly exists in the chair form.[23] Similar situations were observed by Peters and co-workers[25-30] in related systems. Their conclusions were that if $^3J_{H(1),H(2a)}$ [or $^3J_{H(1),H(8a)}$] was small (≤ 4 Hz), then the ring

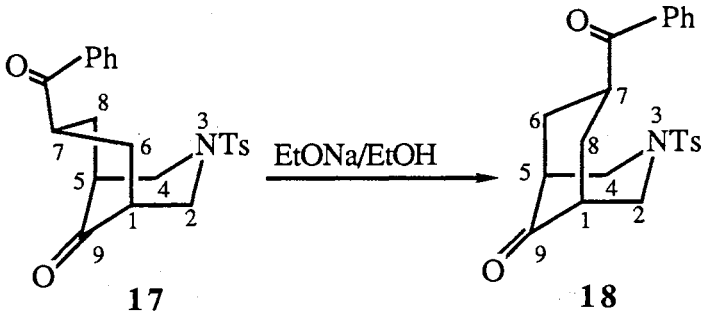
existed predominantly in a chair form, and if these ^3J values were large (≥ 10 Hz), then the ring was predominantly in a boat form.

Raber and co-workers[32] used LSR to determine conformation of bicyclo[3.3.1]-nonan-9-one (**10**) in solution. Their conclusions were based upon predicted shifts and



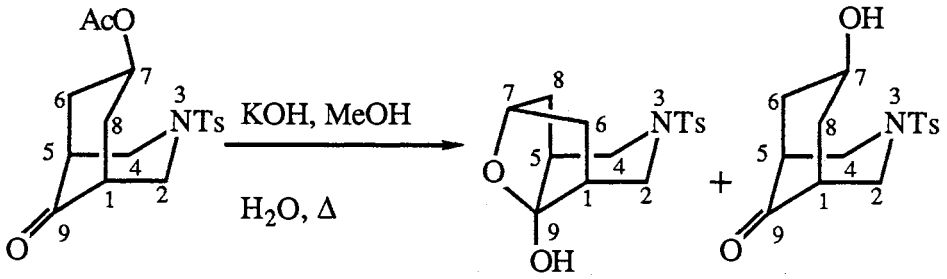
10-CC **10'-BC**

experimental values obtained with Eu(fod)$_3$, which indicated that **10** existed in a CC⇌BC equilibrium. The BC conformer constitutes 22% of the mixture of conformers at 25°C. Speckamp and co-workers[41] were able to predict preferred conformations in solution for a series of 3-tosyl-3-azabicyclo[3.3.1]nonane derivatives based upon ^1H NMR and chemical methods. For example, H(7_{exo}) in **17** occurred at δ 3.24 while H(7_{endo}) in **18** (obtained by epimerization of **17** with EtONa/EtOH) was observed at



17 **18**

δ 5.27. This *downfield* shift was attributed to the *deshielding* effect of the tosyl group, suggesting that **17** exists in a CB conformation while **18** exists in a CC conformation. Another interesting observation was made in the case of acetate **19**. Hydrolysis of acetate **19** resulted in the formation of **20a** and **20b**. The chemical shifts for H(7) were δ 5.92, δ 4.24 and δ 5.08 for **19**, **20a** and **20b**, respectively. They concluded that **19** exists in a CC form with H(7) in the *deshielding* region of the tosyl group, i.e. in the *endo*-position,

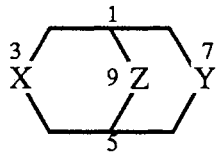


19 **20a** **20b**

with the same being true for **20b**. In contrast, **20a** was believed to exist in a CB form, with H(7) being in *endo* position in the boat ring which was also part of the separate bridged structure as indicated.

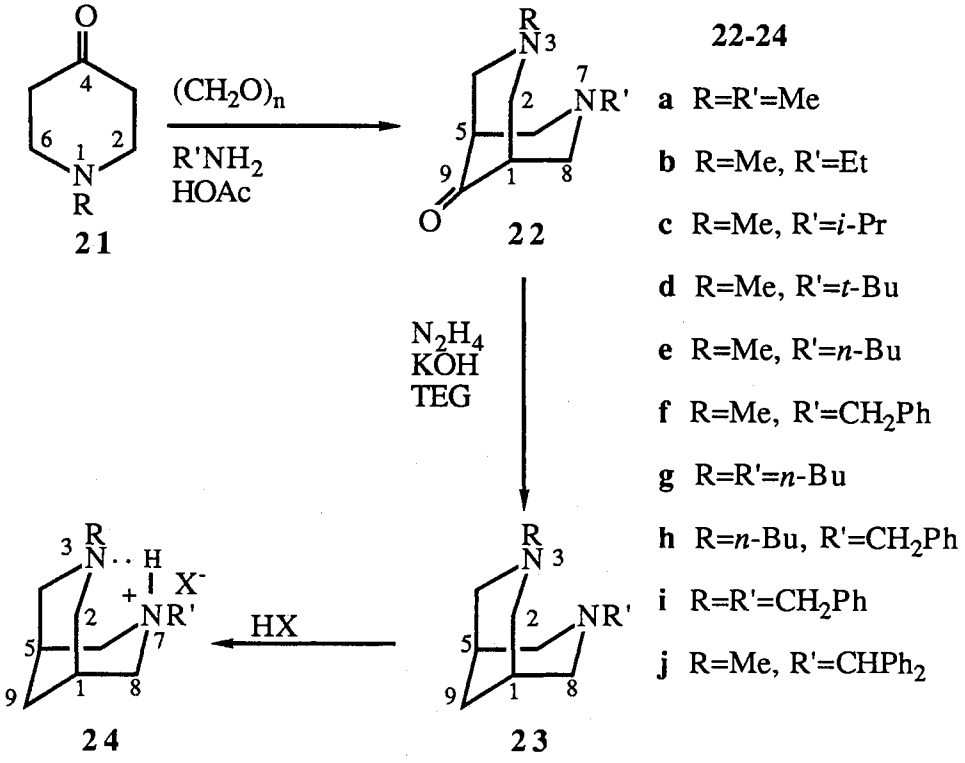
Synthetic Methodology

Several reviews have been published that cover the numerous synthetic routes to the bicyclo[3.3.1]nonane ring system.[19,48] The following discussion will focus on the more popular methods that have been employed in the synthesis of compounds containing the ring system **3**, where X and/or Y are CRR', NR, O, S and Se and Z is C=O or CRR'.



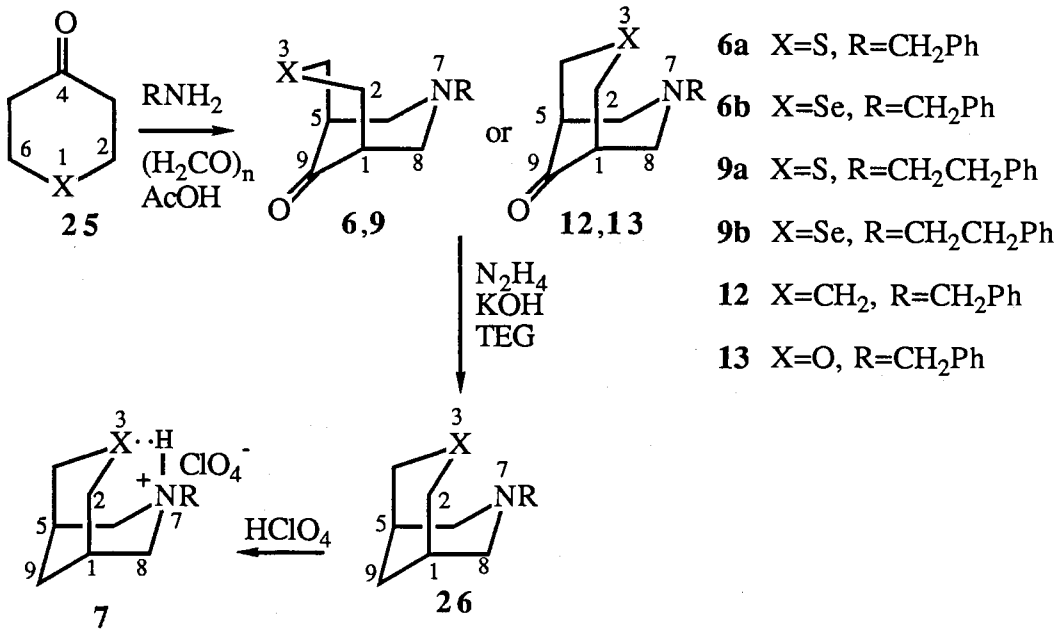
3

Mannich condensation of 1-hetera-4-cyclohexanones **21** with formaldehyde and various primary amines under acidic conditions has been commonly used. Douglas and Ratliff[14] synthesized *N*-methyl-*N'*-alkylbispidones **22a-d** (R=Me, R'=alkyl; bispidone is a common name for the family of 3,7-diazabicyclo[3.3.1]nonan-9-ones) in yields of 40-55%. The bispidines **23** obtained by Wolff-Kishner reduction of the corresponding ketones, were converted to the salts **24** in yields of 60-70%. Ruenitz and Smissman[33,35,38] prepared several *N,N'*-dialkylbispidones **22e-j** via a similar procedure, followed by Wolff-Kishner reduction to the corresponding bispidines. However, they



converted the bispidines into different salts. For example, bispidine **23e** (R=Me, R'=*n*-Bu) was converted to the monohydrobromide **24e** (X=Br) while **23g** (R=R'=*n*-Bu) was converted to monohydrochloride **24g** (X=Cl). Other salts prepared included the mesylate and the sulfate. Binnig and Co-workers[6] followed similar procedures to obtain various N,N'-dialkylbispidines. Ruenitz and co-workers[35] obtained *N*,N'-dibenzylbispidone (**22i**) as a deep red oil in a yield of 83%, while Binnig and co-workers obtained the same as a solid (mp 70-71°C) after distillation (bp 185°C/0.15 mm Hg) and crystallization from light petroleum ether (yield, 60%).

In recent years, previous workers in our research group have made use of the Mannich condensation and Wolff-Kishner reduction to obtain various 3-hetera-7-azabicyclo[3.3.1]nonanes and derivatives.[2,4,5] Thus ketones **6**, **9**, **12** and **13** were obtained starting from appropriate 1-hetera-4-cyclohexanones **25**. Reduction of these bicyclo[3.3.1]nonan-9-ones yielded bicyclo[3.3.1]nonanes **26a-e** which were treated



7, 26

a X=S, R=CH_2Ph

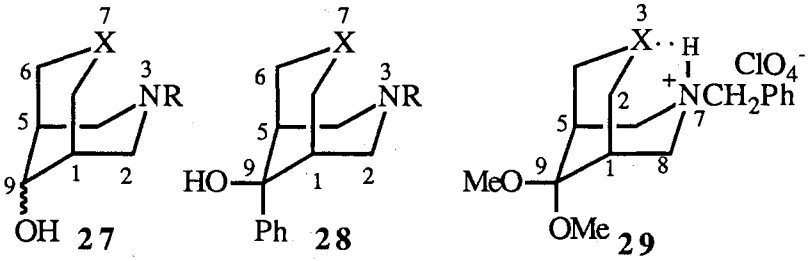
b X=Se, R=CH_2Ph

c X=S, R=CH_2CH_2Ph

d X=Se, R=CH_2CH_2Ph

e X=O, R=CH_2Ph

with $HClO_4$ to afford the salts **7a-e**. The use of the Mannich condensation offers versatility in functional group modification at the 9-position. The carbonyl functional group can be reduced by $NaBH_4$ or $LiAlH_4$ to yield the 9-hydroxy derivative **27**,[2,4,5] or it

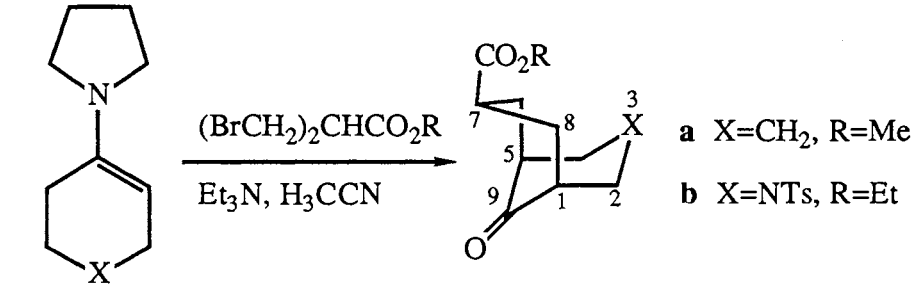


a X=NCH_2Ph

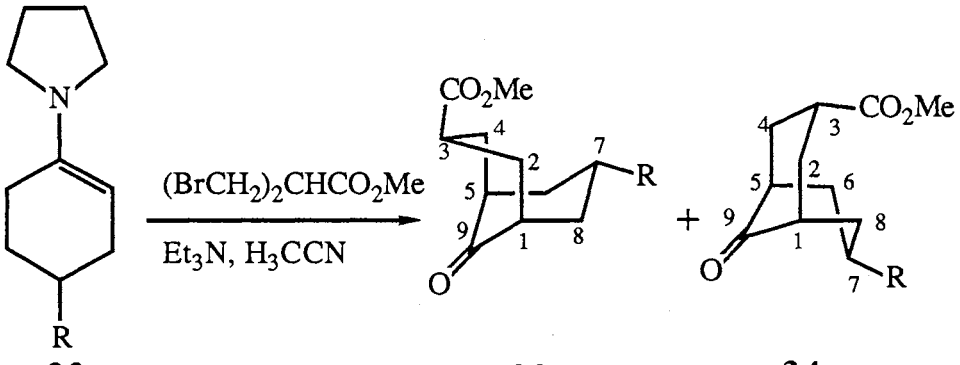
b X=S

can be reduced under Wolff-Kishner conditions to afford the saturated analogues, as stated previously.[2,4-6,14,35,38] Other modifications include treatment of the ketone with Grignard reagent to yield the 9-alkyl(or aryl)-9-hydroxy derivative **28**.[2,4,5] The carbonyl group can also be modified to yield a ketal function at C(9). Thus, the dimethyl ketals **29a** and **29b** were prepared from the appropriate ketone, methanol and perchloric acid.[4]

Annelation of enamines of cyclic ketones **30** have been utilized to obtain certain derivatives of bicyclo[3.3.1]nonan-9-one, namely **31**. In two of these cases the product obtained was in a CB form with an *endo* carboalkoxy group. Peters and co-workers[28] used enamines of 4-substituted cyclohexanones **32** and obtained **33** and **34**. In *all* cases



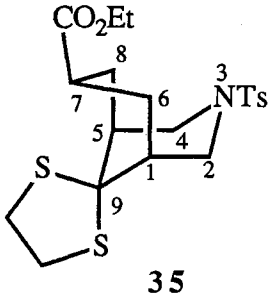
30 **31**



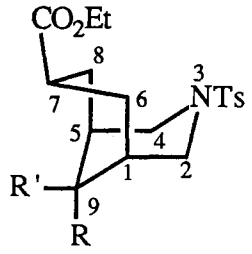
32 **33** **34**

	a	**b**	**c**	**d**
R	H	Me	*i*-Pr	*t*-Bu
Product % Ratio (**33**:**34**)	100:0	63:37	60:40	59:41

the carbomethoxy group was in the *endo*-position. However, as the size of the alkyl group (R) increased, product **34** was formed in greater amounts. Speckamp and co-workers[41,42] prepared several derivatives of keto ester **31b**. A few examples are the



35



36

a R=H, R'=OH

b R=OH, R'=H

thioketal **35**, prepared by treatment of keto ester **31b** with 1,2-ethanedithiol and BF_3 etherate, and the alcohols **36a** and **36b** (in a ratio of 17:3) obtained by $NaBH_4$ reduction of **31b**. Although *no* X-ray data exists on *any* of the structures, spectral evidence supports a boat form for the ring bearing the carboethoxy group. A variety of other methods have been used to synthesize bicyclo[3.3.1]nonane derivatives, and these have been extensively reviewed.[1,3,19,39,48]

Antiarrhythmic Activity

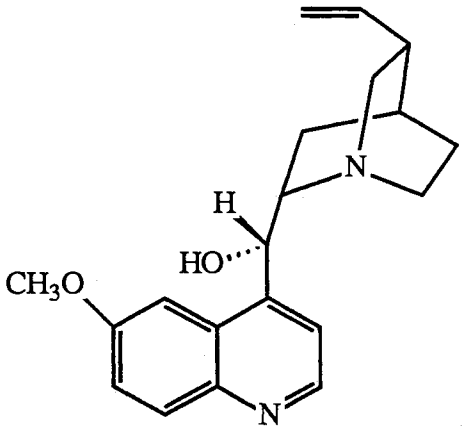
Heart disease is the leading cause of death in this country.[20] Sudden death due to coronary heart disease represents a very large portion of all nontraumatic deaths in the adult population. These deaths in most cases are caused by ventricular fibrillation which may be preceded by ventricular arrhythmias.[15] The underlying cause in most cases is the deposition of fatty plaque along the interior walls of arteries resulting in the restriction of blood flow through the blood vessels, which can ultimately lead to complete blockage of the arteries inducing myocardial infarction.[11]

Following a myocardial infarction nearly all patients exhibit ventricular tachycardia.[10] This is also linked to coronary problems as indicated by the fact that these arrhythmias are nearly always found in patients with advanced coronary heart disease.[10] Other causes of

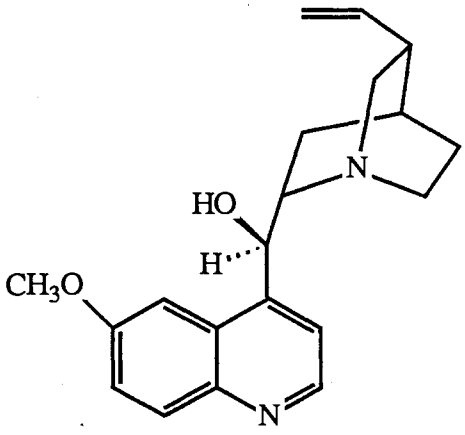
arrhythmias include hypocalcemia, hyperthyroidism, hyperactivity of the sympathetic system, and local ischemia in the heart tissue due to atherosclerosis in the coronary system.[46] Ventricular tachycardia is usually preceded by ventricular premature contractions which are the first signs of an arrhythmia. These can also occur in healthy adults after excessive ingestion of coffee or tea, heavy smoking or emotional excitement.[10]

There are a large number of antiarrhythmic agents in clinical use. However, all of these exhibit a variety of undesirable side effects, some even lethal in certain instances. The most common side effects are cardiotoxicity, gastrointestinal complications, and adverse effects on the central nervous system.[43] Antiarrhythmic properties and toxicities of various drugs in clinical use for the treatment of cardiac arrhythmias have been reviewed extensively.[3,39,45] Some of the more common antiarrhythmic agents in use are the cinchona alkaloids quinidine (**37**) and quinine (**38**), dialantin (**40**), digoxin (**41**), procainamide (**42**) and lidocaine (**43**). Of the various agents in clinical use at this time, lidocaine (**43**) may be the most important. It is usually the first drug administered to patients with acute myocardial infarction.[17] However, the disadvantages with lidocaine (**43**) include a short serum halflife (20-30 minutes) and a few toxic side effects such as sinus arrest, nervous system disorders and the ability to induce new arrhythmias. These side effects are mostly due to excessive doses or advanced liver disease.[17] Since lidocaine (**43**) is the drug of choice in the treatment of many arrhythmias,[17] the activities of the new potential antiarrhythmic agents to be discussed later are compared to that of lidocaine which is used as a standard.

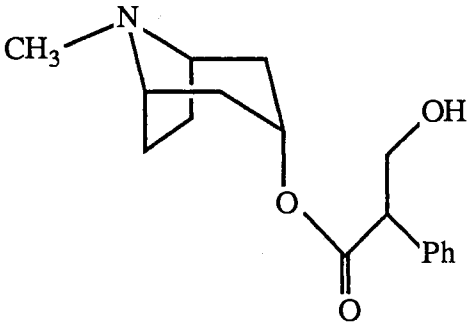
The antiarrhythmic properties of only a few 3,7-dialkyl-3,7-diazabicyclo[3.3.1]-nonanes have been examined in a preliminary manner. Ruenitz and Mokler[33] have reported that the amine salts **24e-j** were reasonably potent. However, their toxicity was fairly high with therapeutic indices for these salts being in the range of 0.87-1.46, and these are listed in Table II. A mouse-chloroform fibrillation assay in mice was used to determine the activity. Following similar methods, Ruenitz and Mokler[34] determined the



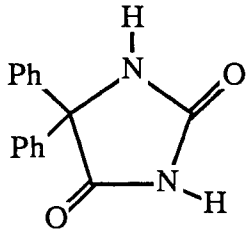
Quinidine (**37**)



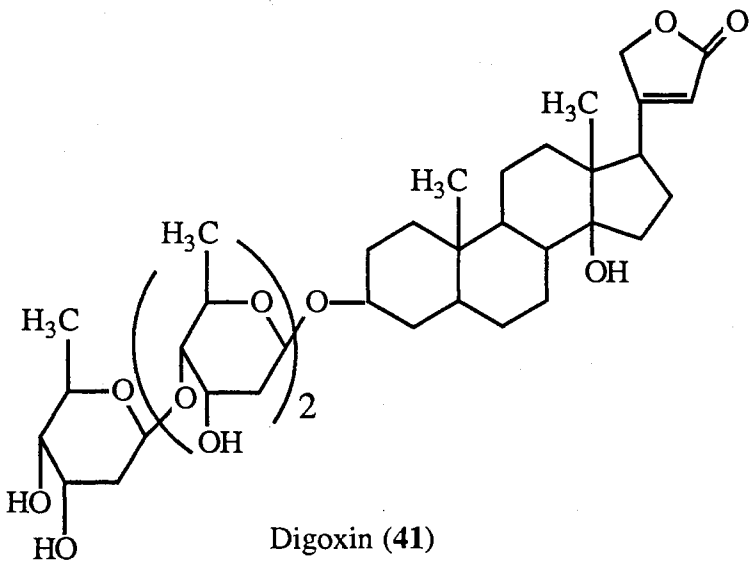
Quinine (**38**)



Atropine (**39**)



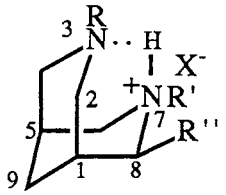
Dilantin (**40**)



Digoxin (**41**)

TABLE II

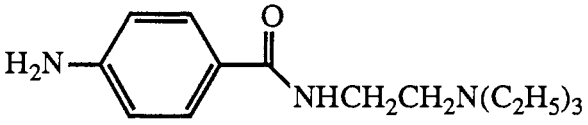
ANTIARRHYTHMIC PROPERTIES OF 3,7-DIALKYL-3-7-DIAZABICYCLO[3.3.1]NONANES [a]



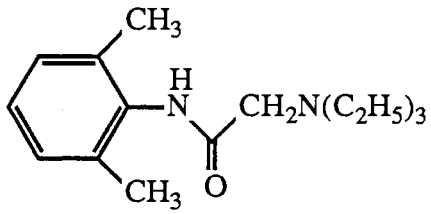
24

Compound	R	R'	R"	X	ED_{50}[b]	LD_{50}[b]	T.I.[c]
e	Me	*n*-Bu	H	Br	192	207	1.08
f	Me	$PhCH_2$	H	Mesylate	154	189	1.23
g	*n*-Bu	*n*-Bu	H	Cl	170	196	1.23
h	*n*-Bu	$PhCH_2$	H	Cl	159	198	1.25
i	$PhCH_2$	$PhCH_2$	H	Cl	160	199	1.24
j	Me	Me	*i*-Pr	2Cl	191	279	1.46
1a[d]	sparteine				150	134	0.89

[a] Determined by mouse-chloroform fibrillation assay: reference 33.
[b] μmol/kg, i.p.
[c] Therapeutic Index (ED_{50}/LD_{50}).
[d] Sulfate.

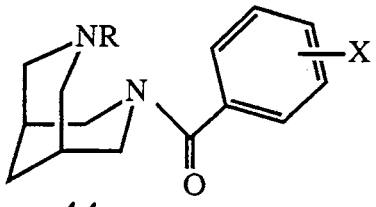


Procainamide (**42**)



Lidocaine (**43**)

antiarrhythmic activity of certain benzamides **44a-e**, in a separate study. All the amides investigated were more potent and less toxic, compared to lidocaine (**43**) with therapeutic indices in the range of 2.1-10.9. The most active derivative was **44a** (X=Cl, R=Me) with ED_{50} of 49 μmol/kg, i.p., LD_{50} of 535 μmol/kg, i.p. and LD_{50}/ED_{50} equal to 10.9.



44

a R=Me, X=4-Cl

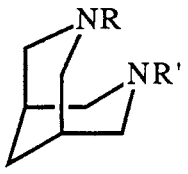
b R=Me, X=H

c R=Me, X=4-MeO

d R=*i*-Pr, X=4-Meo

e R=*i*-Pr, X=H

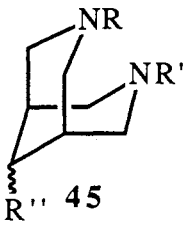
Binnig and co-workers[6] examined certain bispidines **23** for activity, as determined by left auricle refractory period prolongation in guinea pigs. Amines **23i** and **23l** were found to be more potent than lidocaine (**43**). Nador and co-workers[23] have determined the antiarrhythmic properties of a series of 9-substituted 3,7-dialkylbispidines **45**, where R, R'=Me, Et and R"=$ArCO_2$ or ArO. All compounds tested were found to be more active than lidocaine (**43**) in restoring normal sinus rhythm in rats suffering from Aconitine-induced arrhythmias.



23

i R=R'=CH_2Ph

k R=CH_2CH_2Ph, R'=*i*-Pr

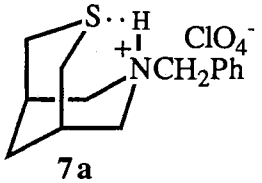


45

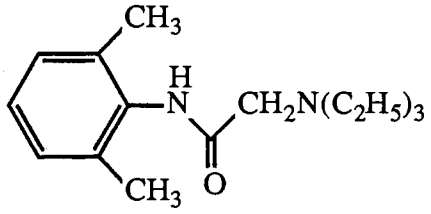
R=Me, Et

R"=$ArCO_2$ or ArO

Studies by Scherlag and co-workers[4] have demonstrated the antiarrhythmic properties of several 3,7-diheterabicyclo[3.3.1]nonanes and derivatives. Compound **7a** (X=S, R=$PhCH_2$) was found to prevent the induction of sustained ventricular tachycardia (SVT) in 8 of 10 dogs that had surgically-induced myocardial infarctions.[39] Moreover, in

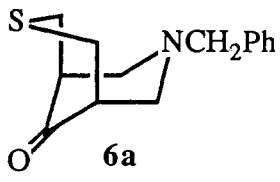


7a

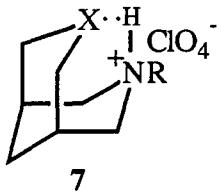


Lidocaine (**43**)

the animals that did exhibit SVT, the heart rate was dramatically slowed by an average of 29% relative to control experiments. In contrast, lidocaine (**43**) permitted induction of SVT in all the animals tested with reduction of the heart rate by an average of only 11% compared to the control. Ketone **6a** showed little antiarrhythmic effect while its hydrated salt **46** was found to have slightly better activity, although it was less active as compared with **7a**.[4] The phenyl alcohol **8** had an overall depressive effect on myocardial conduction in infarcted as well as normal tissue.



6a



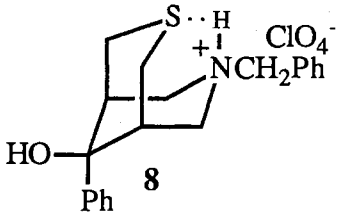
7

a X=S, R=CH_2Ph

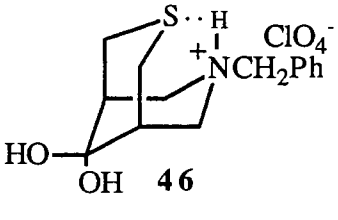
b X=Se, R=CH_2Ph

c X=S, R=CH_2CH_2Ph

d X=Se, R=CH_2CH_2Ph

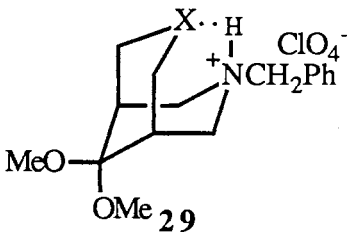


8



46

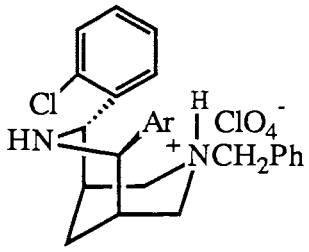
Antiarrhythmic properties of several other very active compounds have been examined with mongrel dogs.[4] For example, compounds **7b-d** showed activity comparable to **7a** at both 3 mg/kg and 6 mg/kg dose levels,[4] while ketal **29b** completely abolished VT at both dose levels and ketal **29a** abolished VT at the higher dose level and lowered the rate of SVT by 46.2% at the lower dose level.[4] Certain 2,4-diaryl derivatives have also been tested for activity.[4] Compound **47** exhibited a proarrhythmic effect and compound **48** had no effect at all while the Se analogue **49** had properties comparable to **7a-d.**



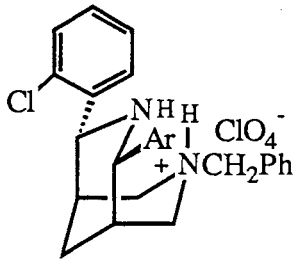
29

a X=NCH_2Ph

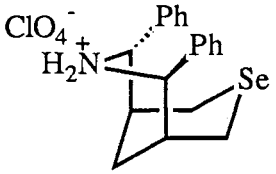
b X=S



47



48



49

It is difficult to compare activities of compounds assayed by different methods. However, presuming that all compounds are operating by the same physiological mechanism, some generalized observations can be made. The presence of *N*-alkyl (methyl, benzyl, β-phenethyl) or *N*-aryloyl group at the 7-position, as well as the presence of S and Se at the 3-position, is generally associated with good activity. In certain cases the 2,4-diaryl derivatives did not show activity while the work of Nador and co-workers[23] suggests aryloxy or aryloate groups at the 9-position exhibit good activity as compared

with lidocaine. The activity of ketals **29a** and **29b** further support the contention that an ether or ester function at C(9) improves the activity. The work of Scherlag and co-workers[4] suggests that it is necessary to have an sp^3 center at C(9), and it should be recalled that ketone **6a** did not exhibit antiarrhythmic activity.

In summary, we can conclude that the presence of an ether (cyclic or acyclic) or an ester function at C(9) [resulting in an sp^3 center], and the presence of S, Se, NR or NC(O)R at the 3- and/or 7-positions in bicyclo[3.3.1]nonane systems results in good antiarrhythmic properties. There is considerable evidence which indicates that large groups (such as aryl) at the 2-, 4-, 6- and 8-positions markedly reduce the antiarrhythmic activity in this family.[4]

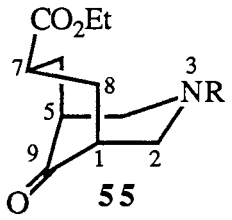
CHAPTER II

RESULTS AND DISCUSSION

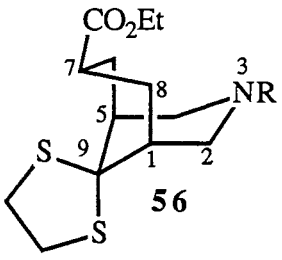
The principle objective of this research was to develop synthetic methodology to obtain certain 3-aza- and 3,7-diazabicyclo[3.3.1]nonane derivatives. Moreover, it was also an objective to screen these heterocycles for potential antiarrhythmic activity in dog models as determined by electrocardiological analysis of dogs with 24-hour infarcted hearts. Such dogs are considered excellent models of the human cardiovascular system for the testing of potential antiarrhythmic agents.[20]

The major accomplishment sof this research are the synthesis of several new and novel 3-aza and 3,7-diazabicyclo[3.3.1]nonane derivatives. Ketones **55a** and **55b**, thioketals **56a** and **56b**, ester **57**, and acid **58**, as well as the monohydroperchlorates **59** and **60**, were prepared. In addition improved preparation of ketone **61** was achieved along with new ketals **62a-c**, monohydroperchlorate **63** and carbamate **64**. Salts **59**, **60**, and **63**, ketals **62a-c** and carbamate **64** were submitted to Dr. B. J. Scherlag (Veterans Administration Hospital, Oklahoma City, OK) for biological testing in dog models.

Previous results have indicated that perhaps certain groups at the 3- and/or 7-positions as well as at C(2,4,6,8) and C(9) in the 3,7-diheterabicyclo[3.3.1]nonane system influence the activity, as stated in the previous chapter.[4,6,23,33,34,38] Salts **7a-d**, as well as ketals **29a** and **29b**, exhibited excellent activity to abolish or reduce the rate of SVT.[4] All of these compounds have certain structural features in common, namely, the presence of an sp^3 center at C(9) and an *N*-benzyl group at the 7-position. In contrast, different groups (S, Se and NCH_2Ph) were present at the 3-position. Therefore, it was reasoned

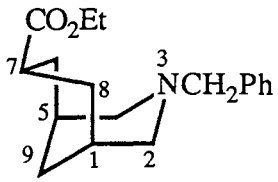


55



56

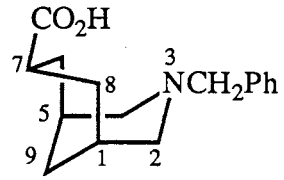
55-56



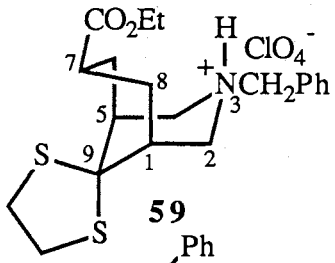
57

a R=CH_2Ph

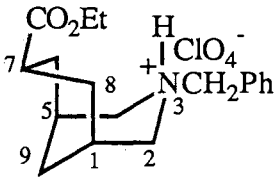
b R=CH_3



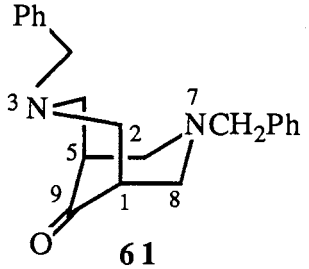
58



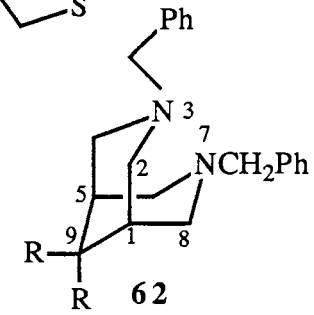
59



60



61

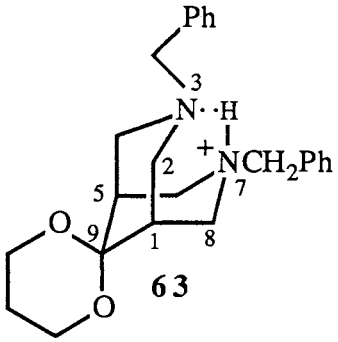


62

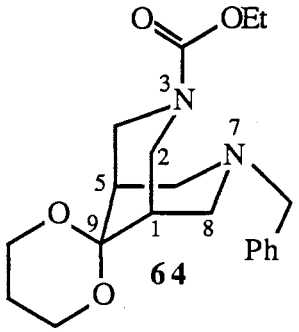
a RR=OCH_2CH_2O

b RR=$OCH_2CH_2CH_2O$

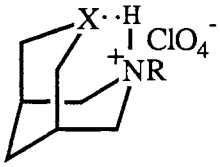
c RR=SCH_2CH_2S



63



64



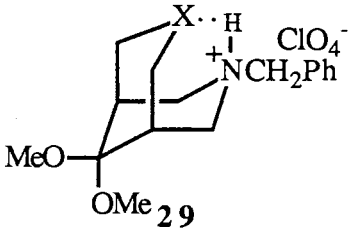
7

a X=S, R=CH_2Ph

b X=Se, R=CH_2Ph

c X=S, R=CH_2CH_2Ph

d X=Se, R=CH_2CH_2Ph



29

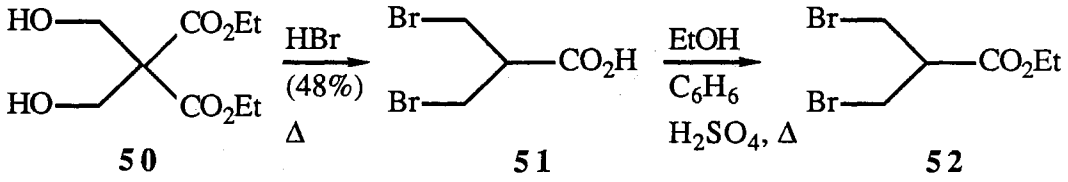
a X=NCH_2Ph

b X=S

that certain structural changes such as the introduction of a $CHCO_2Et$ or an NCO_2Et group at the 7-position, and different ketal groups at C(9), might alter the activity. Thus, another goal was to map structural features which convey optimum antiarrhythmic properties.

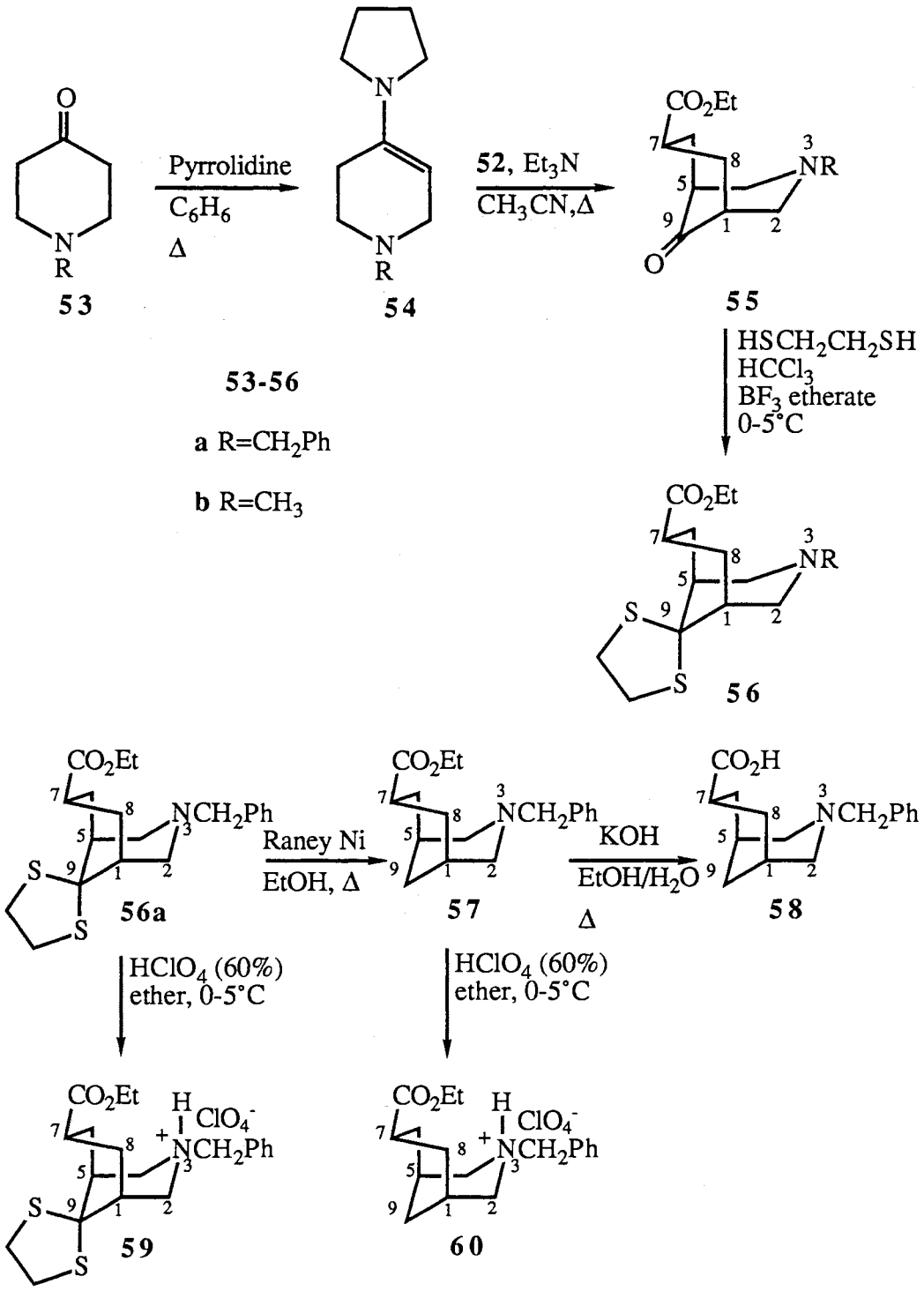
Synthetic Procedures

As discussed in the previous chapter, α,α'-annelation of enamines of cyclic ketones, such as **53**, has been used in the synthesis of certain 3-heterabicyclo[3.3.1]nonan-9-ones.[41] In the convergent synthesis shown below, standard procedures were used to convert the hydroxy ester **50** to the dibromo acid **51** (yield 55.3%).[16] Esterification of



50 **51** **52**

51 afforded the dibromoester **52** (94.9%).[16] Treatment of ketone **53a** (R = NCH_2Ph) with pyrrolidine in benzene solution at reflux gave, after distillation, the enamine **54a** (R = NCH_2Ph, yield 97.0%).[12] Enamine **54b** (R = NCH_3) was obtained via a similar procedure starting from ketone **53b** in a yield of 97.0%. Ketones **55a** and **55b** were synthesized via α,α'-annelation of enamines **54a** and **54b** with **52** in the presence of triethylamine in acetonitrile solution. The products were purified in both cases via column chromatography on silica gel. A solution of 10% ethyl acetate in hexanes was used for elution of **55a** while **55b** was eluted with 20% ethyl acetate in hexanes. Both the ketones were obtained in a yield of 33% as heavy oils. Attempted distillation of these oils resulted in decomposition of the material, and thus, they were used without further purification. It should be noted that Peters[26,27,29] and Speckamp[41] have shown that the reaction of certain enamines of cycloalkanones with ethyl β,β'-dibromoisobutyrate (**52**) afford bicyclic ketones with the carboethoxy group suggested to be in the *endo*-position, as discussed in Chapter I.



53 **54** **55** **56**

53-56

a R=CH_2Ph

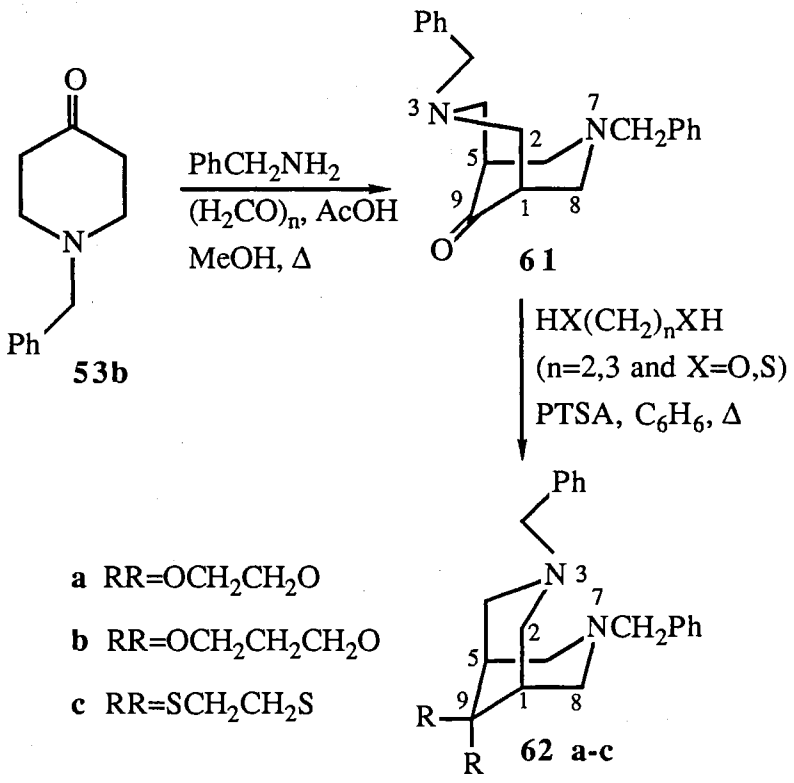
b R=CH_3

56a **57** **58** **59** **60**

Conversion of ketones **55a** and **55b** to thioketals **56a** and **56b** was accomplished by treatment of the appropriate ketone with 1,2-ethanedithiol and BF_3 etherate in chloroform solution at 0-5°C. Thioketals **56a** (42%) and **56b** (40%) were purified by column

chromatography over silica gel using 10% EtOAc in hexanes as the eluting solution. Reduction of thioketal **56a** with Raney Ni resulted in the formation of ester **57** (68%) as an oil. Attempted distillation of this oil resulted in decomposition; hence the ester **57** was used without further purification. Acid **58** (59%) was obtained by saponification of **57** using KOH in 80% ethanol (aq.). Salts **59** (90%) and **60** (68%) were obtained by treating cold ethereal solutions of **56a** and **57**, respectively, with $HClO_4$ (60%).

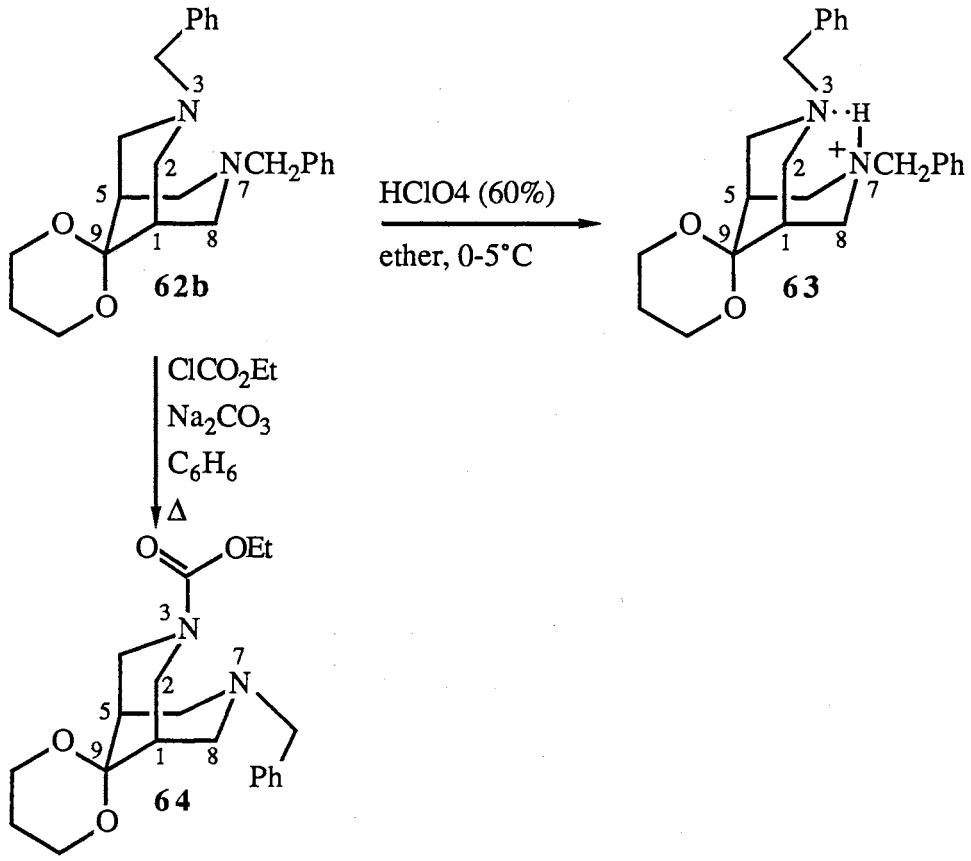
A Mannich condensation of *N*-benzyl-4-piperidinone (**53b**) with benzylamine, paraformaldehyde and acetic acid with methanol was used to prepare ketone **61**. Elaborate



purification procedures (see Experimental) were used to obtain **61** as a white crystalline solid (35.2%, mp 83-83.5°C). Ruenitz and co-workers[35] obtained **61** as a deep red oil (yield, 83%), while Binnig and co-workers[6] reported the same as a solid (60%, mp 70-71°C). Ketone **61** was converted to the ethylene ketal **62a** (64.3%), the trimethylene

ketal **62b** (79.9%) and the thioketal **62c** (30.4%) in the presence of an appropriate diol (or dithiol) and PTSA in benzene.

Treatment of ketal **62b** with $HClO_4$ (60%) in ether solution at 0-5°C yielded the salt **63** (69%). Carbamate **64** (58%) was obtained by reaction of $ClCO_2Et$ with ketal **62b** in



benzene at reflux in the presence of anhydrous Na_2CO_3. When this reaction was attempted without Na_2CO_3, the workup was complicated by the formation of an emulsion during extraction. It is interesting to note that only monodebenzylation occurred although 4.8 equivalents of $ClCO_2Et$ were used. This experiment was repeated using 10 equivalents of $ClCO_2Et$ but only the carbamate was found (54%). Thus, it is tentatively concluded that steric factors, such as an axial N(3)-C(O) bond, inhibit the reaction from proceeding to the second debenzylation step. We assume an initial nucleophilic attack of N(3) on $ClCO_2Et$ gives a tetrahedral intermediate which loses Cl^- to give a salt. Attack of

Cl^- on the CH_2Ph group produces benzyl chloride and **64**. Proton NMR analysis of the crude reaction mixture showed the presence of benzyl chloride.

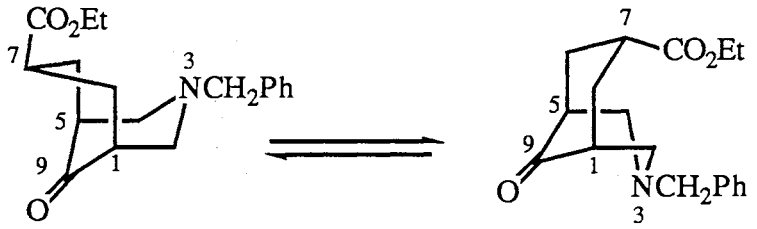
Solubilities of both ketal **62b** and its salt **63** were low in aqueous EtOH. Ketal **62b** had a solubility of 0.8 mg/mL and 4.0 mg/mL in 50% EtOH:H_2O, and 75% EtOH:H_2O, respectively, while salt **63** had a solubility of 1.8 mg/mL and 5.0 mg/mL in the same solutions respectively. Since the solubilities of ketal **62b** and salt **63** are about the same, salts of ketals **62a** and **62c** were not prepared. Solubilities of **62a** and **62b** in 50% EtOH/H_2O are 0.70 mg/mL and 0.60 mg/mL and in 75% EtOH/H_2O are 2.5 mg/mL and 1.8 mg/mL, respectively. The carbamate **64** had the best overall solubility at 11.5 mg/mL and 105 mg/mL in 50% and 75% EtOH/H_2O, respectively. Dr. Scherlag is currently testing ketals **62a-c**, salt **63**, and carbamate **64** for biological activity. The activity profile of these compounds should provide better insight on the activity-solubility relationship in this family of heterocycles.

Conformational Analysis

The identity and conformational analyses of all compounds were based on their IR, ^1H and ^{13}C NMR spectra. Analyses of IR spectra of certain members of the 3-azabicyclo[3.3.1]nonane family, namely, ketones **55a** and **55b**, thioketals **56a** and **56b** and ester **57** revealed the presence of Bohlmann bands[4,7,19] in the 2900-2700 cm^{-1} region. This suggests that the ring bearing the *N*-benzyl group is in chair form with the lone pair on nitrogen in the *endo*-position (axial position). Bohlmann bands are C-H stretching vibrations normally observed in the 2900-2700 cm^{-1} region of the IR spectra of piperidine derivatives when a C-H bond *alpha* to nitrogen is antiperiplanar with the electron pair of nitrogen. The presence of Bohlmann bands was also detected in the IR spectra of analogues **61**, **62a-c** and **64**. The C=O band of the ester groups appeared between 1730-1715 cm^{-1} in the free amines **55a,b**, **56a,b** and **57**, whereas for the salts **59** and **60**, the C=O band appeared at 1700 cm^{-1}. This change in absorption suggests

either a change in ring conformation or that there is an unusual effect of the N^+–H group on the C=O function of the ester. It is possible that intermolecular or intramolecular hydrogen-bonding occurs and causes the C=O frequency to shift to a lower frequency in the salts.

The ^1H NMR analysis of the series of 3-azabicyclononane derivatives **55-60** was complex due to high signal density in the aliphatic region at δ 2-3.3. However, for ketone **55a** the signals for $H(2,4)_{ax}$ [δ 2.82, dd, J = 6.0, 14.4 Hz] and $H(6,8)_{ax}$ [δ 2.18, dd, J = 6.9, 15.9 Hz] could be assigned. The $^3J_{H(1),H(8a)}$ coupling value observed for $H(6,8)_{ax}$ [6.9 Hz] is larger than the $^3J_{H(1),H(2a)}$ coupling value for $H(2,4)_{ax}$ [6.0 Hz] by a very small margin. As discussed in Chapter I, Peters and co-workers[26,27,29] suggested that if $^3J_{H(1),H(8a)}$ [or $^3J_{H(1),H(2a)}$] is ≥ 4 Hz but ≤ 10 Hz then a BC⇌CB equilibrium is favored as in **55a⇌55a'**. The slightly greater value for $^3J_{H(1),H(8a)}$ suggests that the **55a⇌55a'** equilibrium favors **55a** by a small margin but this conclusion must be considered tentative.

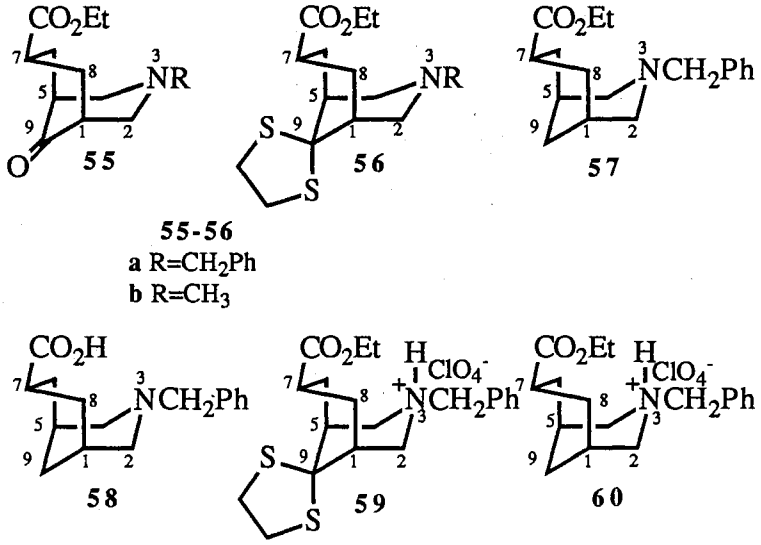


55a **55a'**

Another interesting observation was made while comparing the $H(2,4)_{ax}$, $H(2,4)_{eq}$ and CH_2Ph shifts of free amines **56a** and **57** with the corresponding shifts in the salts **59** and **60**, respectively. The $H(2,4)_{ax}$ signal in these free amines appeared between δ 2.5-2.7, whereas in the salts the signal was observed between δ 3.35-3.50, a *downfield* shift of 0.8-0.92 ppm. Similarly, a *downfield* shift of 0.7-0.95 ppm and 0.8-0.95 ppm was noted for $H(2,4)_{eq}$ and CH_2Ph, respectively. Therefore, it is apparent that protons on carbons *alpha* to the nitrogen are *deshielded* in the presence of protonated nitrogen due to

TABLE III

^{1}H NMR SIGNALS FOR 3-AZABICYCLO[3.3.1]NONANES **55-60** [a]

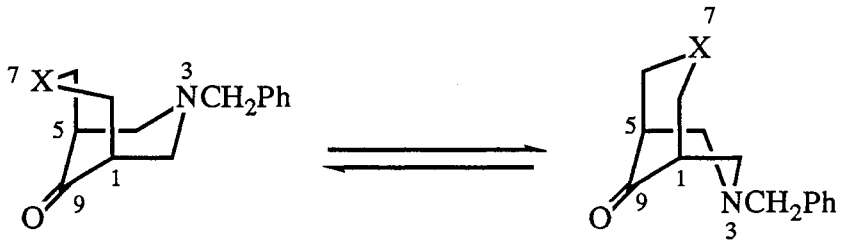


Compound	H(1,5)	$H(2,4)_{ax}$	$H(2,4)_{eq}$	$H(6,8)_{ax}$	$H(6,8)_{eq}$	H(7)	N-R[a]
55a	2.29	2.82	3.04	2.18	2.44[b]	2.44[b]	3.56
55b	2.34	2.52[b]	3.05	2.20	2.52[b]	2.52[b]	2.10
56a	1.90	2.71[b]	2.71[b]	2.34	2.71[b]	2.47	3.44
56b	1.92	2.52[b]	2.52[b]	2.52[b]	2.52[b]	2.52[b]	1.96
57	1.8[b]	2.5[b]	2.77	1.8[b]	2.33	2.5[b]	3.49
58	1.56	2.91	3.01	2.06[b]	2.06[b]	2.47	3.73
59	2.36	3.50	3.50	2.05	2.71	2.90	4.38
60	2.24[b]	3.42[b]	3.42[b]	1.87	2.24[b]	2.95	4.50

[a] R=CH_2Ph in **55a**, **56a** and **57-60**; R=CH_3 in **55a** and **56a**.
[b] These signals are overlapping multiplet patterns.

the decreased electron density around nitrogen. It is noted that the CH_2 of the ethyl function in benzyldiethylamine deuterochloride is *deshielded* by 0.64 ppm compared to the counterpart in the free amine,[11] which is a reasonable model for our system.

The ^1H NMR analyses of the members of 3,7-diazabicyclo[3.3.1]nonane family **61-63** were relatively less complex than the corresponding 3-aza systems **55-60**, since there is a plane of symmetry passing through N(3)-C(9)-N(7). The $H(2,4,6,8)_{ax}$ signals were observed at δ 2.80 ($^3J_{H(1),H(2a)}$ = 6.0 Hz), δ 2.66 ($^3J_{H(1),H(2a)}$ = 2.3 Hz), δ 2.61 ($^3J_{H(1),H(2a)}$ = 2.3 Hz) and δ 2.75 ($^3J_{H(1),H(2a)}$ = 2.6 Hz) in **61**, **62a**, **62b** and **62c**, respectively. It is interesting to note the identical $^3J_{HH}$ value of 6.0 Hz in ketones **55** (for the $^3J_{H(1),H(2a)}$) and **61**. This further supports the contention that these ketones



55 and **61-BC** **55** and **61-CB**

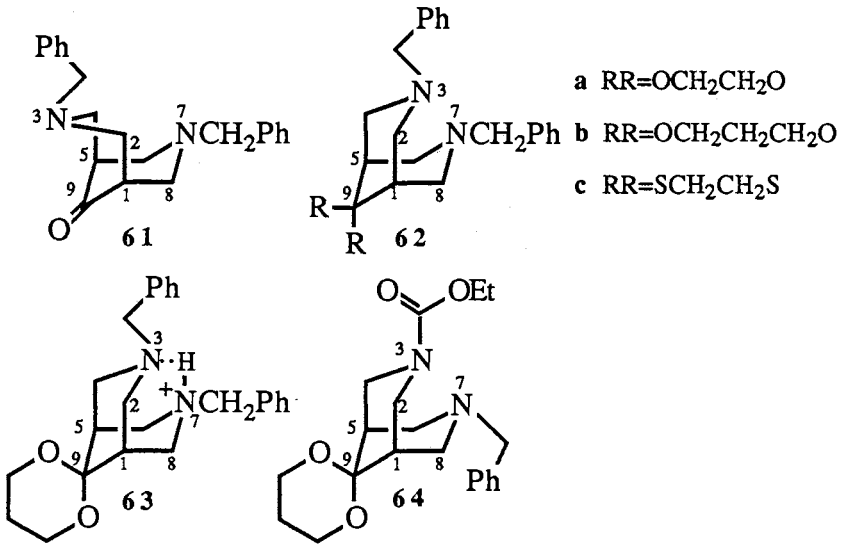
55 X=$CHCO_2Et$

61 X=NCH_2Ph

exist in a BC⇌CB equilibrium in solution. The $^3J_{H(1),H(2a)}$ values (2.3-2.6 Hz) for the ketals **62a-c** are small; thus it can be concluded that these ketals possibly exist in a twin-chair form in solution. In the salt **63**, a $^3J_{H(1),H(2a)}$ coupling is not observed. A related ketal hydroperchlorate **29a** is known to exist in CC form in the solid state, based on X-ray analysis.[39] It is reasonable to believe that **29a** exists in CC form in solution.[4] In analogy with **63**, $^3J_{HH}$ coupling was not observed in **29a**; therefore, **63** also possibly exists in a CC conformation both in the solid state and in solution. The stabilizing force for the CC form in these salts of 3,7-diheterabicyclo[3.3.1]nonanes is probably the intramolecular H-bonding between the N^+-*H* and the free nitrogen.[4]

TABLE IV

^{1}H NMR SIGNALS FOR 3,7-DIAZABICYCLO[3.3.1]NONANES **61-64** [a]



Compound	H(1,5)	$H(2,4)_{ax}$	$H(2,4)_{eq}$	$H(6,8)_{ax}$	$H(6,8)_{eq}$	CH_2Ph
61	2.54	2.80	3.03	2.80	3.03	3.55
62a	1.67	2.66	2.91	2.66	2.91	3.50
62b	2.19	2.61	2.84	2.61	2.84	3.49
62c	2.12	2.75	2.84	2.75	2.84	3.52
63	2.58	2.93	3.05	2.92	3.05	3.84
64[a]	2.08 2.31	3.30 3.35	3.99 4.22	2.47 2.73	2.59 2.92	3.20 3.53

[a] Each of the ring proton is nonequivalent. The assignments have been confirmed by COSY experiment.

Interestingly, in salt **63** the signals for $H(2,4,6,8)_{ax,eq}$ and CH_2Ph were deshielded by only 0.21-0.35 ppm as compared with the signals in free amine **62b**. In contrast, a downfield shift of 0.7-0.95 ppm was observed in the 3-aza analogues **59** and **60** compared with **56** and **57**. The diminished *downfield* shift in **63**, compared to **62b**, may be the result of the hydrogen being shared somewhat equally by the two nitrogens resulting in only a partial charge on each nitrogen.[4] It is also possible that the 3-aza-analogues **56** and **57** are more mobile compared to the 3,7-diaza-analogues **63** (believed to be predominantly in CC form – based on $^3J_{H(1),H(2a)}$ analyses). Thus, protonation of **56** and **57** may cause a greater conformational change in **59** and **60** (compared to **56** and **57**) than in **63** (compared to **62b**). Unfortunately, due to high signal density in the ^1H NMR aliphatic region of **56** and **57**, first order spectral analysis was not possible. Hence $^3J_{H(1),H(2a)}$ values could not be determined. The same was true for the signal of $H(2,4)_{ax}$ in salts **59** and **60**. However, in both **59** and **60** the $H(6,8)_{ax}$ signal was detectable and occurred at δ 2.05 (d, ^2J = 16.1 Hz) and δ 1.87 (d, ^2J = 12 Hz), respectively. The $^3J_{H(1)H(8a)}$ was not detected in both cases. This suggests that the carbocyclic ring is in chair form in salts **59** and **60**.

Thus, it can be tentatively concluded that in bicyclo[3.3.1]nonane systems if $^3J_{H(1),H(2a)}$ (or $^3J_{H(1),H(8a)}$) is very small (≤ 4 or essentially zero), then the chair form is probably the preferred conformation. If the $^3J_{H(1),H(8a)}$ value is detectable (≥ 4 Hz), then a BC⇌CB equilibrium may exist (see Peters and co-workers[26,27,29] – Chapter I).

The ^1H NMR data for carbamate **64** was very interesting with *every* proton on the ring being non-equivalent. Two broad singlets were observed for H(1) and H(5) at δ 2.08 and δ 2.31, while two sets of separate doublets at δ 2.47 (^2J = 11.1 Hz), and δ 2.73 (^2J = 10.8 Hz) and at δ 2.59 (^2J = 10.8 Hz), and δ 2.92 (^2J = 10.7 Hz) correspond to $H(6,8)_{ax}$ and $H(6,8)_{eq}$, respectively. Similarly, different resonances were observed for $H(2,4)_{ax}$, $H(2,4)_{eq}$ and for each CH_2Ph. Of course the NCO_2Et rotation barrier is high and this induces molecular dissymmetry and flattens one ring. However, some protons in the left

ring of **64** may fall in the *deshielding* cone of the carbonyl group. We are currently in the process of determining the structure of carbamate **64** in the solid state via X-ray crystallography. No system of this type in the family of 3,7-diheterabicyclo[3.3.1]-nonanes could be found in the literature for comparison.

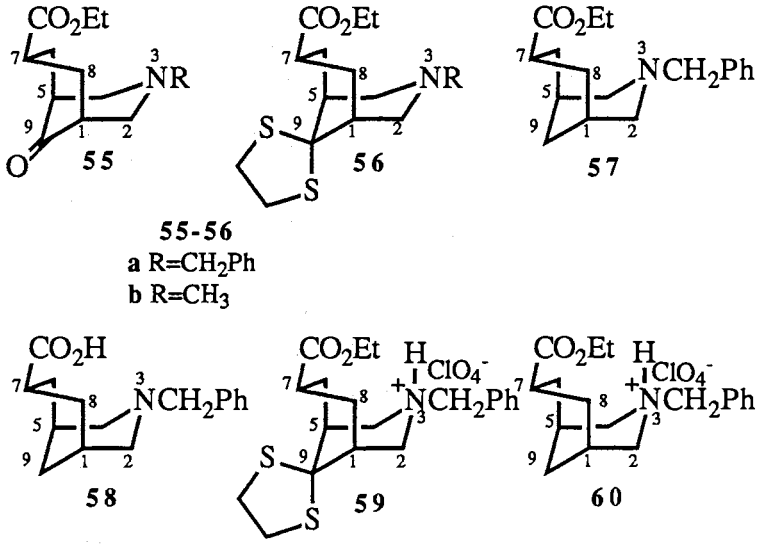
The ^{13}C NMR analysis also proved helpful in a conformational evaluation of these systems and parallels to some extent that found earlier for related systems.[10,17,19,36] Signals for C(9) in ketones **55a,b** and **61** were observed in the region of 213-215 ppm, *upfield* by about 3-5 ppm from the C(9) signal of **12** (believed to be CC form in solution[4]). Therefore, in comparison with the C(9) shift in related systems, as discussed in Chapter I, ketones **55a,b** and **61** appear to exist in a CB form in solution. However, in these systems a CB⇌BC equilibria cannot be ruled out.

Interestingly, the ^{13}C signal for the *C*=O of the ester group in free amines **55a,b**, **56a,b**, and **57** appears in the region of 171.9-173.6 ppm, while in salts **59** and **60** it is deshielded by about 10 ppm and appears at 183.05 and 182.93 ppm, respectively. This observation further supports the conjecture that there is a significant change in the electron density around the ester group upon protonation of nitrogen. It is possible that the carbocyclic ring in **59** and **60** exists in chair form (also supported by ^{1}H NMR data; molecular models do not support internal H-bonding in a BC system). The ^{13}C shifts observed for C=O of esters in **55a,b**, **56a,b**, and **57** are analogous to those reported for similar systems believed to have the ester group in the *endo*-position.[30] Thus Peters and co-workers[30] observed the *endo*-CO_2Me signal in **33a-c** at 174.6, 174.7 and 174.6 ppm, respectively.

Another important observation was made while analyzing the ^{13}C shifts of aromatic carbons. The *ipso* carbon on the aromatic ring in the 3-aza systems **55a,b**, **56a,b**, and **57** appears in the region of 134-135.5 ppm, while in the 3,7-diaza systems **61**, **62a,b,c**, and **64**, the ^{13}C shift occurs in the region of 139-140 ppm. This difference is difficult to understand. The ^{1}H NMR data ($^{3}J_{H(1),H(2a)}$ coupling values) suggests that both the

TABLE V

^{13}C NMR SIGNALS FOR 3-AZABICYCLO[3.3.1]NONANES **55-60** [a]

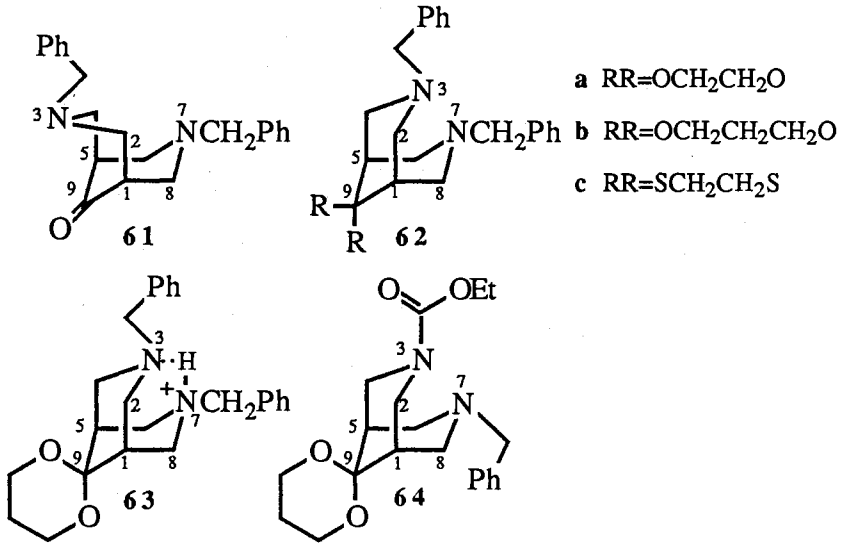


Compound	C(1,5)	C(2,4)	C(6,8)	C(7)	C(9)	N-R[a]	CO_2R'[b]	Ar-*i*-C
55a	45.16	58.06	33.21	37.75	215.92	59.73	172.40	135.10
55b	46.80	60.33	33.85	38.00	216.85	43.25	171.94	—
56a	42.10	54.92	30.25	36.71	74.34	60.14	172.35	134.21
56b	43.72	60.06	31.94	38.28	75.95	45.19	173.61	—
57	28.16	56.77	30.40	38.45	32.49	59.97	173.61	135.37
58	27.25	56.70	29.39	36.37	30.73	61.70	180.47	131.95
59	29.53	56.60	28.42	39.18	68.96	61.81	183.05	131.57
60	25.74	55.96	27.85	39.91	27.84	61.68	182.93	131.25

[a] R = CH_2Ph in **55a**, **56a** and **57-60**, R = CH_3 in **55b** ad **56b**.
[b] R' = Et in **55a,b**, **56a,b**, **57**, **59** and **60**; R' = H in **58**.

TABLE VI

^{13}C NMR SIGNALS FOR 3,7-DIAZABICYCLO[3.3.1]NONANES **61-64** [a]



Compound	C(1,5)	C(2,4)	C(6,8)	C(9)	CH_2Ph	Ar-*i*-C
61	46.76	58.12	58.12	214.70	61.62	138.24
62a	38.78	55.81	55.81	108.20	62.65	139.94
62b	36.00	54.35	54.35	96.76	62.65	140.03
62c	43.59	56.68	56.68	71.93	62.09	139.16
63	33.30	53.43	53.43	93.33	59.72	133.76
64[a]	34.49 35.46	45.25 45.42	54.01 55.19	96.01	62.76	139.06

[a] Each of the ring carbon is nonequivalent. The assignments have been confirmed by HETCOR experiment.

systems exist in CB⇌BC equilibrium in solution. It is possible that in the 3,7-dihetero systems there is greater interaction between the lone pair on nitrogen in the boat ring and the p orbital of π system of C=O at C(9),[10a,b]. This can cause a greater change in the electronic environment at the *ipso* carbon (compared with the 3-aza system). However, in both the systems the *ipso* carbon is shielded by about 4-5 ppm in the corresponding salts, as compared with the free amines.

The ^{13}C signal for C(9) in ketals **56a** and **62b** absorbs at 74.34 and 96.76 ppm, respectively. In the corresponding salts **59** and **63**, C(9) is shielded and appears at 68.96 and 93.33 ppm, respectively. Salt **63** is believed to exist in CC form in the solid state and in solution based upon a comparison of X-ray and NMR data from a similar compound **29a**.[4,39] Unfortunately, the free amine of salt **29a** was not isolated.

Interestingly, in analogy with the ^{1}H NMR data, the ^{13}C NMR data of carbamate **64** revealed that every carbon in the heterocyclic ring was non-equivalent. Thus the signals for C(1,5) were at 34.49 ppm and 35.46 ppm, while those of C(2,4) absorb at 45.25 ppm and 45.42 ppm. The signals for C(6,8) occurred at 54.01 ppm and 55.19 ppm. These assignments have been confirmed by COSY and HETCOR experiments. These diagrams are shown in Figures 1 and 2.

Comparison of ^{1}H and ^{13}C NMR analysis prompts the conclusion that in the 3-azabicyclo[3.3.1]nonane family, the free amines **55a,b**, **56a,b** and **57** exit in a CB form (see also reference 18) or part of a CB⇌BC equilibrium in solution. Salts **59** and **60** probably exist in a CC conformation in solution (solid state conformation of **59** is currently being investigated via X-ray crystallography).

In the 3,7-diazabicyclo[3.3.1]nonane family, a conclusion can be made that ketone **61** exists in a CB form and a CB⇌BC equilibrium is likely, while the ketals **62a,b,c** exist mainly in a CC form in solution, based on ^{1}H and ^{13}C NMR analyses. Salt **63** is possibly in a CC conformation both in solution and in solid state based upon comparison of ^{1}H and ^{13}C NMR analysis with a related system **29a**.

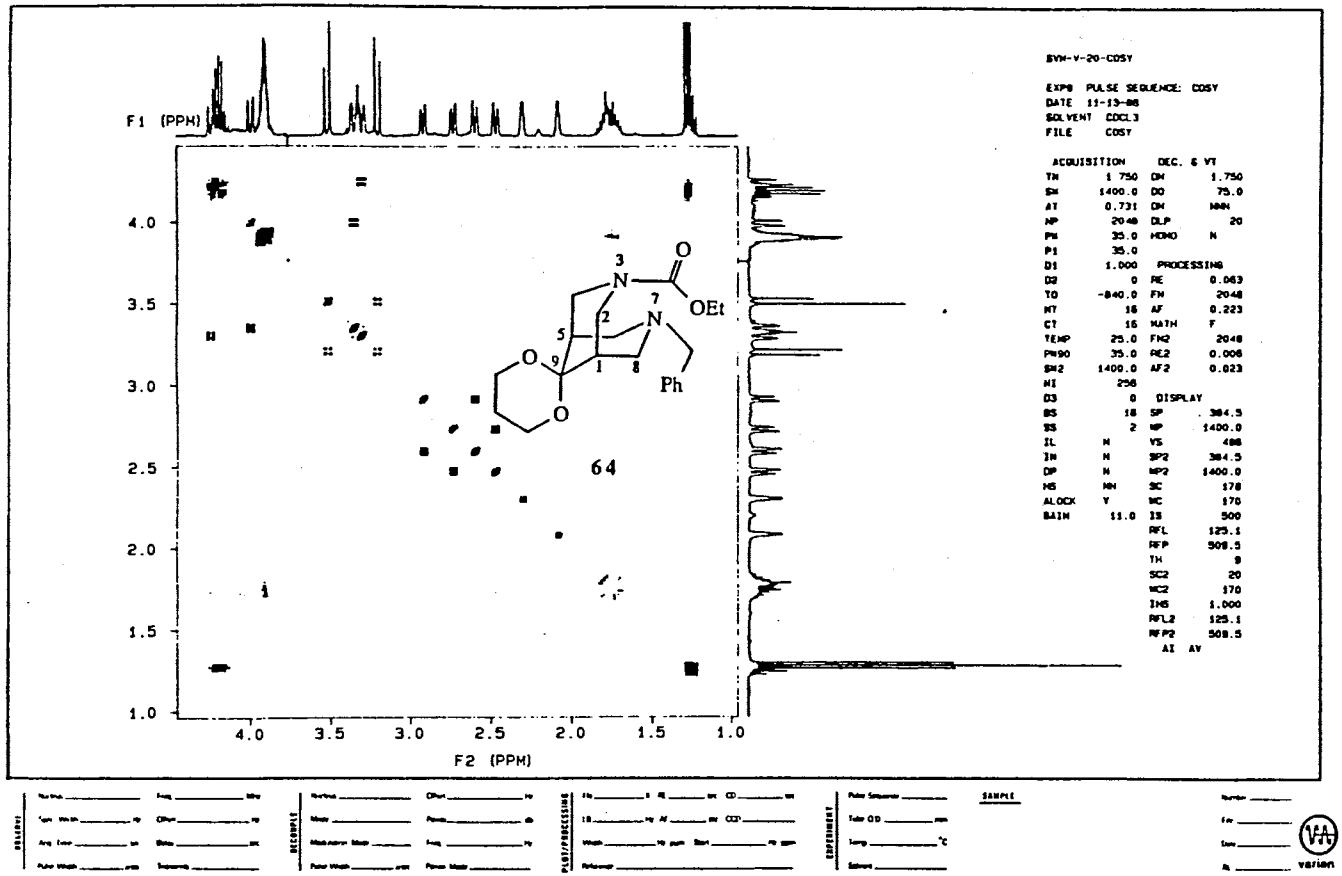


Figure 1. COSY NMR Spectrum of **64**

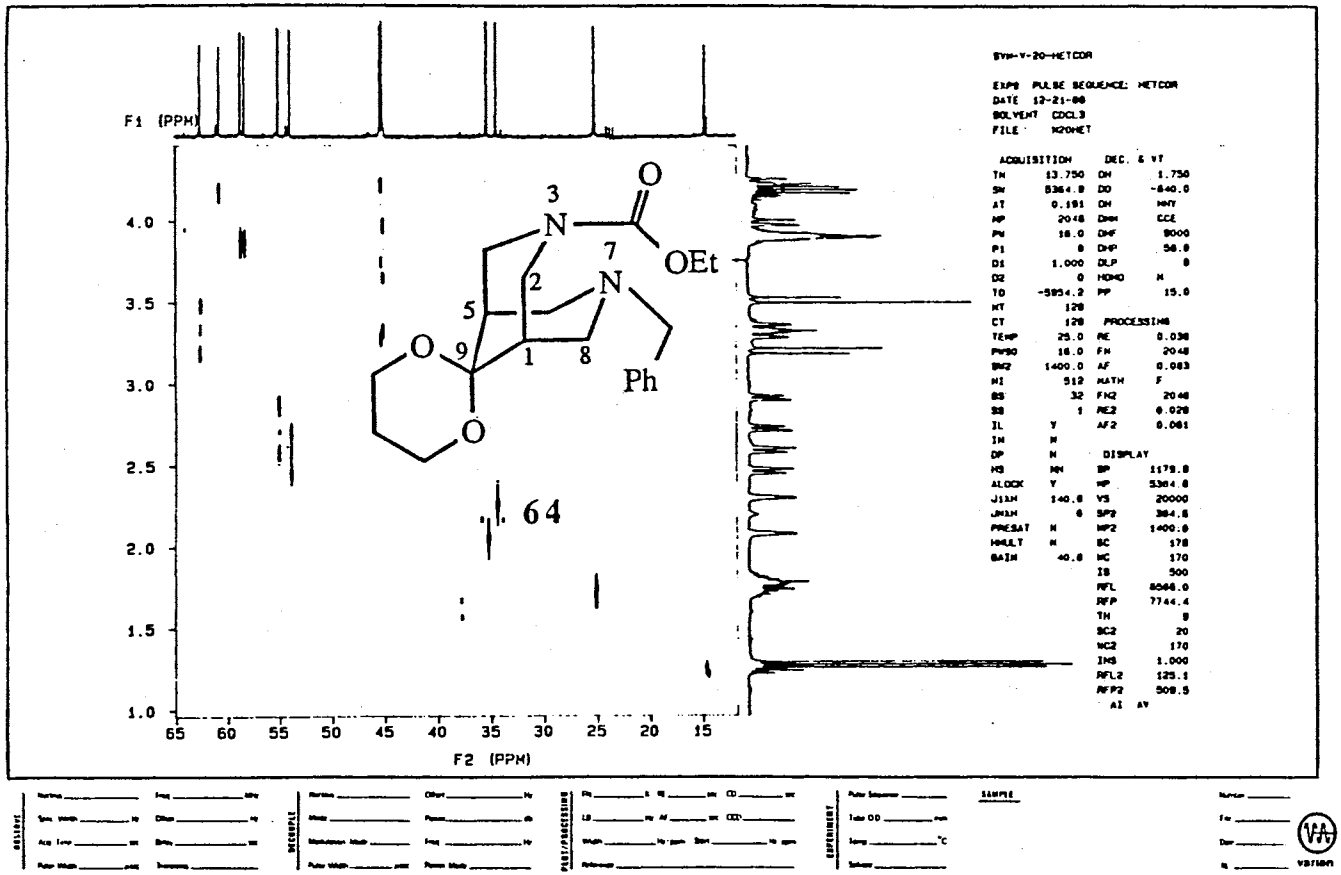
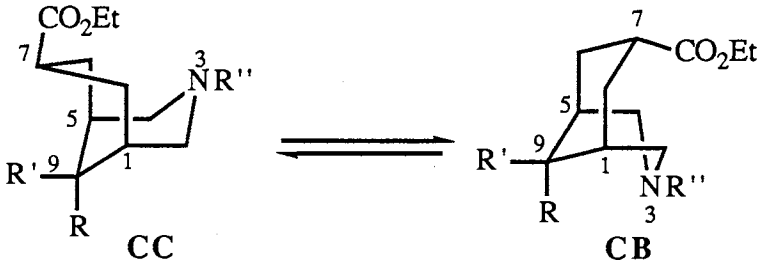


Figure 2. HETCOR NMR Spectrum of **64**



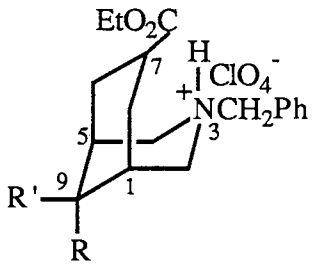
CC **CB**

55a RR'= =O, R''=CH_2Ph

55b RR'= =O, R''=CH_3

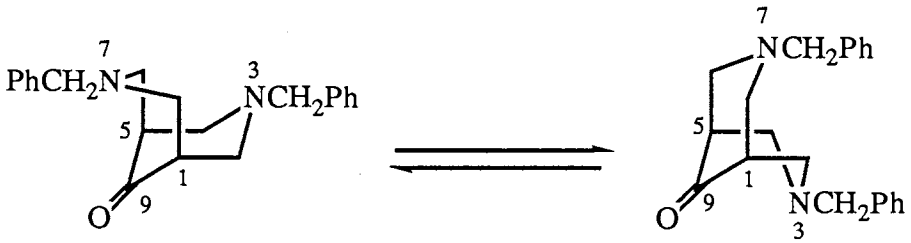
56a RR'=SCH_2CH_2S, R''=CH_2Ph

56b R=R'=H, R''=CH_2Ph

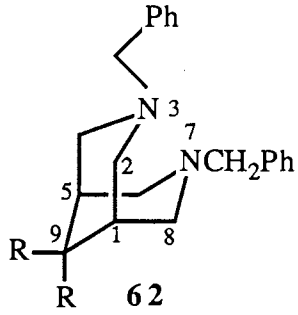


59 RR'=SCH_2CH_2S

60 R=R'=H



61-BC **61-CB**

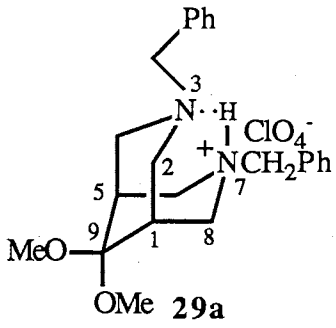


a RR=OCH_2CH_2O

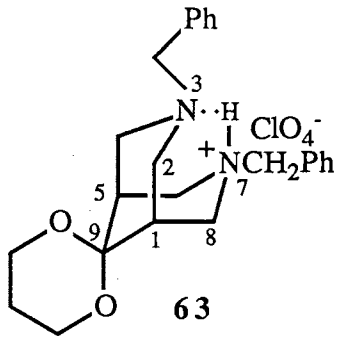
b RR=$OCH_2CH_2CH_2O$

c RR=SCH_2CH_2S

62

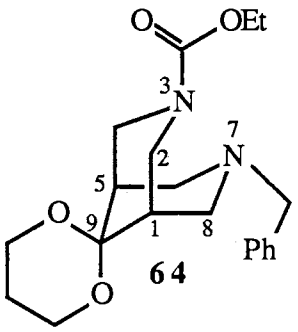


29a

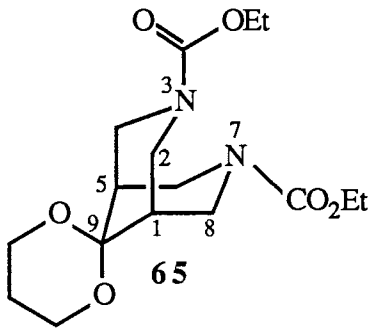


63

The carbamate **64** appears to be in a twin-chair conformation, since $^{3}J_{H(1),H(2a)}$ and $^{3}J_{H(1),H(8a)}$ couplings were not detected in the ^{1}H NMR spectrum. The N(3) ring (with NCO_2Et) in **64** must be flattened to some extent due to non-bonding interaction between the lone pair on amine nitrogen [N(7)] on the left ring with the C=O group of N(3)-CO_2Et in the right ring as shown. Interestingly, ketal **62b** reacted with $ClCO_2Et$ to yield carbamate **64**. Excess of $ClCO_2Et$ used did *not* result in the formation of dicarbamate **65**,



64



65

but only **64** was obtained. This further supports the contention that **64** exists in CC form in solution and has a hindered nitrogen atom attached to the remaining benzyl group.

The biological results are being obtained by Dr. Scherlag. These data will be reported later.

CHAPTER III

EXPERIMENTAL

Melting points were obtained on a Thomas-Hoover apparatus and were uncorrected. All ^{1}H, ^{13}C, and ^{15}N spectra were recorded on a Varian XL-300 unit operating at 299.94 MHz, 75.43 MHz and 30.41 MHz, respectively. Chemical shifts were measured in ppm downfield from TMS [$(CH_3)_4Si$] for ^{1}H and ^{13}C, while ^{15}N signals were measured from external reference $^{15}NH_4NO_3$, which was referenced to $NH_3(l)$. IR spectra were recorded on a Perkin-Elmer 681 spectrometer as KBr pellets or as films. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

All reactions, unless otherwise noted, were performed under an atmosphere of nitrogen with magnetic stirring. The following reagents were obtained from commercial sources and used without further purification: acetic acid (glacial, DuPont), diethyl bis(hydroxymethyl)malonate (Aldrich), ether (anhydrous, Fisher), HBr (48%, Fisher), $HClO_4$ (60%, Baker), *p*-toluenesulfonic acid·H_2O (PTSA·H_2O) (Eastman), Na_2CO_3 (anhydrous, Fisher), and conc. H_2SO_4 (98%, Fisher). The following materials were distilled prior to use under conditions described: acetonitrile (dried over CaH_2, 83-84°C, stored over molecular sieves, 3A, Fisher), benzene (thiophene free, 80-81°C, stored over Na wire, Fisher), benzylamine (35-36°C/0.1 mm Hg, Aldrich), *N*-benzyl-4-piperidinone (111-112°C/0.3 mm Hg, Aldrich), BF_3 etherate (48%, dried over CaH_2, 126-127°C, Aldrich), $HCCl_3$ (60-61°C, stored over $CaCl_2$, Fisher), 1,2-ethanediol (197-198°C, Fisher), 1,2-ethanedithiol (144-146°C, Aldrich), ethyl chloroformate (92-94°C, Aldrich), *N*-methyl-4-piperidinone, 49-50°C/0.3 mm Hg, Aldrich), 1,3-propanediol (126-128°C/12

mm Hg, Aldrich), pyrrolidine (86-87°C, Aldrich), and triethylamine (distilled over KOH, 89-90°C, stored over KOH, Aldrich).

β,β'-Dibromoisobutyric Acid (**51**).

Into a 500-mL, single necked, round-bottomed flask equipped with a heating mantle, a magnetic stirrer, a Claisen distillation head, a condenser and a receiver were placed diethyl bis(hydroxymethyl)malonate (**50**, 37 g, 0.17 mol), and hydrobromic acid (48%, 280 mL, 2.5 mol). The resulting homogeneous solution was distilled for 2.5 h (35°C-126°C), and 100 mL of distillate was collected. Heating was momentarily stopped, and the distillation head, condenser and receiver were removed and replaced with a condenser. The mixture was heated at reflux for 6 h. A brown reaction mixture was poured into a 250 mL Erlenmeyer flask which was allowed to cool to RT (1 h) and then was placed in an ice bath (1 h) to yield acid **51** as a white solid. This white solid was filtered off using a Buchner funnel under suction (aspirator) and was then washed with cold H_2O (50 mL) to afford, after drying (Abderhalden, 78°C, 0.2 mm Hg, P_2O_5, 12 h), acid **51** (19.1 g, 46.3%); mp 96-97°C (lit.[16] 100-102°C). The mother liquor was concentrated to about 75 mL and then cooled to RT (0.5 h), followed by an ice bath (0.5 h), to yield a second crop of the acid **51** (3.7 g, 9.0%); mp 95-97°C. IR (KBr) cm^{-1} 3500-2500 (CO_2H), 1700 (C=O); ^1H NMR ($DCCl_3$) δ 3.27 [m, 1 H, C*H*], 3.79 [m, 4 H, CH_2Br], 10.91 [bs, 1 H, CO_2H]; ^{13}C NMR ($DCCl_3$) ppm 29.80 [t, CH_2Br], 48.38 [d, C*H*], 175.30 [s, CO_2H].

Ethyl β,β'-Dibromoisobutyrate (**52**)

Into a 250-ml, single necked, round-bottomed flask equipped with a soxhlet extractor, condenser, magnetic stirrer and heating mantle were placed dibromo acid **51** (27 g, 0.11 mol), benzene (125 mL), absolute ethanol (50 mL) and conc H_2SO_4 (0.5 ml). Into the soxhlet extractor was placed a thimble containing anhydrous $MgSO_4$ (20 g). The reaction mixture was heated at reflux for 24 h. Solvent was distilled off until about 50 mL

remained. The concentrated reaction mixture was cooled to RT (0.5 h) and H_2O (50 ml) was added followed by slow addition of solid $NaHCO_3$ with stirring until pH was 7. The resulting suspension was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was extracted with ether (3 x 50 mL). The organic layers were combined and washed with H_2O (50 mL) and saturated NaCl (50 ml). This was followed by drying (anhydrous $MgSO_4$, 2 h), filtration and evaporation (rotary evaporator, aspirator) to yield a pale brown liquid which was distilled under reduced pressure to yield the ester **52** (28.3 g, 94.9 %), bp 60-62°C/0.2 mm Hg (lit.[16] 84-86°C/2.5 mm Hg). IR (film) cm^{-1} 1735 (C=O); ^1H NMR ($DCCl_3$) δ 1.30 (t, 3 H, CH_3), 3.20 (m, 1 H, C*H*), 3.78 (m, 4 H, CH_2Br), 4.25 (q, 2 H, OCH_2); ^{13}C NMR ($DCCl_3$) ppm 14.18 (q, CH_3), 30.75 (t, CH_2Br), 48.52 (d, *C*H), 61.66 (t, OCH_2), 169.32 (s, CO_2Et).

1-Benzyl-4-pyrrolidinyl-1,2,3,6-tetrahydropyridine (**54a**)

Into a 250-mL, single necked, round-bottomed flask equipped with a Dean-Stark trap, condenser, magnetic stirrer, heating mantle and a N_2 inlet were placed 1-benzyl-4-piperidinone (**53a**, 10.2 g, 0.055 mol), benzene (125 mL) and pyrrolidine (6.0 g, 0.085 mol). The resulting mixture was heated at reflux for 24 h. The Dean-Stark trap was removed and a simple distillation apparatus was added. Distillation of the solvent was completed at atmospheric pressure followed by another distillation under reduced pressure to yield the enamine **54a** as a pale yellow viscous oil (12.7 g, 97.0%), bp 167-169°C/0.2 mm Hg (lit.[12] 138-140°C/0.05 mm Hg). IR (film) cm^{-1} 1650 (C=C-N); ^1H NMR ($DCCl_3$) δ 1.79 [bs, 4 H, H(9,10)], 2.30 [bs, 2 H, H(3)], 2.56 [t, 2 H, H(2)], 3.00 [bs, 2 H, H(8,11)], 3.05 [bs, 2 H, H(6)], 3.54 [s, 2 H, CH_2Ph], 4.16 [bs, 1 H, H(5)], 7.26-7.33 [m, 5 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 24.69 [t, C(9,10)], 28.31 [t, C(3)], 47.10

[t, C(8,11)], 50.07 [t, C(2)], 52.94 [t, C(6)], 62.68 [t, CH_2Ph], 90.24 [d, C(5)], 126.64, 127.88, 128.92, 138.61 [Ar-*C*], 141.29 [s, C(4)].

1-Methyl-4-pyrrolidinyl-1,2,3,6-tetrahydropyridine (**54b**)

Into a 250-ml, single, necked round-bottomed flask equipped with a Dean-Stark trap, condenser, magnetic stirrer, heating mantle and a N_2 inlet were placed 1-methyl-4-piperidinone (**53b**, 5.65 g, 0.055 mol), benzene (125 mL) and pyrrolidine (6.0 g, 0.085 mol). The resulting mixture was heated at reflux for 24 h. Replacement of the Dean-Stark trap with a simple distillation apparatus followed, and the solvent was distilled off at atmospheric pressure followed by another distillation under reduced pressure to yield the enamine **54b** as a pale yellow viscous oil (8.1 g, 97.0%), bp 72-76°C/0.25 mm Hg (lit.[12] 78-80°C/0.2 mm Hg). IR (film) cm^{-1} 1645 (C=C-N).

Ethyl 3-Benzyl-9-oxo-3-azabicyclo[3.3.1]nonane-7(*endo*)-carboxylate (**55a**)

Into a 250-ml, 3-necked, round-bottomed flask equipped with a heating mantle, magnetic stirrer, condenser, dropping funnel and a N_2 inlet were placed a solution of enamine **54a** [9.9 g, 0.04 mol in CH_3CN (50 mL)] and Et_3N (11.6 mL, 9.1 g, 0.09 mol). The resulting mixture was heated at reflux, and, to the refluxing solution was added dropwise a solution of the dibromo ester **52** (11.1 g, 0.04 mol) in CH_3CN (20 mL) over a period of 0.5 h. During addition, triethylammonium bromide began to precipitate as a white solid, and the reaction mixture turned brown. Heating was continued for 3.5 h after the addition was complete. Solvent was removed (rotary evaporator, aspirator) to yield a dark brown oil to which was added H_2O (50 mL). The mixture was extracted with $HCCl_3$ (4 x 50 mL). The organic layers were combined and washed successively with HCl (1 N, 2 x 50 mL), $NaHCO_3$ (saturated aqueous, 2 x 50 mL) and NaCl (saturated,

2 x 50 mL). After drying (anhydrous Na_2SO_4), the solution was filtered and evaporated (rotary evaporator, aspirator) to yield crude ketone **55a** as a dark brown oil. This dark brown oil was purified by column chromatography over silica gel (150 g; 3.8 x 61 cm; 1 mL/min) using 10 % EtOAc in hexanes as the eluant to yield the ketone **55a** as a pale yellow viscous oil (4.1 g, 33.0%). R_f 0.49 in 9:1 hexanes:EtOAc. IR (film) cm^{-1} 1730 (C=O); ^1H NMR ($DCCl_3$) δ 1.30 [t, 3 H, CH_3], 2.18 [dd, J = 6.9, 15.9 Hz, 2 H, $H(6,8)_{ax}$], 2.29 [bs, 2 H, H(1,5)], 2.44 [m, 3 H, $H(6,8)_{eq}$, $H(7)_{exo}$], 2.82 [dd, J = 6.0, 14.4 Hz, 2 H, $H(2,4)_{ax}$], 3.04 [d, J = 10.6 Hz, 2 H, $H(2,4)_{eq}$], 3.56 [s, 2 H, CH_2Ph], 4.22 [q, 2 H, OCH_2], 7.17-7.30 [m, 5 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 14.35 [q, CH_3], 33.21 [t, C (6,8)], 37.75 [d, C(7)], 46.16 [d, C(1,5)], 58.06 [t, CH_2Ph], 60.34 [t, OCH_2], 127.26, 128.09, 129.50, 135.10 [Ar-*C*], 172.40 [s, CO_2Et], 215.92 [*C*=O]. The oil was used without further purification for suceeding steps since the oil decomposed upon attempted distillation.

Ethyl 3-Methyl-9-oxo-3-azabicyclo[3.3.1]nonane-7(*endo*)carboxylate (**55b**)

Into a 250-ml, 3-necked, round-bottomed flask equipped with a heating mantle, magnetic stirrer, condenser, dropping funnel and a N_2 inlet were placed a solution of enamine **54b** (7.3 g, 0.044 mol in CH_3CN (50 mL) and Et_3N (13 ml,10.2 g, 0.10 mol). The resulting mixture was heated at reflux, and, to the refluxing solution was added dropwise a solution of the dibromo ester **52** (12 g, 0.044 mol) in CH_3CN (20 mL) over a period of 0.5 h. During addition, triethylammonium bromide precipitated as a white solid and the reaction mixture turned brown. Heating was continued for 3.5 h after the addition was complete. Solvent was removed (rotary evaporator, aspirator) to yield a dark brown oil to which was added H_2O (50 mL). The mixture was extracted with $HCCl_3$ (4 x 50 mL). The organic layers were combined and washed successively with HCl (1 N, 2 x 50 mL), $NaHCO_3$ (saturated aqueous, 2 x 50 mL) and NaCl (saturated, 2 x 50 mL). After

drying (anhydrous Na_2SO_4), the solution was filtered and evaporated (rotary evaporator, aspirator) to yield crude ketone **55b** as a dark brown oil. This dark brown oil was purified by column chromatography over silica gel (150 g; 3.8 x 61 cm; 1 mL/min) using 20% EtOAc in hexanes as the eluant to yield the ketone **55b** as a pale yellow viscous oil (3.0 g, 33.0%). R_f 0.53 in 4:1 hexanes:EtOAc. IR (film) cm^{-1} 1730 (C=O); ^1H NMR ($DCCl_3$) δ 1.32 [t, 3 H, CH_3], 2.10 [s, 3 H, N-CH_3], 2.20[m, 2 H, $H(6,8)_{ax}$], 2.34 [bs, 2 H, H(1,5)], 2.52 [m, 5 H, $H(6,8)_{eq}$, $H(7)_{exo}$, $H(2,4)_{ax}$], 3.05 [m, 2 H, $H(2,4)_{eq}$], 4.20 [q, 2 H, OCH_2], ; ^{13}C NMR ($DCCl_3$) ppm 14.34 [q, CH_3], 33.85 [t, C (6,8)], 38.00 [d, C(7)], 43.25 [q, N-CH_3, 46.80 [d, C(1,5)], 60.33 [t, C(2,4)], 60.94 [t, OCH_2], 171.94 [s, CO_2Et], 216.85 [C=O]. Decomposition was observed upon attempted distillation of the oil, and thus it was used without further purification.

Ethyl 3-Benzyl-9,9-(1,3-dithiolan-2-yl)-3-azabicyclo-[3.3.1]nonane-7(*endo*)carboxylate (**56a**)

Into a 100-ml, 3-necked, round-bottomed flask equipped with a magnetic stirrer, condenser, dropping funnel, N_2 inlet and an ice-bath were placed ketone **55a** (3.01 g, 0.01 mol), 1,2-ethanedithiol (2 mL, 2.25 g, 0.024 mol), and dry $HCCl_3$ (50 mL). The resulting mixture was cooled to 0-5°C in an ice-bath. Freshly distilled BF_3 etherate (4 mL, 2.2 g, 0.015 mol) was added dropwise over a period of 0.5 h. The reaction mixture was further stirred at 0-5°C for 1 h and then at RT for 8 h. To the resulting mixture was added $HCCl_3$ (25 mL), and the solution was successively washed with NaOH (1 N, 3 x 50 mL), NaCl (saturated, 50 mL). After drying (anhydrous Na_2SO_4), the solution was filtered and evaporated (rotary evaporator, aspirator) to yield crude thioketal **56a** as a pale yellow viscous oil, which was purified by column chromatography over silica gel (105 g; 2.5 x 76 cm; 0.75 mL/min) using 10% EtOAc in hexanes as the eluant. Thioketal **56a** was obtained as a colorless oil which crystallized out as a white solid on standing at RT (12 h). This white solid was recrystallized from hexanes to yield thioketal **56a** as white

needles (1.6 g, 42.0%), mp 76-78°C. IR (KBr) cm $^{-1}$ 1715 (CO_2Et); ^1H NMR ($DCCl_3$) δ 1.30 [t, 3 H, CH_3], 1.90 [bs, 2 H, H(1,5)], 2.34 [bd, 2 H, $H(6,8)_{ax}$], 2.47 [m, 1 H, H(7)], 2.68-2.83 [m, 6 H, $H(6,8)_{eq}$, $H(2,4)_{ax,\ eq}$], 3.10-3.17 [m, 4 H, SCH_2], 3.44 [s, 2 H, CH_2Ph], 4.19 [q, 2 H, OCH_2], 7.12-7.33 [m, 5 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 14.36 [q,CH_3], 30.25 [t, C(6,8)], 36.71 [d, C(7)], 38.21, 38.64 [t, SCH_2], 42.10 [d, C(1,5)], 54.92 [t,C(2,4)], 60.14 [t, CH_2Ph], 60.27 [t, OCH_2], 127.00, 127.84, 129.91, 134.21 [Ar-*C*], 172.35 [CO_2Et]. Anal. calcd. for $C_{20}H_{27}NO_2S_2$: C, 63.66; H, 7.16; S, 16.97. Found : C, 63.99; H, 7.08; S, 17.23.

Ethyl 3-Methyl-9,9-(1,3-dithiolan-2-yl)-3-azabicyclo-[3.3.1]nonane-7(*endo*)-carboxylate (**56b**)

Into a 100-ml, 3-necked, round-bottomed flask equipped with a magnetic stirrer, condenser, dropping funnel, N_2 inlet and an ice-bath were placed ketone **55b** (6.5 g, 0.028 mol), 1,2-ethanedithiol (4 mL, 4.5 g, 0.048 mol), and dry $HCCl_3$ (50 mL). The resulting mixture was cooled to 0-5°C in an ice-bath. Freshly distilled BF_3 etherate (8 mL, 4.4 g, 0.031 mol) was added dropwise over a period of 0.5 h. The reaction mixture was further stirred at 0-5°C for 1 h and then at RT for 8 h. To the resulting mixture was added $HCCl_3$ (25 mL) and the solution was successively washed with NaOH (1 N, 3 x 50 mL), and NaCl (saturated, 50 mL). After drying (anhydrous Na_2SO_4), filtration and evaporation (rotary evaporator, aspirator) of the solution gave crude thioketal **56b** as a pale yellow viscous oil, which was purified by column chromatography over silica gel (105 g; 2.5 x 76 cm; 0.75 mL/min) using 10 % EtOAc in hexanes as the eluant. Thioketal **56b** was obtained as a colorless oil which crystallized out as a white solid on standing at RT (12 h). Recrystallization from hexanes to yielded thioketal **56b** as white needles (3.5 g, 40.4%), mp 52-54°C. IR (KBr) cm $^{-1}$ 1725 (CO_2Et); ^1H NMR ($DCCl_3$) δ 1.28[t, 3 H, CH_3], 1.92 [bs, 2 H, H (1,5)], 1.96 [s, 3 H, N-CH_3], 2.22-2.81 [m, 9 H, H $(2,4,6,8)_{ax.,\ eq.}$ and H $(7)_{exo}$], 3.26 [s, 4 H, SCH_2], 4.11 [q, 2 H, OCH_2]; ^{13}C NMR

($DCCl_3$) ppm 15.87 [q, CH_3], 31.94 [t, C (6,8)], 38.28 [d, C (7)], 39.71, 40.19 [t, SCH_2], 45.19 [q, N-CH_3], 60.06 [t, C(2,4)], 61.35 [t, OCH_2], 75.95 [s, C(9)], 173.61 [s, $\underline{C}O_2Et$]. Anal. calcd. for $C_{14}H_{23}NO_2S_2$: C, 55.81; H, 7.64; S, 21.26. Found : C, 55.68; H, 7.60; S, 21.37.

Ethyl 3-Benzyl-3-azabicyclo[3.3.1]nonane-7(*endo*)-carboxylate (**57**)

Into a 500-ml, single necked, round-bottomed flask equipped with heating mantle, magnetic stirrer, condenser and nitrogen inlet were placed thioketal **56a** (1.89 g, 0.005 mol), ethanol (200 mL) and Raney nickel (20 mL). Originally, the Raney nickel was dispersed in ethanol, but then mixture was allowed to stand. The Raney nickel precipitated, and the supernatant ethanol was removed via a pipette leaving a final, wet volume of 20 mL of Raney nickel. The resulting mixture was heated at reflux for 18 h and then was allowed to cool to RT. The cooled reaction mixture was filtered, and the solvent was removed (rotary evaporator, aspirator) to yield a thick viscous oil. To this oil was added a saturated solution (50 mL) of NaCl, and the mixture was extracted with $HCCl_3$ (3 x 50 mL). After drying ($MgSO_4$), filtration and evaporation (rotary evaporator, aspirator) of the solution, ester **57** was recovered as a colorless oil (0.97 g, 68.0%). Attempted distillation of this oil resulted in decomposition of the material. IR (film) cm^{-1} 1730 (CO_2Et); ^1H NMR ($DCCl_3$) δ 1.30 [t, 3 H, CH_3], 1.72-1.88 [m, 6 H, H(1,5), $H(6,8)_{ax}$ and H(9)], 2.33 [d, J = 12 Hz, 2 H, $H(6,8)_{eq}$], 2.42-2.58 [m, 3 H, $H(2,4)_{ax}$ and $H(7)_{exo}$], 2.77 [d, J = 12 Hz, 2 H, $H(2,4)_{eq}$], 3.49 [s, 2 H, CH_2Ph], 4.21 [q, 2 H, OCH_2], 7.12-7.38 [m, 5 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 14.48 [t, CH_3], 28.16 [d, C(1,5)], 30.40 [t, C(6,8)], 32.49 [t, C(9)], 38.45 [d, C(7)], 56.77 [t, C(2,4)], 59.97 [t, CH_2Ph], 61.62 [t, OCH_2], 126.88, 127.82, 130.04, 135.37 [Ar-*C*], 173.61 [s, CO_2Et]. The ester was used in the next step without further purification.

3-Benzyl-3-azabicyclo[3.3.1]nonane-
7(*endo*)-carboxylic acid (**58**)

Into a 100-ml, single necked, round-bottomed flask equipped with a heating mantle, magnetic stirrer, condenser and nitrogen inlet were placed ester **57** (0.8 g, 0.003 mol) and a solution of KOH (0.33 g, 0.006 mol) in aqueous ethanol (80%, 25 mL). The resulting solution was heated at reflux for 2 h, followed by cooling to RT. Evaporation (rotary evaporator, aspirator) of the solution gave a white solid which was dissolved in aqueous acetic acid (50%, 20 mL), and the resulting solution was saturated with NaCl and extracted with $HCCl_3$ (4 x 50 mL). The organic layers were combined and dried ($MgSO_4$); filtration and evaporation (rotary evaporator, aspirator) yielded a white solid which was recrystallized (EtOAc) to yield acid **58** as colorless prisms (0.43 g, 59.1%) mp 163-164°C. IR (KBr) cm^{-1} 3450 (broad, OH), 1700 (C=O); ^1H NMR ($DCCl_3$) δ 1.56 [bs, 2 H, H(1,5)], 1.96-2.16 [m, 6 H, $H(6,8)_{ax.,eq.}$ and H(9)], 2.47 [d, J = 12 Hz, 2 H, $H(2,4)_{ax}$], 2.88-2.93 [m, 1 H, H(7)], 3.01 [d, J = 12 Hz, 2 H, $H(2,4)_{eq}$], 3.73 [s, 2 H, CH_2Ph], 7.32-7.48 [m, 5 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 27.25 [d, C(1,5), 29.39 [t, C(6,8)], 30.73 [t, C(9)], 36.37 [d, C(7)], 56.70 [t, C(2,4)], 61.70 [t, CH_2Ph], 128.44, 128.57, 130.86, 131.95 [Ar-*C*], 180.47 [s, CO_2H]. Anal. calcd. for $C_{16}H_{21}NO_2$: C, 74.13; H, 8.10. Found : C, 74.16; H, 8.22.

Ethyl 3-Benzyl-9,9-(ditholan-2-yl)-3-azoniabicyclo-
[3.3.1]nonane-7(*endo*)-carboxylate
perchlorate (**59**)

Into a 250-ml Erlenmeyer flask equipped with a magnetic stirrer were placed thioketal **56a** (1.5 g, 0.004 mol), anhydrous ether (150 mL) and absolute ethanol (5 mL). The resulting solution was cooled in ice-bath for 0.5 h. To this cooled solution was added dropwise $HClO_4$ (60%, 0.85 g, 0.005 mol) over a period of 0.5 h. During the addition a

white solid precipitated. The resulting mixture was stirred in ice-bath for another 1 h, after the addition was complete, and then for 2 h at RT. The white solid obtained by filtration was recrystallized (isopropyl alcohol) to yield thioketal hydroperchlorate **59** as white needles (1.7 g, 90.0%) mp 153-154°C. IR (KBr) cm^{-1} 3400 (N-H), 1700 (CO_2Et), 1100 (ClO_4^-); ^1H NMR ($DCCl_3$) δ 1.30 [t, 3 H, CH_3], 2.05 [d, J = 16.1 Hz, 2 H, $H(6,8)_{ax}$], 2.36 [bs, 2 H, H(1,5)], 2.71 [m, 2 H, $H(6,8)_{eq}$], 3.33 [m, 4 H, SCH_2], 3.50 [m, 2 H, $H(2,4)_{ax}$], 3.68 [d, 2 H, CH_2Ph], 7.43-7.60 [m, 5 H, Ar-*H*], 10.30 [bs, 1H, N-*H*]; ^{13}C NMR ($DCCl_3$) ppm 13.79 [q, CH_3], 28.42 [t, C(6,8)], 29.53 [d, C(7)], 39.18 [d, C(1,5)], 39.51, 39.88 [t, SCH_2], 56.60 [t, C(2,4)], 61.81 [t, CH_2Ph], 63.67 [t, OCH_2], 68.96 [s, C(9)], 127.84, 129.93, 130.31, 131.57 [Ar-*C*], 183.05 [s, CO_2Et]. Anal. calcd. for $C_{20}H_{28}ClNO_6S_2$: C, 50.26; H, 5.86; N, 2.93. Found : C, 50.24; H, 6.12; N, 2.94.

Ethyl 3-Benzyl-3-azoniabicyclo[3.3.1]nonane-7(*endo*)-carboxylate perchlorate (**60**)

Into a 250 ml Erlenmeyer flask equipped with magnetic stirrer were placed ester **57** (0.95 g, 0.003 mol), anhydrous ether (150 mL) and absolute ethanol (5 mL). The resulting solution was cooled in ice-bath and to it was added dropwise $HClO_4$ (60%, 0.75 g, 0.0045 mol) over a period of 0.5 h. During the addition, a white solid precipitated. The resulting mixture was stirred in ice-bath for 1 h, after the addition was complete, and then for 2h at RT. Filtration and recrystallization (isopropyl alcohol) yielded the hydroperchlorate **60** as colorless platelets (0.87 g, 68.0%) mp 130-131°C. IR (KBr) cm^{-1} 3440 (N-H), 1700 (CO_2Et), 1100 (ClO_4^-); ^1H NMR ($DCCl_3$) δ 1.30 [t, 3 H, CH_3], 1.61 [bd, 1 H, $H(9)_{endo}$], 1.87 [d, J = 12 Hz, 2 H, $H(6,8)_{ax}$], 2.05 [bd, 1 H, $H(9)_{exo}$], 2.16-2.31 [m, 4 H, H(1,5) and $H(6,8)_{eq}$], 2.91-2.98 [m, 1 H, H(7)], 3.35-3.48 [m, 4 H, $H(2,4)_{ax.,eq.}$], 4.32 [q, 2 H, OCH_2], 4.50 [d, 2 H, CH_2Ph], 7.38-7.68 [m, 5 H, Ar-*H*], 11.50 [bs, 1 H, N-*H*]; ^{13}C NMR ($DCCl_3$) ppm 13.79 [q, CH_3], 25.74 [d, C(1,5)],

27.85 [t, C(6,8)], 31.91 [d, C(7)], 55.96 [t, C(2,4)], 61.68 [t, CH_2Ph], 63.05 [t, OCH_2], 128.60, 129.98, 131.25 [Ar-*C*], 182.93 [s, CO_2Et]. Anal. calcd. for $C_{18}H_{26}ClNO_6$: C, 55.75; H, 6.71. Found : C, 56.11; H, 6.82.

3,7-Dibenzyl-9-oxo-3,7-diaza-bicyclo[3.3.1]nonane (**61**)

Into a 500-ml, 3-necked, round-bottomed flask equipped with heating mantle, magnetic stirrer, condenser, a dropping funnel and a nitrogen inlet were placed paraformaldehyde (6.7 g, 0.22 mol), methanol (150 mL), benzylamine (11.4 g, 0.11 mol) and AcOH (gl., 6.5 g, 0.11 mol). The resulting mixture was heated at reflux, and to the boiling mixture was added dropwise a solution of 1-benzyl-4-piperidinone (**53a**, 20.0 g, 0.11 mol), AcOH (gl., 6.5 g, 0.11 mol) and methanol (50 mL) over a period of 0.75 h. Heating at reflux was continued for 24 h, followed by cooling to RT. Evaporation (rotary evaporator, aspirator) gave a brown viscous oil which was partitioned between H_2O (100 mL) and ether (100 mL). The aqueous layer was cooled in ice-bath and then made strongly alkaline to pH 12, using NaOH (aq., 10%, 50 mL). This strongly alkaline solution was extracted with ether (5 x 50 mL), and the organic layers were combined and washed with H_2O (50 mL) and NaCl (saturated, 50 mL). After drying (Na_2SO_4), filtration and evaporation (rotary evaporator, aspirator) of the solution gave a brown viscous oil. Digestion of this oil with Skelly 'B' (500 mL), resulted in the formation of a yellow solution. Filtration and evaporation (rotary evaporator, aspirator) of the solution yielded a dark yellow viscous oil. Distillation (molecular still) of this oil gave crude ketone **61** as light yellow oil (15.1 g, 42.9%), bp 195-205°C/2.0x10^{-6} mm Hg. This oil was crystallized (*n*-pentane) to yield ketone **61** as a white solid (12.4 g, 35.2%) mp 83-83.5°C (lit.[6] 70-71°C). IR (KBr) cm^{-1} 1720 (C=O); ^1H NMR ($DCCl_3$) δ 2.54 [bs, 2 H, H(1,5)], 2.80 [dd, J = 6.0, 10.7 Hz, 4 H, $H(2,4,6,8)_{ax.}$], 3.03 [dd, J = 2.3, 10.7 Hz, 4 H, $H(2,4,6,8)_{eq}$], 3.55 [s, 4 H, CH_2Ph], 7.27-7.32 [m, 10 H, Ar-*H*]; ^{13}C NMR

($DCCl_3$) ppm 46.76 [d, C(1,5)], 58.12 [t, C(2,4,6,8)], 61.62 [t, CH_2Ph], 127.13, 128.25, 128.76, 138.24 [Ar-*C*], 214.70 [s, *C*=O]; M.S. calcd for $C_{20}H_{24}N_2O$; M^+, 320.1888. Found : M^+, 320.1890.

3,7-Dibenzyl-9,9-(1,3-dioxalan-2-yl)-3,7-diazabicyclo[3.3.1]nonane (**62a**)

Into a 100-ml, single-necked, round-bottomed flask equipped with heating mantle, magnetic stirrer, condenser, Dean-Stark trap and a nitrogen inlet were placed ketone **61** (1.5 g, 4.68 mmol), benzene (60 mL), 1,2-ethanediol (10.0 g, 0.16 mmol) and PTSA (1.10 g, 5.78 mmol). The resulting mixture was heated at reflux for 24 h. Solvent was evaporated to a volume of about 25 mL, and then the remaining solution was cooled to RT and H_2O (25 mL) was added. The resulting mixture was made basic (pH 12) using aqueous NaOH (10%, 5 mL). This basic mixture was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was extracted with ether (3 x 50 mL). The organic layers were combined and washed with H_2O (50 mL) and saturated NaCl (50 mL). After drying (Na_2SO_4), filtration and evaporation (rotary evaporator, aspirator) of the solution gave a light yellow, viscous oil which solidified upon standing at RT (12 h). Recrystallization (hexanes) yielded ketal **62a** as a white solid (1.1 g, 64.3%) mp 73-74°C. IR (KBr) cm^{-1} 3060, 3025, 2975, 2885, 2785, 1605, 1100, 730, 700; ^1H NMR ($DCCl_3$) δ 1.67 [bs, 2 H, H(1,5)], 2.66 [dd, J = 2.3, 10.7 Hz, 4 H, $H(2,4,6,8)_{ax.}$], 2.91 [d, J = 10.8 Hz, 4 H, $H(2,4,6,8)_{eq.}$], 3.50 [s, 4 H, CH_2Ph], 3.94 [s, 4 H, OCH_2], 7.20-7.49 [m, 10 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 38.78 [d, C(1,5)], 55.81 [t, C(2,4,6,8)], 62.65 [t, CH_2Ph], 63.91 [t, OCH_2], 108.20 [s,C(9)], 126.45, 128.02, 128.70, 139.94 [Ar-*C*]; . Anal. calcd. for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; Found : C, 76.03; H, 8.04.

3,7-Dibenzyl-9,9-(1,3-dioxan-2-yl)-3,7-diazabicyclo[3.3.1]nonane (**62b**)

Into a 250-ml, single-necked, round-bottomed flask equipped with heating mantle, magnetic stirrer, condenser, Dean-Stark trap and a nitrogen inlet were placed ketone **61** (5.0 g, 15.6 mmol), benzene (125 mL), 1,3-propanediol (10.0 g, 0.13 mol) and PTSA (3.50 g, 19.1 mmol). The resulting mixture was heated at reflux for 24 h. Solvent was evaporated to a volume of about 25 mL, and the remaining solution was cooled to RT and H_2O (25 mL) was added. The resulting mixture was made basic (pH 12) using aqueous NaOH (10%, 15 ml). This basic mixture was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was extracted with ether (3 x 50 mL). The organic layers were combined and washed with H_2O (50 mL) and saturated NaCl (50 mL). Drying (Na_2SO_4), filtration and evaporation (rotary evaporator, aspirator) gave a light yellow viscous oil which solidified upon standing at RT (12 h). This solid was recrystallized (hexanes) to yield ketal **62b** as a white solid (4.7 g, 79.7%) mp 118-119°C. IR (KBr) cm^{-1} 3040, 2975, 2975, 2885, 2785, 1610, 1115, 738, 705; ^1H NMR ($DCCl_3$) δ 1.73 [quintet, J = 5.6 Hz, 2 H, OCH_2CH_2], 2.19 [bs, 2 H, H(1,5)], 2.61 [dd, J = 2.3, 10.6 Hz, 4 H, $H(2,4,6,8)_{ax.}$], 2.84 [d, J = 10.3 Hz, 4 H, $H(2,4,6,8)_{eq.}$], 3.49 [s, 4 H, CH_2Ph], 3.88 [t, J = 5.6 Hz, 4 H, OCH_2CH_2], 7.20-7.50 [m, 10 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 25.38 [t, OCH_2CH_2], 36.00 [d, C(1,5)], 54.35 [t, C(2,4,6,8)], 58.40 [t, OCH_2CH_2], 62.65 [t, CH_2Ph], 96.76 [s, C(9)], 126.43, 128.02, 128.69, 140.03 [Ar-*C*]; ^{15}N NMR ($DCCl_3$) ppm 37.81 [N(3,7)]. Anal. calcd. for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.40. Found : C, 76.54; H, 7.95; N, 7.35.

3,7-Dibenzyl-9,9-(1,3-dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]nonane (**62c**)

Into a 250-ml, single necked, round-bottomed flask equipped with heating mantle, magnetic stirrer, condenser, Dean-Stark trap and a nitrogen inlet were placed ketone **61** (5.0 g, 15.6 mmol), benzene (125 mL), 1,2-ethanedithiol (22.5 g, 0.24 mol) and PTSA (3.60 g, 19.1 mmol). The resulting mixture was heated at reflux for 24 h. Solvent was evaporated to a volume of about 25 mL and then the remaining solution was cooled to RT and H_2O (25 mL) was added. The resulting mixture was made basic (pH 12) using aqueous NaOH (10%, 15 ml). This basic mixture was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was extracted with ether (3 x 50 mL). The organic layers were combined and washed with H_2O (50 mL) and saturated NaCl (50 mL). Drying (Na_2SO_4), filtration and evaporation (rotary evaporator, aspirator) of the solution gave a light yellow viscous oil. This oil was crystallized (hexanes, Norit) to yield thioketal **12** as a white solid (1.5 g, 24.7%) mp 102-103°C. Concentration of the mother liquor to 20 mL afforded, after cooling (0°C), a second crop of thioketal **62c** as a white solid (0.35 g, 5.7%; 30.4% total) mp 101-102.5°C. IR (KBr) cm^{-1} 3040, 2935, 2900, 2785 740, 705; ^1H NMR ($DCCl_3$) δ 2.12 [bs, 2 H, H(1,5)], 2.75 [dd, J = 2.6, 11.1 Hz, 4 H, $H(2,4,6,8)_{ax.}$], 2.84 [dd, J = 4.5, 11.1 Hz, 4 H, $H(2,4,6,8)_{eq.}$], 3.14 [s, 4 H, SCH_2], 3.52 [s, 4 H, CH_2Ph], 7.23-7.43 [m, 10 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 38.06 [t, SCH_2], 43.59 [d, C(1,5)], 56.68 [t, C(2,4,6,8)], 62.09 [t, CH_2Ph], 71.93 [s, C(9)], 126.71, 128.10, 128.83, 139.16 [Ar-*C*]. Anal. calcd. for $C_{23}H_{28}N_2S_2$: C, 69.65; H, 7.12; N, 7.06. Found : C, 69.37; H,.7.33; N, 6.88.

3,7-Dibenzyl-9,9-(1,3-dioxan-2-yl)-3,7-diazonia-bicyclo[3.3.1]nonane perchlorate (**63**)

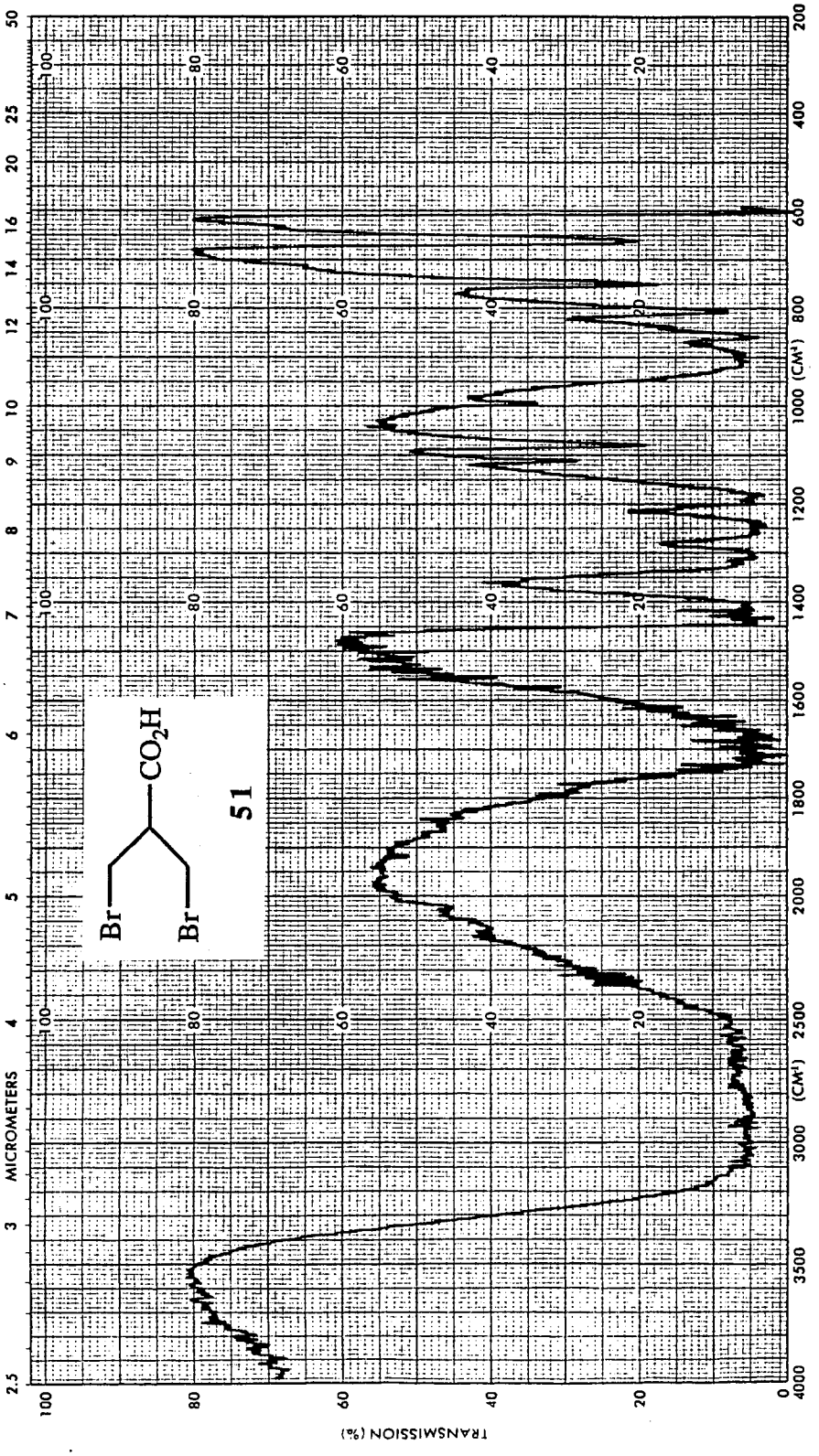
Into a 250-ml Erlenmeyer flask equipped with a magnetic stirrer were placed trimethylene ketal **62b** (1.0 g, 2.7 mmol) and anhydrous ether (125 mL). The resulting solution was cooled in ice-bath (0.5 h). To the cooled solution was added dropwise a solution of $HClO_4$ (60%, 1.0 g, 6.0 mmol) in isopropyl alcohol (2 mL) over a period of 0.5 h. During the addition a white solid precipitated. The resulting mixture was stirred in ice-bath (1.5 h). Filtration (Buchner funnel, aspirator) of the reaction mixture gave a white solid which was washed with cold ether (50 mL). Recrystallization (acetone:pentane) in a diffusion chamber gave, after filtration and drying (Abderhalden, 42°C, P_2O_5, 0.2 mm Hg, 24 h), the hydroperchlorate **63** as white needles (0.90 g, 69.0%) mp 244-245.5°C. IR (KBr) cm^{-1} 3040, 2975, 2885, 1100 (ClO_4^-); ^1H NMR (DMSO-d_6) δ 1.67 [m, 2 H, OCH_2CH_2], 2.58 [bs, 2 H, H(1,5)], 2.93 [d, J = 11.5 Hz, 4 H, $H(2,4,6,8)_{ax.}$], 3.05 [d, J = 11.3 Hz, 4 H, $H(2,4,6,8)_{eq.}$], 3.72-3.95 [m, 8 H, CH_2Ph, OCH_2CH_2], 7.34-7.49 [m, 10 H, Ar-*H*]; ^{13}C NMR (DMSO-d_6) ppm 24.57 [t,OCH_2CH_2], 33.30 [d, C(1,5)], 53.43 [t, C(2,4,6,8)], 58.61 [t, OCH_2CH_2], 59.72 [t, CH_2Ph], 93.33 [s, C(9)], 128.50, 128.71, 128.90, 133.76 [Ar-*C*]; ^{15}N NMR (DMSO-d_6) ppm 52.65 [N(3,7)]. Anal. calcd. for $C_{24}H_{31}ClN_2O_6$: C, 60.19; H, 6.52. Found : C, 60.30; H, 6.33.

Ethyl 7-Benzyl--9,9'-(1,3-dioxan-2-yl)-3,7-diaza-bicyclo[3.3.1]nonane-3(*endo*)-carboxylate (**64**)

Into a 100-ml, single-necked, round-bottomed flask equipped with a heating mantle, magnetic stirrer, condenser and a nitrogen inlet were placed trimethylene ketal **62b** (3.8 g, 10 mmol), benzene (60 mL), Na_2CO_3 (1.5 g, 14 mmol) and $ClCO_2Et$ (5.2 g, 48 mmol). The resulting mixture was heated at reflux for 36 h. After cooling the reaction mixture to

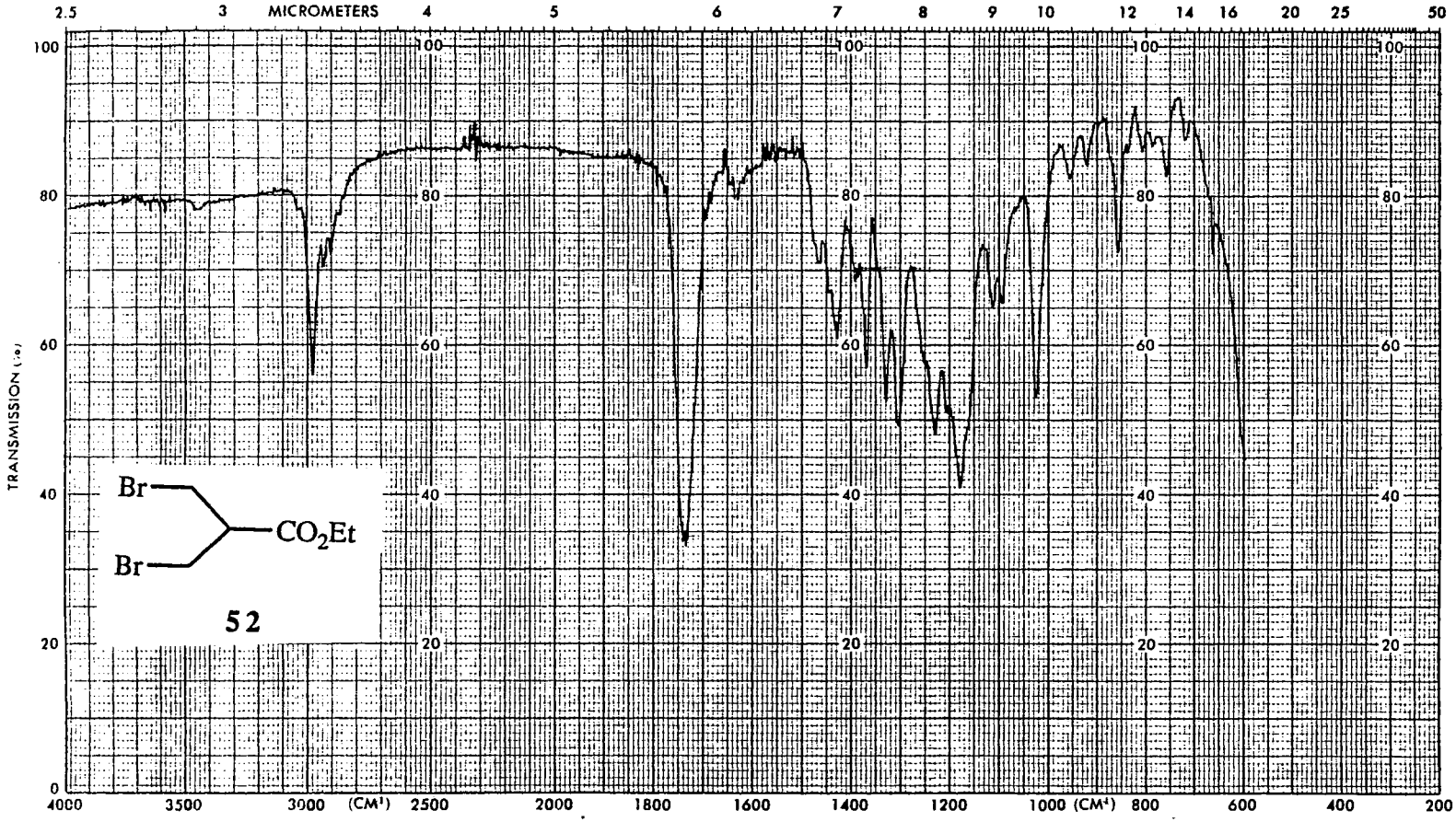
RT, H_2O (30 mL) was added and the organic layer was separated and washed with H_2O (2 x 30 mL) and saturated NaCl (2 x 30 mL). Drying (Na_2SO_4), filtration and evaporation (rotary evaporator, 60°C, 1 mm Hg, 1 h) of the solution afforded a viscous brown oil. This oil, after trituration with hexanes at 0°C, afforded a yellow solid which was recrystallized (hexanes, 30 ml, Norit) to yield carbamate **64** as a white solid (2.1 g, 58.0%) mp 103-104°C. IR (KBr) cm^{-1} 1675 (NCO_2Et); ^1H NMR ($DCCl_3$) δ 1.27 [t, 3 H, CH_3], 1.76 [m, 2 H, OCH_2CH_2], 2.08, 2.31 [bd, 2 H, H(1,5)], 2.47, 2.73 [d, J = 10.9 Hz, 2 H, $H(6,8)_{ax}$], 2.59, 2.92 [d, J = 10.8 Hz, 2 H, $H(6,8)_{eq}$], 3.20, 3.52 [d, J = 13. 2 Hz, 2 H, CH_2Ph], 3.30, 3.35 [m, 2 H, $H(2,4)_{ax}$] 3.88-3.93 [m, 4 H, OCH_2CCH_2], 3.99 [d, J = 13 Hz, 1 H, $H(2,4)_{eq}$], 4.17-4.27 [m, 3 H $H(2,4)_{eq}$, OCH_2CH_3], 7.26-7.28 [m, 5 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 14.84 [q, CH_3], 25.29 [t, OCH_2CH_2], 34.49, 35.46 [d, C(1,5)], 45.25, 45.42 [t, C(2,4)], 54.01, 55.19 [t, C(6,8)], 58.49, 58.88 [t, OCH_2CH_2], 60.97 [t, OCH_2CH_3], 62.76 [t, CH_2Ph], 96.01 [s, C(9)], 126.73, 128.02, 128.69, 139.06 [Ar-*C*], 155.68 [s, NCO_2Et]. Anal. calcd. for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found : C, 66.39; H, 8.00; N, 7.66.

Plate I



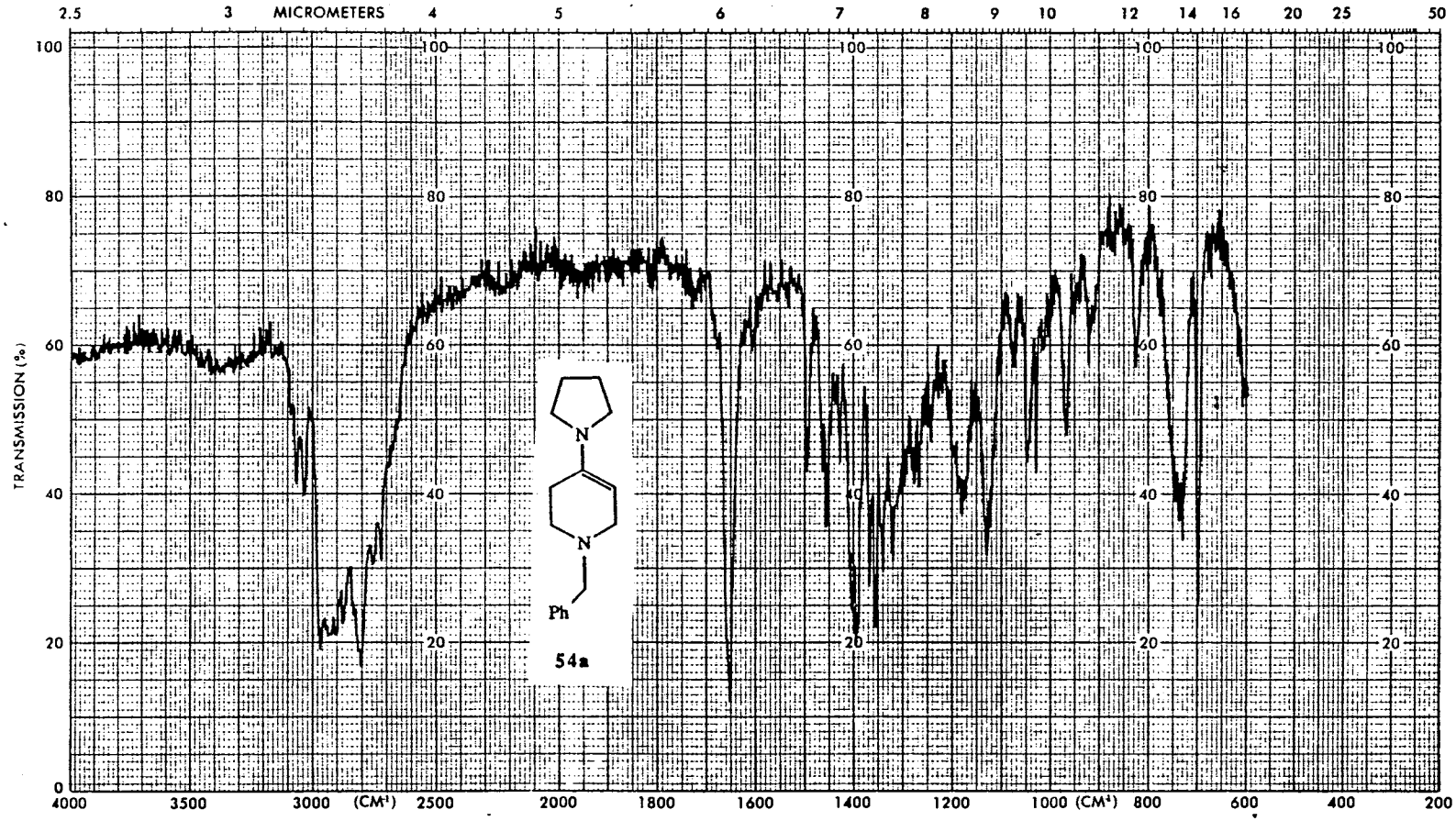
IR Spectrum of **51**

Plate II



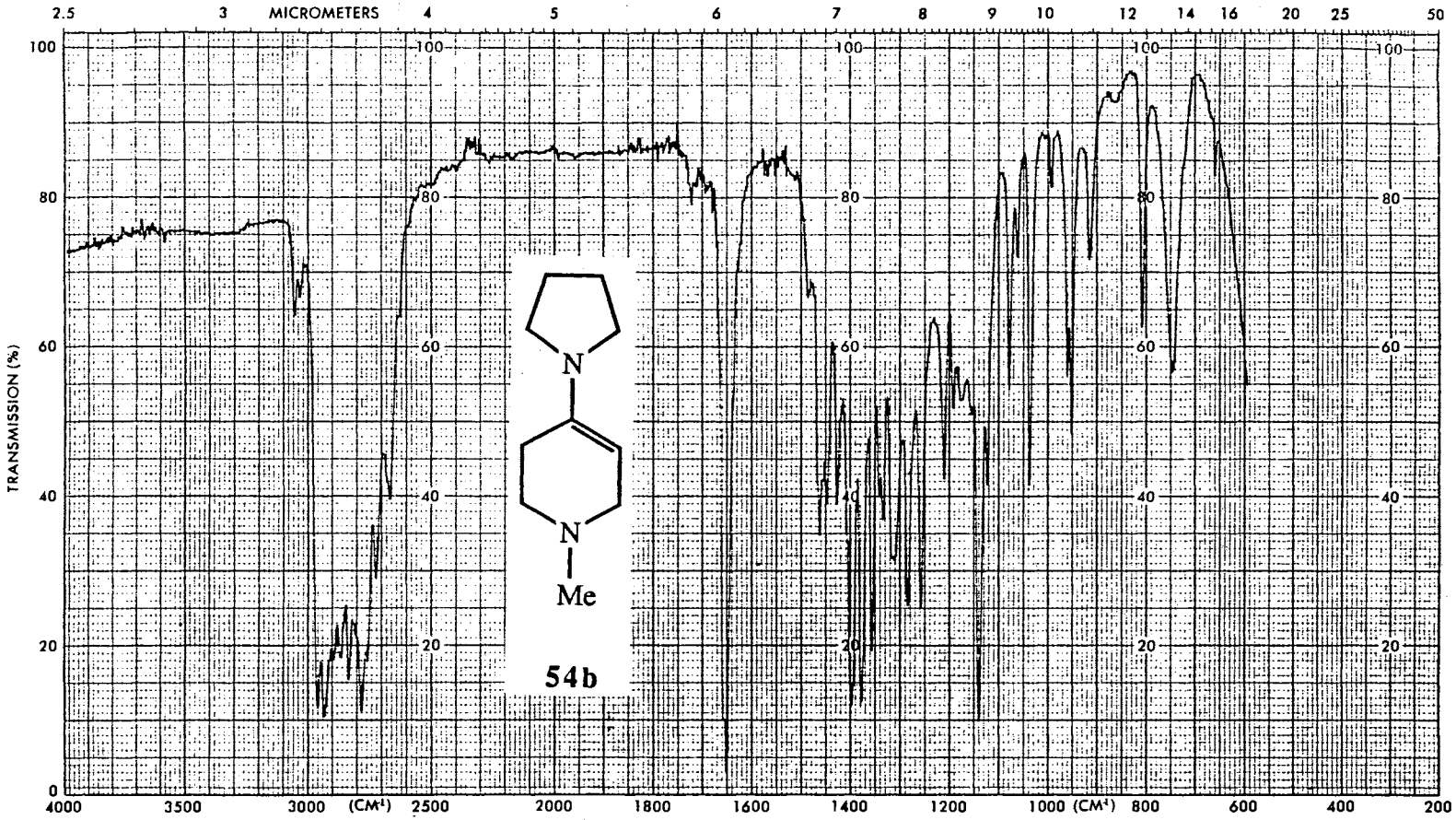
IR Spectrum of **52**

Plate III



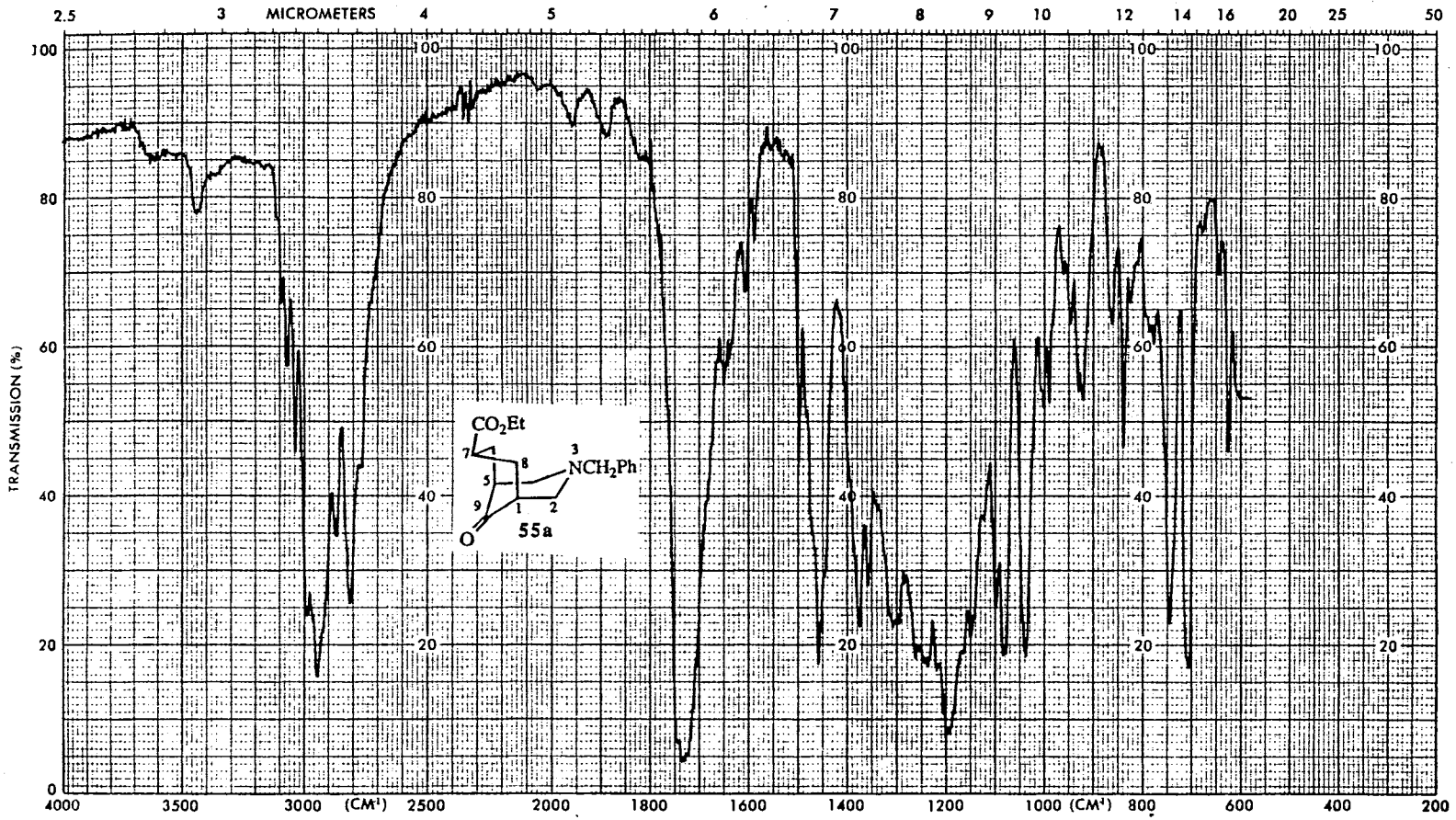
IR Spectrum of **54a**

Plate IV



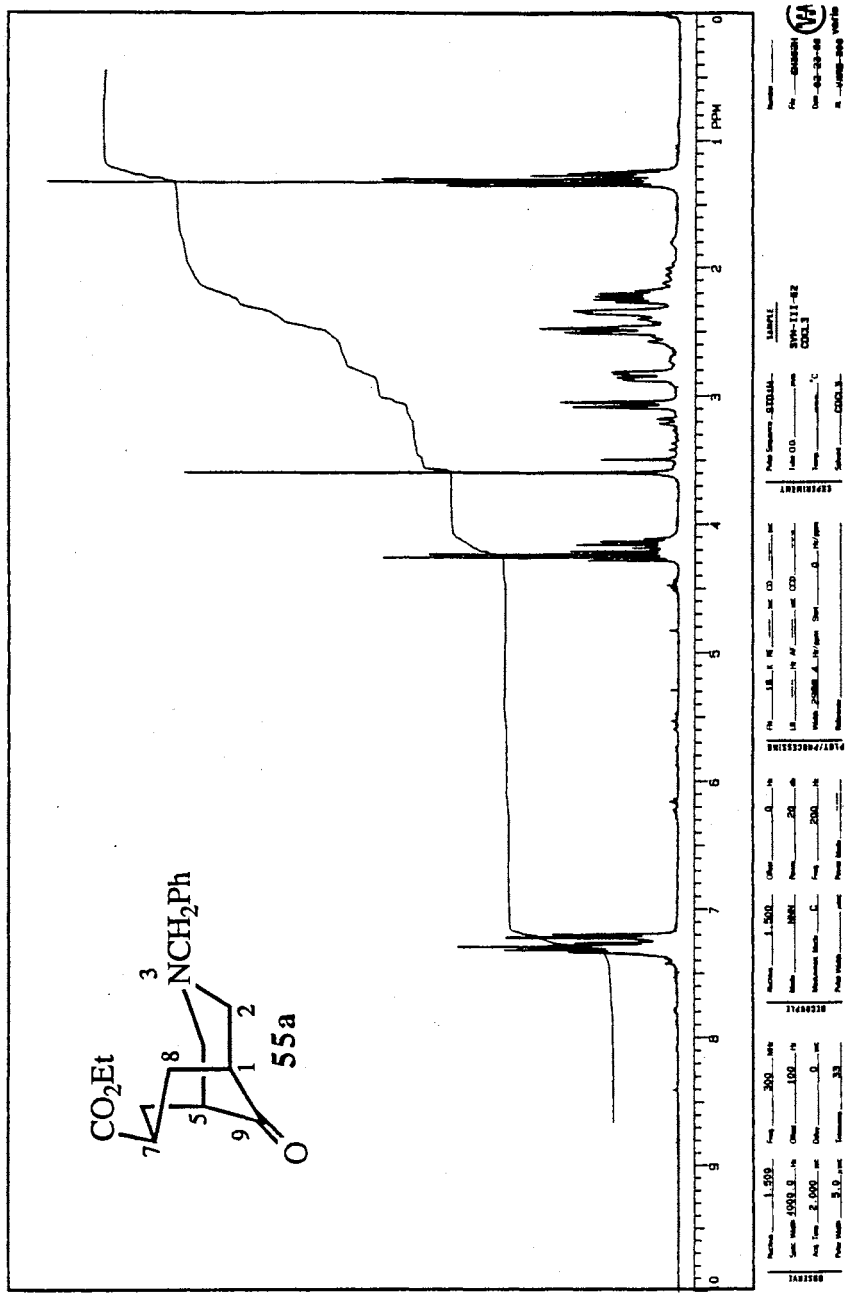
IR Spectrum of **54b**

Plate V



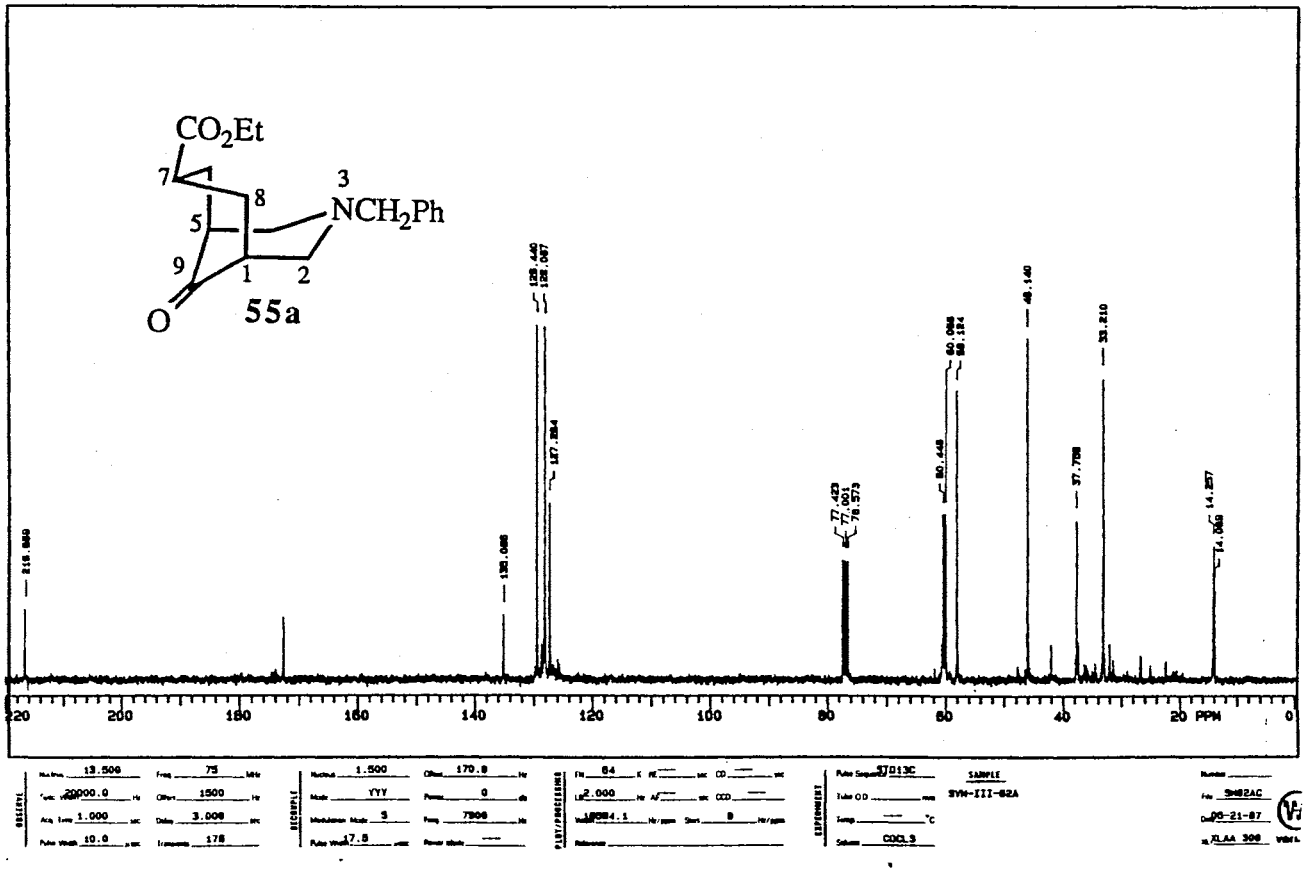
IR Spectrum of **55a**

Plate VI



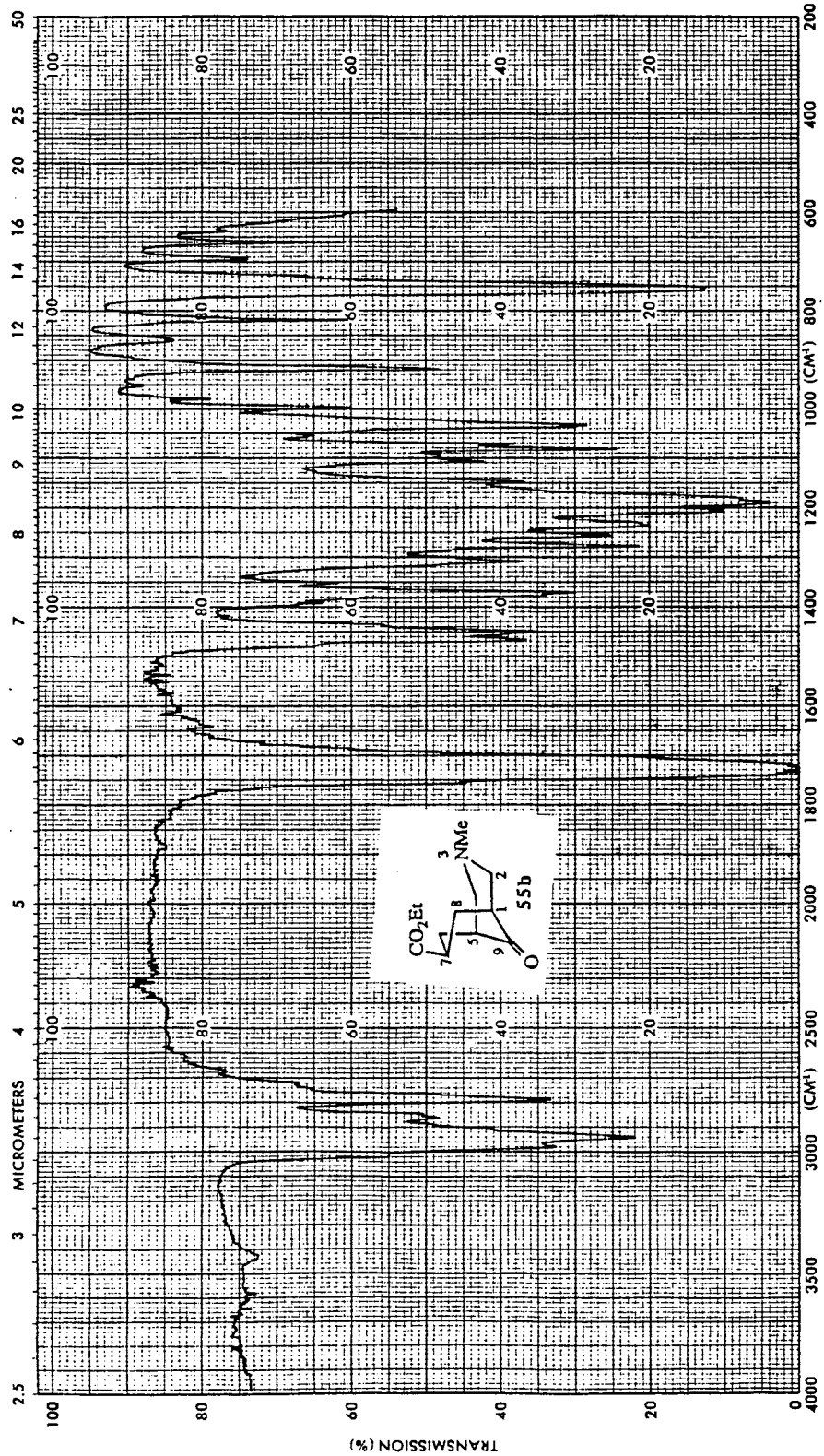
^{1}H NMR Spectrum of **55a**

Plate VII



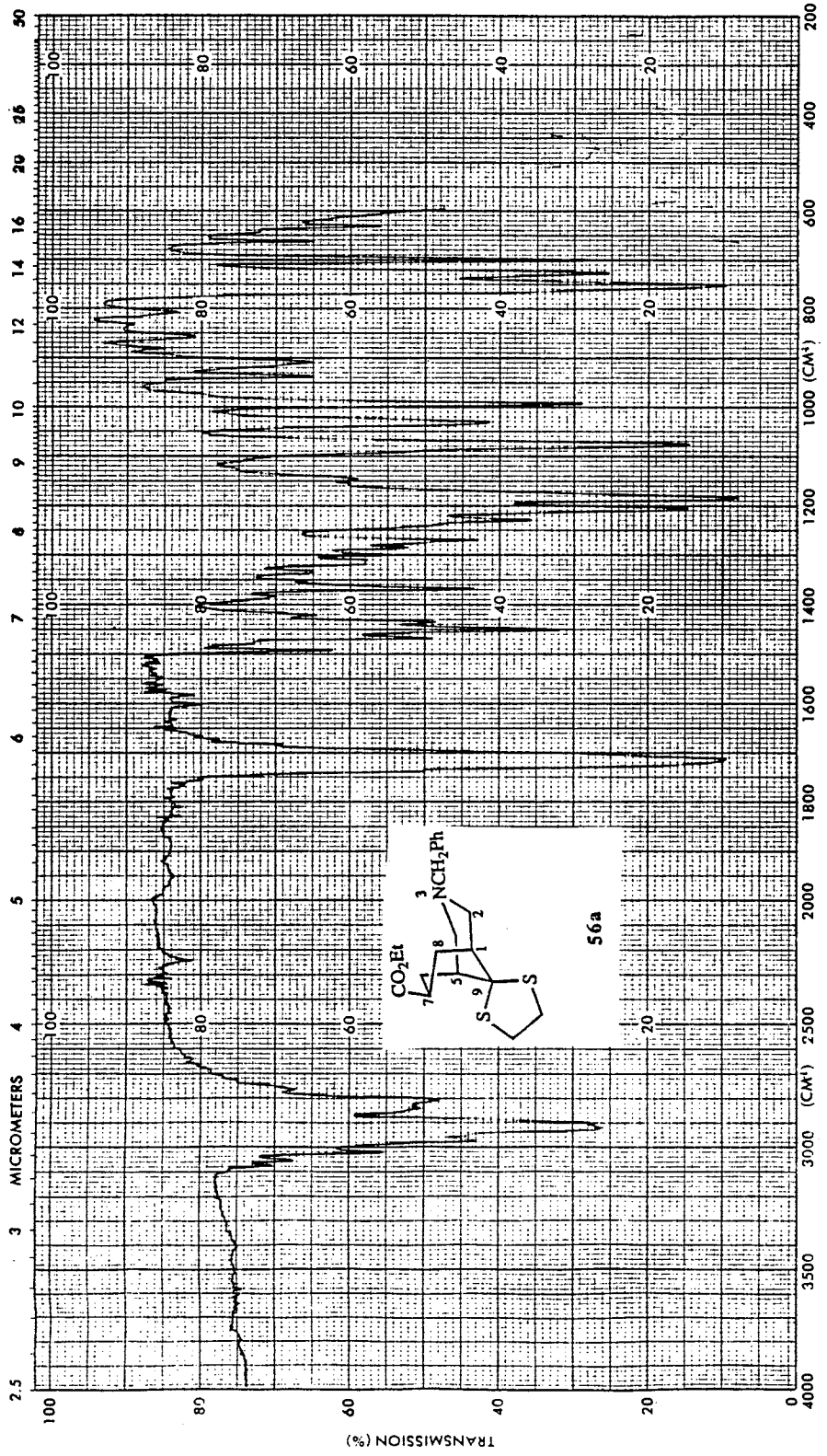
^{13}C NMR Spectrum of **55a**

Plate VIII



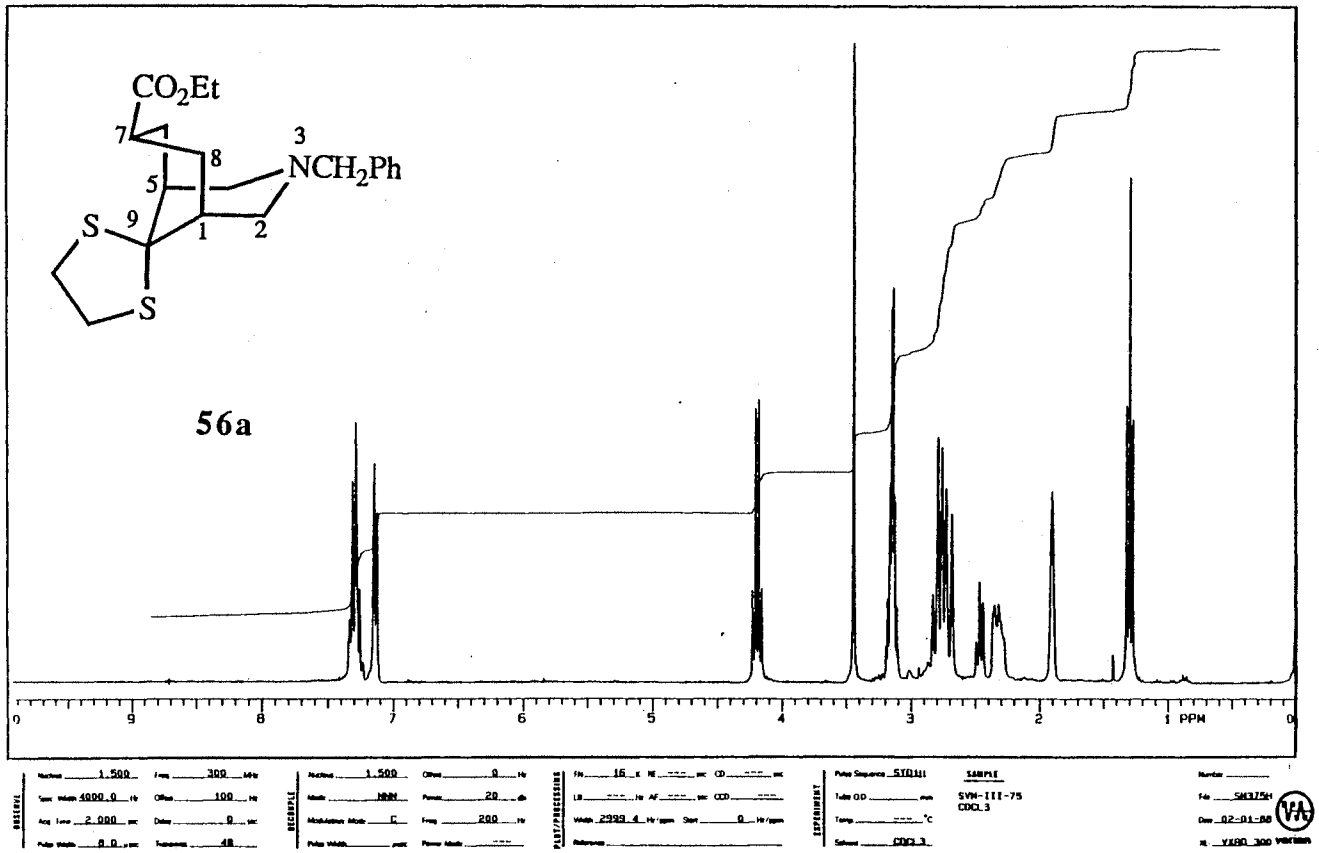
IR Spectrum of **55b**

Plate IX



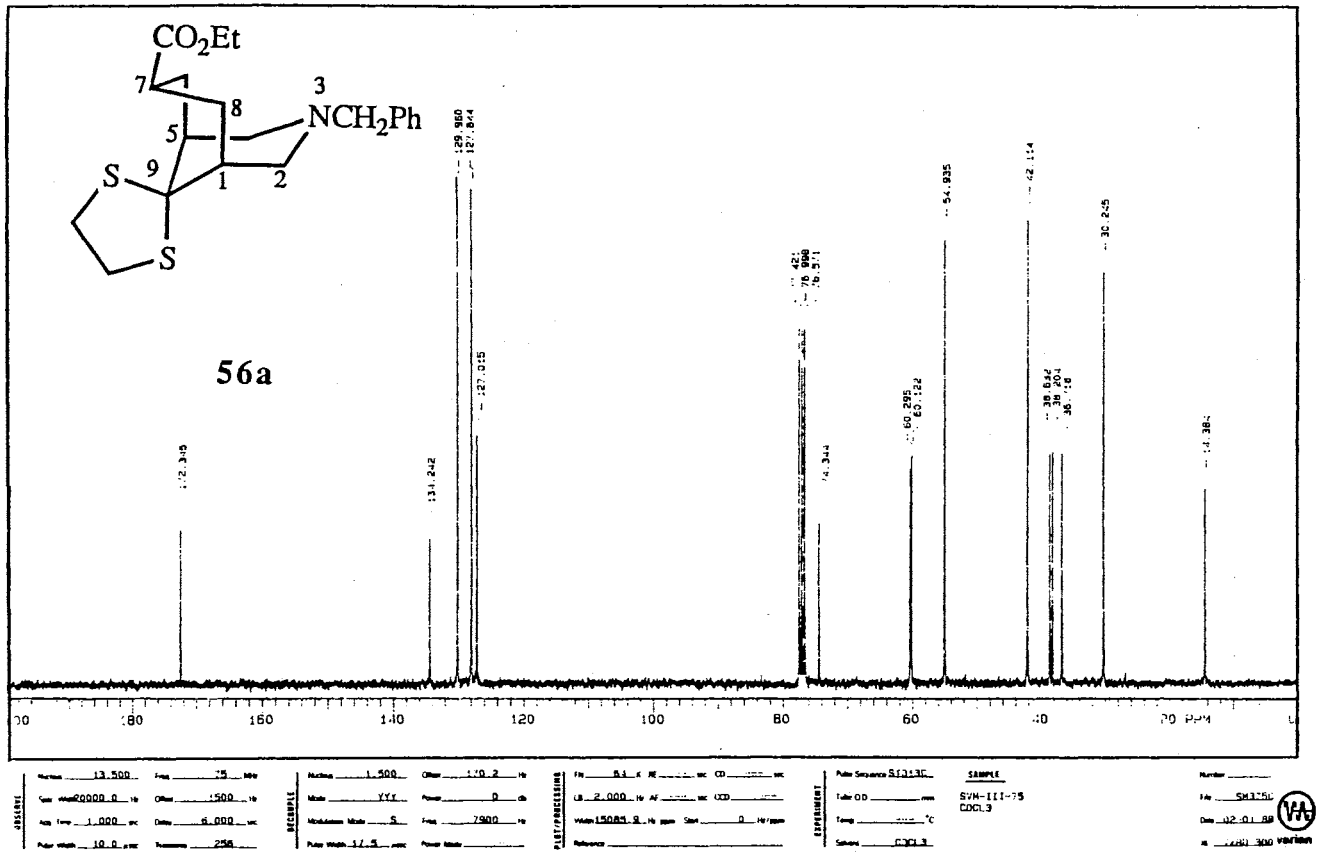
IR Spectrum of **56a**

Plate X



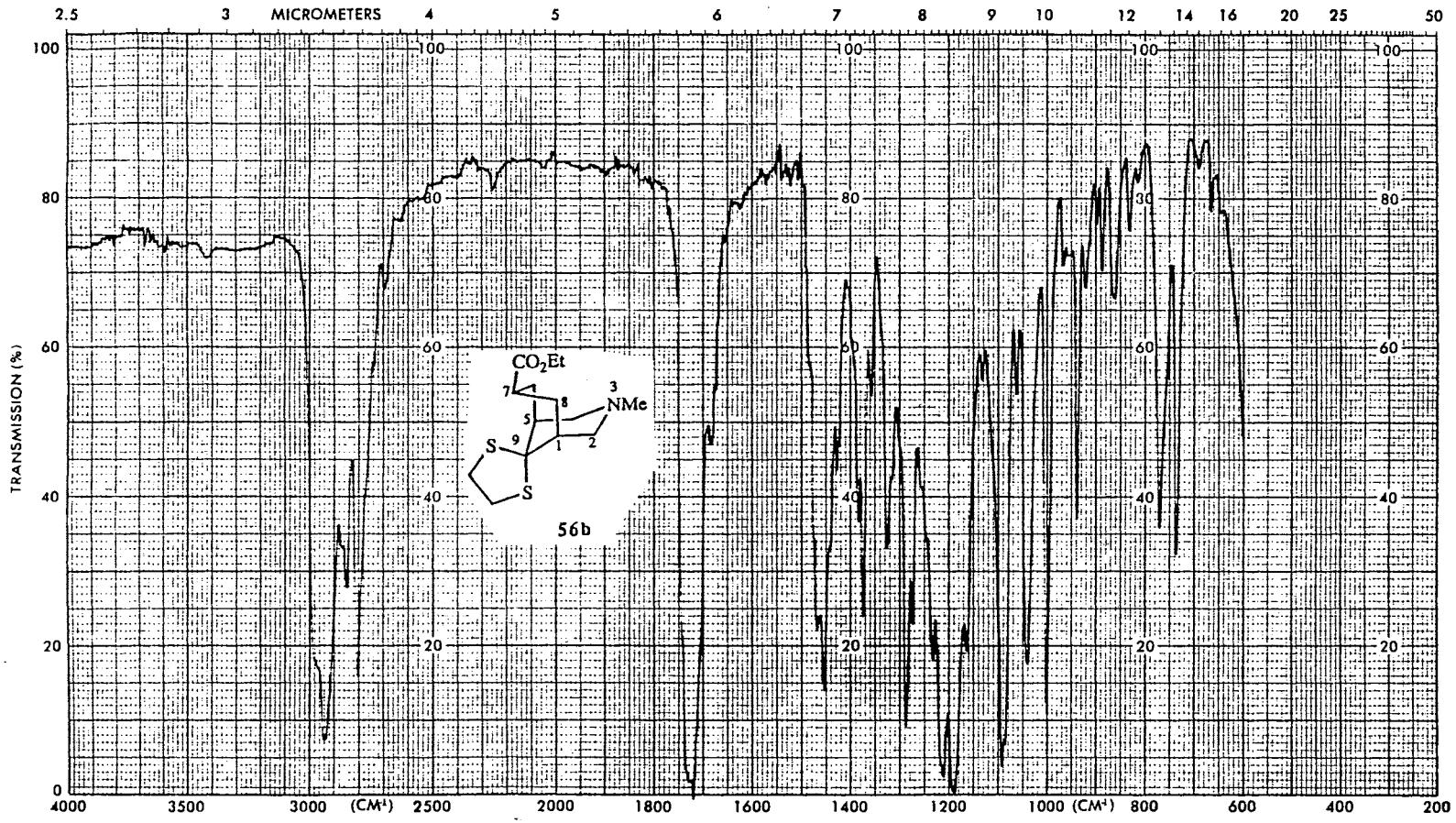
^{1}H NMR Spectrum of **56a**

Plate XI



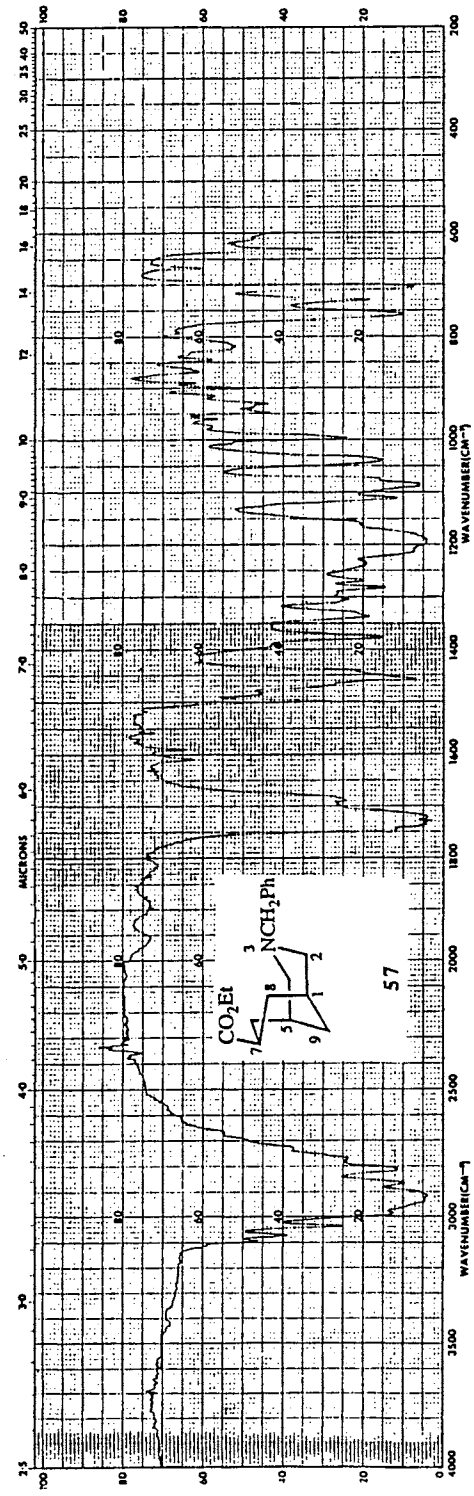
^{13}C NMR Spectrum of **56a**

Plate XII



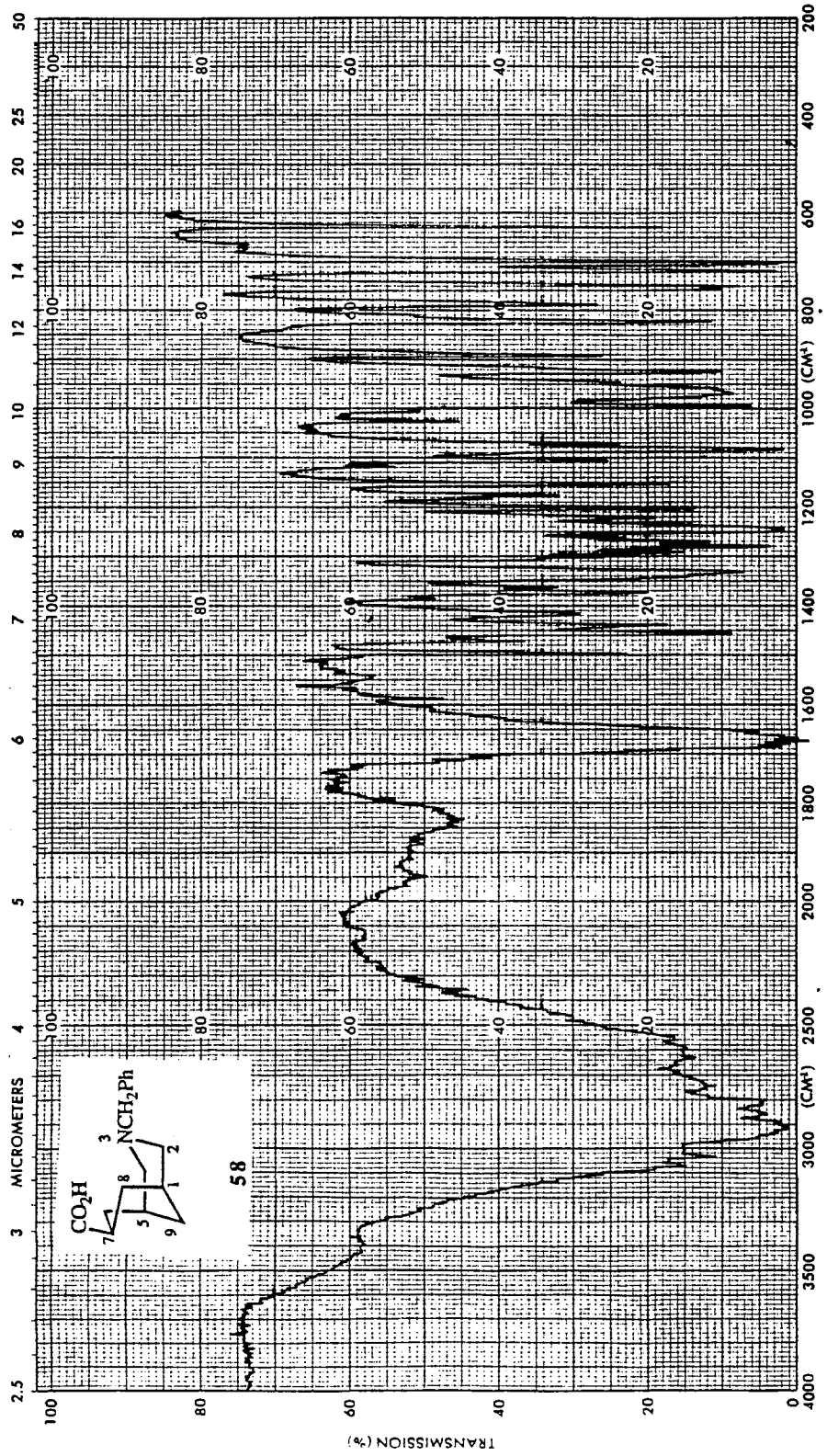
IR Spectrum of **56b**

Plate XIII



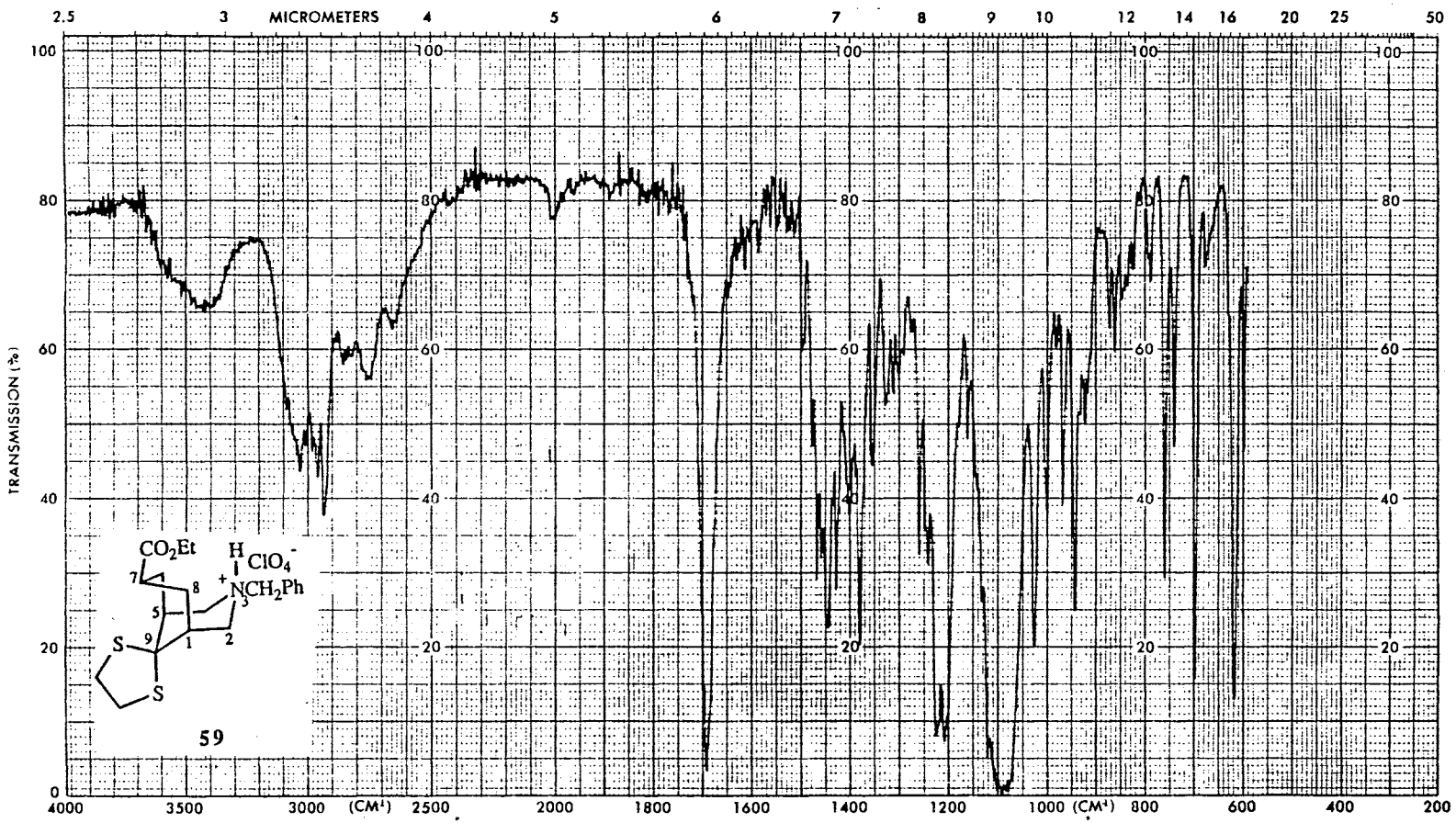
IR Spectrum of **57**

Plate XIV



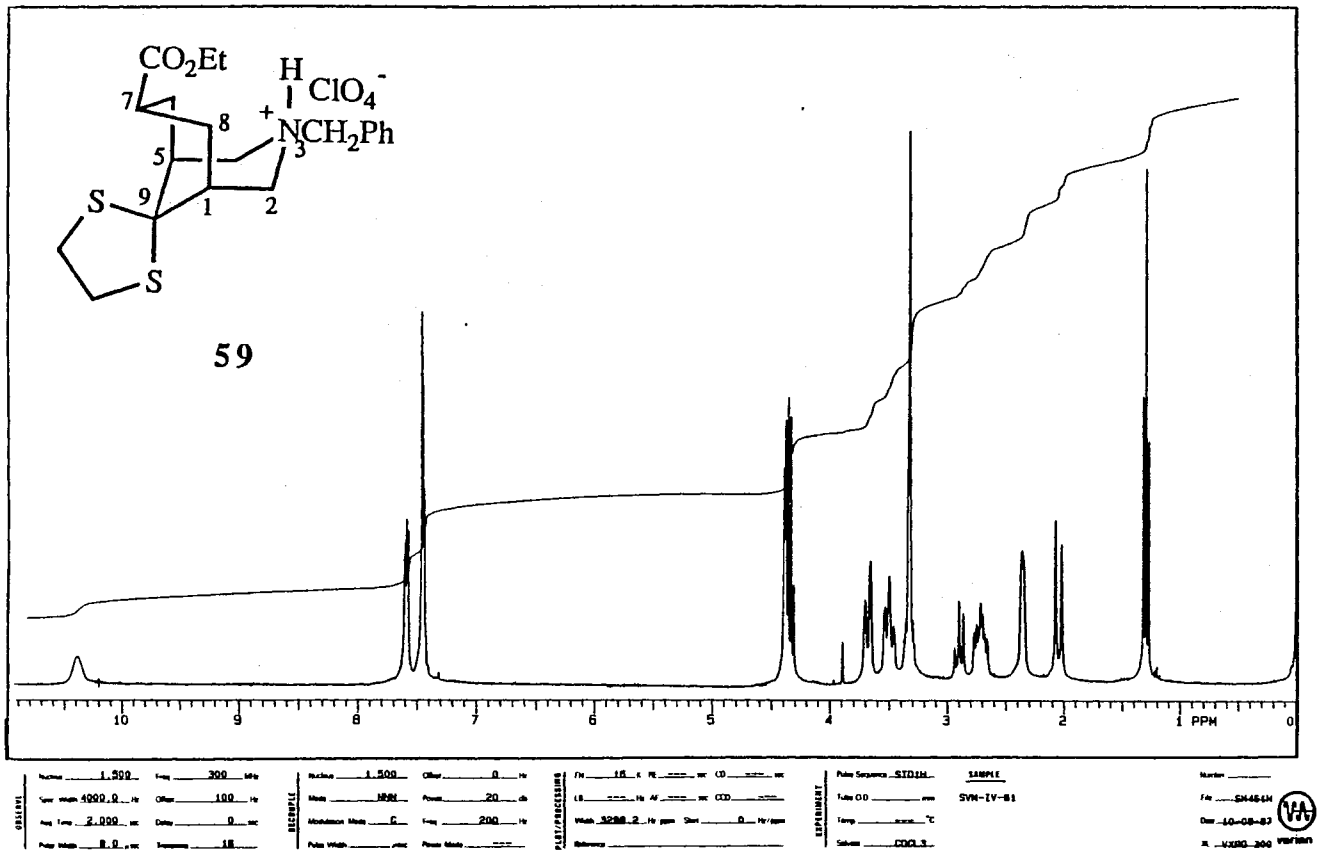
IR Spectrum of **58**

Plate XV



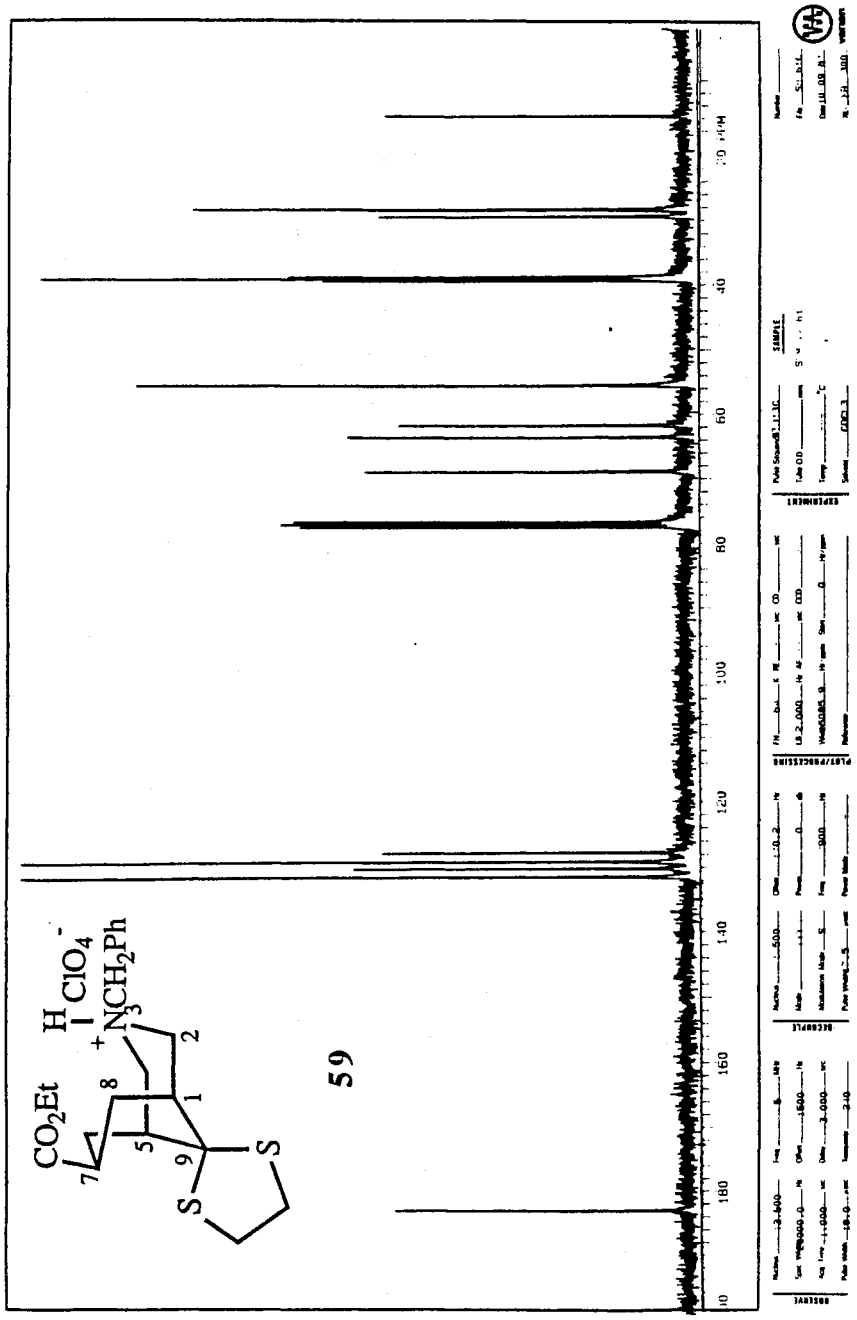
IR Spectrum of **59**

Plate XVI



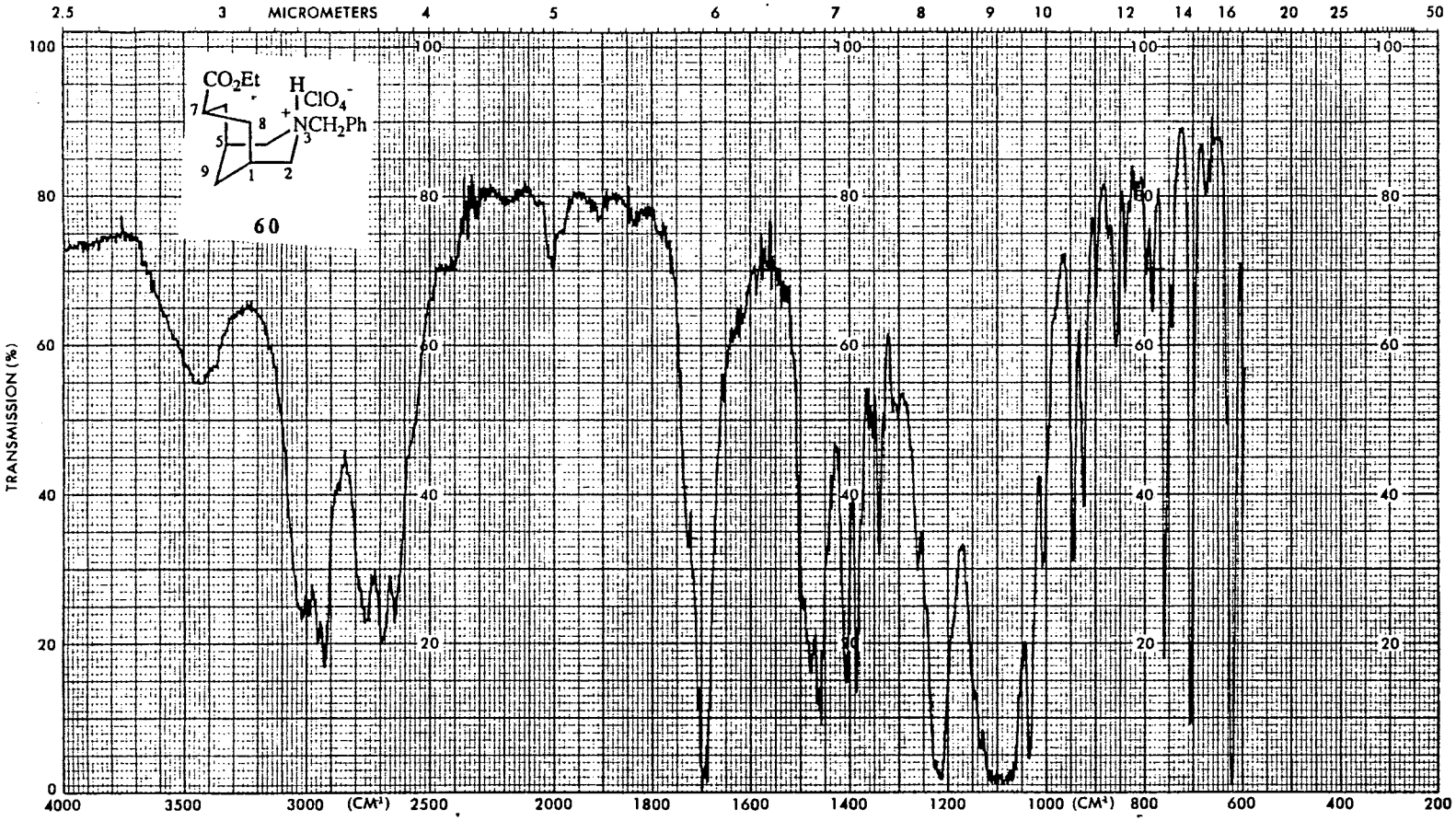
^{1}H NMR Spectrum of **59**

Plate XVII



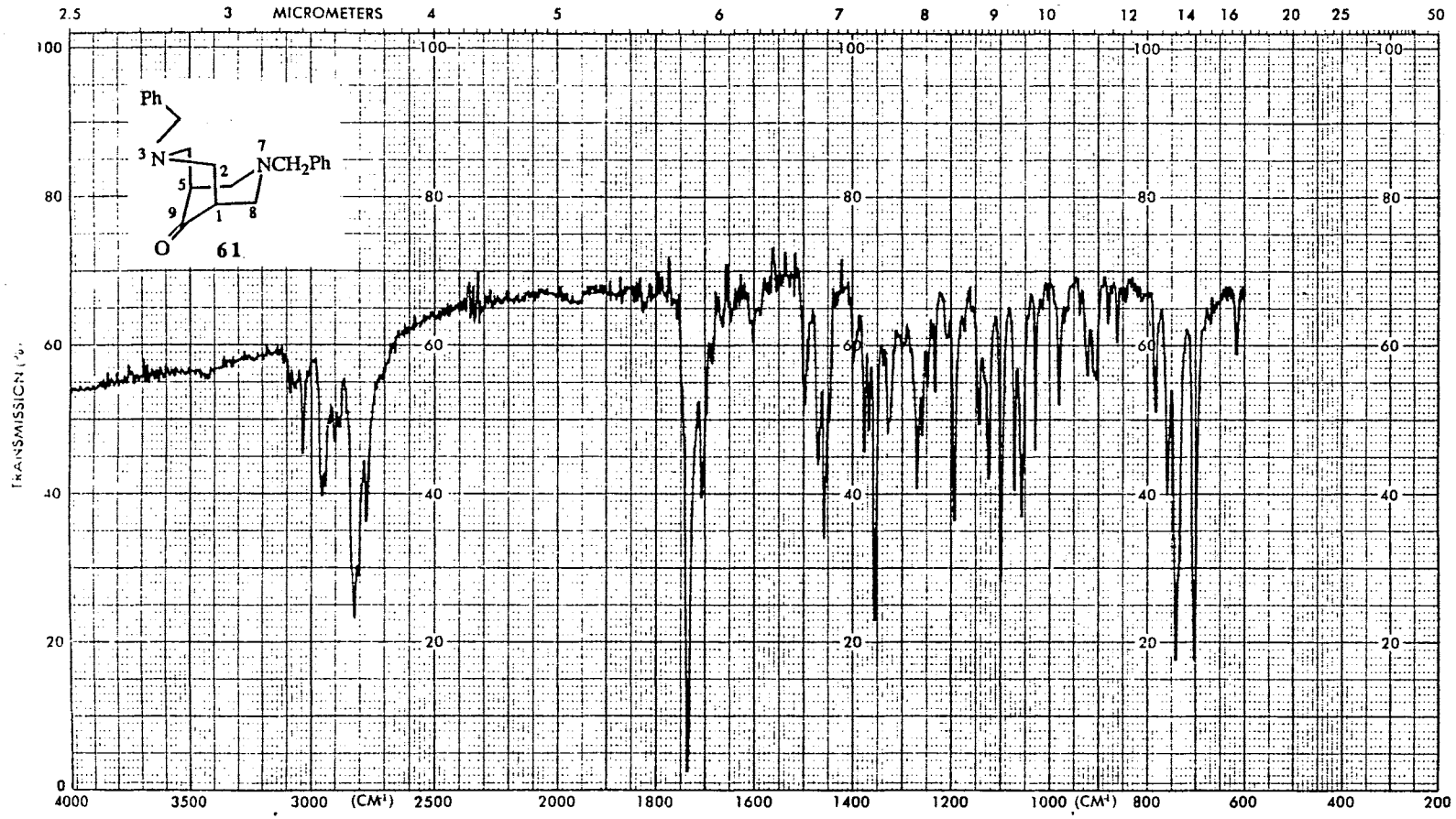
^{13}C NMR Spectrum of **59**

Plate XVIII



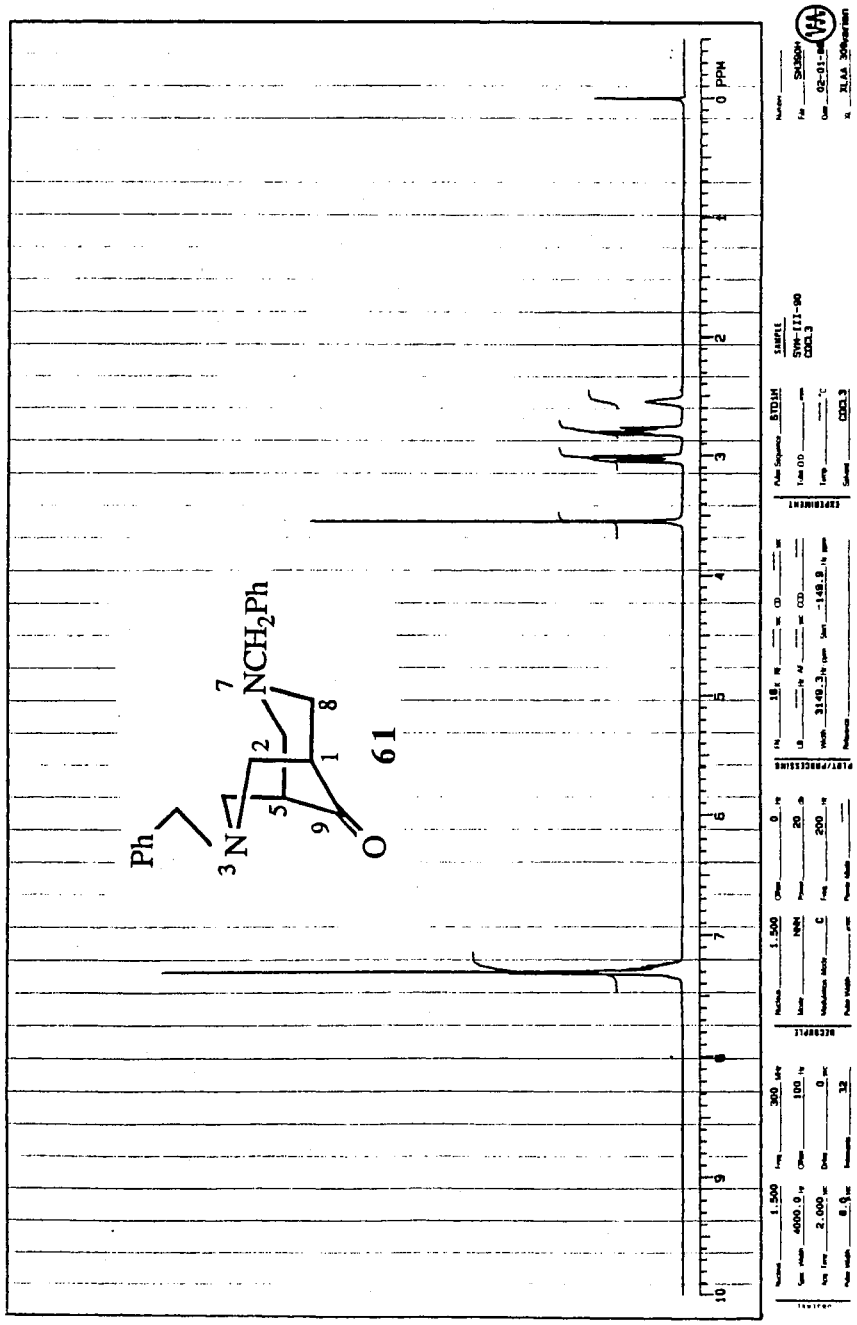
IR Spectrum of **60**

Plate XIX



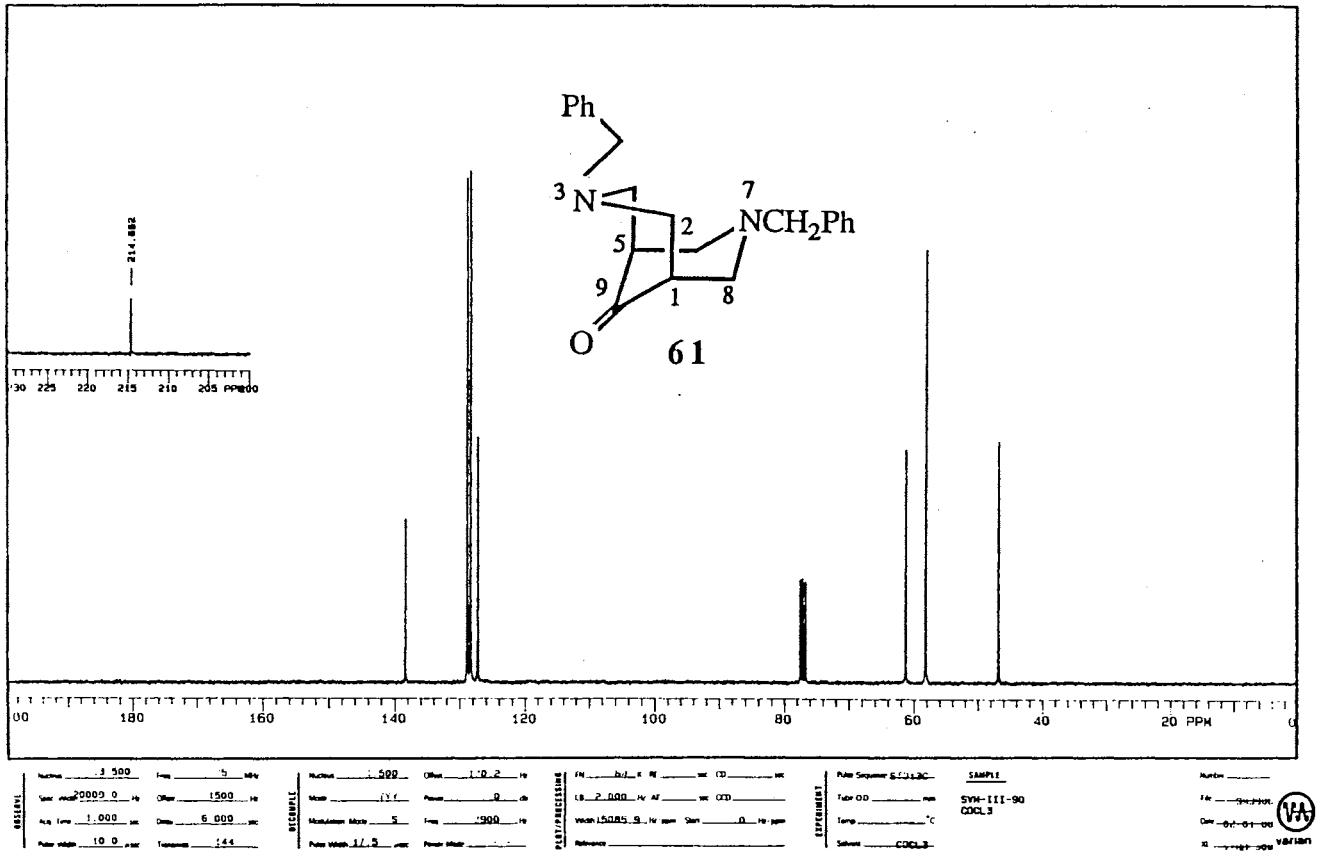
IR Spectrum of **61**

Plate XX



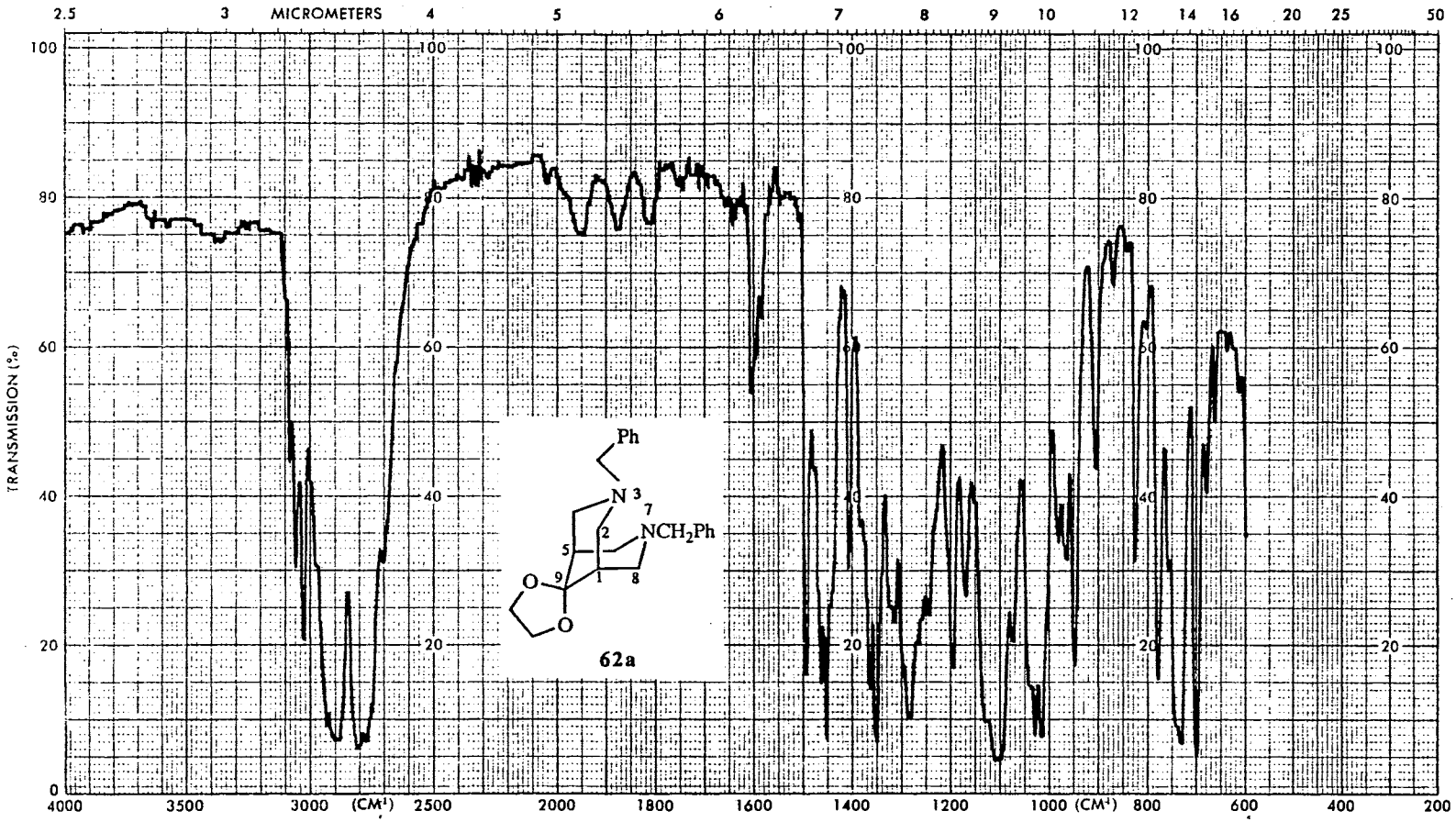
^{1}H NMR Spectrum of **61**

Plate XXI



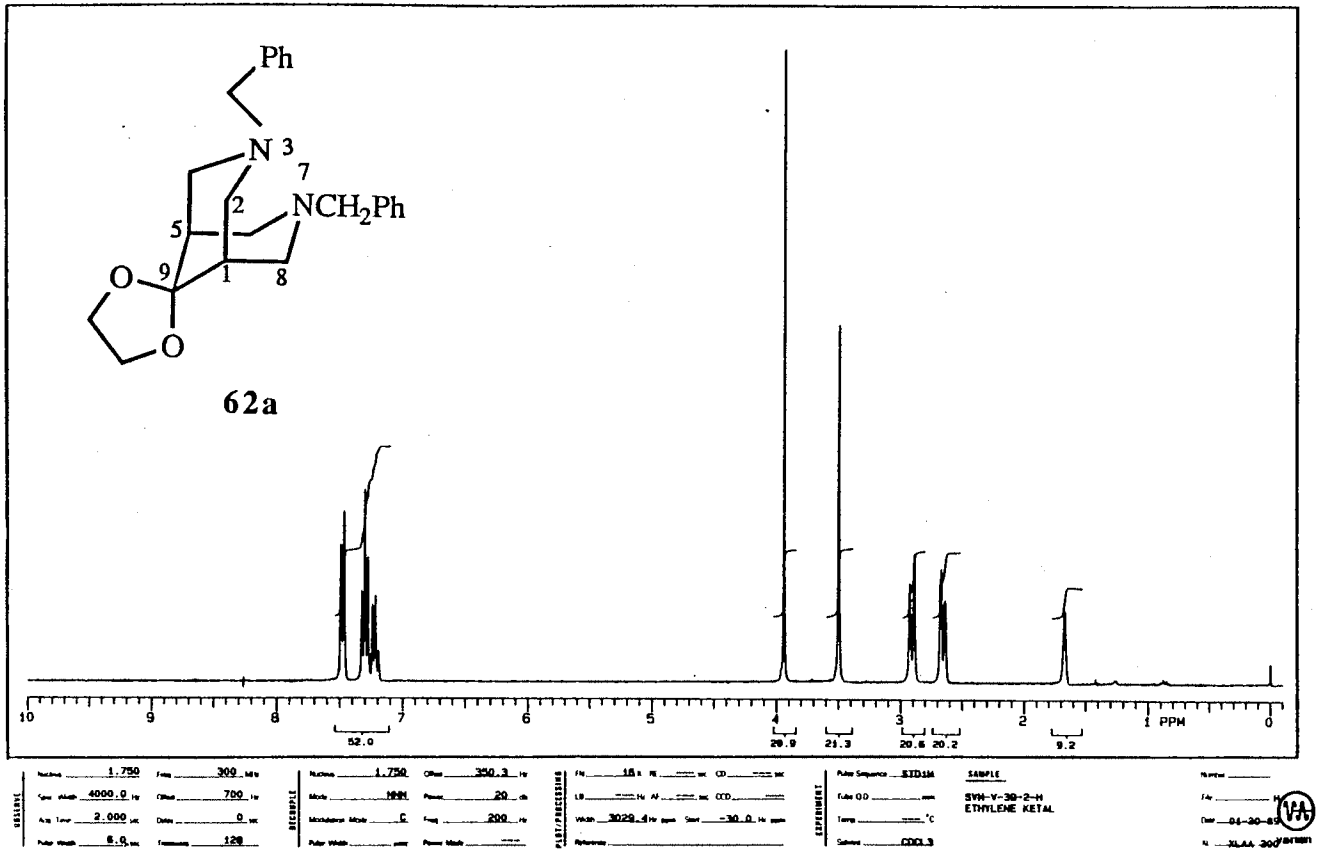
^{13}C NMR Spectrum of **61**

Plate XXII



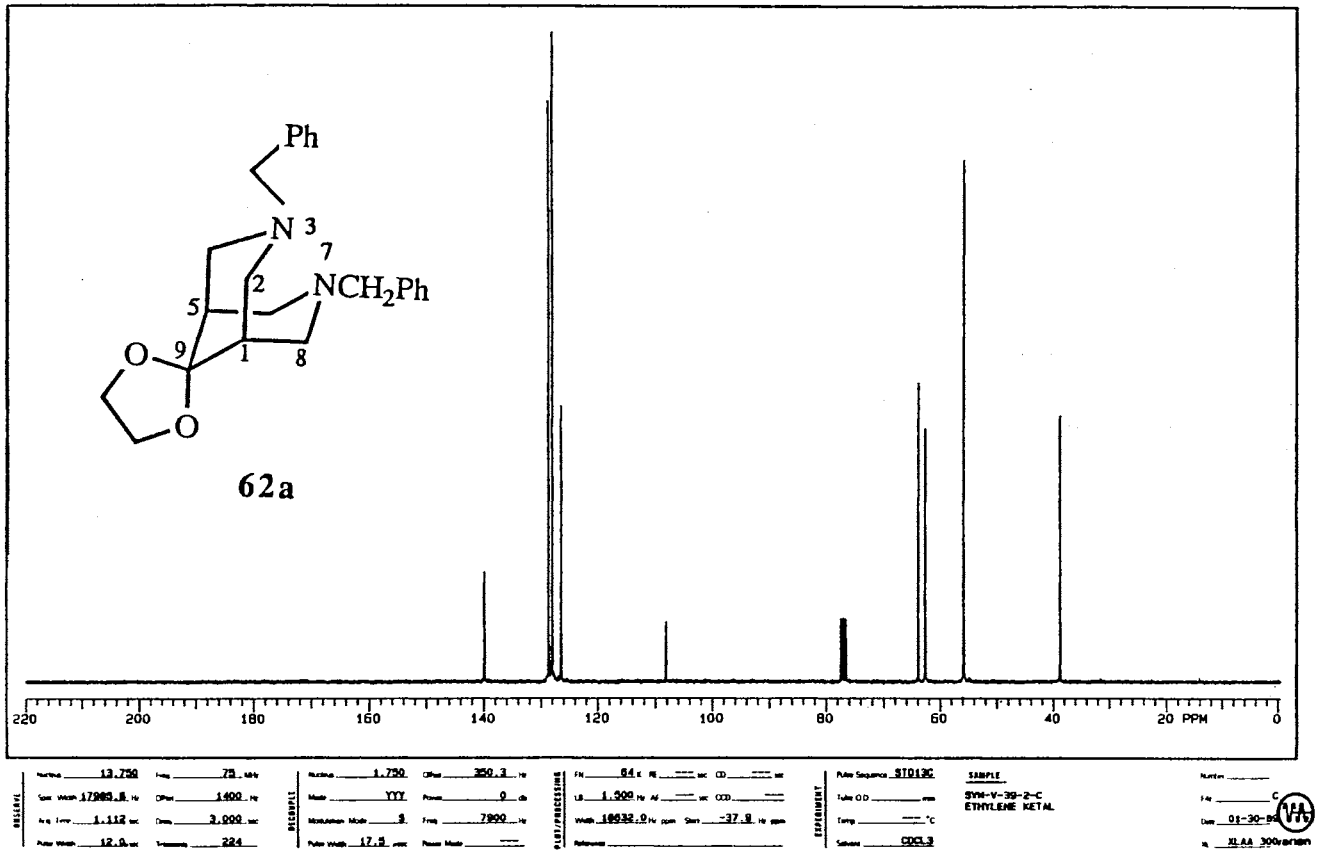
IR Spectrum of **62a**

Plate XXIII



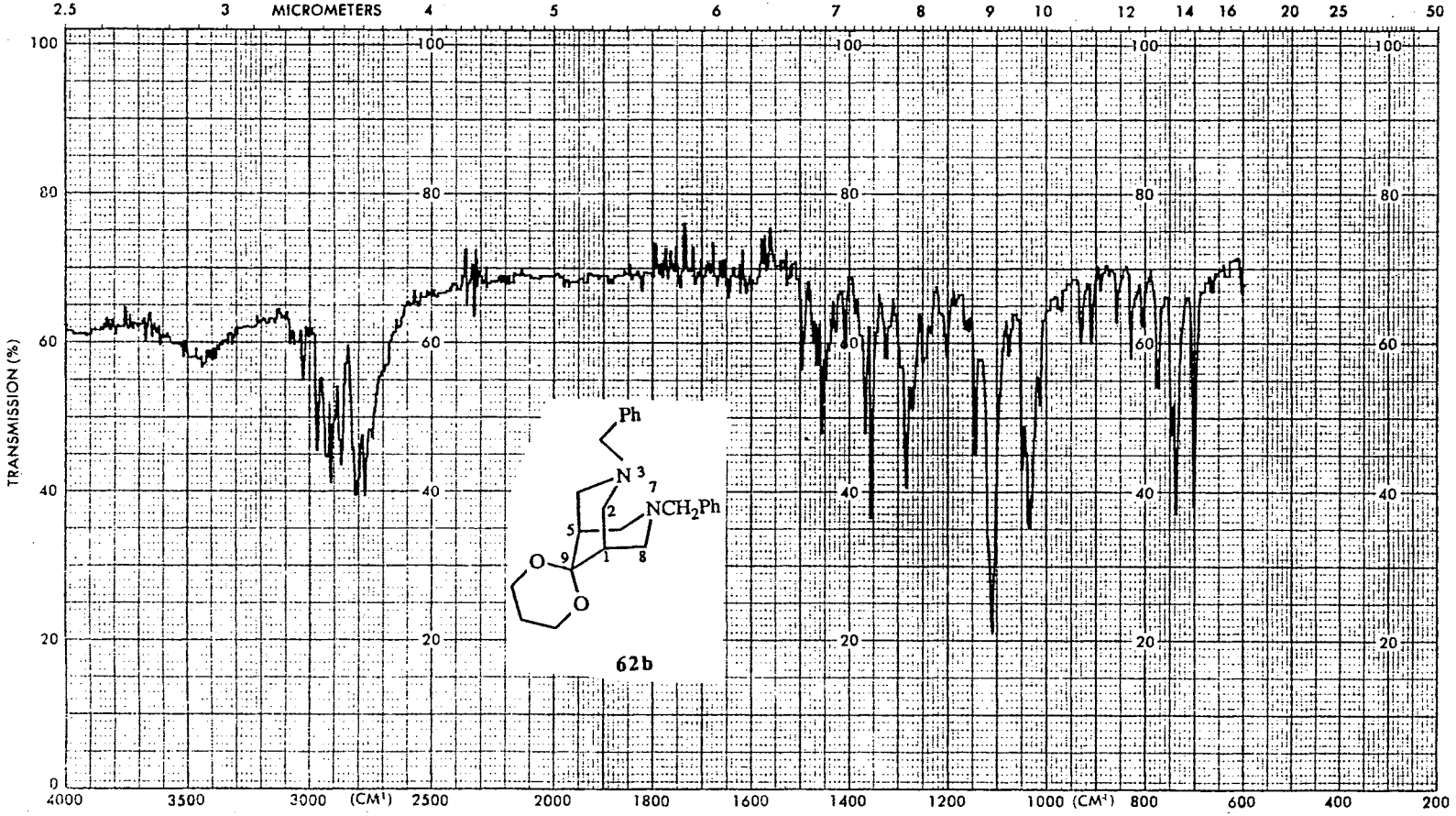
^{1}H NMR Spectrum of **62a**

Plate XXIV



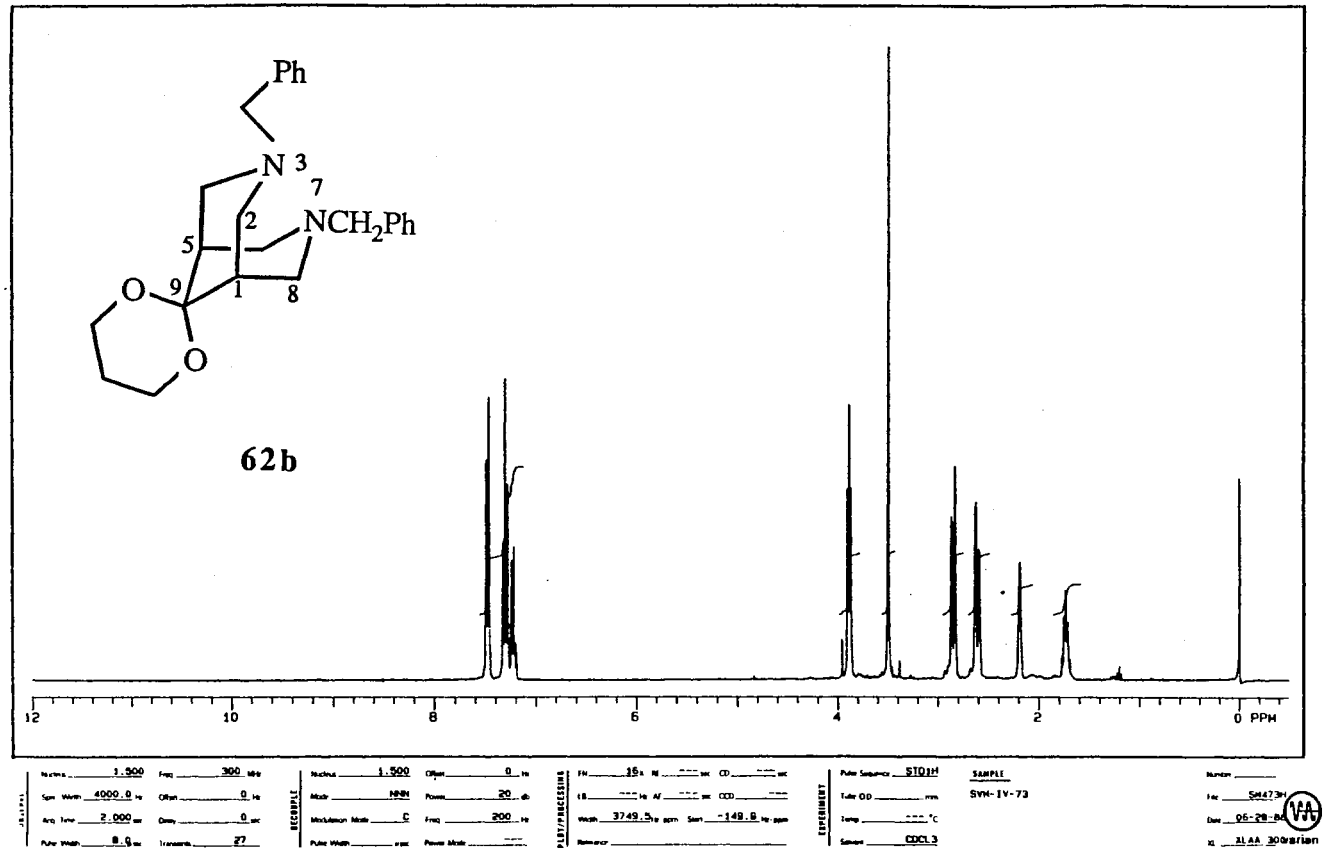
^{13}C NMR Spectrum of **62a**

Plate XXV



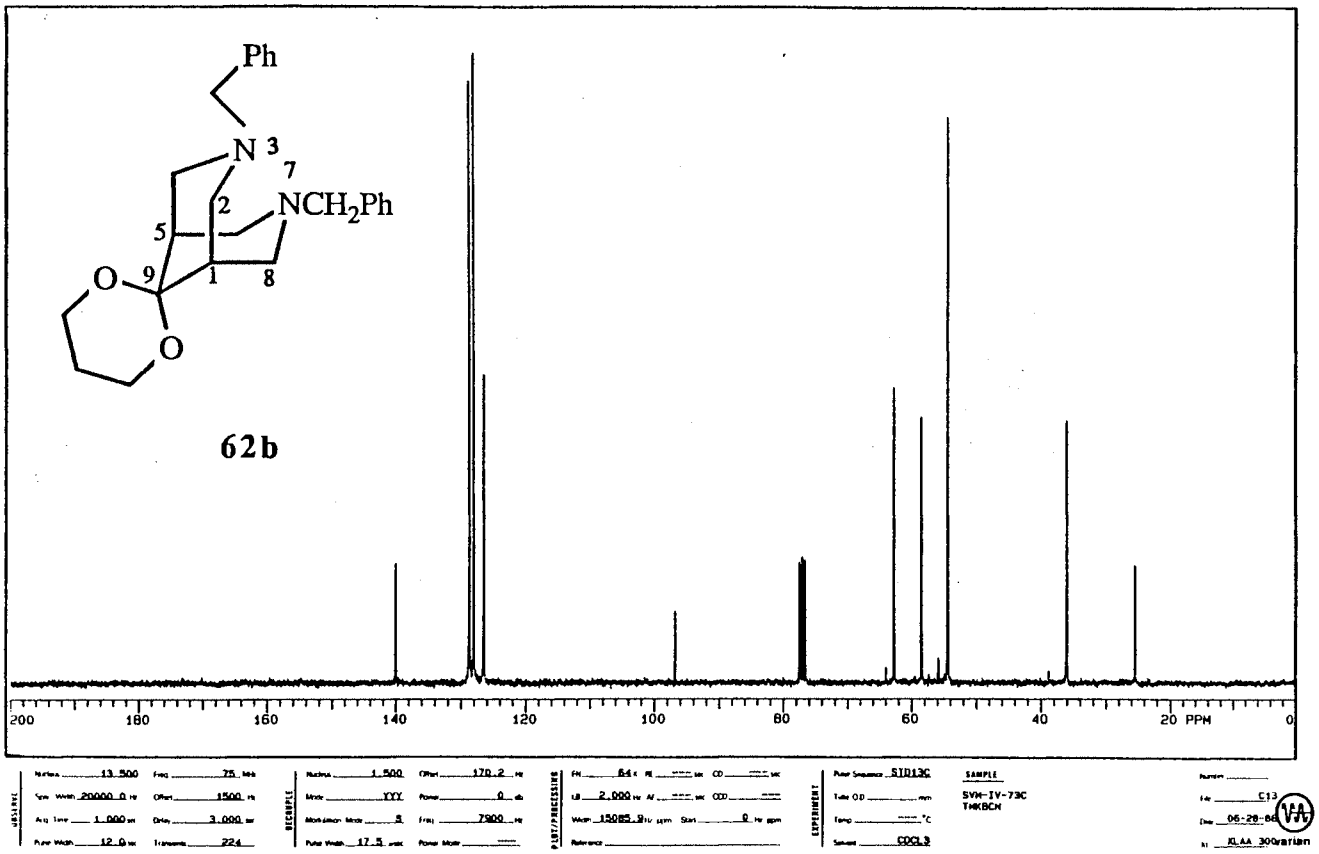
IR Spectrum of **62b**

Plate XXVI



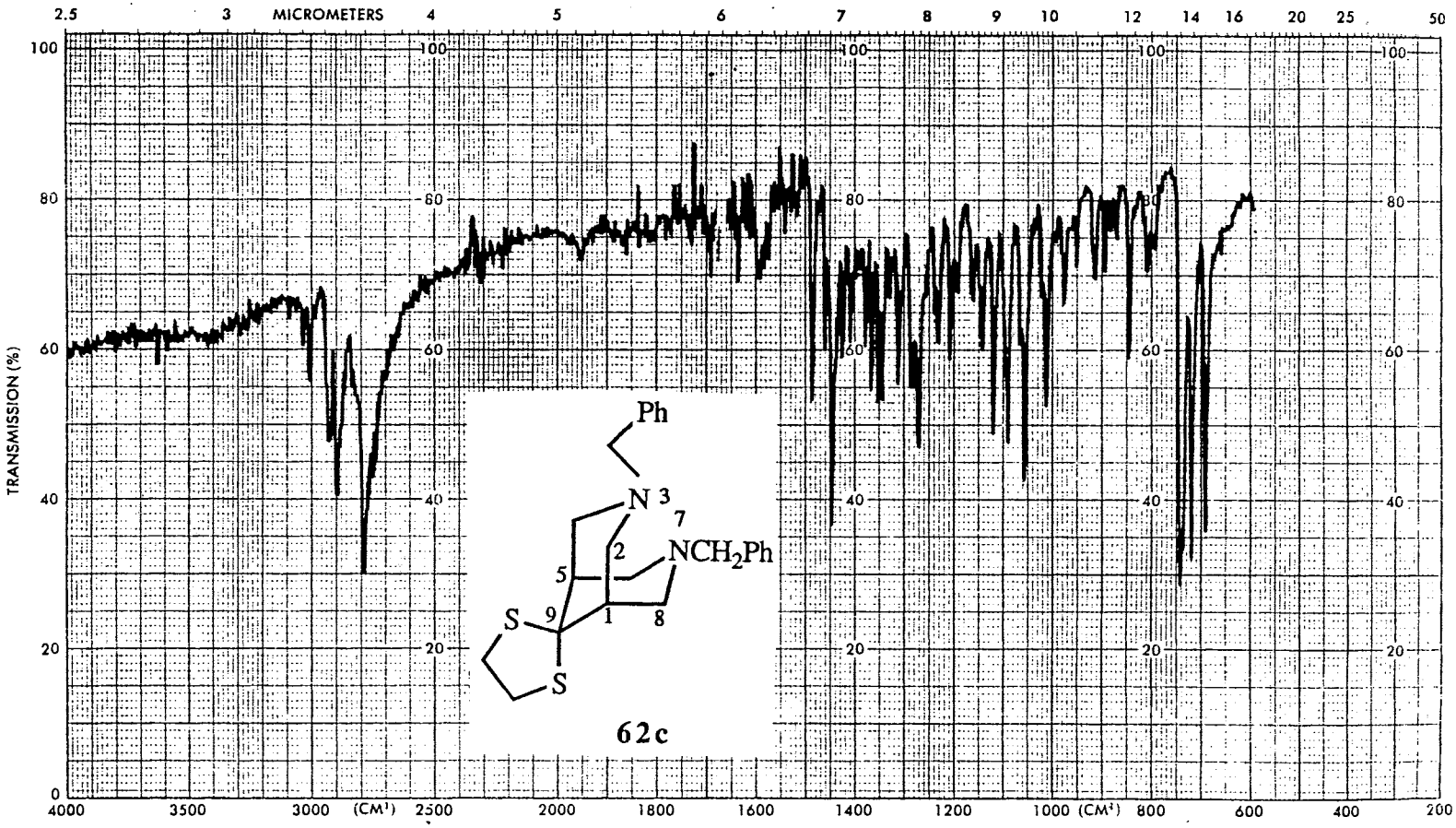
^{1}H NMR Spectrum of **62b**

Plate XXVII



^{13}C NMR Spectrum of **62b**

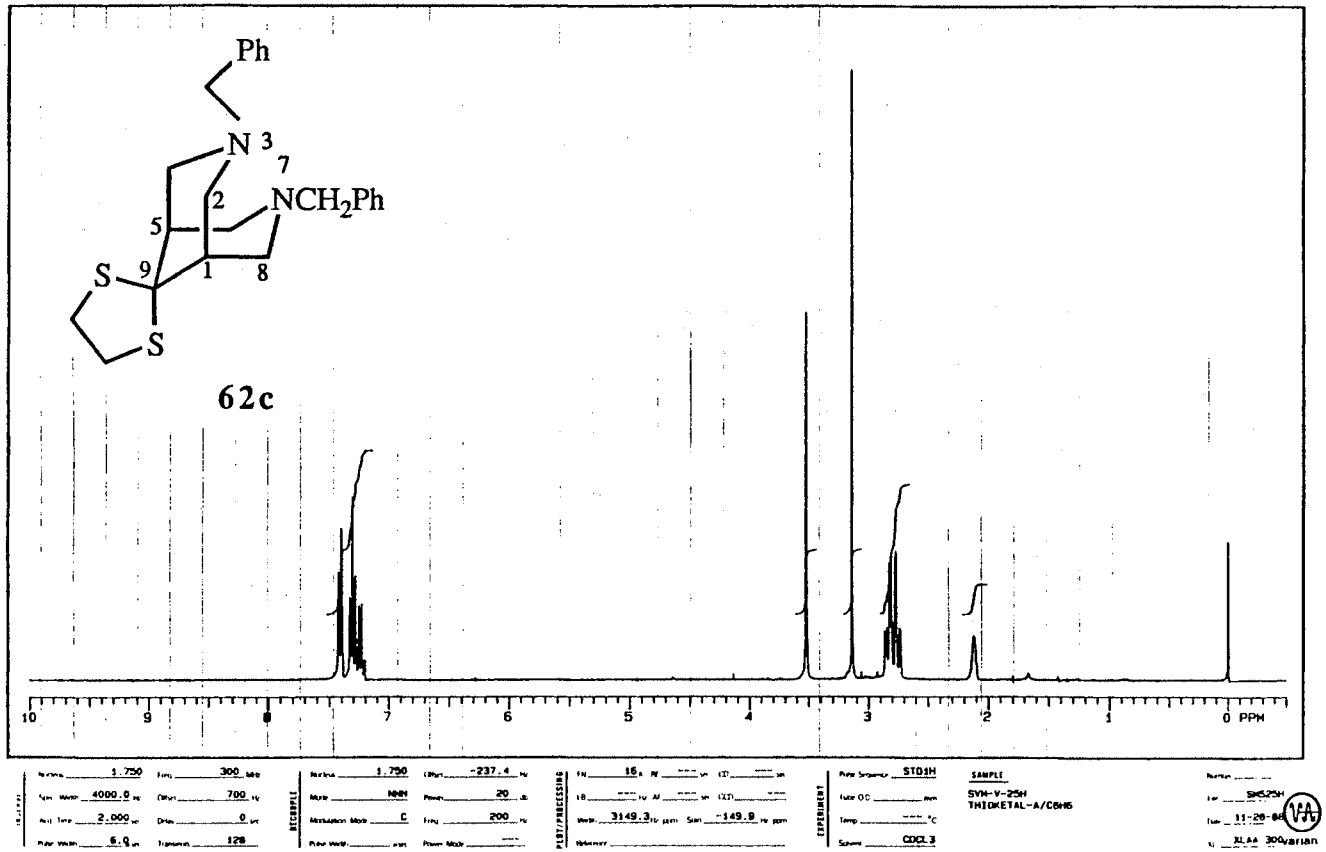
Plate XXVIII



62c

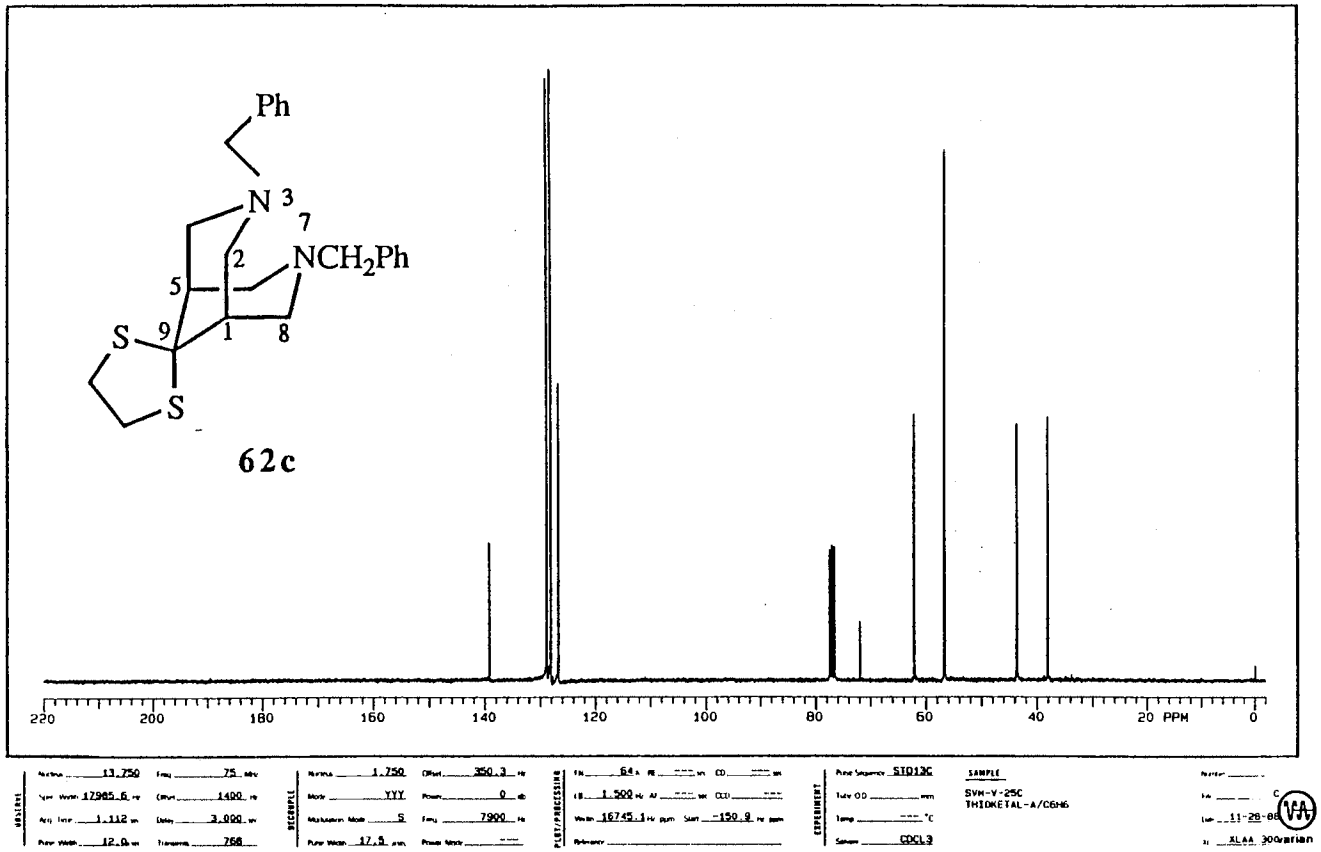
IR Spectrum of **62c**

Plate XXIX



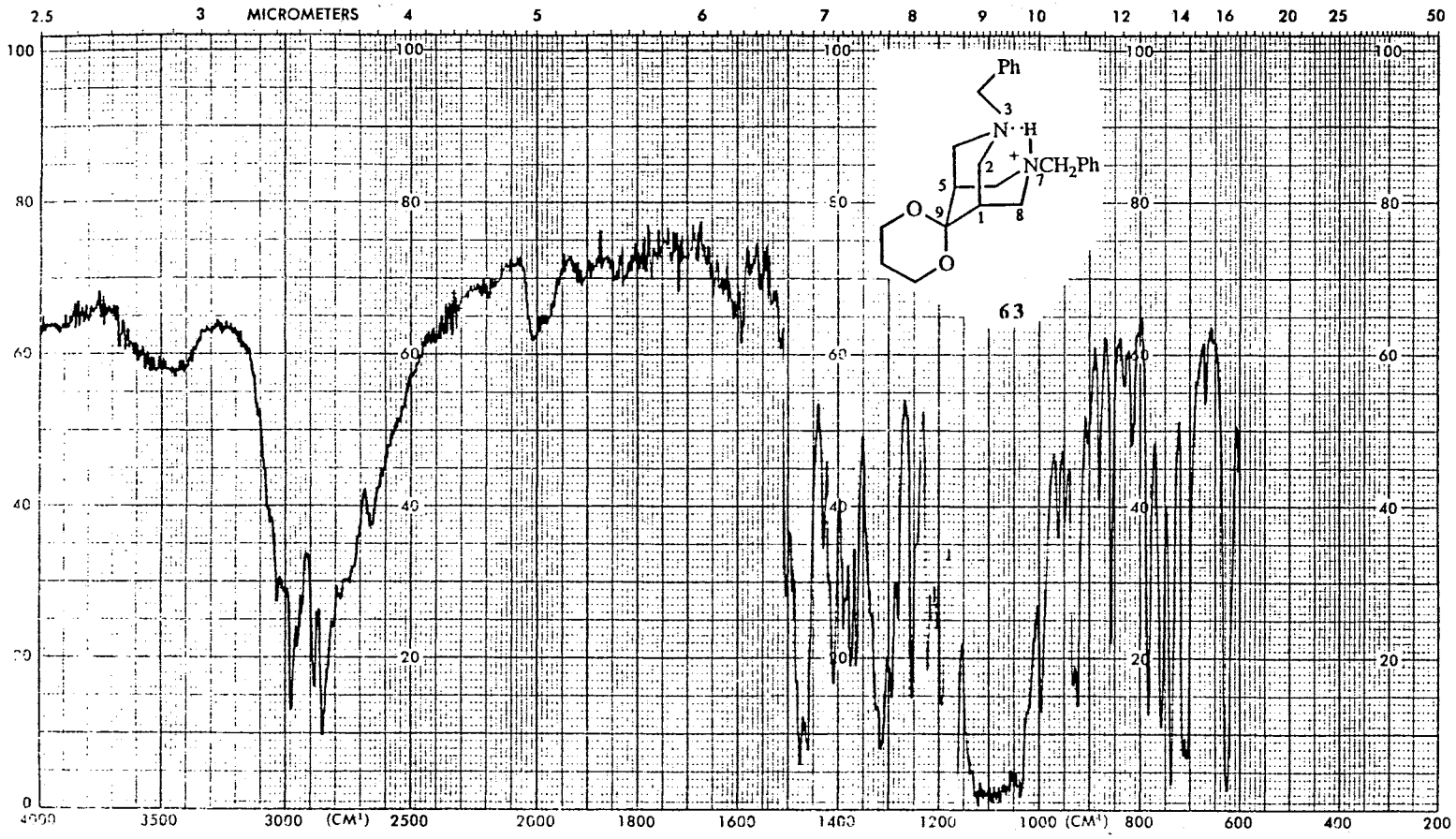
^{1}H NMR Spectrum of **62c**

Plate XXX



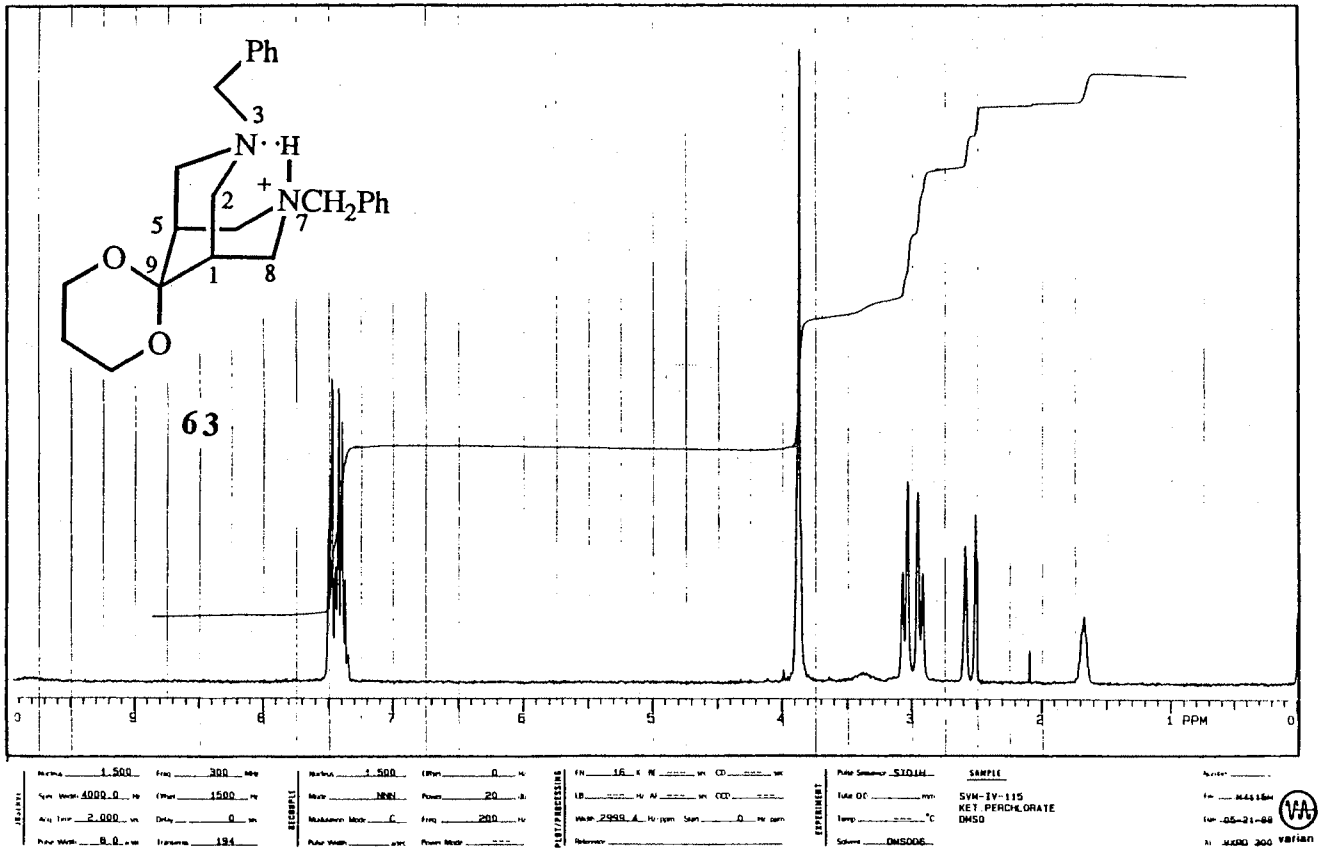
^{13}C NMR Spectrum of **62c**

Plate XXXI



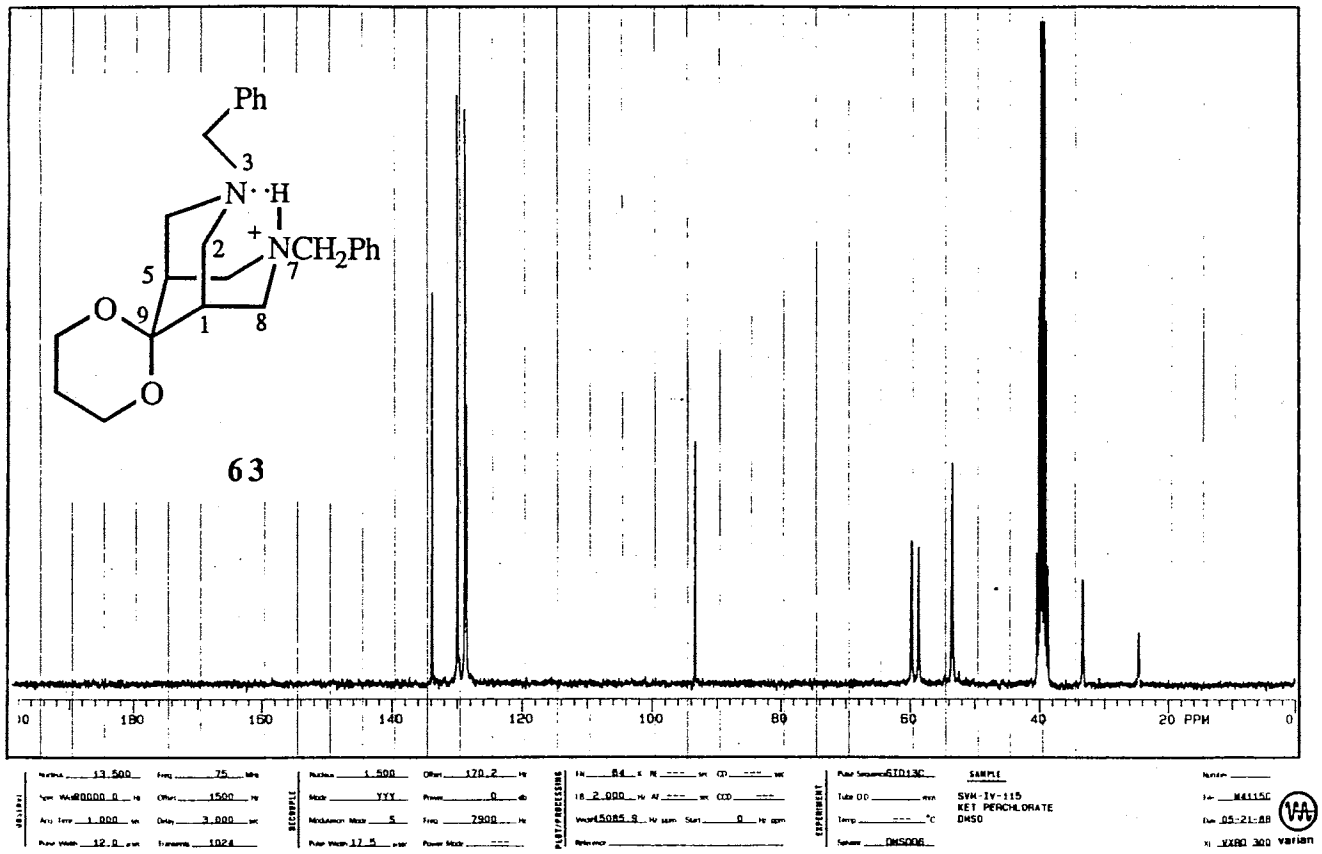
IR Spectrum of **63**

Plate XXXII



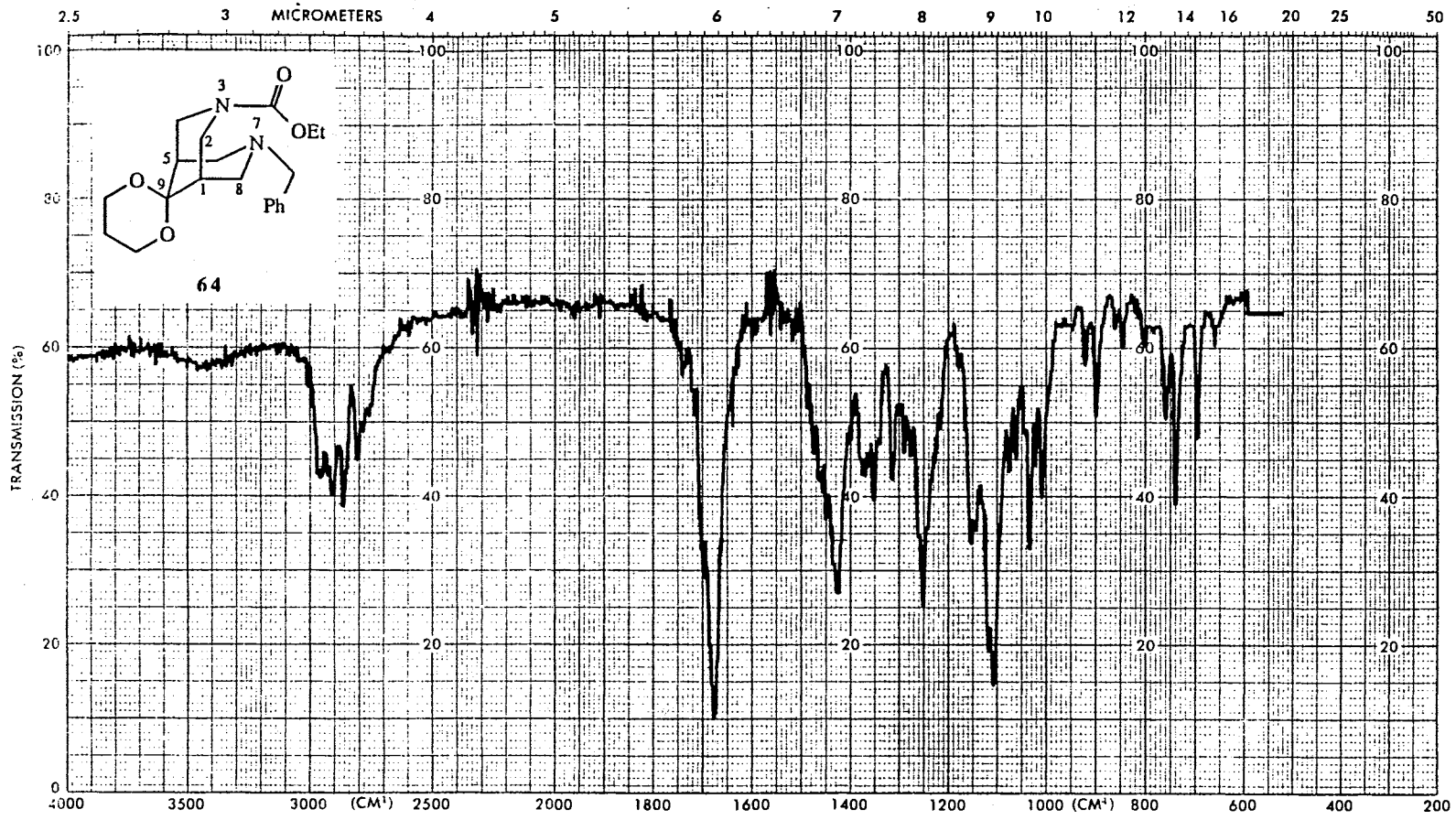
^{1}H NMR Spectrum of **63**

Plate XXXIII



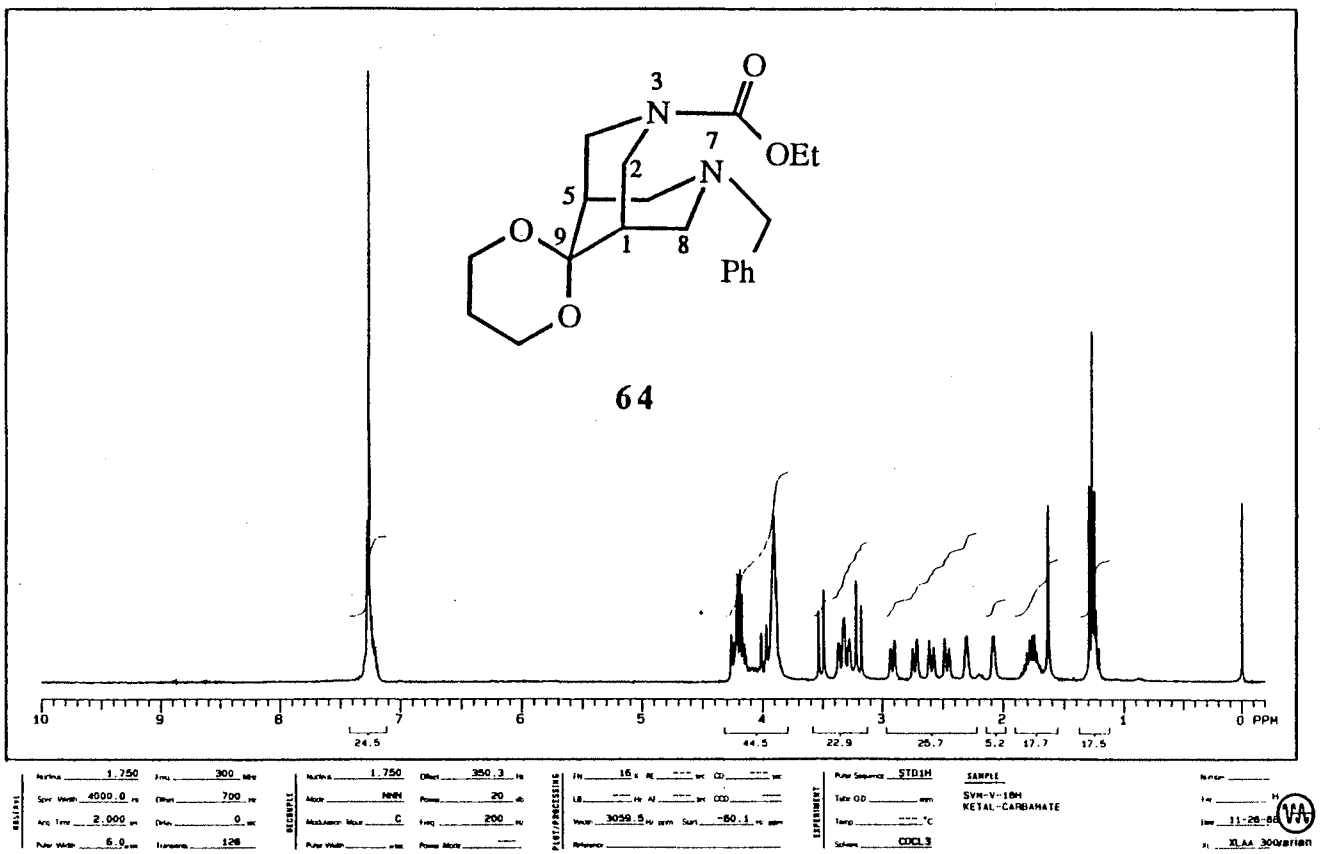
^{13}C NMR Spectrum of **63**

Plate XXXIV



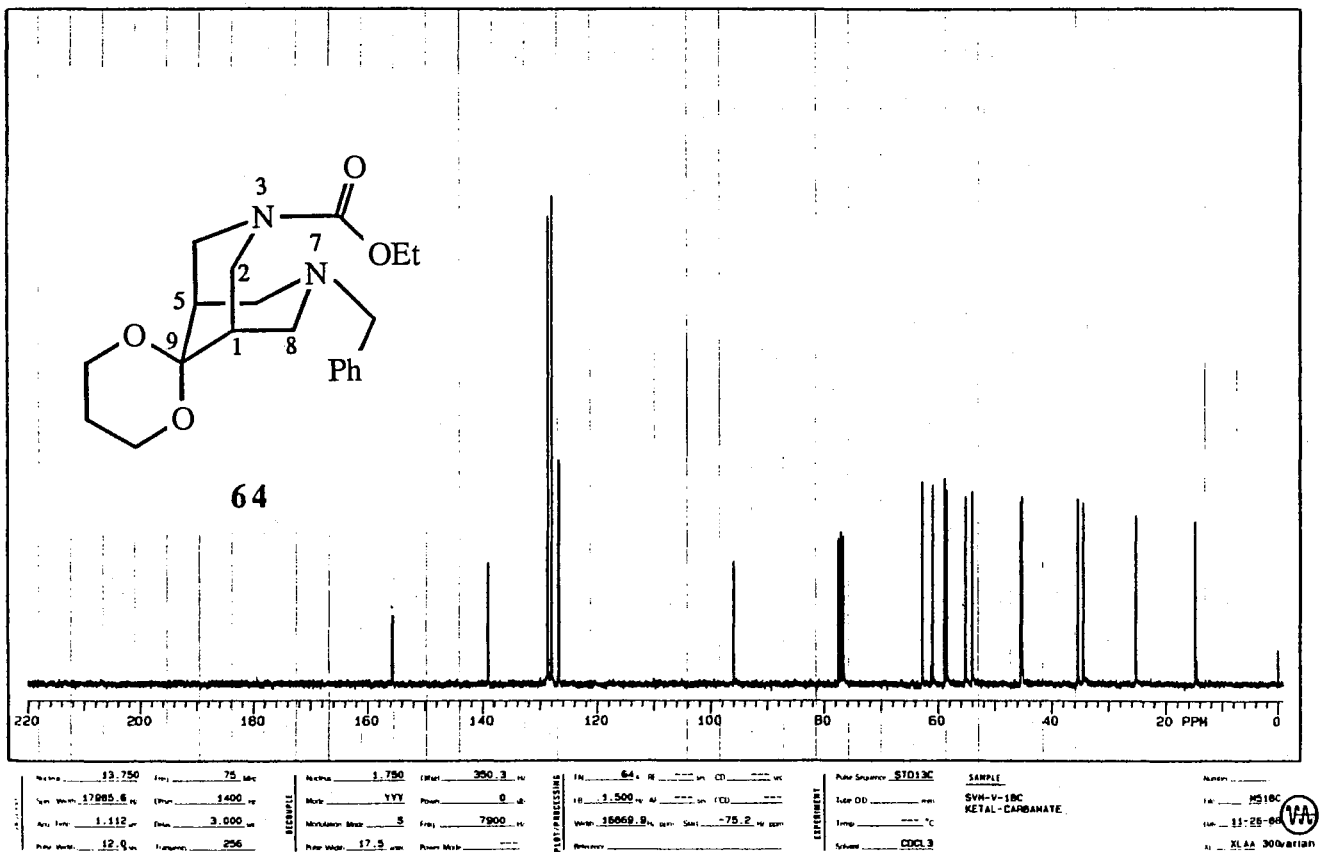
IR Spectrum of **64**

Plate XXXV



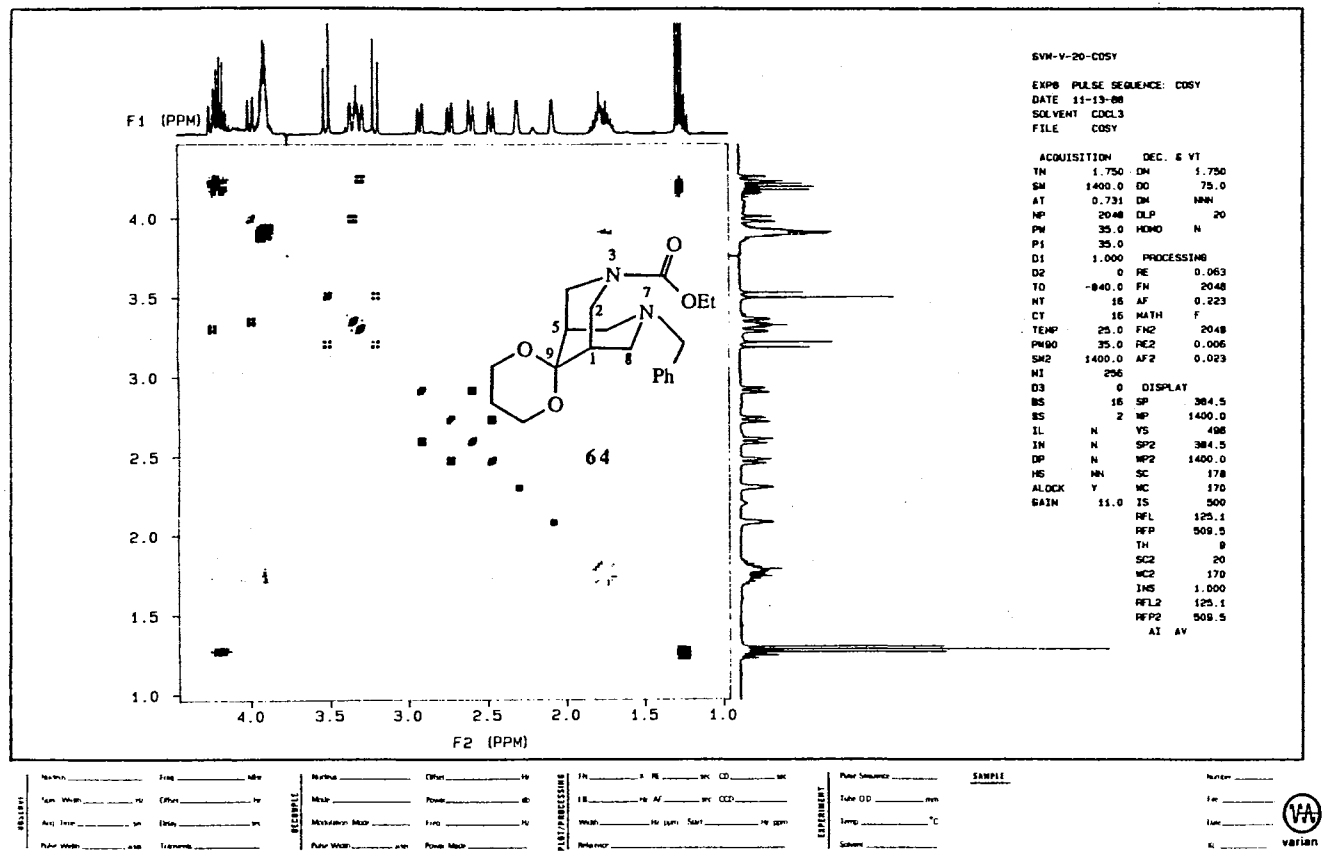
^{1}H NMR Spectrum of **64**

Plate XXXVI



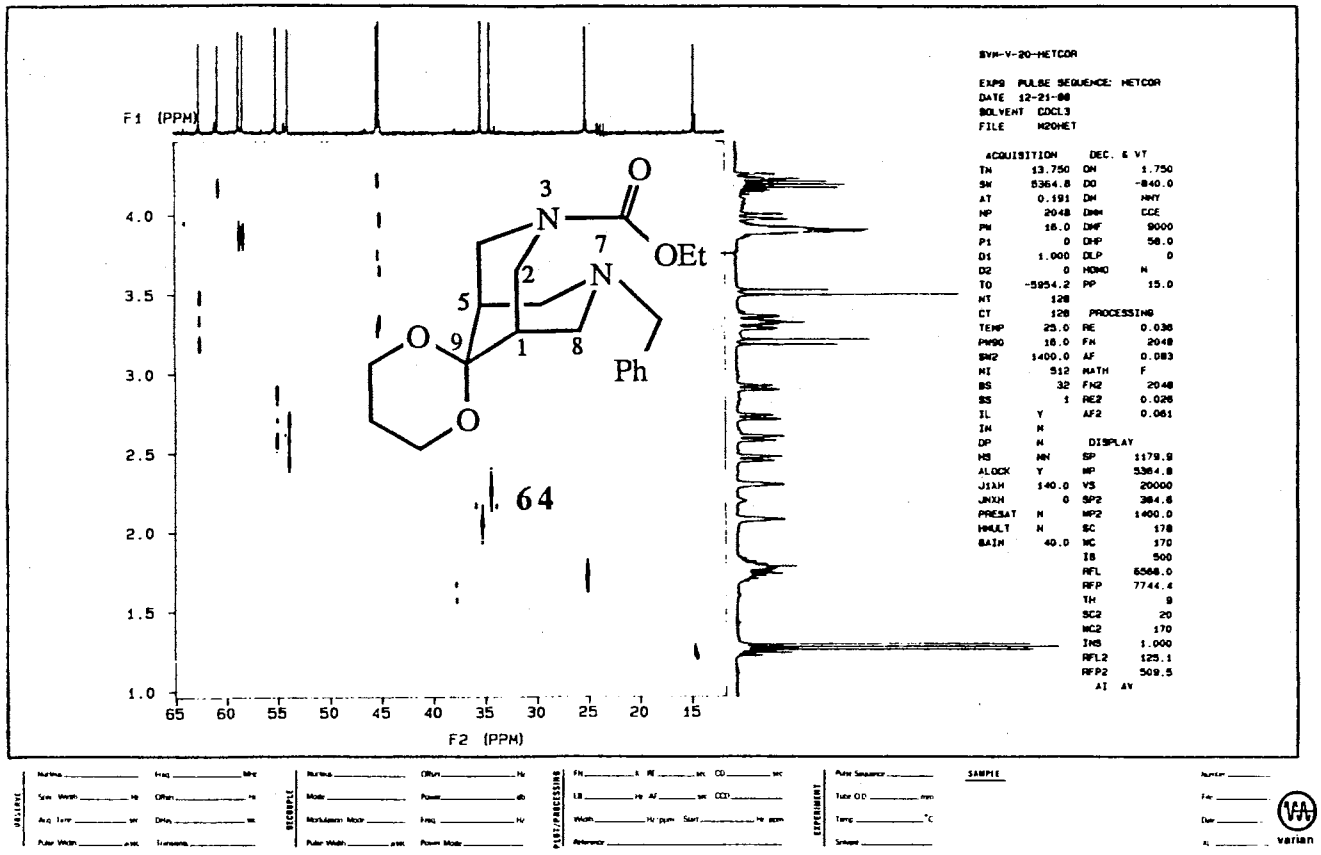
^{13}C NMR Spectrum of **64**

Plate XXXVII



COSY NMR Spectrum of **64**

Plate XXXVIII



HETCOR NMR Spectrum of **64**

BIBLIOGRAPHY

1. Arjunan, P. Doctoral Dissertation, Oklahoma State University, 1980.

2. Arjunan, P.; Berlin, K. D.; Barnes, C. L.; van der Helm, D. *J. Org. Chem.*, **1981**, *46*, 3196.

3. Bailey, B. R., Doctoral Dissertation, Oklahoma State University, 1983.

4. a. Bailey, B. R.; Berlin, K. D.; Holt, E. M.; Scherlag, B. J.; Lazzara, R.; Brachmann, J.; van der Helm, D.; Powell, D. R., Pantaleo, N. S.; Ruenitz, P. C. *J. Med. Chem.*, **1984**, *27*, 758. b. Thompson, M. D.; Smith, G. S.; Berlin, K. D.; Holt, E. M.; Scherlag, B. J.; van der Helm, D.; Muchmore, S. W.; Fidelis, K. A. *J. Med. Chem.*, **1987**, *30*, 780. c. Smith, G. S.; Thompson, M. D.; Berlin, K. D.; Holt, E. M.; Scherlag, B. J.; Patterson, E.; Lazarra, R. *Eur. J. Med. Chem.*, **1989**, in press.

5. Bailey, B. R.; Berlin, K. D.; Powell, D. R.; van der Helm, D. *Phosphorus and Sulfur*, **1984**, *21*, 121.

6. Binnig, F.; Raschack, M.; Treiber, H.-J.; Knoll, A. G. Chemische Fabriken, Germany, U.S. Patent 3,962,449, 1976; *Chem. Abstr.*, **1976**, *84*, 150675x.

7. a. Bohlmann, F.; Schumann, D.; Arndt, C. *Tetrahedron Letters*, **1965**, 2705. b. Wiewiorsky, M.; Edwards, O. E.; Bratek-Wiewiorowska, M. D. *Can. J. Chem.*, **1967**, *45*, 1447.

8. Brown, W. A. C.; Martin, J.; Sim, G. A. *J. Chem. Soc.*, **1965**, 1844.

9. a. Buchanon, G. L. in *Topics in Carbocyclic Chemistry*, Vol. 1, D. Lloyd, Ed.; Logos, Londo, 1969, pp 199. b. Sadtler Research Laboratories, *Nuclear Magenetic Resonance, Standard NMR Spectra*, Philadelphia, Vol. 1, 1966 (no. 152) and Vol. 18, 1971 (No. 11417).

10. Chung, E. K., Ed., *Principles of Cardiac Arrhythmias*, 2nd ed.; Williams and Wilkins, Baltimore, Maryland, 1977.

11. Corday, E.; Swan, H. J. C., Eds. *Myocardial Infarction: New Perspectives in Diagnosis and Management*, Williams and Wilkins, Baltimore, Maryland, 1973.

12. Danishefsky, S.; Cavanaugh, R. *J. Org. Chem.*, **1968**, 2959.

13. a. Diederich, K.-W.; Beeck, J. *Z. Kyeislaufforsch*, **1970**, *59*, 736, *Biol. Abstr.*, **1971**, *52*, 56383. b. Seibner, H. *Duet. Med. Wochenschr.*, **1970**, *95*, 2203; *Biol. Abstr.*, **1971**, *52*, 50974.

14. Douglass, J. E.; Ratliff, T. B. *J. Org. Chem.*, **1968**, *33*, 355.

15. Eisenberg, M. S.; Bergner, L.; Hallstrom, A. P.; Cummins, R. O. *Scientific American*, **1986**, *254*, 37.

16. Ferris, A. F. *J. Org. Chem.*, **1955**, *20*, 780.

17. Fowler, N. O., Ed., *Cardiac Arrhythmias: Diagnosis and Treatment*, Harpers and Row Publishers, Inc., Hagerstown, Maryland, 1977.

18. Henry, T. A. *The Plant Alkaloids*, 4th Edition, The Blackiston Company, Philadelphia, 1949.

19. a. Jeyaraman, R.; Avila, S. *Chem. Rev.*, **1981**, *81*, 149. b. Peters, J. A. *Synthesis*, **1979**, 321. c. Zefirov, N. S. *Russ. Chem. Rev. (Engl. Transl.)*, **1975**, *44*, 196.

20. a. Margulies, E., Ed. *Myocardial Infarction and Cardiac Death*, Academic Press, New York, 1983. b. Sander, H. J. *Chem. Eng. News*, **1982**, *60*, 26.

21. a. Mastryukov, V. S.; Popik, M. V.; Dorofeeva, O. V.; Golubinskii, A. V.; Vilkov, L. V.; Belikova, N. A.; Allinger, N. L. *Tetrahedron Letters*, **1979**, 4339. b. Mastryukov, V. S.; Osina, E. L.; Dorofeeva, O. V.; Popik, M. V.; Vilkov, L. V.; Belikova, N. A. *J. Mol. Struct.*, **1979**, *52*, 211. c. Mastryukov, V. S.; Popik, M. V.; Dorofeeva, O. V.; Golubinskii, A. V.; Vilkov, L. V.; Belikova, N. A.; Allinger, N. L. *J. Am. Chem. Soc.*, **1981**, *103*, 1333.

22. McEuen, J. M.; Nelson, R. P.; Lawton, R. G. *J. Org. Chem.*, **1970**, *35*, 690.

23. Nador, K.; Gabor, K.; Katalin, S.; Paroczai, M.; Karpati, E.; Szporny, L. Richter Gedeon Vegyeszeti Gyar RT, Hungary, U.S. Patent 4,451,473, 1984; *Chem. Abstr.*, **1984**, *99*, 5654v.

24. Ohta, M.; Narahashi, T. *J. Pharmacol. Exp. Ther.*, **1973**, *187*, 47.

25. Peters, J. A.; Baas, J. M. A.; van de Graaf, B.; van der Toorn, J. M.; van Bekkum, H. *Tetrahedron*, **1978**, *34*, 3313.

26. Peters, J. A.; Cranenburgh, P. E. J. P.-V.; van der Toorn, J. M.; Wortel, Th. M.; van Bekkum, H. *Tetrahedron*, **1978**, *34*, 2217.

27. Peters, J. A.; Remijnse, J. D.; van der Wiele, A.; van Bekkum, H. *Tetrahedron Letters*, **1971**, 3065.

28. Peters, J. A.; van der Toorn, J. M.; van Bekkum, H. *Tetrahedron*, **1974**, *30*, 633.

29. Peters, J. A.; van der Toorn, J. M., van Bekkum, H. *Tetrahedron*, **1975**, *31*, 2273.

30. Peters, J. A.; van der Toorn, J. M.; van Bekkum, H. *Tetrahedron*, **1977**, *33*, 349.

31. Quast, H.; Muller, B. *Chem. Ber.*, **1980**, *113*, 2959.

32. Raber, D. J.; Janks, C. M.; Johnston, M. D.; Raber, N. K. *Tetrahedron Letters*, **1980**, 677.

33. Ruenitz, P. C.; Mokler, C. M. *J. Med. Chem.*, **1977**, *20*, 1668.

34. Ruenitz, P. C.; Mokler, C. M. *J. Med. Chem.*, **1979**, *22*, 1142.

35. Ruenitz, P. C.; Smissman, E. E. *J. Heterocyclic Chem.*, **1976**, *13*, 1111.

36. Sim, G. A. *Tetrahedron*, **1983**, *39*, 1181.

37. Smissman, E. E.; Ruenitz, P. C. *J. Org. Chem.*, **1976**, *41*, 1593.

38. a. Smissman, E. E.; Ruenitz, P. C.; Weis, J. A. *J. Org. Chem.*, **1975**, *40*, 251. b. Smissman, E. E.; Ruenitz, P. C. *J. Med. Chem.*, **1976**, *19*, 184. c. Ruenitz, P. C.; Smissman, E. E. *J. Org. Chem.*, **1977**, *42*, 937.

39. Smith, G. S., Doctoral Dissertation, Oklahoma State University, 1986.

40. Smith-Verdier, P.; Florencio, F.; Garcia-Blanco, S. *Acta Cryst.*, **1983**, *C39*, 101.

41. a. Speckamp, W. N.; Dijkink, J.; Dekkers, A. W. J. D.; Huisman, H. O. *Tetrahedron*, **1971**, *27*, 3143. b. Bok, Th. R.; Speckamp, W. N. *Tetrahedron*, **1979**, *35*, 267.

42. Speckamp, W. N.; Dijkink, J.; Huisman, H. O. *J. C. S. Chem. Comm.*, **1970**, 196.

43. a. Stout, D M.; Matier, W. L.; Barcelon-Yang, C.; Reynolds, R. D.; Brown, B. S. *J. Med. Chem.*, **1985**, *28*, 295. b. Stout, D. M.; Matier, W. L.; Barcelon-Yang, C.; Reynolds, R. D.; Brown, B. S. *J. Med. Chem.*, **1984**, *27*, 1347.

44. Takeuchi, Y.; Scheiber, P.; Takada, K. *J. C. S. Chem. Comm.*, **1980**, 403.

45. Thompson, M. D., Doctoral Dissertation, Oklahoma State University, 1985.

46. van Zwieten, P. A.; Schonbaum, E., Eds., *Newer Antiarrhythmic Agents*, In *Prog. Pharmacol.*; Fischer, New York, 1978, Vol. 2, No. 1.

47. Wink, M.; Hartmann, T.; Schiebel, H.-M.; Witte, L. *Planta Med.*, **1980**, *38*, 238; *Biol. Abstr.*, **1980**, *70*, 32302.

48. Zefirov, N. S.; Rogozina, S. V. *Russ. Chem. Rev. (Engl. Transl.)*, **1973**, *42*, 190.

PART II. ^{17}O NMR ANALYSIS OF SUBSTITUTED 1-HETERA-4-CYCLOHEXANONES

CHAPTER I

HISTORICAL

The application of ^{17}O NMR spectroscopy has received considerable attention[13,39,40,43] during this decade as a method for structure and conformation elucidation and as a probe for assessing electronic effects in molecules. Although the first ^{17}O NMR signal was observed as early as in 1951,[1] progress in ^{17}O NMR spectroscopy was very slow until the early sixties.[23,74] Christ and Diehl[14-16] published pioneering work in the field of ^{17}O NMR spectroscopy. For example, ^{17}O chemical shifts were reported for a number of simple alcohols, ethers, carboxylic acids, esters, acid anhydrides, acid halides, aldehydes, ketones, acetals, ketals and nitro compounds.[36-38] Following this early work, little progress occurred in the field until the mid 1970s in terms of applicability to organic chemistry.[19-21] However, a larger number of inorganic compounds were tabulated in a review in 1978.[42]

Oxygen is the earth's most abundant element and forms compounds with all elements except He, Ne and Ar; therefore, the structure of oxygen-containing compounds is a subject of widespread significance.[42] Compared to ^{1}H, ^{13}C, ^{19}F, ^{31}P, ^{15}N and ^{11}B, ^{17}O NMR has received little attention as a structural probe. This void is not surprising since ^{17}O has both a low natural abundance and an appreciable quadrupole moment, making it difficult to observe.[42] However, recent developments in pulsed-FT NMR instrumentation and the availability of ^{17}O enriched materials have alleviated these difficulties. As a result, there has been a fast growing interest in ^{17}O NMR spectroscopy as a structure diagnostic tool in organic chemistry.[13,39,40,43] The following discussion will include an evaluation of the scope and limitations of ^{17}O NMR spectroscopy and the methods employed to

circumvent experimental problems. A comparison will be made of ^{17}O NMR spectroscopy with ^{1}H and ^{13}C NMR spectroscopy in relation to natural abundance, sensitivity, relaxation phenomenon, the influence of groups on chemical shift of ^{17}O, and coupling of other nuclei with ^{17}O. An appraisal of ^{17}O shifts and couplings of representative compounds in different families as an approach to stereochemical diagnosis or electron density variation effects in these families will also be described.

Scope and Limitations

Although oxygen forms compounds with almost all elements, it is one of the most difficult nuclei to observe via NMR spectroscopy due to its low natural abundance (0.037%), and its nuclear spin (I = 5/2) which means it has 6 spin states and a high electric quadrupole moment ($Q = -2.6 \times 10^{-26}$ cm^2) that leads to broad signals. Hence, poor resolution of signal(s)[42] is commonplace. These properties, however, are compensated by large chemical shifts (> 1500 ppm) observed for ^{17}O which aids in the resolution of quadrupole-broadened resonances.

The reactivity of oxygen, coupled with increased availability of ^{17}O enriched materials, simplifies the synthesis of isotopically enriched ^{17}O containing compounds.[42] In general, ^{17}O nuclei have fast relaxation rates or a short T_1 (≤ 0.2 sec),[42] which implies a large number of scans can be acquired in relatively short duration of times.

Recent advances in NMR instrumentation, such as pulsed Fourier transform in place of the continuous wave operations, availability of high field high resolution magnets and field frequency lock (permitting internal lock and improved referencing) have been the most important developments which have led to increased use of ^{17}O NMR spectroscopy in structural analysis.[13,39,40,42,43] For diamagnetic systems, in the absence of rapid site exchange processes, the linewidths of ^{17}O resonances observed in solution are usually limited by quadrupolar relaxation rates. The quadrupolar relaxation time (T_1), is given by equation (1).[42]

$$\frac{1}{T_1} = \frac{3}{125}\left(1+\frac{\eta^2}{3}\right)\left(\frac{(2\pi e^2 Qq)^2}{h^2}\right)\tau \qquad (1)$$

where η - asymmetry parameter at nuclear site

e - elementary charge

Q - nuclear quadrupolar moment

q - electric field gradient

h - Planck's constant

τ_c - rotational correlation time for the whole molecule.

This equation holds under conditions where isotropic molecular tumbling is rapid on the NMR time scale ($\tau_c << \omega_0^{-1}$, where ω_0^{-1} - nuclear Larmor frequency). In this equation e (1.60×19^{-19} C) and h (6.62×10^{-34} J Hz^{-1}) are universal constants and η, Q and q are constants for a given oxygen site within a molecule, which implies that $T_1 \propto 1/\tau_c$. Therefore, to increase T_1 in order to obtain line narrowing, one has to reduce τ_c, i.e. cause the molecule to tumble more rapidly in solution. The Stokes-Einstein-Debye equation (2) can be applied, in general, to obtain a qualitative relationship between the sample conditions and the observed linewidths.[42]

$$\tau_c = \frac{4\pi\eta a^3}{3kT} \qquad (2)$$

where η - solution viscosity (note η has a different meaning here)

T - temperature of solution (in K)

a - molecular radius.

Thus, a lower τ_c can be achieved by raising the temperature of a solution and by lowering solution viscosity. The solution viscosity can be lowered by using a solvent of low viscosity, or using a low concentration of sample. Equation **2** also implies that as the molecular radius increases, the linewidths increase also. Thus, in general, smaller molecules will yield better resolved spectra.

Comparison of NMR Properties of ^{17}O, ^{1}H, and ^{13}C Nuclei

In order to compare ^{17}O NMR analysis with that applied to other common NMR active elements, such as ^{1}H and ^{13}C, a comparision of the NMR properties of the respective nuclei is necessary. Selcted properties of these nuclei are listed in Table I. The data include the spin number (I) which for ^{1}H and ^{13}C is 1/2, in contrast to that for ^{17}O which is 5/2. This means that ^{1}H and ^{13}C nuclei have two spin states (-1/2 and +1/2), whereas ^{17}O nuclei have six spin states (-5/2 to +5/2). Thus, ^{17}O nuclei possess an electric quadrupole moment ($Q = -2.6 \times 10^{-26}$ cm^2) which yields poor resolution as stated previously. The natural abundance of ^{17}O is significantly lower than that of ^{13}C and ^{1}H. This fact, coupled with a low magnetogyric ratio (Table I) results in a very low sensitivity (6.1% of that for ^{13}C and only 1.1×10^{-3} % of that for ^{1}H) for ^{17}O. The implication is that a greater number of scans is required to obtain a good signal-to-noise ratio for ^{17}O spectra. However, the rapid quadrupole relaxation of ^{17}O nuclei (relaxation time ≤ 0.2 sec)[69] causes the FIDs to decay fast, and thus long acquisition times (AT) and delays are not required. In a typical ^{17}O experiment, AT ≤ 0.05 sec and delays above the minimum allowed (by the instrument) are usually not necessary. Thus, a large number of scans can be acquired in a relatively short time. In a normal ^{1}H experiment, AT is 2 s and the delay used is the instrument minimum, while in a ^{13}C experiment, the AT is 1 s and a delay of 3 s is often employed. It can be seen that more than 40 scans for ^{17}O can be accumulated in the time required for one scan in a ^{1}H experiment, while more than 80 scans for ^{17}O can be acquired in the time required for one scan in a ^{13}C experiment.

As noted earlier, the normal spectral region in ^{17}O is relatively wide. The range of -70 to +700 ppm covers most of the common organic oxygen-containing functional groups starting from ether in the upfield region to nitro groups in the downfield region.[7] Some exceptions exist for the ^{17}O spectral region which can extend to about 1600 ppm (the terminal oxygen of ozone is at +1598 ppm[42]). The ^{17}O chemical shifts are generally

TABLE I

NMR PROPERTIES OF ^{1}H, ^{13}C AND ^{17}O NUCLEI[a]

	^{1}H	^{13}C	^{17}O
Spin number, (I)	1/2	1/2	5/2
Electric Quadrupole moment (Q, cm^2)	—	—	-2.6×10^{-26}
Natural abundance (%)	99.985	1.108	0.037
Magnetogyric Ratio ($\gamma/10^7$, rad T^{-1} s^{-1})	26.752	6.728	-3.628
NMR frequency (@ 100 MHz)	100.00	25.15	13.56
Standard reference	TMS	TMS	H_2O
Relative sensitivity	1	1.76×10^{-4}	1.08×10^{-5}
Normal spectral region (ppm)	0 to 12	0 to 220	-70 to +700

[a] Data taken from reference 34.

referenced to external H_2O (0 ppm in a capillary tube) in the appropriate solvent at the desired temperature. Certain common solvents such as acetone (569 ppm) or nitromethane (605 ppm) have been used as secondary reference standards.[69] Recently Boykin and co-workers used a 1% solution of 2-butanone (558 ppm, in acetonitrile) as a secondary internal reference standard.[7]

Caution is needed in comparing ^{17}O chemical shifts which are dependent upon several factors such as the solvent, pH, temperature, hydrogen-bonding, etc. The chemical shift of oxygen in H_2O changes from -18 ppm (in dioxane) to +9 ppm (in NH_3).[59] Temperature variations cause changes from 0 ppm (25°C) to -9 ppm (215°C), while the signal of water vapor at 215°C is at -36 ppm.[30] Christ and co-workers observed that the ^{17}O chemical shift for oxygen in acetone in different solvents ranged from 580 ppm (hexane) to 572 ppm (neat) to 535 ppm (H_2O).[15] Solvents which can hydrogen-bond often cause an upfield shift. Hence, while comparing ^{17}O chemical shifts, it is necessary to consider the effects due to solvent, temperature, etc.

^{17}O Relaxation

The quadrupolar relaxation mechanism is overhelmingly dominant in ^{17}O NMR, at least for diamagnetic compounds.[40] When the conditions of extreme narrowing are fulfilled[39,40] and in the absence of chemical exchange, the longitudinal (T_1) and transverse (T_2) relaxation times are equal and are given by equation (1).[40] Measurement of transverse relaxation times (T_2) is thus possible for a Lorentzian absorption line, as T_2 is related to the line width at half-height ($w_{1/2}$) through equation (3).[40] Consequently, measurement of linewidths at

$$w_{1/2} = 1/\pi\, T_2 \qquad (3)$$

half-height is the easiest method of to determine T_2 values when conditions such as filter broadening, inhomogeneity broadening or unresolved coupling are well controlled.[39]

Direct measurement of T_1 through appropriate pulse sequences [(180° - λ - 90°) and (90° - λ - 90°)] have been performed for ^{17}O in water.[31] Direct T_2 measurement through a pulse sequence (90° - λ - 180°) has shown that the equality $T_1 = T_2$ holds for water.[31] Continuous wave saturation methods have also been employed for the determination of T_1 and T_2 for H_2O, and a lineshape analysis for certain spin-coupled systems gave good results.[40] Some experimental values are provided in Table II. From these values it is clear that at least for small molecules, the relaxation times for ^{17}O are very small. The equality $T_1 = T_2$ is obvious for ^{17}O from the values obtained from different methods. Another interesting feature is that both T_1 and T_2 increase with an increase in temperature, indicating that relaxation rate is faster at higher temperature. This suggests that ^{17}O experiments should be run at higher temperatures with short acquisition times and short or no delays between acquisitions.

Coupling of ^{17}O to Other Nuclei

Due to the low natural abundance of ^{17}O, J_{ox} couplings have not been detected while observing nuclei X bonded to ^{17}O (natural abundance). In order to detect J_{ox} coupling, it is preferable to observe ^{17}O and not X. In addition to the sensitivity problem, it is necessary to consider the quadrupolar "washing out" of the coupling that occurs.[41] Even in an optimum case, the ^{17}O quadrupolar broadening could be greater than the coupling constants.

Some measured coupling constants ($^1J_{ox}$ and $^2J_{ox}$) are given in Tables III and IV. Limited correlations have been found for $^1J_{ox}$ couplings. However, for one-bond couplings, one observes a large increase in J values between O-H and O-Xe. The P-O coupling constants are well known for the P=O bond in phosphonyl compunds.[69] Theoretical calculations made for a series of $O{=}PCl_{3-n}X_n$ compounds within the framework of finite perturbation theory reproduced the general experimental behavior,

TABLE II

EXPERIMENTAL VALUES OF T_1 AND T_2 (IN MSEC)

Compound	Temp. (°C)	Method	T_1	T_2	Ref.
H_2O	29	Pulse	7.1 ± 0.7	6.2 ± 0.7	31
		Saturation	6.8 ± 0.7		31
		Linewidth		6.4 ± 0.2	31
	97	Pulse	26		35
	97	Lineshape		22	22
Methanol	25	Lineshape		4.2	72
Ethanol	25	Lineshape		1.2	72
Acetone	25	Linewidth		6.1	32

TABLE III

$^{1}J_{ox}$ COUPLING CONSTANTS[a]

Compound	X	J (Hz)[b]
CH_3OH	H	85
$(CH_3)_2C=O$	C	22
FSO_2OOF	F	430
F_2O_2	F	424 (t)
H_3PO_2	P	115
H_3PO_3	P	106
$Me_3P\rightarrow O$	P	120
$MeO_3P\rightarrow O$	P	88 (P-OC)
		220 (P→O)
ClO_4^-	^{35}Cl	86
$XeOF_4$	^{129}Xe	692

[a] Values taken from reference 39.
[b] J values are absolute values.

TABLE IV

$^2J_{ox}$ COUPLING CONSTANTS (X = H, F)[a]

Compound	J^{σ} (Hz)	J^{π} (Hz)[b]
HCO_2Me	38 –O–C–H	10.5
	7.5 –O–CH_3	
HCO_2Et	37.5 –O–C–H	13.5
oxirane	6	
$CH_3C(O)H$		4.5
Acrolein		4.2
$CH_3C(O)F$		39
$F_3P{=}O$		31

[a] Values taken from reference 39.

namely that ^{1}J values are smaller for -O-P than for P=O systems, and that in the phosphonyl series OPX_3, ^{1}J increases with substitutuent electronegativity.[33]

In Table III, ^{2}J coupling constants are classified by $^{2}J\sigma$ and $^{2}J\pi$, according to whether the coupling involves only σ bonds or one σ bond and one π bond. In the exception of $^{2}J\pi_{OF}$ and $^{2}J\sigma_{OH}$ in alkyl formates, all ^{2}J values are small and have been obtained from ^{17}O lineshape analysis.[22] The exceptionally high value of $^{2}J\sigma_{OH}$ in ethyl formate is in agreement with the general theory of geminal coupling constants between nuclei adjacent to a carbonyl group.[69]

^{17}O Chemical Shifts in Selected Families

Since the pioneering work of Christ and co-workers,[14-16] various groups have measured the ^{17}O chemical shifts of different families of organic coumpounds. Certain ^{17}O chemical shifts of ethers and alcohols are listed in Tables V and VI, respectively. Considering Tables V and VI containing ^{17}O shifts for ethers and alcohols, one finds a *beta deshielding* effect and a *gamma shielding* effect by a methyl group on the oxygen shift, particularly for ethers. Thus, Kintzinger and Dalseth were able to predict ^{17}O chemical shifts of ethers with a fair degree of accuracy from ^{17}O-^{13}C shift correlations.[21] Crandall and Centeno found similar effects on the ^{17}O chemical shift of alcohols from ^{17}O-^{13}C shift correlations.[17] Eliel and co-workers[26] reported chemical shifts of substituted 1,3-dioxanes and tetrahydropyrans, and these are listed in Table VII. In the case of these cyclic ethers also, a good correlation was observed between ^{13}C-^{17}O chemical shifts. Eliel and co-workers were able to calculate additive-substitution parameters for methyl substituents in 1,3-dioxanes.[26]

The ^{17}O chemical shifts for several aliphatic aldehydes and ketones were measured by Kintzinger and co-workers.[41] Shifts of selected aldehydes and ketones are listed in Table VIII. In the case of aldehydes, there is a clear *beta* and *gamma shielding* effect and a *delta deshielding* effect using acetaldehyde as the standard. A similar effect was observed for

TABLE V

^{17}O CHEMICAL SHIFTS FOR ALIPHATIC ETHERS ROR' [a]

No	R	R'	δ (ppm)	No	R	R'	δ (ppm)
1	Me	Me	-52.5	8	Et	*i*-pr	28.0
2	Me	Et	-22.5	9	Et	*t*-Bu	40.5
3	Me	*n*-Pr	-28.5	10	*n*-Pr	*n*-Pr	-3.5
4	Me	*i*-Pr	-2.0	11	*n*-Pr	*i*-Pr	24.0
5	Me	*t*-Bu	8.5	12	*i*-Pr	*i*-Pr	52.5
6	Et	Et	6.5	13	*i*-Pr	*t*-Bu	62.5
7	Et	*n*-Pr	1.7	14	*t*-Bu	*t*-Bu	76.0

[a] Values taken from reference 21 (pure liquids at 25°C).

TABLE VI

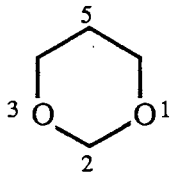
^{17}O CHEMICAL SHIFTS FOR ALIPHATIC ALCOHOLS (ROH) [a]

No	R	δ (ppm)	No	R	δ (ppm)
1	Me	-37.0	5	*n*-Bu	0.0
2	Et	5.9	6	*i*-Bu	-6.8
3	*n*-Pr	-0.5	7	*s*-Bu	34.0
4	*i*-Pr	39.8	8	*t*-Bu	62.3

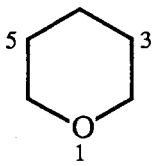
[a] Values taken from reference 17 (pure liquids at 65°C).

TABLE VII

^{17}O CHEMICAL SHIFTS FOR SUBSTITUTED 1,3-DIOXANES AND TETRAHYDROPYRANS [a]



1,3-dioxane



THP[b]

Compound	δ (ppm)
dioxane	35.3
–,2-Me	52.5
–,5-Me	35.5
–,2,2-di-Me	51.8
–,5,5-di-Me	31.1
–,*cis*-4,6-di-Me	58.0
–,*trans*–2,6-di-Me	52.4
–,*r*-2,*trans*-4-*trans*-6-tri-Me	63.3
–,*r*-2,*cis*-4-*cis*-6-tri-Me	76.4
–,2,2,5,5-tetra-Me	47.7
THP[b]	8.8
2-MeTHP	33.6
3-MeTHP	10.3
4-MeTHP	7.7

[a] Values taken from reference 26.
[b] Tetrahydropyran.

TABLE VIII

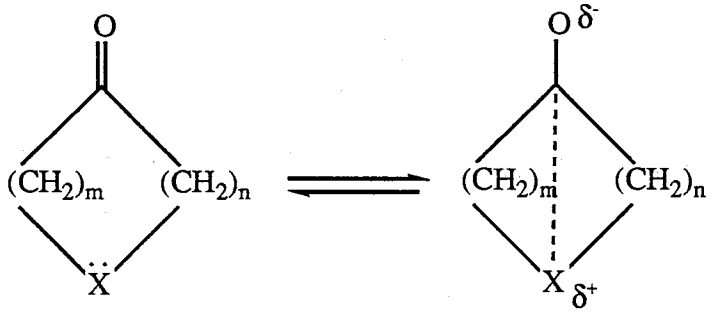
^{17}O CHEMICAL SHIFTS OF ALDEHYDES AND KETONES [R(R')C=O][a]

	R	R'	δ (ppm)
1.	H	Me	592 (550)
2.	H	Et	579.5 (538)
3.	H	*i*-Pr	574.5
4.	H	*t*-Bu	564
5.	H	*n*-Pr	589
6.	Me	Me	569 (523)
7.	Me	Et	557.5
8.	Me	*i*-Pr	557
9.	Me	*t*-Bu	561
10.	Me	*n*-Pr	563
11.	Et	Et	547
12.	Et	*i*-Pr	543.5
13.	Et	*t*-Bu	547.5
14.	Et	*n*-Pr	550

[a] Values taken from reference 41 (pure liquids at 25°C); values in parentheses refer to aqueous solutions.

ketones with the exception of *t*-butyl methyl ketone (entry 9) and *t*-butyl ethyl ketone (entry 13). The signals for the latter should be further upfield compared to the corresponding isopropyl ketones (entries 8 and 12) because there are three methyl groups in the *beta* position in *t*-butyl ketones which should induce greater *upfield* shift as compared with two methyl groups in the isopropyl ketones. However, no explanation was given for this anomolous behavior. Interestingly, from the correlation of ^{17}O ppm in R(R')C=O with $^{13}C'$ shift of the corresponding alkene R(R')C=C'H_2, additivity relationships were constructed for the prediction of ^{17}O shifts.[41] However, the chemical shifts of *aqueous solutions* of aldehydes and ketones give ^{17}O signals which are deshielded by 42-46 ppm coupled to ^{17}O shifts obtained on neat samples. This is indicative of a solvent effect (more pronounced with a polar protic solvent) with a high degree of hydrogen bonding involved.

The ^{17}O chemical shifts of 1-heteracyclohexanones have been useful in studying transannular interaction in 8- and 9-membered rings,[19] and some are listed in Table IX. From the shift values for systems with X = N-Et, m = n = 3 and m = 4, n = 3 and for X = O, m = n = 3, transannular interactions of the type shown in equation (4) is clearly apparent.

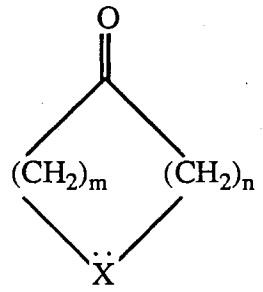


(4)

Crandall and co-workers were the first to measure ^{17}O chemical shifts for a series of alkyl substituted cyclohexanonanes. Table X lists the δ ^{17}O values for a few members of alkyl sustituted cyclohexanones. When a methyl substitutent at a carbon *alpha* [C(2)] to the carbonyl group is oriented equatorially, a large *shielding* effect is observed, whereas

TABLE IX

^{17}O CHEMICAL SHIFTS OF CYCLIC KETONES [a]

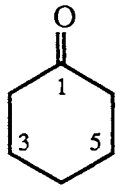


X		CH_2	NEt	O	S
m	n				
2	2	564	561	568	569
3	3	576	516	544	560
4	3	574	471		

[a] Values taken from reference 19; dioxane solution, 28°C.

TABLE X

^{17}O CHEMICAL SHIFTS OF CYCLOHEXANONES[a]

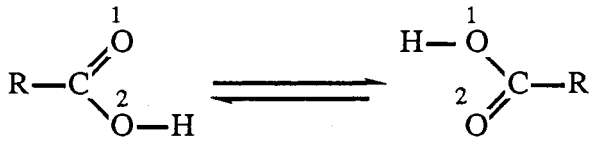


Ketone	$\delta\ ^{17}O$
Cyclohexanone	559.9
2-methyl	548.8
3-methyl	561.8
4-methyl	560.1
2,2-dimethyl	554.9
3,3-dimethyl	572.3
4,4-dimethyl	561.4
cis-2,6-dimethyl	540.8
trans-2,6-dimethyl	550.8
cis-3,5-dimethyl	561.2
trans-3,5-dimethyl	571.3
3,3,5-trimethyl	570.0
3,3,5,5-tetramethyl	576.5
2-ethyl	553.3

[a] Values taken from reference 18; 30% by weight solutions in dioxane, at 28°C.

an axial methyl group causes a *deshielding* effect. Increasing the size of the alkyl group at C(2) also results in a *deshielding* effect. Substituents at a carbon beta [C(3)] to the carbonyl group induces marked *downfield* shifts when axially oriented, whereas only a slight downfield shift is induced when a group is oriented in an equatorial position. More remote substituents in cyclohexanones [such as at the *gamma* position {C(4)}] did not result in significant change in the ^{17}O chemical shifts. The substituent-induced ^{17}O shifts observed, (when methyl substitution is at a carbon adjacent to the carbonyl) have been attributed to changes in internal dihedral angles and a possible contribution from carbonyl group polarization by the substituents.[18] The large deshielding induced by an axial group at C(3) was attributed to a possible through-space interaction.[18]

Table XI lists the ^{17}O chemical shifts for acyl derivatives in the series RC(O)X. Carboxylic acids have only one line, due to the C=O and C-O-H positions being averaged by rapid intermolecular proton transfer [equation (5)]. The carbonyl oxygen in methyl and



(5)

in the ethyl ester of formic acid appears to have the same shift, while the carbonyl oxygen of ethyl acetate is *shielded* by 8 ppm as compared to that in methyl acetate. The ether oxygen in ethyl esters of both formic acid and acetic acid is *deshielded* by 20-30 ppm when compared with the corresponding ^{17}O shifts in the methyl esters. The effect is analogous to that found in ethers.[21] In the case of formamide and acetamide, no significant changes in the ^{17}O ppm value was observed.[39]

Boykin and co-workers[13] noted that as molecular crowding increased around oxygen the magnitude of the chemical shift for ^{17}O in the carbonyl oxygen-containing systems increased. Indeed they detected a clear correlation between estimated torsion angles and the ^{17}O shift. Thus, for example, as the torsion angle of 28° in benzamide increased to

TABLE XI

^{17}O CHEMICAL SHIFTS FOR ACYL DERIVATIVES [RC(O)X]

R	X = OH	OMe	OEt	NH_2	NMe_2
H	253[a]	364 (C=O)[b]	364 (C=O)[b]	310[a]	—
		143 (C–O)[b]	173 (C–O)[b]		
Me	251[a]	355 (C=O)[b]	363 (C=O)[b]	313[a]	—
		148 (C–O)[b]	169 (C–O)[b]		
Ph	250.5[c]	340 (C=O)[c]	—	329[c]	348[c]
		128 (C–O)[c]	—		
2,6-diMe-C_6H_3	280[c]	377 (C=O)[c]	—	353[c]	—
		150 (C–O)[c]	—		

[a] Values taken from reference 39; pure liquids at 25°C.
[b] Values taken from reference 67; pure liquids at ambient temperature.
[c] Values taken from reference 13; 0.5 *M* solutions in H_3CCN at 75°C.

62° in *N,N*-dimethylbenzamide, the ^{17}O chemical shift increased from 329 to 348 ppm, respectively. A similar correlation was noted for aromatic carboxylic acids, esters and amides.[13]

In summary, ^{17}O chemical shifts show promise in structure diagnosis. Kintzinger[20,21] and Kradall[17] found correlations between ^{17}O ppm and certain ^{13}C ppm shifts for alcohols, ethers, aldehydes and ketones. Crandall[18] found a correlation between dihedral angles and the ^{17}O chemical shift in substituted cyclohexanones. Eliel[26] observed good additivity parameters for substituents on the positions alpha, beta, or gamma to oxygen in cyclic ethers. Recently Boykin[7] found good correlations between ^{17}O chemical shifts and variations in torsion angles and/or local van der Waals energy considerations for aryl methyl ketones, aromatic carboxylic acids, and phthalimides. As a result, ^{17}O NMR spectroscopy has emerged as a powerful technique for assessing elecronic effects in molecules due to structural variations.

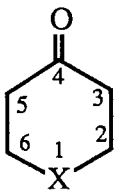
CHAPTER II

RESULTS AND DISCUSSION

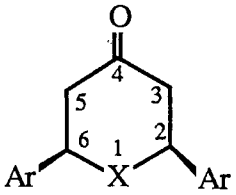
Stereochemical and conformational analysis of substituted 1-hetera-4-cyclohexanones is important since they are vital intermediates in the synthesis of many heterocycles.[38] A few reviews have appeared on the chemistry of these heterocycles.[9] This early work involved the use of IR, ^{1}H NMR and ^{13}C NMR analysis for structural elucidation. However, very little has been done in the area of ^{17}O NMR spectroscopic analysis (see for example ref. 19).

Our work has focused upon a comprehensive study of the stereochemistry in substituted 1-hetera-4-cyclohexanones **1-41** and certain 3,7-diheterabicyclo[3.3.1]nonan-9-ones **42-47** and **49** via ^{17}O NMR spectroscopy. In total, forty-one 1-hetera-4-cyclohexanones were examined for electronic and steric effects as manifested by the analysis of ^{17}O shifts. In this family, the heteroatoms were N, O, P, S, and Se, and the substituents were *cis*-2,6-diaryl, *trans*-2,6-diaryl, *cis*-2,6-diaryl-*trans*-3-methyl, *cis*-2,6-diaryl-*trans*-3,5-dimethyl and 2,2,6,6-tetramethyl groups. In the nitrogen heterocycles, substituents on nitrogen include methyl, isopropyl, benzyl and benzoyl groups, while the substituents on phosphorus are a phenyl group along with the 1-oxide and 1-sulfide derivatives.

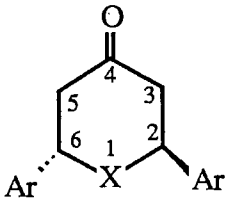
All ^{17}O chemical shifts (ppm), linewidths at half-height ($w_{1/2}$) and shift differences (δ-δ', for example) are listed in Tables XII-XX. Table XII contains ^{17}O shift data for 1-hetera-4-cyclohexanones. The ^{17}O shifts of certain *cis*- and *trans*-2,6 diphenyl analogues are given in Table XIII, while those of selected 2,6-diphenyl-3-methyl- and 2,6-diphenyl-3,5-dimethyl-1-hetera-4-cyclohexanones are provided in Table XV. Table XVII contains



1-12



13-20

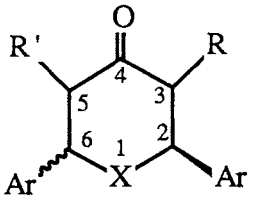


21-24

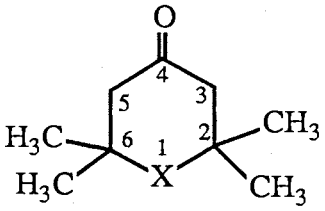
	X
1	CH_2
2	N-H
3	N-Me
4	N-*i*-Pr
5	N-CH_2Ph
6	N-C(O)Ph
7	O
8	S
9	Se
10	P-Ph
11	P(O)-Ph
12	P(S)-Ph

	X	Ar
13	CH_2	Ph
14	NH	Ph
15	N-Me	Ph
16	O	Ph
17	S	Ph
18	Se	*p*-Tol
19	Se	*p*-Anis
20	P-Ph	Ph

	X
21	O
22	S
23	P-Ph
24	P(O)-Ph

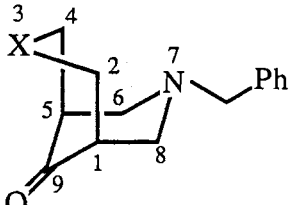


26-35

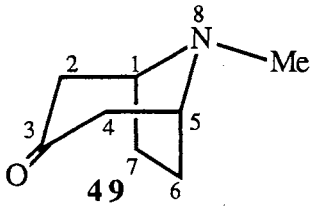


36-41

	X	Ar	R	R'		X
26	N-H	*cis*-Ph	Me	H	**36**	CH_2
27	N-H	*cis*-Ph	Me	Me	**37**	N-H
28	O	*cis-p*-Anis	Me	H	**38**	S
29	O	*cis-p*-Anis	Me	Me	**39**	P-Ph
30	O	*cis-p*-Tol	Me	Me	**40**	P(O)-Ph
31	O	*cis*-Ph	Me	Me	**41**	P(S)-Ph
32	S	*trans*-Ph	H	Me		
33	S	*cis*-Ph	H	Me		
34	P-Ph	*cis*-Ph	Me	H		
35	P(O)-Ph	*cis*-Ph	Me	H		



42-47

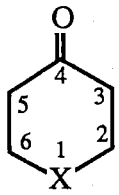


49

	X
42	N-Me
43	N-*i*-Pr
44	N-CH_2Ph
45	O
46	S
47	$CHCO_2Et$

TABLE XII

^{17}O NMR CHEMICAL SHIFTS (ppm, D_3CCN/H_3CCN) FOR **1-12**

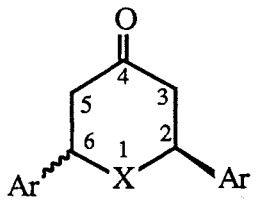


Compd	X	$\delta^{17}O$ (C=O)	$w_{1/2}$ (Hz)	Other ^{17}O Signals
1	CH_2	557.13	76.16	
2	N-H	556.08	131.4	
3	N-Me	560.34	135.6	
4	N-*i*-Pr	558.47	93.7	
5	N-CH_2Ph	559.86	142.3	
6	N-C(O)Ph	566.14	184.6	352.68 (223.2)[a]
7	O	560.42	85.1	10.34 (83.0)[a]
8	S	570.28	87.3	
9	Se	572.32	143.4	
10	P-Ph	564.50	146.9	
11	P(O)-Ph	573.51	184.3	43.58 (156)[b]
12	P(S)-Ph	574.49	210.6	

[a] $w_{1/2}$ in Hz.
[b] $^1J_{PO}$ in Hz.

TABLE XIII

^{17}O NMR CHEMICAL SHIFTS (ppm, D_3CCN/H_3CCN) FOR **13-25**

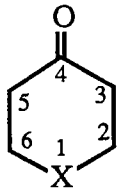


Compd	X	Ar	$\delta^{17}O$ (C=O)	$w_{1/2}$ (Hz)	Other ^{17}O signals
13	CH_2	*cis*-Ph	562.21	317.1	
14	N-H	*cis*-Ph	560.64	408.5	
15	N-Me	*cis*-Ph	562.93	414.0	
16	O	*cis*-Ph	563.71	367.3	49.94 (507.8)[a]
17	S	*cis*-Ph	575.16	258.0	
18	Se	*cis-p*-Tol	578.67	201.4	
19	Se	*cis-p*-Anis	580.34	142.4	48.44 (596.3)[a]
20	P-Ph	*cis*-Ph	572.17	688.1	
21	O	*trans*-Ph	568.11	360.6	45.93 (328.4)[a]
22	S	*trans*-Ph	578.25	523.3	
23	P-Ph	*trans*-Ph	577.14	268.7	
24	P(O)-Ph	*trans*-Ph	582.91	286.8	48.42 (130)[b]
25	$Ph_3P\rightarrow O$				49.22 (162)[b]

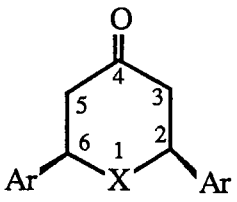
[a] $w_{1/2}$ in Hz.
[b] $^1J_{PO}$ in Hz

TABLE XIV

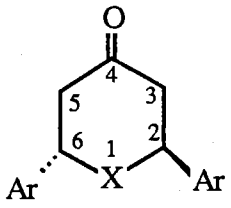
SHIFT DIFFERENCES (ppm) BETWEEN THE 2,6-SUBSTITUTED 1-HETERA-4-CYCLOHEXANONES AND THE CORRESPONDING UNSUBSTITUTED ANALOGUES ($\delta_E - \delta_A$, $\delta_B - \delta_A$, $\delta_C - \delta_A$, AND $\delta_C - \delta_B$)



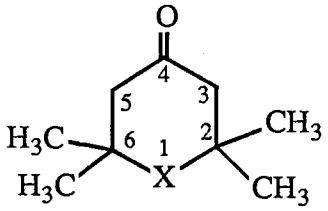
A



B



C

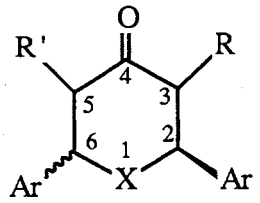


E

X	Compds (**B - A**)	$\delta_E - \delta_A$	Ar	$\delta_B - \delta_A$	$\delta_C - \delta_A$	$\delta_C - \delta_B$
CH_2	**13 - 1**	15.12	Ph	5.08	-	-
N-H	**14 - 2**	12.91	Ph	4.56	-	-
N-Me	**15 - 3**	-	Ph	2.59	-	-
O	**16 - 7**	-	Ph	3.29	7.69	4.40
S	**17 - 8**	16.19	Ph	4.88	7.97	3.09
Se	**18 - 9**	-	*p*-Tol	6.35	-	-
Se	**19 - 9**	-	*p*-Anis	8.02	-	-
P-Ph	**20 - 10**	21.22	Ph	7.67	12.64	4.97
P(O)-Ph	**24 - 11**	18.79	Ph	-	9.40	-
P(S)-Ph	**41 - 12**	20.48	-	-	-	-

TABLE XV

^{17}O NMR CHEMICAL SHIFTS (ppm, D_3CCN/H_3CCN) FOR **26-35**

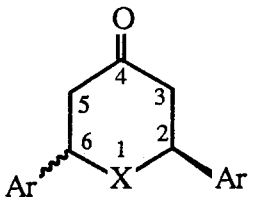


Compd	X	Ar	R	R'	$\delta^{17}O$ (C=O)	$w_{1/2}$ (Hz)	Other ^{17}O signals
26	N-H	*cis*-Ph	Me	H	553.76	593.3	-
27	N-H	*cis*-Ph	Me	Me	542.88	500.7	-
28	O	*cis-p*-Anis	Me	H	555.98	532.8	62.25[a](284.6)[b]
							45.91[c](678.3)[b]
29	O	*cis-p*-Anis	Me	Me	539.39	777.7	66.88[a](379.3)[b]
							46.21[c](582.3)[b]
30	O	*cis-p*-Tol	Me	Me	541.59	485.1	70.32[a](348.3)[b]
31	O	*cis*-Ph	Me	Me	537.84	786.0	67.87[a](262.9)[b]
32	S	*trans*-Ph	H	Me	574.39	390.2	
33	S	*cis*-Ph	H	Me	565.10	594.9	
34	P-Ph	*cis*-Ph	Me	H	564.44	457.0	
35	P(O)-Ph	*cis*-Ph	Me	H	575.53	451.4	30.48(167)[d]

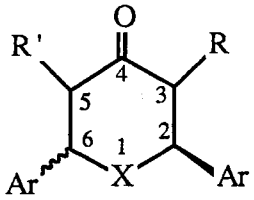
[a] Ring oxygen
[b] $w_{1/2}$ in Hz.
[c] Anisole oxygen
[d] $^1J_{PO}$ in Hz.

TABLE XVI

SHIFT DIFFERENCES (ppm) BETWEEN THE METHYL SUBSTITUTED 2,6-DIPHENYL HETEROCYCLES AND 2,6-DIPHENYL-1-HETERA-4-CYCLOHEXANONES ($\delta_B - \delta_D$)



B

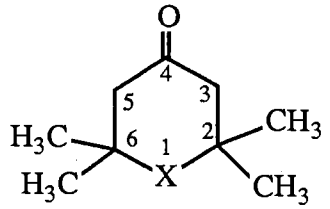


D

X	Ar	R	R'	Compds	$\delta_B - \delta_D$
N-H	*cis*-Ph	Me	H	**14 - 26**	6.88
N-H	*cis*-Ph	Me	Me	**14 - 27**	17.76
O	*cis-p*-Anis	Me	H	**16 - 28**	7.73
O	*cis-p*-Anis	Me	Me	**16 - 29**	16.59
O	*cis*-Ph	Me	Me	**16 - 31**	25.87
P-Ph	*cis*-Ph	Me	H	**20 - 34**	7.73
S	*cis*-Ph	H	Me	**17 - 33**	10.06
S	*trans*-Ph	H	Me	**22 - 32**	3.86

TABLE XVII

^{17}O CHEMICAL SHIFTS (ppm, D_3CCN/H_3CCN) FOR **36-41**

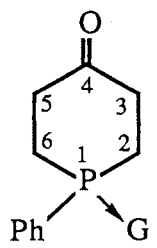


Compd	X	$\delta^{17}O$ (C=O)	$w_{1/2}$ (Hz)	Other ^{17}O signals
36	CH_2	572.25	166.2	
37	N-H	568.99	155.4	
38	S	586.47	173.1	
39	P-Ph	585.72	214.1	
40	P(O)-Ph	592.30	260.6	27.35 (168)[a]
41	P(S)-Ph	594.97	234.7	

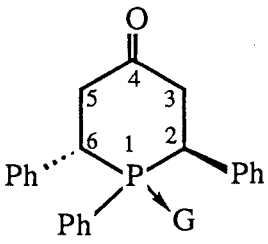
[a] $^1J_{PO}$ in Hz.

TABLE XVIII

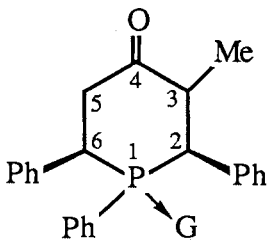
SHIFT DIFFERENCES (ppm) BETWEEN CERTAIN SUBSTITUTED PHOSPHORINANONES



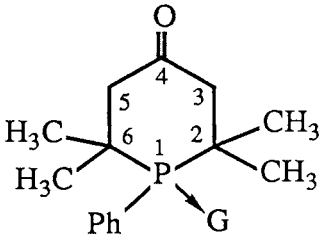
A



B



C



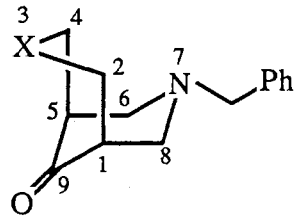
D

1. G =	lone pair (**10**)	lone pair (**23**)	lone pair (**34**)	lone pair (**39**)
2. G =	O (**11**)	O (**24**)	O (**35**)	O (**40**)
3. G =	S (**12**)	-	-	S (**41**)

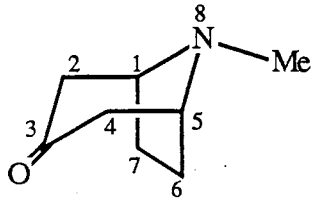
Compd.	$\delta_2 - \delta_1$	$\delta_3 - \delta_1$
A	9.01	9.99
B	5.77	-
C	11.09	-
D	6.58	9.25

TABLE XIX

^{17}O NMR CHEMICAL SHIFTS (ppm, D_3CCN/H_3CCN) FOR **42-48**



42-47



49

Compd	X	$\delta^{17}O$ (C=O)	$w_{1/2}$ (Hz)	Other ^{17}O signal
42	N-Me	545.82	248.5	
43	N-i-Pr	542.01	318.4	
44	N-CH_2Ph	545.07	431.5	
45	O	543.20	209.2	1.00 (173.3)[a]
46	S	559.92	246.5	
47	$CHCO_2Et$	547.17	799.7	339.53[b] (251.2)[a]
				163.98[c] (543.9)[a]
49		573.91	139.2	

[a] $w_{1/2}$ in Hz
[b] C=O of ester
[c] C-O of ester

TABLE XX

SHIFT DIFFERENCES (ppm) BETWEEN BICYCLIC KETONES **42-48** AND THEIR MONOCYCLIC CONSTITUENTS

MC Compds[a]	$\bar{X}\ \delta_I$[b]	BC Compd[c]	δ_{BC}[d]	$\Delta\delta_I - \delta_{BC}$
(**3** + **5**)/2	560.10	**42**	545.82	+ 14.28
(**4** + **5**)/2	559.17	**43**	542.01	+ 17.76
(**5** + **5**)/2	559.86	**44**	545.07	+ 14.79
(**7** + **5**)/2	560.14	**45**	543.20	+ 16.94
(**8** + **5**)/2	565.07	**46**	559.92	+ 5.15
(**1** + **5**)/2	558.50	**47**	547.17	+ 11.33
(**3** +**3**)/2	560.34	**48**	573.91	- 13.57

[a] MC Compds = monocyclic compounds

[b] $\bar{X}\ \delta_I$ = average of the two C=^{17}O shifts for the monocyclic 1-hetera-4-cyclohexanones which constitute the bicyclo[3.3.1]nonan-9-one system.

[c] BC compd = bicyclic compound

[d] δ_{BC} = C=^{17}O shift of bicyclic ketones

TABLE XXI

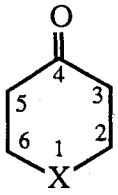
ELECTRONEGATIVITIY (χ) VALUES[a] AND AVERAGE C-X BOND LENGTHS (Å)[b]

X	χ	Bond length (Å)
H	2.1	1.086
C	2.5	1.370
N	3.0	1.285
O	3.5	1.290
P	2.1	1.870
S	2.5	1.680
Si	1.8	1.860
Se	2.4	1.845

[a] Values taken from reference 73
[b] Values taken from reference 54

TABLE XXII

SELECTED BOND LENGTHS (Å), BOND ANGLES (°) AND TORSION ANGLES (°) FOR CERTAIN 1-HETERA-4-CYCLOHEXANONES.

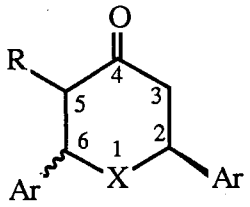


X	CH_2[a]	O[b]	S[c]	Se[d]	P-Ph[e]	P(O)Ph[f]	P(S)Ph[f]
Compd:	**1**	**7**	**8**	**9**	**10**	**11**	**12**
Bond lengths (Å)							
C(2)-X(1)	1.55	1.41	1.80	1.93	1.84	1.80	1.82
Bond angles (°)							
∠C(2)X(1)C(6)	110.8	113.0	97.0	95.0	98.2	101.2	99.8
∠C(2)C(3)C(4)	111.5	110.5	112.5	115.8	114.7	113.1	108.9
∠C(3)C(4)C(5)	115.3	116.0	118.9	118.2	117.7	117.4	117.4
∠C(3)C(2)X(1)	110.8	113.5	113.2	112.2	117.0	109.3	108.9
Torsion angles (°)							
X(1)C(2)C(3)C(4)	53.0	-	57.1	57.0	57.0	59.8	59.2

[a] Electron diffraction: reference 24
[b] Microwave: reference 2
[c] Electron diffraction: reference 61
[d] X-ray diffraction: reference 69
[e] X-ray diffraction: reference 49
[f] X-ray diffraction: reference 71

TABLE XXIII

SELECTED BOND LENGTHS (Å), BOND ANGLES (°) AND TORSION ANGLES (°) FOR CERTAIN SUBSTITUTED 1-HETERA-4-CYCLOHEXANONES.

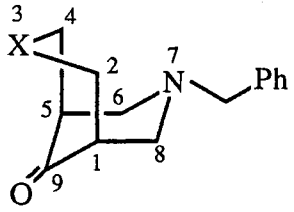


	A[a]	**B**[a]	**C**[b]	**D**[b]	**E**[c]
X	O (**16**)	O (**21**)	S (**32**)	S	P-Ph (**34**)
Ar	*cis*-Ph	*trans*-Ph	*trans*-Ph	*trans*-Ph	*cis*-Ph
R	H	H	Me	Et	Me
Bond lengths (Å)					
C(2)-X(1)	1.44	1.43	1.83	1.83	1.85
bond angles(°)					
∠C(2)X(1)C(6)	113	112	99	100	100
∠C(2)C(3)C(4)	114	112	114	113	118
∠C(3)C(4)C(5)	114	114	117	118	119
∠C(3)C(2)X(1)	110	110	111	112	108
Torsion angles (°)					
X(1)C(2)C(3)C(4)	48	52	57	55	62
X(1)C(6)C(5)C(4)	52	53	58	58	58

[a] X-ray diffraction: reference 28
[b] X-ray diffraction: reference 55
[c] X-ray diffraction: reference 57

TABLE XXIV

SELECTED BOND LENGTHS (Å), BOND ANGLES (°) AND TORSION ANGLES (°) FOR CERTAIN 3,7-DIHETERABICYCLO[3.3.1]NONAN-9-ONES



X	N-Me[a] (**42**)	S[b] (**46**)	Se[b]
Bond length (Å)			
C(2)X(3)	1.43	1.81	1.95
C(6)N(7)	1.46	1.46	1.45
Bond angles (°)			
∠C(2)X(3)C(4)	110.4	98	95.3
∠C(6)N(7)C(8)	111.2	112.7	110.8
∠C(2)C(1)C(9)	108.6	111.7	113.3
∠C(8)C(1)C(9)	106.0	106.4	105.5
Torsion Angles			
X(3)C(2)C(1)C(9)	1.9	2.9	46.3
N(7)C(8)C(1)C(9)	59.8	58.9	68.2

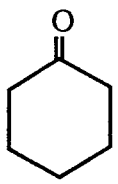
[a] X-ray diffraction: reference 64
[b] X-ray diffraction: reference 70

chemical shifts for 2,2,6,6-tetramethyl-substituted analogues. Bicyclic compounds **42-48** are included in Table XIX. Linewidths at half height or $^{1}I_{PO}$ values in Hz are given in Tables XII, XIII, XV, XVII, and XIX where appropriate. Differences in ^{17}O shifts from C=^{17}O groups in substituted 1-hetera-4-cyclohexanones and the corresponding parent compounds are in Tables XIV, XVI, XVIII, and XX.

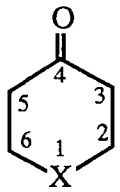
An extensive search of the literature revealed that only compounds **1**,[16,18-20] **7**,[19] **8**,[19] **25**,[60] and **36**[18] had been previously examined by ^{17}O NMR spectroscopy. In analyzing results, it is useful to compare chemical shifts with a standard(s) which was selected to be the parent unsubstituted compound(s) listed in Table XII. Sharp trends in *shielding* and *deshielding* for C=^{17}O were observed with substituents at various positions. For example, *deshielding* effects are detected when phenyl or methyl groups were present at the 2- and/or 6-positions in all systems. Increased *deshielding* was observed for *trans*-2,6-diphenyl analogues as compared with the *cis*-2,6-diphenyl analogues. A *shielding* effect was seen when methyl groups were present at the 3- and 5-positions. Negligible changes in C=^{17}O shifts occurred in 1-aza- and 1-oxa-analogues as compared with cyclohexanone (**1**). In contrast, the corresponding S, Se and P heterocycles (Table XII) showed a significant *downfield* shift (for C=^{17}O) as compared with cyclohexanone (**1**).

For the C-^{17}O shift in pyranones, a *deshielding* effect was observed with substituents at the 2-, 3-, 5- and 6-positions. In the case of 4-phosphorinanone 1-oxides, a *shielding* effect was observed for ^{17}O in P→^{17}O as steric crowding increased around the P→O group along with a concomitant increase in the $^{1}J_{PO}$ value. For certain 3,7-diheterabicyclo[3.3.1]nonan-9-ones, a *shielding* effect on the C=^{17}O resonance was seen and was analogous to the effect elicited by substituents at the 3- and 5-positions (Table XV) in the 1-hetera-4-cyclohexanones. In contrast, the related system tropinone (**48**) exhibited a *deshielding* for C=^{17}O [compared to that in *N*-methyl-4-piperidinone (**3**)] and was quite similar to that found in 2- and 6-substituted 1-hetera-4-cyclohexanones compared to the corresponding parent 1-hetera-4-cyclohexanones.

Inspection of data in Table XII reveals that the heteroatoms N and O do *not* cause a significant change in C=^{17}O chemical shift compared to that in cyclohexanone. However, within the family of isosteric heteroatoms, O, S and Se, a *downfield* trend is observed. This trend appears to be related to the C(2,6)-X bond length (Tables XXI-XXIII), i.e. as the bond length increases, the ^{17}O shift value also increases [average C(2)-Se>C(2)-S>C(2)-O].[73] The reverse is true in terms of electronegativity (Table XXI) of the heteroatom, i.e. as the electronegativity (χ) of the heteroatom decreases, the shift value increases [$\chi_O > \chi_S > \chi_{Se}$].[54]



1



2-12

A similar correlation is observed in the family of isosteric heteroatoms N and P. The shift for **10** (X = P-Ph) is 4.2 ppm downfield from that of **3** (X = N-CH_3) and 4.6 ppm downfield from that of **5** (X = N-CH_2Ph)[(average C(2)-P>C(2)-N)[73] and ($\chi_N > \chi_P$)[54]]. This trend indicates that the C=^{17}O chemical shifts in 1-hetera-4-cyclohexanones depend upon the electronegativity of the heteroatom and possibly upon the distance of the heteroatom from the carbonyl group. The chemical shift of cyclohexanone (**1**) does not fit in this trend since carbon is not isosteric with either O or N. However, it is possible that the C=^{17}O shift of **1** will correlate with 1-silicon analogues.[66] The trend within the nitrogen heterocycles **3-5** (Table XII) is also interesting as a 1.9 ppm upfield shift is observed for **4** (X = *N*-*i*-Pr) and only a 0.5 ppm upfield shift for **5** (X = *N*-CH_2Ph) when compared with **3** (X = *N*-CH_3). This observation further supports the contention that an increase in electron density on the heteroatom causes an *upfield* C=^{17}O shift, as, for example, with the system **3** (*N*-CH_3–560.34 ppm) versus the system **4** [*N*-$CH(CH_3)_2$–558.47 ppm]. Substituting a benzoyl group for a benzyl group causes a *downfield* shift of

6.3 ppm, but this is not surprising in lieu of the trends observed since electron density on the nitrogen in **6** [X = $NC(O)C_6H_5$] is reduced via delocalization of electrons over the carbonyl group of the amide function as compared to electron density on the nitrogen in **5** (X = NCH_2Ph).

That hydrogen-bonding influences the ^{17}O shift (Table XII) has been well established,[13,42] and it is known that such interaction causes weakening of the carbonyl bond and induces an *upfield* shift by as much as about 50 ppm in aldehydes and ketones compared to standards.[42] We have observed an upfield C=^{17}O shift of 4.3 ppm in **2** (X = *N*-H) as compared with **3** (X = *N*-CH_3). This change is smaller than in most cases reported in literature.[42] For example, salicylaldehyde and 1,2-cyclohexanedione exhibit *upfield* shifts of 63 and 69 ppm as compared with benzaldehyde and cyclohexanone,[42] respectively. Smaller changes observed in our case are possibly due to the concentrations of our test samples which are quite low (0.16 M) and less subject to dipole-dipole interactions.

Phosphorus containing heterocycles **10, 11** and **12** form another interesting series (Table XII). In this family, large *downfield* C=^{17}O shifts are observed in oxide **11** (573.5 ppm) and sulfide **12** (574.4 ppm) as compared with **10** (564.5 ppm). These *downfield* shifts are not surprising since in **11** and **12** there is a partial positive charge on phosphorus, analogous to the case of nitrogen heterocycle **6**. It is noteworthy that sulfide **12** is more *deshielded* than the oxide **11**, since oxygen (in P→^{17}O) is more electronegative than sulfur in (P→S). This might be due to $\Sigma\chi_{PO}$ (5.6) > $\Sigma\chi_{PS}$ (4.6) and the different bond length of C(2)-P(S) in **12** (1.816 Å) compared to C(2)-P(0) in **11** (1.801 Å).[71] It was observed that in phosphorus heterocycles **11** and **12** a large upfield shift occurs in ^{13}C=O resonance compared to that in phosphine **10**.[71] It has also been noted that a few substituents on phosphorus influence the ^{13}C shifts in a non-linear fashion.[71]

Hirsch and Havinga[36] have compared the ^{13}C chemical shifts of C(4) in both 1-heteracyclohexanes and 1-hetera-4-cyclohexanones. These authors propose that an electric field effect is probably the major interaction between the heteroatom group and the *gamma* carbon [C(4)] in these systems. In all compounds investigated $^{13}C(4)$ is shifted *upfield* relative to cyclohexane (or cyclohexanone). The upfield shifts were largest for quaternary nitrogen heterocycles, which cannot donate electrons to the carbonyl groups; thus any transannular electron donation must be minimal in such 1-hetera-4-cyclohexanones.[36]

It has also been suggested that the hybridization of nitrogen affected the electron density at each carbon in six-membered nitrogen heterocycles.[36] Eliel and co-workers[25] indicated that the *gamma* shielding effect is more pronounced for second-row heteroatoms (S and P). They proposed a hyperconjugate type interaction of free-electron pairs centered on second-row heteroatoms with the C(2)-C(3) bond accompanied by a subsequent alteration of the electron density at the *gamma* carbon [C(4)]. These workers also noted that the ^{13}C shifts depend upon the heteroatom row and not upon the electronegativity of the heteroatom.[25]

Lambert and co-workers[45] suggested that the introduction of a heteroatom in six-membered rings can alter the basic magnetic resonance parameters (chemical shifts and coupling constants) considerably, because of changes in the electronegativity of the heteroatom, changes in the magnitude and sign of the diamagnetic anisotropy of the C-X bond, changes in the shape of the ring, and the presence of lone pairs on heteroatoms that are capable of new electronic interactions. Some of these early observations based on ^{1}H and ^{13}C NMR analysis of six-membered heterocycles appear to be supported, in part, by ^{17}O NMR analysis, particularly for 1-hetera-4-cyclohexanones. The changes in C=^{17}O shift observed seem to depend upon the electronegativity of the heteroatom within the heteroatom row as well as the distance of the heteroatom from the carbonyl group. Conceivably there is some type of hyperconjugate interaction between the free electron pair on the heteroatom with the carbonyl carbon. This in turn, could cause a change in the

electron density on the carbonyl oxygen. The ring shape in S, Se and P heterocycles is puckered to some extent, while in N and O heterocycles the ring is in a near perfect chair form.[45] The shape of the ring may also have some influence on the C=^{17}O shift.

Boykin[13] has suggested three conceivable explanations for the C=^{17}O chemical shift of a functional group. (1) There is predictable *deshielding* of ^{17}O when there is greater double bond character present in a C=O bond or there is reduced electron density on oxygen in the same group. (2) The case of increased shielding is reasonable when the carbonyl group assumes more single bond character or there is increased electron density on oxygen. (3) A change in shielding on C=^{17}O can be caused by rotation of the C-C(O)-C groups to minimize the internal strain which might be offset (resulting in zero net change) by a contribution to the shielding of ^{17}O by a nearby group such as located at C(2,6). Changes in chemical shifts are also attributed to changes in van der Waals interactions which are relieved by rotation of groups around a single bond. Thus, it is possible that in our 1-hetera-4-cyclohexanones (where a *deshielding* trend has been observed in the same vertical group, namely with S and Se, compared with O heterocycles and with P compared with N heterocycles) there is a significant change in van der Waals interactions or that there is increased double bond character for the C=O bond.

Inspection of data in Table XIII reveals that *cis*-2,6-diphenyl groups cause significant *downfield* C=^{17}O shifts (~ 5 ppm) [compared with that for unsubstituted 1-hetera-4-cyclohexanones in Table XII], and appropriate shift differences are listed in Table XIV. In this family of *cis*-2,6-diphenyl-1-hetera-4-cyclohexanones, a trend towards a *downfield* shift of ^{17}O signals is seen within the isosteric families of O, S and Se (11.5 and 3.3 ppm, respectively, between **16**, **17** and **17**, **18**) and N and P (9.2 ppm between **15** and **20**). This is analogous to the trend previously described for the unsubstituted 1-hetera-4-cyclohexanones. The effect (Table XIV) of *cis*-2,6-diphenyl substituents on the C=^{17}O chemical shift causes an average *downfield* shift of 4.9 ± 1.6 ppm in **13**-**20** compared with the respective unsubstituted analogues (Table XII). This change is significantly

greater than the effect of *cis*-dimethyl groups in equivalent positions in cyclohexanone (a downfield shift of 1.3 ppm) as observed by Crandall and co-workers.[18] Recently Li and Chesnut[46] found a good correlation between local van der Waals energies and observed ^{13}C chemical shifts in several substituted cyclohexanes and were able to predict with a good degree of accuracy the ^{13}C chemical shifts of substituted cyclohexanones. The work of Boykin[13] and Li and Chesnut[46] seems to suggest that local van der Waals interactions form an important factor which govern the chemical shifts. Thus, such van der Waals interactions may be more pronounced in systems with large substituents such as in *cis*-2,6-diphenyl-1-hetera-4-cyclohexanones compared to that in *cis*-3,5-dimethylcyclohexanone.

The C=^{17}O resonances are shifted *downfield* in the *trans*-2,6-diphenyl-substituted systems by about 9.4 ppm in **21**, **22**, **23**, and **24** compared to **7**, **8**, **10** and **11** and are listed in Table XIII. Interestingly, this deshielding effect is close in value to that for *trans*-3,5-dimethylcyclohexanone, which is 11.4 ppm downfield from cyclohexanone.[18] Crandall and co-workers[18] reasoned that the large *deshielding* C=^{17}O shift induced by an axial C(3)-CH_3 bond in 3-methylcyclohexanone as compared to cyclohexanone (**1**) is possibly due to a through-space interaction involving the $CH_{3(axial)}$-C(3) bond and the C=O groups. They suggested that the substituent axial carbon-carbon bond [CH_3-C(3)] in such compounds is reasonably proximate and roughly parallel to the axis of the p orbital on carbon of the C=O group. In our work, this conclusion is further supported by X-ray data[55] which indicates that one ortho hydrogen atom in the axial phenyl group is in close proximity to the carbonyl group in crystalline **32** (Table XV). Moreover, in our examples **21-24** the *downfield* C=^{17}O shift (Table XIII) presumably is due to the *deshielding* effect (compared with the *cis*-analogues) by the axial Ar–C bond. An average *downfield* shift of 9.4 ± 2.0 ppm is seen for **21-24** with respect to the unsubstituted 1-hetera-4-cyclohexanones (Table XII) and 4.2 ± 0.8 ppm compared with the *cis*-2,6-diphenyl

analogues (Table XIII). These shift differences are listed in Table XIV.

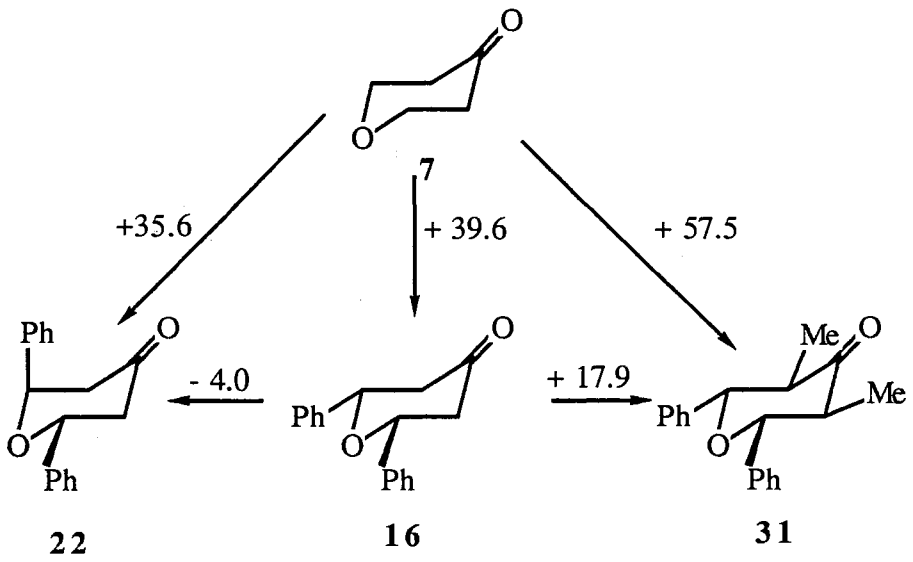
Analysis of data presented in Table XV reveals a significant *upfield* shift upon introduction of methyl groups at the 3- and 5-positions (compared with *cis*-2,6-diphenyl analogues). As a reference, the parent compounds for systems listed in Table XV are the corresponding 2,6-diphenyl analogues listed in Table XIII. Shift differences between the nonmethylated and methylated compounds are listed in Table XVI. An introduction of one methyl group (Table XV) at the 3-position in **26, 28, 33** and **34** causes an average ^{17}O *upfield* shift of 8.1 ± 1.2 ppm compared with that for **14, 16, 17** and **20**. This shielding trend is analogous to that observed in 2-methyl-substituted (-11.0 ppm) and in 2,6-dimethyl-substituted (-8.0 ppm) cyclohexanones (as compared with cyclohexanone) and in 2-methyl-4-*t*-butylcyclohexanone (-8.1 ppm) compared with 4-*t*-butylcyclohexanone.[18]

The C=^{17}O resonances are shifted *downfield* by about 17.5 ppm in tetramethylated systems **36, 37, 38, 39, 40**, and **41** (Table XVII) compared with unsubstituted systems **1, 2, 8, 10, 11** and **12**, respectively. The shift differences are listed in Table XIV. In a similar situation involving cyclohexanone as the standard, where methyl groups were successively substituted at the 3- and 5-positions, the following trends were observed:[18] 3(e)-CH_3 (+1.9), 3(e),5(e)-$(CH_3)_2$ (+1.3), 3,3-$(CH_3)_2$ (+12.4), 3(e),5(a)-$(CH_3)_2$ (+11.4), 3,3,5(e)-$(CH_3)_3$ (+10.1), and 3,3,5,5-$(CH_3)_4$ (+16.6) [values in parenthesis are *downfield* shifts from cyclohexanone]. Thus, it can be seen that the large *downfield* shifts observed in the tetramethyl analogues are mainly due to the methyl groups in *axial* positions. This large *deshielding* of C=^{17}O shifts induced by axial methyl groups at C(2) and C(6) is difficult to understand. Perhaps, it is similar to the case of *trans*-2,6-diphenyl analogues. It is also conceivable that a significant rotation of the carbonyl group occurs around the single bonds to relieve van der Waals interactions[13] and results in a significant downfield ^{17}O shift. The effect on C=^{17}O shift by the tetramethyl groups appears to be an average deshielding of 17.5 ± 3.0 ppm for six systems (Table XIV). The deviations from the mean are not very large when considering the different parameters that might be

influencing ^{17}O shifts and the linewidths of ^{17}O signals which limit reproducibility of data to within ± 1 ppm. Delseth and Kintzinger[20] measured ^{17}O chemical shifts for several aliphatic aldehydes and ketones and concluded that the shift data for various groups was additive with a standard deviation of 2.5 ppm.

We have observed interesting trends for the chemical shifts of *ether oxygen* atom in each substituted tetrahydro-4-pyranone (Scheme I) in this work. Values above the arrows are for shielding (-) or deshielding (+) effects due to substituents. When compared to standard **7**, *cis*-phenyl groups in the 2- and 6-positions caused a *deshielding* effect of

Scheme I



39.6 ppm as found in **16.** Whereas, when the phenyl groups are *trans*-oriented, a slightly diminished deshielding effect of 35.6 ppm is noted (in **22**). A similar situation has been observed by Eliel and co-workers[43] in certain 1,3-dioxanes. Ether oxygen in *cis*-4,6-dimethyl-1,3-dioxane is deshielded by 22.7 ppm whereas in *trans*-4,6-dimethyl-1,3-dioxane, C-^{17}O-C is deshielded by 17.1 ppm (compared with 1,3-dioxane). Increased deshielding for C-^{17}O is observed in the dimethyl analogue **31** compared to **7** (+57.5 ppm) or to **16** (+17.9 ppm). Unfortunately, no related model systems could be found in

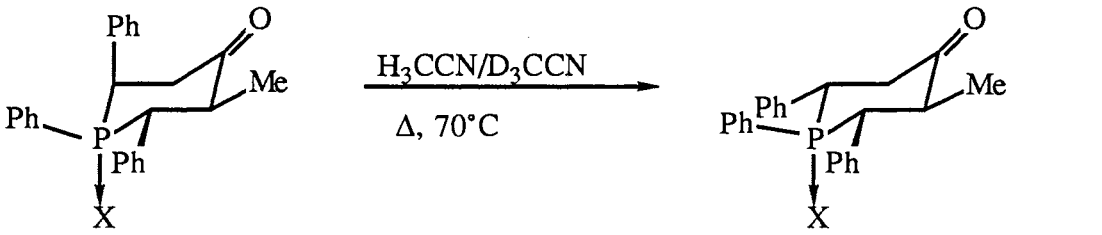
the literature. However, we note that in tetrahydro-4-pyranones with equatorial substituents at the 2-, 3-, 5- and 6-positions, a deshielding effect occurs for C=^{17}O which proved helpful in the study of conformations in bicyclo[3.3.1]nonan-ones containing a tetrahydropyran ring system which will be discussed shortly.

We have observed the ^{17}O chemical shift of the oxygen in P→^{17}O of 4-phosphorinanone 1-oxides (Tables XII, XIII, XIV and XVII), and we were also able to detect the P→^{17}O coupling in these systems. The P→^{17}O signal in triphenylphosphine oxide (**25**) is at 49.2 ppm (Table XIII) with $^{1}J_{PO}$ = 162 Hz (lit.[60] 160 Hz), while 1-phenyl-4-phosphorinanone 1-oxide (**11**) has a P→^{17}O shift of 43.6 ppm (Table XII) with $^{1}J_{PO}$ = 156 Hz. The chemical shift in **24**, which has *trans*-phenyl groups in the 2- and 6-positions, is 48.4 ppm with $^{1}J_{PO}$ = 130 Hz. The oxygen atom of P→^{17}O in **24** is *deshielded* by 4.8 ppm (compared to that in **11**) and is accompanied by a decrease in the $^{1}J_{PO}$ value (156 Hz in **11** and 130 Hz in **24**) which is not unreasonable because of the drastic difference in environment around the P→^{17}O bond in the two systems. There is a greater change in the P→^{17}O shift and the $^{1}J_{PO}$ value in **35** (Table XV) compared to **11** and **24**, the values for **35** being 30.5 ppm and 167 Hz, respectively. The 2,6-phenyl groups in **24** are in a *trans*-arrangement, while in **35** the 2,6-phenyl groups are *syn* to one another; however, there is a methyl group in the 3-position in **35** which appears to shield the P→^{17}O group and change the $^{1}J_{PO}$ value. In the 2,2,6,6-tetramethyl analogue **40** (Table XVII), the oxygen in P→^{17}O is even more *shielded* at 27.4 ppm (compared to **11**, **25**, and **35**, see Table XV) and has a $^{1}J_{PO}$ value of 167 Hz. This seems to suggest that as steric effects increase around P→O groups, there is a *shielding* effect with concomitant increase in the $^{1}J_{PO}$ value.

We have observed a novel case of isomerization in two members of the 4-phosphorinanone family under the conditions of our experiment, and this is outlined in Scheme II. Using an authentic sample[58] of *trans*-isomer **34'**, heating in the solvents shown for 16 hours produced a C=^{17}O resonance at 564.60 ppm which persisted even

after 24 hours. However, with authentic sample[58] of *cis*-isomer **34**, a signal for C=^{17}O appeared at 564.44 ppm within 20 hours. Thus, it was concluded that only the C=^{17}O signal for **34** was observed in both experiments which was supported by the $w_{1/2}$ of 460 Hz and 457 Hz for the two signals, respectively. The differences in δ and $w_{1/2}$ values are within experimental error. Unfortunately, the ^{17}O signals could not be observed prior to the times specified and this prevented any observations of the decay of **34'** or **35'**.

Scheme II



34' X = lone pair

35' X = O

34 X = lone pair

35 X = O

The same situation was observed for *trans*-oxide **35'** and *cis*-oxide **35**, i.e. heating authentic **35'** in the system gave only **35** for which a C=^{17}O signal occurred at 575.53 ppm with an ^{17}O signal from P→^{17}O at 30.48 ppm ($^{1}J_{P\rightarrow O}$ = 167 Hz). The data for the product from heating **35'** was essentially identical. These observations were not totally unexpected, as we had reported a similar case of isomerization in this family under quite different conditions.[58] Previously noted was that the *trans*-isomer **34'** isomerized to the *cis*-isomer **34** when the former was heated in a sealed glass tube under N_2 to a temperature of 200-210°C for 2 h. Although heating of keto phosphine **34'** to 70°C seems modest, possibly inherent strain induced by steric congestion around the P atom is sufficient to promote the isomerization at the lower temperature in acetonitrile.

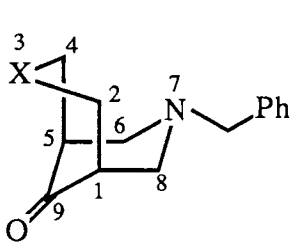
In Table XVIII, we listed all phosphorus heterocycles examined. We recognized that **10-12**, **23-24**, and **39-40** are likely dynamic systems in solution in contrast to **34** and

35 which are likely biased. Consequently, the ^{17}O shifts for the former molecules must be considered average values for C=^{17}O. It is clear in all families that ^{17}O shifts for all P-oxides and P-sulfides occur *downfield* compared to the corresponding phosphines, with the signals for P-sulfides being at lowest field. It is noteworthy that as substitution of a proton by a methyl group occurs *alpha* to the C=O group such as X=P is changed to X=P→O, (compare **34** and **35**), a large deshielding of ^{17}O in C=^{17}O occurs. As steric congestion increases around phosphorus, as in **40** versus **41**, the shift differences in the ^{17}O resonances in the C=^{17}O groups are quite large. We suspect that the larger size of the S atom is not compensated enough by the longer P→S bond in **41** (compared to the P→O bond in **40**) with the result being a marked downfield effect on the ^{17}O resonance in C=^{17}O. Possibly, in **41** there is some ring distortion because of crowding around phosphorus. It has been presumed[47] that P→G (X = O, S, etc.) bonds in systems like **10-12**, **23**, **24**, **34**, **35**, and **39-41** have a propensity to occupy an axial position predominantly. Therefore, it is tempting to speculate that the large sulfur causes a *deshielding effect on the* C=^{17}O resonance because of non-bonding through-space interactions such as dipole-dipole interactions or changes in local van der Waals interactions.[13,46] Moreover, even in an axial position, the P→S group may induce a twist in the ring to relieve the strain in **41**. This in turn might result in a closer position of S in the P→S groups to the C in C=O.

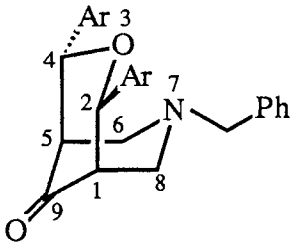
We have an interest in the conformational analysis of 3,7-diheterabicyclo[3.3.1]-nonanes and their derivatives as potential antiarrhythmic agents.[70] Present in these bicyclic ketones are two 1-hetera-4-cyclohexanone moieties. It will be recalled that some trends in C=^{17}O shifts induced by substituents were visible in the 1-hetera-4-cyclohexanones examined (Tables XII, XV and XVI). Substituting methyl groups at the 3(e)- and 5(e)-positions in cyclohexanones resulted in an *upfield* shift of about 20 ppm (Table XVI). Crandall and co-workers[18] noted that substituting methyl groups in the 2(a)-position in cyclohexanone and related cyclohexanones resulted in *downfield* shifts of 2-6

ppm in C=^{17}O. In analogy, bicyclic systems **42** and **46** (Table XIX) have *axial* C–C bonds at positions *alpha* to the C=O group. Single crystal X-ray analyses have been reported for **42**[64] and **46**,[70] and selected data for these compounds are listed in Table XXIV. Both compounds exist in a chair-boat conformation in the solid state. The C(1)-C(2) and C(4)-C(5) bonds are *axially* oriented to the *N*-benzyl-4-piperidinone ring.

The ^{17}O chemical shifts of bicyclic ketones **42-48** are listed in Table XIX. The shift differences between these bicyclic ketones and their monocyclic counterparts are listed in Table XX and were calculated as follows. The chemical shifts of the C=^{17}O bicyclic ketone were subtracted from the average of the chemical shifts of the carbonyl oxygens for the two 1-hetera-4-cyclohexanones making up the bicyclic ketone skeleton. For example, in ketone **42** which contains both *N*-methyl and an *N*-benzyl-4-piperidinone rings, the ^{17}O shift of carbonyl oxygen was subtracted from the *average* of the C=^{17}O shift for *N*-methyl- and *N*-benzyl-4-piperidinones. These differences reveal an *upfield* shift compared with the monocyclic ketones. In analogy with the observation of Crandall and co-workers,[18] we expected a *downfield* shift of about 2-6 ppm, contrary to a significant *upfield* shift of about 5-17 ppm observed in these bicyclic ketones with axially oriented substituents which are also alpha to the carbonyl group. Such *upfield* shifts seem possible only if there is significant interaction between the lone pair on the heteroatom and the p orbital of the carbon of the C=^{17}O carbonyl group, a result which could cause increased electron density on the carbonyl oxygen or increased single bond character in C=O. Thus, in ketone **42** (X = *N*-CH_3) an *upfield* shift of 14.28 ppm is noted, while in ketone **46**



42-47



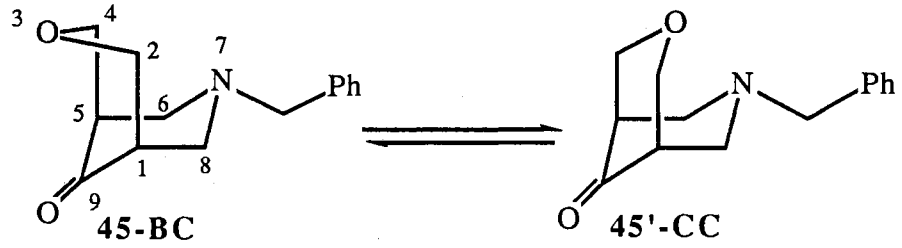
48 (Ar=*o*-ClC_6H_4)

(X = S) an upfield shift of only 5.15 ppm is observed. The torsion angles X(3)-C(2)-C(1)-C(9) [1.9° (**42**)[64] and 2.9° (**46**)[70] and X(3)-C(4)-C(5)-C(9) [-0.4° (**42**)[64] and -2.6° (**46**)[70]] (Table XXIV) are not significantly different in these two compounds. However, the bond lengths of C(2)-X(3) and C(4)-X(3) are quite different (1.46 Å and 1.81 Å in **42**[64] and **46**,[70] respectively). Thus the lone pair on nitrogen of the *N*-CH_3 group in **42** may be closer to the carbonyl group than is the lone pair on sulfur in **46** which also is in a flattened ring. In **42**, a boat–chair seems plausible to cause significant *shielding* of the carbonyl group, whereas in **46** we observe a diminished *upfield* ^{17}O shift.

It appears that a boat–chair conformation is preferred in acetonitrile at 70° for **42** and probably for **46** although the latter has less influence by S on altering charge in C=^{17}O because of the flattened ring and long C–S bonds. Three other members of this family, namely **43**, **44**, and **45**, also follow the same trend and hence appear to be in a boat–chair (BC) conformation with the ring containing the *N*-benzyl group in a chair conformation. An average upfield shift for ^{17}O in the C=^{17}O in ketones **42-45** is 15.8 ± 1.3 ppm, as determined by the method in Table XX and discussed previously. We presume that C(2)–X and C(4)–X bond lengths are comparable in **42-45**. Moreover, we assume in **43**, where X = O, the C(2,4)–X bonds are of comparable length as found in **7**[2] (1.41 Å) and in 7-benzyl-2,4-di(2-chlorophenyl)-7-aza-2-oxabicyclo[3.3.1]nonan-9-one (**48**, 1.42 Å).[3]

Another interesting observation was made in detecting the chemical shift of *ether oxygen* in the ketone **45** (Table XIX). The ether C-^{17}O shift is at 1.0 ppm and is shielded by 9.3 ppm as compared with tetrahydro-4-pyranone (**7**, Table XII). This *upfield* C-^{17}O shift in **45** is contrary to the *downfield* shift of 17.9 ppm observed for the methylated tetrahydro-4-pyranone (**31**, Scheme I) and a downfield shift of 1.5 ppm observed in 3-methyltetrahydropyran.[26] While accounting for this observation, the differences in conformation, electronic environment, and steric factors should be considered. The tetrahydropyran ring in the compounds outlined in Scheme I and in 3-methyl-tetrahydropyran[26] exists in a chair conformation, while in ketone **45**, the ^{17}O data suggest

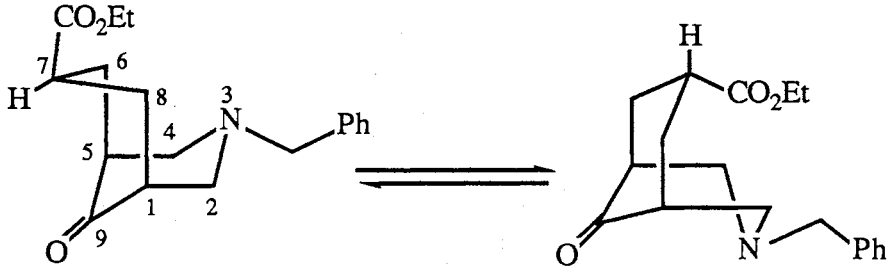
that a *boat* conformation or perhaps a boat chair equilibrium is present. A chair–boat boat–chair equilibrium has been observed, via dynamic NMR studies, in a related system with phenyl groups at the 1,5-positions.[68] Moreover, there is probably a significant interaction between a lone pair on oxygen in the tetrahydropyran ring of **45** and the p orbital of the π system in C=^{17}O. The chair–chair conformer **45'** might be less stable due



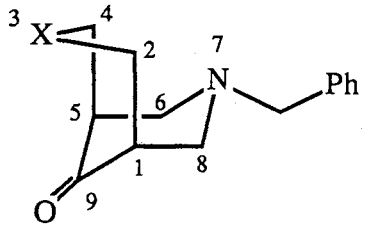
to nonbonding repulsive interactions between the lone pairs on nitrogen and oxygen. Moreover, solvation of the system in boat–chair conformation might be easier as compared with the chair–chair conformer, thus leading to greater stabilization of the boat–chair conformer in acetonitrile. It is possible that both of these factors can cause a *downfield* C=^{17}O shift, but solvation may be the more important factor. Taken on the whole, the above observations support a boat–chair (BC, X = O) conformation for **45** in D_3CCN/H_3CCN.

Ketone **47** also appears to be in boat–chair (BC, X = $CHCO_2Et$) conformation. For certain related bicyclic ketones, a boat–chair conformation has been suggested by Speckamp and Peters based on ^1H and ^{13}C NMR analysis.[12] The C=^{17}O shift in ketone **47** is 547.17 ppm, which is upfield by 11.33 ppm from the average of the ^{17}O shifts of both *N*-benzyl-4-piperidinone (**5**) and cyclohexanone (**1**). This shift difference value is slightly smaller than those observed for ketones **42**-**45**. Speckamp and Peters suggested that the carboethoxy group is in the *endo*-position and that the ring bearing the carboethoxy group is in boat conformation in related systems.[12] If their observations hold for keto ester **47**, then the ketone C=^{17}O should experience a *downfield* shift and not an *upfield* shift as observed for ketones **42**-**46**. However, there is no electronegative atom

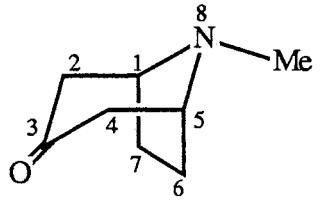
or group present in the 7-*exo*-position of **47**, which would produce a shielding effect on the ketone C=^{17}O (the carboethoxy group in the *endo* position cannot cause such an effect – compare **47** with **42-46**). Thus, it is possible that there is a boat–chair (BC, **47**) chair–boat (CB, **47'**) equilibrium in this system. Consequently, this C=^{17}O NMR study seems to suggest that 7-benzyl-7-aza-3-heterabicyclo[3.3.1]nonan-9-ones **42-47** exist in boat–chair (BC) conformations in acetonitrile at 70°C.



47 BC **47' CB**



42-46



49

An interesting model system related to **42-47** is tropinone (**49**). The ^{17}O chemical shift of tropinone (**49**) is 573.91 ppm which is *downfield* by 13.57 ppm compared with *N*-methyl-4-piperidinone (**3**). An analogous effect was observed in the study of several cyclohexanones with methyl groups in the 3(a)- and 5(a)-positions [*downfield* shift for ^{17}O of 15.3 ppm, compared to cyclohexanone (**1**)][18] whereas when the methyl groups were in the 3(e)- and 5(e)-positions, a *downfield* shift of only 1.3 ppm was detected.[18] This supports the 6-membered ring in **49** as being in a *chair* conformation with the ethylene bridge axially oriented. Solid state conformation of **48** has not been established, from a literature search.

In summary, forty-one 1-hetera-4-cyclohexanones have been examined via ^{17}O NMR spectroscopy for the purpose of determining whether or not a correlation exists between $\delta^{17}O$ in C-^{17}O and stereochemical and electronic properties of the systems. Correlation between the ^{17}O shifts and the electronegativity of heteroatoms and the C-X bond lengths have been observed. Substituents at the 2- and 6-positions in the ring result in *downfield* shifts, while equatorial substituents at the 3- and 5-positions result in *upfield* shifts. The C=^{17}O chemical shifts of 3,7-diheterabicyclo[3.3.1]nonan-9-ones **42-47** suggest that these systems may exist in boat–chair (BC) conformations in acetonitrile. Thus, the trends observed for $\delta^{17}O$ from analysis of C-^{17}O strongly suggest that such data can be most instructive in diagnosing stereochemical features in 1-hetera-4-cyclohexanones.

CHAPTER III

EXPERIMENTAL

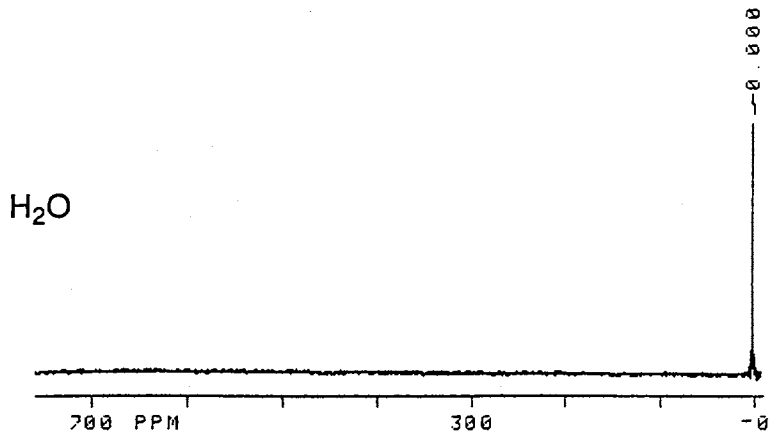
All compounds used in this study were commercially available or were prepared via literature procedures. The following commercially available compounds were purified by distillation prior to use, under conditions described: acetonitrile (dried over CaH_2, 83-84°C, stored over molecular sieves, 3A, Fisher), cyclohexanone (**1**) (154-156°C, Aldrich), *N*-methyl-4-piperidinone (**3**) (49-50°C/0.3 mm Hg, Aldrich), *N*-isopropyl-4-piperidinone (**4**) (38-41°C/0.5 mm Hg, Aldrich), *N*-benzyl-4-piperidinone (**5**) (111-112°C/0.3 mm Hg, Aldrich), and tetrahydro-4*H*-pyran-4-one (**7**) (166-167°C, Aldrich). Tropinone (**48**, Aldrich) was recrystallized (hexanes, mp 44-44.5°C). 4-Piperidinone (**2**) and 2,2,6,6-tetramethyl-4-piperidinone (**37**) were purchased (Aldrich) as hydrochlorides and then dissolved in H_2O to give a solution which was made basic to pH 12 (10% aq. NaOH solution). The free amines were extracted (ether) from the basic solution, after drying (Na_2SO_4), the extracts were subjected to evaporation (rotary evaporator, aspirator). The crude amines were oils and were used without further purification. The following materials were obtained from commercial sources and were also used without further purification: acetonitrile-d_3 (99 atom % D, Aldrich), 1-benzoyl-4-piperidinone (**6**) (mp 55-59°C, Aldrich), triphenylphosphine oxide (**21**, Aldrich) and 3,3,5,5-tetramethylcyclohexanone (**36**, Aldrich). The following compounds were prepared previously and fully identified: tetrahydro-4*H*-thiopyran-4-one (**8**),[29,55] 4-selenanone (**9**),[69] 1-phenyl-4-phosphorinanone (**10**),[65] 1-phenyl-4-phosphorinanone 1-oxide (**11**),[50] 1-phenyl-4-phosphorinanone 1-sulfide (**12**),[71] *cis*-3,5-diphenylcyclohexanone (**13**),[6,55] *cis*-2,6-diphenyl-4-piperidinone (**14**),[7,55] *r*-2,*cis*-6(e)-diphenyl-1(e)-*trans*-methyl-4-piperidinone

(**15**),[7,55] *cis*-2,6-diphenyltetrahydro-4*H*-pyran-4-one (**16**),[10,6] *cis*-2,6-diphenyltetrahydro-4*H*-thiopyran-4-one (**17**),[8,55] *cis*-2,6-di(4-methylphenyl)-4-selenanone (**18**),[52] *cis*-2,6-di(4-methoxyphenyl)-4-selenanone (**19**),[44,52] *r*-1,*trans*-2(e),6(e)-triphenyl-4-phosphori-nanone (**20**),[48,58] *trans*-2,6-diphenyltetrahydro-4*H*-pyran-4-one (**22**),[10,55] *trans*-2,6-diphenyltetrahydro-4*H*-thiopyran-4-one (**23**),[27,55] *r*-1,*trans*-2(e)-*cis*-6(a)-triphenyl-4-phosphorinanone (**24**),[48,58] *r*-1,*trans*-2(e)-*cis*-6(e)-triphenyl-4-phosphori-nanone 1-oxide (**25**),[57,58] *r*-2,*cis*-6(e)-diphenyl-*trans*-3(e)-methyl-4-piperidinone (**26**),[7,55] *r*-2,*cis*-6(e)-diphenyl-*trans*-3(e),5(e)-dimethyl-4-piperidinone (**27**),[7,55] *r*-2,*cis*-6(e)-di(4-methoxy-phenyl)-*trans*-3(e)-methyltetrahydro-4*H*-pyran-4-one (**28**),[62] *r*-2,*cis*-6(e)-di(4-methoxy-phenyl)-*trans*-3(e),5(e)-dimethyltetrahydro-4*H*-pyran-4-one (**29**),[62] *r*-2,*cis*-6(e)-di(4-methylphenyl)-*trans*-3(e),5(e)-dimethyltetrahydro-4*H*-pyran-4-one (**30**),[62] *r*-2,*cis*-6(e)-diphenyl-*trans*-3(e),5(e)-dimethyltetrahydro-4*H*-pyran-4-one (**31**),[37,55] *r*-2,*trans*-6(a)-diphenyl-*cis*-3(e)-methyltetrahydro-4*H*-thiopyran-4-one (**32**),[55] *r*-2,*cis*-6(e)-diphenyl-*trans*-3(e)-methyltetrahydro-4*H*-thiopyran-4-one (**33**),[55] *r*-1,*trans*-2(e)-*cis*-6(e)-triphenyl-*cis*-3(e)-methyl-4-phosphorinanone (**34**),[56] *r*-1,*trans*-2(e)-*cis*-6(e)-triphenyl-*cis*-3(e)-methyl-4-phosphorinanone 1-oxide (**35**),[56] 2,2,6,6-tetramethyltetrahydro-4*H*-thiopyran-4-one (**38**),[53,55] 1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanone (**39**),[57] 1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanone 1-oxide (**40**),[4] 1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanone 1-sulfide (**41**),[75] 3-benzyl-7-methyl-3,7-diazabicyclo-[3.3.1]nonan-9-one (**42**),[63] 7-benzyl-3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**43**),[76] 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**44**),[11,51] 7-benzyl-7-aza-3-oxabicyclo-[3.3.1]nonan-9-one (**45**),[3] 7-benzyl-7-aza-3-thiabicyclo[3.3.1]nonan-9-one (**46**),[5] and 3-benzyl-3-azabicyclo[3.3.1]nonan-9-one, 7-carboxylic acid, ethyl ester, *endo* (**47**).[51]

The ^{17}O NMR spectra were recorded on a Varian XL-400 spectrometer equipped with a 10-mm broad-band, variable temperature probe operating at 54.2 MHz. All spectra were acquired at natural abundance ^{17}O at 70°C in a 2:1 (v/v) mixture of acetonitrile (H_3CCN)

and acetonitrile-d_3 (D_3CCN, 99 atom % D). The concentration of most ketones examined was 0.16 M, except for the selenium and phosphorus containing ketones **18**, **19**, **20**, **24**, **25**, **34** and **35**. The latter were examined as saturated solutions at 70°C (due to poor solubility in H_3CCN:D_3CCN mixture, the concentration is estimated to be about 0.05-0.10 M). Distilled, deionized water was used as an external reference in a 5 mm tube, placed concentrically within a sample tube of 10 mm o.d. containing 2:1 mixture of H_3CCN:D_3CCN. The oxygen of water was referenced to 0 ppm. The spectra of ketones were added to the spectrum of water using the add-sub routine. The instrumental settings were: spectral width 44248 Hz, 1024 data points, 40 μs pulse width (PW 90 = 50 μs), 1 ms acquisition delay, 0.012 sec acquisition time and 1 x 10^5 to 4 x 10^6 scans. The spectra were recorded with sample spinning and deuterium lock. The signal-to-noise ratio was improved by applying a 20 Hz exponential broadening factor to the FID prior to Fourier transformation. The digital resolution was improved to ± 1.4 Hz by zero filling to 16K data points prior to Fourier transformation. The reproducibility of the chemical shift data is estimated to be greater than ± 1.0 ppm.

Plate I

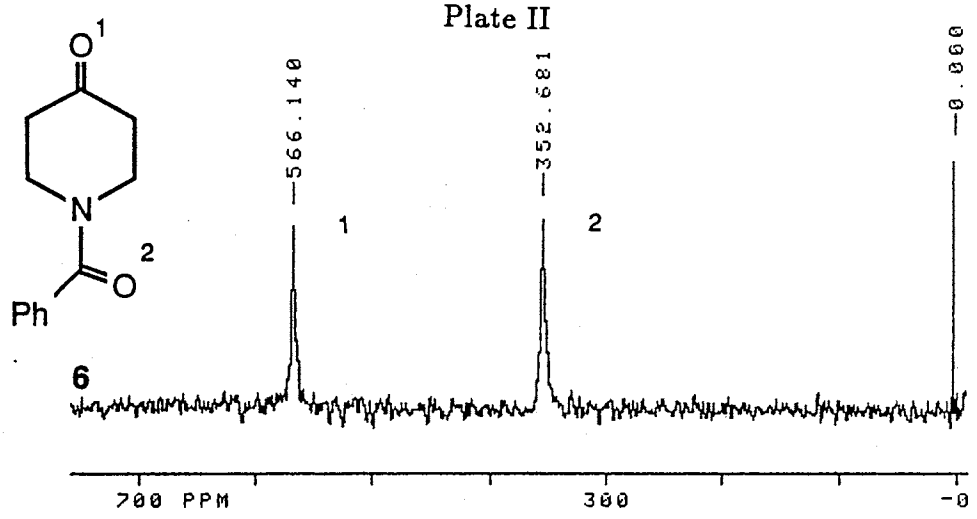


ACQUISITION				PROCESSING	
SFRQ	54.2	DATE	10-04-88	SE	0.016
TN	17.000	SOLVNT	CD3CN	LB	20.000
SW	44247.8	FILE	HOAN70	RE	NOT USED
AT	0.012			CD	NOT USED
NP	1024	DECOUPLING		CCD	NOT USED
BS	1024	DN	1.500	AF	NOT USED
SS	0	DO	1999.8	FN	16384
PW	40.0	DM	NNN	MATH	F
P1	0	DHP	NOT USED	WERR	VTM
D1	1.00E-3	DLP	20	WEXP	VTM
D2	0	HOMO	N	WBS	WFT
TO	18729.5			WNT	WFT
NT	1.00E 6	FLAGS			
CT	10240	IL	N	SPECIAL	
		IN	N	TEMP	70.0
		DP	Y	PW90	50.0
		HS	NN		
		ALOCK	Y		
		USER			

CALC OF LINEWIDTH AT HALF HEIGHT
LINEWIDTH = 71.83 HZ
DIGITAL RESOLUTION= 1.351 HZ

^{17}O NMR Spectrum of H_2O

Plate II



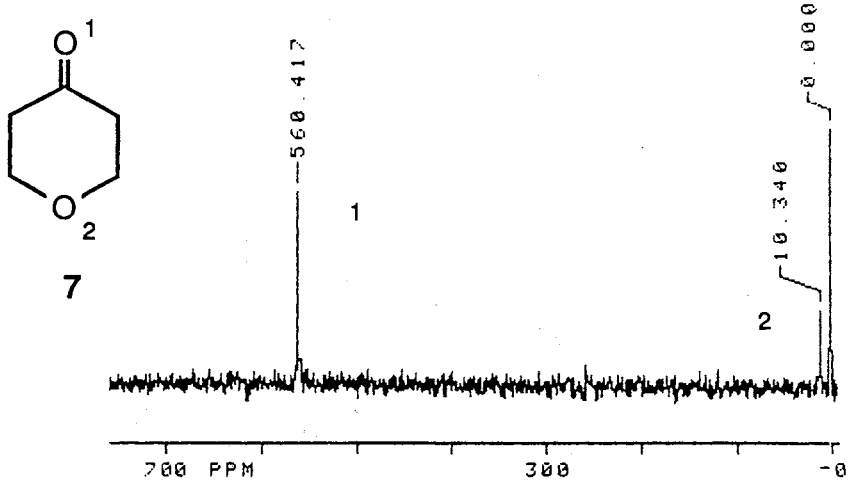
ACQUISITION				PROCESSING	
SFRQ	54.2	DATE	10-24-88	SE	0.016
TN	17.000	SOLVNT	CD3CN	LB	20.000
SW	44247.8	FILE	A12070	RE	NOT USED
AT	0.006			CD	NOT USED
NP	512	DECOUPLING		CCD	NOT USED
BS	16384	DN	1.500	AF	NOT USED
SS	0	DO	1999.8	FN	16384
PW	40.0	DM	NNN	MATH	F
P1	0	DHP	NOT USED	WERR	VTM
D1	0	DLP	20	WEXP	VTM
D2	0	HOMO	N	WBS	WFT
TO	18729.5			WNT	WFT
NT	1.00E 6	FLAGS			
CT	327680	IL	N	SPECIAL	
		IN	N	TEMP	70.0
		DP	Y	PW90	50.0
		HS	NN		
		ALOCK	Y		
		USER			

CALC OF LINEWIDTH AT HALF HEIGHT
LINEWIDTH = 184.55 HZ
DIGITAL RESOLUTION= 1.351 HZ

CALC OF LINEWIDTH AT HALF HEIGHT
LINEWIDTH = 223.17 HZ
DIGITAL RESOLUTION= 1.351 HZ

^{17}O NMR Spectrum of **6**

Plate III



7

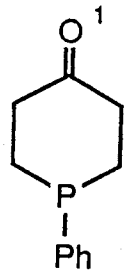
ACQUISITION				PROCESSING	
SFRQ	54.2	DATE	10-04-88	SE	0.016
TN	17.000	SOLVNT	CD3CN	LB	20.000
SW	44247.8	FILE	A5070A	RE	NOT USED
AT	0.012			CD	NOT USED
NP	1024	DECOUPLING		CCD	NOT USED
BS	4096	DN	1.500	AF	NOT USED
SS	0	DO	1999.8	FN	16384
PW	40.0	DM	NNN	MATH	F
P1	0	DHP	NOT USED	WERR	VTM
D1	1.00E-3	DLP	20	WEXP	VTM
D2	0	HOMO	N	WBS	WFT
TO	18729.5			WNT	WFT
NT	1.00E 6	FLAGS			
CT	106496	IL	N	SPECIAL	
		IN	N	TEMP	70.0
		DP	Y	PW90	50.0
		HS	NN		
		ALOCK	Y		
		USER			

CALC OF LINEWIDTH AT HALF HEIGHT
LINEWIDTH = 85.08 HZ
DIGITAL RESOLUTION= 1.351 HZ

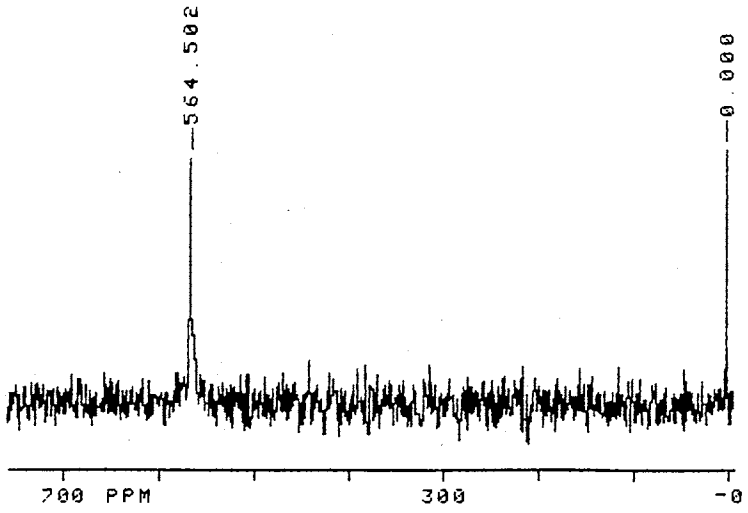
CALC OF LINEWIDTH AT HALF HEIGHT
LINEWIDTH = 82.97 HZ
DIGITAL RESOLUTION= 1.351 HZ

^{17}O NMR Spectrum of 7

Plate IV



10

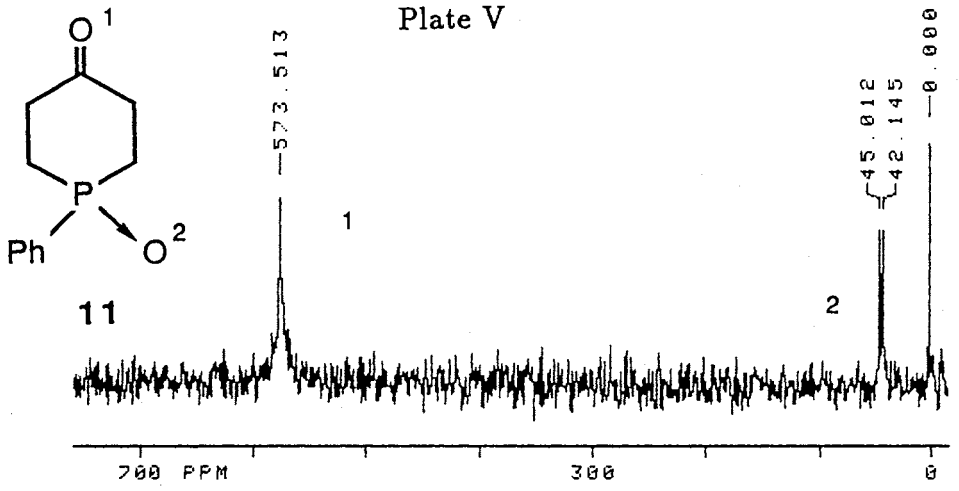


ACQUISITION				PROCESSING	
SFRQ	54.2	DATE	10-04-88	SE	0.016
TN	17.000	SOLVNT	CD3CN	LB	20.000
SW	44247.8	FILE	A7070A	RE	NOT USED
AT	0.012			CD	NOT USED
NP	1024	DECOUPLING		CCD	NOT USED
BS	4096	DN	1.500	AF	NOT USED
SS	0	DO	1999.8	FN	16384
PW	40.0	DM	NNN	MATH	F
P1	0	DHP	NOT USED	WERR	VTM
D1	1.00E-3	DLP	20	WEXP	VTM
D2	0	HOMO	N	WBS	WFT
TO	18729.5			WNT	WFT
NT	1.00E 6	FLAGS			
CT	114688	IL	N	SPECIAL	
		IN	N	TEMP	70.0
		DP	Y	PW90	50.0
		HS	NN		
		ALOCK	Y		
		USER			

CALC OF LINEWIDTH AT HALF HEIGHT
LINEWIDTH = 146.93 HZ
DIGITAL RESOLUTION= 1.351 HZ

^{17}O NMR Spectrum of **10**

Plate V



ACQUISITION				PROCESSING	
SFRQ	54.2	DATE	10-04-88	SE	0.016
TN	17.000	SOLVNT	CD3CN	LB	20.000
SW	44247.8	FILE	A10070	RE	NOT USED
AT	0.012			CD	NOT USED
NP	1024	DECOUPLING		CCD	NOT USED
BS	16384	DN	1.500	AF	NOT USED
SS	0	DO	1999.8	FN	16384
PW	40.0	DM	NNN	MATH	F
P1	0	DHP	NOT USED	WERR	VTM
D1	0	DLP	20	WEXP	VTM
D2	0	HOMO	N	WBS	WFT
TO	18729.5			WNT	WFT
NT	1.00E 6	FLAGS			
CT	557056	IL	N	SPECIAL	
		IN	N	TEMP	70.0
		DP	Y	PW90	50.0
		HS	NN		
		ALOCK	Y		
		USER			

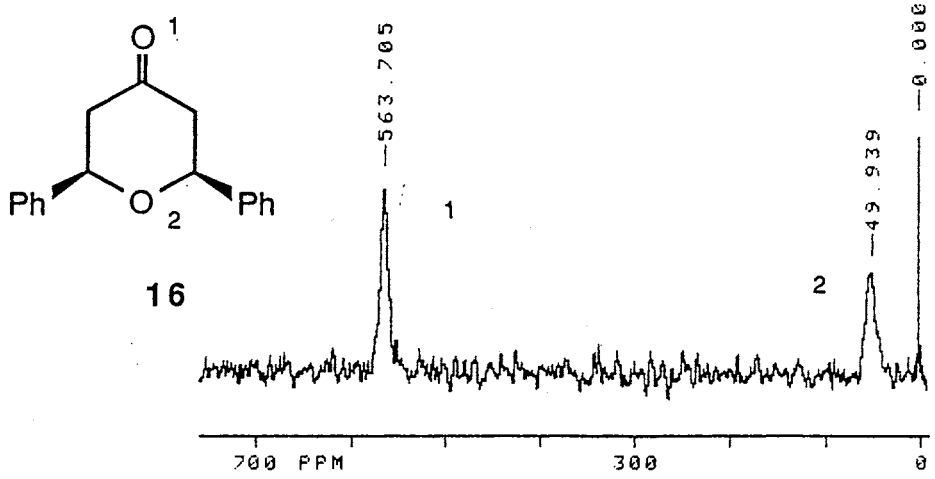
SPECTRAL LINES FOR TH= 48.53

INDEX	FREQ	PPM	INTENSITY
01	31095.1	573.513	67.993
02	2440.5	45.012	56.279
03	2285.0	42.145	56.411
04	0	0	87.441

CALC OF LINEWIDTH AT HALF HEIGHT
LINEWIDTH = 184.32 HZ
DIGITAL RESOLUTION= 1.351 HZ

^{17}O NMR Spectrum of **11**

Plate VI



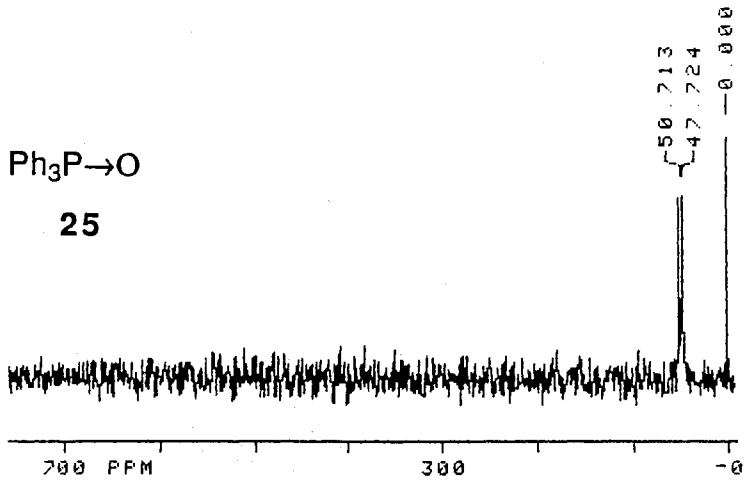
ACQUISITION				PROCESSING	
SFRQ	54.2	DATE	10-04-88	SE	0.016
TN	17.000	SOLVNT	CD3CN	LB	20.000
SW	44247.8	FILE	B4070A	RE	NOT USED
AT	0.006			CD	NOT USED
NP	512	DECOUPLING		CCD	NOT USED
BS	4096	DN	1.500	AF	NOT USED
SS	0	DO	1999.8	FN	16384
PW	40.0	DM	NNN	MATH	F
P1	0	DHP	NOT USED	WERR	VTM
D1	0	DLP	20	WEXP	VTM
D2	0	HOMO	N	WBS	WFT
TO	18729.5			WNT	WFT
NT	1.00E 6	FLAGS			
CT	335872	IL	N	SPECIAL	
		IN	N	TEMP	70.0
		DP	Y	PW90	50.0
		HS	NN		
		ALOCK	Y		
		USER			

CALC OF LINEWIDTH AT HALF HEIGHT
LINEWIDTH = 367.26 HZ
DIGITAL RESOLUTION= 1.351 HZ

CALC OF LINEWIDTH AT HALF HEIGHT
LINEWIDTH = 507.79 HZ
DIGITAL RESOLUTION= 1.351 HZ

^{17}O NMR Spectrum of **16**

Plate VII



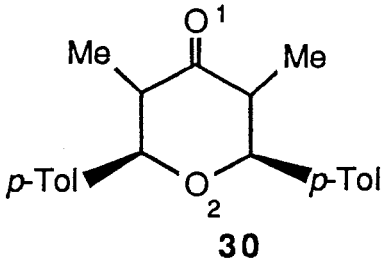
ACQUISITION				PROCESSING	
SFRQ	54.2	DATE	10-04-88	SE	0.016
TN	17.000	SOLVNT	CD3CN	LB	20.000
SW	44247.8	FILE	B9070A	RE	NOT USED
AT	0.012			CD	NOT USED
NP	1024	DECOUPLING		CCD	NOT USED
BS	16384	DN	1.500	AF	NOT USED
SS	0	DO	1999.8	FN	16384
PW	40.0	DM	NNN	MATH	F
P1	0	DHP	NOT USED	WERR	VTM
D1	0	DLP	20	WEXP	VTM
D2	0	HOMO	N	WBS	WFT
TO	18729.5			WNT	WFT
NT	1.00E 6	FLAGS			
CT	245760	IL	N	SPECIAL	
		IN	N	TEMP	70.0
		DP	Y	PW90	50.0
		HS	NN		
		ALOCK	Y		
		USER			

SPECTRAL LINES FOR TH= 58.13

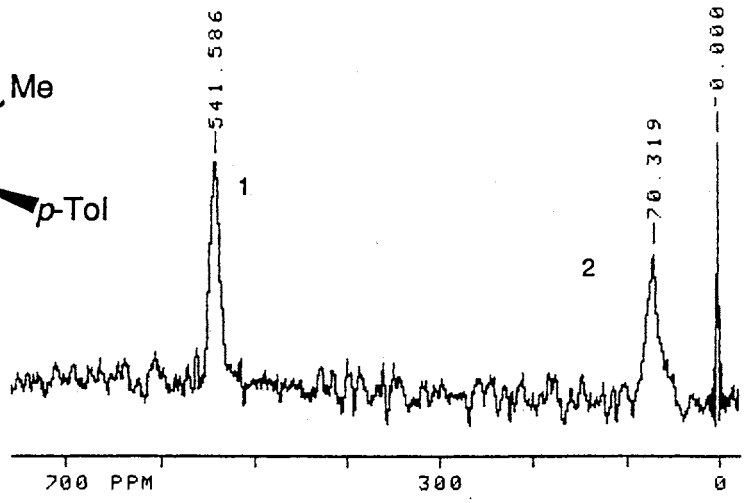
INDEX	FREQ	PPM	INTENSITY
01	2749.6	50.713	62.056
02	2587.6	47.724	62.280
03	0	0	82.059

^{17}O NMR Spectrum of **25**

Plate VIII



30



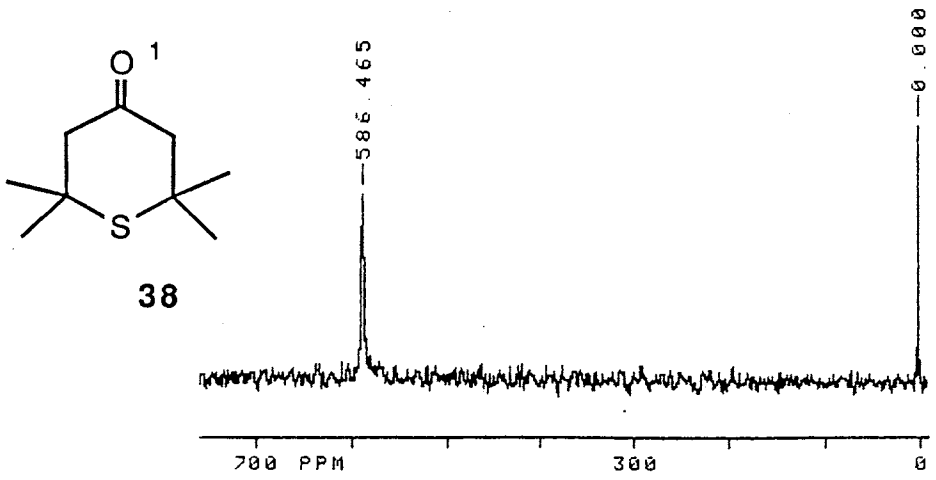
ACQUISITION				PROCESSING	
SFRQ	54.2	DATE	10-04-88	SE	0.016
TN	17.000	SOLVNT	CD3CN	LB	20.000
SW	44247.8	FILE	D4070A	RE	NOT USED
AT	0.006			CD	NOT USED
NP	512	DECOUPLING		CCD	NOT USED
BS	16384	DN	1.500	AF	NOT USED
SS	0	DO	1999.8	FN	16384
PW	40.0	DM	NNN	MATH	F
P1	0	DHP	NOT USED	WERR	VTM
D1	0	DLP	20	WEXP	VTM
D2	0	HOMO	N	WBS	WFT
TO	18729.5			WNT	WFT
NT	1.00E 6	FLAGS			
CT	376832	IL	N	SPECIAL	
		IN	N	TEMP	70.0
		DP	Y	PW90	50.0
		HS	NN		
		ALOCK	Y		
		USER			

CALC OF LINEWIDTH AT HALF HEIGHT
LINEWIDTH = 485.13 HZ
DIGITAL RESOLUTION= 1.351 HZ

CALC OF LINEWIDTH AT HALF HEIGHT
LINEWIDTH = 348.27 HZ
DIGITAL RESOLUTION= 1.351 HZ

^{17}O NMR Spectrum of **30**

Plate IX

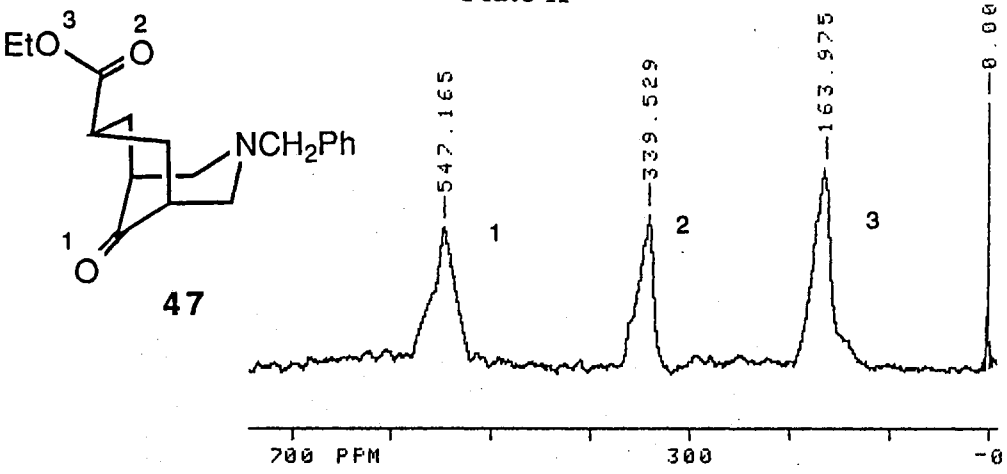


ACQUISITION				PROCESSING	
SFRQ	54.2	DATE	10-04-88	SE	0.016
TN	17.000	SOLVNT	CD3CN	LB	20.000
SW	44247.8	FILE	E3070A	RE	NOT USED
AT	0.006			CD	NOT USED
NP	512	DECOUPLING		CCD	NOT USED
BS	16384	DN	1.500	AF	NOT USED
SS	0	DO	1999.8	FN	16384
PW	40.0	DM	NNN	MATH	F
P1	0	DHP	NOT USED	WERR	VTM
D1	0	DLP	20	WEXP	VTM
D2	0	HOMO	N	WBS	WFT
TO	18729.5			WNT	WFT
NT	1.00E 6	FLAGS			
CT	196608	IL	N	SPECIAL	
		IN	N	TEMP	70.0
		DP	Y	PW90	50.0
		HS	NN		
		ALOCK	Y		
		USER			

CALC OF LINEWIDTH AT HALF HEIGHT
LINEWIDTH = 173.10 HZ
DIGITAL RESOLUTION= 1.351 HZ

^{17}O NMR Spectrum of **38**

Plate X



ACQUISITION				PROCESSING	
SFRQ	54.2	DATE	10-24-88	SE	0.016
TN	17.000	SOLVNT	CD3CN	LB	20.000
SW	44247.8	FILE	F7070A	RE	NOT USED
AT	0.012			CD	NOT USED
NP	1024	DECOUPLING		CCD	NOT USED
BS	16384	DN	1.500	AF	NOT USED
SS	0	DO	1999.8	FN	16384
PW	40.0	DM	NNN	MATH	F
P1	0	DHP	NOT USED	WERR	VTM
D1	0	DLP	20	WEXP	VTM
D2	0	HOMO	N	WBS	WFT
TO	18729.5			WNT	WFT
NT	4.98E 6	FLAGS			
CT	1.46E 6	IL	N	SPECIAL	
		IN	N	TEMP	70.0
		DP	Y	PW90	50.0
		HS	NN		
		ALOCK	Y		
		USER			

CALC OF LINEWIDTH AT HALF HEIGHT
LINEWIDTH = 799.68 HZ
DIGITAL RESOLUTION= 1.351 HZ

CALC OF LINEWIDTH AT HALF HEIGHT
LINEWIDTH = 251.16 HZ
DIGITAL RESOLUTION= 1.351 HZ

CALC OF LINEWIDTH AT HALF HEIGHT
LINEWIDTH = 534.91 HZ
DIGITAL RESOLUTION= 1.351 HZ

^{17}O NMR Spectrum of **47**

BIBLIOGRAPHY

1. Alder, F.; Yu, F. C. *Phys. Rev.*, **1951**, *81*, 1067.

2. Alonso, J. L. *J. Mol. Spec.*, **1980**, *84*, 520.

3. Arjunan, P.; Berlin, K. D.; Barnes, C. L.; van der Helm, D. *J. Org. Chem.*, **1981**, *46*, 3196.

4. Asinger, F.; Saus, S.; Michel, E. *Monatsh. Chem.*, **1968**, *99*, 1695.

5. Bailey, B. R.; Berlin, K. D.; Powell, D. R.; van der Helm, D. *Phosphorus and Sulfur*, **1984**, *21*, 121.

6. Balasubramanian, M.; D'souza, A. *Tetrahedron*, **1968**, *24*, 5399.

7. Balasubramanian, M.; Padma, N. *Tetrahedron*, **1963**, *19*, 2135.

8. Baliah, V.; Chellathurai, T. *Indian J. Chem.*, **1971**, *9*, 960.

9. (a) Baliah, V.; Jeyaraman, R.; Chandrasekaran, L. *Chem. Rev.*, **1983**, *83*, 379. (b) Eliel, E. L.; Pietrusiewicz, K. M. *^{13}C NMR of Nonaromatic Heterocyclic Compounds* In *Topics in Carbon-13 Spectroscopy*, Levy, G. C., Ed.; Wiley-Interscience, New York, 1979, Ch. 3, pp. 171-282. (c) Lambert, J. B.; Featherman, S. I. *Chem. Rev.*, **1975**, *75*, 611.

10. Baxter, C. A. R.; Whiting, D. A. *J. Chem. Soc. C*, **1968**, 1174.

11. Binnig, F.; Raschack, M.; Treiber, H.-J.; Knoll A. G. Chemische Fabriken, Germany; U.S. Patent 3,962,449, 1976; *Chem. Abstr.*, **1976**, *84*, 150675x.

12. (a) Bok, Th. R.; Speckamp, W. N. *Tetrahedron*, **1979**, *35*, 267. (b) Peters, J. A.; Baas, J. M. A.; van de Graff, B.; van der Toorn, J. M.; van Bekkum, H. *Tetrahedron*, **1978**, *34*, 3313. (c) Peters, J. A.; van der Toorn, J. M.; van Bekkum, H. *Tetrahedron*, **1974**, *30*, 633.

13. Boykin, D. W.; Baumstark, A. L. *Tetrahedron*, **1989**, In press.

14. Christ, H. A. *Helv. Phys. Acta*, **1960**, *33*, 572.

15. Christ, H. A.; Diehl, P. *Helv. Phys. Acta*, **1963**, *36*, 170.

16. Christ, H. A.; Diehl, P.; Schneider, H. R.; Dahn, H. *Helv. Chimica Acta*, **1961**, *44*, 865.

17. Crandall, J. K.; Centeno, M. A. *J. Org. Chem.*, **1979**, *44*, 1183.

18. Crandall, J. K.; Centeno, M. A.; Borrensen, S. *J. Org. Chem.*, **1979**, *44*, 1184.

19. Dahn, H.; Schlunke, H.-P.; Temler, J. *Helv. Chimica Acta*, **1972**, *55*, 907.

20. Delseth, C.; Kintzinger, J.-P. *Helv. Chimica Acta*, **1976**, *59*, 466.

21. Delseth, C.; Kintzinger, J.-P. *Helv. Chimica Acta*, **1978**, *61*, 1327.

22. Delseth, C.; Kintzinger, J.-P. *Org. Magn. Reson.*, **1978**, *11*, 38.

23. Dharmatti, S. S.; Sundara Rao, K. J.; Vijayaraghavan, R. *Nuovo Cimento*, **1959**, *11*, 656; *Chem Abstr.*, **1959**, *53*, 16703b.

24. Dillen, J.; Geise, H. J. *J. Mol. Struct.*, **1980**, *69*, 137.

25. Eliel, E. L.; Bailey, W. F.; Kopp, L. D.; Willer, R. L.; Bertrand, R.; Christensen, K. A.; Dalling, D. K.; Duch, M. W.; Wenkert, E.; Schell, F. M.; Cochron, D. W. *J. Am. Chem. Soc.*, **1975**, *97*, 322.

26. Eliel, E. L.; Pietrusiewicz, K. M.; Jewell, L. M. *Tetrahedron Letters*, **1979**, *38*, 3649.

27. El-Kholy, I. E.-S.; Rafla, F. K. *Tetrahedron Lett.*, **1965**, *20*, 1437.

28. Fakler, T M. Masters Thesis, Oklahoma State University, 1987.

29. Fehnel, E. A.; Carmack, M. *J. Am. Chem. Soc.*, **1948**, *70*, 1813.

30. Florin, A. E.; Alei, M. *J. Chem. Phys.*, **1967**, *47*, 4268.

31. Garrett, B. B.; Denison, A. B.; Rabideau, S. W. *J. Phys. Chem.*, **1967**, *71*, 2606.

32. Goldammer, E. V.; Hertz, H. G. *J. Phys. Chem.*, **1970**, *74*, 3734.

33. (a) Gray, G. A.; Albright, T. A. *J. Am. Chem. Soc.*, **1976**, *98*, 3857. (b) Gray, G. A.; Albright, T. A. *J. Am. Chem. Soc.*, **1977**, *99*, 3243.

34. Harris, R. K. in *Nuclear Magnetic Resonance Spectroscopy A Physicochemical View*, Pitman, London, 1983, pp 230-233.

35. Hindman, J. C.; Svirmickas, A.; Wood, M. *J. Phys. Chem.*, **1967**, *71*, 1266.

36. Hirsch, J. A.; Havinga, E. *J. Org. Chem.*, **1976**, *41*, 455.

37. Japp, F. R.; Maitland, W. *J. Chem. Soc.*, **1904**, 1473.

38. Jeyaraman, R.; Avila, S. *Chem. Rev.*, **1981**, *31*, 149.

39. Kintzinger, J.-P. *Oxygen NMR Characteristic Parameters and Application*, in *NMR Basic Principles and Progress, Volume 17, Oxygen-17 and Silicon-*

29, Diehl, P.; Fluck, E.; Kosfeld, R., Eds.; Springer-Verlag, New York, 1981, pp. 1-64.

40. Kintzinger, J.-P. *Oxygen-17 NMR*, in *NMR of Newly Accessible Nuclei*, Laszlo, P., Ed.; Academic Press, New York, 1983, Vol. 2, pp. 79-104.

41. Kintzinger, J.-P.; Lehn, J. M. *Mol. Phys.*, **1968**, *14*, 133.

42. Klemperer, W. G. *Angew. Chem. Intern. Ed. Engl.*, **1978**, *17*, 246.

43. Klemperer, W. G. in *The Multinuclear Approach to NMR Spectroscopy*, Lambert, J. B.; Riddel, F. G., Eds.; Reidel, Dordrecht, Holand, 1983, pp. 245-260.

44. Lalezari, I.; Ghanbarpour, F.; Ghapgharan, M. N.; Jafrinamin, R. *J. Heterocyclic Chem.*, **1974**, *11*, 469.

45. Lambert, J. B.; Featherman, S. I. *Chem. Rev.*, **1975**, *75*, 611.

46. (a) Li, S.; Chesnut, D. B. *Magn. Reson. Chem.*, **1985**, *23*, 625. (b) Li, S.; Chesnut, D. B. *Magn. Reson. Chem.*, **1986**, *24*, 93.

47. (a) Macdonnell, G. D.; Berlin, K. D.; Baker, J. R.; Ealick, S. E.; van der Helm, D.; Marsi, K. L. *J. Am. Chem. Soc.*, **1978**, *100*, 4535. (b) Featherman, S. I.; See, S. O.; Quin, L. D. *J. Org. Chem.*, **1974**, *39*, 2899.

48. Markl, G.; Fischer, D. E.; Olbrich, H. *Tetrahedron Letters*, **1970**, 645.

49. McPhail, A. T.; Breen, J. J.; Quin, L. D. *J. Am. Chem. Soc.*, **1971**, *93*, 2574.

50. Morris, D. L.; Berlin, K. D. *Phosphorus*, **1972**, *1*, 305.

51. Mulekar, S. V.; Otiv, S. R.; Berlin, K. D. unpublished results.

52. Nanjappan, P.; Ramalingam, K.; Herd, M. D.; Arjunan, P.; Berlin, K. D. *J. Org. Chem.*, **1980**, *45*, 4622.

53. Naylor, R. F. *J. Chem. Soc.*, **1949**, 2749.

54. Pauling L., *The Nature of Chemical Bond*, 3rd Edition, Cornell University Press, Ithaca, New York, 1960.

55. (a) Ramalingam, K.; Berlin, K. D.; Satyamurthy, N.; Sivakumar, R. *J. Org. Chem.*, **1979**, *44*, 471; (b) Ramalingam, K.; Berlin, K. D.; Loghry, R. A.; van der Helm, D.; Satyamurthy, N. *J. Org. Chem.*, **1979**, *44*, 477.

56. Rampal, J. B.; Berlin, K. D.; Edasery, J. P.; Satyamurthy, N.; van der Helm, D. *J. Org. Chem.*, **1981**, *46*, 1166.

57. Rampal, J. B.; Macdonnel, G. D.; Edasery, J. P.; Berlin, K. D.; Rahman, A.; van der Helm, D.; Pietrusiewicz, K. M. *J. Org. Chem.*, **1981**, *46*, 1156.

58. Rampal, J. B.; Satyamurthy, N.; Bowen, J. M.; Purdie, N.; Berlin, K. D. *J. Am. Chem. Soc.*, **1981**, *103*, 7602.

59. Reuben, J. *J. Am. Chem. Soc.*, **1969**, *91*, 5725.

60. Sammons, R. D.; Frey, P. A.; Bruzick, K.; Tsai, M.-D. *J. Am. Chem. Soc.*, **1983**, *105*, 5455.

61. Seip, R.; Seip, H. M.; Smith, Z. *J. Mol. Struct.*, **1976**, *32*, 279.

62. Selvaraj, K.; Nanjappan, P.; Ramalingam, K.; Ramarajan, K. *J. Chem. Soc. Perkin Trans. II*, **1983**, 49.

63. (a) Smith, G. S.; Berlin, K. D. unpublished results; (b) Smissman, E. E.; Ruenitz, P. C. *J. Org. Chem.*, **1976**, *41*, 1593.

64. Smith-Verdier, P.; Florencio, F.; Garcia-Blanco, S. *Acta Cryst.*, **1983**, *39C*, 101.

65. Snider, T. E.; Morris, D. L.; Srivastava, K. C.; Berlin, K. D. *Org. Syn.*, **1973**, *53*, 98.

66. Soderquist, J. A.; Shiau, F.-Y.; Lemesh, R. A. *J. Org. Chem.*, **1984**, *49*, 2565. This work contains citation to 1,1-dimethyl-1-sila-4-cyclohexanone but no ^{17}O shift was reported.

67. Sugawara, T.; Kawada, Y.; Katoh, M.; Iwamura, H. *Bull. Chem. Soc. Jpn.*, **1979**, *52*, 3391.

68. Takeuchi, Y.; Scheiber, P.; Takada, K. *J. C. S. Chem. Comm.*, **1980**, *403*.

69. Thompson, M. D.; Holt, E. M.; Berlin, K. D.; Sherlag, B. J. *J. Org. Chem.*, **1985**, *50*, 2580.

70. (a) Thompson, M. D.; Smith, G. S.; Berlin, K. D.; Holt, E. M.; Scherlag, B. J.; van der Helm, D.; Muchmore, S. W.; Fidelis, K. A. *J. Med. Chem.*, **1987**, *30*, 780. (b) Bailey, B. R.; Berlin, K. D.; Holt, E. M.; Scherlag, B. J.; Lazzara, R.; Brachmann, J.; van der Helm, D.; Powell, D. R.; Pantaleo, N. S.; Ruenitz, P. C. *J. Med. Chem.*, **1984**, *27*, 758.

71. Venkataramu, S. D.; Berlin, K. D.; Ealick, S. E.; Baker, J. R.; Nichols, S.; van der Helm, D. *Phosphorus and Sulfur*, **1979**, *7*, 133.

72. Versmold, H.; Yoon, C. *Ber. Bunsenges. Phys. Chem.*, **1972**, *76*, 1164; *Chem. Abstr.*, **1973**, *78*, 9890h.

73. Weast, R. C., Ed., *CRC Handbook of Chemistry and Physics*, CRC Press, Inc., Boca Raton, Florida, 1981-1982, 62nd Edition, F-176.

74. Weaver, H. E.; Tolbert, B. M.; La Force, R. C. *J. Chem. Phys.*, **1955**, *23*, 1956.

75. Welcher, R. P.; Day, N. E. *J. Org. Chem.*, **1962**, *27*, 1824.

76. Zisman, S. A.; Berlin, K. D. unpublished results.

VITA

Satish Vasant Mulekar

Candidate for the Degree of

Doctor of Philosophy

Thesis: PART I. SYNTHESIS AND ANTIARRHYTHMIC PROPERTIES OF SUBSTITUTED 3,7-DIAZABICYCLO[3.3.1]NONANES AND 3-AZABICYCLO[3.3.1]NONANES, AND DERIVATIVES

PART II. ^{17}O NMR ANALYSIS OF SUBSTITUTED 1-HETERA-4-CYCLOHEXANONES

Major Field: Chemistry

Biographical:

Personal Data: Born in Khalapur, Maharashtra, India on October 18, 1957, the son of Vasant V. and Shailaja V. Mulekar; married to Madhuri S. Nagardeolekar, May 15, 1985.

Education: Graduated from Sainik School, Bijapur, India in 1974; received the Bachelor of Science Degree in Chemistry from A. S. C. College, University of Bombay, India, in 1979; completed requirements for Doctor of Philosophy degree in Chemistry at Oklahoma State University in May 1989.

Professional Experience: Chemist, R & D, Indian Organic Chemicals Ltd., India, June 1977-June 1978; Chemist, R & D, Godrej Soaps Ltd., Bombay, India, June 1978-July 1982; Graduate Teaching Assistant, Department of Chemistry, Oklahoma State University, August 1982-May 1989; Research Assistant (NIH), Department of Chemistry, Oklahoma State University, January 1985-August 1986.

Professional Organizations: American Chemical Society, Phi Lambda Upsilon.