A STUDY OF STEREOCHEMICAL AND SUBSTITUENT EFFECTS ON ANTIARRHYTHMIC ACTIVITY OF SELECTED 3-AZABICYCLO[3.3.1]NONANES AND DERIVATIVES

By

STAN ALAN ZISMAN

Bachelor of Science

Cameron University

Lawton, Oklahoma

1985

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
December, 1989

A STUDY OF STEREOCHEMICAL AND SUBSTITUENT EFFECTS ON ANTIARRHYTHMIC ACTIVITY OF SELECTED 3-AZABICYCLO[3.3.1]NONANES AND DERIVATIVES

Thesis Approved:

K D Berlin
Thesis Advisor

Richard A. Bruce

Richard C Essenburg

Warren T Ford

Norman N. Durham
Dean of Graduate College

ACKNOWLEDGMENTS

Completion of this work was made possible by the contributing efforts of certain members of the faculty and staff, as well as several colleagues to which I am indebted. I would like to thank Dr. K. D. Berlin, not only for his suggestions and guidance regarding this project, but also for his advice and personal insight outside of the lab. I would also like to give special recognition to Dr. Richard Bunce, Dr. Richard Essenberg, and Dr. Warren T. Ford for serving as members of my committee. Efforts of Stan Sigle for technical assistance with the NMR spectrometers, Dr. Dick van der Helm for crystallographic work, Dr. Benjamin Scherlag for antiarrhythmic assays, and Drs. Sangiah and Clarke for performance of the pharmacological profiles, to whom I am very grateful, are acknowledged as well. Several fellow students and co-workers have also played significant roles, both past and present, in making life all the more wonderful who include: Satish Mulekar, Shankar Subramanian, Francis Clement, Marwan El Masri, Greg Garrison, Jonathan Gale, Gary Smith, Prasanna Sunthankar, Tim Fakler, Vicki Pruitt, Dr. Shanshank Otiv, Shirish Rajadhyaksha, Lyle Spruce, Betsy Rice, Terry Keimig, Sudha Varma, and Vicki Taylor.

Financial support was provided by the Department of Chemistry, the National Heart, Lung, and Blood Institute (National Institute of Health), as well as the Presidential Water Resources Fellowship. A heartfelt thanks is extended to the Water Resources Board for having provided my salary stipend throughout my tenure here at the university.

Though my life over the past two years has seemed to collapse around me due to the tragic death of my father, my loving wife, Jennifer has provided the necessary encouragement for me to endure and withstand the pain amidst the stress which accompanies such tedious work. My mother, Frances Zisman, and two sisters, Julie

Zisman and Jan Zisman, maintained that "I was always loved at 1105 Holly, if nowhere else" and for this I am thankful. Finally and foremost, I give thanks to the Lord, Jesus Christ for having blessed me in so many ways, comforting me in my time of need.

I would like to dedicate this small portion of my life's work to my father, Allen L. Zisman, who was and remains my source of inspiration. My principle motivator, he encouraged me to push ahead to the first doctoral degree ever obtained by a member of the Zisman family and with that in mind, we rejoice together. We fought the good fight, we finished the race, we kept the faith. I made it Daddy.

TABLE OF CONTENTS

Chapter Page

LIST OF TABLES

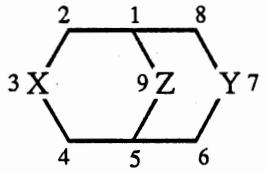
LIST OF FIGURES

LIST OF PLATES

CHAPTER I

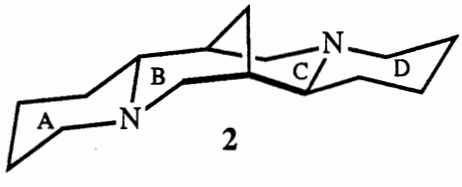
HISTORICAL

Certain members of the 3-hetera-7-azabicyclo[3.3.1]nonane ring system **1** have been of interest not only for unique conformational and stereochemical considerations but also

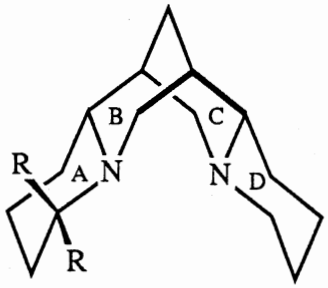


1

as potential analgesic and antiarrhythmic agents.[30] These compounds are related in structure to members of the family of naturally occurring lupine alkaloids.[55] Such alkaloids possess fused structures which are locked in rigid conformations such as the chair-boat (CB) form of sparteine (**2**) and the chair-chair (CC) forms of both α-iso-



2

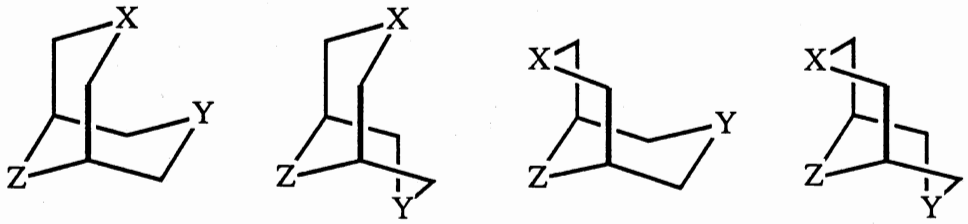


3a R = H
3b R, R = O

sparteine (**3a**) and isolupanine (**3b**). Sparteine (**2**) has been found to exhibit moderate biological activity in the management of cardiac arrhythmias; however, toxic side effects such as nervousness, difficulty in breathing, convulsions, and loss of muscular control

have limited its application.[49,60] Nowacki and Wezyk determined the oral and intravenous mean lethal dosages of sparteine **2** in rabbits to be 32 and 810 mg/kg, respectively.[47]

The two inner B and C rings of the lupine alkaloids **2-3** constitute the structural backbone of the 3,7-diheterabicyclo[3.3.1]nonanes **1**.[55] Dynamic properties unique to these bicyclic systems may result in equilibration between four different conformations: chair-chair **1-CC**, chair-boat **1-CB**, boat-chair **1-BC**, and boat-boat **1-BB**.[30] Identical



1-CC **1-CB** **1-BC** **1-BB**

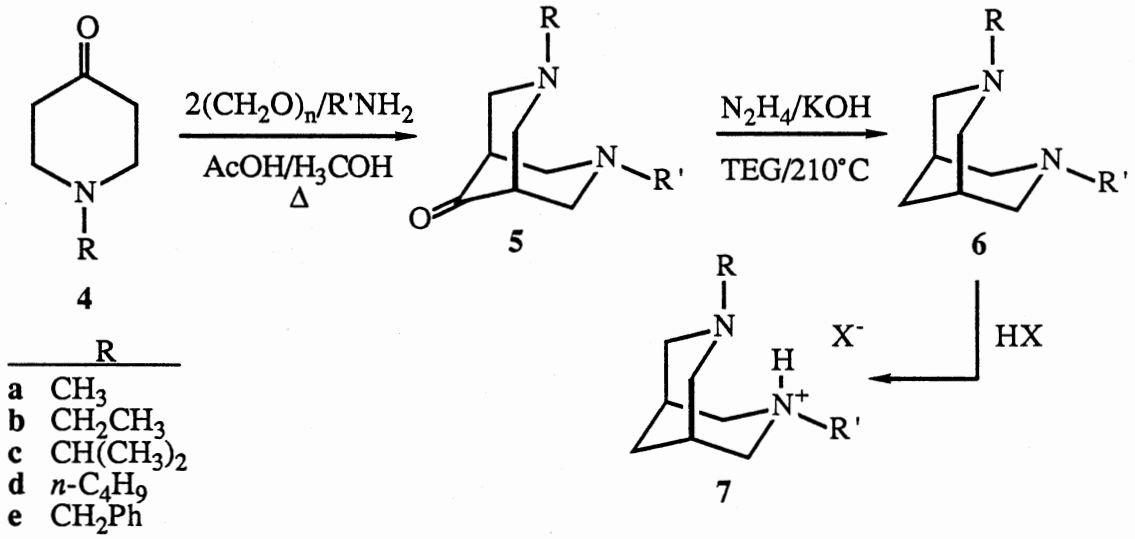
forms of the CB and BC forms exist when X and Y are equivalent. Several members of this family possess significant analgesic as well as antiarrhythmic properties which have warranted extended investigations[6,11,46,55] Analysis of the preferred conformations of these systems is critical in order to further explain the observed biological activity and the mode of action of these agents.[30,75]

This discussion will focus on 3,7-diheterabicyclo[3.3.1]nonanes **1** and certain derivatives in which chemical and physical properties will be previewed with special emphasis on structure-activity relationships. Synthetic methodologies employed to construct the 3,7-diheterabicyclo[3.3.1]nonane moiety **1** will be reviewed initially, followed by an examination of the conformational and stereochemical properties of such systems. Antiarrhythmic properties of certain derivatives of this family, as compared to known clinical standards, will be explored along with the various methods employed to acquire such data. Finally, an evaluation of the mechanism of metabolic degradation and the identification of active metabolites of some related agents will be discussed.

Synthetic Methodology

Synthetic routes to 3,7-diheterabicyclo[3.3.1]nonanes **1** prior to the 1980's have been extensively reviewed.[30,75] Syntheses that have been employed more recently, which include modifications to the bicyclic framework where X and/or Y = NR, O, S, and Se and Z = (C=O) or CRR', will be the main topic of discussion. Illustration of some of the more popular methods and presentation of new novel strategies, which have been used to obtain more functionalized analogs, will be the principal objective.

A double Mannich condensation of the 1-alkyl-4-piperidinones **4** with paraformaldehyde and various primary amines in acidic media has proven to be one of the more



R	
a	CH_3
b	CH_2CH_3
c	$CH(CH_3)_2$
d	*n*-C_4H_9
e	CH_2Ph

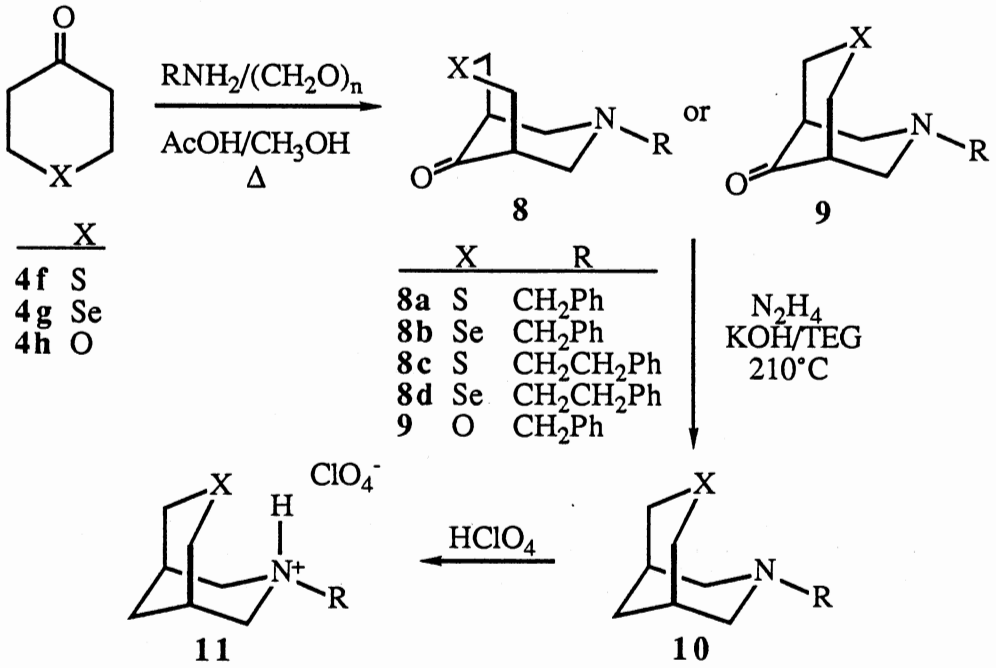
5-7

R	R'	R	R'
a CH_3	CH_3	**j** CH_2Ph	CH_2Ph
b CH_3	CH_2CH_3	**k** $CH(CH_3)_2$	CH_2CH_2Ph
c CH_3	$CH(CH_3)_2$	**l** CH_2Ph	$CH_2C_6H_3$-3,4-$(Cl)_2$
d CH_3	$C(CH_3)_3$	**m** CH_2Ph	$CH_2C_6H_4$-3-Cl
e CH_3	*n*-C_4H_9	**n** CH_2Ph	$CH_2C_6H_4$-3-F
f CH_3	CH_2Ph	**o** CH_2Ph	$CH_2C_6H_4$-3-CF_3
g CH_3	$CHPh_2$	**p** CH_2Ph	$CHPh_2$
h *n*-C_4H_9	*n*-C_4H_9	**q** CH_2Ph	$C(Ph)_2CH_3$
i *n*-C_4H_9	CH_2Ph		

commonly employed methods for constructing the bicyclic ketone framework. Douglass and Ratliff, for example, synthesized a series of 3,7-dialkylbispidones **5a-d** ("bispidone"

is a commonly used name synonymous with 3,7-diazabicyclo[3.3.1]nonan-9-one) by this method in modest yields (40-55%). The ketones were then reduced under Wolff-Kishner conditions to the bispidines **6a-d**, followed by conversion to the perchlorates **7a-d** in yields of 60-70%.[18] Reunitz and Mokler[55] determined the lipophilicity of similar agents by examining the distribution coefficients (between octanol and a pH 7.4 aqueous buffer) of various bispidine salts **7e-j** which had been derived by similar procedures as those employed by Douglass and Ratliff. Binnig and co-workers found application for this method in which a series of 3,7-dialkylbispidines **6k-q** and their salts **7k-q** were produced in comparable yields.[11]

Our research group has developed specific procedures for the synthesis of a variety of 3-hetera-7-azabicyclo[3.3.1]nonanes and certain derivatives.[4,6,7,67] Starting from the



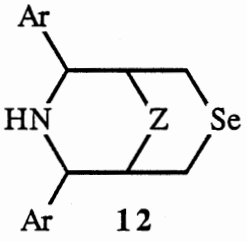
X	
4f	S
4g	Se
4h	O

X	R	
8a	S	CH_2Ph
8b	Se	CH_2Ph
8c	S	CH_2CH_2Ph
8d	Se	CH_2CH_2Ph
9	O	CH_2Ph

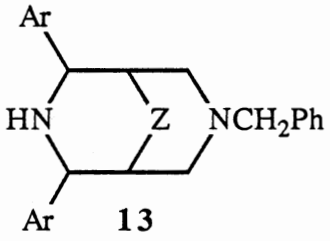
11, 12

X	R	
a	S	CH_2Ph
b	Se	CH_2Ph
c	S	CH_2CH_2Ph
d	Se	CH_2CH_2Ph
e	O	CH_2Ph

appropriate 1-hetera-4-cyclohexanones **4**, ketones **8** or **9** (it has not been established if a BC or CC form is dependent upon X or R) could be obtained via a double Mannich condensation. Wolff-Kishner conditions gave the corresponding reduced products **10** which were then treated with perchloric acid to give the respective salts **11**. Similarly, 6,8-diarylsubstituted analogs of the 3-hetera-7-azabicyclo[3.3.1]nonanes were prepared, such as illustrated in the general formulas **12** and **13**.[6,67]

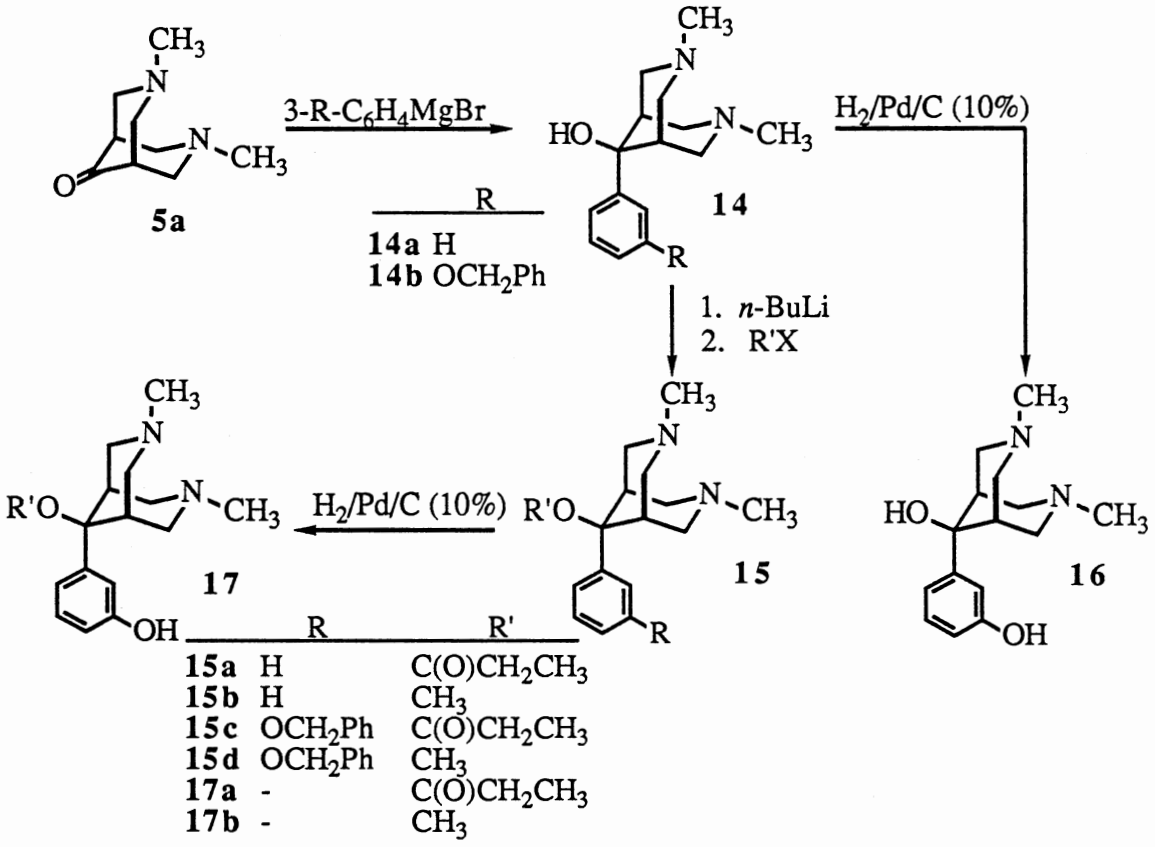


12



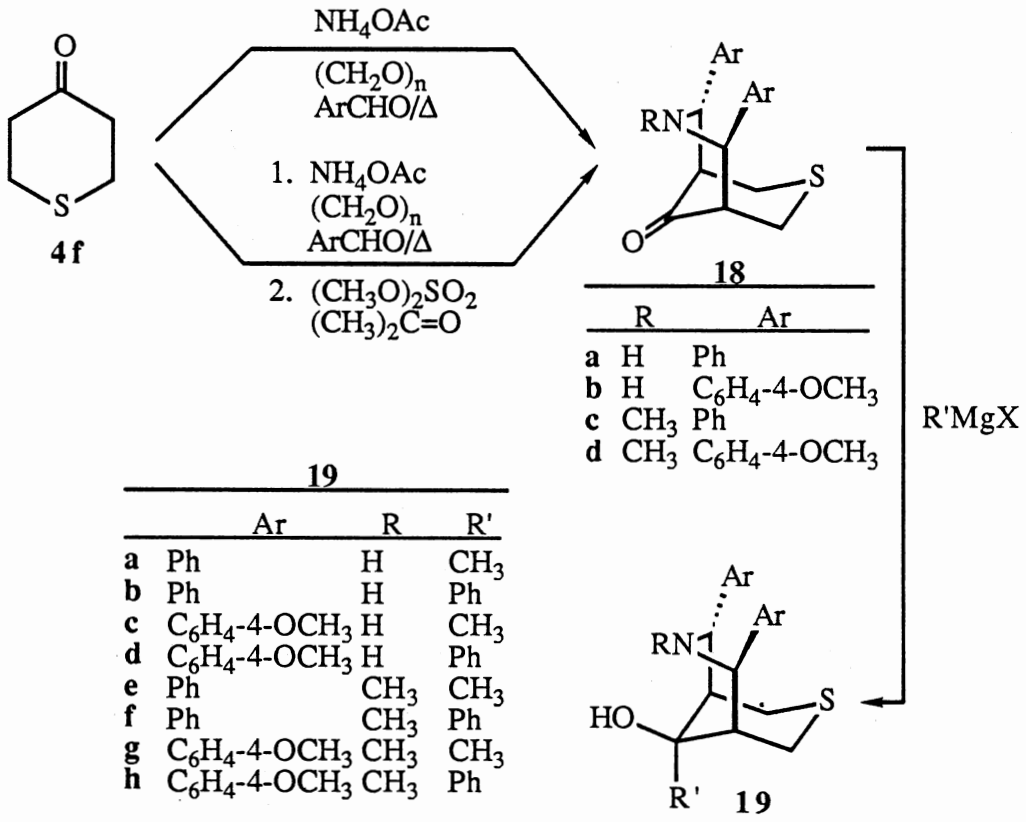
13

Salva and co-workers sought to modify the 9-position of these bicyclic systems via a reaction of ketone **5a** with phenylmagnesium bromide which gave alcohol **14a** (95%).[57]



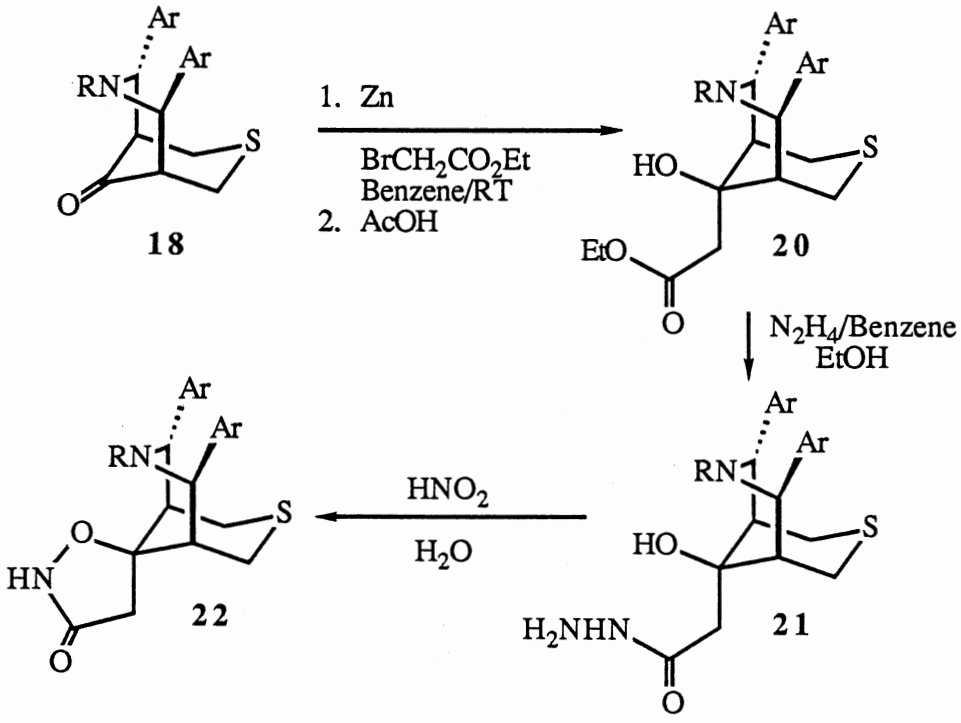
Treatment of alcohol **14a** with the appropriate alkylation agent and *n*-butyllithium gave **15a** and **15b**, respectively. Condensation of ketone **5a** with 3-benzyloxyphenylmagnesium bromide gave the alcohol **14b** which was then debenzylated with H_2/Pd/C (10%) to afford the diol **16**. After **14b** was derivatized to **15c** and/or **15d**, hydrogenolysis of each product gave **17a** and **17b**, respectively.[57]

Attempted alteration of the 9-position was also included in the work of Llama and Trigo.[40] Several 6,8-diaryl-3-thia-7-azabicyclo[3.3.1]nonan-9-ones **18** were synthesized via a double Mannich condensation of 4-thianone (**4f**) with an aromatic aldehyde and ammonium acetate in ethanol. Treatment of ketones **18a** or **18b** with dimethyl sulfate

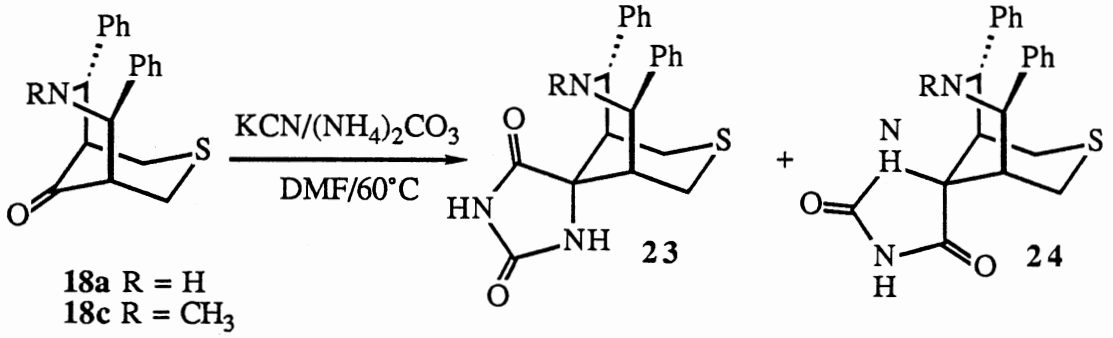


in acetone gave the respective methyl-substituted ketones **18c** and **18d** in high yields. Alcohols **19** (68-77%) could then be obtained from the reaction of ketones **18** with the appropriate Grignard reagent. Addition of a Reformatsky reagent to **18** led to esters **20**.

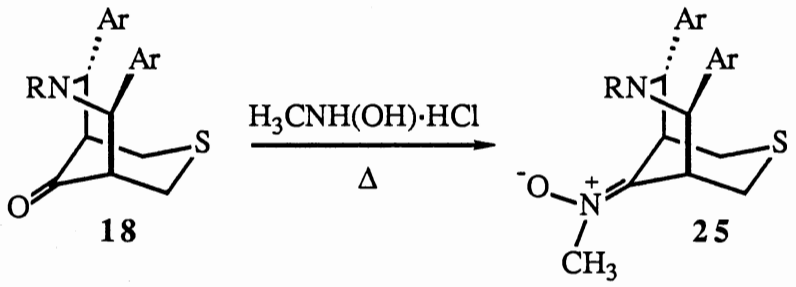
Hydrazides **21** (78-85%) were isolated upon treatment of esters **20** with hydrazine hydrate in benzene. Formation of oxazolidines **22** (40-48%) was accomplished by reaction of



$NaNO_2$/HCl with the respective hydrazides **21**. Treatment of ketones **18a** and **18c** with KCN and ammonium carbonate in DMF gave the hydantoin isomers **23** and **24** (50-



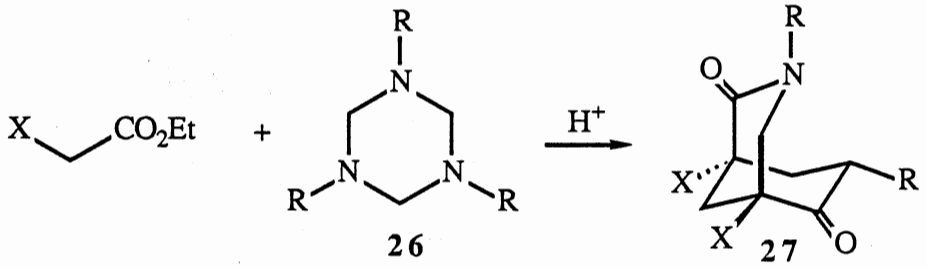
52%). Nitrone derivatives (68-73%) **25** were also made when ketones **18** were subjected to treatment with *N*-methylhydroxylammonium chloride in KOH/CH_3OH.[40]



25-26	
	R
a	H
b	CH_3

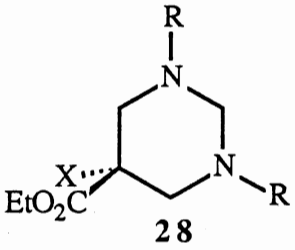
20-22, 25		
	Ar	R
a	Ph	H
b	Ph	CH_3
c	C_6H_4-4-OCH_3	H
d	C_6H_4-4-OCH_3	CH_3

Recently, it was discovered that 3,5-trialkyltriazines **26** (which is a masked R-$\overset{+}{N}$=CH_2 synthon)[17] could be converted to lactams **27** (18-77%) in acid media as illustrated below.



X = CN, CO_2Et, 4-CH_3-$C_6H_4SO_2$, PhC(O)

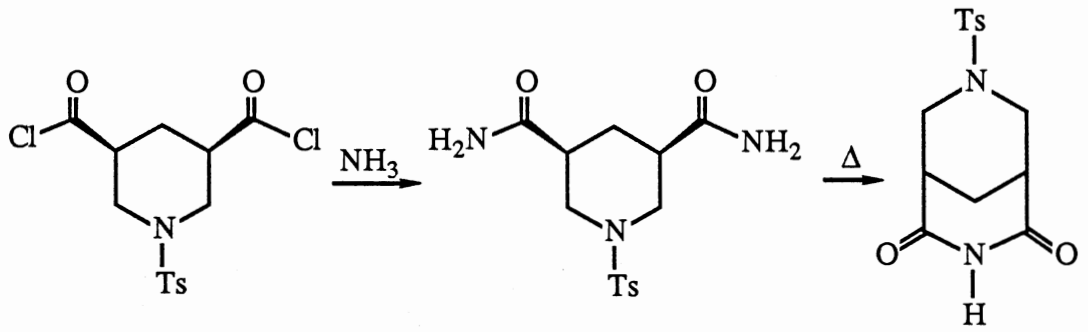
R = CH_3, CH_2CH_3, CH_2Ph



(Suspected Intermediate)

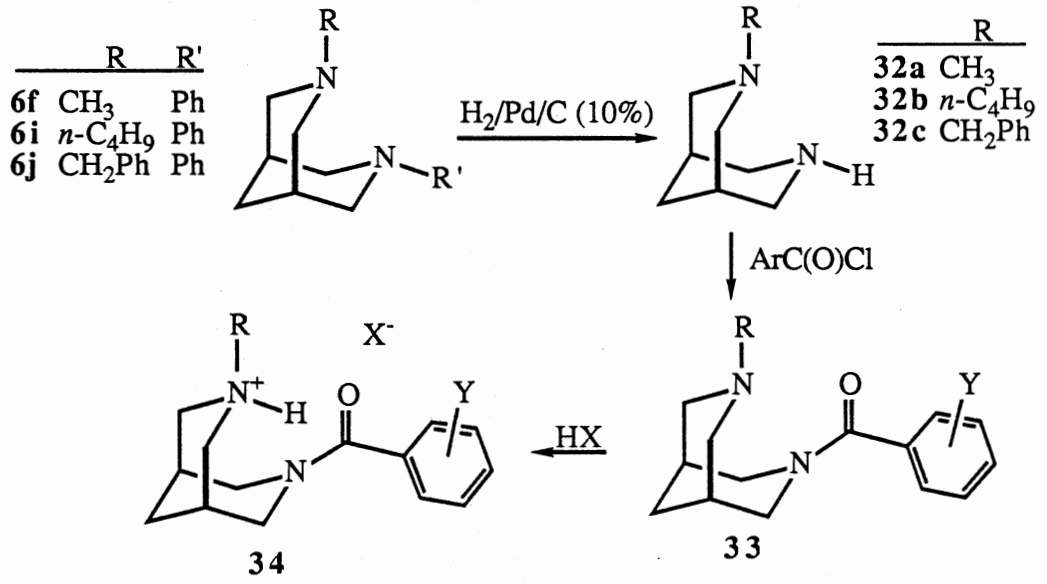
Initial formation of the suspected hexahydro pyrimidine intermediate **28** was apparently followed by several rearrangements to the final product **27**.

Stetter also synthesized several bispidine derivatives which possessed the lactam function.[64] Amidation of a di-acid chloride **29** as shown gave diamide **30** which was then heated and cyclized neat to the novel 2,4-imide **31**.[64]



29 **30** **31**

Reunitz and Mokler were able to debenzylate certain bispidine derivatives **6f** and **6i** to give the secondary amines **32a** and **32b** in 97-100% yield, respectively, which could then



	R	R'
6f	CH_3	Ph
6i	*n*-C_4H_9	Ph
6j	CH_2Ph	Ph

	R
32a	CH_3
32b	*n*-C_4H_9
32c	CH_2Ph

33 **34**

33, 34

	R	Y	X^-
a	CH_3	H	$O_2CH{=}CHCO_2H$
b	CH_3	4-OCH_3	$O_2CH{=}CHCO_2H$
c	CH_3	3,4,5-$(OCH_3)_3$	$O_2CH{=}CHCO_2H$
d	CH_3	4-$(Cl)_2$	$O_2CH{=}CHCO_2H$
e	CH_3	3,4-$(Cl)_2$	$O_2CH{=}CHCO_2H$
f	*n*-C_4H_9	H	Cl
g	*n*-C_4H_9	4-OCH_3	$O_2CH{=}CHCO_2H$
h	*n*-C_4H_9	4-Cl	$O_2CH{=}CHCO_2H$
i	*n*-C_4H_9	3,4-$(Cl)_2$	$O_2CH{=}CHCO_2H$
j	CH_2Ph†	4-NO_2	-
k	CH_2Ph	H	HSO_4

†This compound exists only as a derivative of **33** and not as a salt.

35

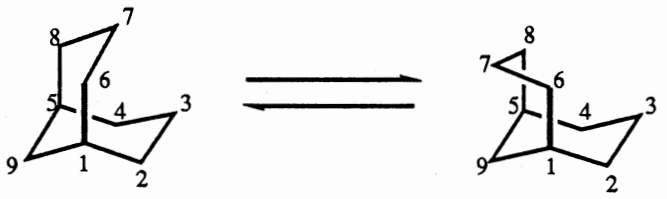
be acylated to amides **33a-i.** In turn, the latter were converted to the appropriate salts **34a-i** (57-97%).[55] Similarly, Binnig and co-workers[11] acylated the secondary amine **32c** with the appropriate acid chloride to give **33j** and **33k.** Amide **33k** was treated with sulfuric acid to give the sulfate salt **34k.** Reduction of the nitro derivative **33j** with H_2/Pt/C (5%) was followed by conversion to the fumarate **35.**

Conformational Aspects

Conformational mobility, a property which is inherent to the bicyclo[3.3.1]nonane ring system, has stimulated a variety of studies concerned with the delineation of stereochemical and conformational preferences.[30,74] As was previously described, the 3,7-diheterabicyclo[3.3.1]nonanes **1** can exist in four possible conformations when X and Y are nonequivalent. Although X-ray analysis can supply positive proof of structure for a crystalline state, debates frequently occur over unequivocal structural assignments for a compound in solution. Several factors are relevant to the situation, namely: (1) steric repulsion of the heteroatoms, (2) dipole repulsion, (3) lone pair orbital repulsion or (4) intramolecular hydrogen bonding. All of these parameters can play roles in the stabilization of one conformer over another.[30,74] Evaluation of the recent literature regarding conformational properties of the 3,7-diheterabicyclo[3.3.1]nonanes, as well as certain carbocyclic model systems and other related heterocycles, will be the focus of the following discussion.

Variable temperature studies[43] involving bicyclo[3.3.1]nonane (**36**) revealed a ΔE~1.5-2.5 kcal/mol for the CC$\rightleftharpoons$BC equilibrium a (where ΔE represents the energy requirement for interconversion of the two possible conformations). Although the CC form is preferred in **36**, the BC form in **36** is in higher concentration than is the boat form in the chair-boat equilibrium of cyclohexane where ΔE~2.1-2.7 kcal/mol. Analyses revealed only 5% of the BC form of **36** at 65°C with 20% at 400°C. Molecular mechanics

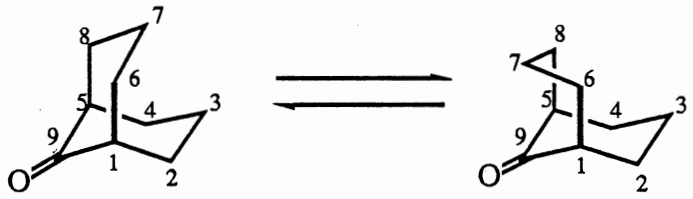
calculations agree well with these data in which a ΔE of 2.3 kcal/mol was calculated for **36**.[43] Earlier electron diffraction studies[50] predicted a ΔE of 2.5 kcal/mol with a contri-



36-CC **36-BC**

bution by the BC form of 4.6% at 65°C and 23.6% at 400°C. Thus, a direct relation was observed between the amount of the BC conformer and temperature.

Solid state ^{13}C NMR studies of bicyclo[3.3.1]nonan-9-one (**37**) at 42°C suggested a predominance of the CC form.[70] The ^{13}C shifts recorded in this experiment did not

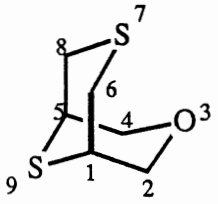


37-CC **37-BC**

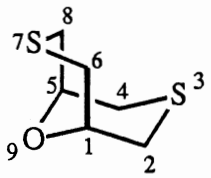
deviate significantly from those observed for **37** in C_6D_{12} solution. This conclusion was further supported from work by Raber[54] in which **37** was characterized via examination of the ^1H shifts induced by the lanthanide shift reagent $Eu(fod)_3$, on a CCl_4 solution. A distribution of 78:22 favoring the CC conformer was observed by comparing the experimental shifts with those predicted by the pseudocontact equations using geometries obtained from empirical force field (EFF) calculations. Predominance of the CC conformation for **37** was supported by each of these independent studies.

Factors governing the conformational equilibria of the 3,7-diheterabicyclo[3.3.1]-nonanes **1** differ somewhat when compared to those for the simplified carbocyclic

systems. The X-ray analyses[76] of 3-oxa-7,9-dithiabicyclo[3.3.1]nonane (**38**) and 9-oxa-3,7-dithiabicyclo[3.3.1]nonane (**39**), for example, revealed the existence of CC and BC forms, respectively. The predominance of the CC conformation in bicyclo[3.3.1]nonane (**36**), where the ideal calculated C(3)···C(7) distance is ~2.52 Å (calculated for **36**), can



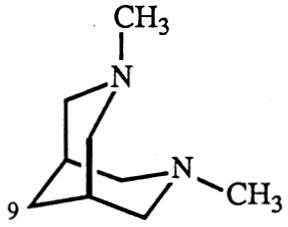
38-CC



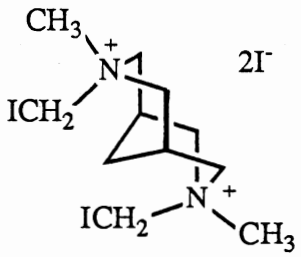
39-BC

not always be extrapolated to more complex systems. Lone pair repulsion between O(3) and S(7) in **38** is reflected in an increase of the O(3)···S(7) distance to 3.12 Å. Repulsion from non-bonding electron pairs on S would destabilize a CC form for **39** so that a predominance of the BC form is observed where the S(3)···S(7) distance is close to 4.24 Å.[76]

Investigations by Douglass and Ratliff[18] of 3,7-dimethylbispidine (**6a**) evaluated conformational preferences by both dipole and NMR techniques. Calculated dipoles of 1.10 D (CC), 1.10 D (CB), and 1.84 D (BB) did not match well with the experimental value of 2.02 D. However, as the CC conformation is flattened, the calculated dipole approaches a maximum value of 1.90 D when the axes of the nitrogen lone pairs are



6a

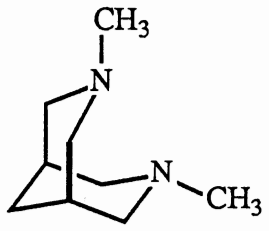


40

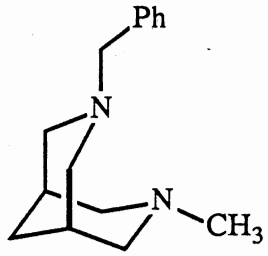
parallel. Comparison of ^{1}H NMR shifts of the γ-methylene protons [H(9)] of **6a** with those of the known chair form of *N*-methyl-4-piperidine strongly support a CC form for

6a. Isolation of what was postulated to be a rare BB form **40** was achieved from reaction of **6a** with diiodomethane. Nevertheless, the lack of unequivocal proof has led to some speculation concerning the structure of **40**.

Photoelectric spectroscopy (PES) techniques have been employed to determine the gas phase conformation of **6a**[39] in which two bands (corresponding to the ionization processes in which electrons are removed from the "lone pair" orbitals on the nitrogen atoms) separated by 0.51 eV were observed. Two plausible explanations for this phenomenon were proposed: (1) the sample could be a mixture in which each conformer is character-



6a

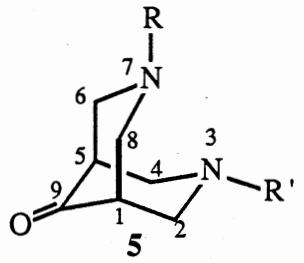


6f

ized by a single band or (2) the sample could be one conformer having two non-equivalent nitrogen lone pair ionization potentials. There is no intuitively obvious rationale for the latter unless there is significant influence of the initial radical on the ionization potential of the electron on the second nitrogen lone pair. Molecular orbital calculations (MINDO/3 and MNDO) predicted that a CC form for **6a** is significantly more stable and should be present to the extent of 96.9-99.8%. A similar assignment of a CC conformation was suggested for analogous 3-benzyl-7-methylbispidine (**6f**) as assessed by NMR and IR spectral methods.[15]

Application of ^{1}H NMR, ^{13}C NMR, and IR spectral techniques by Galvez and coworkers,[3,23] resulted in the structural elucidation of several 3,7-dialkylbispidones **5**. Evidence suggests that ketones **5** adopt a flattened CC conformation in solution, and an increase in distortion from an ideal CC occurs in the series from the methyl to the isopro-

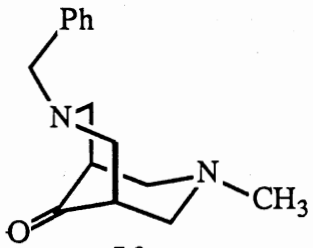
pyl substituent.[3] A slight increase in [$\delta_{H(2,4)ax}$ - $\delta_{H(6,8)ax}$] from **5a** to **5c** in the ^{1}H NMR spectra was observed. A decrease in the trans-coplanarity of R'N: with C-H(2,4)$_{ax}$ bonds is noted as the R' increases in size (greater than methyl) as compared to the H_3CN: and C-H(6,8)$_{ax}$ groups. Thus, the ring with R'>CH_3 is more flattened than the ring containing H_3CN in **5b**, **5c**, **5f**, **5r**, and **5s**.[3,23] A trend of increasing values [0 (**5a**), 2.59 (**5b**),



5

R	R'	R	R'
5a CH_3	CH_3	**5a** CH_3	CH_3
5b CH_3	CH_2CH_3	**5f** CH_3	CH_2Ph
5c CH_3	$CH(CH_3)_2$	**5j** CH_2Ph	CH_2Ph
5r CH_3	$CH_2CH_2CH_3$	**5s** CH_3	CH_2CH_2Ph

6.29 (**5c**), and 2.10 (**5d**)][23] for [$\delta_{C(6,8)}$ - $\delta_{C(2,4)}$] in the ^{13}C NMR spectra in the series **5a** to **5c** also supports a more flattened CC conformation as the size of the *N*-alkyl substituent increases. These observations were also noted for ketones **5a**, **5f**, **5j**, and **5s**.[3]

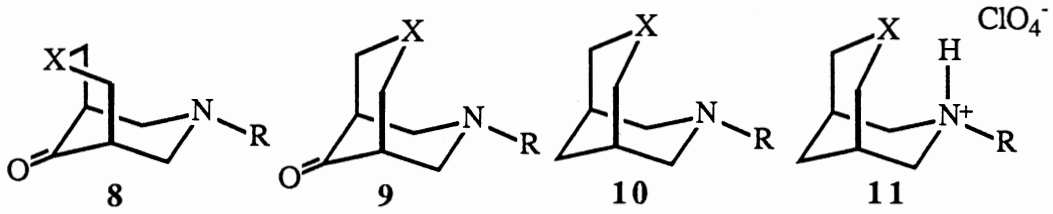


5f

37

However, an X-ray analysis of **5f** verified the BC conformation in the solid state.[63] The ^{13}C NMR spectral assignments made by Galvez's group for CC conformations for **5** in solution compare well with the data obtained for the aforementioned carbocyclic ketone **37**.[54]

Our group has characterized, through a variety of techniques, several members of the 3-hetera-7-azabicyclo[3.3.1]nonane family, which include[4,6,7,67] ketones **8-9** as well as the reduced forms **10** and salts **11** . An X-ray analysis of ketones **8a** and **8b** revealed a preference for a BC conformation which was further supported by variable temperature NMR studies of **8a** in solution.[6] A flattened CC conformation was determined for **9** in solution.[4] Reduction of the ketones **8** or **9** gave the free amines **10** which were converted

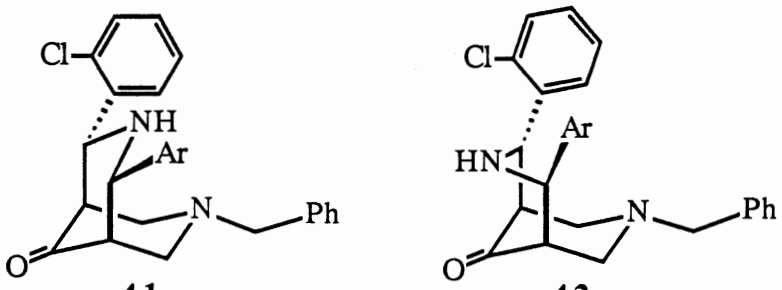


8 **9** **10** **11**

8, 9			10, 11		
	X	R		X	R
8a	S	CH_2Ph	**a**	S	CH_2Ph
8b	Se	CH_2Ph	**b**	Se	CH_2Ph
8c	S	CH_2CH_2Ph	**c**	S	CH_2CH_2Ph
8d	Se	CH_2CH_2Ph	**d**	Se	CH_2CH_2Ph
9	O	CH_2Ph	**e**	O	CH_2Ph

to the corresponding salts **11**, both of which were assigned CC forms in solution. Solids **11a** and **11b** were also confirmed as CC forms using single crystal X-ray analyses.[6]

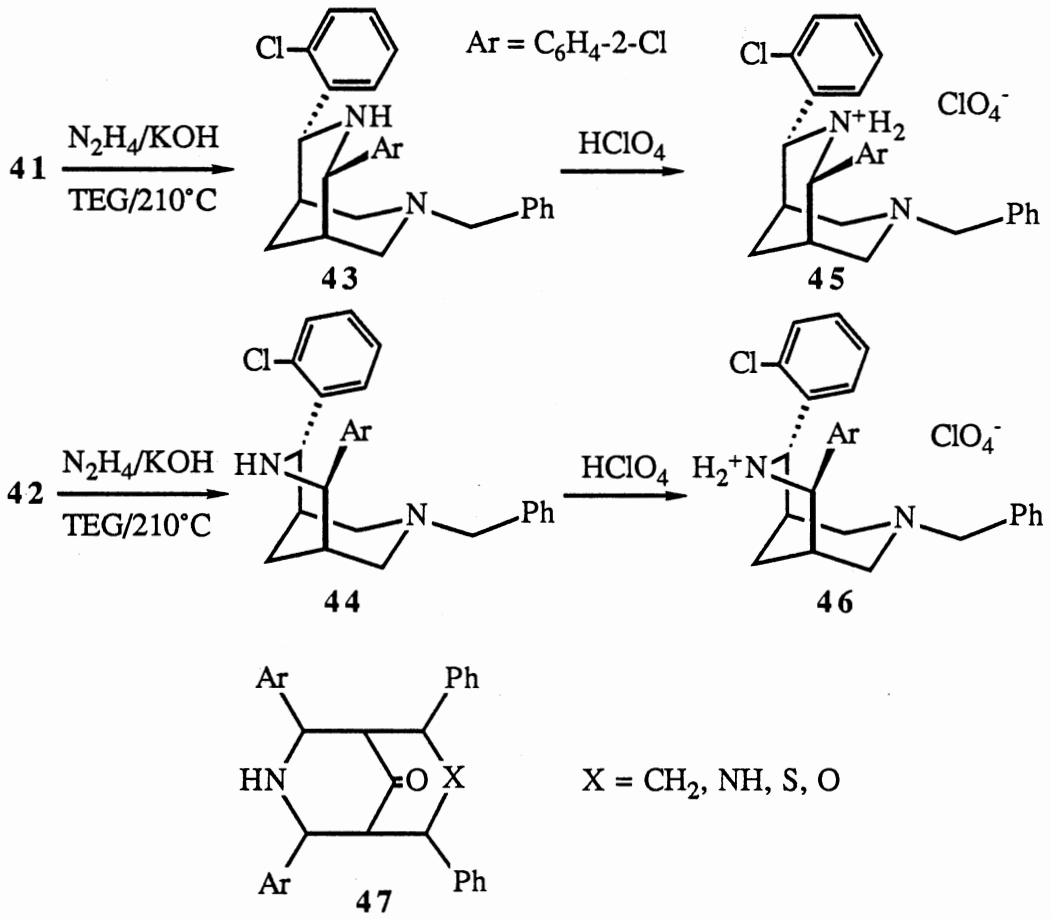
Limited literature citations[6,53] involve the isolation of both CC and BC isomeric ketones from a *single reaction* vessel. For example, the diaryl-substituted, isomeric ketones **41** and **42** were isolated and confirmed by NMR and X-ray analyses to be in a



41 **42**

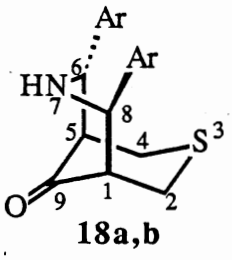
Ar = C_6H_4-2-Cl

CC and BC conformation, respectively, and stable in solution as well as in the solid state. Vigorous reduction conditions, followed by protonation in acidic media, did not alter the stereochemistry in amines **43** and **44** or in the respective salts **45** and **46**. Quast and co-workers isolated a series of tetraaryl-substituted, isomeric ketones **47** which adopted both BC and CB conformations.[53]

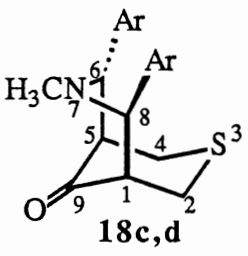


Llama and Trigo[40] have shown that conformationally biased systems such as the 6,8-diaryl-3-thia-7-azabicyclo[3.3.1]nonan-9-ones **18** react stereoselectively (under certain conditions) due to steric restrictions imposed by the boat form of the 4-piperidinone ring. Analysis of ketones **18**, using NMR and IR spectral methods, supports the existence of a BC form. Reactions of the ketones with Grignard reagents gave exclusively the β-alco-

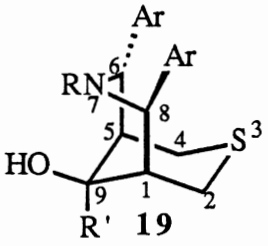
hols **19**. Formation of such β-alcohols is clearly favored since the approach of the nucleophile is hindered from the side with the nitrogen atom in the boat form. Possible



18a,b



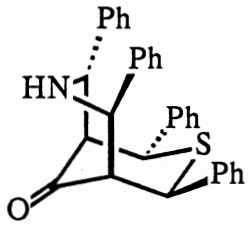
18c,d



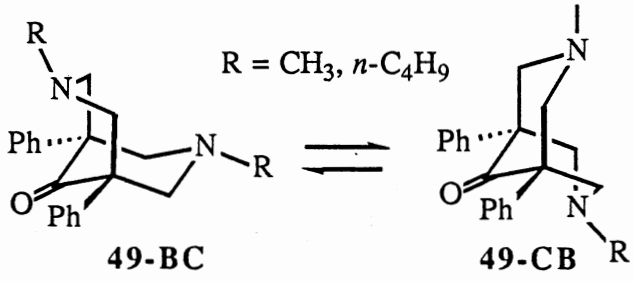
19

paramagnetic influence (it is assumed NOE irradiation experiments at specific atoms were attempted but the paper is not clear on this matter) by aromatic substituents at C(6) and C(8) on a C(9) methyl substituent is neglible in alcohols **19** (R' = CH_3) which further supports the assigned conformation of a BC form.

Confirmation of similar systems such as **48**[51] by X-ray analysis in the solid state and NMR analysis in solution ($DCCl_3$) supports the existence of a BC conformer. A CC conformer for **48** would appear to be energetically unfavorable since bulky phenyl substituents would have to occupy axial positions in the molecule. At this time, however, no data are available to discern if more than one conformer is available for this ketone in solution.



48

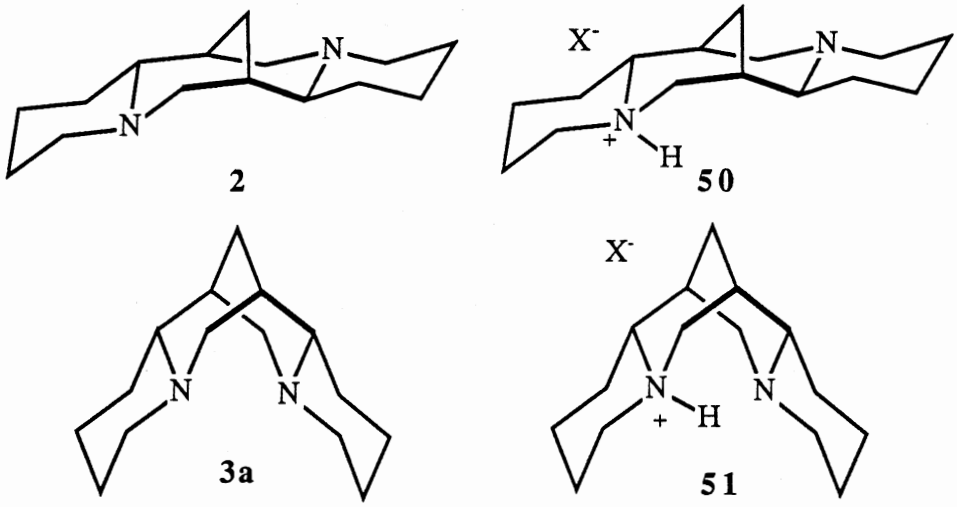


49-BC **49-CB**

There has been extensive research on conformational equilibria in solution in which the preference for a CC, CB, BC, or BB form for the 3-hetera-7-azabicyclo[3.3.1]nonanes **1** has been proposed.[30,75] However, the debate remains as to whether an equilibrium exists between *all* of the respective conformers. Variable temperature NMR spectral studies of **49**, for instance, revealed the existence of a BC⇌CB equilibrium in solution.[65]

Three different peaks were observed at ambient temperature in the aliphatic region of the ^{13}C NMR spectrum and only one AB quartet for the methylene protons was seen in the ^{1}H NMR spectrum. Lowering the temperature resulted in a broadening of the CH_2 singlet in the ^{13}C spectrum, which first coalesced at -63°C and then split into two distinct signals with a maximum chemical shift difference of 6.0 ppm. These data are consistent with the "freezing out" of one structural form which possessed two-fold symmetry and implying a BC⇌CB equilbrium. The possibility of other equilibria operating, such as the double twist boat⇌double twist boat or a CB⇌CC equilibria could not be ruled out. Surprisingly, these types of studies have not been common for bicyclo[3.3.1]nonane systems.

Several members of the lupine alkaloids, such as sparteine (**2**), which possess the backbone of the bispidine moiety in the inner B and C rings, have been examined by IR, NMR, and X-ray analyses for structural preferences.[14,52,56,61,71] Sparteine (**2**)[14,52,61,71] and its salt **50**[61] were found to prefer a CB conformation while α-isosparteine (**3a**)[52,71] and its salt **51**[61] assumed a CC conformation. A thorough understanding of the stereo-



chemical and conformational arrangements preferred by these natural products might aid in the delineation of certain structural characteristics which are inherent to the 3-hetera-7-aza-

bicylo[3.3.1]nonanes and provide insight as to how they might function as antiarrhythmics since chelation of calcium is not an unreasonable possibility by members of **1** and related systems. Intuitively, it would seem as if CC conformers would be more active as antiarrhythmics if calcium chelation were of major importance. This has not been investigated.

Antiarrhythmic Activity

Sudden cardiac death refers to an unexpected cessation in breathing and circulation which results from underlying heart disease such as atherosclerosis of the coronary arteries. Death can generally be attributed to ventricular fibrillation (chaotic contraction of the ventricles without pumping action) which is usually preceded by ventricular arrhythmias.[21] This condition can be related to myocardial ischemia (reduced blood flow to the heart muscle) which in most cases is caused by deposition of fatty plaque along the interior walls of certain arteries and may lead to complete blockage of the arteries with induction of myocardial infarction.[16] Approximately 400,000 people die each year in the United States from cardiovascular disease, and close to 60-65% experience a sudden malfunction of the heart while engaged in normal activities. Although the death rate resulting from coronary disease is on a slight decline, it remains the number one killer in the United States.[44]

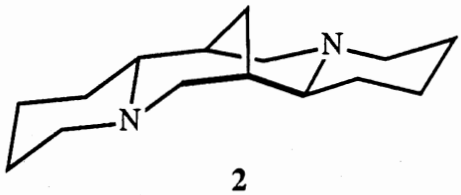
Most patients experience ventricular tachycardia (VT, irregular beating pattern of the heart in which the pumping action has been significantly reduced) as a late complication of myocardial infarction. There are relatively few agents to treat patients suffering from this disorder. Antiarrhythmic agents seem to be effective in no more than one third of these patients.[36] Moreover, efficacy of the available agents appears dependent upon the nature of each patient's VT. Although other new potential antiarrhythmic drugs exist, there is little evidence to suggest that any possess more potent activity with less side effects than those agents available now.

Currently, there is a modest variety of clinical agents for management of heart arrhythmias.[41] The rationale for an agent's use is usually based upon the following criteria: (1)

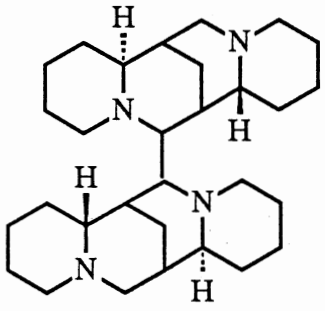
knowledge of the electrophysiologic mechanisms leading to the genesis of the condition, (2) knowledge of electropharmacologic properties of the agent in cardiac cells at the proposed site of origin and (3) an understanding of the pharmacokinetics of the agent. Adverse side effects, which include conversion of nonstained VT to sustained ventricular tachycardia (SVT), can occur. Thus, the choice of an agent can be critical since selection of the wrong agent can be fatal.[36]

Clinical standards (Table I) such as lidocaine (**52**), encainide (**53**), quinidine (**54**), lorcainide (**55**), disopyramide (**56**), and procainamide (**57**) have proven effective toward the treatment of cardiac arrhythmias in many cases. Lidocaine (**52**), for example, is considered the drug of choice in the emergency intravenous therapy of patients with ventricular arrhythmias.[41] Mode of action, pharmacokinetics, metabolism, and potential side effects of each of these standards, as well as new experimental agents, have been thoroughly reviewed.[16,36,41,44] New potential antiarrhythmic agents, to be discussed shortly, have been compared in biological assays with known clinical standards.[6,11,46,55]

Antiarrhythmic properties of sparteine (**2**) have been well established;[19] however, a new novel form of this classic alkaloid, bis-sparteine (**58**)[25] was synthesized and screened



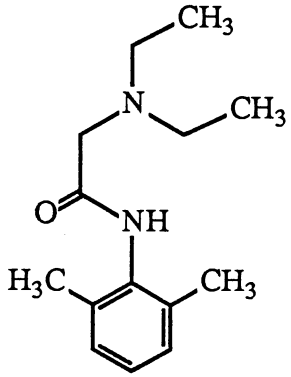
2



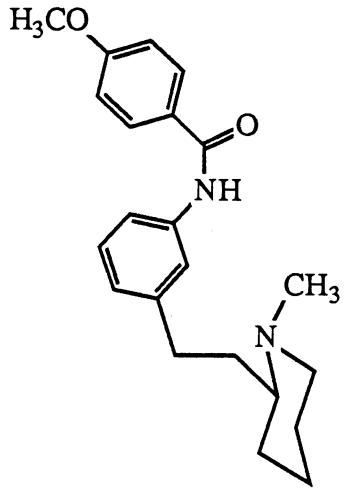
58

for activity toward aconitine-induced arrhythmias in guinea pigs. Low toxicity levels and efficacy of the agent proved its superiority to its monomeric parent, sparteine (**2**).

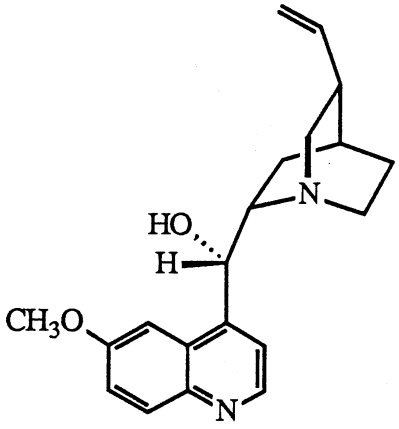
In the late 1970's, Reunitz and Mokler[55] synthesized and tested a series of 3,7-dialkyl-bispidine salts **7e-j** [versus the known clinical standard, disopyramide (**56**)] employing



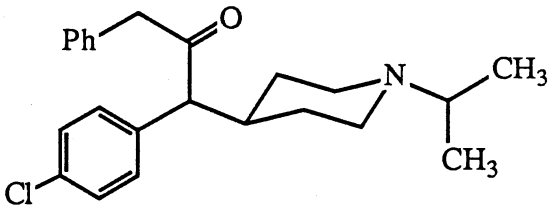
Lidocaine
52



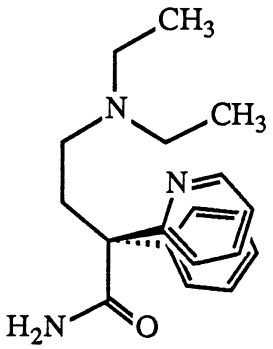
Encainide
53



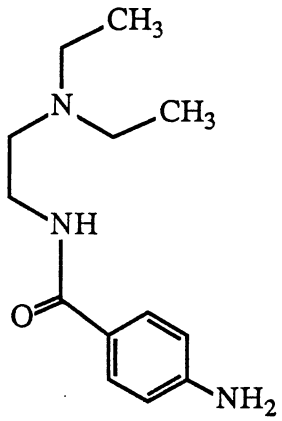
Quinidine
54



Lorcainide
55



Disopyramide
56



Procainamide
57

TABLE I[a]

PROPERTIES OF CLINICAL ANTIARRHYTHMIC AGENTS

Agent	Therapeutic Action	Side Effects
Lidocaine (**52**)	agent of choice for ventricular arrhythmias	dizziness, confusion seizure
Encainide (**53**)	treatment of WPW syndrome[b] and premature ventricular repolarizations	induces ventricular fibrillation
Quinidine (**54**)	terminates atrial flutter	nausea, anorexia headache, confusion
Lorcainide (**55**)	treatment of ouabain-induced arrhythmias	sleep disorders headache
Disopyramide (**56**)	suppresses both supraventricular and ventricular tachycardias; can act as an anticholinergic	dry mouth, blurred vision, constipation
Procainamide (**57**)	treatment of WPW syndrome[b] and supraventricular arrhythmias	nausea, arthritis, diarrhea

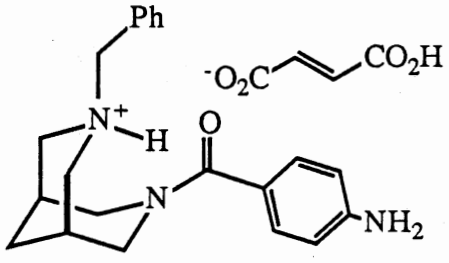
[a] Reference 41.

[b] WPW refers to Wolff-Parkinson-White Syndrome, which is a condition where a patient suffers attacks of paroxysmal tachycardia as evidenced by an electrocardiogram. This implies a bundle branch block-like pattern with a short PR interval.

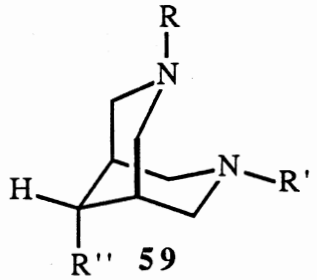
a mouse-chloroform fibrillation assay. Potency of these agents was reasonably high, although the acute toxicities (where therapeutic indices were on the order of 0.89-1.25) were less attractive (Table II). Slight modification to the framework of the bispidines, in which benzamide functions were incorporated to give structures **34a-i**, had a dramatic effect (Table III) upon the observed antiarrhythmic effect. Employing a similar assay[55] as described previously, the amides **34a-i** were significantly more potent and less toxic with therapeutic indices of 1.05-10.89. Compounds **34a** and **34d** (Table II) were found to be more active than even disopyramide (**57**) in these trials in terms of the observed ED_{50} values and therapeutic indices.

Binnig made bispidine analogs **6j-k** which were screened (Table IV) for antiarrhythmic activity in guinea pigs and found both to be quite active compared to lidocaine (**52**) in therapeutic breadth (value which reflects the safety margin between the desired rhythm regulating effect and the undesired impairing of the contractional forces of the heart). Similarly, salts of **7** were tested against quinidine (**54**) and both **7j** and **7l** (Table V) had superior effectiveness. In addition to the antiarrhythmic properties, bispidine derivatives **7** possessed calcium antagonistic, antiphlogistic, and thrombocyte aggregation inhibiting ability.[11]

Amide **35** was screened by Binnig and found to be more effective than sparteine (**2**) as an antiarrhythmic agent in rats and had the further advantage in that little or no constrictive



35

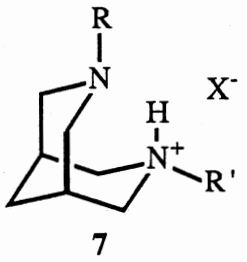


59

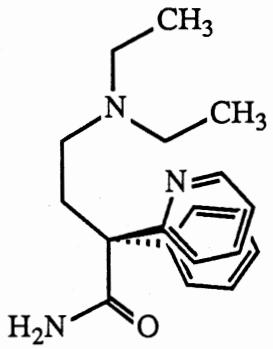
effects on vascular muscle were observed *in vitro*.[11] Adverse hypertensive effects were not observed for this novel amide **35** in contrast to those of sparteine (**2**).[11]

TABLE II[a]

ANTIARRHYTHMIC ACTIVITY OF BISPIDINE DERIVATIVES **7**



7



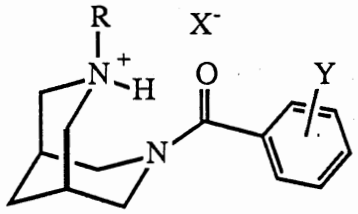
Disopyramide
56

Agent[b]	R	R'	ED_{50}[c]	LD_{50}[d]	Th. Index[e]
7e[f]	CH_3	*n*-C_4H_9	192	207	1.08
7f[g]	CH_3	CH_2Ph	154	189	1.23
7g[h]	CH_3	$CHPh_2$	259	225	0.87
7h[h]	*n*-C_4H_9	*n*-C_4H_9	170	196	1.23
7i[h]	*n*-C_4H_9	CH_2Ph	159	198	1.25
7j[h]	CH_2Ph	CH_2Ph	160	199	1.24
Disopyramide (**56**)			60	504	8.40

[a]Reference 55.
[b]Mouse-chloroform fibrillation assay in adult mice.
[c]Mean potency (μmole/kg ip).
[d]Mean toxicity (μmole/kg ip).
[e]Therapeutic Index = LD_{50}/ED_{50}.
[f]Monohydrobromide derivative.
[g]Monomesylate derivative.
[h]Monohydrochloride derivative.

TABLE III[a]

ANTIARRHYTHMIC ACTIVITY OF BENZAMIDE DERIVATIVES **34**



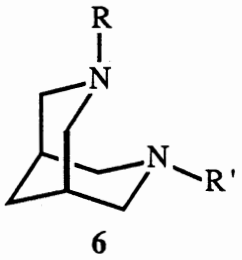
34

Agent[b]	R	Y	ED_{50}[c]	LD_{50}[d]	Th. Index[e]
34a	CH_3	H	85	621	7.29
34b	CH_3	4-OCH_3	78	463	5.93
34c	CH_3	3,4,5-$(OCH_3)_3$	137	535	3.91
34d	CH_3	4-Cl	49	535	10.89
34e[f]	CH_3	3,4-$(Cl)_2$	470	492	1.05
34f	*n*-C_4H_9	H	242	500	2.07
34g	*n*-C_4H_9	4-OCH_3	106	488	4.60
34h	*n*-C_4H_9	4-Cl	134	463	3.45
34i	*n*-C_4H_9	3,4-$(Cl)_2$	223	605	2.71
Disopyramide (**56**)			90	517	5.77

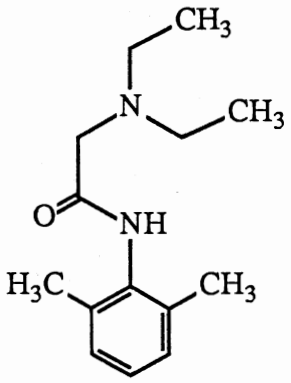
[a]Reference 55.
[b]Mouse-chloroform fibrillation assay in adult mice.
[c]Mean Potency (μmole/kg ip).
[d]Mean Toxicity (μmole/kg ip).
[e]Therapeutic Index = LD_{50}/ED_{50}.
[f]Monohydrochloride derivative (others were fumarate derivatives).

TABLE IV[a]

ANTIARRHYTHMIC ACTIVITY OF BISPIDINES **6**



6



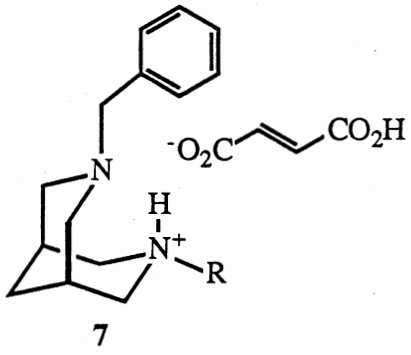
Lidocaine
52

Agent[b]	R	R'	Antiarrhythmic effect (ED_{25})[c]	Inotropic effect (LD_{25})[d]	Therapeutic Breadth[e]
6k	$CH(CH_3)_2$	CH_2CH_2Ph	0.13	0.07	2.0
6j	CH_2Ph	CH_2Ph	0.034	0.26	2.0
Lidocaine (**52**)			0.47	0.48	1.0

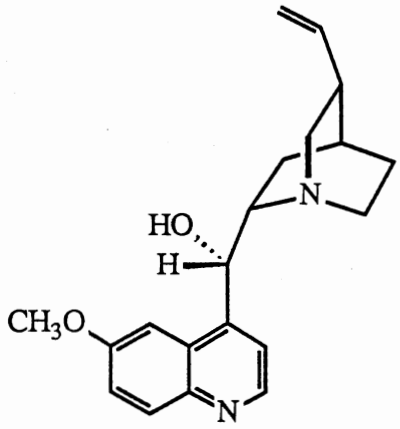
[a]Reference 11.
[b]Measuring the refractory period elongation of the left auricle of guinea pigs.
[c]Effective dose to produce 25% extension of refractory period (mg/kg).
[d]Effective dose to lower contractile force by 25% (mg/kg).
[e]Ratio of antiarrhythmic effect to inotropic effect relative to lidocaine (**53**).

TABLE V[a]

ANTIARRHYTHMIC PROPERTIES OF BISPIDINES **7**



7



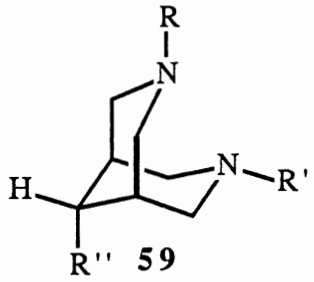
Quinidine
54

Agent	R	ED_{50}[b]	Max. Effect Dose[c]	Toxic Dose[d]	Q[e]
7l	$CH_2C_6H_3$-3,4-$(Cl)_2$	15.6	215	464	29.7
7m	$CH_2C_6H_4$-3-Cl	16.6	46	100	6.0
7n	$CH_2C_6H_4$-4-F	20.2	100	215	10.6
7o	$CH_2C_6H_4$-3-CF_3	25.4	100	215	2.5
7p	$CH(Ph)_2$	20.4	215	464	22.8
7q	$CH_2CH(Ph)_2$	13.0	46	100	7.7
Quinidine (**54**)		42.7	215	464	10.9

[a]Aconitine-induced arrhythmias in rats (Reference 11).
[b]Effective dose (mg/kg) for the increase by 50% in the duration of aconitine infusion.
[c]Maximum tolerated dose (mg/kg) to achieve maximum duration effect.
[d]Dose (mg/kg) at which toxic side effects, such as cyanosis or ECG change, occur.
[e]Q = Toxic Dose/ED_{50}.

TABLE VI[a]

ANTIARRHYTHMIC ACTIVITY OF BISPIDINES **59**



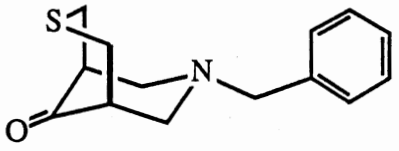
59

Agent[b]	R	R'	R''	ED_{50}[c]	LD_{50}[d]	T.I.[e]	R.I.[f]
59a[g]	CH_3	CH_3	O_2C-2-Napthyl	0.11	17.0	154	58
59b	CH_3	CH_3	O_2CPh	0.08	9.0	112	39
59c[h]	CH_3	CH_3	OC_6H_4-4-Cl	0.9	52.0	58	21
59d	CH_3	CH_3	O_2C-9-Xanthenyl	0.27	14.0	52	16
59e[i]	CH_3	C_2H_5	$O_2CC_6H_4$-4-Cl	0.6	26.0	43	15
59f[h]	CH_3	CH_3	OPh	1.15	39.0	34	12
59g[h]	CH_3	C_2H_5	OC_6H_4-4-Cl	1.25	41.0	33	12
59h[i]	C_2H_5	C_2H_5	$O_2CC_6H_4$-4-Cl	0.4	11.0	28	10
59i[h]	CH_3	CH_3	$O_2CC_6H_4$-4-Cl	0.25	5.0	20	7
Lidocaine (**52**)				10.0	28.5	3	1

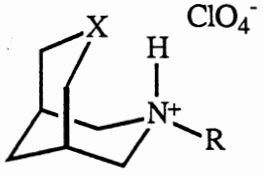
[a]Reference 46.
[b]Aconitine-induced arrhythmias in rats.
[c]Effective dose (mg/kg) to restore normal sinus rhythm in 50% of rats tested.
[d]Dose (mg/kg) causing mortality in 50% of tested rats.
[e]Therapeutic index (T.I.) = LD_{50}/ED_{50}.
[f]Relative Index (R.I.) = T.I. (agent)/T.I. [lidocaine (**52**)].
[g]Methanesulfonate derivative.
[h]Fumarate derivative.
[i]Dihydrochloride derivative.

Bispidine derivatives **59**, with ether or alcohol functionality at the 9-position, exhibited enhanced activity (Table VI) in aconitine-induced arrhythmias in rats.[46] These amines displayed 5 to 58 times more favorable therapeutic effects than lidocaine (**52**) and also possessed calcium antagonistic capability. Furthermore, it was observed that these agents can increase the stimulus threshold which is the impulse time and the refractory period, thereby aiding in the elimination of certain rhythm disorders.

Our group, in collaboration with Dr. Scherlag and co-workers, has synthesized and screened the antiarrhythmic efficacy of several 3-hetera-7-azabicyclo[3.3.1]nonane derivatives using lidocaine (**52**) as the standard.[6] The ability of these compounds to alleviate sustained ventricular tachycardias (SVT), which were generated by electrical stimulation of animal hearts impaired with surgically-induced myocardial infarctions, was evaluated. Although the ketone **8a** had little antiarrhythmic activity, salt **11a** prevented the



8a



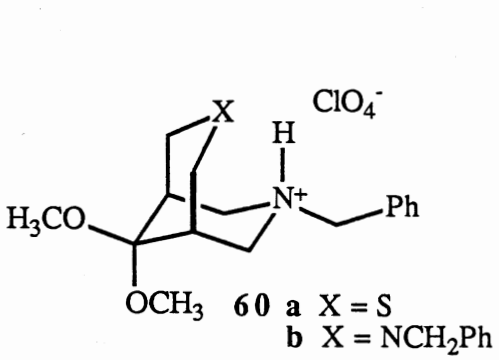
11

	X	R
a	S	CH_2Ph
b	Se	CH_2Ph
c	S	CH_2CH_2Ph
d	Se	CH_2CH_2Ph

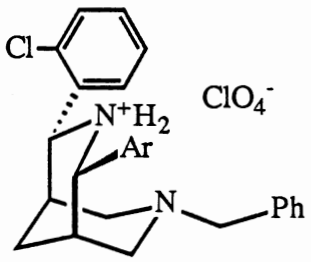
induction of SVT in 8 of 10 animals and also had the additional effect of suppressing the heart rate by 29% relative to the control experiments.[6] Lidocaine (**52**) , however, did not diminish the SVT in every animal and reduction of the heart rate was only 11%.[6] Salt **11a** also inhibited the induction of reentry of the VT, relative to lidocaine (**52**). Moreover, **52** was virtually ineffective against ventricular escape rhythms or arrhythmias due to enhanced autonomic activity in the ventricles.[59]

Several other potentially active derivatives have been produced.[6] For example, while compounds **11b-d** displayed activity comparable to **11a** at dose levels of 3 mg/kg and 6 mg/kg, ketal **60a** showed complete abolition of the SVT at both dose levels while **60b** displayed abolition of the SVT at the 6 mg/kg dosage with reduction in the rate of the SVT

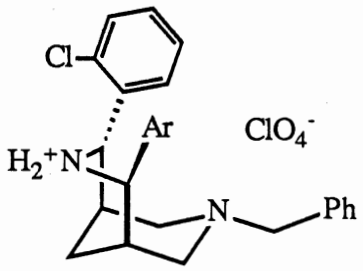
by 46% at the lower dosage. Salt **45** had no effect on the SVT while the isomeric salt **46** exhibited *proarrhythmic* effects. A related selenium adduct **61** displayed little antiarrhythmic action as compared to **11a**.[6]



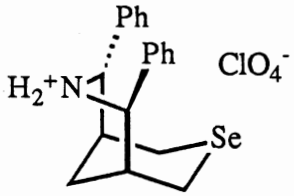
60 **a** X = S
b X = NCH_2Ph



45 Ar = C_6H_4-2-Cl



46



61

One can conclude that although trends in activity in a series can be observed within specific testing procedures, problems may arise when comparing compounds which are screened using different procedures. Certainly, several members of these 3-hetera-7-azabicylo[3.3.1]nonanes deserve special attention considering the volume of evidence accumulating that the family does have useful antiarrhythmic properties.

Metabolism

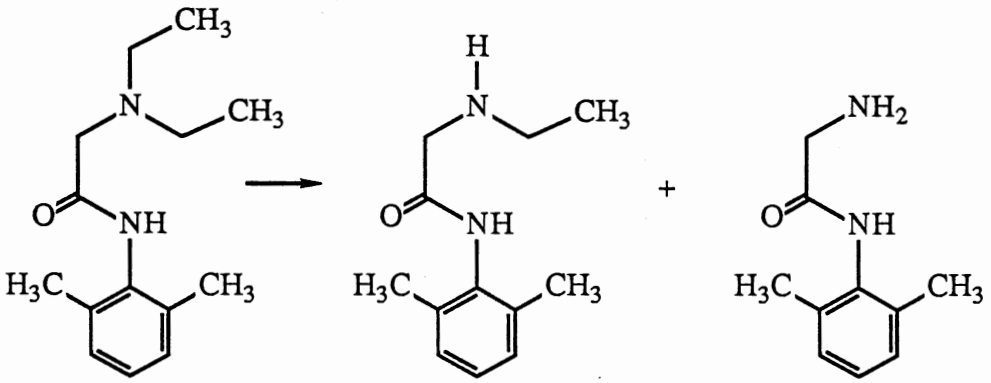
The pharmacokinetic requirements, the mode of action and the clinical effectiveness of standards and new experimental antiarrhythmic agents have prompted examinations of metabolites from useful agents. Considering that many of these agents have a narrow therapeutic range, and the fact that more accurate techniques for measuring plasma concentrations have been developed, the ability to correlate plasma concentrations with the drug's

effectiveness and toxicity are now possible.[35] Although such correlations are not always observed, there are factors which can explain the discrepancies: (1) mediation of drug effects by the generation of metabolic side products, (2) persistence of drug-induced cellular alterations after drug elimination, (3) failure to detect prolonged retention of the drug at the myocardial effector site by conventional methods, and (4) indirect effects which are mediated by the autonomic nervous system or via hemodynamic changes and assay nonspecificity.[41] The potential significance of metabolites as the active components with antiarrhythmic properties from any agent is clear.[35]

To fully explain the role of metabolites as potential antiarrhythmics requires isolation, purification, identification and evaluation in biological assays to determine the pharmacological activity. Understanding the biological profile of any agent, as well as the metabolites therefrom, is critical in order to individualize therapy for patients.[35] Clinical determinations reveal that there is also the presence of interindividual differences among patients in the response to these agents.[19] Factors such as age, diet, co-administration of drugs, underlying disease factors, as well as the pharmacogenetics of a person can produce marked variation in the ability to metabolize drugs. Pharmacogenetics refers to the hereditary variations in the response to these agents which can help to explain the variety of reactions which occur in individual patients. An understanding of the mode of action and pharmacological aspects of both the precursor and its metabolites becomes necessary in order to evaluate the overall clinical capability of these agents.[35]

Detailed examinations involving several known antiarrhythmic agents via pharmacological studies have been accomplished in order to evaluate the mode of action of the parent and the metabolites which might be derived therefrom. In the following survey, the discussion will focus on the metabolic studies of certain clinical standards and also some related systems. Known metabolites, as well as the pharmacokinetics of seven agents, will be briefly reviewed.

Lidocaine (**52**) is primarily metabolized in the liver which is extremely efficient in removing the agent from circulation.[41] Oxidative *N*-dealkylation is the major route in lidocaine metabolism, although several metabolites have been identified.[13,41] Initial products formed from this dealkylation are monethylglycinexylidide [MEGX] (**62**) and glycinexylidide [GX] (**63**). Metabolites such as MEGX (**62**) possess some antiarrhythmic properties while GX (**63**) potentiates convulsant action of **52** and **62**.[13] Lidocaine

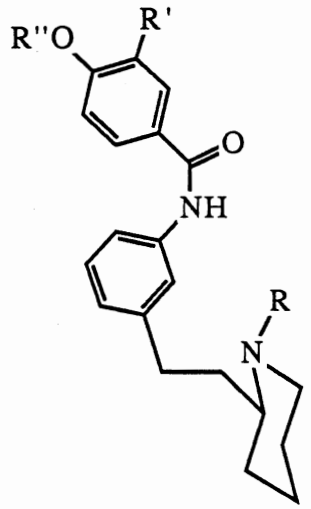


Lidocaine **52** MEGX **62** GX **63**

(**52**) undergoes hepatic elimination up to 80% of the prescribed oral dosage with only about 3% being excreted unchanged in the urine.[41]

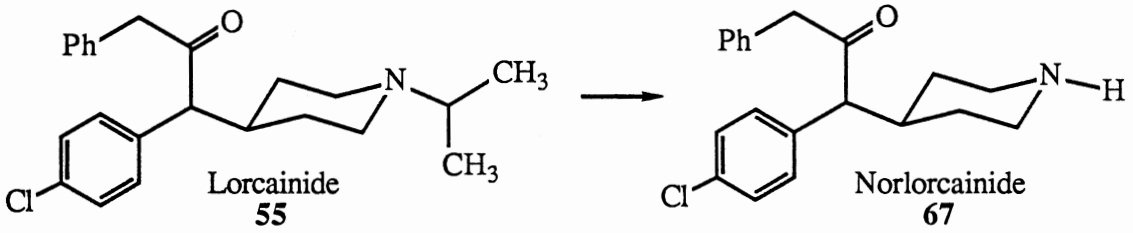
Development of encainide (**53**) as an investigational agent was delayed due to lack of knowledge concerning its pharmacokinetics. Aggravation of ventricular arrhythmias, including induction of ventricular fibrillation, is the main limitation in its application. Three main metabolites have since been identified as: *O*-demethylencainide [ODE] (**64**), 3-methoxy-*O*-demethylencainide [MODE] (**65**), and *N*-demethylencainide [NDE] (**66**).[35,41] Metabolite ODE (**64**) has been found to be 50 times more effective in alleviating aconitine-induced ventricular arrhythmias while MODE (**65**) was equipotent compared to **53** in suppressing ouabain-induced arrhythmias.[35] Hepatic metabolism is responsible for elimination of encainide (**53**) and this should be accounted for in long term

oral therapy due to the important antiarrhythmic efficacy of the metabolites.[41] Toxic side effects in humans have not been fully assessed for encainide (**53**).



	R	R'	R''
Encainide (**53**)	CH_3	H	CH_3
ODE (**64**)	CH_3	H	H
MODE (**65**)	CH_3	OCH_3	H
NDE (**66**)	H	H	CH_3

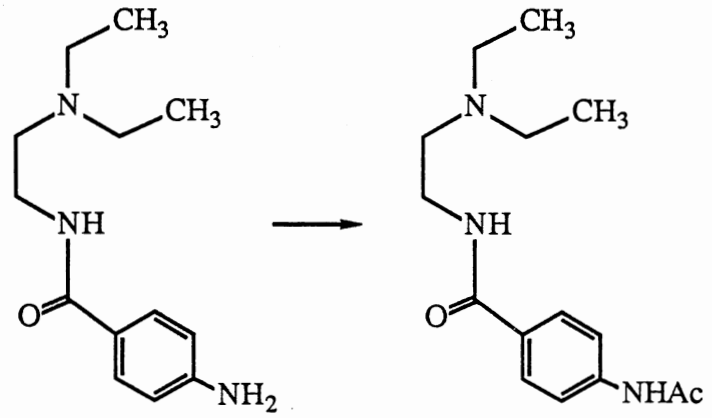
Complete elimination of lorcainide (**55**) occurs by hepatic metabolism with only 2% being excreted unchanged in the urine.[41] Surveys reveal the major metabolite to be norlorcainide (**67**), which has been isolated and found to be quite active in controlling ventricular arrhythmias.[35] This dealkylated metabolite **67** is the product of a first pass



metabolism of **55** and is not produced in significant amounts following acute intravenous administration.[35] Considering the equipotent effectiveness of the metabolite **67** relative to its parent **55**, one can note the significant role **67** plays in the clinical efficacy of **55**.[41]

Procainamide (**57**), is rapidly distributed in the body and is primarily metabolized in the liver by the polymorphic enzyme *N*-acetyltransferase.[41] Conversion of **57** to its major metabolite, *N*-acetylprocainamide [NAPA] (**68**), was discovered in rhesus monkeys as well as in humans.[41] Hydrolysis also accounts for 2 to 10% of the administered dosage

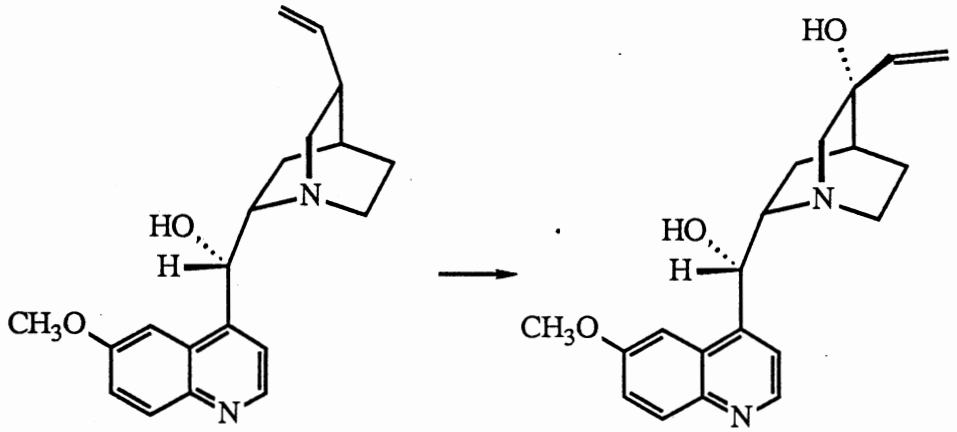
being converted to *p*-aminobenzoic acid. Electrophysiologic and antiarrhythmic properties of NAPA (**68**) are quite comparable to those of the parent **57**. Renal clearance of **57** is pH dependent (decrease in excretion with increase in pH) and can have an effect on its prolonged efficacy.[41]



Procainamide
57

NAPA
68

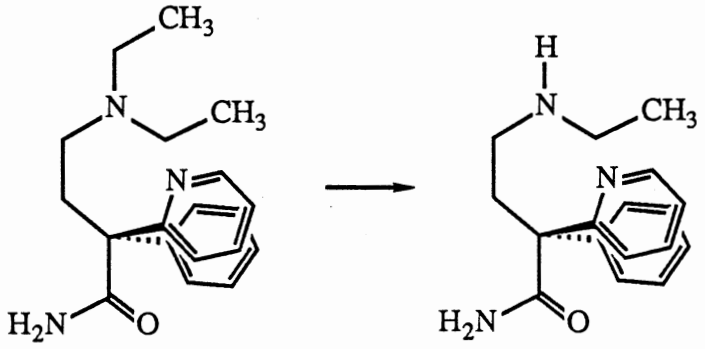
Other agents have been analyzed in similar fashion. Quinidine (**54**) is metabolized (85%) to the hydroxylated metabolite **69**[9] which possesses very little antiarrhythmic activity, while excretion of unchanged **54** is *inversely* related to the pH of the urine



Quinidine
54

69

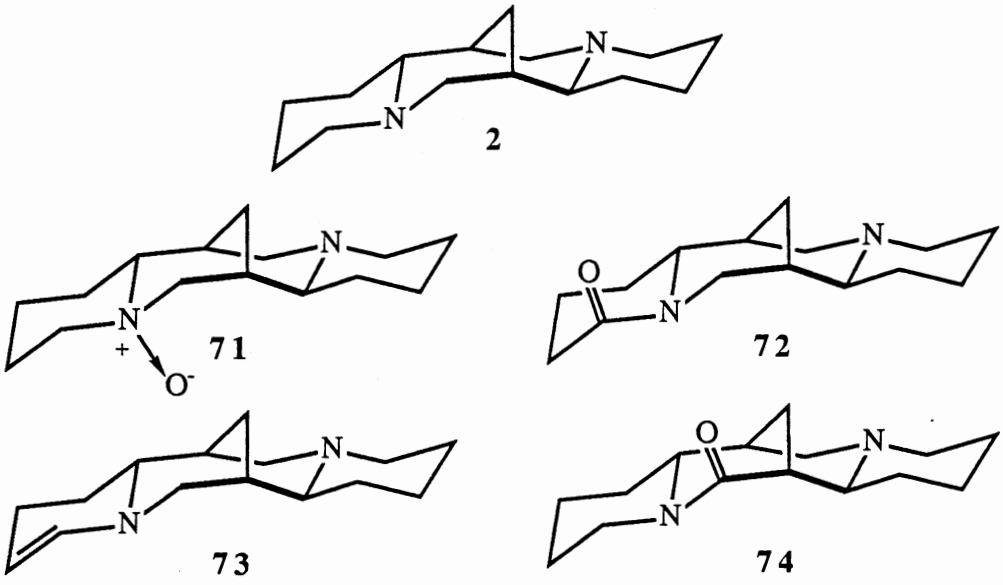
(decrease in excretion of the agent with increase in pH). Metabolism and disposition of disopyramide (**56**) is not well understood, although it has been determined that the major metabolite **70** (*N*-dealkylated product) is formed in the liver and has about 50% as much antiarrhythmic action as the parent **56**.[41] Metabolism of sparteine (**2**) in humans favors



Disopyramide
56

70

formation of the *N*-oxidized product **71** as the major metabolite.[20] Small amounts of the amide **72**, as well as **73** and **74**, have been detected in studies involving plants.[72]



2

71

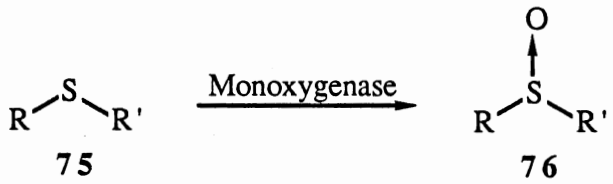
72

73

74

Incorporation of the sulfur moiety into several potential antiarrhythmic agents has stimulated debate on the possible metabolic pathway which agents of this nature might

follow. Holland[27] suggested that monoxygenases (enzymes found in plants and animals) were capable of oxidizing these type of sulfur substrates like **75** to the sulfoxides **76**.[27]



75 **76**

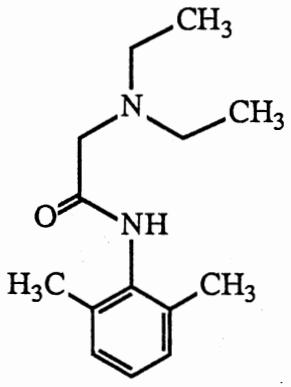
One might therefore predict that the metabolic pathway for certain 3-thia-7-azabicyclo-[3.3.1]nonanes might proceed in a related fashion to some degree.

Several members of the 3-hetera-7-azabicyclo[3.3.1]nonanes have displayed significant antiarrhythmic action in animal models.[6,11,46,55] Unfortunately, the mode of action and pharmacokinetics are still not well understood in most of these systems. From these model systems, one might be able to outline some of the parameters which have an influence on the uptake and metabolism of these agents. Currently, there is investigative work in progress which should help to define the pharmacological boundaries of this family.

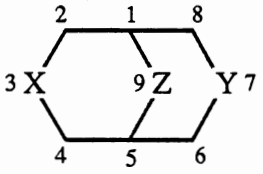
CHAPTER II

RESULTS AND DISCUSSION

Members of the 3-hetera-7-azabicyclo[3.3.1]nonanes[30] possess very promising pharmacological properties as supported by a variety of assays which demonstrate such activity.[6,11,46,55,57,75] Several of these compounds display superb antiarrhythmic action compared to the clinical standard lidocaine (**52**) as determined in electrocardiological analyses of dog models with a 24 hour infarcted heart.[6] Since canine subjects are con-



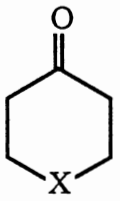
Lidocaine
52



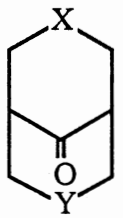
1

sidered close models of the human cardiovascular system in these types of assays,[42] the potential utility of these agents to help alleviate arrhythmic conditions, which can lead to sudden death, is promising. Slight modifications in structure in the 3-hetera-7-azabicyclo-[3.3.1]nonanes **1** can significantly alter the observed antiarrhythmic action[6,11,46,55] (as previously described in Chapter I); therefore, further characterization of structure-activity relationships should allow the incorporation of structural features which might elicit optimum activity.

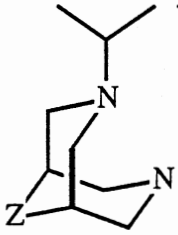
One major objective of this research was to develop methodology to obtain a series of 3-hetera-7-azabicyclo[3.3.1]nonan-9-ones which could be converted to 3-hetera-7-azabicyclo[3.3.1]nonanes and the corresponding hydroperchlorates with potential antiarrhythmic properties. In a modified Mannich[66] type condensation, starting from ketones **4**, it has been possible to synthesize 3-hetera-7-azabicyclo[3.3.1]nonan-9-ones **77**, and certain



4



77



78

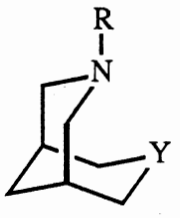
Z	
a	$C(OH)_2^{\dagger}$
b	$C(OH)OEt^{\dagger}$
c	C=N-OH

$^{\dagger}HClO_4$ salts

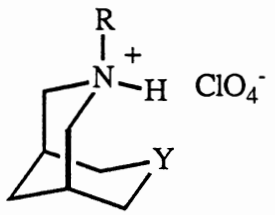
X	
c	$NCH(CH_3)_2$
f	S

77

X	Y
a $NCH(CH_3)_2$	NCH_2Ph
b $NCH(CH_3)_2$	$NCH_2C_6H_4$-4-Cl
c $NCH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$
d $NCH(CH_3)_2$	S
e $NCH_2C_6H_4$-3-I	S



79

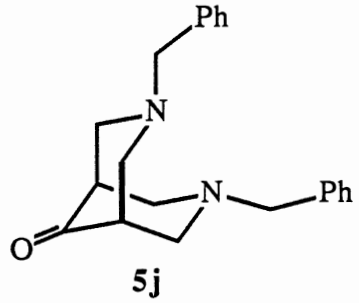


80

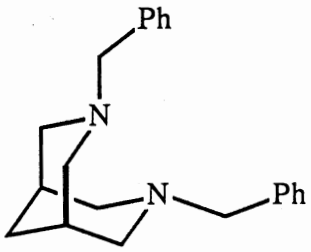
79, 80

R	Y
a $CH(CH_3)_2$	NCH_2Ph
b $CH(CH_3)_2$	$NCH_2C_6H_4$-4-Cl
c $CH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$
d $CH(CH_3)_2$	NH
e $CH(CH_3)_2$	S
f $CH_2C_6H_4$-3-I	S

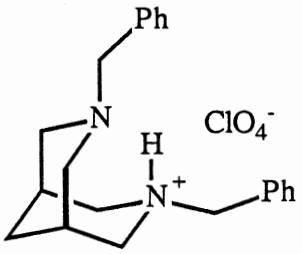
derivatives **78** thereof, which were reduced to the amines **79** that in turn were transformed to the hydroperchlorates **80**. Certain intermediates and known members, such as ketones **5j** and **8a**, amines **6j** and **10a** and salts **7j** and **11a** have been reported here for the sake of completeness and to aid in later discussion.



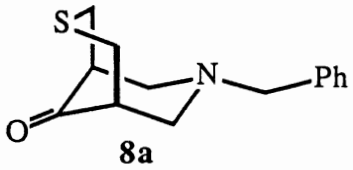
5j



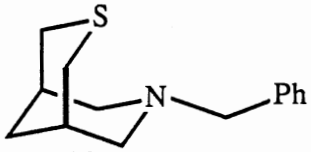
6j



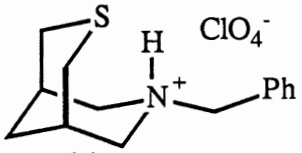
7j



8a

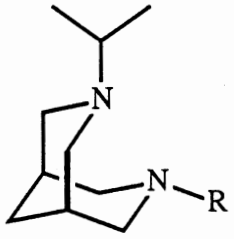


10a

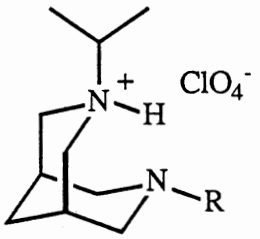


11a

An ancilliary objective was to uncover a useful method to prepare the related amides **81** and certain salts **82** which not only could exhibit antiarrhythmic characteristics but could be potential metabolites of members **79** and/or **80**. In addition, amides **81** and **82** should be more hydrophilic for improved drug formulation.



81



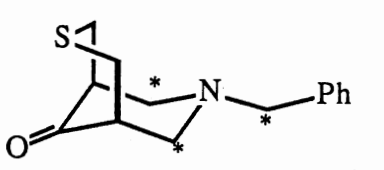
82

81, 82†

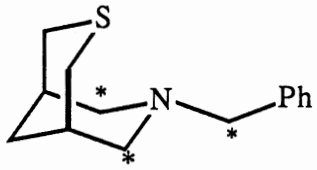
R
a C(O)Ph†
b $C(O)C_6H_4$-4-Cl
c $C(O)C_6H_3$-3,4-$(OCH_3)_2$†
d $C(O)C_6H_2$-3,4,5-$(OCH_3)_3$
e SO_2Ph

†$HClO_4$ salts

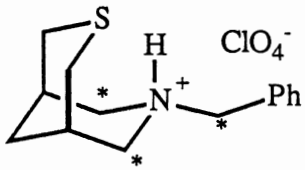
In an investigation to determine the principal metabolites from **11a**, we developed a method[77] to prepare the labelled ketone **8a***, amine **10a***, and the hydroperchlorate **11a***. In collaboration with pharmacologists/toxicologists in the OSU College of Veterinary



8a* *C = ^{14}C

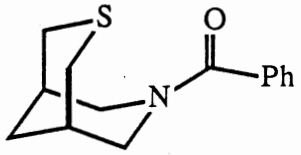


10a*

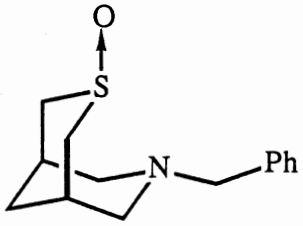


11a*

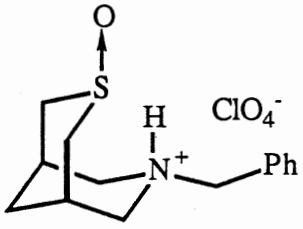
Medicine (Dr. Clarke and Dr. Sangiah), we have established a profile of metabolites[58] found in the urine of rats. Identification of one major metabolite **83** has been accomplished via mass spectral analysis in collaboration with Dr. Geno of the OSU Department of Chemistry.[58] Potential metabolites **84** and **85** were synthesized as was the model lactam system **86** (which might be derived from amine **6j** or salt **7j**).



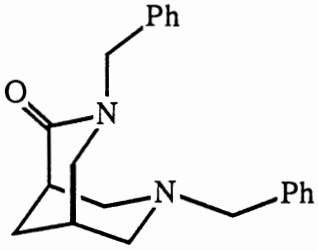
83



84



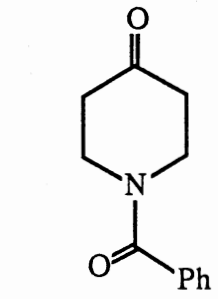
85



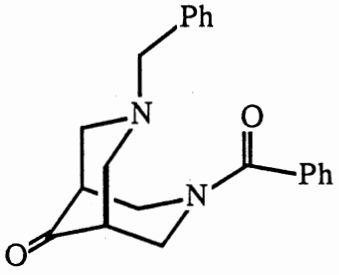
86

Ketoamide **87** was derived under Mannich[66] condensation conditions from **4h** and was then reduced to the amide **33k.** This was converted to the perchlorate **88.** These

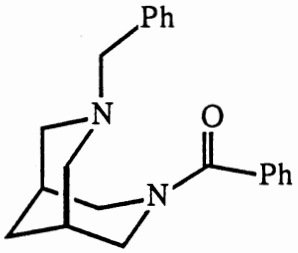
compounds were of interest for comparision with the metabolite profile. We derived an efficient route to **33k** since it and its sulfate **34k** had only been reported once with just a melting point for **34k** (181°C) being recorded.[11]



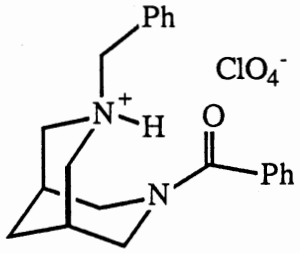
4i



87



33k

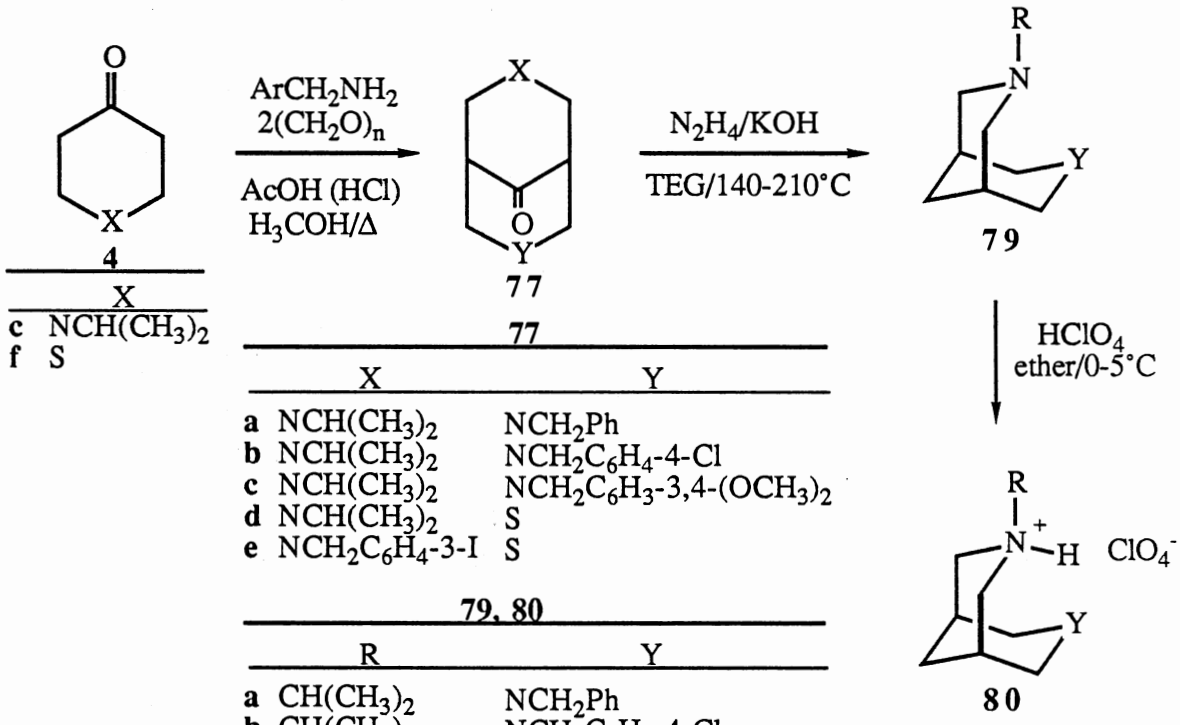


88

Synthetic Methodology

A double Mannich condensation[66] of 1-hetera-4-cyclohexanones **4c** and **4f** was utilized in the synthesis of 3-hetera-7-azabicyclo[3.3.1]nonan-9-ones **77**. Condensation of **4c** or **4f**, an amine, paraformaldehyde, and acetic acid (and/or concentrated hydrochloric acid in methanol) gave ketones **77**. It was discovered that the addition of one equivalent of HCl (37%) to the Mannich reaction mixture significantly increased the isolated yield for **77a** from 20-50% to a consistent 56-57% (although this phenomenon is not completely understood, slight alterations in pH could play a role in the reaction kinetics which in turn could affect the distribution of products). Elaborate purification procedures (see Chapter III) were followed to obtain ketones **77** (22.6-57.5%).

Wolff-Kishner reduction[68] of the ketones **77** in the presence of hydrazine, KOH, and triethylene glycol at elevated temperature (140-210°C) gave the amines **79** as oils which were characterized spectrally and used without further purification. Salts **80** were obtained upon treatment of a chilled (0-5°C), ethereal solution of **79** with $HClO_4$ (60%).



4	
	X
c	$NCH(CH_3)_2$
f	S

77

	X	Y
a	$NCH(CH_3)_2$	NCH_2Ph
b	$NCH(CH_3)_2$	$NCH_2C_6H_4$-4-Cl
c	$NCH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$
d	$NCH(CH_3)_2$	S
e	$NCH_2C_6H_4$-3-I	S

79, 80

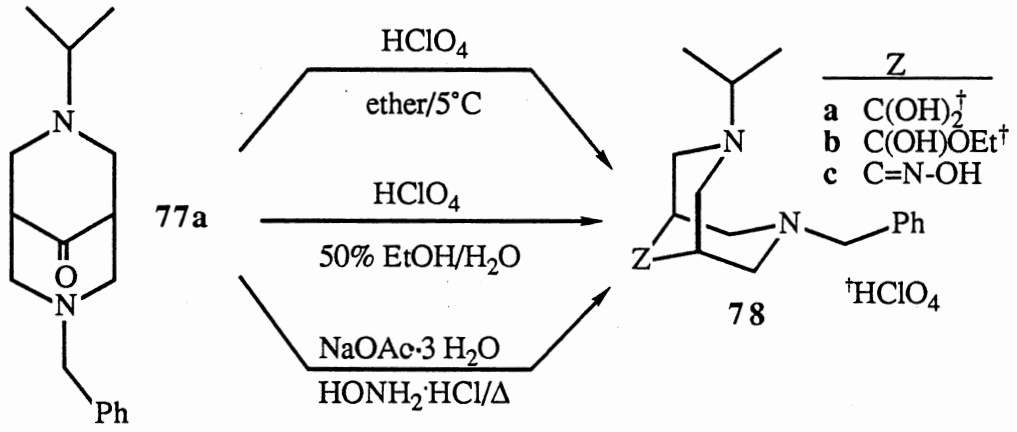
	R	Y
a	$CH(CH_3)_2$	NCH_2Ph
b	$CH(CH_3)_2$	$NCH_2C_6H_4$-4-Cl
c	$CH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$
d	$CH(CH_3)_2$	NH
e	$CH(CH_3)_2$	S
f	$CH_2C_6H_4$-3-I	S

It must be noted that, in order to effect the reduction of these ketones, the temperature must be high enough to reduce the hydrazone which is formed *in situ* but also should be low enough to prevent thermal decomposition of the starting material. For example, when ketone **77c** is reduced at 200-210°C, the clear reaction mixture turned dark brown upon heating although subsequent treatment with 60% $HClO_4$ gave the hydroperchlorate **80d** (apparently at this elevated temperature, hydrazine effectively behaves as a source of

hydrogen which cleaves the benzylic substituent). In a separate experiment, a reduction in the temperature range to 150-160°C with **77c** gave the desired product **79c** which was then isolated as a hydroperchlorate **80c.**

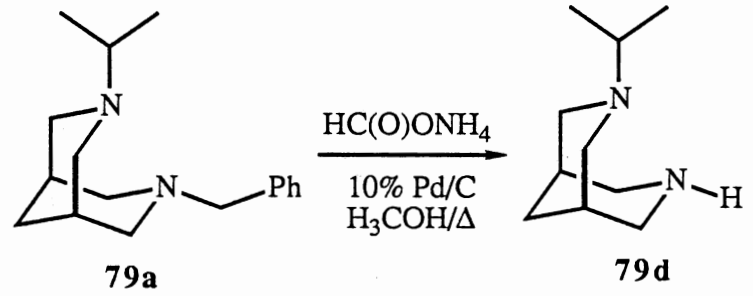
Similarly, bicyclic ketones **77d** and **77e** were derived using this synthetic scheme from 4-thianone (**4f**) and were obtained in yields of 41.6% and 57.5%, respectively. Reduction of ketones **77d** and **77e** gave the amines **79e** and **79f**, respectively, which were immediately converted to the respective salts **80e** (63.6%) and **80f** (27.7%).

Certain derivatives of ketone **77a** were prepared and characterized. The chemistry of 3-hetera-7-azabicyclo[3.3.1]nonan-9-ones **1** has been extensively studied.[30] For example, treatment of ketone **77a** with $HClO_4$ (60%) in ether at 5°C gave the diol **78a** (48.7%);[5] however, when identical conditions were employed using 50% EtOH/H_2O as the solvent, the novel hemiketal **78b** could be obtained following tedious purification procedures (21.7%). A boiling mixture of the ketone **77a** in hydroxylamine hydrochloride and sodium acetate trihydrate in EtOH afforded the oxime **78c** (62.3%).[8] Oximes are rare for these ketones.



Observations by Reunitz and Binnig suggest that amides derived from the bispidine family possess antiarrhythmic properties.[46,55] In our work, several new amide derivatives were targeted as potential antiarrhythmics. Debenzylation of bispidine **79a** in a boiling

mixture of ammonium formate, 10% Pd/C (catalytic), and methanol gave the secondary amine **79d** as an oil (93.0%) which was characterized spectrally and used without further purification. The use of ammonium formate as a hydrogen source (especially in debenzylation) has only been recently examined and has been proven to be a quite novel and mild method for effecting this type of $ArCH_2N$-C cleavage.[1] Amine **79d** could then be acylated using a modified Schotten-Baumann procedure[73] in which the amine was stirred at RT with the appropriate acylation agent in a biphase mixture of CH_2Cl_2 and 10% NaOH to



R
a C(O)Ph†
b $C(O)C_6H_4$-4-Cl
c $C(O)C_6H_3$-3,4-$(OCH_3)_2$†
d $C(O)C_6H_2$-3,4,5-$(OCH_3)_3$
e SO_2Ph

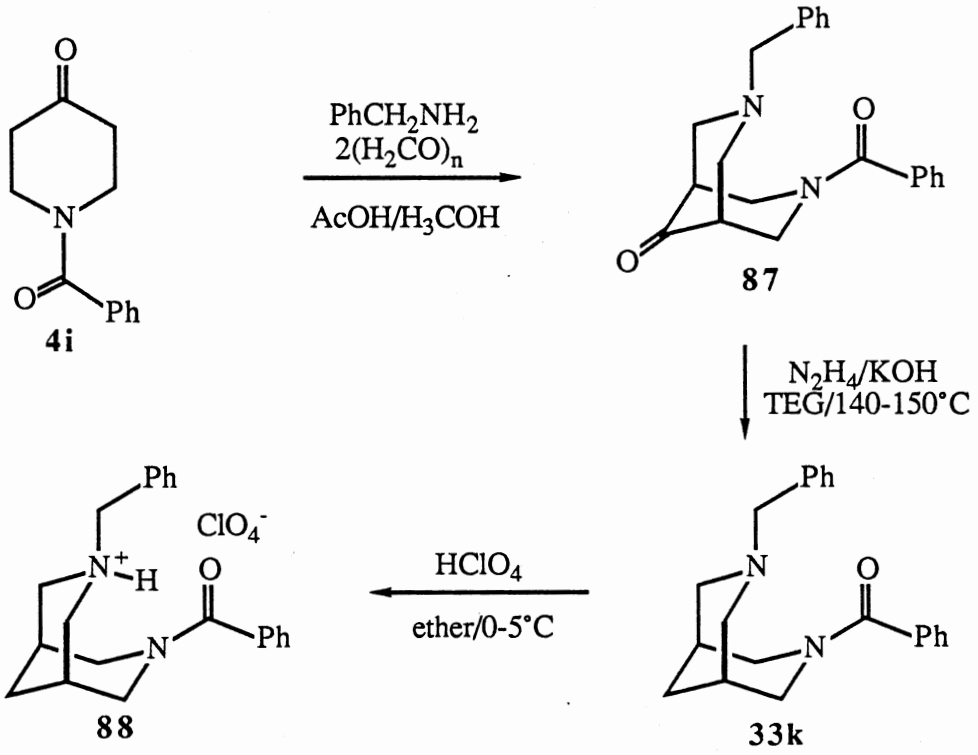
81, 82†

†$HClO_4$ salts

give the crude amides **81**. Chromatography over neutral alumina afforded the desired purified product **81a** as an oil (82.4%) while amides **81b-d** were isolated (73.1-80.4%) as solids. Compounds **81a** and **81c** were then converted to the respective hydroper-

chlorate salts **82a** (91.3%) and **82c** (69.2%). In a similar fashion, the secondary amine **79d** was converted to the sulfonamide **81e** (28.6%) although formation of the hydroperchlorate was not attempted.

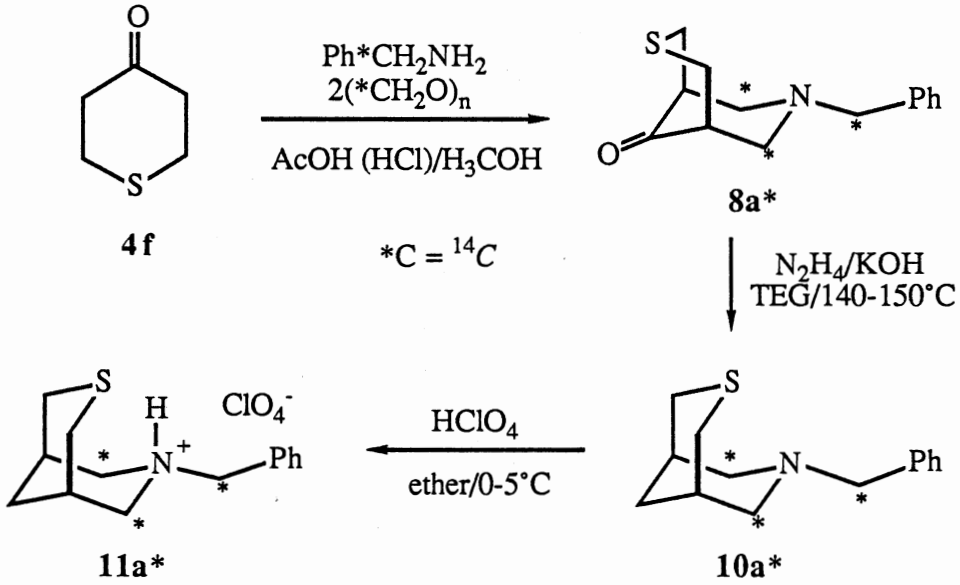
The novel ketoamide **87** could be obtained from Mannich[66] condensation of *N*-benzoyl-4-piperidinone (**4i**) with benzylamine, paraformaldehyde, and glacial acetic acid in methanol. After workup, the product was isolated (38.3%) as a low melting solid (mp 22-24°C) following chromatography over silica gel. Wolff-Kishner[68] reduction of **87**, followed by chromatography over silica gel, afforded the amide **33k** (68.9%) as a solid.



Salt **88** was obtained upon treatment of a chilled (5°C), ethereal solution of **33k** with $HClO_4$. Although Binnig[11] had previously reported the synthesis of **33k** and its sulfate salt **34k**, the only physical data to support his findings was the melting point (181°C) of **34k**. The method which is described herein is superior to that reported by Binnig[11] in that the number of steps required for the isolation of **33k** has been reduced with concomitant

improved yields. Our results have further application considering that the amide group *survives* the vigorous conditions of the Wolff-Kishner[68] reduction, and selective reduction of the ketone carbonyl group is accomplished. A review of the literature indicated that this finding is quite unique with no previous citations regarding this type of selectivity. It is has been reported that ester functions are hydrolyzed under these severe conditions which further supports the novelty of this reaction.[68] These results might also have use in natural product syntheses where selective reductions are often required.

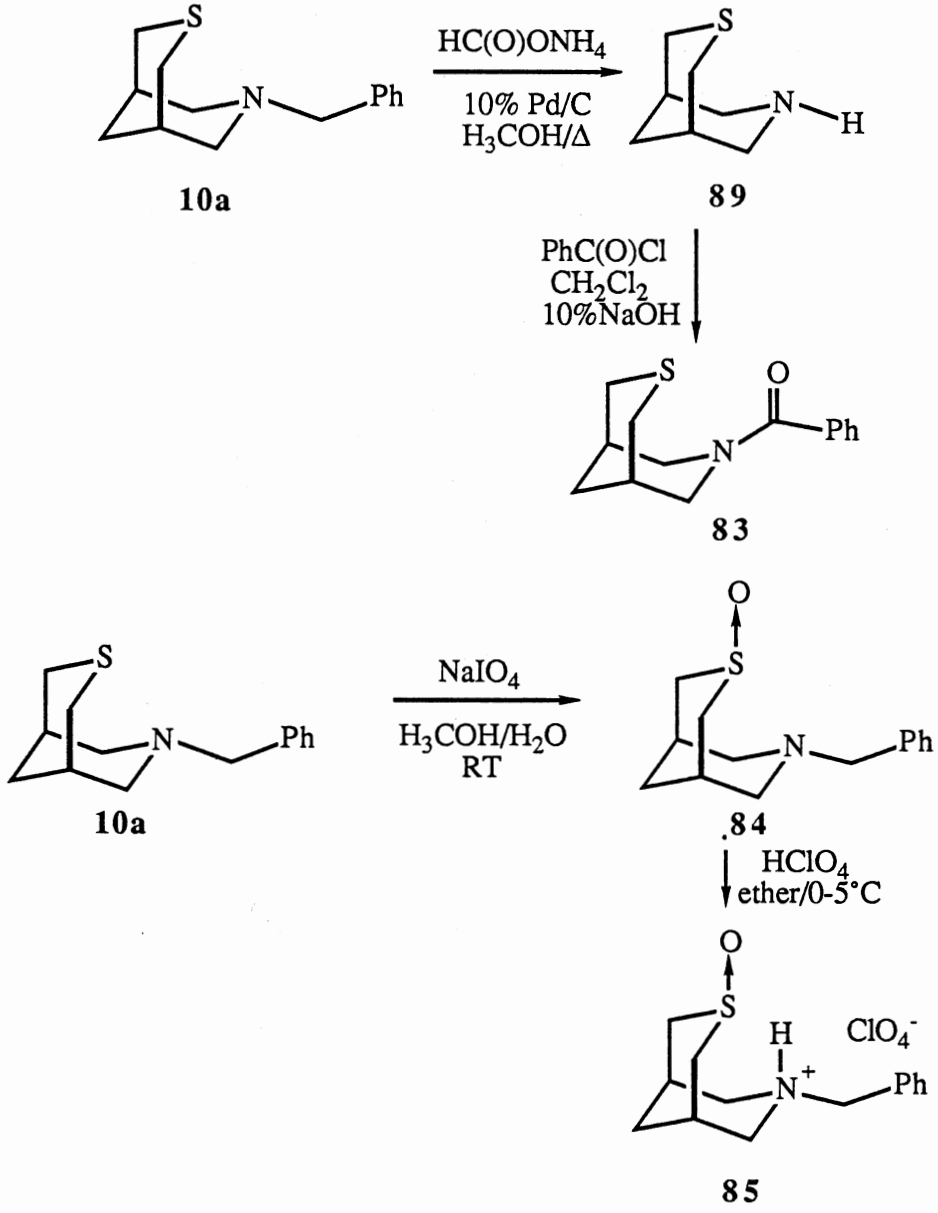
Currently, the pharmacological properties of the active experimental agent **11a** are under investigation.[58] In order to monitor the physiological distribution and metabolic properties of the agent, it was necessary to synthesize the radioactive form[77] **11a*** as



well as potential metabolites (which might be derived upon feeding a diluted form of **11a*** to an animal model). A double Mannich[66] condensation of 4-thianone (**4f**) with diluted ^{14}C -labelled benzylamine and ^{14}C-labelled paraformaldehyde, as well as glacial acetic acid, HCl (37%), and methanol, was used to synthesize the labelled ketone **8a*** which was purified by sublimation. Physical properties of labelled **8a*** were totally comparable to the unlabelled counterpart[6] (note that ^{14}C label has been incorporated at the positions

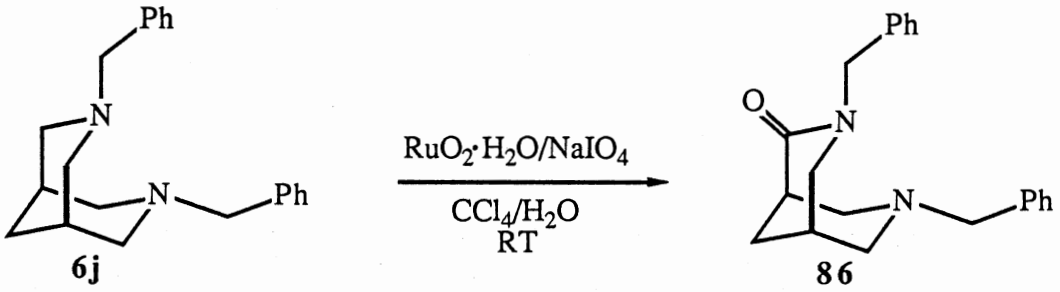
alpha to the nitrogen atom). Reduction of the ketone using Wolff-Kishner conditions to **10a*** was followed by conversion to the labelled hydroperchlorate **11a*** whose physical properties were entirely comparable to those of the unlabelled compound **11a**.[6,77]

Potential metabolites (which might be derived upon feeding a diluted **11a*** with **11a** to an animal model) were also synthesized. For example, debenzylation of unlabelled **10a** with ammonium formate[1] in the presence of Pd/C and methanol (as previously described) gave the amine **89** as a crude gum. This gum could then be acylated with benzoyl chloride



in a biphase mixture of 10% $NaOH/CH_2Cl_2$ to give the crude amide **83**. Chromatography over neutral alumina afforded the pure amide **83**. Amide **83** is a potential metabolite which could be derived from benzylic oxidation and will be discussed in more detail shortly. Oxidation of the sulfide **10a**, using a modified procedure of that developed by Johnson[31] with $NaIO_4$ in CH_3OH/H_2O at RT, gave the sulfoxide **84** (76.9%) which, upon treatment with $HClO_4$ (60%), afforded the salt **85** (78.1%). Sulfoxides **84** and **85** are potential metabolites which could be derived from metabolic oxidation at the S atom in **11a**. Such oxidation has been shown previously[27] to be common for sulfides and will be discussed shortly.

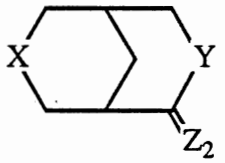
Currently, potential metabolites of other species are being targeted for synthesis. Our initial entry to this area has been to obtain lactam **86** via oxidation of amine **6j**. A biphase mixture of $RuO_2 \cdot H_2O/NaIO_4$[69] in CCl_4/H_2O at RT did produce the lactam **86** (28.9%). Preliminary results from this experiment are encouraging, and conditions are being modified to determine the scope of the reaction in related systems. A recent review described the versatility of RuO_4 (formed *in situ* from $RuO_2 \cdot H_2O/NaIO_4$) as an oxidant for organic transformations.[69]



6j **86**

Several derivatives, namely **33k**, **80a**, **80c**, **80e**, **81e**, **82a**, **83**, **84**, **85**, **86**, and **88** have been or are currently being tested by Dr. Benjamin Scherlag of the VA Medical Center in Oklahoma City, Oklahoma, for antiarrhythmic activity. Pharmacological studies have been and are being performed by Dr. Clarke and Dr. Sangiah[58] of the OSU College of Veterinary Medicine with the radioactive form **11a*** which should provide insight into

the mode of action and metabolism of this agent as well as related species. Data accumulated from these studies should help to further define the boundaries for structure-activity relationships.

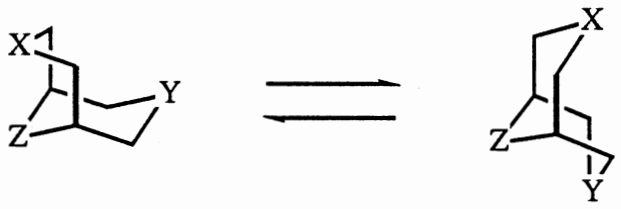


	X	Y	Z_2
33k	NCH_2Ph	NC(O)Ph	H_2
80a†	$NCH(CH_3)_2$	NCH_2Ph	H_2
80c†	$NCH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$	H_2
80e†	$NCH(CH_3)_2$	S	H_2
81e	$NCH(CH_3)_2$	NSO_2Ph	H_2
82a†	$NCH(CH_3)_2$	NC(O)Ph	H_2
83	S	NC(O)Ph	H_2
84	S→O	NCH_2Ph	H_2
85†	S→O	NCH_2Ph	H_2
86	NCH_2Ph	NCH_2Ph	O
88†	NCH_2Ph	NC(O)Ph	H_2

†$HClO_4$ Salts

Conformational Aspects

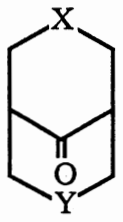
Delineation of conformational preferences in these 3-hetera-7-azabicyclo[3.3.1]nonanes **1** (Y = N) by ^1H, ^{13}C and ^{15}N NMR spectroscopy in solution as well as X-ray



1-BC **1-CB**

crystal analysis in the solid state is critical. Not only are the analyses useful as diagnostic probes for structure elucidation, but such data are also important to understand the observed biological properties and mode of action of these agents. Positive confirmation of structure in the solid state is provided by X-ray crystal analyses, but debate over preferred

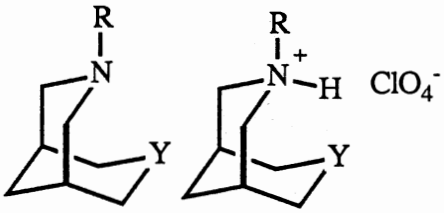
conformations in solution continues. Though a recent study by Takeuchi[65] seems to suggest that a BC⇌CB equilibrium may be in operation in many of compounds **1** in solution, other work has indicated that these systems adopt one conformation preferentially over another.[3,23] Unequivocal proof of conformation in solution of these compounds is difficult to obtain at this time. However, we propose a rational explanation concerning structural preferences in solution as supported by our data and which further substantiates some previous work. Ketones **77**, amides **81** and **83**, as well as salts **80** and **82** derived therefrom, will be the subject of this discussion.



77

77

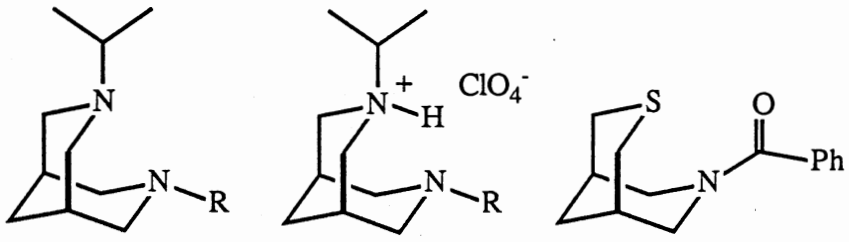
	X	Y
a	$NCH(CH_3)_2$	NCH_2Ph
b	$NCH(CH_3)_2$	$NCH_2C_6H_4$-4-Cl
c	$NCH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$
d	$NCH(CH_3)_2$	S
e	$NCH_2C_6H_4$-3-I	S



79 **80**

79, 80

	R	Y
a	$CH(CH_3)_2$	NCH_2Ph
b	$CH(CH_3)_2$	$NCH_2C_6H_4$-4-Cl
c	$CH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$
d	$CH(CH_3)_2$	NH
e	$CH(CH_3)_2$	S
f	$CH_2C_6H_4$-3-I	S



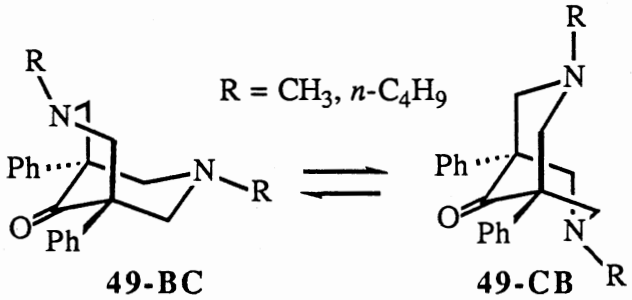
81 **82** **83**

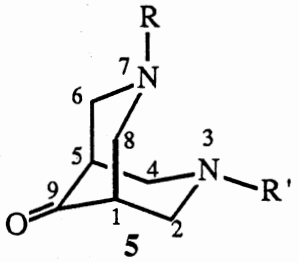
81, 82 †

	R
a	C(O)Ph†
b	$C(O)C_6H_4$-4-Cl
c	$C(O)C_6H_3$-3,4-$(OCH_3)_2$†
d	$C(O)C_6H_2$-3,4,5-$(OCH_3)_3$
e	SO_2Ph

†HClO4 salt

Variable temperature ^{13}C NMR spectral studies of **49**[65] (as previously described, Chapter I) were shown to support a BC⇌CB equilibrium for **49**. Galvez[3,23] and workers, however, opted for the assignment of flattened CC forms for the ketones **5(a,b,c,f, j, r,** and **s)** based on IR, ^{1}H and ^{13}C NMR spectral evaluations with the greatest distortion of the CC conformer occurring in **5c**.[23] Recently, ^{17}O NMR spectroscopy was employed as a diagnostic tool for structural determination and ketones **5j**,[6d] **8a** and **77a.** The BC



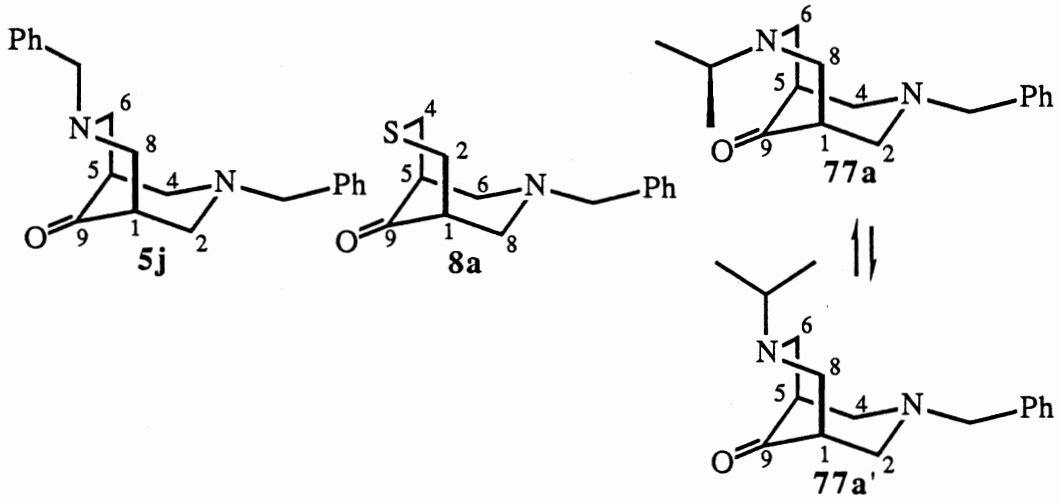


5

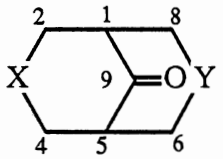
	R	R'		R	R'
5a	CH_3	CH_3	**5a**	CH_3	CH_3
5b	CH_3	CH_2CH_3	**5f**	CH_3	CH_2Ph
5c	CH_3	$CH(CH_3)_2$	**5j**	CH_2Ph	CH_2Ph
5r	CH_3	$CH_2CH_2CH_3$	**5s**	CH_3	CH_2CH_2Ph

conformations in D_3CCN solution at 70°C were assigned for each compound based upon the observed ^{17}O shifts.[6d] In each case, the ring bearing the benzyl group possessed the chair form and thus appears to be somewhat biased, at least in **8a** and **77a.** An upfield shift for C=*O* of 5-7 ppm [due to increased shielding at *C*(9) and decreased shielding of the C=*O*] was observed for each which appeared feasible only if a significant interaction

existed between the lone pair of the heteroatom and the p orbital of the carbon of the carbonyl group. Thus, it was suggested that a BC conformer would give rise to such an effect.



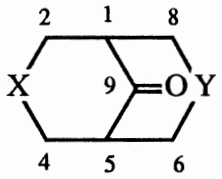
An analysis of ketones **77** by ^{1}H (Table VII), ^{13}C (Table VIII), and ^{15}N (Table IX) NMR spectroscopy seems to suggest that certain conformational bias does exist. Unfortunately, the ^{1}H NMR spectra (Table VII) were not of great value in structure



	X	Y
8a	S	NCH_2Ph
8b	Se	NCH_2Ph
8c	S	NCH_2CH_2Ph
8d	Se	NCH_2CH_2Ph
9	O	NCH_2Ph
77a	$NCH(CH_3)_2$	NCH_2Ph
77b	$NCH(CH_3)_2$	$NCH_2C_6H_4$-4-Cl
77c	$NCH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$
77d	S	$NCH(CH_3)_2$
77e	S	$NCH_2C_6H_4$-3-I

TABLE VII

^{1}H NMR SPECTRAL DATA FOR KETONES 77[a] (δ VALUES)

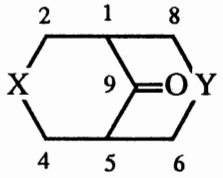


	X	Y	H(1,5)	Ring *H*	C*H*$(CH_3)_2$	C*H*$_3$	C*H*$_2$Ar	Ar-*H*	Other
77a	$NCH(CH_3)_2$	NCH_2Ph	2.58	2.87,3.03	2.87	1.02	3.53	7.30	-
77b	$NCH(CH_3)_2$	$NCH_2C_6H_4$-4-Cl	2.58	2.80-3.05	2.80-3.05	1.03	3.49	7.27	-
77c	$NCH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$	2.59	2.81-2.90 2.98,3.08	2.81-2.90	1.03	3.47	6.86	3.87, 3.88
77d	$NCH(CH_3)_2$	S		2.75-2.90	2.75-2.90	1.04	-	-	-
77e	$NCH_2C_6H_4$-3-I	S	2.72-3.18	2.72-2.90	-	-	3.51	7.07-7.71	-

[a]$DCCl_3$ solutions referenced to TMS (tetramethylsilane) at 0 ppm.

TABLE VIII

^{13}C NMR SPECTRAL DATA FOR KETONES **77**[a] (PPM)

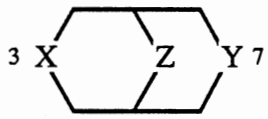


	X	Y	C(1,5)	C(2,4)	C(6,8)	*C*=O	*C*H_2Ph	*C*H	*C*H_3	Ar-*C*
77a	NCH(CH_3)$_2$	NCH_2Ph	46.93	53.71	58.07	215.20	61.25	53.41	18.25	127.09, 128.25 128.69, 138.67
77b	NCH(CH_3)$_2$	N$CH_2C_6H_4$-4-Cl	46.85	53.76	57.92	215.04	60.48	53.40	18.25	128.40, 129.95 132.74, 137.21
77c	NCH(CH_3)$_2$	N$CH_2C_6H_3$-3,4-(OCH_3)$_2$	46.85	53.86	58.01	215.27	60.93	53.40	18.17	110.60, 111.46 120.68, 131.30 148.04, 148.90
77d	S	NCH(CH_3)$_2$	47.52	34.16	54.16	213.68	-	53.76	18.30	-
77e	S	N$CH_2C_6H_4$-3-I	46.95	35.05	58.20	213.00	60.69	-	-	94.43, 127.98 130.23, 136.44 137.64, 140.63

[a]$DCCl_3$ solution reference to TMS (tetramethylsilane) at 0 ppm.

TABLE IX

^{15}N NMR SPECTRAL DATA (PPM)[a]



	X	Y	Z	N(3)	N(7)
77a[b]	$NCH(CH_3)_2$	NCH_2Ph	C=O	40.80	39.25
77b[b]	$NCH(CH_3)_2$	$NCH_2C_6H_4$-4-Cl	C=O	40.31	39.18
77c[b]	$NCH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$	C=O	40.93	39.66
77d[b]	S	$NCH(CH_3)_2$	C=O	-	39.27
78a[b]	$NCH(CH_3)_2$	NCH_2Ph	C=N-OH	42.05	37.85
78b[c]	$\overset{+}{N}(H)CH(CH_3)_2$	NCH_2Ph[d]	$C(OH)_2$	59.18	48.93
78c[c]	$\overset{+}{N}(H)CH(CH_3)_2$	NCH_2Ph[d]	C(OH)OEt	59.14	48.85
80a[c]	$\overset{+}{N}(H)CH(CH_3)_2$	NCH_2Ph[d]	CH_2	60.47	50.90
80b[c]	$\overset{+}{N}(H)CH(CH_3)_2$	$NCH_2C_6H_4$-4-Cl[d]	CH_2	60.57	50.34
80c[c]	$\overset{+}{N}(H)CH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$[d]	CH_2	59.43	52.22
80d[c]	$\overset{+}{N}(H)CH(CH_3)_2$	NH[d]	CH_2	48.33	39.50
80e[c]	S	$\overset{+}{N}(H)CH(CH_3)_2$[d]	CH_2	-	58.47
80f[c]	S	$\overset{+}{N}(H)CH_2C_6H_4$-3-I[d]	CH_2	-	54.17
84[b]	S→O	NCH_2Ph	CH_2	-	49.37
85[c]	S→O	$\overset{+}{N}(H)CH_2Ph$[d]	CH_2	-	56.45

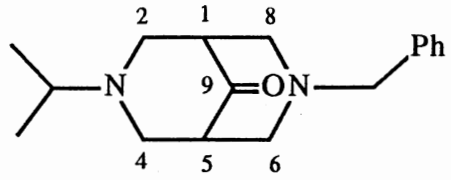
[a]All spectra were obtained at RT using an 8 M $^{15}NH_4NO_3$ external standard (19.73 ppm) which was cross-referenced to liquid NH_3 at 0 ppm (Reference 38).
[b]$DCCl_3$.
[c]DMSO-d_6.
[d]Counterion is ClO_4^-.

elucidation due to the complexity of the spectra from overlap of signals. However, the ^{13}C NMR (Table VIII) spectra proved quite informative in making structural assignments. In each case, C(6,8) had shifts between 57.9-58.1 ppm which is of a similar range of shifts (57.5-59.0 ppm) observed in the analogous systems **8** and **9** where the ring bearing the benzyl substituent assumes a chair.[6] Noteworthy shielding of C(2,4), where shifts are on the order of 53.7-53.9 ppm, can be explained by the steric compression from gamma-gauche interactions with the isopropyl substituent (this effect is pronounced when the isopropyl group assumes an equatorial position in a chair conformer).[2] Also, the C(9) shifts in solution have been found to be at *higher* field in the BC conformers (211.5-212.4 ppm) but are deshielded by up to 5-6 ppm (217.2-218.6 ppm) in the CC forms.[6] The shielding effect observed in the BC conformers may be caused by influence of the heteroatom which assumes an arrangement in which the lone pair of electrons of the heteroatom is directed toward C(9); thus, C(9) is somewhat shielded due to the enhanced electron density at *C*(9)=O.[6] Shifts of 215.0-215.3 ppm for ketones **77a-c** are somewhat intermediary to the range cited previously and suggest that a preference of CC or BC might not be valid. Thus, a more definitive means of analysis was sought.

Variable temperature ^{13}C NMR spectral studies of **77a** in solution (60:27:13 D_2CCl_2:-$DCCl_3$:CCl_4; fp -111°C)[24] were employed as a means of exploring the conformational boundaries of this system. A solution (70 mg/mL) of **77a** was analyzed over a temperature range of -100°C to RT (22°C) with significant changes in the chemical shifts (Table X). As the temperature was lowered, increased *deshielding* was observed for C(9), with a correlation coefficient of -0.999, while increased *shielding* was observed for *C*H(CH_3)$_2$, CH(*C*H$_3$)$_2$, *ipso*-Ar-*C* (*i*-Ar-*C*), C(6,8), *C*H$_2$Ph, C(1,5), and C(2,4) with correlation coefficients of 0.995, 0.998, 0.772, 0.798, 0.998, 0.997, and 0.994, respectively [for plots of the difference in shift from RT ($\Delta\delta$) vs temperature (Fig. 1)]. Position C(9) was influenced the most dramatically when the $\delta_{C=O}$ shifts varied from 214.62 ppm at RT to 217.34 ppm at -100°C with a slope of -0.022 ppm/°C.

TABLE X

VARIABLE TEMPERATURE ^{13}C NMR SPECTRAL DATA OF **77a**[a]



	C(1,5)		C(2,4)		C(6,8)		C(9)		CH_2Ph		*i*-Ar-*C*		$CH(CH_3)_2$		$CH(CH_3)_2$	
Temp.	ppm	Δδ	ppm	Δδ	ppm	Δδ	ppm	Δδ	ppm	Δδ	ppm	Δδ	ppm	Δδ	ppm	Δδ
22°C	47.08	0	53.84	0	58.25	0	214.62	0	61.42	0	138.93	0	53.61	0	18.29	0
0°C	46.91	-0.17	53.67	-0.17	58.15	-0.1	215.07	0.45	61.31	-0.11	138.85	-0.08	53.53	-0.08	18.20	-0.09
-20°C	46.76	-0.32	53.52	-0.32	58.08	-0.17	215.50	0.88	61.22	-0.20	138.80	-0.13	53.47	-0.14	18.12	-0.17
-40°C	46.65	-0.43	53.37	-0.47	58.03	-0.22	215.93	1.31	61.11	-0.31	138.77	-0.16	53.41	-0.20	18.03	-0.26
-60°C	46.53	-0.55	53.21	-0.63	58.00	-0.25	216.38	1.76	61.01	-0.41	138.77	-0.16	53.36	-0.25	17.95	-0.34
-80°C	46.42	-0.66	53.05	-0.79	58.03	-0.22	216.85	2.23	60.89	-0.53	138.78	-0.15	53.31	-0.30	17.86	-0.43
-85°C	46.39	-0.69	52.90	-0.94	58.06	-0.19	217.00	2.38	60.84	-0.58	138.79	-0.14	53.30	-0.31	17.84	-0.45
-90°C	46.36	-0.72	-	-	58.06	-0.19	217.11	2.49	60.84	-0.58	138.80	-0.13	53.29	-0.32	17.82	-0.47
-100°C	46.32	-0.76	-	-	-	-	217.34	2.72	-	-	-	-	53.28	-0.33	17.74	-0.55

[a]Sample in 60:27:13 D_2CCl_2:$DCCl_3$:CCl_4 (Reference 24).

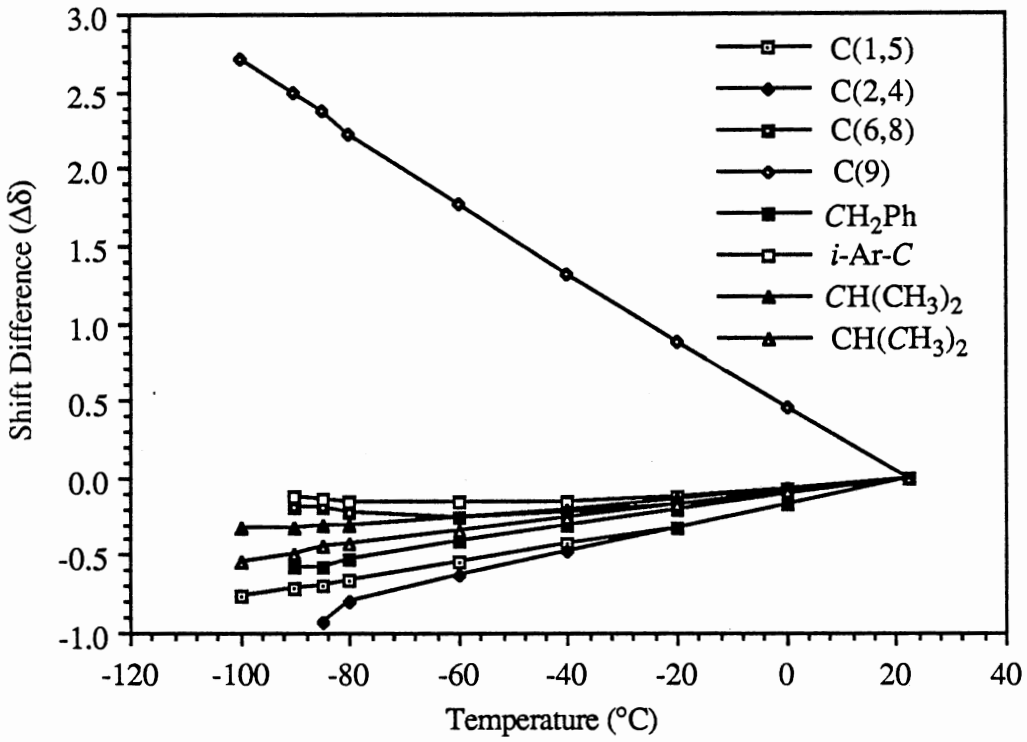
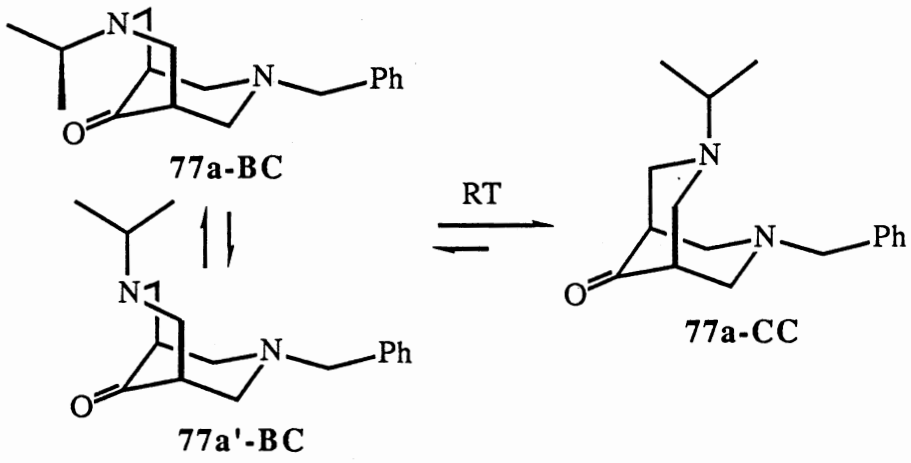


Figure 1. Variable Temperature Plot for **77a**

An explanation of this phenomena can be envisioned if two assumptions are made: (1) that atomic inversion at the nitrogen centers is operating and discernable, or (2) from previous data, the ring bearing the benzyl substituent is locked in a chair form.[6] Conse-

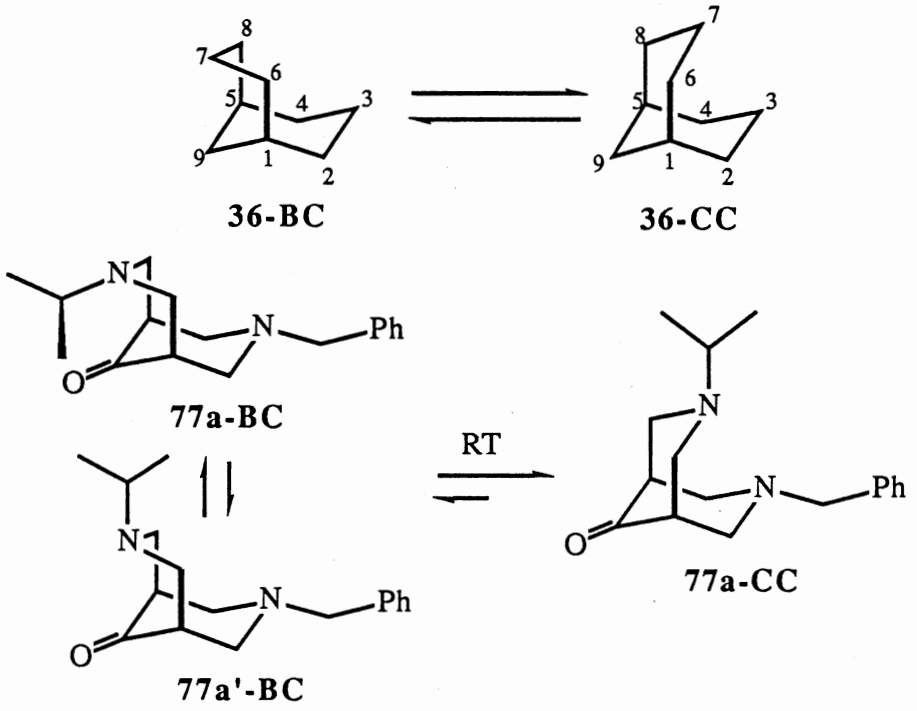


quently, the observed variable temperature shifts seem to support an equilibrium between either a BC or flattened CC form rather than a CC conformer with near perfect chair forms.

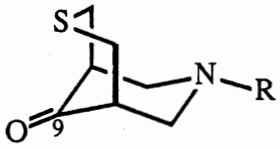
Based on these data, the BC⇌CC equilibrium seems to be favored with increasing predominance of the flattened CC form at lower temperature. Although the flagpole bowsprit interaction of the boat form is generally considered destabilizing in saturated ring systems,[22] the flattened piperidinone ring containing the isopropyl substituent might be able to tolerate such a flattened boat form **77a-BC** in equilibrium with a chair form. Thus, one might expect a significant shielding (NMR average shifts) effect by the isopropyl group on the carbonyl carbon at higher temperature which is what is observed (shielding increases at higher temperature due to an increase in population of the BC conformer. Increased deshielding with an increase in temperature is observed for the carbons in $CH(CH_3)_2$ due to a reduced population of the flattened CC form **77a-CC** and perhaps a greater influence by the deshielding cone of the carbonyl group in the BC conformer. At lower temperatures, a higher concentration of the CC conformer is apparently realized. An X-ray analysis of crystalline **77a** is in progress. The question of position of the $CH(CH_3)_2$ group as being pseudo axial (as in **77a-BC**) or pseudo equatorial (as in **77a'-BC**) remains unanswered. In contrast, the lone electron pair on N(3) might also cause enhanced shielding of C(9) if the former was in an orbital in a *pseudo axial* position. It is not possible to deduce the exact or average position of the lone electron pair on N(3) as seen on the NMR time scale with the data available.

A similar trend was observed for bicyclo[3.3.1]nonane (**36**)[43] using variable temperature electron diffraction (as previously described in Chapter I), in which a BC⇌CC equilibrium was determined to exist with less predominance of the CC observed at elevated temperatures. Moreover, recent ^{17}O NMR spectral results in our lab[6d] indicate that in D_3CCN at 70°C, **77a** preferred the BC conformation which further supports the trend described here. However, our conclusions were based upon the change in ^{13}C NMR shifts (Fig. 1) which correlate with a reduced population of the CC form at RT compared to that at the lower temperatures. Thus, if this same trend is followed above RT, a better correlation with the preferred BC conformation might be expected. Although the higher

temperature experiment was not attempted, it is our position that the equilibrium described in this discussion provides a rational explanation for the data collected at or below RT.



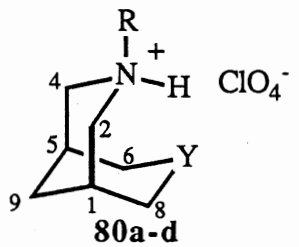
Ketones **77e** and **77f** were also examined. Experiments using variable temperature NMR spectral analysis[6a] (from -120°C to RT) on **8a** revealed that a preference for the BC conformer of **8a** was evident over the entire temperature range. Based upon very similar

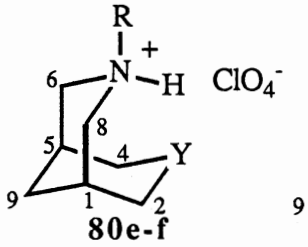


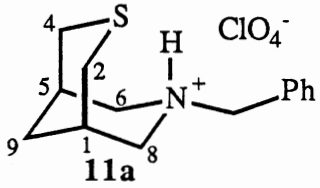
	R
8a	CH_2Ph
77e	$CH(CH_3)_2$
77f	$CH_2C_6H_4$-3-I

^1H, ^{13}C and ^{15}N NMR spectral shifts for **77e** and **77f**, as compared with those of **8a**, it was concluded that these ketones most probably exist in the BC conformation as well. For example, the C(9) shift of **77e** (213.68 ppm) and **77f** (213.00 ppm) agree well with the shift observed for **8a** (212.8 ppm)[6] where the carbonyl is shielded by the sulfur atom in the boat ring. It was presumed[6] that the BC form present in solid **8a** persisted in solution.

Reduced forms of certain 3,7-diheterabicyclo[3.3.1]nonanes and their salts have been examined[6,18,38] and found to almost exclusively prefer the CC conformer in solution. In our work, salts **80** were characterized by ^{1}H (Table XI), ^{13}C (Table XII), and ^{15}N (Table IX) NMR spectral techniques and have also been postulated to exist in CC conformations. Certain factors can explain the preference for CC conformers in salts **80**, namely: (1) hydrogen bonding between the heteroatoms, and (2) a boat ring could result in severe







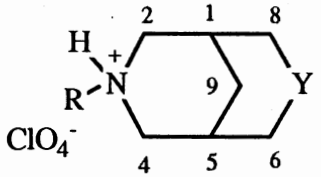
80

	R	Y
a	$CH(CH_3)_2$	NCH_2Ph
b	$CH(CH_3)_2$	$NCH_2C_6H_4$-4-Cl
c	$CH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$
d	$CH(CH_3)_2$	NH
e	$CH(CH_3)_2$	S
f	$CH_2C_6H_4$-3-I	S

bow-sprit interactions[22] with the C(9) protons. Although the ^{1}H NMR spectral analyses of these salts **80** are relatively uninformative as far as structural features are concerned, the ^{13}C NMR spectra (Table XII) display certain diagnostic trends. In salts **80e** and **80f**, C(6,8), which are alpha to the more electronegative N, are *deshielded* relative to those alpha to S. Moreover, the *C*$H(CH_3)_2$ shift is *deshielded* in salts **80** relative to the ketone precursors **77** which suggests that protonation occurs on the N of the $NCH(CH_3)_2$ moiety (positively charged N withdraws electron density from the C of the alpha CH and *deshields* it). This *deshielding* is *not* observed at C(2,4) due to the fact that the stabilized CC form of the salts **80** possesses a pronounced *gamma shielding effect* by the C(6)···N(7) and N(7)···C(8) bonds on C(2,4), possibly offsetting, to some degree, any

TABLE XI

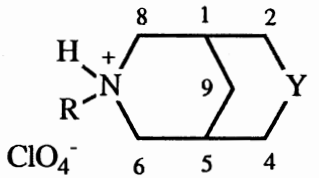
^{1}H NMR SPECTRAL DATA FOR $HClO_4$ SALTS **80**[a] (δ VALUES)



80a-d

80

	R	Y
a	$CH(CH_3)_2$	NCH_2Ph
b	$CH(CH_3)_2$	$NCH_2C_6H_4$-4-Cl
c	$CH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$
d	$CH(CH_3)_2$	NH
e	$CH(CH_3)_2$	S
f	$CH_2C_6H_4$-3-I	S



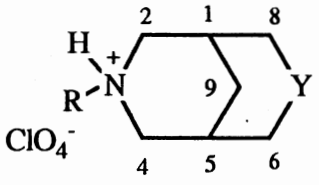
80e-f

	H(1,5)	$H(2,4)_{ax}$	$H(2,4)_{eq}$	$H(6,8)_{ax}$	$H(6,8)_{eq}$	H(9)	$CH(CH_3)_2$	CH_3	CH_2Ar	Ar-*H*
80a	2.14	3.11	3.32	2.47	3.11	1.62, 1.82	3.47	1.18	3.52	7.30-7.43
80b	2.14	3.16	3.34	2.41	3.04	1.61, 1.82	3.44-3.52	1.19	3.44-3.52	7.44
80c	2.14	3.04-3.14	3.28	2.50	3.05-3.14	1.64, 1.80	3.39	1.15	3.49	6.86-7.08
80d	2.00	3.09	3.36	2.51	2.96	1.60, 1.82	2.72	0.99	-	-
80e	2.35	2.78	3.14	3.29-3.57	3.62	1.76, 1.91	3.29-3.57	1.28	-	-
80f	2.36	2.70	3.09	3.35	3.58	1.81	-	-	4.24	7.32-8.03

[a]DMSO-d_6 solutions referenced to TMS (tetramethylsilane) at 0 ppm.

TABLE XII

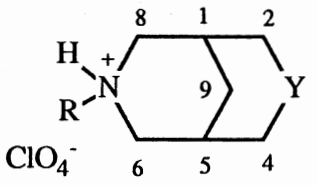
^{13}C NMR SPECTRAL DATA FOR $HClO_4$ SALTS **80**[a] (PPM)



80a-d

80

	R	Y
a	$CH(CH_3)_2$	NCH_2Ph
b	$CH(CH_3)_2$	$NCH_2C_6H_4$-4-Cl
c	$CH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$
d	$CH(CH_3)_2$	NH
e	$CH(CH_3)_2$	S
f	$CH_2C_6H_4$-3-I	S



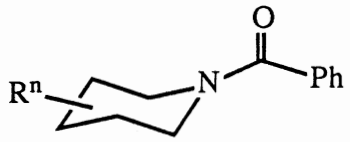
80e-f

	C(1,5)	C(2,4)	C(6,8)	C(9)	*C*H$(CH_3)_2$	CH(*C*$H_3)_2$	*C*H_2Ph	Ar-*C*
80a	27.24	52.85	56.85	29.67	56.00	16.11	61.15	127.65, 128.35 129.38, 136.35
80b	27.25	52.77	56.75	29.60	56.25	16.10	60.42	128.28, 131.27 132.14, 135.72
80c	27.23	52.74	56.85	29.79	55.78	16.25	60.89	111.23, 113.01 122.02, 128.00 148.38, 148.66
80d	26.43	52.71	48.47	30.04	53.64	17.29	-	-
80e	25.51	30.69	52.36	28.35	58.66	-	-	-
80f	25.78	30.65	56.53	28.48	-	-	60.04	95.40, 129.93 131.08, 132.47 138.18, 138.93

[a]DMSO-d_6 solutions referenced to TMS (tetramethylsilane) at 0 ppm.

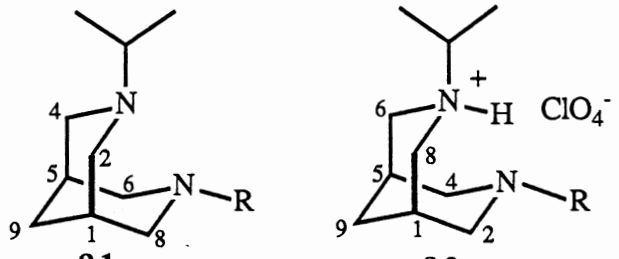
deshielding contributions which result from protonation. For instance, the shifts for C(2,4) in **77a-c** are 53.71-53.86 ppm versus 52.74-52.85 ppm in salts **80a-c**. In constrast, C(6,8) have signals at 57.92-58.01 ppm in **77a-c** while in **80a-c** the signals occur at 56.75-56.95 ppm.

The ^{15}N spectral analysis (Table IX) proved to be quite instructive regarding location of the site of protonation in the mixed salts **80a-d**. For compounds which were closely related, the ^{15}N shifts displayed little variation. Based upon shifts for simple piperidine systems[38] and those of compounds **11a** (^{15}N shift = 54.16 ppm), **80e** (^{15}N shift = 58.47 ppm) and **80f** (^{15}N shift = 54.17 ppm), assignments could be made for the mixed salts **80a-d** (Table IX). Analysis of diazasubstituted salts **80a-c** revealed that N(3) (^{15}N shift = 59.43-60.47 ppm) was significantly downfield from N(7) (^{15}N shift = 50.34-52.22 ppm) due to protonation of N(3). Both N(3) and N(7) in **80a-c** are deshielded, relative to their ketone counterparts, which suggests that upon protonation hydrogen bonding occurs between the N atoms and the one proton, resulting in deshielding of both N atoms. Similar hydrogen bonding is thought to be present in salts **80e** and **80f** as well. Determination of the site of protonation in the aforementioned mixed salts **80a-c** is important in order to further characterize their interactions as potential medicinal agents.



89

Amides **81** and **83** and certain salts **82** possess several unique features which contribute to the observed conformational properties. Several *N*-benzoylated-piperidines **89** have been studied [26,33] using variable temperature ^{1}H NMR[33] and ^{13}C NMR[26] spectroscopy in solution. Since these simple amides seem to display preferred conformations at



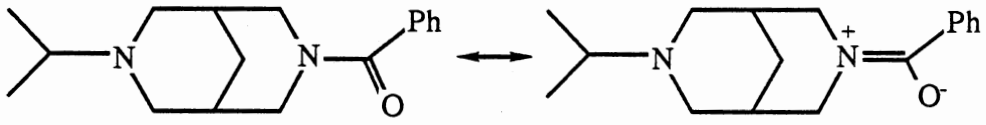
81 **82** **83**

81, 82 †

R
a C(O)Ph†
b $C(O)C_6H_4$-4-Cl
c $C(O)C_6H_3$-3,4-$(OCH_3)_2$†
d $C(O)C_6H_2$-3,4,5-$(OCH_3)_3$
e SO_2Ph

†$HClO_4$ salts

RT, it is evident that such an effect might be observed in amides **81**, **82**, and **83**. This conformational preference probably results from an energy saving process resulting from reorientation and overlap of the carbon p orbital of the carbonyl π system with the nitrogen lone pair (substituents attached to either C or N of the amide lie in the same plane with these C and N atoms).[33] Familiar resonance forms for this phenomena are illustrated for **81a**. Amide rotational barriers exhibited by similar benzamides have been found to be



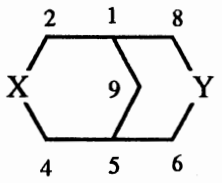
81a

approximately 14-15 kcal/mole from ^1H and ^{13}C NMR spectral analysis in $DCCl_3$.[26] Thus, in the case of amides **81**, **82**, and **83** nonequivalence for the CH_3 carbons, C(1) and C(5), C(2) and C(4), and C(6) and C(8) is observed (which should coalesce at elevated temperature). The ^1H NMR (Table XIII) and ^{13}C NMR (Table XIV) assignments for the amides **81** and **83** were based upon related systems and further supported by HETCOR 2D NMR analysis (Chapter III) of **81b**.

Johnson[33] and co-workers found that simple benzamides of piperidines, as well as the ring containing the benzamide function in 3-benzoyl-3-azabicyclo[3.3.1]nonane (**90**),

TABLE XIII

^{1}H NMR SPECTRAL DATA FOR AMIDES **33k, 81, 83**[a] (δ VALUES)



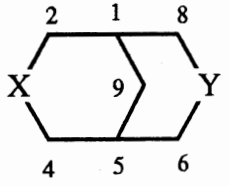
	X	Y
33k	NC(O)Ph	NCH_2Ph
81a	NC(O)Ph	$NCH(CH_3)_2$
81b	$NC(O)C_6H_4$-4-Cl	$NCH(CH_3)_2$
81c	$NC(O)C_6H_3$-3,4-$(OCH_3)_2$	$NCH(CH_3)_2$
81d	$NC(O)C_6H_2$-3,4,5-$(OCH_3)_3$	$NCH(CH_3)_2$
81e	NSO_2Ph	$NCH(CH_3)_2$
83	S	NC(O)Ph

	H(1)	H(5)	H(2)		H(4)		H(6)		H(8)		*CH*	*CH_3*	H(9)
			Ax	Eq	Ax	Eq	Ax	Eq	Ax	Eq			
33k	1.98	1.68-1.78	3.05-3.13	4.79	2.19	3.05-3.13	2.27	2.88	3.26	3.75	-	-	1.68-1.78
81a	1.97	1.65-1.78	3.04-3.07	4.77	2.41	3.04-3.07	2.50	2.72	3.30	3.74	2.62	0.96, 1.07	1.65-1.78
81b	1.93	1.63-1.75	3.03-3.06	4.77	2.41	3.03-3.06	2.50	2.71	3.31	3.71	2.59	0.95, 1.05	1.63-1.75
81c	1.96	1.62-1.75	3.00-3.09	4.77	2.43	3.00-3.09	2.51	2.74	3.32	3.83-3.94	2.62	0.96, 1.06	1.62-1.75
81d	1.96	1.64-1.79	3.02-3.07	4.77	2.44	3.02-3.07	2.57	2.76	3.31	3.80-3.92	2.66	0.96, 1.09	1.64-1.79
81e[b]	1.94	1.94	2.89	2.36	2.89	3.36	2.35	2.69	2.35	2.69	2.53	0.86	1.40
83	2.15	1.78-1.93	3.41	3.89	2.39	3.12-3.21	2.77	3.12-3.21	3.12-3.21	4.98	-	-	1.78-1.93

[a]Samples were run in $DCCl_3$ (unless otherwise indicated) referenced to TMS (tetramethylsilane) at 0 ppm.
[b]Sulfonamide does not possess the property of nonequivalence due to resonance.

TABLE XIV

^{13}C NMR SPECTRAL DATA FOR AMIDES **33k**, **81**, **83**[a] (PPM)

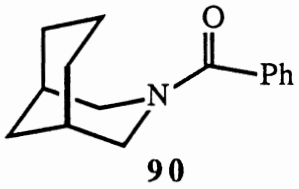


	X	Y
33k	NC(O)Ph	NCH_2Ph
81a	NC(O)Ph	$NCH(CH_3)_2$
81b	$NC(O)C_6H_4$-4-Cl	$NCH(CH_3)_2$
81c	$NC(O)C_6H_3$-3,4-$(OCH_3)_2$	$NCH(CH_3)_2$
81d	$NC(O)C_6H_2$-3,4,5-$(OCH_3)_3$	$NCH(CH_3)_2$
81e	NSO_2Ph	$NCH(CH_3)_2$
83	S	NC(O)Ph

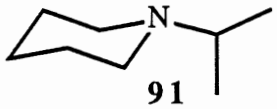
	C(1)	C(2)	C(4)	C(5)	C(6)	C(8)	C(9)	CH_3	$CH(CH_3)_2$	Ar-*C*	N(*C*=O)	Other
33	29.02	46.43	52.22	29.50	58.63	58.51	31.97	-	-	126.81, 126.88 128.27, 128.72 129.02, 137.46 138.19	170.11	63.99
81a	29.06	46.55	52.19	29.76	54.75	52.62	32.29	16.30, 19.33	54.34	126.75, 128.24 128.67, 137.75	170.09	-
81b	29.07	46.68	52.22	29.80	54.79	52.56	32.29	16.37, 19.35	54.38	128.35, 128.51 134.67, 136.11	169.03	-
81c	29.13	46.71	52.25	29.86	54.68	52.65	32.36	16.46, 19.15	54.35	110.50, 119.64 130.23, 148.78 149.39	169.90	55.88, 55.93
81d	29.02	46.64	51.73	29.78	54.95	52.48	32.25	15.87, 19.42	54.39	103.83, 133.32 138.22, 153.21	169.66	56.13, 60.86
81e[b]	27.39[c]	48.88	48.88	27.39	52.66	52.66	28.95	17.57	53.42	126.90, 129.01 132.36, 136.79		
83	26.53	31.73	32.34	26.87	52.12	46.07	31.78	-	-	126.46, 128.41 128.83, 137.35	170.38	-

[a]Samples were run in $DCCl_3$ (unless otherwise noted) referenced to TMS (tetramethylsilane) at 0 ppm.
[b]DMSO-d_6 solution.
[c]Sulfonamide does not possess the property of nonequivalence resulting from resonance.

prefer the chair form. Moreover, the chair form of *N*-isopropylpiperidine (**91**) has been shown to be favored with the isopropyl substituent in an equatorial position.[2,12] These

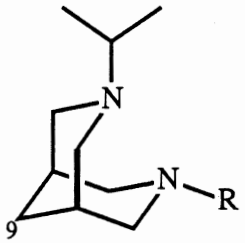


90



91

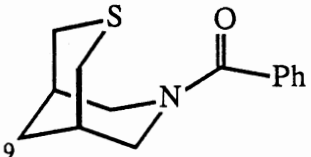
data have been compared to that found in our work. For example, shifts for C(9) in the ^{13}C NMR spectra for amides **81** and **83** (32-32.3 ppm) were similar to those in the known CC system of **43** (35.9 ppm) but not with the BC form of its isomeric structure **44**



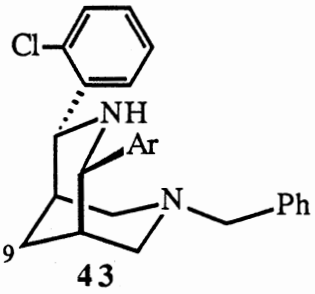
81

81

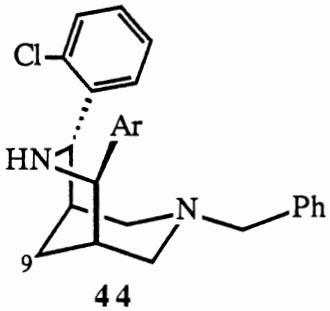
R	
a	C(O)Ph
b	$C(O)C_6H_4$-4-Cl
c	$C(O)C_6H_3$-3,4-$(OCH_3)_2$
d	$C(O)C_6H_2$-3,4,5-$(OCH_3)_3$
e	SO_2Ph



83



43



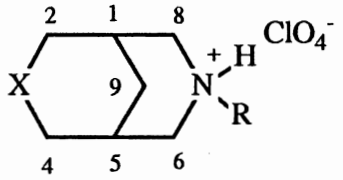
44

(24.6 ppm).[6] Possibly a flattened CC form persists in solution for amides **81** and **83**, although a CB⇌CC equilibrium may not be ruled out.

Similar conclusions were drawn for the amide salts **82** and **88** whose ^1H (Table XV) and ^{13}C (Table XVI) spectral data were accumulated at 80°C in DMSO-d_6 solution (a

TABLE XV

^{1}H NMR SPECTRAL DATA FOR AMIDE SALTS **82, 88**[a] (δ VALUES)



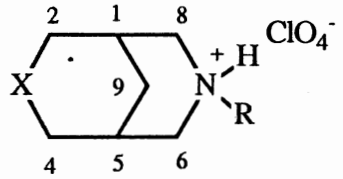
	X	R
82a	NC(O)Ph	$CH(CH_3)_2$
82c	$NC(O)C_6H_3$-3,4-$(OCH_3)_2$	$CH(CH_3)_2$
88	NC(O)Ph	CH_2Ph

	H(1,5)	$H(2,4)_{ax}$	$H(2,4)_{eq}$	$H(6,8)_{ax}$	$H(6,8)_{eq}$	H(9)	$CH(CH_3)_2$	$CH(CH_3)_2$	Ar-*H*	N-*H*	Other
82a[b]	2.51	3.65	4.23	3.30	3.94	1.97, 2.18	3.83	1.55	7.45-7.50	7.85	-
82c[c]	2.27	3.19-3.28	3.97	3.12	3.42-3.56	1.74, 1.91	3.42-3.56	1.33	6.94-7.03	7.81	-
88[c]	2.26	3.25-3.33	3.89	3.09-3.13	3.25-3.33	1.77, 1.86	-	-	7.27-7.65	8.03	4.33

[a]Referenced to TMS (tetramethylsilane) at 0 ppm.
[b]$(D_3C)_2C{=}O$ solution.
[c]DMSO-d_6 solution.

TABLE XVI

^{13}C NMR SPECTRAL DATA FOR AMIDE SALTS **82**, **88**[a] (PPM)

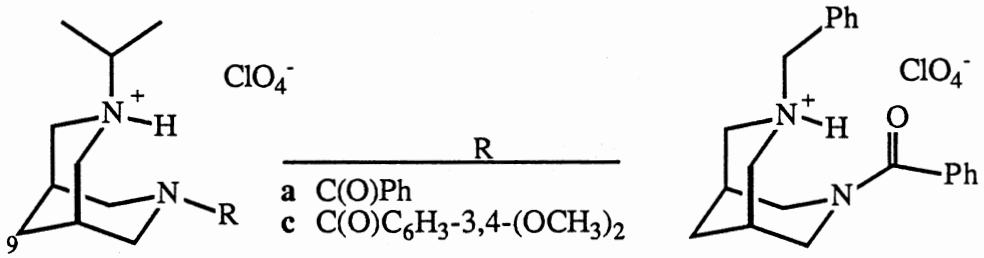


	X	R
82a	NC(O)Ph	$CH(CH_3)_2$
82c	$NC(O)C_6H_3$-3,4-$(OCH_3)_2$	$CH(CH_3)_2$
88	NC(O)Ph	CH_2Ph

	C(1,5)	C(2,4)	C(6,8)	C(9)	*C*H(CH$_3$)$_2$	*C*H$_3$	*C*=O	Ar-*C*	Other
82a	26.69	48.80	52.31	27.62	59.91	16.34	172.86	127.05, 128.30, 129.40, 136.40	-
82c	26.81	49.06	52.40	27.80	59.97	16.34	172.97	111.85, 112.10, 120.44, 128.68 148.74, 150.26	55.88, 55.92
88	26.84	48.87	56.34	28.13	-	-	172.90	126.90, 128.24, 129.04, 129.30 129.53, 129.89, 131.05, 136.12	61.60

[a]Samples were run at 80°C in DMSO-d_6 solution and referenced to TMS (tetramethylsilane) at 0 ppm.

higher temperature was necessary to obtain coalesced, intensified signals). This suggests that the rotational barrier for these salts is much lower than for the unprotonated amides at RT.



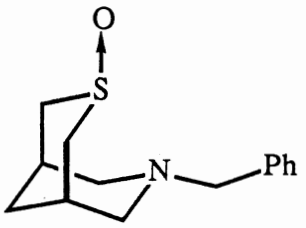
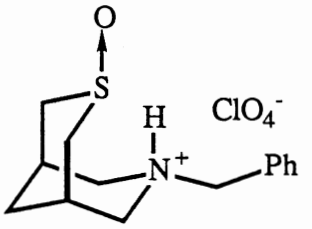
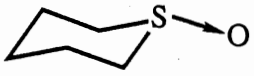
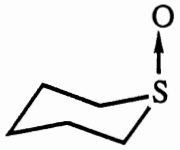
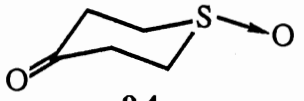
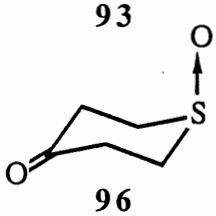
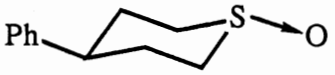
82 **88**

Spectral techniques have also been applied in the delineation of the configuration of the S→O bond in sulfoxides **84** and **85**. In Table XVII are shown the geminal $^2J_{H-H}$ coupling constants for several simple sulfoxides as well as for **84** and **85**. This coupling constant is larger in absolute value for protons alpha to the axial S→O bond ($^2J_{H-H}$~14 Hz) than for the protons alpha to the equatorial S→O bond ($^2J_{H-H}$~12 Hz).[37] Coupling constants for **92**[37], **93**[29], and **94**[29]were determined experimentally as were those for the conformationly biased **95**[45] while the $^2J_{H-H}$ value for **96**[37] was estimated from analogous substituted chair conformers. Therefore, coupling constants for **84** (11.7 Hz) and **85** (11.6 Hz) suggest a preference for an equatorial configuration for the S→O bond.

Unequivocal assignments of conformational preference for many of our compounds in solution cannot be established, but data accumulated for these systems using various spectral techniques can aid in predicting the most probable structural assignment. Currently, compounds **77a** and **84** have been sent for X-ray analysis and will provide some insight into the conformation which is the most stable in the solid state. A better understanding of conformational properties in solution and in the solid state of these heterocycles may help to explain the observed biological properties.

TABLE XVII

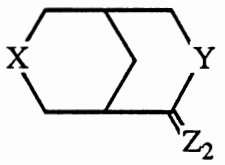
GEMINAL $^2J_{H-H}$ COUPLING CONSTANTS FOR PROTONS ALPHA TO THE S ATOM

 **84**	11.7		
 **85**	11.6		
 **92**	11.7[a]	 **93**	13.7[a]
 **94**	~12.0[b]	 **96**	13.4[c]
 **95**	11.7[d]		

[a] Reference 37.
[b] Reference 45; estimated value.
[c] Reference 45.
[d] Reference 29.

Antiarrhythmic Activity

The antiarrhythmic properties of **80a**, **80c**, **80e**, **82a**, **83**, **84**, **85**, and **86** were assessed by Dr. Benjamin Scherlag of the Veterans Administration Hospital in Oklahoma City, Oklahoma. These compounds were studied in anesthesized mongrel dogs which

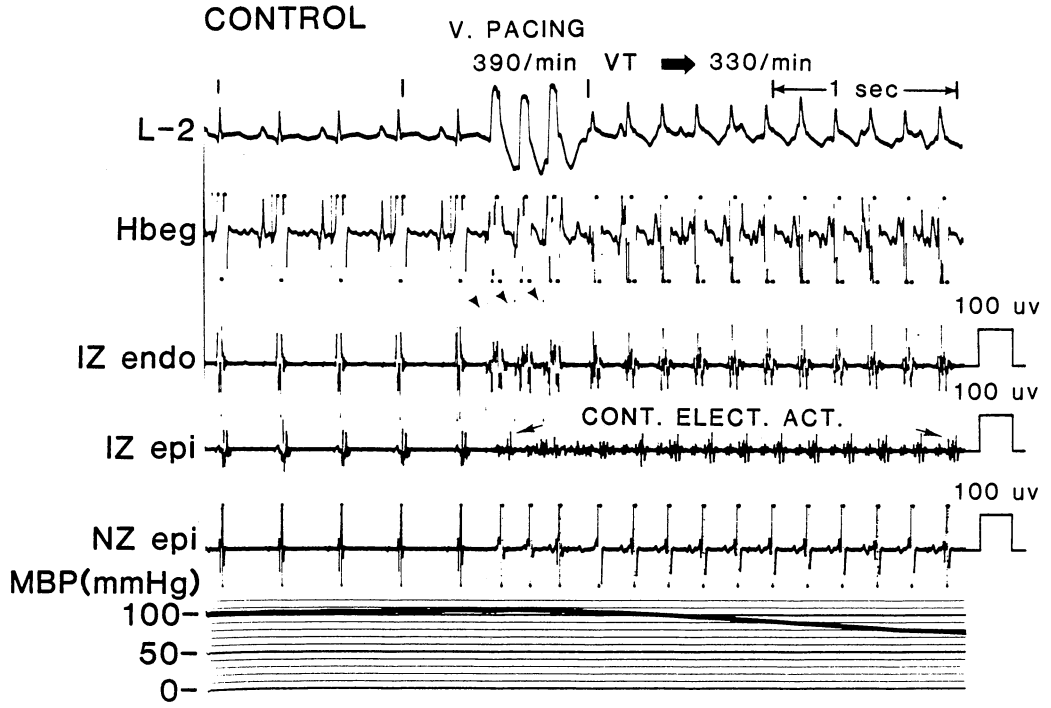


	X	Y	Z_2
80a†	$NCH(CH_3)_2$	NCH_2Ph	H_2
80c†	$NCH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$	H_2
80e†	$NCH(CH_3)_2$	S	H_2
82a†	$NCH(CH_3)_2$	NC(O)Ph	H_2
83	S	NC(O)Ph	H_2
84	S→O	NCH_2Ph	H_2
85†	S→O	NCH_2Ph	H_2
86	NCH_2Ph	NCH_2Ph	O

†$HClO_4$ salts

were examined after the left anterior coronary artery had been ligated and the animal was allowed to recover over 24 h.[6,59] This ligation results in a transmural myocardial infarction of the heart in which multifocal, accelerated idioventricular rhythms are observed interdispersed with the beats of the normal sinus rhythm. Electrical output from the heart is monitored via specially constructed composite electrodes[6,59] which are secured to obtain electrical recordings during induced ventricular arrhythmias. Figure 2 shows five typical tracings which are monitored in addition to the blood pressure during each experiment.

Ventricular pacing is achieved by the delivery of pacing pulses from an electrical stimulator attached to the right ventricle via a plunge technique where the electrode is placed into the outflow tract area.[6,59] Ventricular arrhythmias were then induced by subjecting the heart to three beat bursts at rates between 240-390 beats/min. A sustained

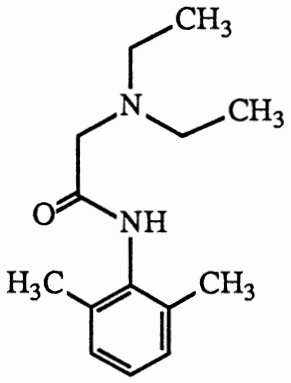


Traces from above are Lead II (L-2) electrocardiograms, His bundle electrogram (Hbeg), electrode catheter recording from the endocardial surface of the infarcted zone (IZ endo), a composite electrode recording from the epicardial surface overlying the infarct zone (IZ epi), and a similar composite electrode recording from the noninfarcted or normal epicardial surface on the posterior left ventricle (NZ epi). The calibrated blood pressure tracing is shown at the bottom.

Figure 2. The Induction of Sustained Ventricular Tachycardia.

ventricular tacycardia (SVT) is defined as a series of ventricular ectopic beats lasting at least 30 seconds or more than 100 consecutive ectopic beats, which are usually uniform at a rate of 250 beats/min or more.[6,59] Non-sustained ventricular tachycardia (NSVT) were defined as a series of ectopic beats, usually uniform, lasting for less than 30 seconds or consisting of fewer than 100 beats at a rate of at least 250 beats/min. Figure 2 is an example of SVT . An increase in the rate of the VT is observed for each of the electrical tracings and also a fractionation of the conduction pattern from the epicardial surface of the infarcted zone (reminiscent of SVT). A drop in mean blood pressure is also observed due to the decrease in pumping action of the heart.[6,59]

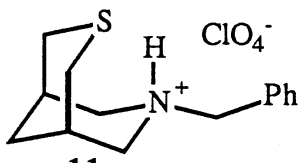
Upon induction of the SVT, the test agents, at dose levels of 3 and 6 mg/kg, were administered intravenously in a bolus of compound dissolved in 1:1 EtOH/H_2O solution. It might be noted that previous studies[6,59] found no significant effects on various related electrophysiological properties nor on blood pressure which were related to the injected 1:1% EtOH/H_2O solution alone. Lidocaine (**52**), served as the benchmark standard for



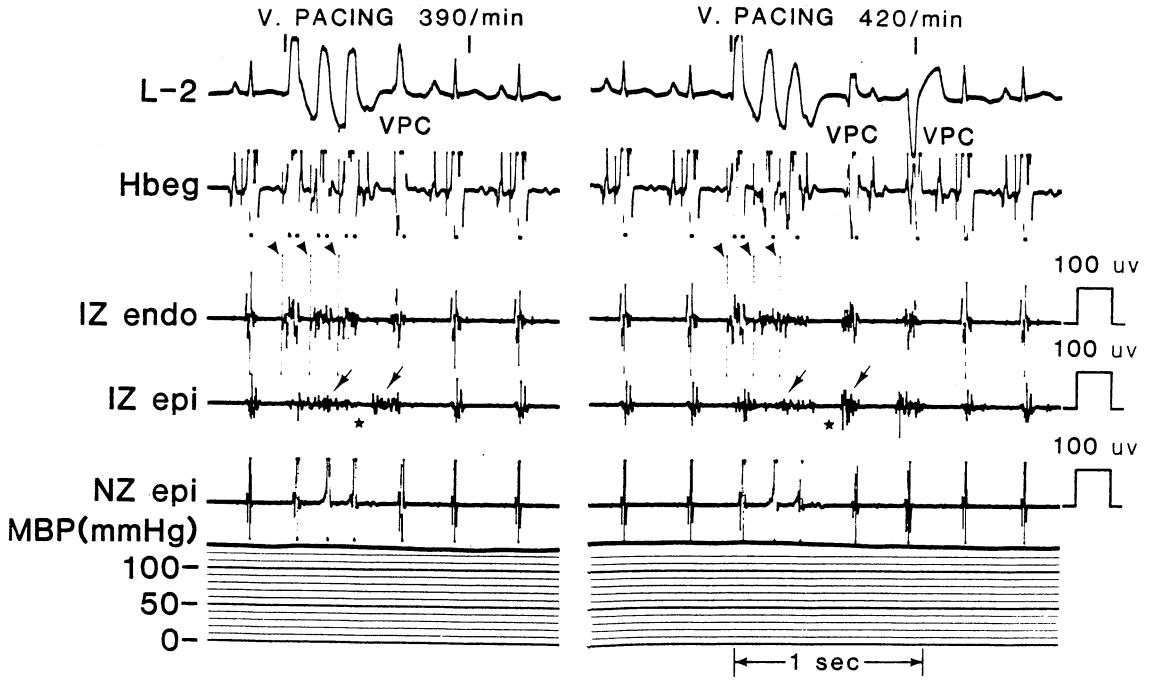
Lidocaine
52

comparative purposes, since it is currently the drug of choice in the treatment of SVT.[41] Each test compound was administered over a 3-5 min period and the testing procedures were completed in that time frame. In the experiment, the effect of the injected agent upon the SVT (change in the rate or complete abolition) was observed relative to the same animal in the absence of any agent, the latter serving as a control. Twenty to forty minutes after administration of the agent, provocative ventricular pacing is employed to determine the dissipation of the drug's effect.[6,59]

Figure 3 illustrates the inhibition of the induced tachycardia after the intravenous administration of previously discussed **11a** at pacing rates of both 390 beats/min and 420 beats/min, respectively. In this case, an ideal response to the agent was observed in which the SVT was completely abolished (notice that the IZ epi conduction pattern is no longer fractionated and each tracing returns to a normal rate) and the blood pressure is elevated by 10-15%. Thus, this particular agent possesses the ability to effect two desired physical



11a



Traces from above are Lead II (L-2) electrocardiograms, His bundle electrogram (Hbeg), electrode catheter recording from the endocardial surface of the infarcted zone (IZ endo), a composite electrode recording from the epicardial surface overlying the infarct zone (IZ epi), and a similar composite electrode recording from the noninfarcted or normal epicardial surface on the posterior left ventricle (NZ epi). The calibrated blood pressure tracing is shown at the bottom.

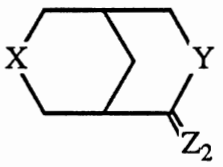
Figure 3. Inhibition of Induced Tachycardia After Intravenous Injection of **11a** (6mg/kg).

transformations of clinical interest: (1) abolition of the SVT and (2) increase in blood pressure which is critical in restoring the pumping action of the heart.[6,59]

In view of the structure-activity relationships which have been previously examined (see Chapter I),[6,11,46,55,75] it was the intended goal of this project to apply this prior knowledge to the development of new antiarrhythmic agents which possess the structural

features necessary for optimum activity. Similar studies, as discussed earlier, have been or are currently being carried out using lidocaine (**52**) as the standard along with the very active agent **11a.**

While salts **80a, 80c** and **82a** completely abolished the SVT at both 3 and 6 mg/kg dosages, salt **80e** had little effect (Table XVIII). Potential metabolites **83, 84,** and **85** of



	X	Y	Z_2
33k	NCH_2Ph	NC(O)Ph	H_2
80a†	$NCH(CH_3)_2$	NCH_2Ph	H_2
80c†	$NCH(CH_3)_2$	$NCH_2C_6H_4$-3,4-$(OCH_3)_2$	H_2
80e†	$NCH(CH_3)_2$	S	H_2
81e	$NCH(CH_3)_2$	NSO_2Ph	H_2
82a†	$NCH(CH_3)_2$	NC(O)Ph	H_2
83	S	NC(O)Ph	H_2
84	S→O	NCH_2Ph	H_2
85†	S→O	NCH_2Ph	H_2
86	NCH_2Ph	NCH_2Ph	O
88†	NCH_2Ph	NC(O)Ph	H_2

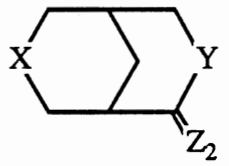
†$HClO_4$ salts

the known active agent **11a** were not especially effective although a small reduction in the rate of the SVT was observed. Interestingly, lactam **86,** which is a potential metabolite of 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonane (**6j**), had very little antiarrhythmic action.

In view of the results obtained by Reunitz[55] and Binnig,[11] in which incorporation of an amide moiety seems to enhance antiarrhythmic action, we were also encouraged by the results obtained for amide **82a.** Complete abolition of the SVT was observed at both doses for **82a.** Thus, this potential metabolite of **80a** (which had similar properties) might serve to prolong the efficacy of **80a** over an extended period. Currently, compounds **33k, 81e,** and **88** are under investigation and results are expected at a later time.

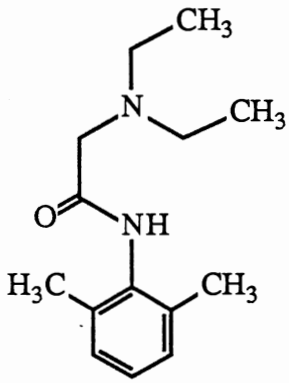
TABLE XVIII

ANTIARRHYTHMIC PROPERTIES OF
3-HETERA-7-AZABICYCLO[3.3.1]-
NONANE DERIVATIVES



	X	Y	Z_2
11a†	S	NCH_2Ph	H_2
80a†	$NCH(CH_3)_2$	NCH_2Ph	H_2
80c†	$NCH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$	H_2
80e†	$NCH(CH_3)_2$	S	H_2
82a†	$NCH(CH_3)_2$	NC(O)Ph	H_2
83	S	NC(O)Ph	H_2
84†	S→O	NCH_2Ph	H_2
85	S→O	NCH_2Ph	H_2
86	NCH_2Ph	NCH_2Ph	O

†$HClO_4$ salts

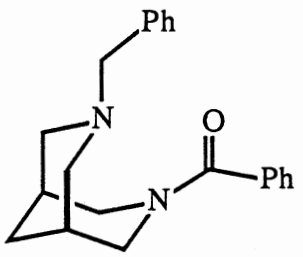


Lidocaine
52

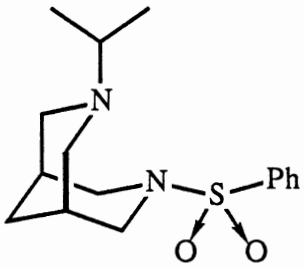
Compound	Rate of SVT[a] 3 mg/kg	Rate of SVT[a] 6 mg/kg
Lidocaine (**52**)	Reduced rate of VT	Reduced Rate of VT
11a	NSVT[b]	NSVT
80a	NSVT	NSVT
80c	NSVT	NSVT
80e	No action	No action
82a	NSVT	NSVT
83	Reduced rate of VT	Reduced rate of VT
84	Reduced rate of VT	Reduced rate of VT
85	Reduced rate of VT	Reduced rate of VT
86	Reduced rate of VT	Reduced rate of VT

[a]SVT = Sustained ventricular tachycardia of animal heart following electrical pacing.

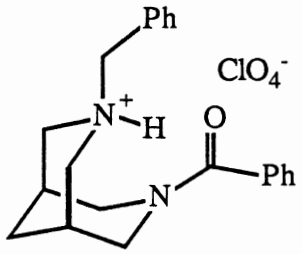
[b]NSVT = Nonsustained ventricular tachycardia.



33k

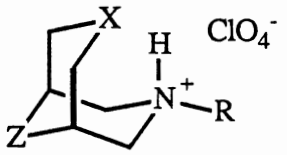


81e

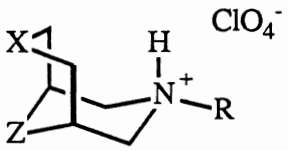


88

Compounds **80a**, **80b**, and **82a** compared favorably in terms of antiarrhythmic activity to lidocaine (**52**) and also have potency equal to that of the active species **11a**. Thus, the modifications of the structure **11a** have proven successful. From the accumulated data gathered to date, certain conclusions can be drawn concerning certain structure-activity relationships. Antiarrhythmic action is generally observed in the general structures **97** and

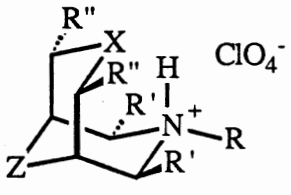


97

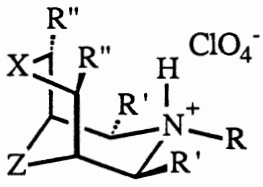


98

98 when X = S, Se, NCH_2Ph or NC(O)Ar, Z = CH_2, $(COR')_2$, or $(CSR')_2$ and R = CH_2Ph or $CH(CH_3)_2$. The presence of at least one *N*-benzyl or *N*-benzoyl group substituent appears critical since the absence of either is consistently associated with reduced antiarrhythmic action.[6] Further research in this area is also dependent upon observations in regard to structural features which depress the action of the agent. In the general



100



101

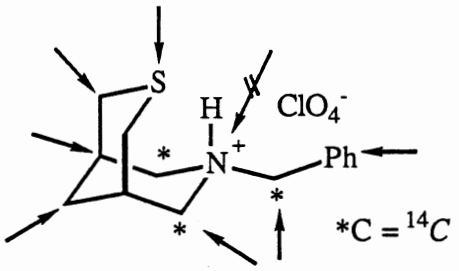
structures **99** and **100**, if X = S, Se, or NCH_2Ph (known to be present in many active agents), the effectiveness of the compound is rather minimal if either of the following conditions hold: (1) R' or R" > H or (2) Y = $C(OH)_2$ or C(OH)Ar.[6]

Metabolism

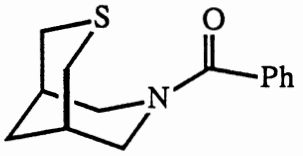
In order to individualize therapy and monitor the optimum response of a patient to a given compound, it is critical to characterize the pharmacologic effects and potencies of the agent and its metabolites.[35] After administration of a parent test compound, detection by indirect methods in the blood is the only means of determining its absolute presence, and confirmation is only gained if the parent is detected in eliminated wastes. Although direct comparison of the biological activity of the parent and the metabolites can be made in animal models, the final assessment for potential clinical utility can only be surmised after administration to human patients. It is also well established that a relationship between the concentration of the agent in the plasma and the pharmacological activity may lead to early detection of metabolites.[35]

In a collaborative effort with Dr. Clarke and Dr. Sangiah of the OSU College of Veterinary Medicine,[58] the pharmacological profile of the ^{14}C radiolabelled form of the known active experimental agent **11a*** (**11a** first synthesized by Bruce Bailey[6] of our lab) was performed using adults rats. A study of the distribution of the agent in the blood and vital organs with time as well as an examination of various metabolites present in the urine was undertaken.[58]

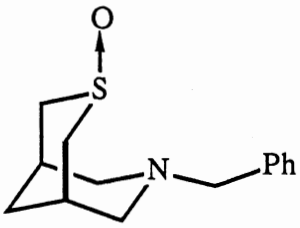
Prior to the pharmacological studies, potential metabolites **83**, **84**, and **85** were synthesized. It was reasoned that although several potential sites of metabolic oxidation of **11a*** are feasible, the sulfur atom and the benzylic position were probably the most vulnerable sites. The nitrogen atom appears screened in molecular models and is also protonated. Finally, the ^{14}C labelled salt **11a*** was synthesized [with ^{14}C label incorporated at positions $^{*}C(2,4)$ and $^{*}CH_2Ph$] and used in a diluted form in the study.[56]



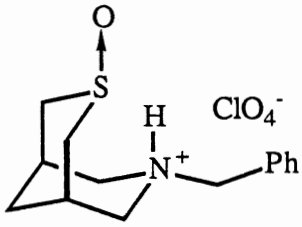
11a*



83



84

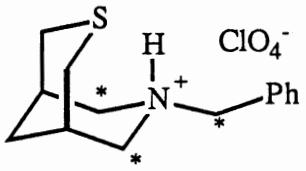


85

To determine the concentration of the agent in the blood (Table XIX) with time, rats were administered a solution of the diluted radioactive compound **11a*** (1.332×10^7 dpm/kg, 10 mg/kg) either orally through a syringe in the stomach or intravenously via intracardial injection.[58] Aliquots of the blood were then removed at various times and the level of radioactivity was monitored with time over a 24 hour period. Although the level of radioactivity was measured (and not the actual concentration of the test agent), it was tentatively assumed that a direct relationship existed between the concentration of the test agent and the radioactivity. The highest level of radioactivity (mean value) from **11a*** in the oral administration was reached after 30 min while after the intravenous injection, the upper level (mean value) of **11a*** was achieved almost immediately (Table XIX). With both the oral and intravenous dosages, the level of radioactivity decayed in similar fashion over time as seen in Table XIX and Figure 4. Thus, it would appear that an intravenous injection of this agent would be preferred clinically since the highest level of the drug is

TABLE XIX

DISTRIBUTION OF **11a*** IN BLOOD OF RATS[a]



11a* *C = ^{14}C

	Mean Radioactivity (dpm/mL)	
Time (h)	Intravenous	Oral
0.03	6644	-
0.08	5905	-
0.17	5460	1134
0.33	4913	2025
0.50	4343	2771
1.0	3623	2383
2.0	2272	1884
3.0	2087	-
4.0	1842	1905
6.0	1828	1462
10.0	1039	1026
16.0	413	347
24.0	171	134

[a]Administered diluted dosage: 1.33×10^7 dpm/kg or 10 mg/kg.

available to act almost immediately. It must also be noted that no adverse side effects were observed in the animals over several days after administration of **11a***, which suggested that the toxicity of **11a*** is minimal (although these are preliminary results).

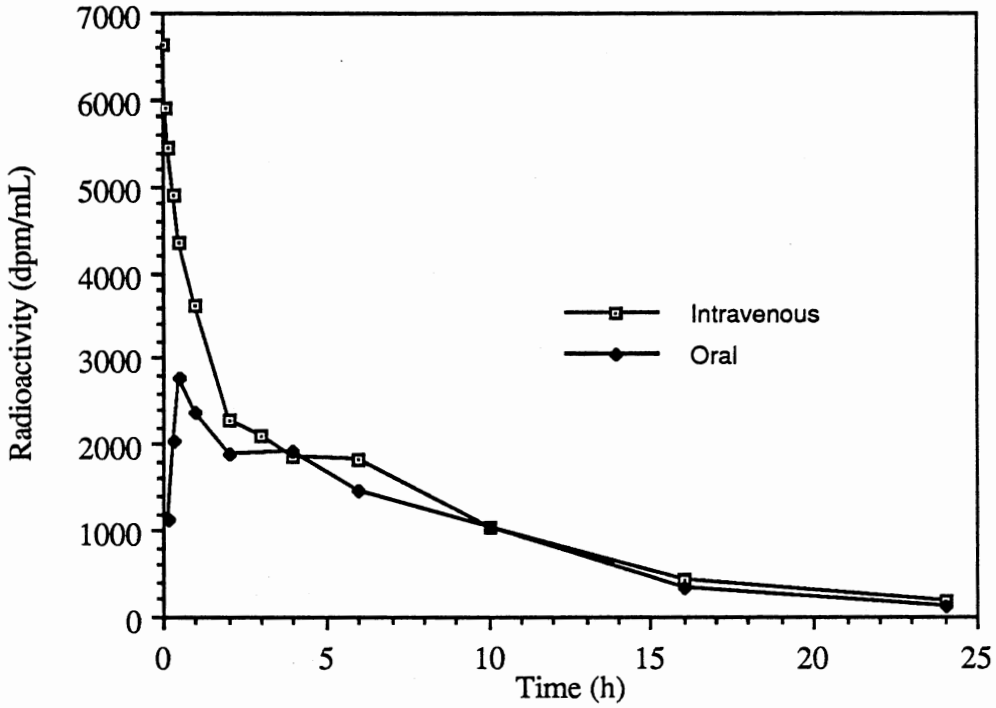
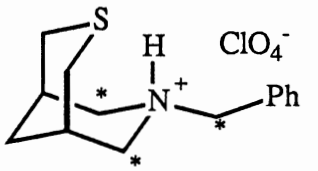


Figure 4. Concentration of **11a*** in Blood.

The pharmacodynamics of the test agent **11a*** were also determined in rats given an intravenous injection of a diluted form of the labelled salt **11a*** (1.332×10^7 dpm/mg, 10 mg/kg).[58] Radioactivity was then monitored with time : organs of the body: blood, brain, fat , heart, kidney, an that upper levels (mean maximum radioactivity) are ach these critical regions. Concentrations were highest in tl was metabolized. Another significant feature was that the brain which suggested that **11a*** may not be effecti

TABLE XX

DISTRIBUTION OF **11a*** IN VITAL AREAS OF RAT BODY[a]



11a* *C = ^{14}C

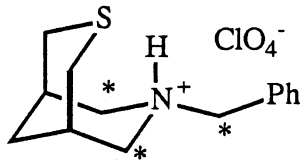
Monitored Area	Time at Max. Level (h)	Mean Radioactivity (dpm/g or dpm/mL[b])
Blood	0.5	5655
Kidney	0.5	33279
Liver	0.5	77499
Heart	0.25	4980
Fat	0.25	6541
Brain	0.25	1523

[a]Administered via intravenous, diluted dosage of (1.33×10^7 dpm/kg or 10 mg/kg).

[b]Blood concentrations were measured in dpm/mL.

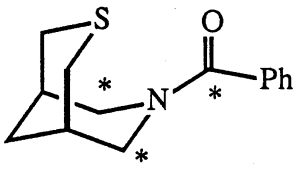
barrier and therefore may possess very little central nervous system activity.[58] This is a very important property for new antiarrhythmic agents.

Finally, rats were administered a diluted dosage of the test compound **11a*** (1.33 x 10^7 dpm/mg, 10 mg/kg) and the urine was collected and basified (pH~13) to neutralize any salts present. Extraction of the urine with ethyl acetate, followed by evaporation of the solvent under N_2, gave a residue which was analyzed using high resolution mass spectrometry in collaboration with Dr. Geno of the OSU Department of Chemistry.[58] The data in Table XXI reveal that the fragmentation pattern and relative intensities of a major component in the urine match quite well with the previously synthesized metabolite amide **83**. Peaks in the spectrum coincided only to a small degree with those for sulfoxide **84**, and

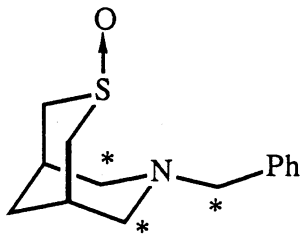


11a*

*C = ^{14}C



83*



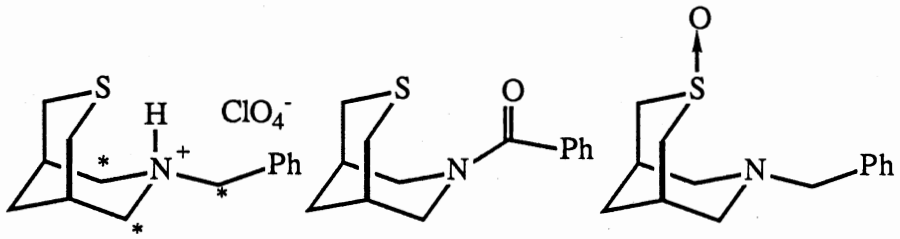
84*

therefore the fit was not compelling (Table XXI) that **84*** was formed *in vivo*. It was concluded that the major metabolite present in the urine was the amide **83*** which is the product derived probably through benzylic oxidation.[58]

These results suggest that the oxidation of the benzylic site in these heterocycles might be favored. Although salt **11a** possesses significant antiarrhythmic action, its major metabolite **83** displays little activity, which suggests that the overall efficacy of **11a** is

TABLE XXI

MASS SPECTRAL ANALYSIS OF **11a*** POTENTIAL METABOLITES IN RAT URINE[a]

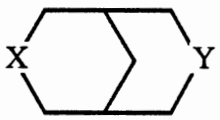


11a* *C = ^{14}C **83** **84**

m/z	Intensity		m/z[b]	Intensity
	Extract	**83**	**84**	
77	39	56	91	100
105	100	100	106	20
134	8	5	158	6
142	64	54	232	80
148	19	17	249	10
186	11	9		
199	12	8		
214	6	6		
247	67	63		

[a]Administered an intravenous diluted dosage of 1.33×10^7 dpm/kg or 10 mg/kg.
[b]These are m/z values for authentic **84**.

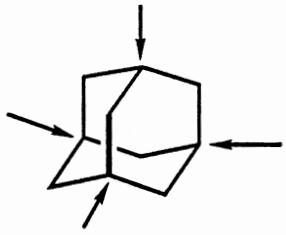
restricted with time. However, if salt **80a** (whose activity was equipotent to **11a**) should follow the same metabolic pathway to amide **82a** (activity also equipotent to **11a**), then the overall effectiveness of the parent agent **80a** should be preserved with time. This theory may also apply to related salts **80b-c** and potential metabolites **81b-c** and **82(a,c)**.



	X	Y
80a†	$NCH(CH_3)_2$	NCH_2Ph
80b†	$NCH(CH_3)_2$	$NCH_2C_6H_4$-4-Cl
80c†	$NCH(CH_3)_2$	$NCH_2C_6H_3$-3,4-$(OCH_3)_2$
81a	$NCH(CH_3)_2$	NC(O)Ph
81b	$NCH(CH_3)_2$	$NC(O)C_6H_4$-4-Cl
81c	$NCH(CH_3)_2$	$NC(O)C_6H_3$-3,4-$(OCH_3)_2$
82a†	$NCH(CH_3)_2$	NC(O)Ph
82c†	$NCH(CH_3)_2$	$NC(O)C_6H_3$3,4-$(OCH_3)_2$

†$HClO_4$ salts

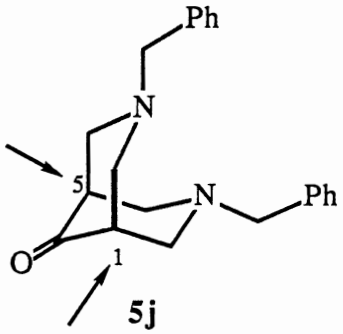
In an attempt to develop methodology to introduce oxygen at bridgehead positions [since bridgehead carbons C(1,5) are conceivably vulnerable to metabolic oxidation] in the



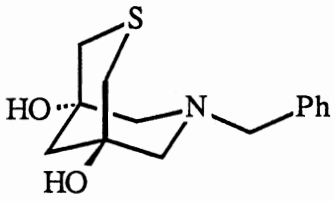
101

3,7-diheterabicyclo[3.3.1]nonanes, a variety of oxidizing agents were evaluated. As a model system, adamantane (**101**) is reported to undergo oxidation at the bridgehead carbons when treated with chromium trioxide in acetic acid/acetic anhydride at RT.[10] Similar conditions were employed for the attempted selective oxidation of model system

5j. Although a reaction proceeded, a complex mixture resulted from which it has not been possible to isolate a pure product. Chromatography with a variety of substrates might cause some separation of products. Other reagents were attempted; however, the product of interest was not isolated or starting material was recovered in each case. For example,



5j

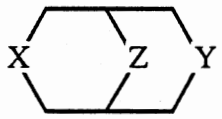


102

oxidation of **5j** with $Pb(OAc)_4$ in trifluoroacetic acid/benzene[34] at reflux for 14 hours resulted in recovered starting material (73%). Agents such as Na_2O_2,[28] and several new potentially useful oxidation agents such as In_2O_3, Li_2MnO_3, $Li_2CrO_4 \cdot H_2O$, and Li_2O_2 were also employed. In each case, starting material was recovered in modest to good yields. However, significant reaction did occur with Li_2MnO_3 and $LiCrO_4 \cdot H_2O$ although unseparable mixtures were obtained. These studies had as an objective to develop an oxidative method that might yield **102** although it was recognized that sulfur was vulnerable to most oxidizing agents. Thus, deoxygenation of sulfur would have to be accomplished separately.[48]

Considering the fact that hundreds of thousands of U.S. citizens die from conditions which arise from cardiovascular disorders each year,[41] the results are encouraging. Several members of the 3-hetera-7-azabicyclo[3.3.1]nonane family **1** (Y = N) have displayed significant antiarrhythmic action in animal models and, coupled with a further understanding of pharmacological properties of these agents,[58] we are currently working

in a collaborative effort with a pharmaceutical company to complete the analyses of these agents in order to initiate clinical trials.



1

CHAPTER III

EXPERIMENTAL

All ^{1}H, ^{13}C, and ^{15}N spectral data were obtained on a Varian XL-300 NMR spectrometer operating at 299.94, 75.43, and 30.41 MHz, respectively. Chemical shifts for ^{1}H and ^{13}C NMR spectra were recorded in δ or ppm values downfield from TMS [$(CH_3)_4Si$], while ^{15}N NMR signals were reported in ppm downfield from NH_3 (*liquid*, 0 ppm) using 8 M $^{15}NH_4NO_3$ (19.73 ppm) as an external reference. IR spectra were acquired on a Perkin Elmer 681 IR spectrometer. Melting points, which were uncorrected, were recorded on a Thomas-Hoover capillary melting point apparatus. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Syntheses were executed, unless otherwise indicated, under an atmosphere of N_2 with magnetic stirring. The following reagents were obtained commercially and used without further purification: glacial acetic acid (Dupont), benzylamine hydrochloride ($^{14}CH_2$, ICN), 4-chlorobenzoyl chloride (99%, Aldrich), 4-chlorobenzylamine (98%, Aldrich), chromium (VI) oxide (99%, Aldrich), 3,4-dimethoxybenzoyl chloride (98%, Aldrich), hydrazine (95%, Fisher), hydroxylamine hydrochloride (Fisher), 3-iodobenzylamine hydrochloride (98%, Lancaster), indium oxide (Arconium), isopropylamine (99%, Aldrich), lead tetraacetate (Aldrich), lithium chromate (Alfa), lithium manganese (IV) oxide (Alfa), lithium peroxide (95.3%, Alfa), Pd/C (10%, Alfa), paraformaldehyde (Fisher), paraformaldehyde (^{14}C, ICN), perchloric acid (60%, Baker), potassium hydroxide (85%, Baker), ruthenium (IV) oxide hydrate (13%, Alfa), sodium acetate trihydrate (Mallinckrodt), sodium hydroxide (97%, Fisher), sodium metaperiodate (Mallinckrodt), sodium peroxide (97%, Baker) and 3,4,5-trimethoxybenzoyl choride (98%, Aldrich). The

following compounds required distillation prior to use: benzenesulfonyl chloride (bp 82-84°C/1 mm Hg, Eastman), benzoyl chloride (bp 46°C/1 mm Hg, Eastman), benzylamine (bp 57-59°C/4.2 mm Hg, Lancaster), *N*-benzyl-4-piperidinone (bp 120-122°C/1 mm Hg, Lancaster), 3,4-dimethoxybenzylamine (bp 105-115°C/0.2 mm Hg, Lancaster) and *N*-isopropyl-4-piperidinone (bp 38-41°C/0.05 mm Hg, Aldrich). Ammonium formate (Baker) was recrystallized from CH_3OH and dried (vacuum pump, overnight, 0.2 mm Hg) in a dessicator prior to use (mp 118-120°C). 4-Thianone (mp 61-62°C) was prepared by known methods[32] and was sublimed (45°C/0.5 mm Hg) before use. All solvents were reagent grade and used without further purification, unless otherwise indicated. Silica gel ("Davisil 62", 60-200 mesh, Davison Chemical), and Alumina (neutral, 70-230 mesh, Merck) were employed in chromatographic separations with reagent grade solvents as eluants. **Caution**: *Although no difficulties were experienced in handling the hydroperchlorates cited herein, all work should be done in a hood and with extreme care as indicated.*

3,7-Dibenzyl-3,7-diazabicyclo-
[3.3.1]nonan-9-one (**5j**)

A 500-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with a N_2 inlet, a 250-mL addition funnel and a glass stopper. A mixture of benzylamine (10.71 g, 100 mmol), HCl (37%, 4.93 g, 50 mmol), glacial.acetic acid (6.0 g, 100 mmol) and paraformaldehyde (6.31 g, 210 mmol) in CH_3OH (100 mL) was brought to gentle reflux with stirring under N_2 over 15 min. A solution of *N*-benzyl-4-piperidinone (**4e**, 18.93 g, 100 mmol) and glacial acetic acid (6.01 g, 100 mmol) in CH_3OH (100 mL) was then added dropwise over 1 h and this was followed by a period of reflux for an additional 18 h. Upon cooling the mixture to RT, the solvent was removed (rotary evaporator) and the resulting red oil was redissolved in H_2O (100 mL). Combined extracts (ether, 2 x 100 mL) of the acidic aqueous layer were

discarded. Basification of the chilled (10°C, via ice water bath) water layer to pH~12 was effected by the addition of 10% NaOH. Combined extracts (ether, 4 x 60 mL) were dried (Na_2SO_4, 1 h), filtered and concentrated (rotary evaporator) to give a viscous red oil. This oil was digested with Skelly B (2 x 250 mL, 20 min), and the supernatant extracts were concentrated and then distilled (190-215°C/10^{-5} mm Hg) to give an oil. Crystallization of the oil was induced by dissolving the oil in hot pentane (800 mL) and then chilling (-10°C) the solution to give 14.66 g (45.8%) of white crystalline **5j**; mp 82.5-83.5°C (lit.[11] mp 70-71°C). Concentration (hot plate) of the mother liquor to ~80 mL produced a second crop (0.81 g, 2.5%): mp 81.5-82.0°C. The total yield was (15.47 g, 48.3%).

3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonane (**6j**)

A 70-mL, five-necked, jacketed flask was equipped with a magnetic stirrer, a heating mantle, a condenser, a lower take-off condenser with a N_2 inlet, a thermometer and two glass stoppers. After the addition of the ketone (**5j**, 2.0 g, 6.24 mmol), KOH pellets (85%, 4.94 g, 56.1 mmol) and hydrazine (95%, 2.11 g, 32.1 mmol) in triethylene glycol (40 mL), the apparatus was flushed with N_2, and the mixture was heated at 140-150°C for 4 h using boiling *o*-xylene (bp 144°C) in the jacket. Cooling the solution to RT was followed by the addition of chilled water (80 mL). Combined extracts (ether, 3 x 75 mL) of the suspension were washed with saturated NaCl (75 mL), dried (Na_2SO_4, overnight), filtered and concentrated (rotary evaporator) to a yellow oil (1.83 g, 95.7%) which displayed no carbonyl stretch in the IR spectrum. This oil was used without further purification.

7-Benzyl-3-thia-7-azabicyclo[3.3.1]-
nonan-9-one (**8a**)

A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with a N_2 inlet and two glass stoppers. A mixture containing

benzylamine (0.43 g, 4 mmol), paraformaldehyde (0.96 g, 32 mmol), CH_3OH (15 mL), HCl (37%, 0.20 g, 2 mmol), and glacial acetic acid (0.36 g, 6 mmol) was stirred under N_2 at RT. In one portion, 4-thianone (**4f**, 0.47 g, 4 mmol) was added to the mixture which was then heated at reflux under N_2 for 6 h. Evaporation (rotary evaporator) of the solvent gave a red oil which was diluted with H_2O (30 mL) and then the mixture was extracted with ether (2 x 40 mL), the latter being discarded. Basification (pH~12) of the aqueous layer by the addition of NaOH pellets (97%, 0.26 g, 6 mmol) formed a cloudy yellow suspension which was extracted with ether (4 x 30 mL). Combined extracts were dried (Na_2SO_4, 4 h), filtered, and concentrated (rotary evaporator) to afford a yellow solid. This solid was digested in Skelly B (300 mL, bp 60-68°C) for 30 min and the supernatant was decanted. Evaporation (rotary evaporator) of the solvent gave crude ketone **8a** as a solid which was heated *in vacuo* (110°C/0.1 mm) in a sublimation apparatus to give 0.4 g (40.4%) of pure ketone **8a**; mp 94.5-95.5°C (lit.[6] mp 91-93°C).

7-Benzyl -3-thia-7-azabicyclo[3.3.1]-
nonan-9-one *6,8,10-*$^{14}C_3$ (**8a***)

Caution: *Special precautions should be taken when handling radioactive chemicals. All reactions should be carried out in a well ventilated hood with protective shields to prevent possible contamination of the lab area. Protective safety goggles as well as quality rubber gloves should also be worn at all times since exposure to the potentially dangerous* ^{14}C *materials could be fatal.* A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with N_2 inlet and two glass stoppers. To a mixture containing benzylamine (0.43 g, 4 mmol), [^{14}C] benzylamine HCl [1 mg, 7 x 10^{-3} mmol, 0.5 mCi (minimum activity, ICN)] in H_2O (2.5 mL), and deoxygenated CH_3OH (15 mL) was added HCl (37%, 0.1 g, 1 mmol) followed by glacial acetic acid (0.36 g, 6 mmol). Addition in one portion of paraformaldehyde (0.96 g, 32 mmol) and [^{14}C] paraformaldehyde [1 mg, 3.3 x 10^{-2} mmol, 0.5 mCi (minimum activity,

ICN)] was followed by subsequent addition of 4-thianone (**4f**, 0.47 g, 4 mmol) all at once with stirring. After the mixture was heated at reflux under N_2 for 6 h, the solution was concentrated (rotary evaporator) to 2-3 mL and then diluted with H_2O (30 mL). The aqueous solution was extracted with ether (2 x 30 mL), and the latter was discarded. Chilling (via ice water bath) of the aqueous layer to below 5°C was followed by basification (pH~12) with NaOH pellets (97%, 0.29 g, 7 mmol) which resulted in the formation of a cloudy suspension. Combined extracts (ether, 4 x 30 mL) were dried (Na_2SO_4, overnight), filtered and concentrated (rotary evaporator) to give a viscous oil, which was then digested in 200 mL of Skelly B (bp 60-68°C) for 0.5 h. Concentration (rotary evaporator) of the supernatant afforded a yellow oil which was subjected to heating at high vacuum (110°C/0.1 mm Hg) in a sublimation apparatus to give 0.13 g of ketone **8a***; mp 91-93°C; (lit.[6] mp.91-93°C). The residue which remained was again dissolved in ether (~50 mL), and the latter solution was dried (Na_2SO_4, overnight), filtered, and concentrated (rotary evaporator) to an oil. Digestion of the oil was effected in 50 mL of Skelly B for 0.5 h, and the supernatant was concentrated (rotary evaporator) to a viscous oil. This material was heated under vacuum (110°C/0.1 mm Hg) in a sublimation apparatus and gave 0.05 g of slightly crude ketone **8a***; mp 78-80°C (lit.[6] mp 91-93°C). A mixture melting point determination with the first crop was 86-88°C without significant depression. This gave a total yield of 0.18 g (17.7%) of ketone **8a*** which was used without further purification in the next step.

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane (**10a**)

To a mixture of KOH pellets (85%, 3.20 g, 48.5 mmol) and the ketone (**8a**, 1.0 g, 4.04 mmol) in triethylene glycol (25 mL) was added hydrazine (95%, 1.36 g, 40.4 mmol) in a 70-mL, jacketed flask equipped with a magnetic stirrer, a heating mantle, a condenser, a lower take-off condenser with a N_2 inlet and two glass stoppers. A heating temperature of 140-150°C over 4 h under N_2 was produced by boiling *o*-xylene in the jacket. After

cooling to RT, the solution was first diluted with chilled H_2O (40 mL) and then extracted with ether (3 x 40 mL). Combining the extracts, followed by drying (Na_2SO_4, 4 h), filtering and concentrating (rotary evaporator then vacuum pump, overnight, RT/0.2 mm Hg) the solution gave 0.90 g (95.4%) of a light yellow oil (slightly crude) which displayed no C=O stretch in the IR spectrum, and this oil was used without further purification.

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane
Hydroperchlorate *6,8,10*-$^{14}C_3$ (**11a***)

Caution: *Special precautions should be taken when handling radioactive chemicals. All reactions should be carried out in a well ventilated hood with protective shields to prevent possible contamination of the lab area. Protective safety goggles as well as quality rubber gloves should also be worn at all times since exposure to the potentially dangerous ^{14}C materials could be fatal.* To a mixture of KOH pellets (85%, 0.48 g, 8.5 mmol) and the ketone (**8a***, 0.18 g, 0.71 mmol) in triethylene glycol (5 mL) was added hydrazine (95%, 0.23 g, 7.1 mmol) in one portion in a 50-mL, jacketed flask equipped with a magnetic stirrer, a condenser, a lower take-off condenser and two glass stoppers. A heating temperature of 140-150°C for 4 h was produced by boiling *o*-xylene (bp 144°C) in the jacket. After cooling to RT, the solution was diluted with chilled H_2O (30 mL) and extracted with ether (4 x 20 mL). Combined extracts were dried (Na_2SO_4, overnight) and filtered. Cooling of the ethereal solution to below 5°C was followed by the dropwise addition of $HClO_4$ (60%, 1 mL) over 10 min with stirring, which resulted in the formation of a white precipitate. Crude salt **11a*** was filtered, recrystallized (95% EtOH), and dried over P_2O_5 (78°C/0.1 mm Hg) to give 0.14 g (58.6%) of white crystals of salt **11a***; mp 154.5-155.0°C; (lit 155-156°C).[6] A stock solution (3.49 mg/mL) of salt **11a*** was prepared using DMSO, H_2O and 0.1 N HCl (40:53.5:6.5 by volume). Samples were made by diluting 4 μL of the stock solution with 10 mL of Aquasol 2 scintillation cocktail (New England Nuclear Research Products).[58] Measurements of activity were obtained at

room temperature using a TRI-CARB liquid scintillation analyzer, model 1900 CA (Packard Instrument Company). An average count of 19,800 DPM was observed for each sample and the specific activity was determined to be 0.64 μCi/mg. In similar fashion, samples were prepared from stock solution of the salt **11a*** in methanol and the specific activity was determined to be 0.63 μCi/mg.

3-Benzoyl-7-benzyl-3,7-diazabicyclo-
[3.3.1]nonane (**33k**)

A 150-mL, five-necked, jacketed flask was equipped with a magnetic stirrer, a heating mantle, a condenser, a lower take-off condenser with a N_2 inlet and three glass stoppers. To a mixture of KOH pellets (85%, 1.24 g, 18.8 mmol) and the ketone (**87**, 3.0 g, 8.97 mmol) in triethylene glycol (75 mL) was added hydrazine (95%, 0.61 g, 17.9 mmol) in one portion. A heating temperature of 140-150°C for 3.5 h under N_2 was produced by boiling *o*-xylene (bp 144°C) in the jacket. Cooling of the solution to RT was followed by the addition of chilled H_2O (120 mL). Combined extracts of the resulting suspension (CH_2Cl_2, 3 x 120 mL) were washed with 10% NaOH (50 mL) and saturated NaCl (50 mL), dried (Na_2SO_4, overnight), filtered and concentrated (rotary evaporator) to a viscous yellow oil. Chromatography of the oil was performed on silica gel (81 g, 1.9 cm x 90 cm) using 3% CH_3OH/CH_2Cl_2 as eluant. The fractions ($R_f = 0.58$) were saved and the remaining impure material was rechromatographed on silica gel (50 g, 2.1 cm x 51 cm) in the same fashion. Fractions from both columns ($R_f = 0.58$) were combined, concentrated (rotary evaporator then vacuum pump, overnight, RT/0.2 mm Hg) to give a clear oil which crystallized upon standing and afforded 1.98 g (68.9 %) of the amide **33k**; mp 81-82°C. IR (KBr) cm^{-1} 3080, 3055, 3025 (Ar C-H), 2935, 2910, 2880, 2850, 2805, 2770, 2750, 2715, 2690 (C-H), 1630 (C=O); ^1H NMR ($DCCl_3$) δ 1.68-1.78 [m, 3 H, H(5) and H(9)], 1.98 [bs, 1 H, H(1)], 2.19 [bd, 1 H, $H(4)_{ax}$, J = 11.1 Hz], 2.27 [bd, 1 H, $H(6)_{ax}$, J = 11.2 Hz], 2.88 [bd, 1 H, $H(6)_{eq}$, J = 11.2 Hz], 3.05-3.13 [m, 2 H, $H(2)_{ax}$ and

$H(4)_{eq}$], 3.26 [bd, 1 H, $H(8)_{ax}$, J = 14.1 Hz], 3.34 (d, 1 H, ArCH_2, J = 13.2 Hz), 3.48 (d, 1 H, ArCH_2, J = 13.1 Hz), 3.75 [bd, 1 H, $H(8)_{eq}$, J = 13.5 Hz], 4.79 [bd, 1 H, $H(2)_{eq}$, J = 13.3 Hz], 7.23-7.38 (m, 10 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 29.02 [C(1)], 29.50 [C(5)], 31.97 [C(9)], 46.43 [C(2)], 52.22 [C(4)], 58.51 [C(8)], 58.63 [C(6)], 63.99 (ArCH_2), 126.81, 126.88, 128.27, 128.72, 129.02, 137.46, 138.19 (Ar-*C*), 170.11 (*C*=O). Anal. Calcd. for $C_{21}H_{24}N_2O$: C, 78.72; H, 7.55. Found: C, 78.76; H, 7.74.

7-Benzyl-3-isopropyl-3,7-diazabicyclo-
[3.3.1]nonan-9-one (**77a**)

A 500-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a 250-mL addition funnel, a condenser with a N_2 inlet and a glass stopper. A mixture of benzylamine (10.71 g, 100 mmol), HCl (37%, 9.86 g, 100 mmol), glacial acetic acid (3.0 g, 50 mmol) and paraformaldehyde (6.31 g, 210 mmol) in deoxygenated (N_2 bubbled in for 1 h) CH_3OH (100 mL) was stirred at reflux for 15 min under N_2. A solution of *N*-isopropyl-4-piperidinone (**4c**, 14.12 g, 100 mmol) and glacial acetic acid (6.0 g, 100 mmol) in CH_3OH (100 mL) was then added dropwise to the mixture over 30 min, followed by stirring at reflux for an additional 18.5 h. Concentration (rotary evaporator) of the solution gave an oil which was redissolved in H_2O (100 mL). An ether extract (100 mL) of this acidic solution was discarded. Basicification (pH~13) of the water layer was achieved by the addition of 10% NaOH, resulting in the formation of a milky suspension which was extracted (ether, 4 x 60 mL). Combined extracts were dried (Na_2SO_4, 1 h), filtered and concentrated (rotary evaporator) to a viscous red oil, which, when distilled (175-185°C/10^{-5} mm Hg), afforded a light yellow oil (15.6 g, 57.2%), that solidified when refrigerated at -10°C; mp 46-47.5°C. This solid could be recrystallized (pentane) to give an analytical sample of **77a**; mp 49-50°C. IR (KBr) cm^{-1} 3095, 3070, 3035 (Ar-H), 2975, 2900, 2820 (C-H), 1745 (C=O), 1605, 1495 (C=C), 740, 700 (C-H

out of plane, mono); ^{1}H NMR ($DCCl_3$) δ 1.02 (d, 6 H, C*H*$_3$), 2.58 [bs, 2 H, H(1,5)], 2.87 [m, 5 H, ring protons and C*H*$(CH_3)_2$], 3.03 (dd, 4 H, ring protons), 3.53 (s, 2 H, ArC*H*$_2$), 7.30 (m, 5 H, Ar-*H*) ^{13}C NMR ($DCCl_3$) ppm 18.25 (*C*H_3), 46.93 [C(1,5)], 53.41 [*C*H$(CH_3)_2$], 53.71 [C(2,4)], 58.07 [C(6,8)], 61.25 (Ar*C*H_2), 127.09, 128.25, 128.69, 138.67 (Ar-*C*), 215.20 (*C*=O); ^{15}N NMR ($DCCl_3$) ppm 39.25 [N(7)], 40.80 [N(3)]. Anal. Calcd. for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 75.18; H, 8.61; N, 10.24.

7-(4-Chlorobenzyl)-3-isopropyl-3,7-diaza-bicyclo[3.3.1]nonan-9-one (**77b**)

A 200-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with a N_2 inlet, a 50-mL addition funnel and a glass stopper. A mixture of 4-chlorobenzylamine (7.08 g, 50 mmol), paraformaldehyde (3.15 g, 105 mmol), glacial acetic acid (3.0 g, 50 mmol) and CH_3OH (35 mL) was brought to gentle reflux with stirring under N_2 for 15 min. To the mixture was added dropwise a solution of *N*-isopropyl-4-piperidinone (**4c**, 7.06 g, 50 mmol) and glacial acetic acid (3.0 g, 50 mmol) in CH_3OH (25 mL) over 1 h. Boiling of the mixture was continued for an additional 24 h. After concentrating (rotary evaporator) to a viscous red oil, the reaction mixture was then diluted with H_2O (100 mL) and extracted (ether, 3 x 100 mL), the latter being discarded. Chilling (via ice water bath) of the aqueous layer to below 10°C was followed by basification (pH~13) with KOH pellets (85%, 6.6 g, 100 mmol). Combined extracts (ether, 3 x 60 mL) were dried (Na_2SO_4, 4 h), filtered and concentrated (rotary evaporator) to give a viscous red oil. This oil was digested in pentane (100 mL) for 20 min and the supernatant was decanted and concentrated (rotary evaporator). Distillation of the resulting oil (195-205°C/10^{-5} mm Hg) gave 5.25 g of a yellow oil which solidified upon standing. Recrystallization of the solid from pentane gave 3.46 g (22.6%) of white crystalline **77b**; mp 68-69°C. IR (KBr) cm^{-1} 3030 (Ar C-H), 2955, 2880, 2800 (C-H),

1730 (C=O), 800 (C-H out of plane, para); ^{1}H NMR ($DCCl_3$) δ 1.03 (d, 6 H, CH_3, J = 6.3 Hz), 2.58 [bs, 2 H, H(1,5)], 2.80-3.05 [m, 9 H, ring protons and $CH(CH_3)_2$], 7.27 (s, 4 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 18.25 (CH_3), 46.85 [C(1,5)], 53.40 [$CH(CH_3)_2$], 53.76 [C(2,4)], 57.92 [C(6,8)], 60.48 (ArCH_2), 128.40, 129.95, 132.74, 137.21 (Ar-*C*), 215.04 (*C*=O); ^{15}N NMR ($DCCl_3$) ppm 39.18 [N(3)], 40.31 [N(7)]. Anal. Calcd. for $C_{17}H_{23}ClN_2O$: C, 66.55; H, 7.56. Found: 66.47; H, 7.52.

3-(3,4-Dimethoxybenzyl)-7-isopropyl3,7-diaza-bicyclo[3.3.1]nonan-9-one (**77c**)

A 200-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with a N_2 inlet, a 50-mL addition funnel and a glass stopper. A mixture containing 3,4-dimethoxybenzylamine (8.36 g, 50 mmol), paraformaldehyde (3.15 g, 105 mmol) and CH_3OH (35 mL) was made acidic with the addition of glacial acetic acid (3.0 g, 50 mmol). Stirring the mixture under N_2 for 20 min was followed by the dropwise addition of *N*-isopropyl-4-piperidinone (**4c**, 7.06 g, 50 mmol) and glacial acetic acid (3.0 g, 50 mmol) in CH_3OH (25 mL) over 1.25 h. Boiling of the mixture was continued for an additional 23 h. This new mixture was evaporated (rotary evaporator) to give a red viscous oil. After dissolving the oil in H_2O (100 mL), the solution was extracted (ether, 2 x 100 mL), the latter being discarded. Chilling (via ice water bath) of the water layer below 10°C, followed by basification (pH~12) with KOH pellets (6.6 g, 100 mmol), produced an orange suspension which was extracted (CH_2Cl_2, 4 x 80 mL). Combined extracts were dried (Na_2SO_4, overnight), filtered and concentrated (rotary evaporator) to give a crude oil. This oil was digested in Skelly B (250 mL, bp 60-68°C) for 0.5 h and the supernatant was decanted. Evaporation (rotary evaporator) of the solvent gave an oil which, when distilled (175-205°C/10^{-4} mm Hg) afforded a yellow oil. Adding Skelly B induced crystallization to give 4.32 g (26%) of off white ketone **77c**; mp 79.5-80.5°C. IR (KBr) cm^{-1} 3095, 3015 (Ar-H), 2980, 2955, 2920, 2855, 2810 (C-H), 1745

(C=O), 1620, 1605 (C=C); ^{1}H NMR ($DCCl_3$) δ 1.03 (d, 6 H, C*H*$_3$, J = 6.6 Hz), 2.59 [bs, 2 H, H(1,5)], 2.81-2.90 [m, 5 H, ring protons and C*H*$(CH_3)_2$], 2.98 (dd, 2 H, ring protons, J = 10.7 Hz, J' = 3.2 Hz), 3.08 (dd, 2 H, ring protons, J = 10.7 Hz, J' = 2.99 Hz), 3.47 (s, 2 H, ArC*H*$_2$), 3.87 (s, 3 H, OC*H*$_3$), 3.88 (s, 3 H, OC*H*$_3$), 6.80-6.92 (m, 3 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 18.17 (*C*H_3), 46.85 [C(1,5)], 53.40 [*C*H$(CH_3)_2$], 53.86 [C(2,4)], 55.76, 55.86 (O*C*H_3), 58.01 [C(6,8)], 60.93 (Ar*C*H_2), 110.60, 111.46, 120.68 131.30, 148.04, 148.90 (Ar-*C*), 215.27 (*C*=O); ^{15}N NMR ($DCCl_3$) ppm 39.66 [N(7)], 40.93 [N(3)]. Anal. Calcd. for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49. Found: C, 68.70; H, 8.53.

7-Isopropyl-3-thia-7-azabicyclo-
[3.3.1]nonan-9-one (**77d**)

A three-necked, 300-mL, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with a N_2 inlet and two glass stoppers. A mixture containing $(H_3C)_2CHNH_2$ (2.96 g, 50 mmol), paraformaldehyde (12.01 g, 400 mmol) and CH_3OH (188 mL) was made acidic with glacial acetic acid (4.5 g, 75 mmol). In one portion, 4-thianone (**4f**, 5.81 g, 50 mmol) was added followed by stirring at reflux for 21 h. Evapo-ration (rotary evaporator) of the solvent gave a red oil, which was diluted with H_2O (200 mL) and extracted with ether (2 x 100 mL), the latter being discarded. Basification (pH~12) of the aqueous layer by the addition of NaOH pellets (3.0 g, 75 mmol) resulted in the formation of a yellow suspension which was extracted with CH_2Cl_2 (4 x 100 mL). Combined extracts were dried ($MgSO_4$, overnight), filtered, and concentrated (rotary evaporator) to afford a yellow oil which solidified upon standing. This solid was digested in 250 mL of Skelly B (bp 60-68°C) for 30 min, and the supernatant was decanted. Evaporation (rotary evaporator) of the solvent, followed by heating the crude solid *in vacuo* (95-110°C/0.3 mm Hg) in a sublimation apparatus gave a sticky white solid (mp 54-57°C). Recrystallization (Skelly B) afforded 4.15 g (41.6%) of

white flakes of ketone **77d**; mp 59-60°C. IR (KBr) cm^{-1} 2965, 2935, 2900, 2875, 2805 (C-H), 1730 (C=O); ^1H NMR ($DCCl_3$) δ 1.04 (d, 6 H, CH_3, J = 6.7 Hz), 2.75-2.90 [m, 5 H, ring protons, $CH(CH_3)_2$, and H(1,5)], 3.05-3.13 (m, 4 H, ring protons), 3.24-3.29 (m, 2 H, ring protons); ^{13}C NMR ($DCCl_3$) ppm 18.30 (q, CH_3), 34.16 [t, C(2,4)], 47.52 [d, C(1,5)], 53.76 [d, $CH(CH_3)_2$], 54.16 [t, C(6,8)], 213.68 (s, C=O); ^{15}N NMR ($DCCl_3$) ppm 39.27 [N(7)]. Anal. Calcd. for $C_{10}H_{17}NOS$: C, 60.26; H, 8.60. Found: C, 60.40; H, 8.65.

7-(3-Iodobenzyl)-3-thia-7-azabicyclo-
[3.3.1]nonan-9-one (**77e**)

A 100 mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with a N_2 inlet and two glass stoppers. A mixture containing 3-iodobenzylamine (1.19 g, 5.10 mmol), paraformaldehyde (1.22 g, 40.8 mmol), and CH_3OH (30 mL) was made acidic with glacial acetic acid (0.46 g, 7.65 mmol). In one portion, 4-thianone (**4f**, 0.59 g, 5.10 mmol) was added and the resulting mixture was heated under N_2 at reflux for 21 h. Evaporation (rotary evaporator) of the solvent gave a reddish oil, which was dissolved in H_2O (40 mL). Basification (pH~13) of the solution by the dropwise addition of 10% NaOH resulted in the formation of a milky suspension which was extracted with ether (5 x 40 mL). Combined extracts were dried (Na_2SO_4, overnight), filtered and concentrated (rotary evaporator) to a yellow oil. Digestion of the oil occurred in Skelly B (125 mL, bp 60-68°C) for 30 min, and the supernatant was decanted. Further digestion of the residual material was effected in pentane (2 x 125 mL) for 30 min. Combined supernatant extracts were concentrated (rotary evaporator, then vacuum pump overnight, RT/0.2 mm Hg) to give 0.84 g (57.5%) of a crude viscous oil which was used without further purification in the next step. IR (film) cm^{-1} 3055 (Ar C-H), 2930, 2825 (C-H), 1735 (C=O), 885, 790, 695 (C-H out of plane, meta); ^1H NMR ($DCCl_3$) δ 2.72-3.18 [m, 10 H, ring protons and H(1,5)], 3.51 (s,

2 H, ArCH_2), 7.07-7.71 (m, 4 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 35.05 [C(2,4)], 46.95 [C(1,5)], 58.20 [C(6,8)], 60.69 (Ar*C*H_2), 94.43, 127.98, 130.23, 136.44, 137.64, 140.63 (Ar-*C*), 213.00 (*C*=O).

7-Benzyl-3-isopropyl-3,7-diazabicyclo[3.3.1]-nonan-9,9-diol Hydroperchlorate (**78a**)

A 50-mL Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. A solution of $HClO_4$ (60%, 0.92 g, 5.22 mmol) in $(H_3C)_2CHOH$ (2 mL) was added dropwise over 20 min to a stirred, cold (5°C, via ice water bath) solution of the ketone (**77a**, 0.5 g, 1.84 mmol) in dry ether (20 mL) which produced a light yellow gum. After decantation, the remaining material was dissolved in H_2O (35 mL), decolorized with Norit, filtered and refrigerated overnight at -10°C. Crystals formed and were filtered and then recrystallized (H_2O) to give 0.35 g (48.7%) of the salt **78a**; mp 143-144°C. IR (KBr) cm^{-1} 3400 (O-H), 3040 (Ar C-H), 2900, 2850 (C-H), 1630 (C=C), 1080 (Cl-O); ^{1}H NMR (DMSO-d_6) δ 1.17 (d, 6 H, CH_3), 1.95 [s, 2 H, H(1,5)], 2.82 (d, 2 H, ring protons), 2.97 (d, 2 H, ring protons), 3.23-3.57 [m, 5 H, ring protons and CH(CH_3)$_2$], 3.57 (s, 2 H, ArCH_2), 6.19 (s, 1 H, O*H*), 6.21 (s, 1 H, O*H*) 7.38 (m, 5 H, Ar-*H*); ^{13}C NMR (DMSO-d_6) ppm 16.24 (*C*H_3), 50.65 [C(2,4)], 53.79 [C(6,8)], 55.34 [*C*H(CH_3)$_2$], 60.40 (Ar*C*H_2), 89.43 [C(9)], 127.83, 128.53, 129.54, 136.53 (Ar-*C*); ^{15}N NMR (DMSO-d_6) ppm 48.93 [N(7)], 59.18 [N(3)]. Anal. Calcd. for $C_{17}H_{27}ClN_2O_6$: C, 52.24; H, 6.96. Found: C, 52.16; H, 6.88.

7-Benzyl-9-ethoxy-3-isopropyl-3,7-diazabicyclo-[3.3.1]nonan-9-ol Hydroperchlorate (**78b**)

A 50-mL Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. A solution of $HClO_4$ (60%, 0.9 g, 5.4 mmol) was added dropwise over 15 min to a stirred solution of the ketone (**77a**, 0.5 g, 1.80 mmol) in 50% C_2H_5OH/H_2O (30 mL).

Concentration (hot plate) of the solution (~20 mL) and then refrigeration (-10°C) gave an oily residue. Upon addition of CH_2Cl_2 (~1 mL) and after standing at RT, the oil dissolved and then crystallization occurred. Filtration and recrystallization (C_2H_5OH/ether, 8:2) afforded 0.16 g (21.7%) of white salt **78b**; mp 114-115°C. IR (KBr) cm^{-1} 3410 (O-H), 3080, 3055, 3025 (Ar C-H), 2975, 2930, 2880, 2845 (C-H), 1020-1170 (Cl-O); ^1H NMR (DMSO-d_6) δ 1.12 (t, 3 H, OCH_2CH_3), 1.16 (d, 6 H, CH_3), 2.14 [bs, 2 H, H(1,5)], 2.71 (d, 2 H, ring protons), 2.97 (d, 2 H, ring protons), 3.37 [m, 5 H, ring protons and $CH(CH_3)_2$], 3.48 (q, 2 H, OCH_2CH_3), 3.55 (s, 2 H, $ArCH_2$), 6.41 (s, 1 H, -OH), 7.38 (m, 5 H, Ar-H); ^{13}C NMR (DMSO-d_6) ppm 15.32 (q, OCH_2CH_3), 16.24 (q, CH_3), 35.85 [d, C(1,5)], 50.45 [t, C(2,4)], 53.41 [t, C(6,8)], 54.05 (t, OCH_2CH_3), 55.28 [d, $CH(CH_3)_2$], 60.26 (t, $ArCH_2$), 92.26 [s, C(9)], 127.73, 128.37, 129.38, 136.33 (Ar-C); ^{15}N NMR (DMSO-d_6) ppm 48.85 [N(7)], 59.14 [N(3)]. Anal. Calcd. for $C_{19}H_{31}ClN_2O_6$: C, 54.48; H, 7.46; N, 6.69. Found: C, 54.34; H, 7.34; N, 6.67.

7-Benzyl-3-isopropyl-3,7-diazabicyclo-[3.3.1]nonan-9-one Oxime (**78c**)

A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with a N_2 inlet and two glass stoppers. A mixture of the ketone (**77a**, 0.5 g, 1.84 mmol), hydroxylamine hydrochloride (0.26 g, 3.67 mmol) and sodium acetate trihydrate (0.62 g, 4.59 mmol) in C_2H_5OH (20 mL) was stirred at reflux under N_2 for 5 h. After removing (rotary evaporator) the solvent, the remaining solid was redissolved in H_2O (40 mL), and the pH was adjusted to 7.5 by the addition of $NaHCO_3$ (solid). Extracts ($HCCl_3$, 4 x 30 mL) of the solution were combined, dried (K_2CO_3, 2 h), filtered, and concentrated (rotary evaporator) to a viscous oil which solidified when refrigerated at -10°C. Recrystallization (hexane) of the crude solid gave 0.33 g (62.3%) of off-white crystalline oxime **78c**; mp 112.5-113.5°C. IR (KBr) cm^{-1} 3200 (O-H), 3100, 3040 (Ar C-H), 2970, 2940, 2900, 2850, 2800 (C-H), 1685 (C=N), 1605 (C=C); ^1H

NMR ($DCCl_3$) δ 1.05 (d, 6 H, CH_3, J = 6.6 Hz), 2.56-2.88 [m, 10 H, ring protons, CH_3, and H(5)], 3.51 (s, 2 H, $ArCH_2$), 3.78 [bs, 1 H, H(1)], 7.30 (m, 5 H, Ar-*H*), 9.13 (*OH*); ^{13}C NMR ($DCCl_3$) ppm 18.11 (CH_3), 18.22 (CH_3), 30.08 [C(1)], 36.62 [C(6)], 51.99 [C(2)], 52.87 [C(4)], 53.53 [$CH(CH_3)_2$], 57.06 [C(8)], 58.21 [C(8)], 58.21 [C(6)], 61.43 ($ArCH_2$), 126.94, 128.15, 128.86, 138.76 (Ar-*C*), 161.78 (*C*=N); ^{15}N NMR ($DCCl_3$) ppm 37.85 [N(7)], 42.05 [N(3)]. Anal. Calcd. for $C_{17}H_{25}N_3O$: C, 71.05; H, 8.77; N, 14.62. Found: C, 71.16; H, 8.81; N, 14.67.

7-Benzyl-3-isopropyl-3,7-diaza-
bicyclo[3.3.1]nonane (**79a**)

To a mixture of KOH pellets (85%, 13.6 g, 206 mmol) and the ketone (**79a**, 7.0 g, 25.7 mmol) in triethylene glycol (120 mL) was added hydrazine (95%, 3.47 g, 103 mmol) in one portion in a 200-mL, jacketed flask equipped with a magnetic stirrer, a heating mantle, a condenser, a lower take-off condenser with a N_2 inlet and two glass stoppers. A heating temperature of 200-210°C for 4 h under N_2 was produced by boiling tetralin (bp 207°C) in the jacket. Cooling of the solution to RT was followed by the addition of chilled water (150 mL). Combined extracts (ether, 4 x 60 mL) of the suspension were washed with 10% NaOH (60 mL) and saturated NaCl (60 mL), dried (Na_2SO_4, 1 h), filtered and concentrated (rotary evaporator then vacuum pump, overnight, RT/0.2 mm Hg) to a yellow oil (6.33 g, 95.3%). Analysis of compound **79a** showed no carbonyl stretch in the IR spectrum and thus was used without further purification.

3-Isopropyl-3,7-diazabicyclo-
[3.3.1]nonane (**79d**)

A 200-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with a N_2 inlet, and two glass stoppers. To a stirred mixture of amine (**79a**, 5.53 g, 21.4 mmol) and 10% Pd/C (0.64 g, 30 mg/mmol of amine) in

CH_3OH (80 mL) was added anhydrous HCO_2NH_4 (3,37 g, 53.5 mmol) in one portion. Stirring the mixture at reflux under N_2 for 30 min, cooling the new mixture to RT, and filtering through a Celite pad was followed by concentration (rotary evaporator) of the resulting solution to give a viscous oil. The oil was then dissolved in H_2O (80 mL) and the pH was adjusted to ~12 by the addition of 10% NaOH. Combined extracts (CCl_4, 4 x 40 mL) of the aqueous solution were dried (Na_2SO_4, 30 min), filtered and concentrated (rotary evaporator then vacuum pump, 10 min, RT/0.2 mm Hg) to give a yellow oil (3.35 g, 93.0%) which was used without further purification. IR (film) cm^{-1} 3315 (N-H), 2965, 2900, 2850, 2790, 2760, 2725 (C-H); ^1H NMR ($DCCl_3$) δ 1.01 (d, 6 H, CH_3, J = 6.7 Hz), 1.60-1.67 [m, 3 H, H(1,5) and H(9)], 1.79-1.84 [m, 1 H, H(9)], 2.53-2.59 [m, 3 H, $H(6,8)_{ax}$ and $CH(CH_3)_2$], 2.90-3.06 [m, 4 H, $H(6,8)_{eq}$, $H(2,4)_{ax}$ and $H(2,4)_{eq}$], 3.56 (bs, 1 H, N-*H*); ^{13}C NMR ($DCCl_3$) ppm 18.12 (CH_3), 30.04 [C(1,5)], 33.62 [C(9)], 52.86 [C(6,8)], 54.59 [$CH(CH_3)_2$], 54.65 [C(2,4)].

7-Benzyl-3-isopropyl-3,7-diazabicyclo-
[3.3.1]nonane Hydroperchlorate (**80a**)

A 125-mL Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a stirred, chilled (5°C) solution of the amine (**79a**, 0.84 g, 3.25 mmol) in dry ether (50 mL) was added dropwise a solution of $HClO_4$ (60%, 1.08 g, 6.50 mmol) in $(H_3C)_2CHOH$ (3 mL) over 20 min. After the mixture was stirred an additional hour, a white powdery material was filtered, and then dissolved in CH_3OH. Decolorizing with Norit, filtering, and concentrating (rotary evaporator) the solution gave a solid that was recrystallized (CH_3OH) to give 0.65 g (49.4%) of salt **80a**; mp 152.0-152.5°C. IR (KBr) cm^{-1} 3050, 3030 (Ar C-H), 2970, 2940, 2910, 2810 (C-H), 1090 (Cl-O); ^1H NMR (DMSO-d_6) δ 1.18 (d, 6 H, CH_3), 1.62 [d, 1 H, H(9), J = 12.4 Hz], 1.82 [d, 1 H, H(9), J = 12.7 Hz], 2.14 [bs, 2 H, H(1,5)], 2.47 (d, 2 H, $H(6,8)_{ax}$, J = 11.4 Hz], 3.11 [m, 4 H, $H(2,4)_{ax}$ and $H(6,8)_{eq}$], 3.32 [d, 2 H, $H(2,4)_{eq}$, J = 11.8 Hz], 3.47 [h, 1 H,

$CH(CH_3)_2$], 3.52 (s, 2 H, ArCH_2-), 7.30-7.46 (m, 5 H, Ar-*H*); ^{13}C NMR (DMSO-d_6) ppm 16.11 (q, CH_3), 27.24 [d, C(1,5)], 29.67 [t, C(9)], 52.85 [t, C(2,4), 56.00 [d, $CH(CH_3)_2$], 56.85 [t, C(6,8)], 61.15 (t, ArCH_2), 127.65, 128.35, 129.38, 136.35 (Ar-C); ^{15}N NMR (DMSO-d_6) ppm 50.90 [N(7)], 60.47 [N(3)]. Anal. Calcd. for $C_{17}H_{27}ClN_2O_4$: C, 56.90; H, 7.58; N, 7.81. Found: C, 56.70; H, 7.45; N, 7.84.

7-(4-Chlorobenzyl)-3-isopropyl-3,7-diazabicyclo-[3.3.1]nonane Hydroperchlorate (**80b**)

To a mixture of KOH pellets (85%, 1.72 g, 26.1 mmol) and the ketone (**77b**, 1.0 g, 3.26 mmol) in triethylene glycol (30 mL) was added hydrazine (95%, 0.44 g, 13.0 mmol) in one portion in a 150-mL, jacketed flask equipped with a magnetic stirrer, a heating mantle, a condenser, a lower take-off condenser with a N_2 inlet and three glass stoppers. A heating temperature of 200-210°C for 4 h under N_2 was produced by boiling tetralin (bp 207°C) in the jacket. Cooling of the solution to RT was followed by the addition of chilled water (40 mL). Combined extracts of the resulting suspension (ether, 4 x 30 mL) were washed with 10% NaOH (30 mL) and saturated NaCl (30 mL), dried (Na_2SO_4, 4 h), filtered and concentrated (rotary evaporator) to a light yellow oil which displayed no carbonyl stretch in the IR spectrum and was used without further purification. Dissolution of the oil in ether (60 mL) at ~5°C (via ice water bath) was followed by the dropwise addition of a solution of $HClO_4$ (60%, 0.68 g, 4.08 mmol) in $(H_3C)_2CHOH$ (1 mL) over 5 min. The resulting, precipitated solid was filtered and recrystallized (95% EtOH) to give 0.81 g (63.3%) of white crystals of **80b**; mp 140-141°C. IR (KBr) cm^{-1} 3060, 3020 (Ar C-H), 2970, 2920, 2830 (C-H), 1485 (C=C), 1085 (Cl-O), 790 (C-H out of plane, para); ^1H NMR (DMSO-d_6) δ 1.19 (d, 6 H, CH_3, J = 6.7 Hz), 1.61 [d, 1 H, H(9), J = 12.7 Hz], 1.82 [d, 1 H, H(9), J = 12.2 Hz], 2.14 [bs, 2 H, H(1,5)], 2.41 [bd, 2 H, $H(6,8)_{ax}$, J = 11.2 Hz], 3.04 [bd, 2 H, $H(6,8)_{eq}$, J = 11.1 Hz], 3.16 [bd, 2 H, $H(2,4)_{ax}$, J = 11.2 Hz], 3.34 [bd, 2 H, $H(2,4)_{eq}$, J = 11.7 Hz], 3.44-3.52 [m, 3 H, $CH(CH_3)_2$ and ArCH_2],

7.44 (s, 4 H, Ar-*H*); ^{13}C NMR (DMSO-d_6) ppm 16.10 (CH_3), 27.25 [C(1,5)], 29.60 [C(9)], 52.77 [C(2,4)], 56.25 [$CH(CH_3)_2$], 56.75 [C(6,8)], 60.42 (ArCH_2), 128.28, 131.27, 132.14, 135.72 (Ar-*C*); ^{15}N NMR (DMSO-d_6) ppm 50.34 [N(7)], 60.57 [N(3)]. Anal. Calcd. for $C_{17}H_{20}Cl_2N_2O_4$: C, 51.92; H, 6.66. Found: C, 51.74; H, 6.57.

7-(3,4-Dimethoxybenzyl)-3-isopropyl-3,7-diaza-bicyclo[3.3.1]nonane Hydroperchlorate (**80c**)

To a mixture of KOH pellets (85%, 2.38 g, 36 mmol) and the ketone (**77c**, 1.0 g, 3 mmol) in triethylene glycol (25 mL) was added hydrazine (95%, 1.01 g, 30 mmol) in one portion in a 70-mL, jacketed flask equipped with a magnetic stirrer, a heating mantle, a condenser, a lower take-off condenser with a N_2 inlet and two glass stoppers. A heating temperature of 150-160°C for 3.5 h was achieved by using tetralin (bp 207°C) in the jacket. After cooling to RT, the solution was diluted with cold H_2O (50 mL) and extracted with ether (3 x 40 mL). Combined extracts were washed with 10% NaOH (50 mL) and saturated NaCl (50 mL), dried (Na_2SO_4, overnight), filtered and concentrated (rotary evaporator) to afford a yellow oil (0.78 g). Dissolution of the oil in ether (50 mL) in a 125-mL Erlenmeyer flask with magnetic stirring and cooling (5°C, via ice water bath) was followed by the dropwise addition of a solution of $HClO_4$ (60%, 0.51 g, 3.06 mmol) over 10 min. Filtering the precipitate, washing the latter with ether (~50 mL), and then recrystallizing (95% EtOH) gave 0.79 g (62.9%) of white salt **80c**; mp 127.5-128.0°C (dec). IR (KBr) cm^{-1} 3020 (Ar C-H), 2955, 2930, 2840, 2815, 2790 (C-H), 1610 (C=C), 1090 (Cl-O); ^{1}H NMR (DMSO-d_6) δ 1.15 (d, 6 H, CH_3, J = 6.7 Hz), 1.64 [d, 1 H, H(9), J = 12.1 Hz], 1.80 [d, 1 H, H(9), J = 13.0 Hz], 2.14 [bs, 2 H, H(1,5)], 2.50 [d, 2 H, $H(6,8)_{ax}$, J = 10.4 Hz], 3.05-3.14 [m, 4 H, $H(6,8)_{eq}$ and $H(2,4)_{ax}$], 3.28 [d, 2 H, $H(2,4)_{eq}$, J = 11.6 Hz], 3.39 [m, 1 H, $CH(CH_3)$, J = 6.7 Hz], 3.49 (s, 2 H, ArCH_2), 3.75, 3.76 (two s, 6 H, OCH_3), 6.86-7.08 (m, 3 H, Ar-*H*); ^{13}C NMR (DMSO-d_6) ppm 16.25 (CH_3), 27.23 [C(1,5)], 29.79 [C(9)], 52.74 [C(2,4)], 55.31, 55.36 (OCH_3),

55.78 [*C*H(CH$_3$)$_2$], 56.85 [C(6,8)], 60.89 (Ar*C*H$_2$), 111.23, 113.01, 122.02, 128.00, 148.38, 148.66 (Ar-*C*); ^{15}N NMR (DMSO-d_6) ppm 52.22 [N(7)], 59.43 [N(3)]. Anal. Calcd. for $C_{19}H_{31}ClN_2O_6$: C, 54.48; H, 7.46. Found: C, 54.76; H, 7.61.

3-Isopropyl-3,7-diazabicyclo[3.3.1]-
nonane Hydroperchlorate (**80d**)

The same apparatus and procedure as for **80c** were employed except: (1) an increase in temperature to 200-210°C (boiling tetralin in jacket) was effected over 5 h; (2) the addition of $HClO_4$ (60%, 0.13 g, 0.75 mmol) was over 5 min; and (3) the salt **80d** was recrystallized from $(H_3C)_2CHOH$ to give 90 mg (11.2%) of white needles of **80d**; mp 188-189°C. IR (KBr) cm^{-1} 3510, 3450 (N-H), 2970, 2935, 2890, 2835 (C-H), 1090 (Cl-O); ^{1}H NMR (DMSO-d_6) δ 0.99 (d, 6 H, C*H*$_3$, J = 6.6 Hz), 1.60 [d, 1 H, H(9), J = 12.6 Hz], 1.82 [d, 1 H, H(9), J = 12.7 Hz], 2.00 [bs, 2 H, H(1,5)], 2.51 [m, 2 H, H(6,8)$_{ax}$], 2.72 [heptet, 1 H, C*H*(CH$_3$)$_2$, J = 6.6 Hz], 2.96 [d, 2 H, H(6,8)$_{eq}$, J = 11.2 Hz], 3.09 [d, 2 H, H(2,4)$_{ax}$, J = 12.3 Hz], 3.35 (bs, 2 H, N-*H*), 3.36 [d, 2 H, H(2,4)$_{eq}$, J = 12.7 Hz]; ^{13}C NMR (DMSO-d_6) ppm 17.29 (*C*H$_3$), 26.43 [C(1,5)], 30.04 [C(9)], 48.47 [C(6,8)], 52.71 [C(2,4)], 53.64 [*C*H(CH$_3$)$_2$]; ^{15}N NMR (DMSO-d_6) ppm 39.50 [N(7)], 48.33 [N(3)]. Anal. Calcd. for $C_{10}H_{21}ClN_2O_4$: C, 44.69; H, 7.88. Found: C, 44.58; H, 7.97.

7-Isopropyl-3-thia-7-azabicyclo[3.3.1]-
nonane Hydroperchlorate (**80e**)

To a mixture of KOH pellets (85%, 3.96 g, 60 mmol) and the ketone (**77d**, 1.0 g, 5 mmol) in triethylene glycol (25 mL) was added hydrazine (95%, 1.69 g, 50 mmol) in one portion in a 70-mL, jacketed flask equipped with a magnetic stirrer, a heating mantle, a condenser, a lower take-off condenser with a N_2 inlet and two glass stoppers. A heating temperature of 200-210°C for 5 h was produced by boiling tetralin (bp 207°C) in the

jacket. After cooling to RT, the solution was diluted with chilled water (100 mL) and extracted with ether (4 x 50 mL). Combined extracts were washed with 10% NaOH (50 mL) and saturated NaCl (50 mL), dried (Na_2SO_4, overnight), filtered and concentrated (rotary evaporator) to give a yellow oil (0.8 g). Dissolution of the oil in ether (50 mL) in a 125 mL flask [with magnetic stirring and cooling (5°C) with an external ice bath] was followed by dropwise addition of a solution of $HClO_4$ (60%, 1.08 g, 6.45 mmol) in $(H_3C)_2CHOH$ (3 mL) over 10 min. Stirring of the mixture an additional 10 min, filtering the precipitated salt, and then washing the latter with ether (~50 mL) gave an off-white solid. Dissolving the salt in hot 95% EtOH and decolorizing the solution with Norit, followed by filtering, and cooling, afforded 0.91 g (63.6%) of salt **80e** as white solid; mp 281-282.5°C. IR (KBr) cm^{-1} 3060 (N-H), 3000, 2960, 2935 (C-H), 1090 (Cl-O); ^1H NMR (DMSO-d_6) δ 1.28 (d, 6 H, CH_3), 1.76 [d, 1 H, H(9), J = 13.3 Hz], 1.91 [d, 1 H, H(9), J = 12.9 Hz], 2.35 [bs, 2 H, H(1,5)], 2.78 [bd, 2 H, $H(2,4)_{ax}$, J = 12.2 Hz], 3.14 [bd, 2 H, $H(2,4)_{eq}$, J = 13.6 Hz], 3.29-3.57 [m, 3 H, $H(6,8)_{ax}$ and C$H(CH_3)_2$], 3.62 [d, 2 H, $H(6,8)_{eq}$, J = 12.7 Hz], 9.07 (bs, 1 H, N-*H*); ^{13}C NMR (DMSO-d_6) ppm 16.19 (q, CH_3), 25.51 [d, C(1,5)], 28.35 [t, C(9)], 30.69 [t, C(2,4)], 52.36 [t, C(6,8)], 58.66 [d, $CH(CH_3)_2$]; ^{15}N NMR (DMSO-d_6) ppm 58.47 [N(7)]. Anal. Calcd. for $C_{10}H_{20}ClNO_4S$: C, 42.03; H, 7.05. Found: C, 42.10; H, 7.18.

7-(3-Iodobenzyl)-3-thia-7-azabicyclo[3.3.1]-
nonane Hydroperchlorate (**80f**)

To a mixture of KOH pellets (85%, 0.48 g, 7.2 mmol) and the ketone (**77e**, 0.224 g, 0.60 mmol) in triethylene glycol (10 mL) was added hydrazine (95%, 0.20 g, 6.0 mmol) in one portion in a 50-mL, jacketed flask equipped with a magnetic stirrer, a heating mantle, a condenser, a lower take-off condenser with a N_2 inlet and two glass stoppers. A heating temperature of 140-150°C for 4 h was produced by boiling *o*-xylene (bp 144°C) in the jacket. After cooling to RT, the solution was diluted with cold H_2O (30 mL) and was

then extracted with ether (4 x 30 mL). Combined extracts were washed with 10% NaOH (30 mL) and saturated NaCl (30 mL), dried (Na_2SO_4, overnight), filtered and concentrated (rotary evaporator) to give a yellow oil (209 mg). Dissolution of the oil in ether (25 mL) in a 50 mL flask [with magnetic stirring and cooling (5°C) using an external ice bath] was followed by the dropwise addition of a solution of $HClO_4$ (60%, 0.15 g, 0.87 mmol) in $(H_3C)_2CHOH$ (1 mL) over 10 min. Filtration of the precipitate and then washing the latter with ether (~50 mL) gave a solid which changed to an oil. This oil was dissolved in 95% EtOH, and the solution was decolorized with Norit, filtered and left to stand at RT overnight. White crystalline salt **80f** was collected (77 mg, 27.7%); mp 169.5-170°C. IR (KBr) cm^{-1} 3045 (Ar C-H), 2950, 2915, 2825 (C-H), 1570 (C=C), 1085 (Cl-O), 780, 765 (C-H out of plane, meta); ^1H NMR (DMSO-d_6) δ 1.81 [m, 2 H, H(9)], 2.36 [bs, 2 H, H(1,5)], 2.70 [d, 2 H, $H(2,4)_{ax}$, J = 13.6 Hz], 3.09 [d, 2 H, $H(2,4)_{eq}$, J = 13.7 Hz], 3.35 [m, 2 H, $H(6,8)_{ax}$], 3.58 [d, 2 H, $H(6,8)_{eq}$, J = 11.9 Hz], 4.22 (s, 2 H, ArCH_2), 4.24 (s, 1 H, ArCH_2), 7.32-8.03 (m, 4 H, Ar-*H*), 9.20 (bs, 1 H, N-*H*); ^{13}C NMR (DMSO-d_6) ppm 25.78 [C(1,5)], 28.48 [C(9)], 30.65, [C(2,4)], 56.53 [C(6,8)], 60.04 (ArCH_2), 95.40, 129.93, 131.08, 132.47, 138.18, 138.93 (Ar-*C*); ^{15}N NMR (DMSO-d_6) ppm 54.17 [N(7)]. Anal. Calcd. for $C_{14}H_{19}ClINO_4S$: C, 36.58; H, 4.17; N, 3.05; I, 27.60. Found: C, 36.87; H, 4.15; N, 2.99; I, 27.64.

3-Benzoyl-7-isopropyl-3,7-diaza-bicyclo[3.3.1]nonane (**81a**)

A three-necked, 50-mL, round-bottomed flask was equipped with a magnetic stirrer, an ice bath, a condenser with a N_2 inlet, a 10-mL addition funnel and a glass stopper. To a stirred solution of the amine (**79d**, 1.14 g, 6.77 mmol) and NaOH (10%, 6.80 g, 16.9 mmol) in CH_2Cl_2 (15 mL) in one portion. Dropwise addition of a solution of benzoyl chloride (1.05 g, 7.45 mmol) in CH_2Cl_2 (5 mL) to the mixture over 15 min under N_2 was followed by stirring an additional 2.75 h. Addition of H_2O (30 mL) was followed by

extraction with CH_2Cl_2 (3 x 25 mL). Combined extracts were dried (Na_2SO_4, 1 h), filtered, and concentrated (rotary evaporator) to give a yellow oil. Chromatography of the oil was performed over neutral alumina (100 g, 2.1 cm x 33 cm) with ethyl acetate as eluant. Fractions ($R_f = 0.70$) were combined and concentrated (rotary evaporator then vacuum pump, overnight, RT/0.2 mm Hg) to give 1.52 g (82.4%) of amide **81a** as an oil which was used without further purification. IR (film) cm^{-1} 3085, 3065, 3035 (Ar C-H), 2970, 2925, 2865, 2805, 2780, 2750 (C-H), 1635 (C=O), 730, 710 (C-H out of plane, mono); ^1H NMR ($DCCl_3$) δ 0.96 (d, 3 H, C*H*$_3$, J = 6.4 Hz), 1.07 (d, 3 H, C*H*$_3$, J = 6.6 Hz), 1.65-1.78, [m, 3 H, H(5) and H(9)], 1.97 [bs, 1 H, H(1)], 2.41 [d, 1 H, $H(4)_{ax}$, J = 10.3 Hz), 2.50 [d, 1 H, $H(6)_{ax}$, J = 11.0 Hz], 2.62 [m, 1 H, C*H*$(CH_3)_2$, J = 6.5 Hz], 2.72 [d, 1 H, $H(6)_{eq}$, J = 10.6 Hz], 3.03-3.07 [m, 2 H, $H(2)_{ax}$ and $H(4)_{eq}$], 3.30 [d, 1 H, $H(8)_{ax}$, J = 13.2 Hz], 3.74 [d, 1 H, $H(8)_{eq}$, J = 12.8 Hz], 4.77 [d, 1 H, $H(2)_{eq}$, J = 13.9 Hz], 7.28-7.41 (m, 5 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 16.30 (*C*H_3), 19.33 (*C*H_3), 29.06 [C(1)], 29.76 [C(5)], 32.29 [C(9)], 46.55 [C(2)], 52.19 [C(4)], 52.62 [C(8)], 54.34 [*C*H$(CH_3)_2$], 54.75 [C(6)], 126.75, 128.24, 128.67, 137.75 (Ar-*C*), 170.09 (*C*=O).

3-(4-Chlorobenzoyl)-7-isopropyl-3,7-diaza-bicyclo[3.3.1]nonane (**81b**)

A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, a 10-mL addition funnel and two glass stoppers. To a mixture of the amine (**79d**, 0.60 g, 3.57 mmol) in CH_2Cl_2 (5 mL) and 10% NaOH (3.58 g, 8.93 mmol) was added dropwise a solution of 4-chlorobenzoyl chloride (0.69 g, 3.92 mmol) in CH_2Cl_2 (5 mL) over 15 min. Stirring of the mixture was continued for an additional 3 h under N_2. An aqueous mixture, upon addition of H_2O (30 mL) was extracted (CH_2Cl_2, 4 x 25 mL). Combined extracts were dried (Na_2SO_4, 2 h), filtered and concentrated (rotary evaporator) to give a viscous yellow oil. Chromatography of the oil was performed on

neutral alumina (69 g, 1.7 cm x 30 cm) using 60:40 hexanes/ethyl acetate as eluant. Fractions (R_f = 0.41) were saved and concentrated (rotary evaporator then vacuum pump, overnight, RT/0.2 mm Hg) to give 0.86 g (80.4%) of off-white solid **81b**; mp 97-98°C. IR (KBr) cm^{-1} 3085, 3070 (Ar C-H), 2965, 2935, 2865, 2800, 2770 (C-H), 1630 (C=O); ^1H NMR ($CDCl_3$) δ 0.95 (d, 3 H, C*H*$_3$, J = 6.5 Hz), 1.05 (d, 3 H, C*H*$_3$, J = 6.4 Hz), 1.63-1.75 [m, 3 H, H(5) and H(9)], 1.97 [bs, 1 H, H(1)], 2.41 [bd, 1 H, $H(4)_{ax}$, J = 10.6 Hz], 2.50 [bd, 1 H, $H(6)_{ax}$, J = 11.2 Hz], 2.59 [heptet, 1 H, C*H*$(CH_3)_2$, J = 6.5 Hz], 2.71 [bd, 1 H, $H(6)_{eq}$, J = 11.0 Hz], 3.03-3.06 [m, 2 H, $H(2)_{ax}$ and $H(4)_{eq}$], 3.31 [bd, 1 H, $H(8)_{ax}$, J = 12.8 Hz], 3.71 [bd, 1 H, $H(8)_{eq}$, 13.1 Hz], 4.77 [bd, 1 H, $H(2)_{ax}$, J = 13.2 Hz], 7.27-7.37 (m, 4 H, Ar-*H*); ^{13}C NMR ($CDCl_3$) ppm 16.37, 19.35 (*C*H_3), 29.07 [C(1)], 29.80 [C(5)], 32.29 [C(9)], 46.68 [C(2)], 52.22 [C(4)], 52.56 [C(8)], 54.38 [*C*H$(CH_3)_2$], 54.79 [C(6)], 128.35, 128.51, 134.67, 136.11 (Ar-*C*), 169.03 (*C*=O). Anal. Calcd. for $C_{17}H_{23}ClN_2O$: C, 66.55; H, 7.56. Found: C, 66.45; H, 7.71.

3-(3,4-Dimethoxybenzoyl)-7-isopropyl-
3,7-diazabicyclo[3.3.1]nonane (**81c**)

A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, a 10-mL addition funnel and two glass stoppers. To a mixture of the amine (**79d**, 0.60 g, 3.57 mmol) in CH_2Cl_2 (5 mL) and 10% NaOH (3.58 g, 8.93 mmol) was added dropwise a solution of 3,4-dimethoxybenzoyl chloride (0.80 g, 3.92 mmol) in CH_2Cl_2 (10 mL) over 15 min. Stirring of the mixture was continued for an additional 3 h under N_2. An aqueous mixture, upon addition of H_2O (30 mL) was extracted (CH_2Cl_2, 4 x 25 mL). Combined extracts were dried (Na_2SO_4, 2 h), filtered and concentrated (rotary evaporator) to give a viscous yellow oil. Chromatography of the oil was performed on neutral alumina (74 g, 1.7 cm x 32 cm) using 60:40 ethyl acetate/-hexanes as eluant. Fractions (R_f = 0.31) were saved and concentrated (rotary evaporator then vacuum pump, overnight, RT/0.2 mm Hg) to give 0.87 g (73.1%) of off-white solid

81c; mp 67.5-69.5°C. IR (KBr) cm^{-1} 3055 (Ar C-H), 2950, 2915, 2845, 2820, 2770, 2750, 2710 (C-H), 1625 (C=O); ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, C*H*$_3$, J = 6.4 Hz), 1.06 (d, 3 H, C*H*$_3$, J = 6.5 Hz), 1.62-1.75 [m, 3 H, H(5) and H(9)], 1.96 [bs, 1 H, H(1)], 2.43 [bd, 1 H, $H(4)_{ax}$, J = 9.7 Hz], 2.51 [bd, 1 H, $H(6)_{ax}$, J = 10.5 Hz], 2.62 [heptet, 1 H, C*H*$(CH_3)_2$, J = 6.4 Hz], 2.74 [bd, 1 H, $H(6)_{eq}$, J = 9.9 Hz], 3.00-3.09 [m, 2 H, $H(4)_{eq}$ and $H(2)_{ax}$], 3.32 [bd, 1 H, $H(8)_{ax}$, J = 13.2 Hz], 3.83-3.94 [m, 7 H, $H(8)_{eq}$ and OC*H*$_3$], 4.77 [bd, 1 H, $H(2)_{eq}$, J = 13.3 Hz], 6.84-6.94 (m, 3 H, Ar-*H*); ^{13}C NMR ($CDCl_3$) ppm 16.46, 19.15 (*C*H_3), 29.13 [C(1)], 29.86 [C(5)], 32.36 [C(9)], 46.71 [C(2)], 52.25 [C(4)], 52.65 [C(8)], 54.35 [*C*$H(CH_3)_2$], 54.68 [C(6)], 55.88, 55.93 (O*C*H_3), 110.50, 119.64, 130.23, 148.78, 149.39 (Ar-*C*), 169.90 (*C*=O). Anal. Calcd. for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49. Found: C, 68.58; H, 8.47.

7-Isopropyl-3-(3,4,5-trimethoxybenzoyl)-
3,7-diazabicyclo[3.3.1]nonane (**81d**)

A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, a 10-mL addition funnel and two glass stoppers. To a mixture of the amine (**79d**, 0.60 g, 3.57 mmol) in CH_2Cl_2 (5 mL) and 10% NaOH (3.58 g, 8.93 mmol) was added dropwise a solution of 3,4,5-trimethoxybenzoyl chloride (0.92 g, 3.92 mmol) in CH_2Cl_2 (5 mL) over 15 min. Stirring of the mixture was continued for an additional 3 h under N_2. An aqueous mixture, upon addition of H_2O (30 mL) was extracted (CH_2Cl_2, 4 x 25 mL). Combined extracts were dried (Na_2SO_4, 2 h), filtered and concentrated (rotary evaporator) to give a viscous yellow oil. Chromatography of the oil was performed on neutral alumina (74 g, 1.7 cm x 32 cm) using 60:40 ethyl acetate/-hexanes as eluant. Fractions (R_f = 0.34) were saved and concentrated (rotary evaporator then vacuum pump, overnight, RT/0.2 mm Hg) to give 1.02 g (79.1%) of off-white solid **81d**; mp 67.5-69.5°C. IR (KBr) cm^{-1} 3055 (Ar C-H), 2985, 2955, 2910, 2890, 2780 (C-H), 1620 (C=O); ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, C*H*$_3$, J = 6.5 Hz), 1.09 (d, 3 H,

C*H*$_3$, J = 6.7 Hz), 1.64-1.79 [m, 3 H, H(5) and H(9)], 2.05 [bs, 1 H, H(1)], 2.44 [bd, 1 H, H(4)$_{ax}$, J = 10.6 Hz], 2.57 [bd, 1 H, H(6)$_{ax}$, J = 10.8 Hz], 2.66 [heptet, 1 H, C*H*(CH$_3$)$_2$, J = 6.6 Hz], 2.71 [bd, 1 H, H(6)$_{eq}$, J = 11.0 Hz], 3.02-3.07 [m, 2 H, H(4)$_{eq}$ and H(2)$_{ax}$], 3.31 [bd, 1 H, H(8)$_{ax}$, J = 13.2 Hz], 3.80-3.92 [m, 10 H, H(8)$_{eq}$ and OC*H*$_3$], 4.77 [bd, 1 H, H(2)$_{eq}$, J = 13.5 Hz], 7.29 (s, 2 H, Ar-*H*); ^{13}C NMR (CDCl$_3$) ppm 15.87, 19.42 (*C*H$_3$), 29.02 [C(1)], 29.78 [C(5)], 32.35 [C(9)], 46.64 [C(2)], 51.73 [C(4)], 52.48 [C(8)], 54.39 [*C*H(CH$_3$)$_2$], 54.95 [C(6)], 56.13, 60.86 (O*C*H$_3$), 103.83, 133.32, 133.21, 138.22, 153.21 (Ar-*C*), 169.66 (*C*=O). Anal. Calcd. for C$_{20}$H$_{30}$N$_2$O$_4$: C, 66.27; H, 8.34. Found: C, 66.04; H, 8.32.

3-Benzenesulfonyl-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (**81e**)

A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, an ice bath, a 10-mL addition funnel and a glass stopper. To a stirred, ice cold (5°C) mixture of the amine (**79d**, 1.03 g, 6.12 mmol) and NaOH pellets (97%, 0.76 g, 18.4 mmol) in H_2O (7 mL) and CH_2Cl_2 (5 mL) was added dropwise a solution of benzenesulfonyl chloride (2.16 g, 12.2 mmol) in CH_2Cl_2 (5 mL) over 30 min. Stirring of the mixture was continued for an additional 17.5 h at RT. The reaction mixture was then partitioned between H_2O (30 mL) and CH_2Cl_2 (30 mL) followed by basification (pH~12) of the aqueous phase. Extracts (CH_2Cl_2, 3 x 30 mL) of the remaining water layer were combined with the initial organic layer. The solution was washed with 10% NaOH (30 mL) then saturated NaCl (30 mL), dried (Na_2SO_4, overnight), filtered and concentrated (rotary evaporator) to give an orange viscous oil. Chromatography of the oil was performed on silica gel (39 g, 1.6 cm x 62 cm) using 10% CH_3OH/CH_2Cl_2. Fractions (R_f = 0.44) were saved, concentrated (rotary evaporator) and re-eluted on neutral alumina (90 g, 2.5 cm x 18 cm) employing ethyl acetate as eluant. Fractions (R_f = 0.53) were saved and concentrated (rotary evaporator). A colored impurity persisted which was

removed by once again eluting over silica gel (21 g, 1.6 cm x 33 cm) using 5% CH_3OH/-CH_2Cl_2 as eluant. Fractions (Rf = 0.34) were combined and concentrated (rotary evaporator then vacuum pump, overnight, RT/0.2 mm Hg) to give 0.54 g (28.6%) of white solid **81e**; mp 85.5-86.5°C. IR (KBr) cm^{-1} 3060 (Ar C-H), 2960, 2910, 2890, 2865, 2820 (C-H), 1585 (C=C), 1340, 1170 (S=O), 760, 720 (C-H out of plane, mono); ^1H NMR (DMSO-d_6) δ 0.88 (d, 6 H, CH_3, J = 6.5 Hz), 1.40 [bs, 2 H, H(9)], 1.94 [bs, 2 H, H(1,5)], 2.35 [bd, 2 H, $H(6,8)_{ax}$, J = 10.3 Hz], 2.53 [heptet, 1 H, C$H(CH_3)_2$, J = 6.5 Hz], 2.69 [bd, 2 H, $H(6,8)_{eq}$, J = 10.3 Hz], 2.89 [dd, 2 H, $H(2,4)_{ax}$, J = 11.2 Hz, J' = 4.5 Hz], 3.36 [d, 2 H, $H(2,4)_{eq}$, J = 10.9 Hz], 7.58-7.75 (m, 5 H, Ar-*H*); ^{13}C NMR (DMSO-d_6) ppm 17.57 (*C*H_3), 27.39 [C(1,5)], 28.95 [C(9)], 48.88 [C(2,4)], 52.66 [C(6,8)], 53.42 [*C*H$(CH_3)_2$], 126.90, 129.01, 132.36, 136.79 (Ar-*C*). Anal. Calcd. for $C_{16}H_{24}N_2O_2S$: C, 62.31; H, 7.85. Found: C, 62.48; H, 7.69.

3-Benzoyl-7-isopropyl-3,7-diazabicyclo-
[3.3.1]nonane Hydroperchlorate (**82a**)

A 125-mL Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a chilled (5°C), stirred solution of the amide (**81a**, 1.52 g, 5.58 mmol) in ether (60 mL) was added dropwise a solution of $HClO_4$ (60%, 1.17 g, 6.98 mmol) over 10 min followed by stirring for an additional 10 min. Filtration gave salt **82a** as a white solid which was washed with dry ether (50 mL), stirred with hot CH_3OH (30 mL), then refrigerated (overnight, -10°C), filtered and dried (vacuum pump, overnight, 61°C/0.2 mm Hg) to afford 1.90 g (91.3%) of pure salt **82a**; mp 226-227°C (dec): IR (KBr) cm^{-1} 3150 (N-H), 2990, 2960, 2935, 2920, 2885 (C-H), 1635 (C=O), 1100 (Cl-O), 740, 710 (C-H out of plane, mono); ^1H NMR [$(D_3C)_2CO$] δ 1.55 (d, 6 H, CH_3, J = 6.6 Hz), 1.97 [bd, 1 H, H(9), J = 13.0 Hz], 2.18 [bd, 1 H, H(9), J = 13.2 Hz], 2.51 [bs, 2 H, H(1,5)], 3.30 [bd, 2 H, $H(6,8)_{ax}$, J = 13.2 Hz], 3.65 [m, 2 H, $H(2,4)_{ax}$], 3.83 [h, 1 H, -C$H(CH_3)_2$, J = 6.8 Hz], 3.94 [bd, 2 H, $H(6,8)_{eq}$, J = 12.3 Hz], 4.23 [bd, 2 H, $H(2,4)_{eq}$, J = 13.2 Hz],

7.45-7.50 (m, 5 H, Ar-*H*), 7.85 (bs, 1 H, N-*H*); ^{13}C NMR (DMSO-d_6, 80°C) ppm 16.34 (CH_3), 26.69 [C(1,5)], 27.62 [C(9)], 48.80 [C(2,4)], 52.31 [C(6,8)], 59.91 [$CH(CH_3)_2$], 127.05, 128.30, 129.40, 136.40 (Ar-*C*), 172.86 (*C*=O). Anal. Calcd. for $C_{17}H_{25}ClN_2O_5$: C, 54.76; H, 6.76. Found: C, 54.43; H, 6.78.

3-(3,4-Dimethoxybenzoyl)-7-isopropyl-3,7-diaza-bicyclo[3.3.1]nonane Hydroperchlorate (**82c**)

A 50-mL Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a chilled (5°C), stirred solution of the amide (**81c**, 0.30 g, 0.90 mmol) in ether (30 mL) was added dropwise a solution of $HClO_4$ (60%, 0.18 g, 1.08 mmol) in $(H_3C)_2CHOH$ (1 mL) over 10 min. A white precipitate resulted which was filtered and then stirred in hot CH_3OH (10 mL) for 20 min; the mixture was filtered and dried (Abderhalden, P_2O_5, overnight, RT/0.2 mm Hg) to give 0.27 g (69.2%) of white solid **82c**; mp 235-236°C (dec). IR (KBr) cm^{-1} 3130 (N-H), 3010 (Ar C-H), 2975, 2945, 2920 (C-H), 1635 (C=O), 1095 (Cl-O); ^{1}H NMR (DMSO-d_6, 80°C) δ 1.33 (d, 6 H, C*H*$_3$, J = 6.7 Hz), 1.74 [bd, 1 H, H(9), J = 12.8 Hz], 1.91 [bd, 1 H, H(9), J = 13.2 Hz], 2.27 [bs, 2 H, H(1,5)], 3.12 [bd, 2 H, H(6,8)$_{ax}$, J = 13.7 Hz], 3.19-3.28 [m, 2 H, H(2,4)$_{ax}$], 3.42-3.56 [m, 3 H, H(6,8)$_{eq}$ and C*H*(CH$_3$)$_2$], 3.78, 3.81 (two s, 6 H, OC*H*$_3$), 3.97 [bd, 2 H, H(2,4)$_{eq}$, J = 13.6 Hz], 6.94-7.03 (m, 3 H, Ar-*H*), 7.81 (bs, 1 H, N-*H*); ^{13}C NMR (DMSO-d_6, 80°C) ppm 16.34 (CH_3), 26.81 [C(1,5)], 27.80 [C(9)], 49.06 [C(2,4)], 52.40 [C(6,8)], 55.88, 55.92 (OCH_3), 59.97 [$CH(CH_3)_2$], 111.85, 112.10, 120.44, 128.68, 148.74, 150.26 (Ar-*C*), 172.97 (*C*=O). Anal. Calcd. for $C_{19}H_{29}ClN_2O_7$: C, 52.72; H, 6.75. Found: C, 52.35; H, 6.77.

7-Benzoyl-3-thia-7-azabicyclo[3.3.1]nonane (**83**)

A 10-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, an ice bath, a condenser with a N_2 inlet, and a glass stopper. To a chilled (5°C) solution of

NaOH pellets (0.1 g, 2.38 mmol) in H_2O (1.7 mL) was added a solution of the amine (**89**, 0.17 g, 1.19 mmol) in CH_2Cl_2 (1 mL). This was followed by the dropwise addition of a solution of benzoyl chloride (0.2 g, 1.43 mmol) over ~5 min. After stirring for 30 min at 0-5°C, 30 min at RT, and then 15 min over a steam bath, the mixture was diluted with H_2O (15 mL), and the mixture was extracted (CH_2Cl_2, 3 x 15 mL). Combining the extracts, drying (Na_2SO_4, overnight), filtering, and concentrating (rotary evaporator) the solution gave a viscous yellow oil. Chromatography of the oil on alumina (38 g, 2.4 cm x 17 cm) employed ethyl acetate as eluant and afforded amide **83** (R_f = 0.47) as white crystals (157 mg, 53.3%); mp 95-96°C. IR (KBr) cm^{-1} 3065, 3045 (Ar C-H), 3000, 2985, 2940, 2910, 2855, 2835 (C-H), 1635 (C=O), 745, 720 (C-H out of plane, mono); ^1H NMR ($DCCl_3$) δ 1.78-1.93 [m, 3 H, H(9) and H(1)], 2.15 [bs, 1 H, H(5)], 2.39 [d, 1 H, $H(4)_{ax}$, J = 13.9 Hz], 2.77 [d, 1 H, $H(6)_{ax}$, J = 12.3 Hz], 3.12-3.21 [m, 3 H, $H(4)_{eq}$ and $H(6)_{eq}$], 3.41 [d, 1 H, $H(2)_{ax}$, J = 12.8 Hz], 3.89 [d, 1 H, $H(2)_{eq}$, J = 13.4 Hz], 4.98 [d, 1 H, $H(8)_{eq}$, J = 13.1 Hz], 7.38-7.44 (m, 5 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 26.53 [C(1)], 26.87 [C(5)], 31.73 [C(2)], 31.78 [C(9)], 32.34 [C(4)], 46.07 [C(8)], 52.12 [C(6)], 126.46, 128.41, 128.83, 137.35 (Ar-*C*), 170.38 (*C*=O). Anal. Calcd. for $C_{14}H_{17}NOS$: C, 67.98; H, 6.93. Found: C, 68.01; H, 7.07.

7-Benzyl-3-thia-7-azabicyclo-
[3.3.1]nonane 3-oxide.(**84**)

A 200-mL, round-bottomed flask was equipped with a magnetic stirrer, an ice bath and a condenser with a N_2 inlet. To a stirred, chilled (5°C) solution of the amine (**10a**, 1.4 g, 6 mmol) in CH_3OH (60 mL) was added dropwise a solution of $NaIO_4$ (1.35 g, 6.3 mmol) in H_2O (15 mL) over 10 min. After stirring for 1 h, the suspension was filtered and washed with CH_3OH (50 mL); the filtrate was concentrated (rotary evaporator) to a residue which was partitioned between CH_2Cl_2 and H_2O (40 mL each). Additional extracts ($HCCl_3$, 3 x 40 mL) of the aqueous layer were combined with the initial extract,

and the solution was dried (Na_2SO_4, overnight) and concentrated (rotary evaporator) to afford an oil which solidified upon standing. Recrystallization ($HCCl_3$/pentane) of the solid using a diffusion chamber gave 1.15 g (76.9%) of rhombic crystals of **84**; mp 140-141°C. IR (KBr) cm^{-1} 3085, 3065, 3030 (Ar C-H), 2955, 2920, 2895, 2815 (C-H), 1495, (C=C), 1020 (S=O), 740, 705 (C-H out of plane, mono); ^1H NMR ($DCCl_3$) δ 1.59 [bd, 1 H, H(9), J = 13.3 Hz], 1.86 [bd, 1 H, H(9), J = 13.2 Hz], 2.20 [d, 2 H, $H(2,4)_{ax}$, J = 11.7 Hz], 2.37 [bs, 2 H, H(1,5)], 2.62 [d, 2 H, $H(6,8)_{ax}$, J = 12.0 Hz], 2.78 [d, 2 H, $H(2,4)_{eq}$, J = 11.8 Hz], 3.51 [d, 2 H, $H(6,8)_{eq}$, J = 11.7 Hz], 3.55 (s, 2 H, ArCH_2), 7.25-7.39 (m, 5 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 31.86 [t, C(9)], 32.59 [d, C(1,5)], 57.42 [t, C(2,4)], 58.59 [t, C(6,8)], 62.88 (ArCH_2), 127.20, 128.39, 129.12, 137.67 (Ar-*C*); ^{15}N NMR ($DCCl_3$) ppm 49.37 [N(7)]. Anal. Calcd. for $C_{14}H_{19}NOS$: C, 67.43; H, 7.68. Found: C, 67.61; H, 7.73.

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane-
3-oxide Hydroperchlorate (**85**)

A 50-mL Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a stirred, chilled (5°C) solution of the sulfoxide (**84**, 0.47 g, 1.88 mmol) in ether (20 mL) and $(H_3C)_2CHOH$ (3 mL) was added dropwise a solution of $HClO_4$ (60%, 0.63 g, 3.75 mmol) in $(H_3C)_2CHOH$ (3 mL) over 10 min. Filtering of the precipitate formed, washing the latter with ether (~50 mL) and then recrystallizing (95% EtOH) the solid gave 0.51 g (78.1%) of crystalline salt **85**; mp 137-138°C. IR (KBr) cm^{-1} 3090 (Ar C-H), 2970, 2950 (C-H), 1465 (C=C), 1095 (Cl-O), 745, 705 (C-H out of plane, mono); ^1H NMR (CD_3OD) δ 1.70 [bd, 1 H, H(9), J = 14.0 Hz], 2.01 [bd, 1 H, H(9), J = 13.9 Hz], 2.61 [bd, 2 H, $H(2,4)_{ax}$, J = 11.8 Hz], 2.69 [bs, 2 H, H(1,5)], 3.06 [bd, 2 H, $H(2,4)_{eq}$, J = 11.8 Hz], 3.36 [bd, 2 H, $H(6,8)_{ax}$, J = 13.1 Hz], 3.94 (s, 2 H, ArCH_2), 4.19 [bd, 2 H, $H(6,8)_{eq}$, J = 12.9 Hz], 7.35-7.42 (m, 5 H, Ar-*H*); ^{13}C NMR (CD_3OD) ppm 30.80 [C(9)], 36.27 [C(1,5)], 53.94 [C(2,4)], 58.56 [C(6,8)], 61.07 (ArCH_2), 129.43,

129.78, 131.49, 135.29 (Ar-*C*); ^{15}N NMR (DMSO-d_6) ppm 56.45 [N(7)]. Anal. Calcd. for $C_{14}H_{20}ClNSO_5$: C, 48.06; H, 5.76. Found: C, 47.84; H, 5.74.

3,7-Dibenzyl-3,7-diazabicyclo-
[3.3.1]nonan-2-one (**86**)

A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, a 50-mL addition funnel and a glass stopper. To a solution of $NaIO_4$ (2.49 g, 11.62 mmol) in H_2O (22.4 mL) was added RuO_2xH_2O (0.1 g) which produced a dark green solution. After the apparatus was flushed with N_2, a solution of the amine (**6j**, 0.89 g, 2.9 mmol) in CCl_4 (16 mL) was added in one portion to produce a blackened mixture. The mixture was stirred at RT for 72 h and then the organic layer was separated. Further extraction of the aqueous phase was effected with CCl_4 (20 mL) followed by $HCCl_3$ (3 x 20 mL). Combined extracts were treated with isopropyl alcohol (3 mL) to destroy excess oxidant and were then filtered through a Celite pad. After washing the extracts with 5% sodium thiosulfate (50 mL), the extracts were dried (Na_2SO_4, overnight), filtered and concentrated (rotary evaporator) to a yellow oil. Elution of the oil on neutral alumina (84 g, 2.4 cm x 19 cm) using first ether (50 mL) and then ethyl acetate (150 mL) as eluants gave a solid material (R_f = 0.60, ethyl acetate). This material was recrystallized from ether (6 mL) which was first refrigerated to -10°C for 2 h then placed in a diffusion chamber of pentane for 1 h. Filtration afforded (0.27 g, 28.9%) of the lactam **86**; mp 96.0-96.5°C. IR (KBr) cm^{-1} 3070, 3050, 3020 (Ar C-H), 2945, 2920, 2855, 2785, 2760 (C-H), 1645 (C=O), 1600 (C=C) 740, 710 (C-H out of plane, mono); ^1H NMR ($DCCl_3$) δ 1.69 [d, 1 H, H(9), J = 12.7 Hz], 1.88 [d, 1 H, H(9), J = 12.7 Hz], 2.05-2.09 [m, 2 H, ring proton and H(1)], 2.24 (dd, 1 H, ring proton, J = 10.74 Hz, J' = 2.23 Hz), 2.66 [m, 2 H, ring proton and H(5)], 3.08 [d, 1 H, ring proton, J = 11.8 Hz], 3.25-3.36 [m, 3 H, ring proton and H(11)], 3.59 [d, 1 H, H(11), J = 13.2 Hz], 4.24 [d, 1 H, H(10), J = 14.8 Hz], 5.06 [d, 1 H, H(10), J = 14.7 Hz], 7.08-7.38

(m, 10 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 27.94 [C(9)], 28.07 [C(5)], 39.07 [C(1)], 49.84 [C(10)], 51.60 [C(4)], 57.07 [C(8)], 59.03 [C(6)], 62.70 [C(11)], 126.88, 127.14, 128.17, 128.40, 128.49, 128.72, 137.39, 138.13 (Ar-*C*), 172.77 (*C*=O). Anal. Calcd. for $C_{21}H_{24}N_2O$: C, 78.72; H, 7.55. Found: C, 78.39; H, 7.78.

3-Benzoyl-7-benzyl-3,7-diazabicyclo-
[3.3.1]nonan-9-one (**87**)

A 200-mL, three-necked, round-bottomed flask was equipped with magnetic stirrer, a heating mantle, a condenser with N_2 inlet, a 50-mL addition funnel and a glass stopper. A mixture containing benzylamine (5.36 g, 50 mmol), paraformaldehyde (3.15 g, 105 mmol) and CH_3OH (35 mL) was made acidic with the addition of glacial acetic acid (3.0 g, 50 mmol). Stirring of the mixture under N_2 at reflux for 10 min was followed by the dropwise addition of *N*-benzoyl-4-piperidinone (**4i**, 10.16 g, 50 mmol) and glacial acetic acid (3.0 g, 50 mmol) in CH_3OH (40 mL) over 1 h. This mixture was stirred at reflux for an additional 23 h, and then the solvent was removed (rotary evaporator) to give a dark viscous oil. This oil was partioned between H_2O (150 mL) and 50/50 ether/Skelly B (150 mL), the latter being discarded. Chilling (10°C, via ice water bath) of the aqueous mixture followed by basification (pH~12) with KOH pellets (85%, 6.6 g, 100 mmol) produced a suspension which was extracted with CH_2Cl_2 (3 x 75 mL). Combined extracts were dried (Na_2SO_4, overnight), filtered and concentrated (rotary evaporator) to give a crude dark gum. Chromatography of the material was performed on silica gel (200 g, 2.9 cm x 97 cm) using 1.5% CH_3OH/CH_2Cl_2 as eluant. Fractions (R_f = 0.39) were combined, concentrated (rotary evaporator then vacuum pump, overnight, RT/0.2 mm Hg) to give 6.41 g (38.3%) of **87** as a light yellow low-melting solid; mp 22-24°C. IR (film) cm^{-1} 3060, 3005 (Ar C-H), 2940, 2910, 2860, 2805, 2765 (C-H), 1740 (C=O, ketone), 1635 (C=O, amide); ^1H NMR ($DCCl_3$) δ 2.34 [bs, 1 H, H(5)], 2.54 [bs, 1 H, H(1)], 2.59-2.70 (m, 3 H, ring protons), 3.57-3.66 (ArCH_2), 4.13 (bd, 1 H, ring proton, J = 13.1

Hz), 5.18 (bd, 1 H, ring proton, J = 13.3 Hz], 7.26-7.44 (m, 10 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 47.45 [C(1)], 47.61 [C(5)], 48.08 [C(2)], 53.51 [C(4)], 58.99 [C(8)], 59.17 [C(6)], 62.13 (Ar*C*H_2), 126.97, 127.46, 128.52, 129.06, 129.53, 136.10, 136.95 (Ar-*C*), 170.57 (*C*=O, amide), 212.62 (*C*=O, ketone). Anal. Calcd. for $C_{21}H_{22}N_2O_2 \cdot 1/2$ H_2O: C, 73.45; H, 6.75. Found: C, 73.68; H, 6.69.

3-Benzoyl-7-benzyl-3,7-diazabicyclo-
[3.3.1]nonane hydroperchlorate (**88**)

A 50-mL, Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a chilled (5°C), stirred solution of the amide (**33k**, 0.50 g, 1.60 mmol) in ether (30 mL) was added dropwise a solution of $HClO_4$ (60%, 0.33 g, 1.95 mmol) in $(CH_3)_2CHOH$ (1 mL) over 5 min. Stirring the mixture an additional 5 min, filtering, washing with ice cold ether (50 mL), and then drying (vacuum pump, 12 h/110°C/0.2 mm Hg) gave 0.64 g (97.6%) of the salt **88**; mp 248-249°C (dec). IR (KBr) cm^{-1} 3135 (N-H), 2980, 2945, 2905, 2870 (C-H), 1625 (C=O), 1085 (Cl-O); ^{1}H NMR (DMSO-d_6, 80°C) δ 1.77 [bd, 1 H, H(9), J = 13.1 Hz], 1.86 [bd, 1 H, H(9), J = 13.2 Hz], 3.09-3.13 [bd, 2 H, $H(6,8)_{ax}$ J = 13.0 Hz], 3.25-3.33 [m, 4 H, $H(6,8)_{eq}$ and $H(2,4)_{ax}$], 3.89 [m, 2 H, $H(2,4)_{eq}$,. J = 11.9 Hz], 4.33 (bs, 2 H, ArCH_2), 7.27-7.65 (m, 10 H, Ar-*H*), 8.03 (bs, 1 H, N-*H*); ^{13}C NMR (DMSO-d_6, 80°C) ppm 26.84 [C(1,5)], 28.13 [C(9)], 48.87 [C(2,4)], 56.34 [C(6,8)], 61.60 (Ar*C*H_2), 126.90, 128.24, 129.04, 129.30, 129.53, 129.89, 131.05, 136.12 (Ar-*C*), 172.90 (*C*=O). Anal. Calcd. for $C_{21}H_{25}ClN_2O_5$: C, 59.93; H, 5.99. Found: C, 60.11; H, 6.24.

3-Thia-7-azabicyclo[3.3.1]nonane (**89**)

A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with a N_2 inlet and two glass stoppers. In one portion, anhydrous HCO_2NH_4 (1.11 g, 17.1 mmol) was added under N_2 to a mixture of the amine

(**10a**, 0.90 g, 3.86 mmol) and 10% Pd/C (0.90 g) in anhydrous CH_3OH (25 mL). With stirring, the mixture was brought to reflux for 30 min, filtered through a Celite pad on a fritted funnel (which was washed thoroughly with CH_2Cl_2), and then concentrated to give a gummy oil with suspended solid. This material was again dissolved in CH_2Cl_2 (~15 mL), and the suspension was filtered to remove any unreacted ammonium formate. The filtrate was then concentrated (rotary evaporator) to near saturation and placed in a diffusion chamber of ether overnight. Crude amine became an oil; however, the mother liquor, containing predominantly starting material, could be decanted. Chromatography of the oil employed a gradient elution of CH_3OH/CH_2Cl_2 (300 mL of 10% CH_3OH/CH_2Cl_2, 50 mL of 20% CH_3OH/CH_2Cl_2, 100 mL of 50% CH_3OH/CH_2Cl_2, and 100 mL of CH_3OH) on silica gel (35 g, 1.5 cm x 62 cm) and afforded 0.32 g (56.9%) of amine **89** (R_f = 0.11, 10% CH_3OH/CH_2Cl_2) as a light, gummy solid which was used without further purification. ^1H NMR ($DCCl_3$) δ 1.84, 2.04 [two bd, 2 H, H(9)], 2.31 [bs, 2 H, H(1,5)], 2.80 [bd, 2 H, $H(2,4)_{ax}$, J = 12.3 Hz], 3.20 [bd, 2 H, $H(2,4)_{eq}$, J = 13.7 Hz], 3.45 [m, 2 H, $H(6,8)_{ax}$], 3.73 [bd, 2 H, $H(6,8)_{eq}$, J = 13.2 Hz], 7.59 (bs, 1 H, N-*H*); ^{13}C NMR ($DCCl_3$) ppm 24.88 [d, C(1,5)], 29.79 [t, C(9)], 32.17 [t, C(2,4)], 47.8 [t, C(6,8)].

Attempted In_2O_3 Oxidation of **5j**

A 25-mL, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, and a condenser with a N_2 inlet. A stirred mixture of the ketone (**5j**, 0.50 g, 1.56 mmol), glacial HOAc (4 mL), HCl (37%, 1/2 mL), In_2O_3 (0.43 g, 1.56 mmol) and H_2O (5 mL) was brought to reflux under N_2 and maintained for 45 h. Cooling of the mixture to RT was followed by basification to pH~12 using 10% NaOH. This mixture was diluted with H_2O (30 mL) and then extracted with ether (3 x 25 mL). Combined extracts were dried (Na_2SO_4, overnight), filtered, and concentrated (rotary evaporator) to give 0.48 g

(96.0%) of crude starting ketone **5j**. The literature contained no record of In_2O_3 being employed in organic syntheses.

Attempted Li_2MnO_3 Oxidation of **5j**

A 30-mL, four-necked, jacketed flask was equipped with a magnetic stirrer, a heating mantle, a condensor, a condenser with a N_2 inlet and a glass stopper. To a stirred mixture of the ketone (**5j**, 0.25 g, 0.78 mmol) and glacial HOAc (5 mL) was added Li_2MnO_3 (0.18 g, 1.56 mmol) in small portions over 1 h. A slight exothermic reaction occurred which was followed by heating at 56°C (boiling acetone in jacket) for 17 h. This mixture was filtered and then diluted with saturated NaCl (10 mL). Combined extracts (CH_2Cl_2, 3 x 10 mL) were washed with H_2O (10 mL), dried (K_2CO_3, overnight), filtered and concentrated (rotary evaporator) to give 0.11 g (44.0%) of crude starting material **5j**. The material which remained in the aqueous layer could not be isolated or characterized. The literature contained no record of Li_2MnO_3 being employed in organic syntheses.

Attempted Li_2CrO_4 H_2O Oxidation of **5j**

A 25 mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with a N_2 inlet and two glass stoppers. Addition of the ketone (**5j**, 0.25 g, 0.78 mmol) and glacial acetic acid (5 mL) was followed by the additon of Li_2CrO_4 H_2O (0.27 g, 1.56 mmol) in small portions over 1 h at RT. Stirring of the mixture was continued for 4 days. This mixture was diluted with saturated NaCl (10 mL) and then extracted (CH_2Cl_2, 3 x 10 mL). Combined extracts were washed with H_2O (2 x 20 mL), dried (K_2CO_3, overnight), filtered and concentrated (rotary evaporator) to give 0.10 g (40%) of crude starting material **5j**. The material which remained in the aqueous layer could not be separated or characterized. The literature contained no record of $Li_2CrO_4 \cdot H_2O$ being employed in organic syntheses.

Attempted Na_2O_2 Oxidation of **5j**

A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, a 10-mL addition funnel and a glass stopper. To a stirred mixture of the ketone (**5j**, 0.50 g, 1.56 mmol), Na_2O_2 (1.95 mmol, 25.0 mmol), and EtOH (25 mL) was added H_2O (5 mL) dropwise over 2 h at RT. Stirring was continued for another 14 h followed by dilution with H_2O (25 mL). Combined extracts (CH_2Cl_2, 3 x 20 mL) were dried (Na_2SO_4, overnight), filtered and concentrated (rotary evaporator) to give 0.47 g (94.0%) of crude starting material **5j**. The procedure employed was similar in nature to conditions previously cited in the literature.[28]

Attempted Li_2O_2 Oxidation of **5j**

A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, condenser with a N_2 inlet and two glass stoppers. A mixture of the ketone (**5j**, 0.50 g, 2.0 mmol), Li_2O_2 (95%, 0.11 g, 2.2 mmol) and THF (25 mL) was stirred at reflux under N_2 for 7 h and then cooled to RT. After diluting with 10% NaOH (25 mL), the mixture was extracted (ether, 3 x 25 mL). Combined extracts were washed with 10% NaOH (25 mL) and saturated NaCl (25 mL), dried (Na_2SO_4, overnight), filtered and concentrated (rotary evaporator) to give 0.47 g (94.0%) of crude starting material **5j**. The literature contained no record of Li_2O_2 being employed in organic syntheses.

Attempted CrO_3 Oxidation of **5j**

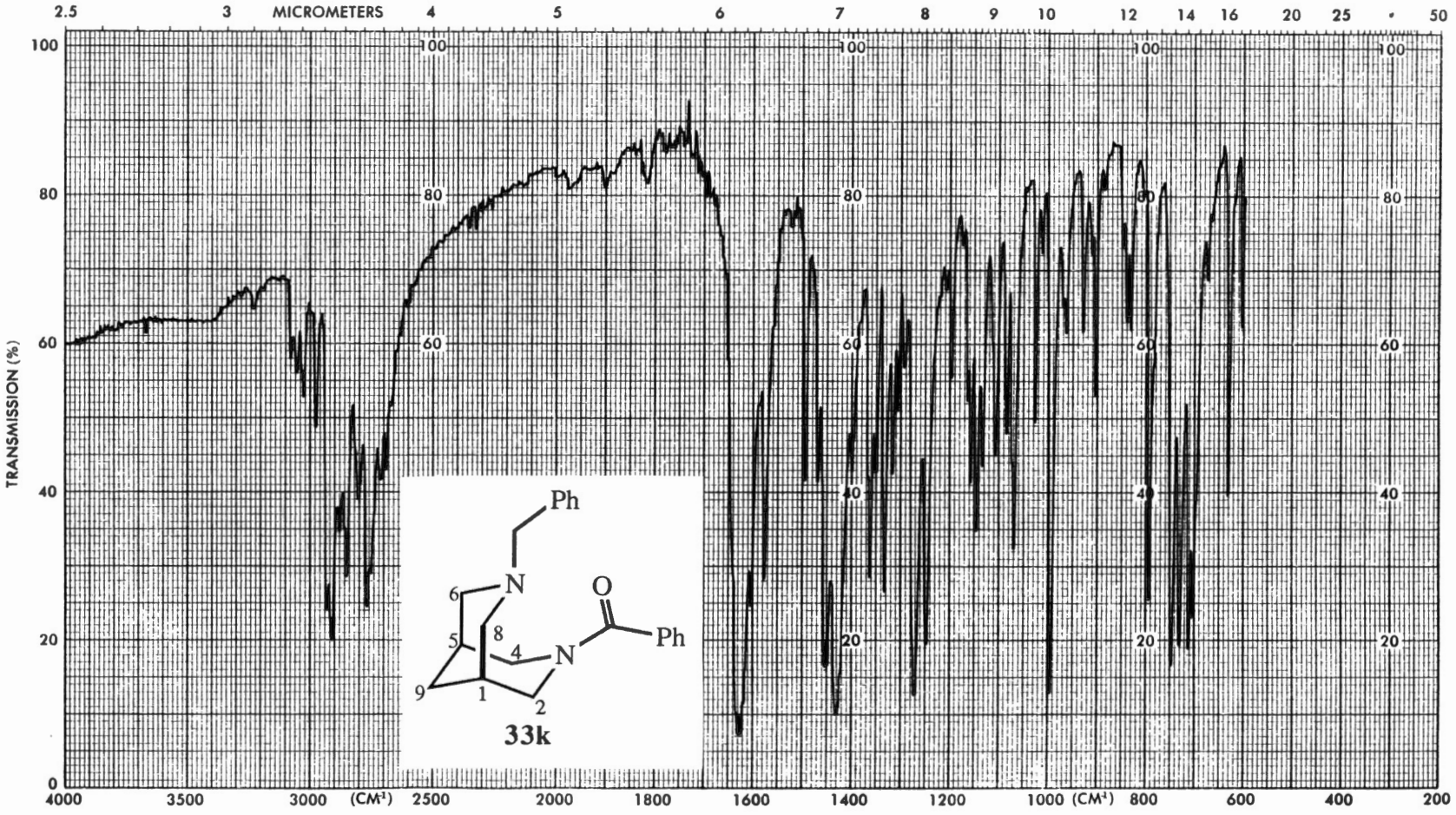
A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, an ice bath, a condenser with a N_2 inlet and two glass stoppers. To a stirred, chilled (0°C) solution of the ketone (**5j**, 1.0 g, 3.12 mmol), glacial acetic acid (10 mL) and acetic anhydride (10 mL) was added CrO_3 (0.62 g, 6.24 mmol) in small portions over 1 h. Warming of the stirred mixture to RT resulted in a color change from red to green over 5

h. Excess oxidant was then destroyed by slow addition of isopropyl alcohol (2 mL) followed by dilution with chilled H_2O (50 mL). Combined extracts (ether, 2 x 30 mL) were discarded. Chilling of the aqueous phase (10°C) was followed by basification to pH~12 using 50% NaOH. Combined extracts (ether, 4 x 30 mL) were dried (Na_2SO_4, overnight), filtered and concentrated (rotary evaporator) to give 0.32 g (32.0%) of crude starting material **5j**. The material which remained in the aqueous layer could not be separated or characterized. The procedure employed was similar in nature to conditions previously cited in the literature.[10]

Attempted $Pb(OAc)_4$ Oxidation of **5j**

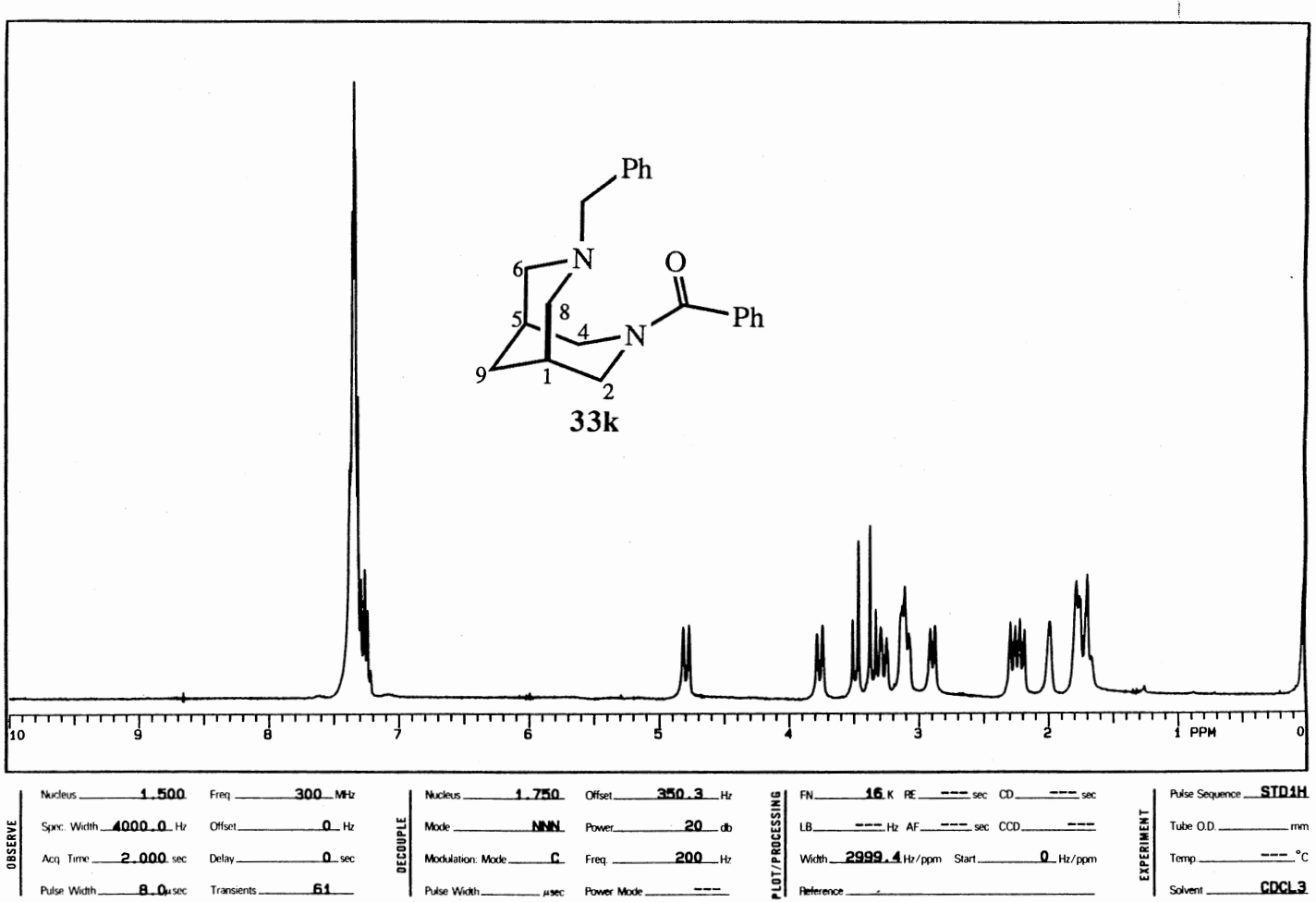
A 15-mL, two-necked, round-bottomed flask was equipped with magnetic stirrer, a heating mantle, a condenser with a N_2 inlet and a glass stopper. A mixture of the ketone (**5j**, 0.64 g, 2.0 mmol), $Pb(OAc)_4$ (1.11 g, 2.5 mmol), trifluoroacetic acid (7.13 g, 2.5 mmol), LiCl (20 mg) and benzene (5 mL) was stirred at reflux under N_2 for 14 h. This brownish mixture was diluted with H_2O (60 mL) and basified with NaOH pellets to pH~12. Combined extracts (ether, 3 x 50 mL) were dried (Na_2SO_4, overnight), filtered and concentrated to give 0.49 g (73.4%) of crude starting material **5j**. The material which remained in the aqueous layer could not be separated or characterized. The procedure employed was similar in nature to conditions previously cited in the literature.[34]

Plate I



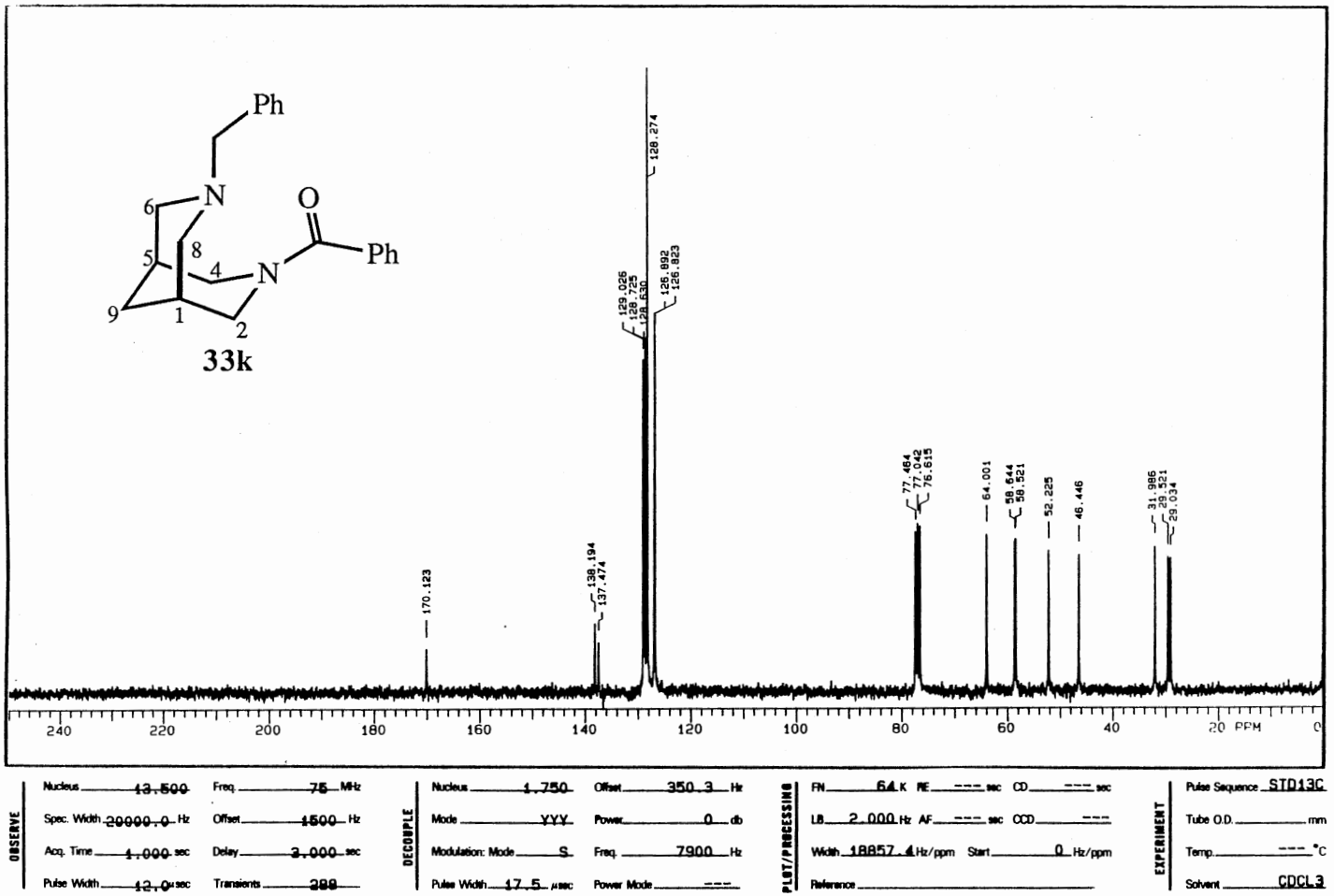
IR Spectrum of **33k**

Plate II



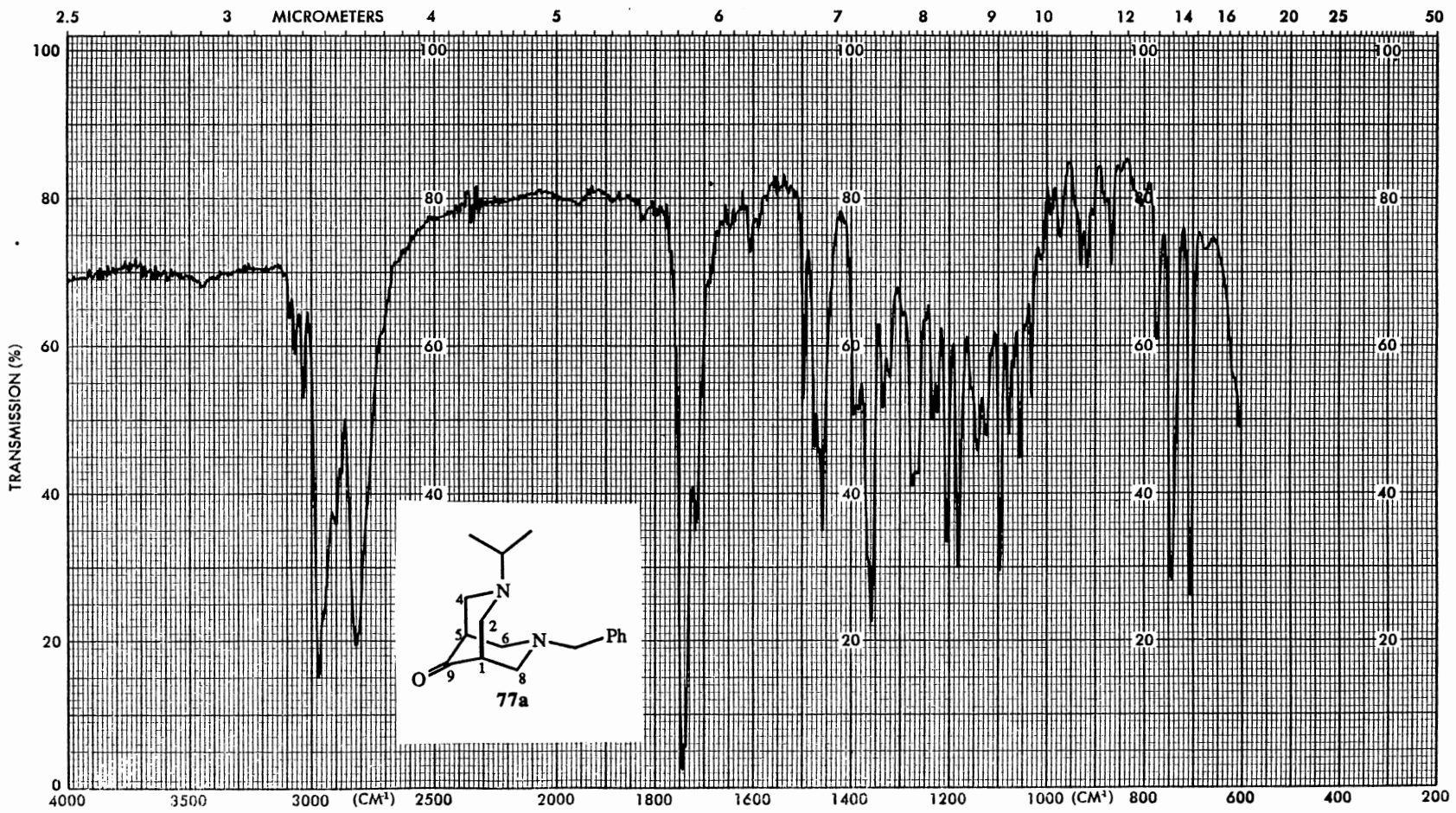
^{1}H NMR Spectrum of **33k**

Plate III



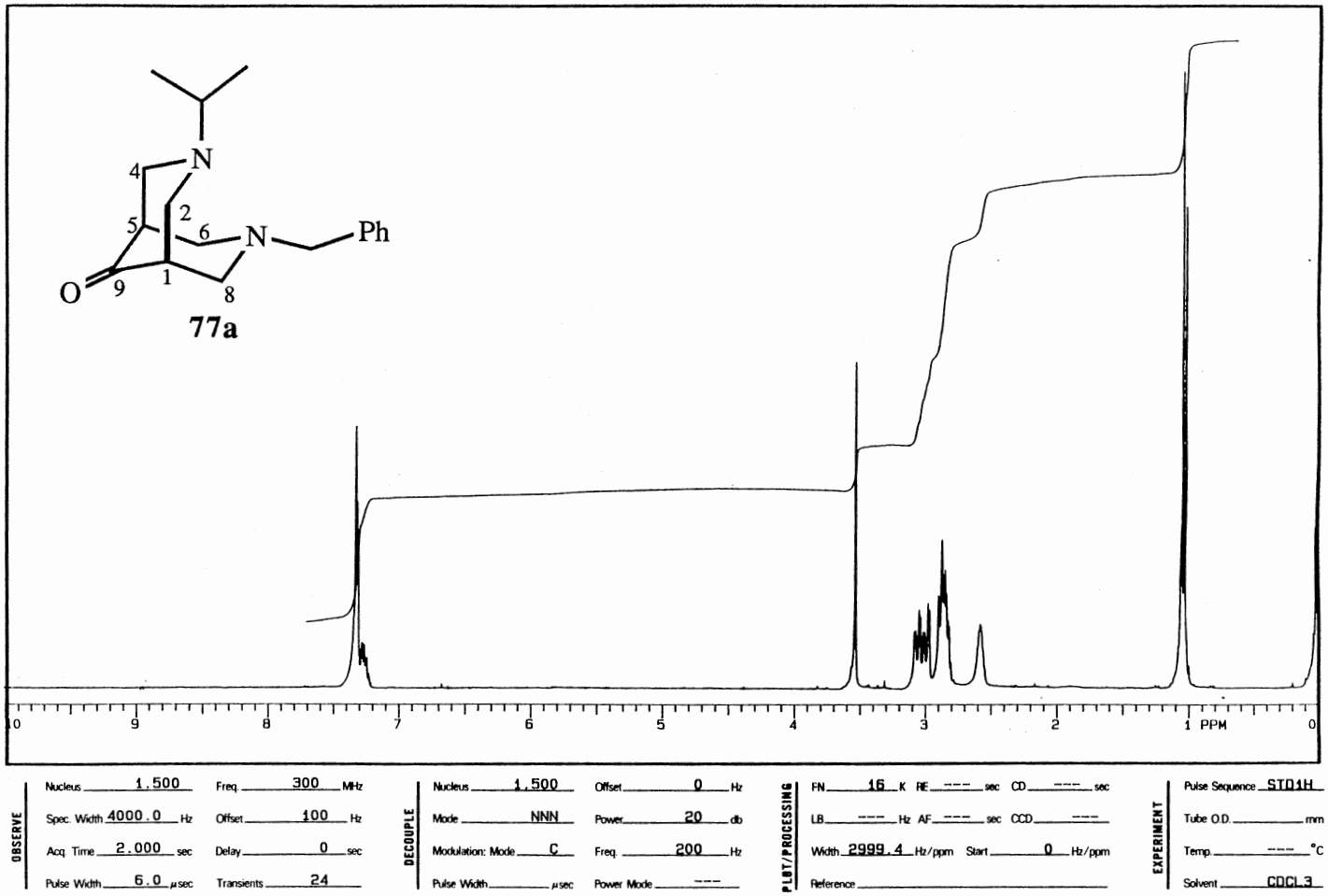
^{13}C NMR Spectrum of **33k**

Plate IV



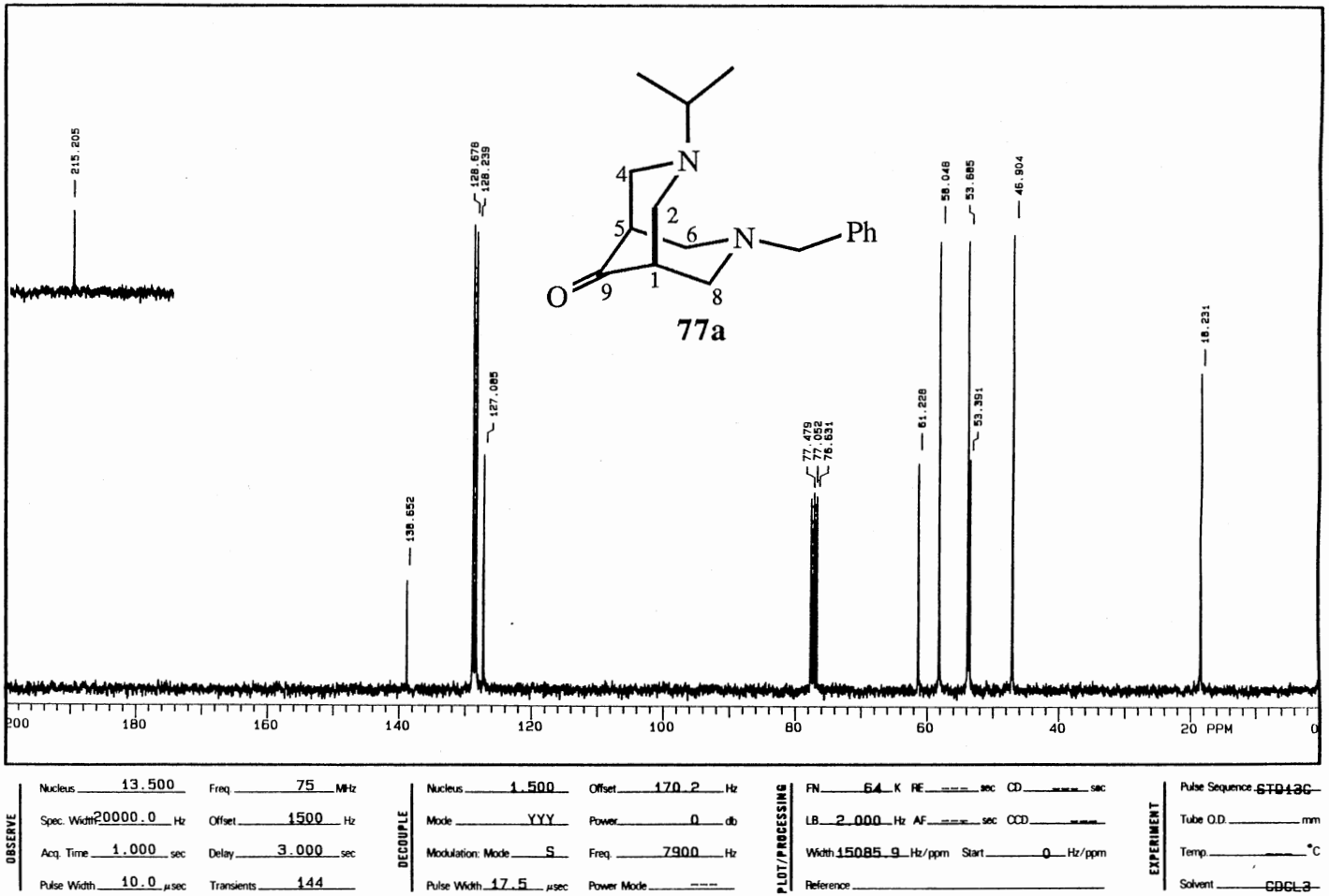
IR Spectrum of **77a**

Plate V



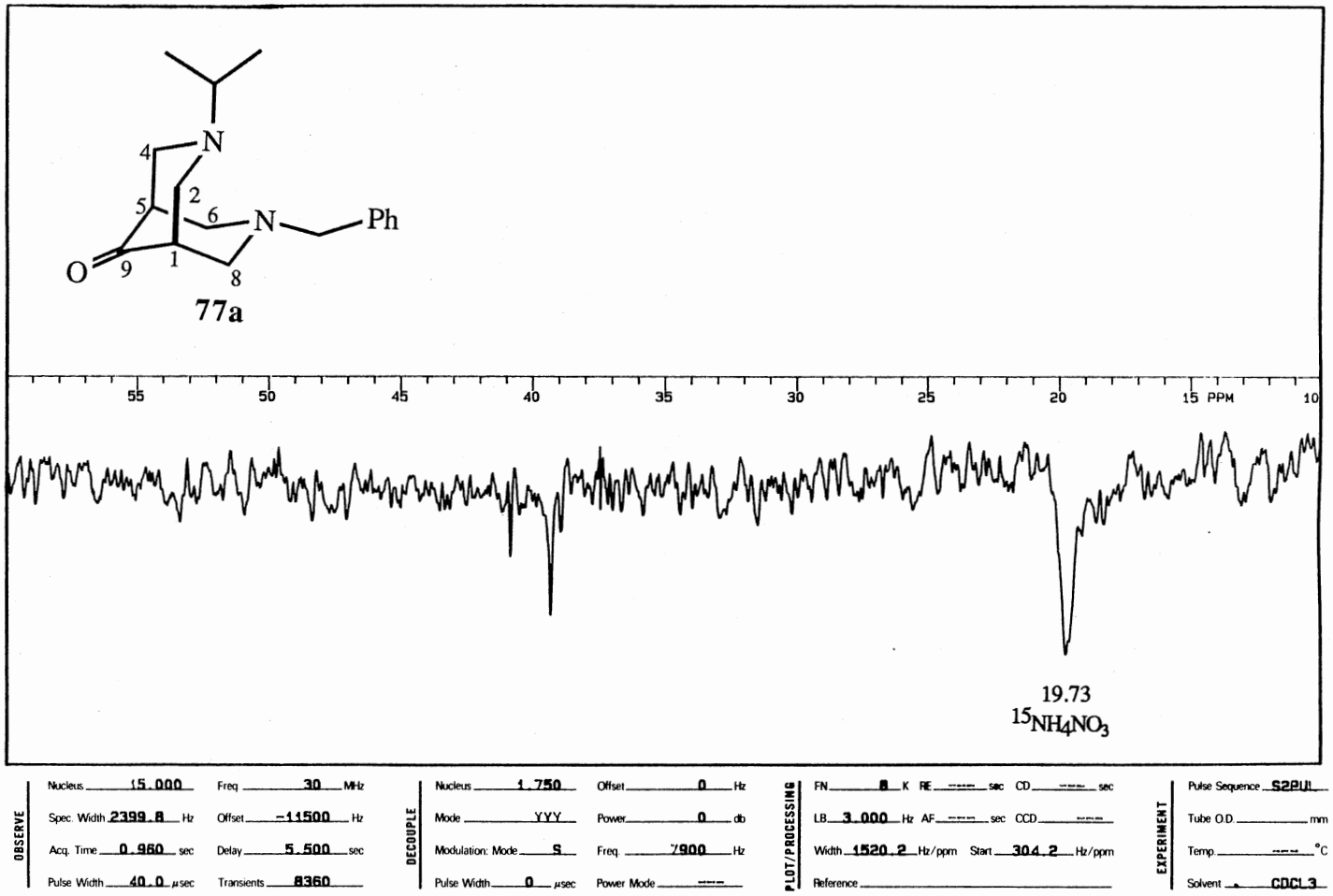
^{1}H NMR Spectrum of **77a**

Plate VI



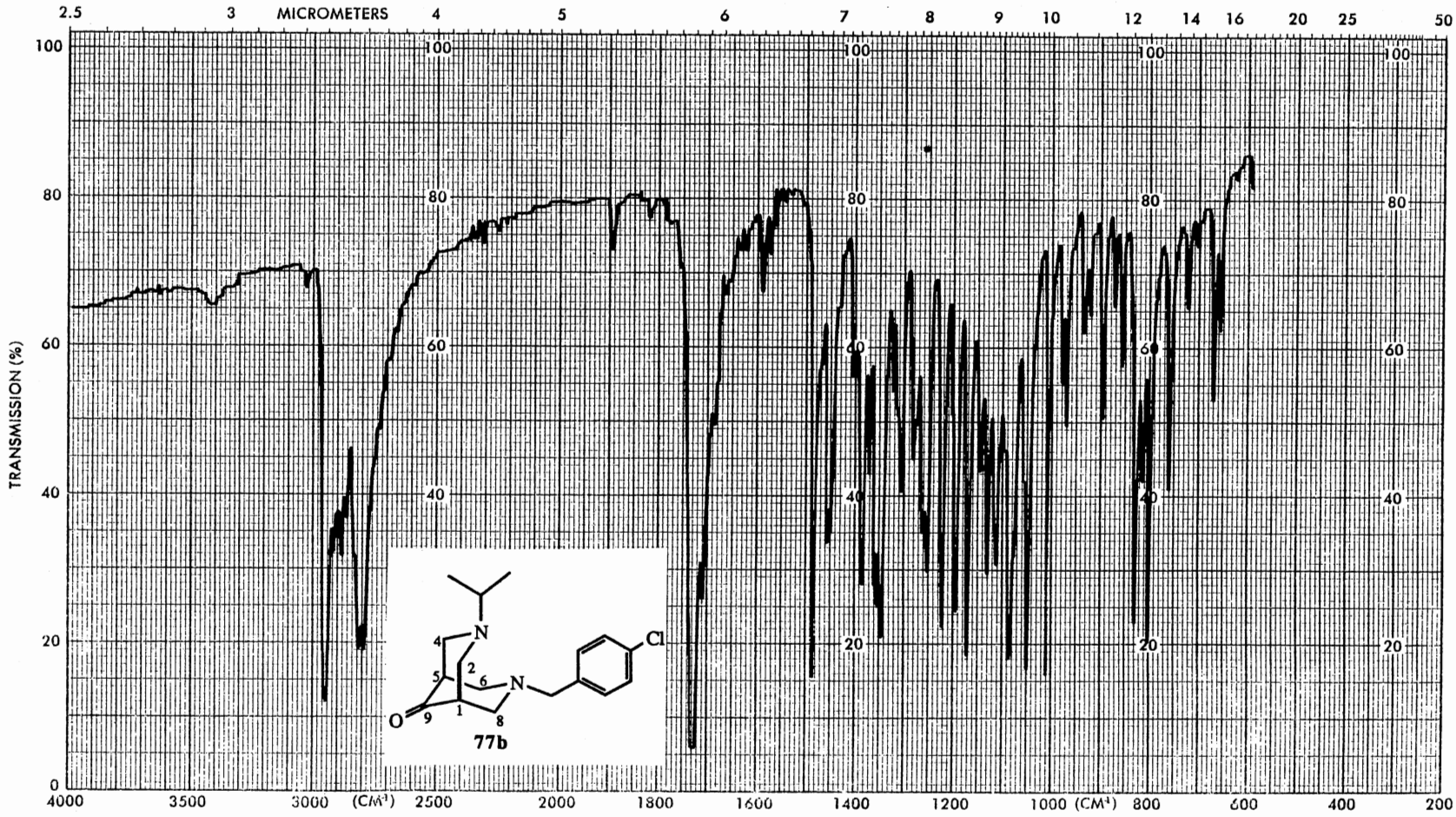
^{13}C NMR Spectrum of **77a**

Plate VII



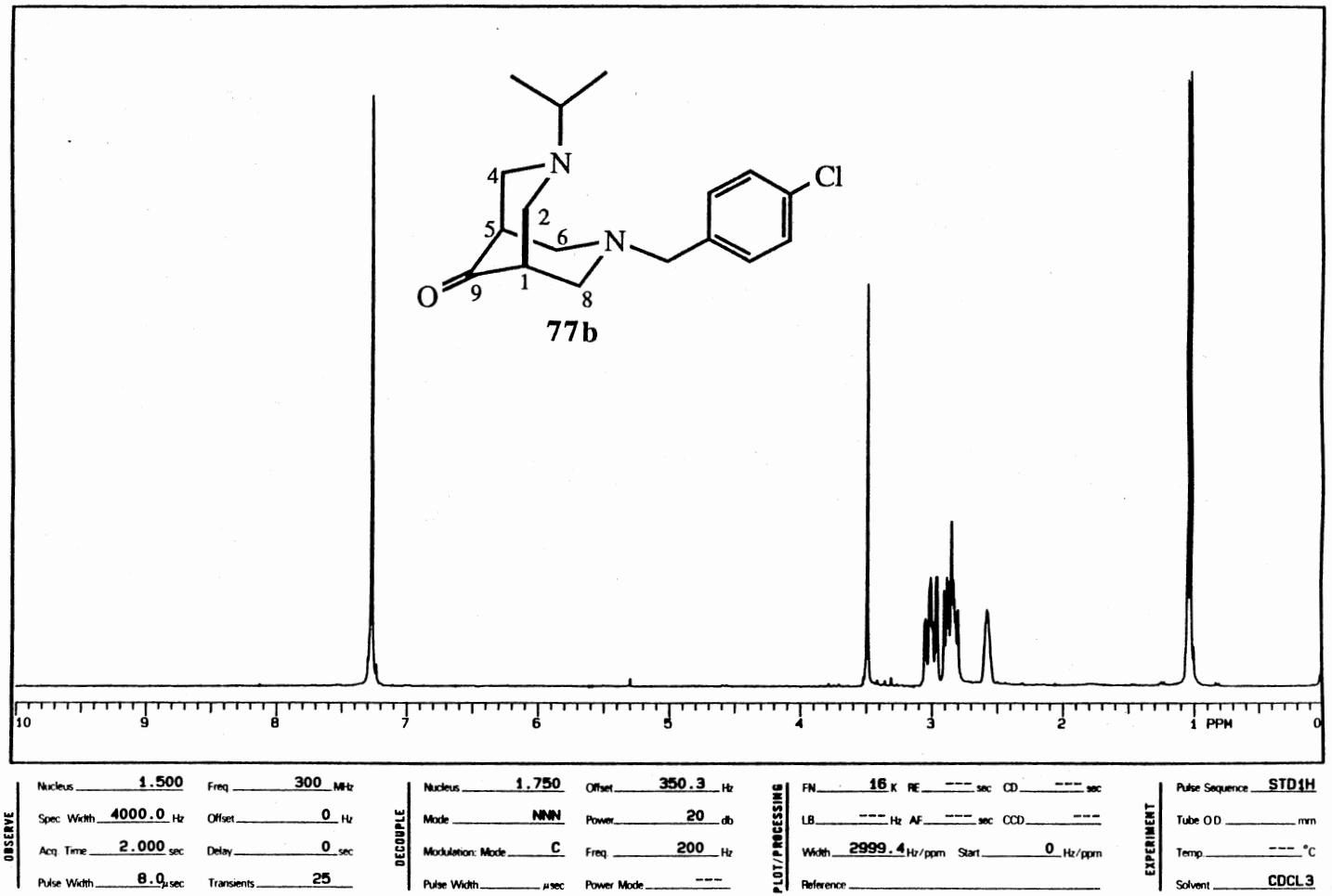
^{15}N NMR Spectrum of **77a**

Plate VIII



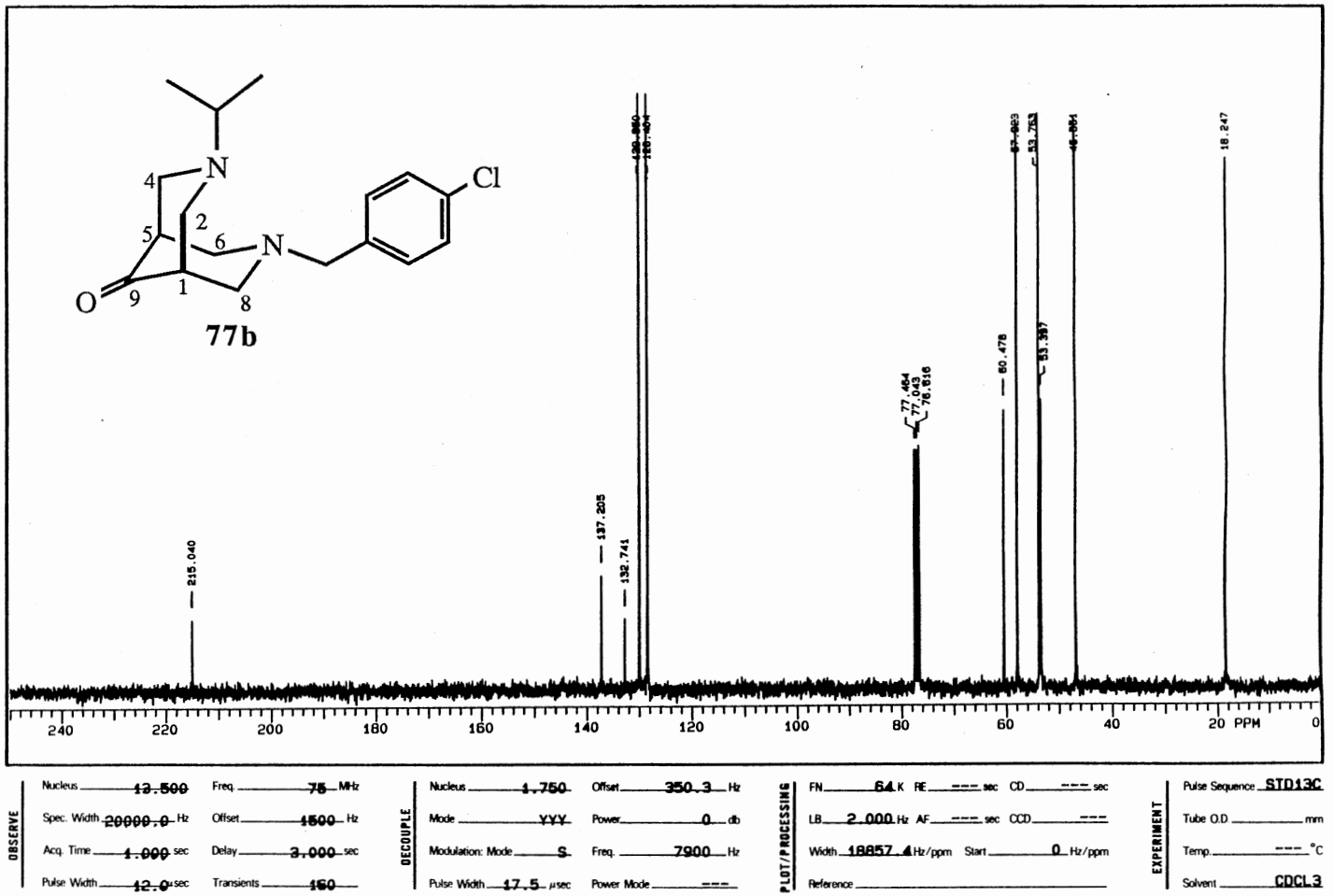
IR Spectrum of **77b**

Plate IX



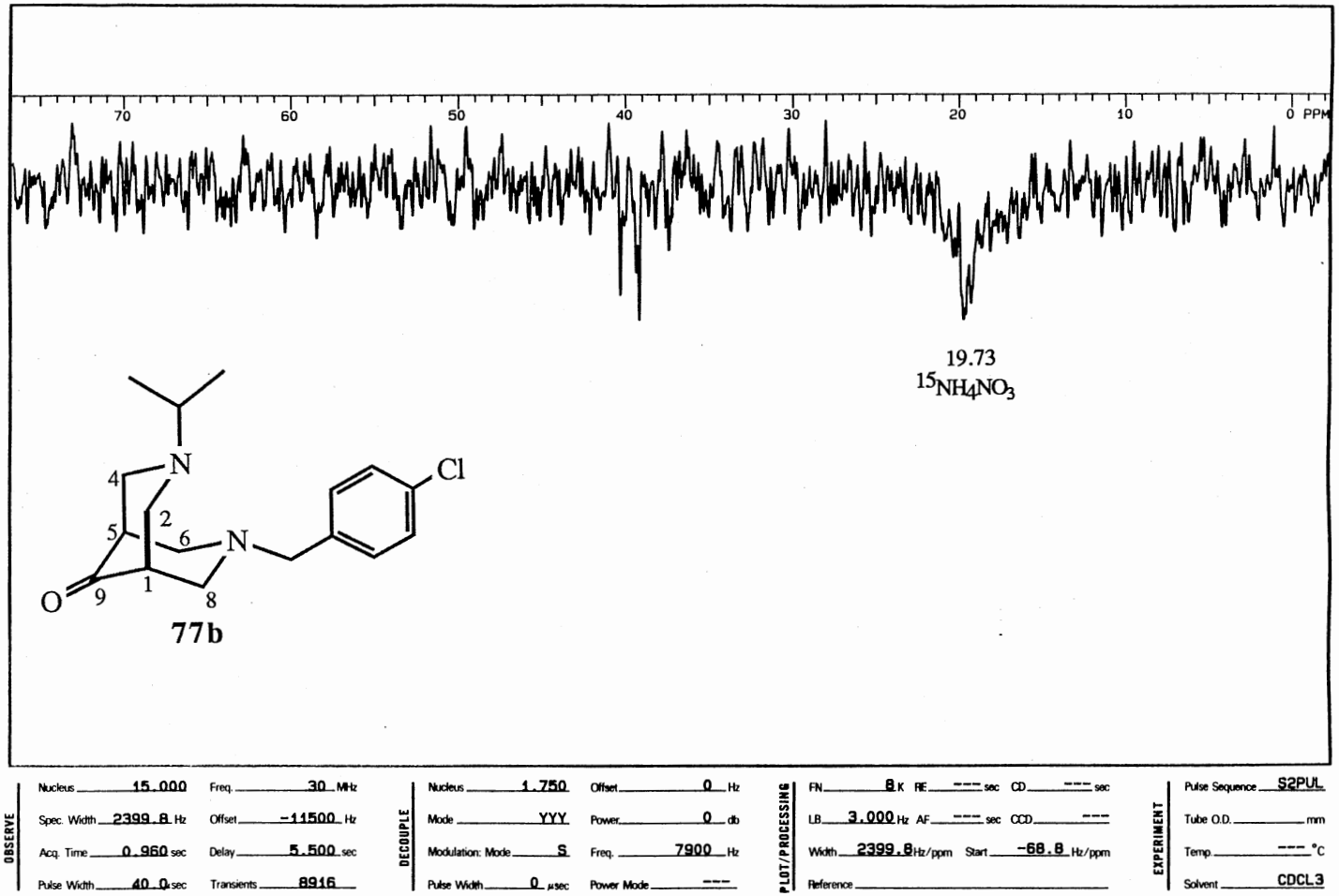
^{1}H NMR Spectrum of **77b**

Plate X



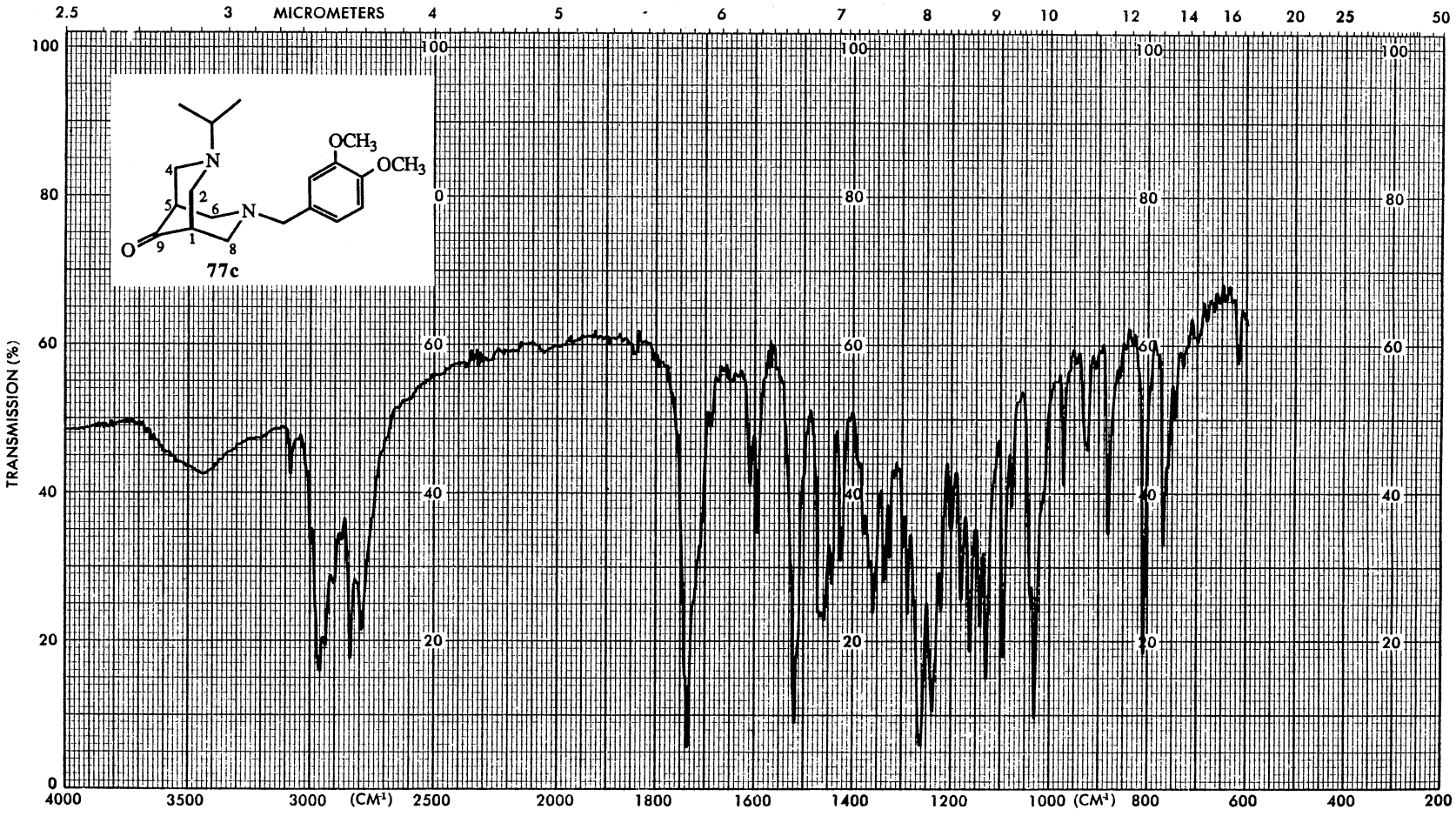
^{13}C NMR Spectrum of **77b**

Plate XI



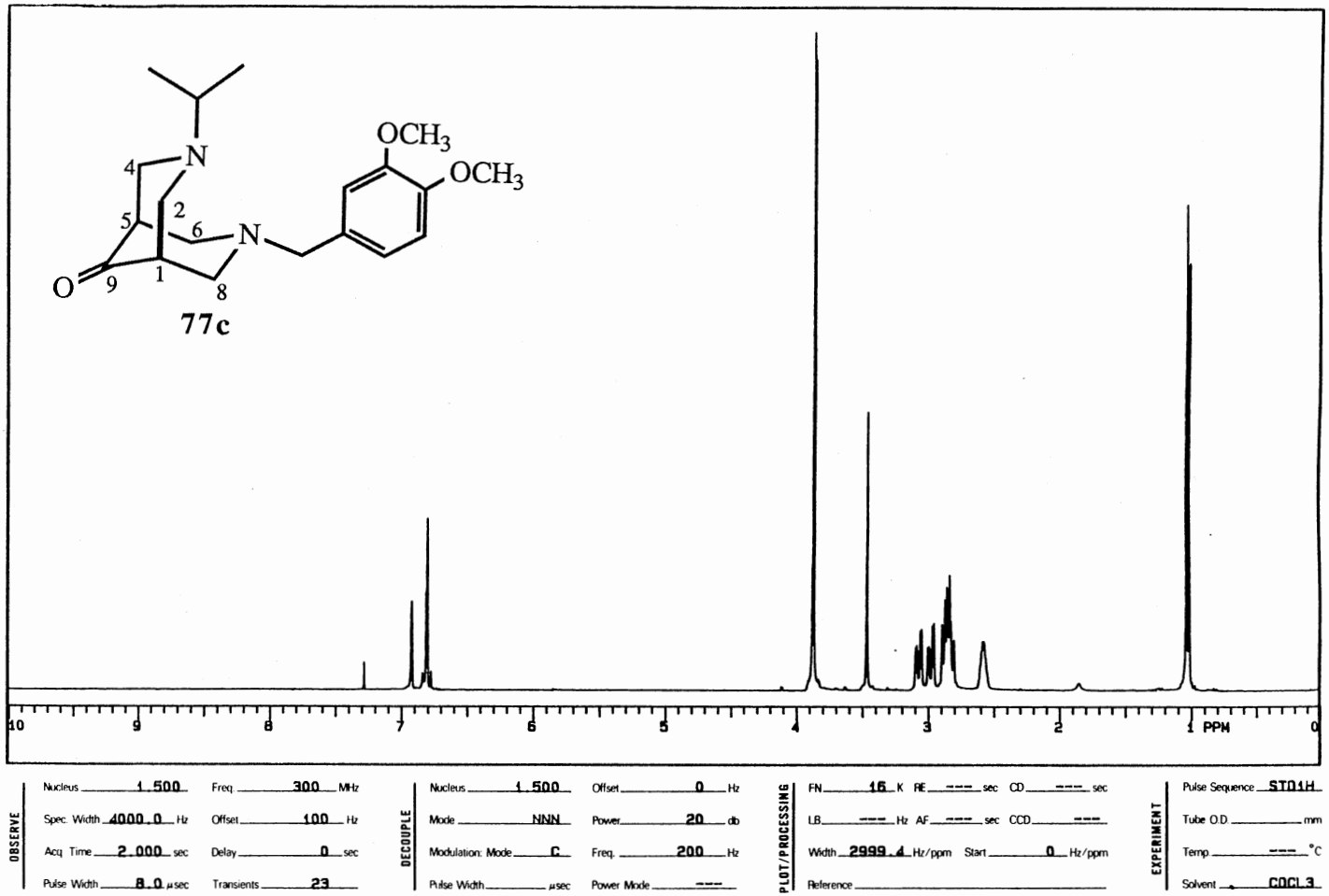
^{15}N NMR Spectrum of **77b**

Plate XII



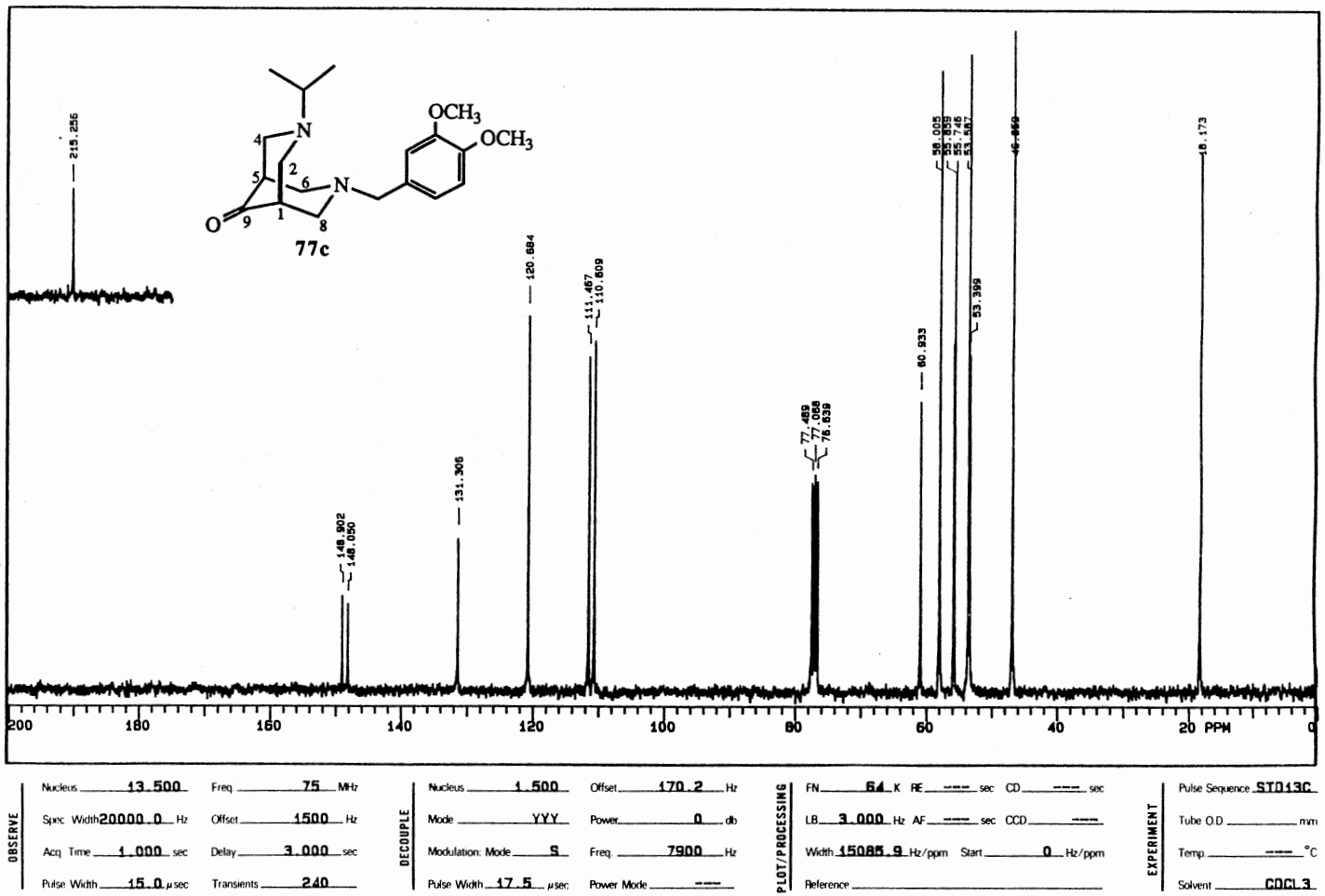
IR Spectrum of **77c**

Plate XIII



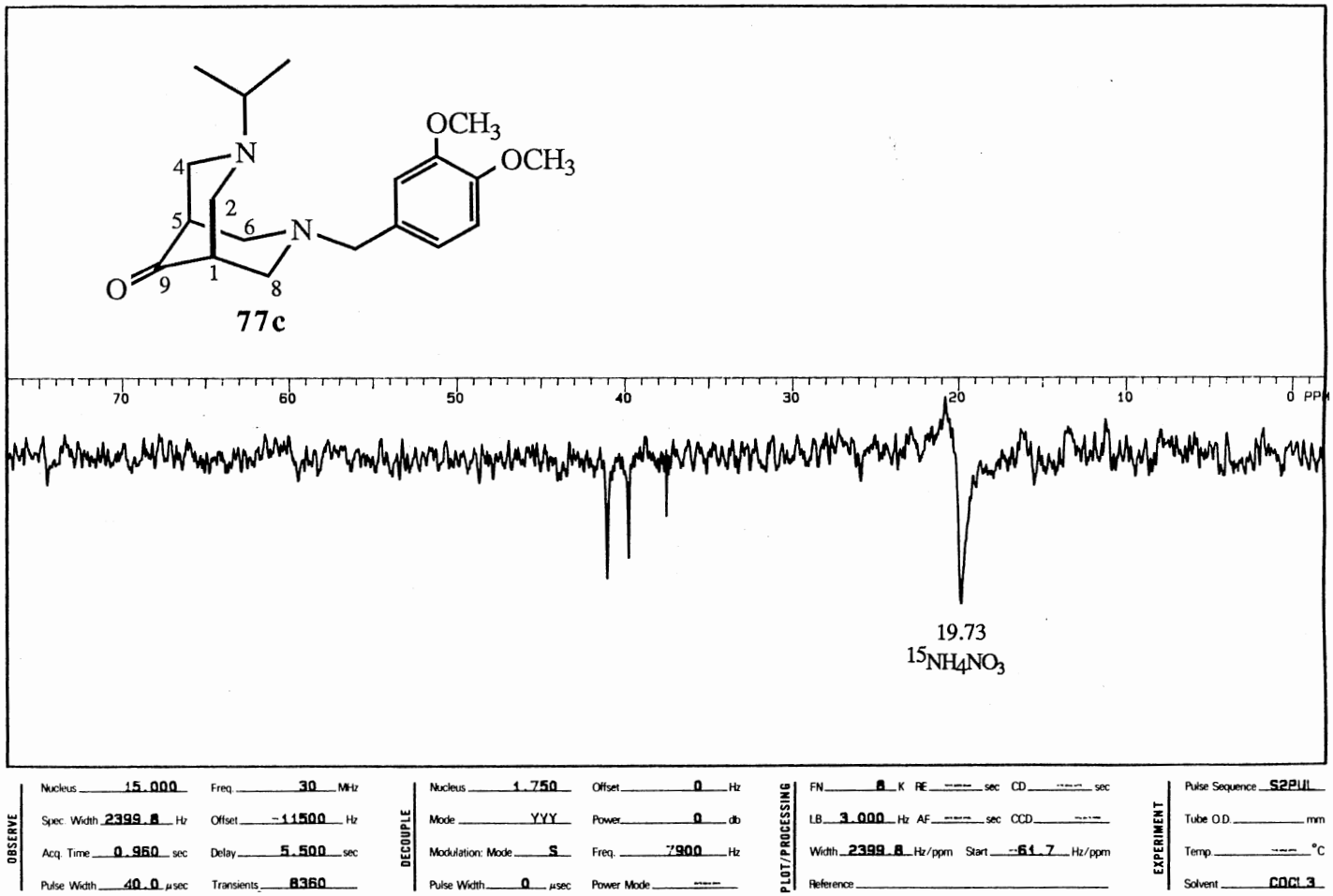
^{1}H NMR Spectrum of **77c**

Plate XIV



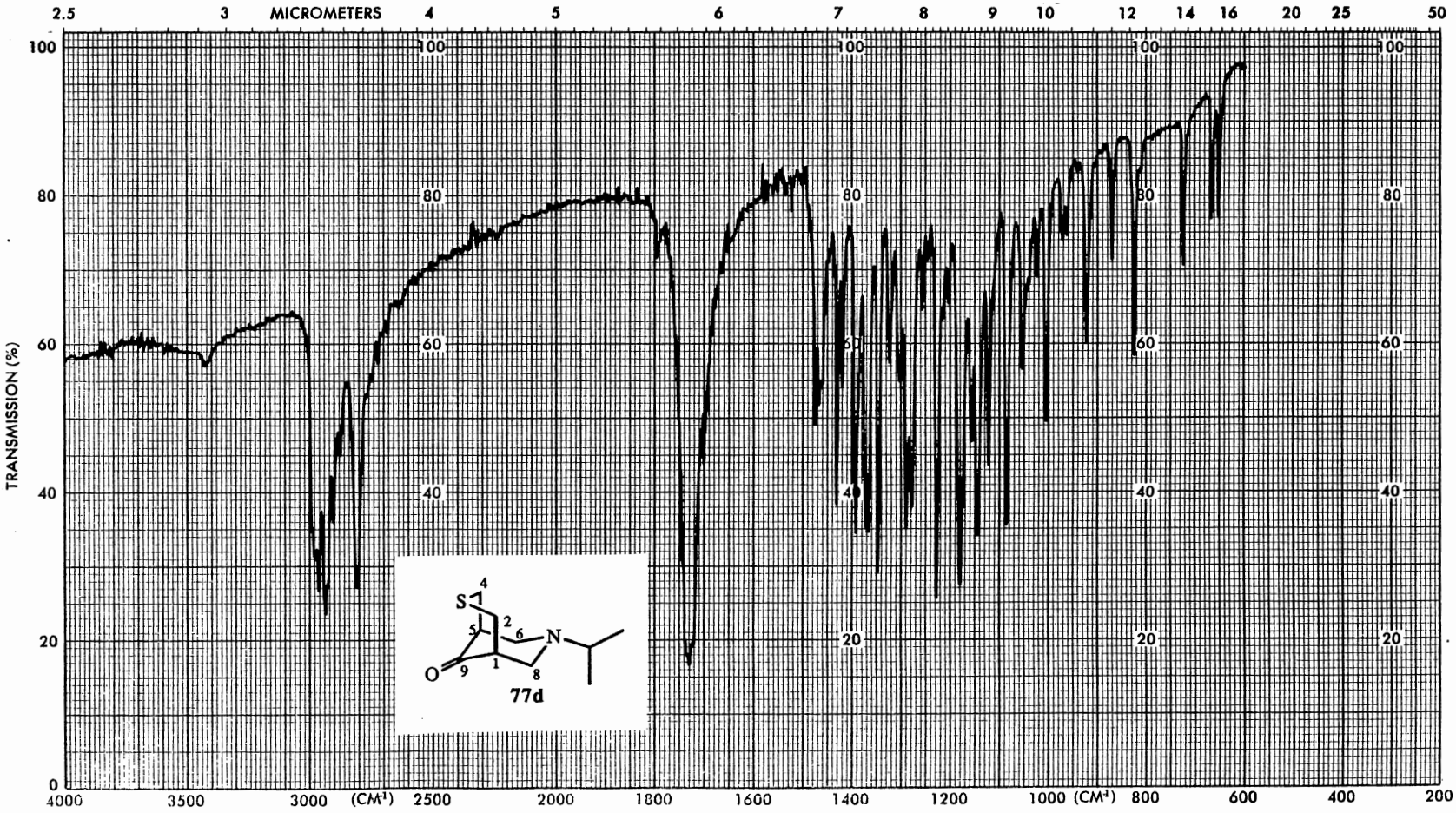
^{13}C NMR Spectrum of **77c**

Plate XV



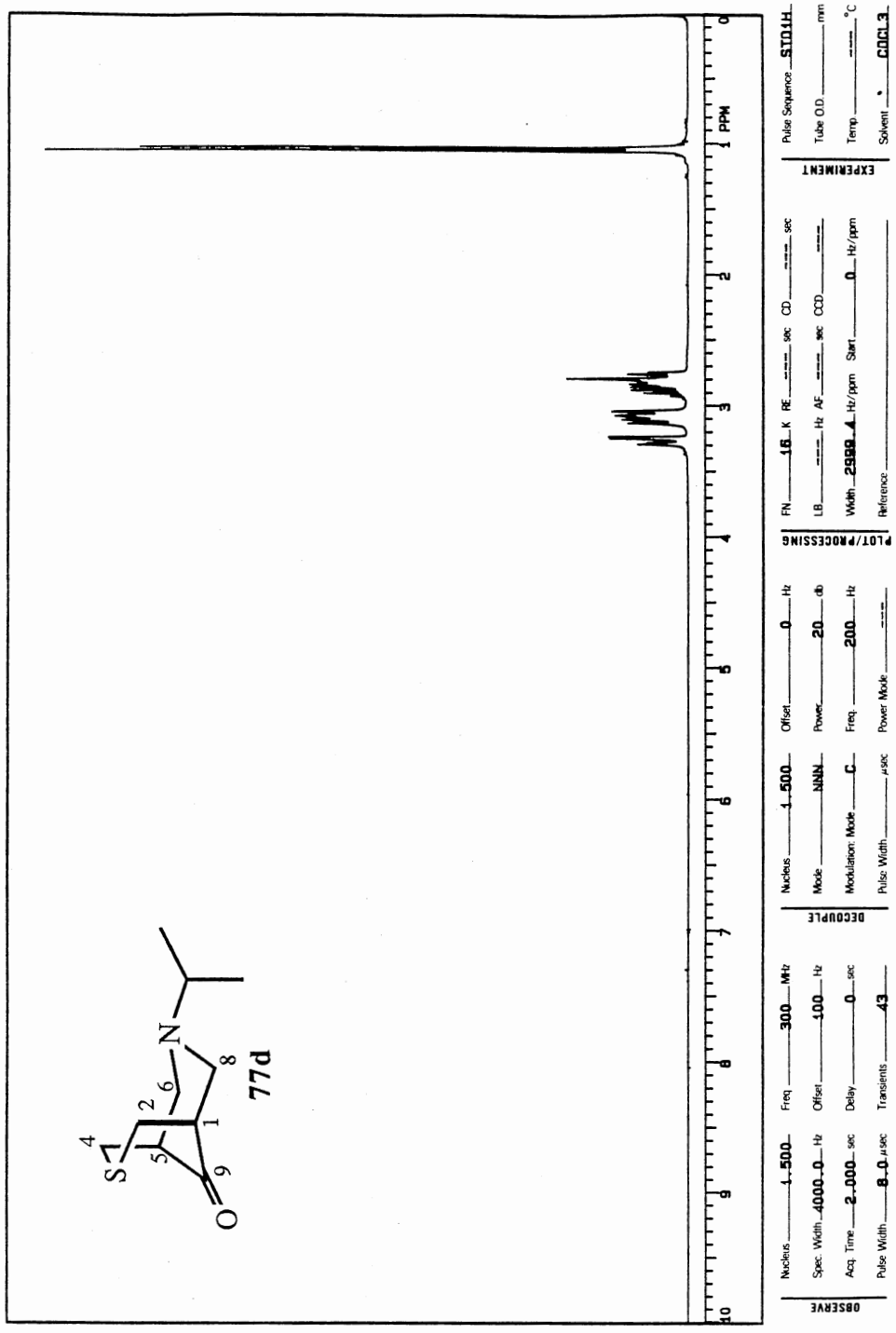
^{15}N NMR Spectrum of **77c**

Plate XVI



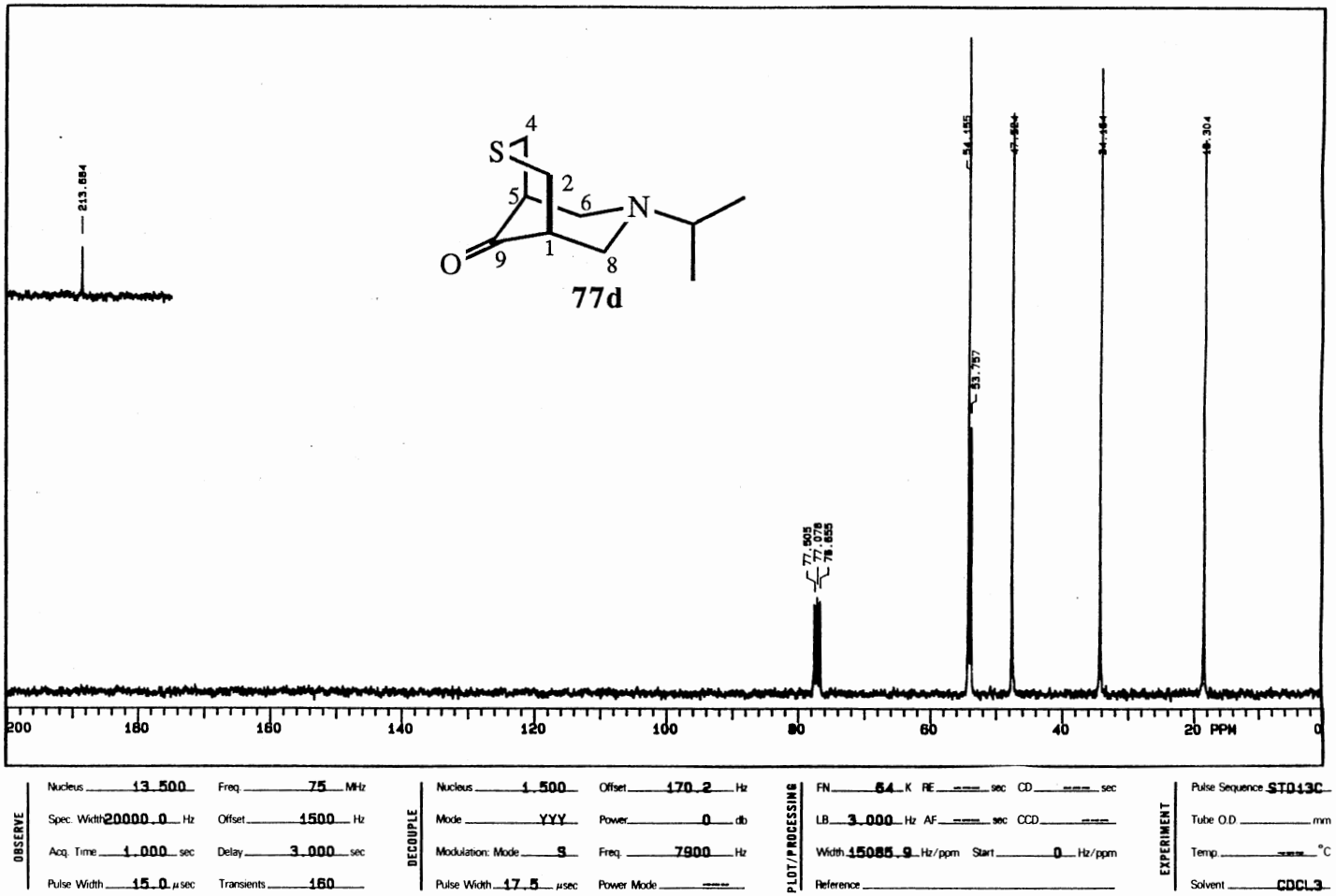
IR Spectrum of **77d**

Plate XVII



^{1}H NMR Spectrum of **77d**

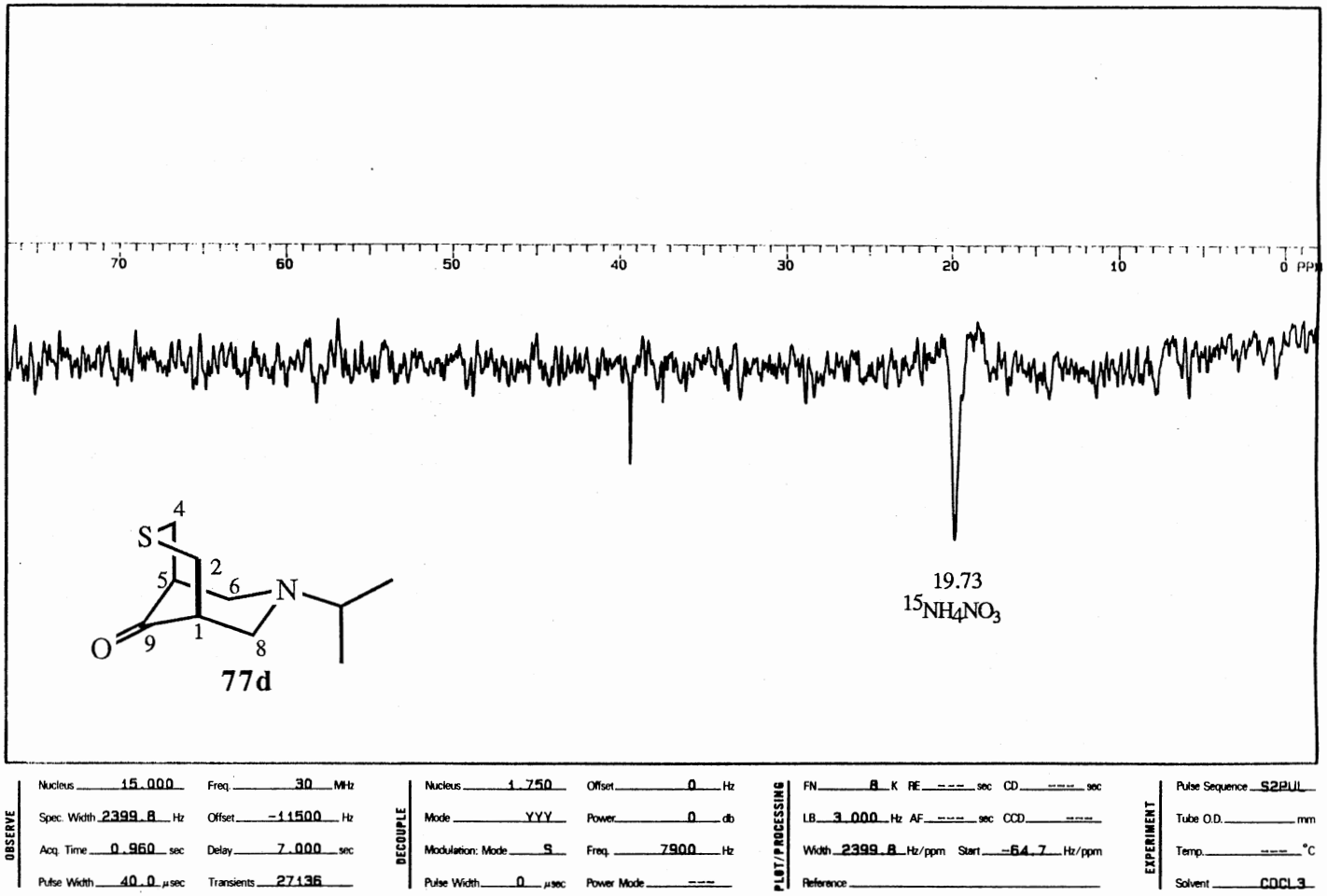
Plate XVIII



77d

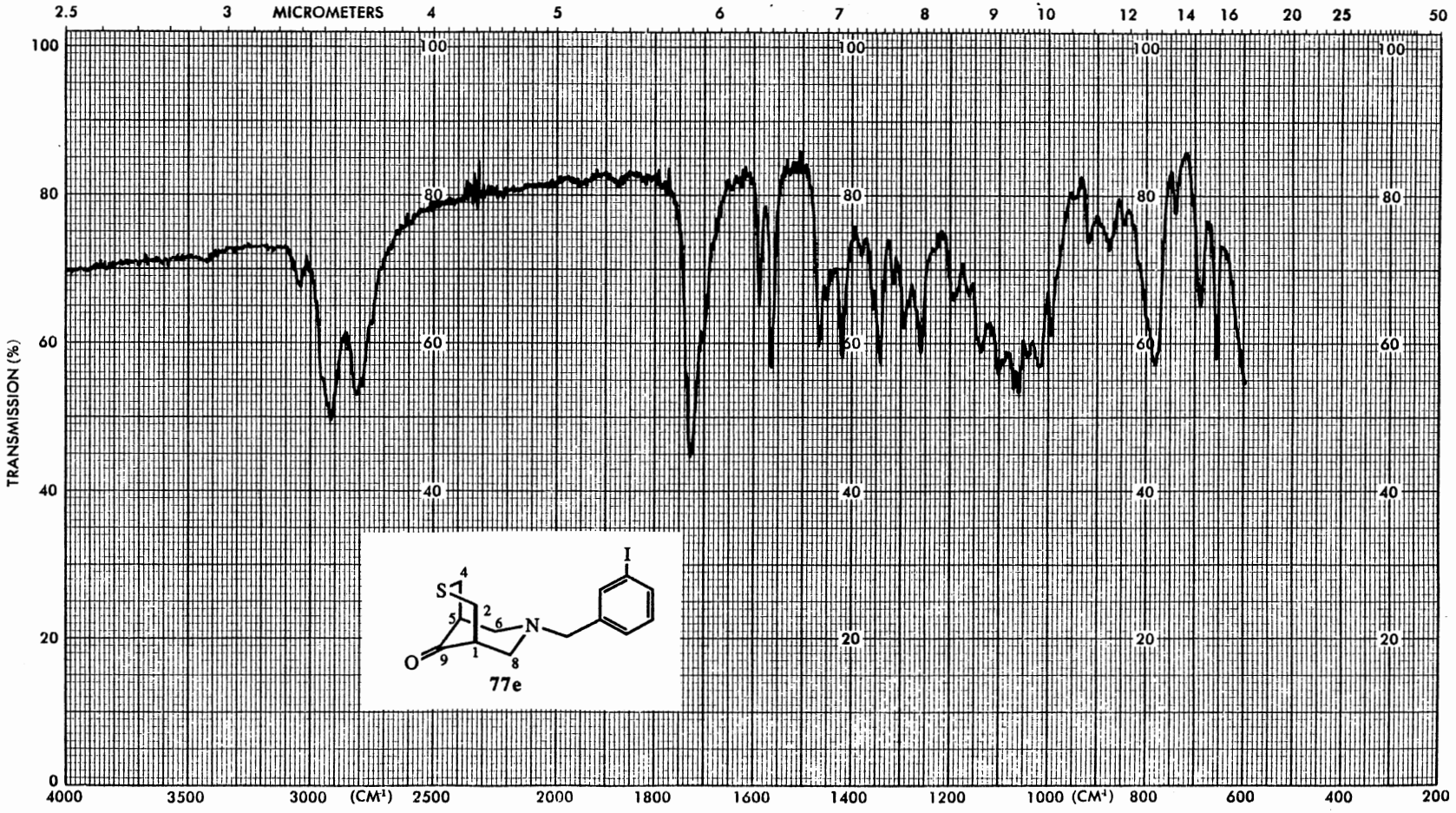
^{13}C NMR Spectrum of **77d**

Plate XIX



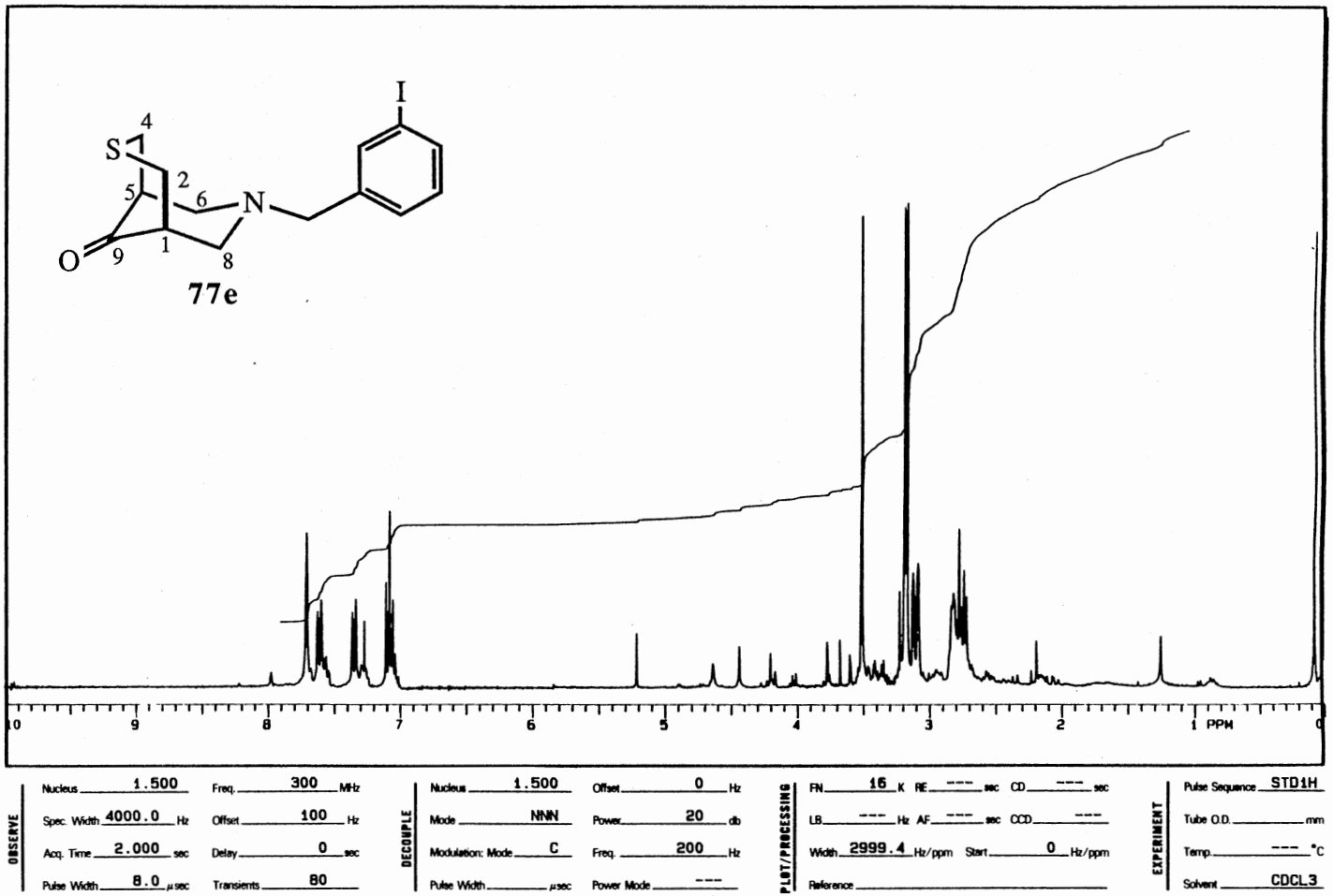
^{15}N NMR Spectrum of **77d**

Plate XX



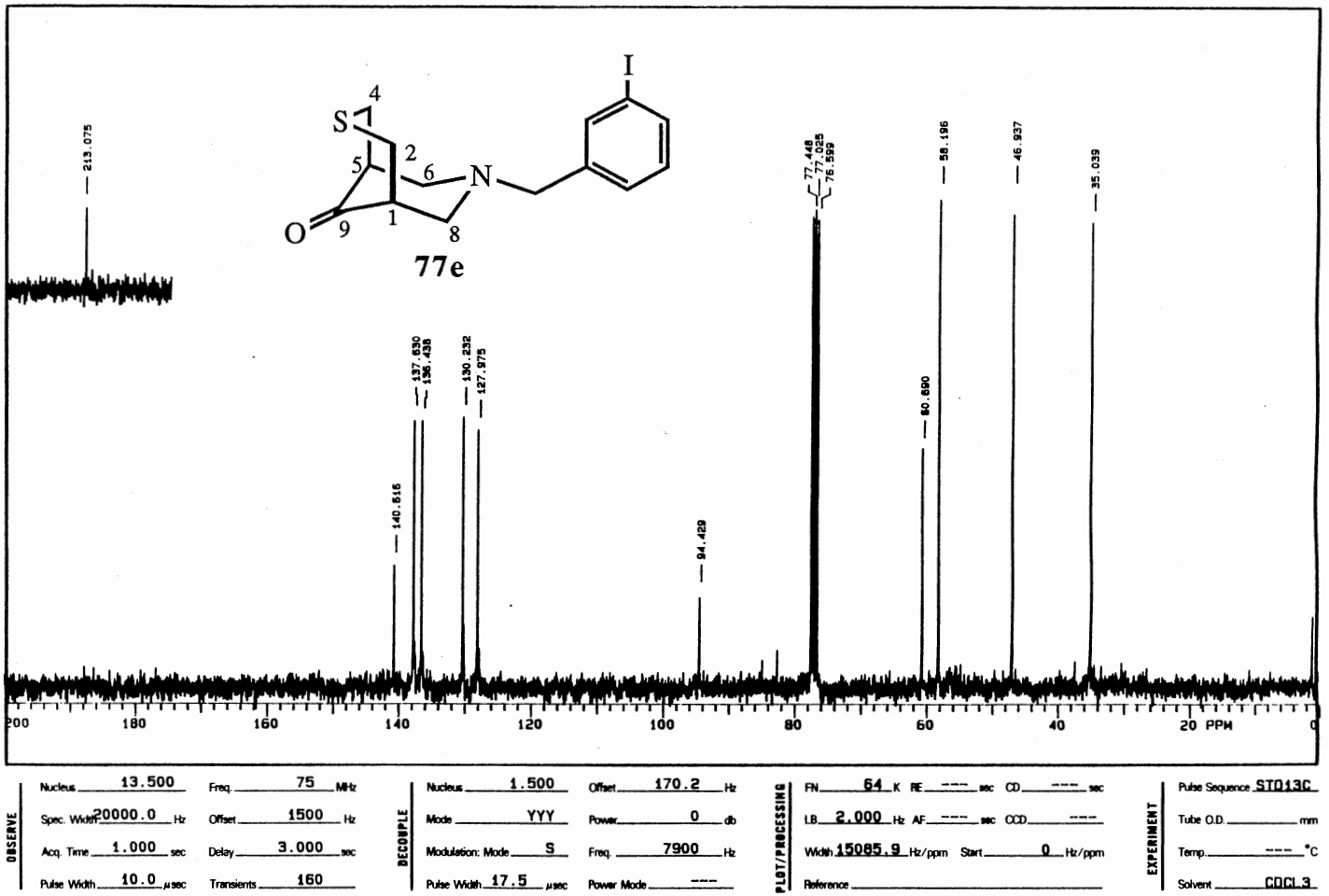
IR Spectrum of **77e**

Plate XXI



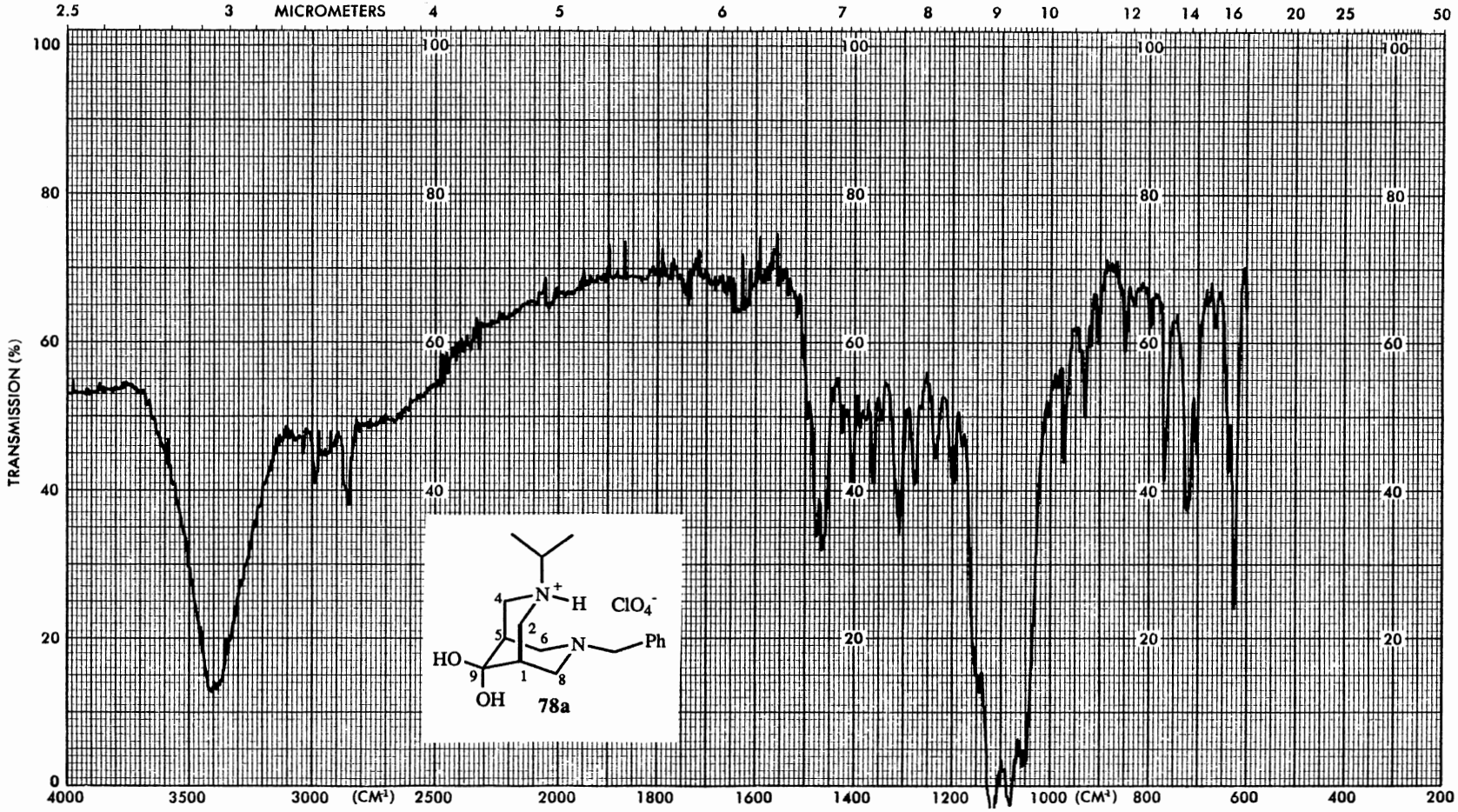
^{1}H NMR Spectrum of **77e**

Plate XXII



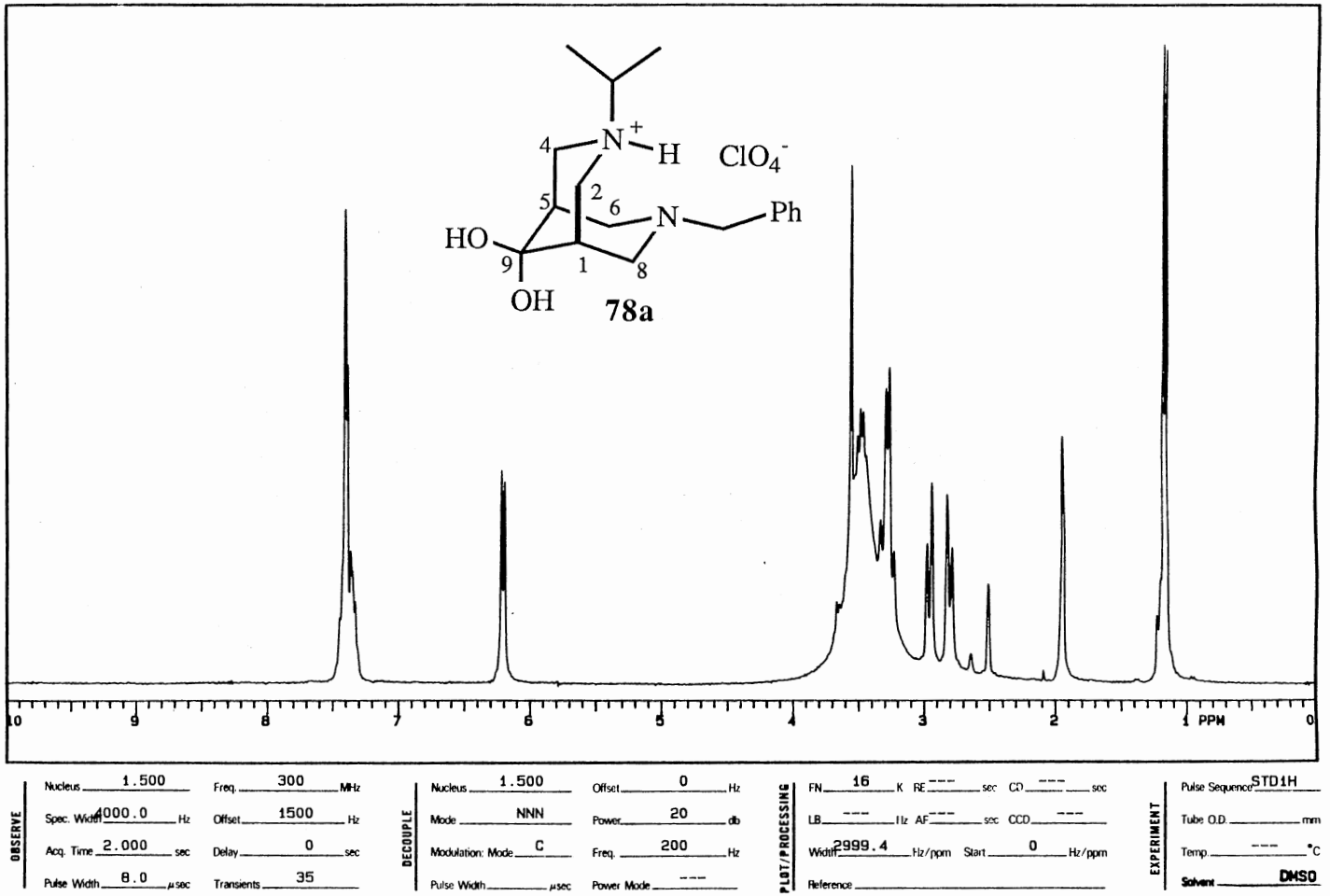
^{13}C NMR Spectrum of **77e**

Plate XXIII



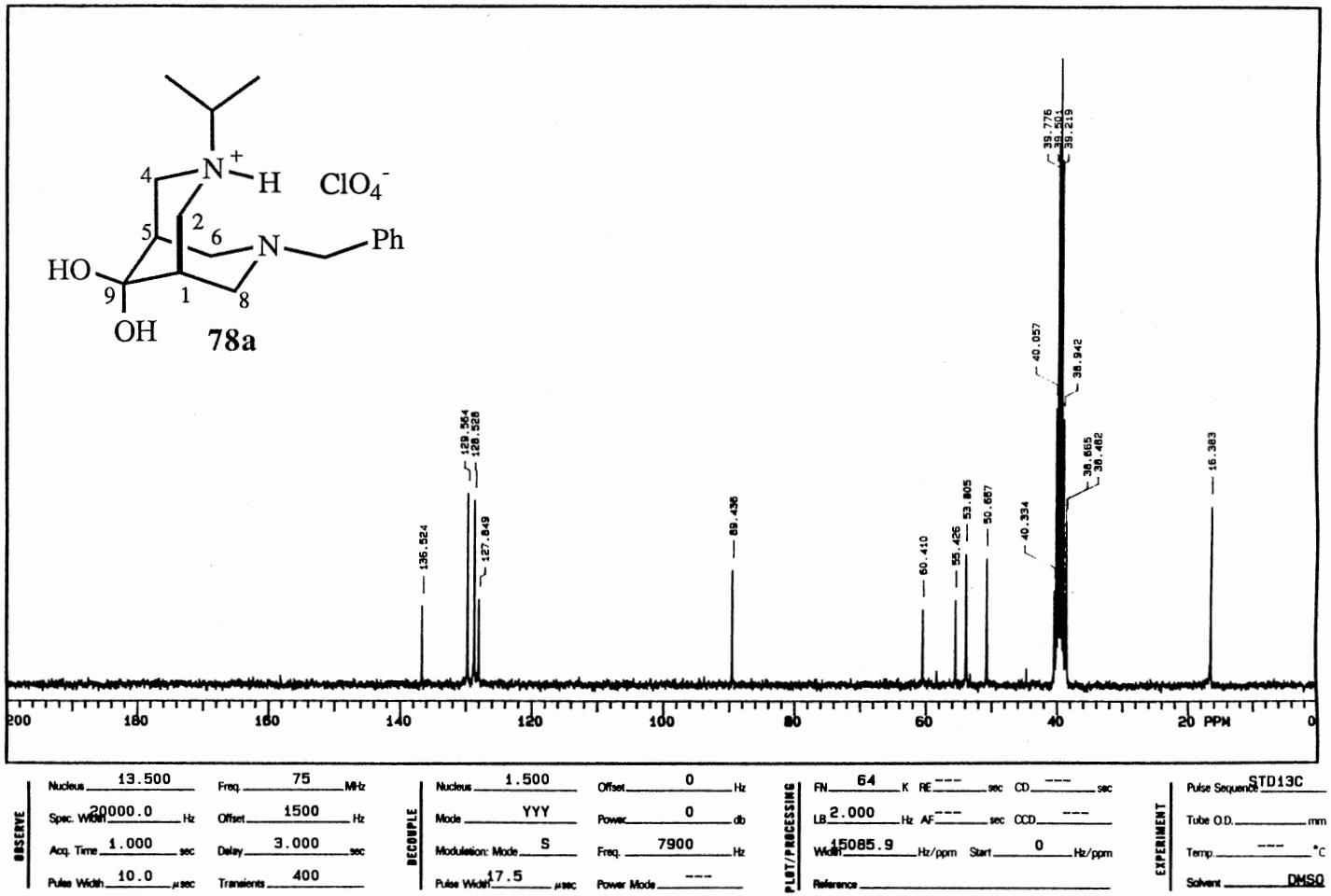
IR Spectrum of **78a**

Plate XXIV



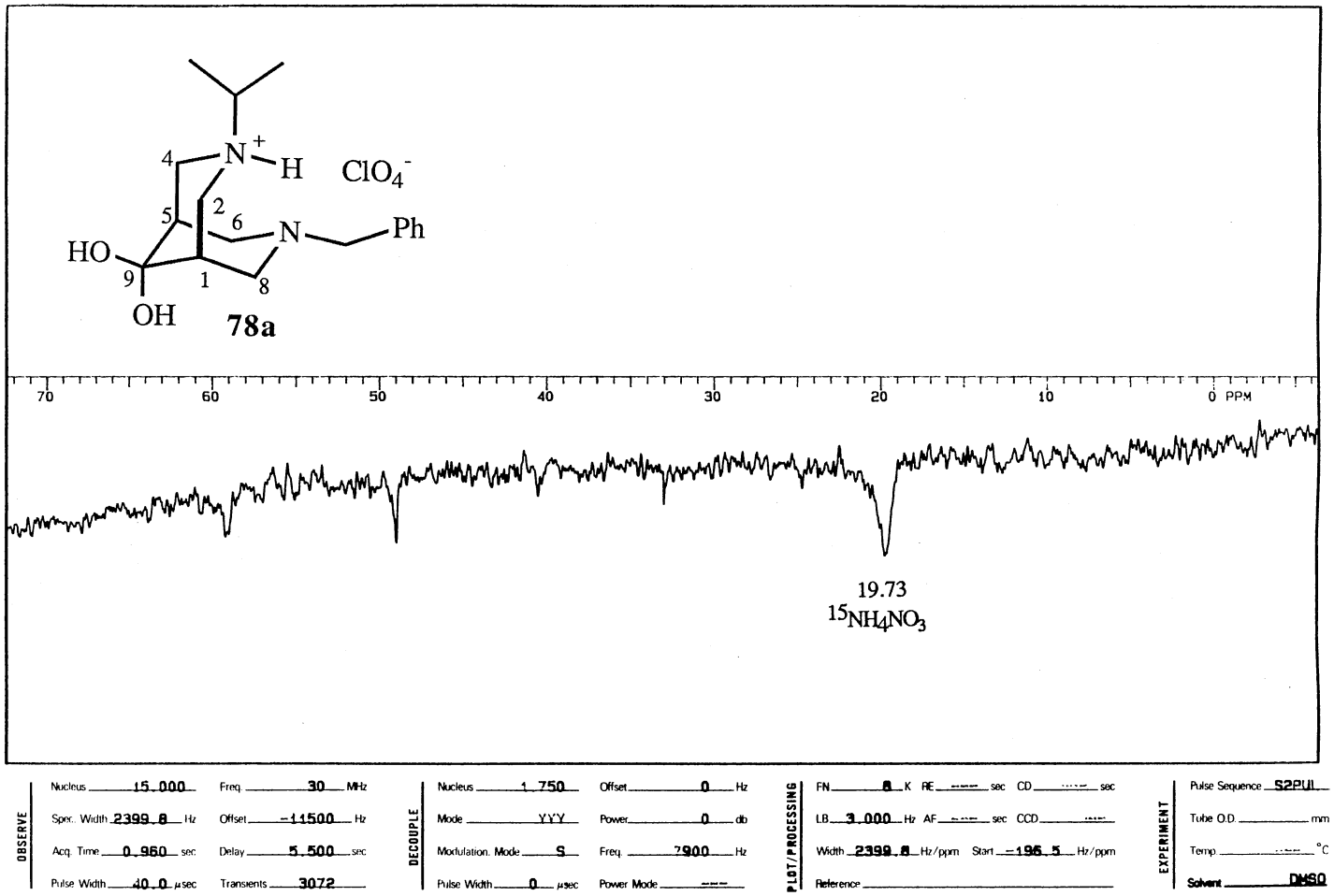
^{1}H NMR Spectrum of **78a**

Plate XXV



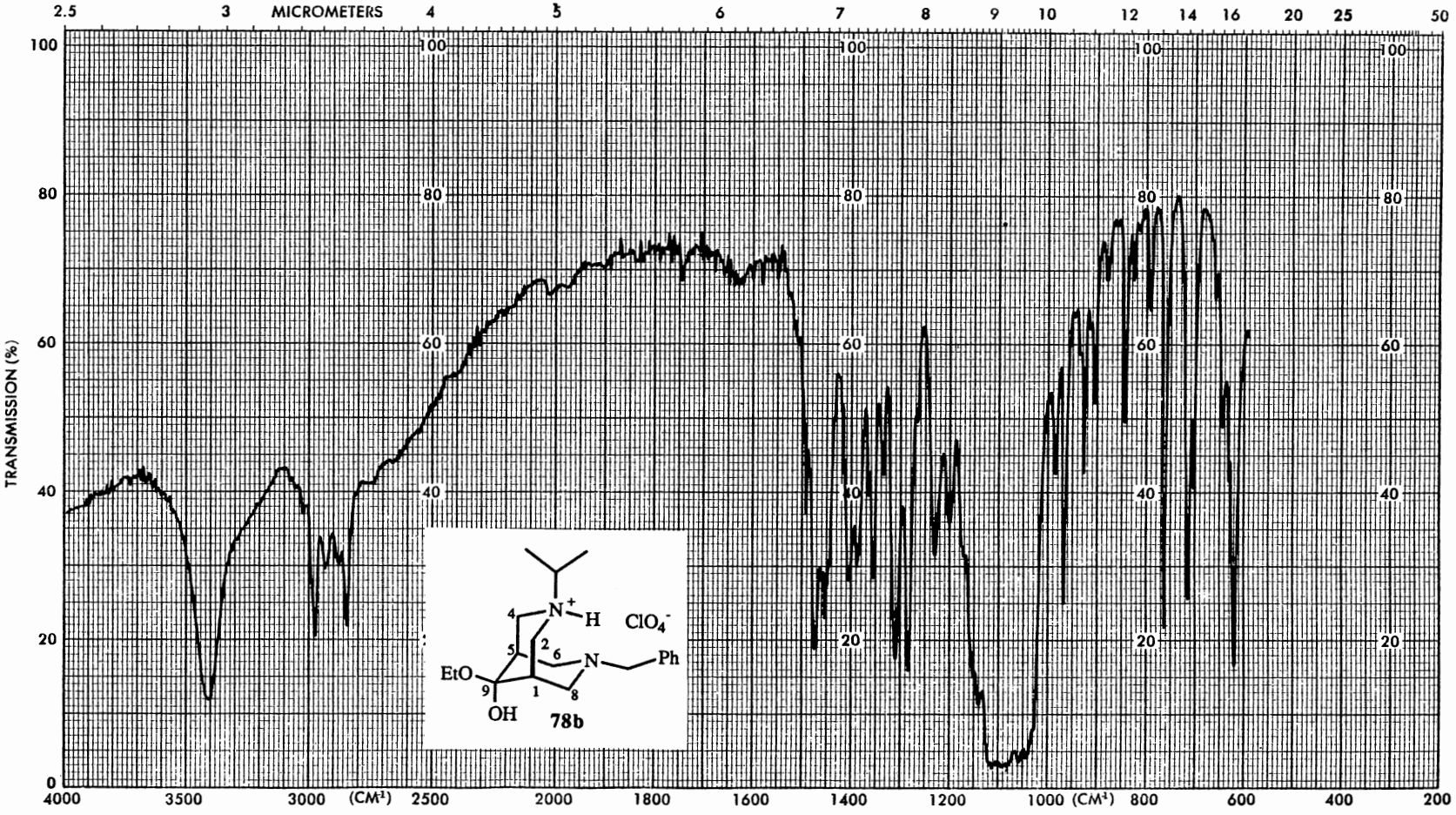
^{13}C NMR Spectrum of **78a**

Plate XXVI



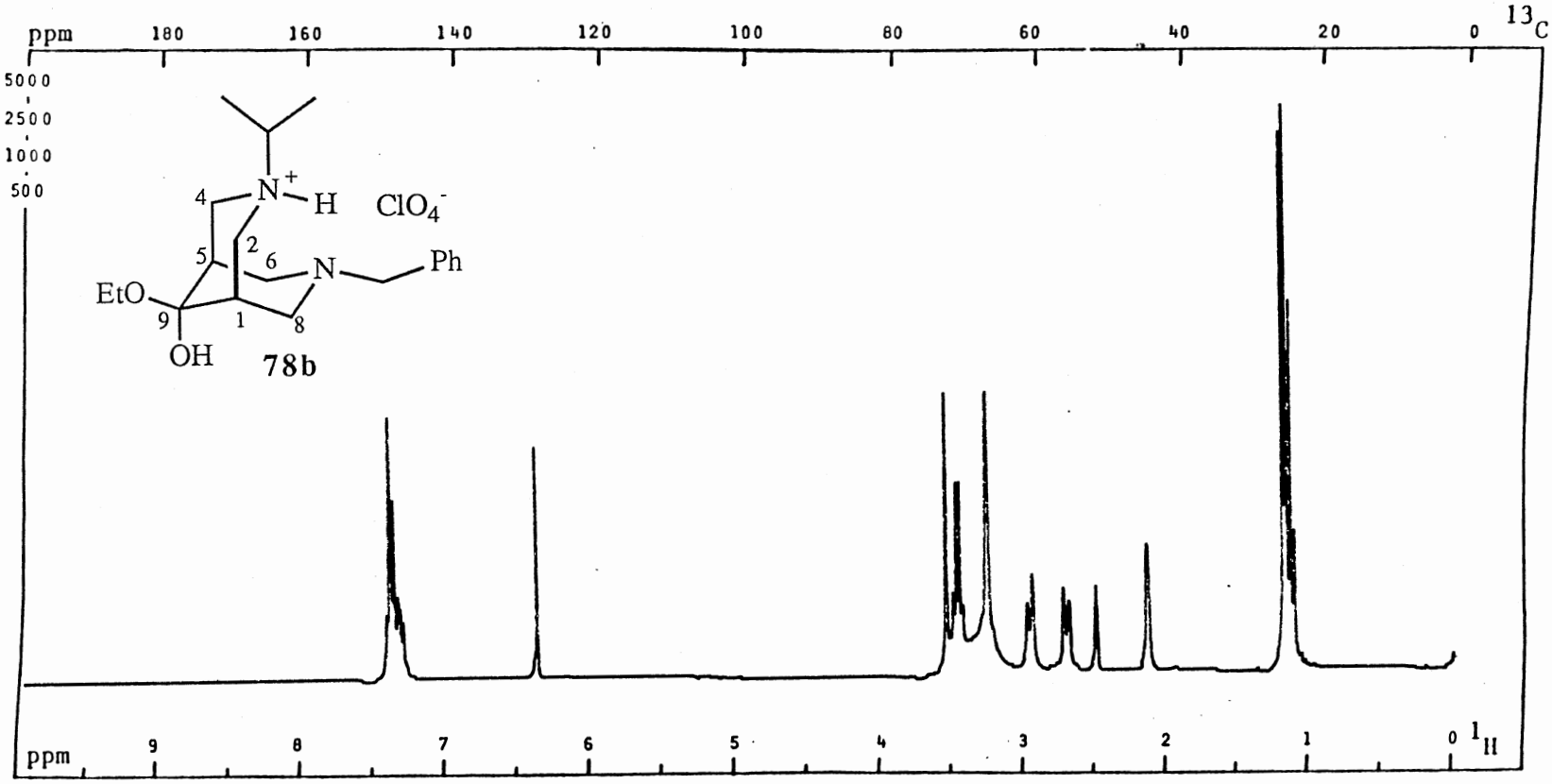
^{15}N NMR Spectrum of **78a**

Plate XXVII



IR Spectrum of **78b**

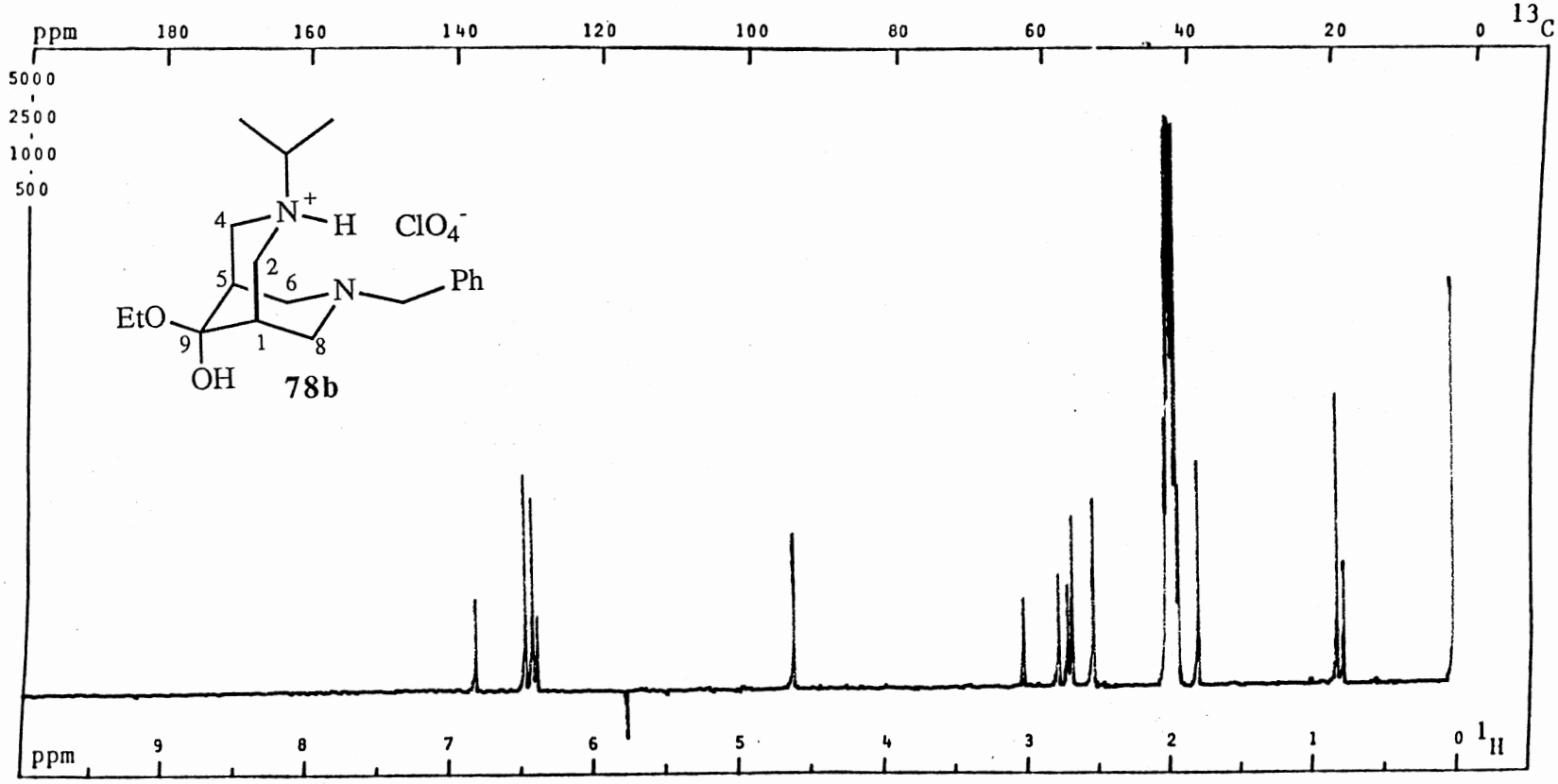
Plate XXVIII



Nucleus: 1.5	Freq: 300 MHz	WC: 2999.4 Hz	Temp: RT
Spec. Width: 4000 Hz	Offset: 1500 Hz	PW/RF: 12 µs/dB	Solvent: DMSO
Acq. Time: 2.0 sec	Delay: 0 sec	Size: 16 K	
Pulse Width: 10.0 sec	Transients: 64	LB: - Hz	

^{1}H NMR Spectrum of **78b**

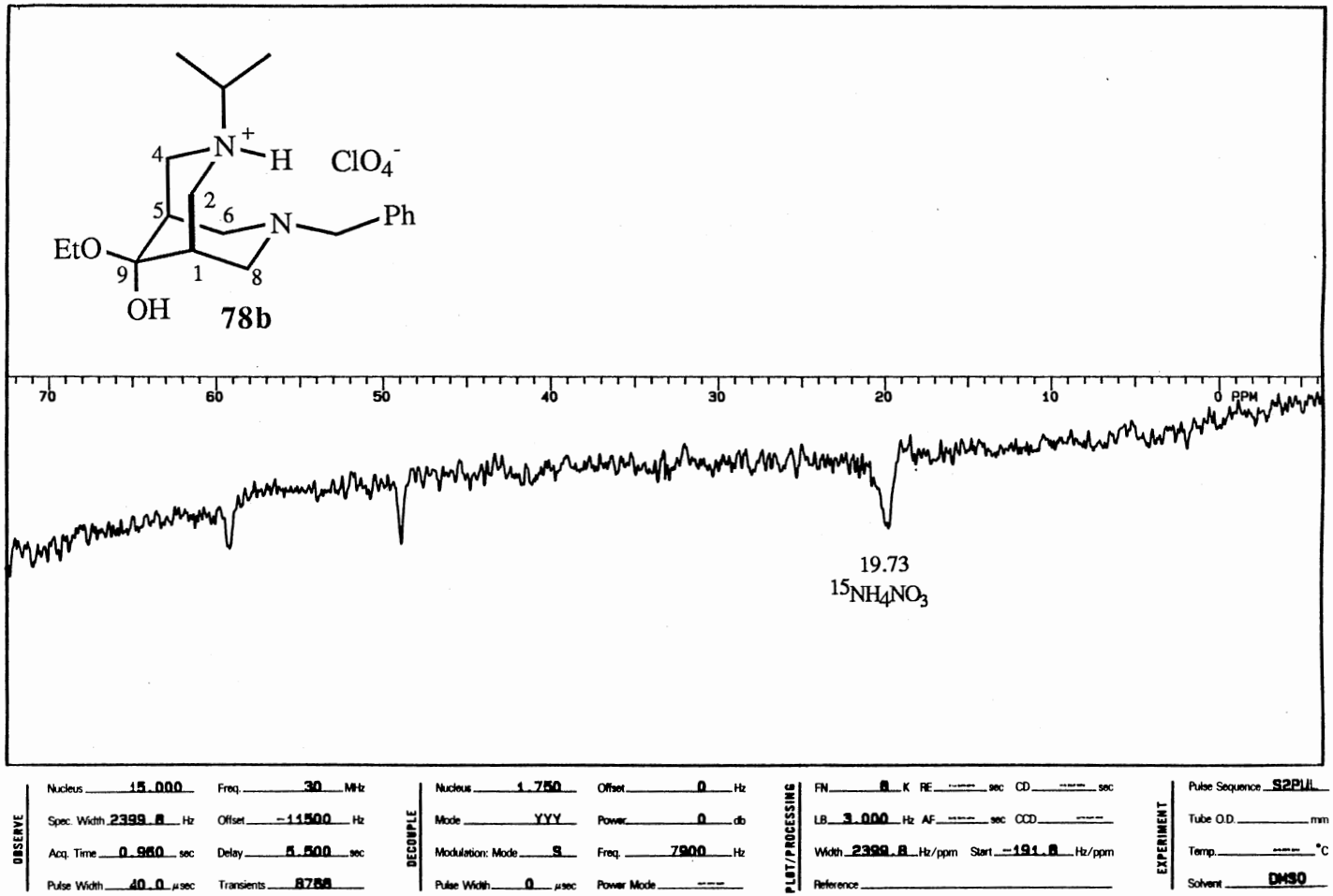
Plate XXIX



Nucleus: 13.5	Freq: 75 MHz	WC: 15085.9 Hz	Temp: RT
Spec. Width: 20000 Hz	Offset: 1500 Hz	PW/RF: 12 µs/dB	Solvent: DMSO
Acq. Time: 1.0 sec	Delay: 3.0 sec	Size: 32 K	
Pulse Width: 10.0 sec	Transients: 400	LB: 2.0 Hz	

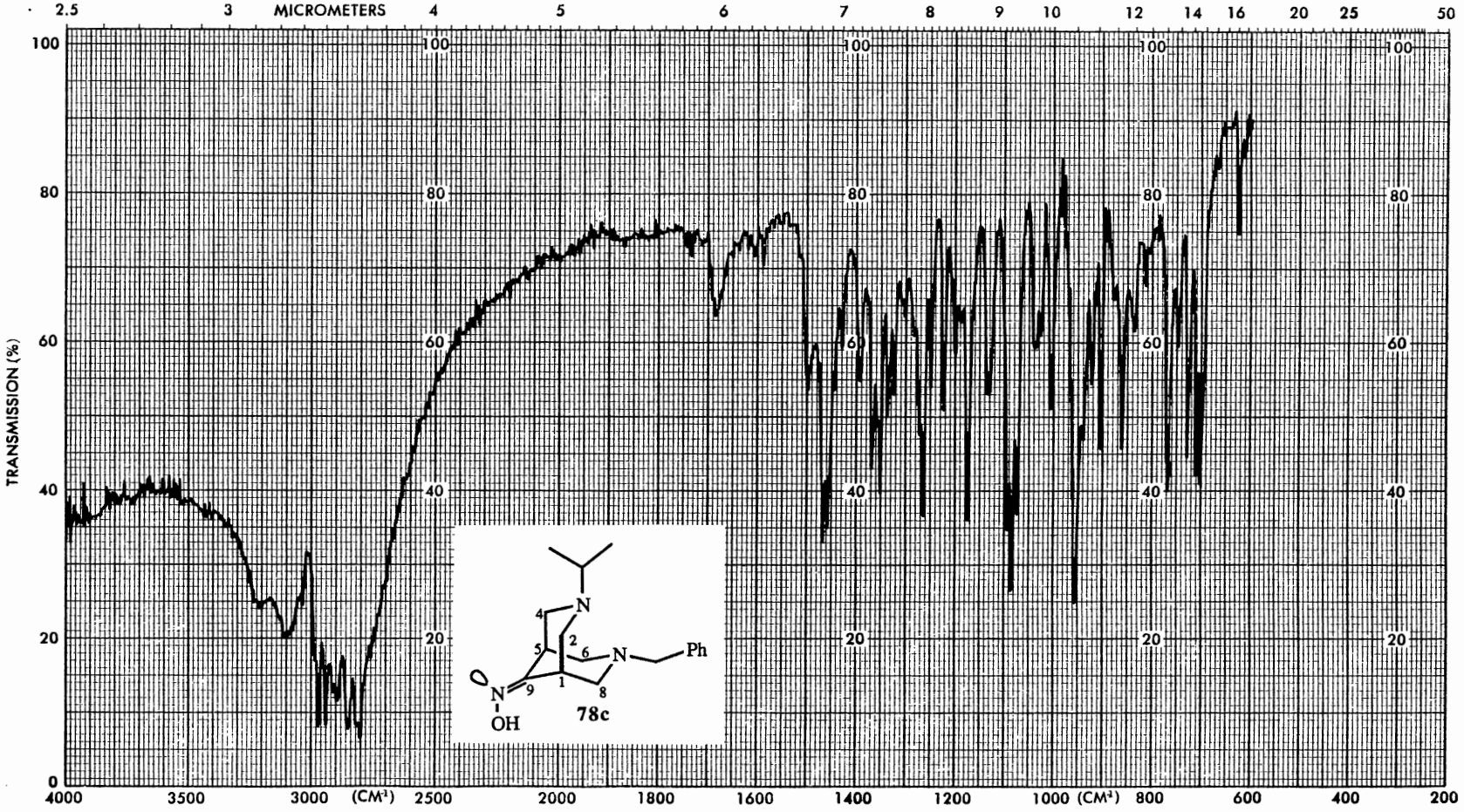
^{13}C NMR Spectrum of **78b**

Plate XXX



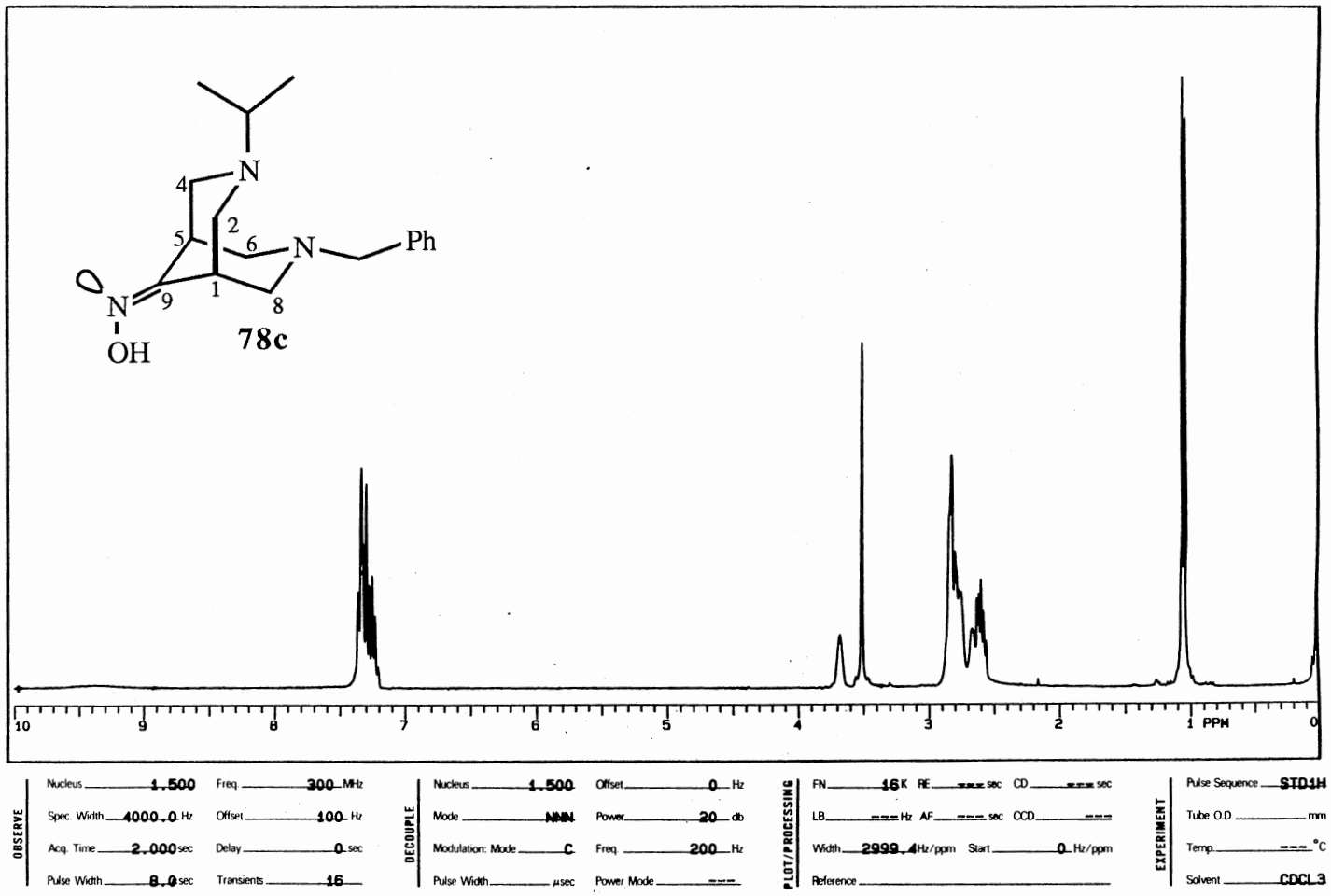
^{15}N NMR Spectrum of **78b**

Plate XXXI



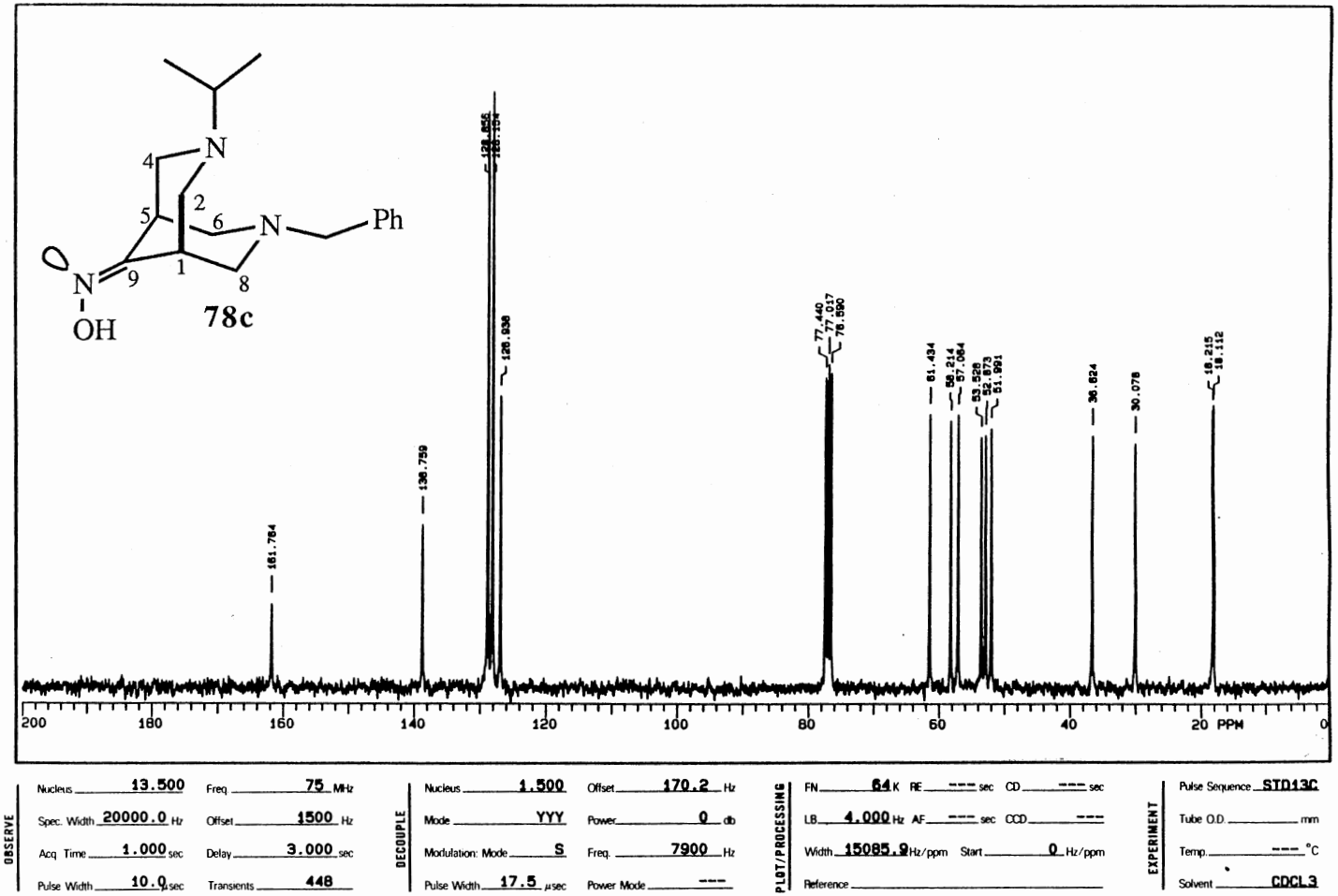
IR Spectrum of **78c**

Plate XXXII



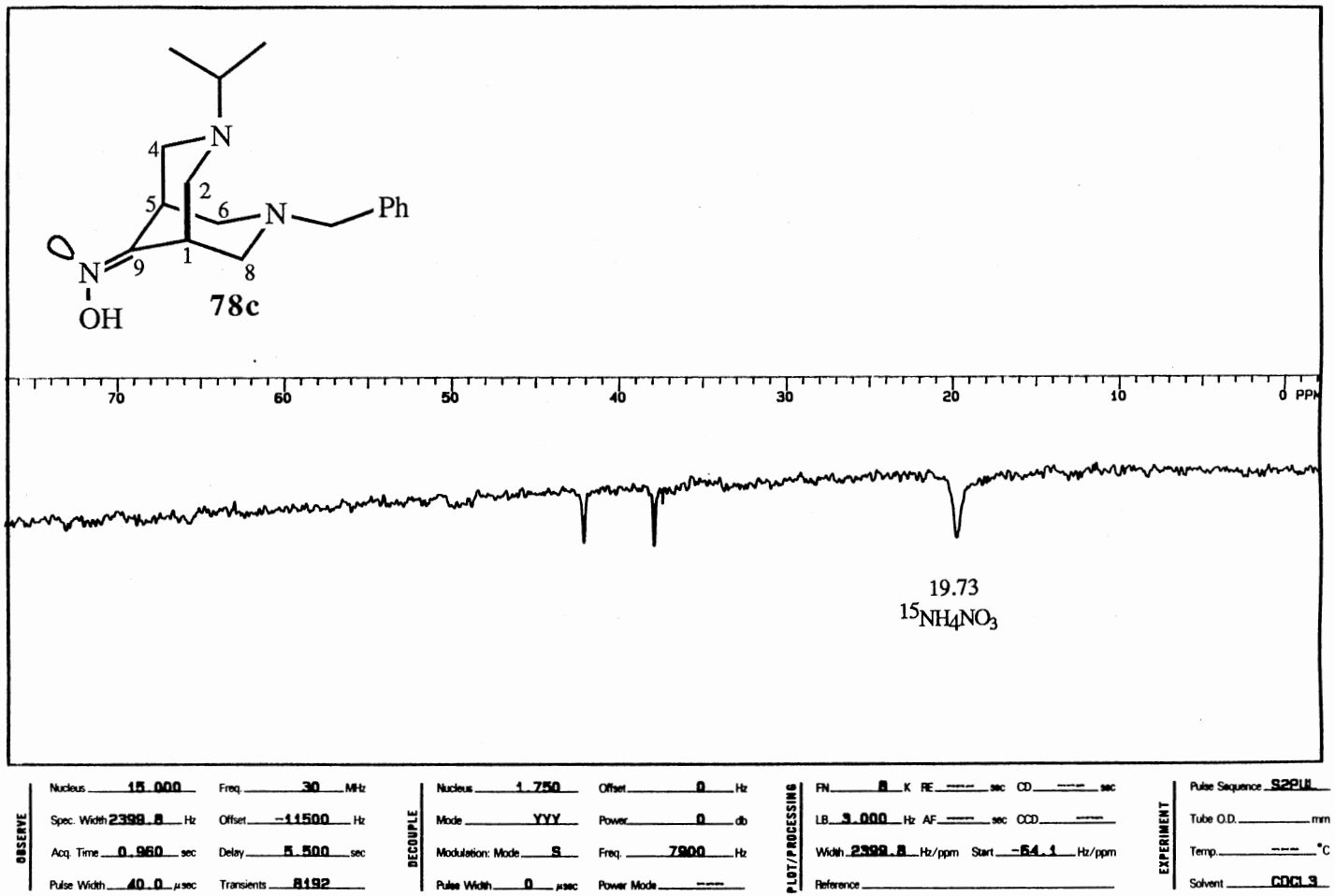
^{1}H NMR Spectrum of **78c**

Plate XXXIII



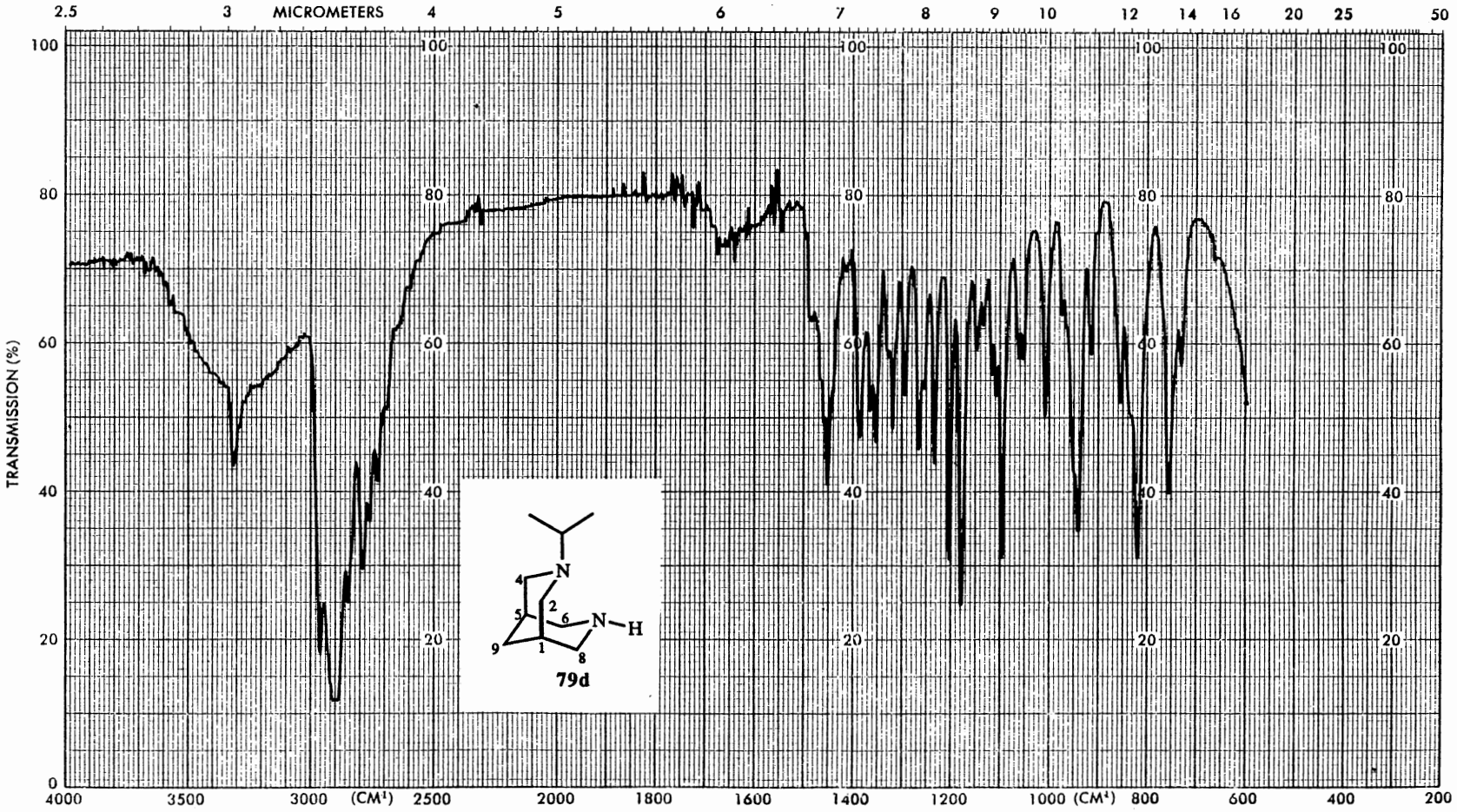
^{13}C NMR Spectrum of **78c**

Plate XXXIV



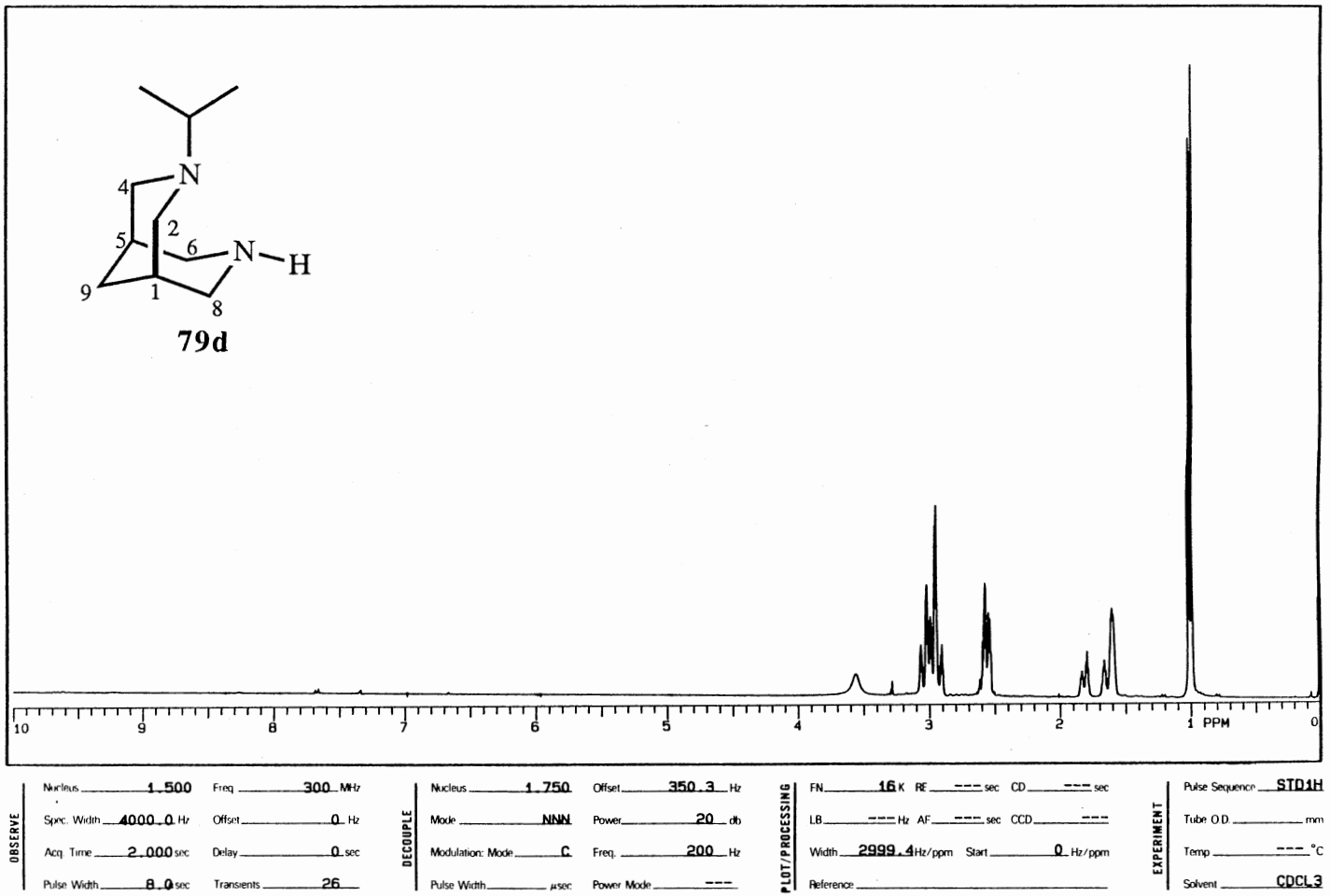
^{15}N NMR Spectrum of **78c**

Plate XXXV



IR Spectrum of **79d**

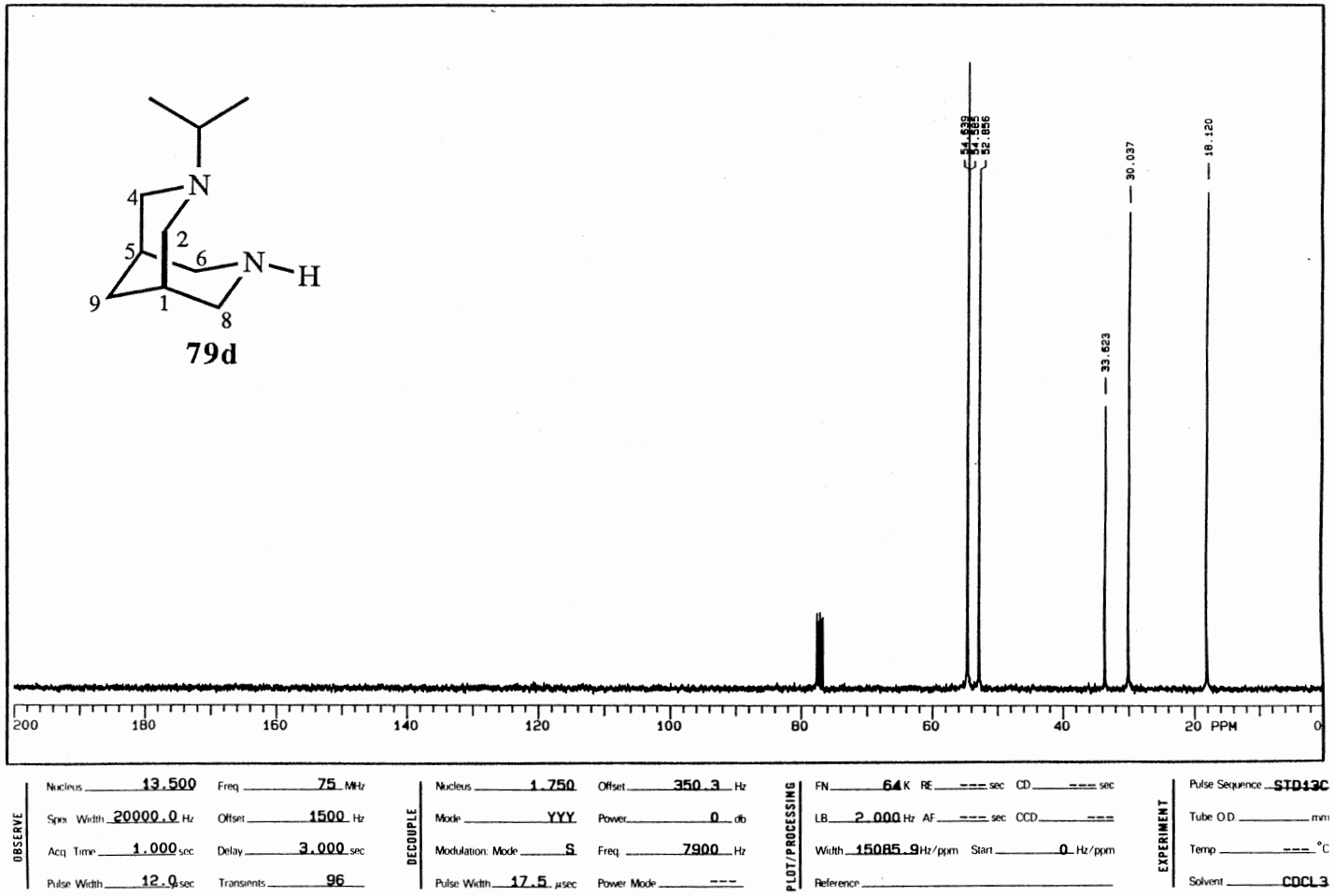
Plate XXXVI



79d

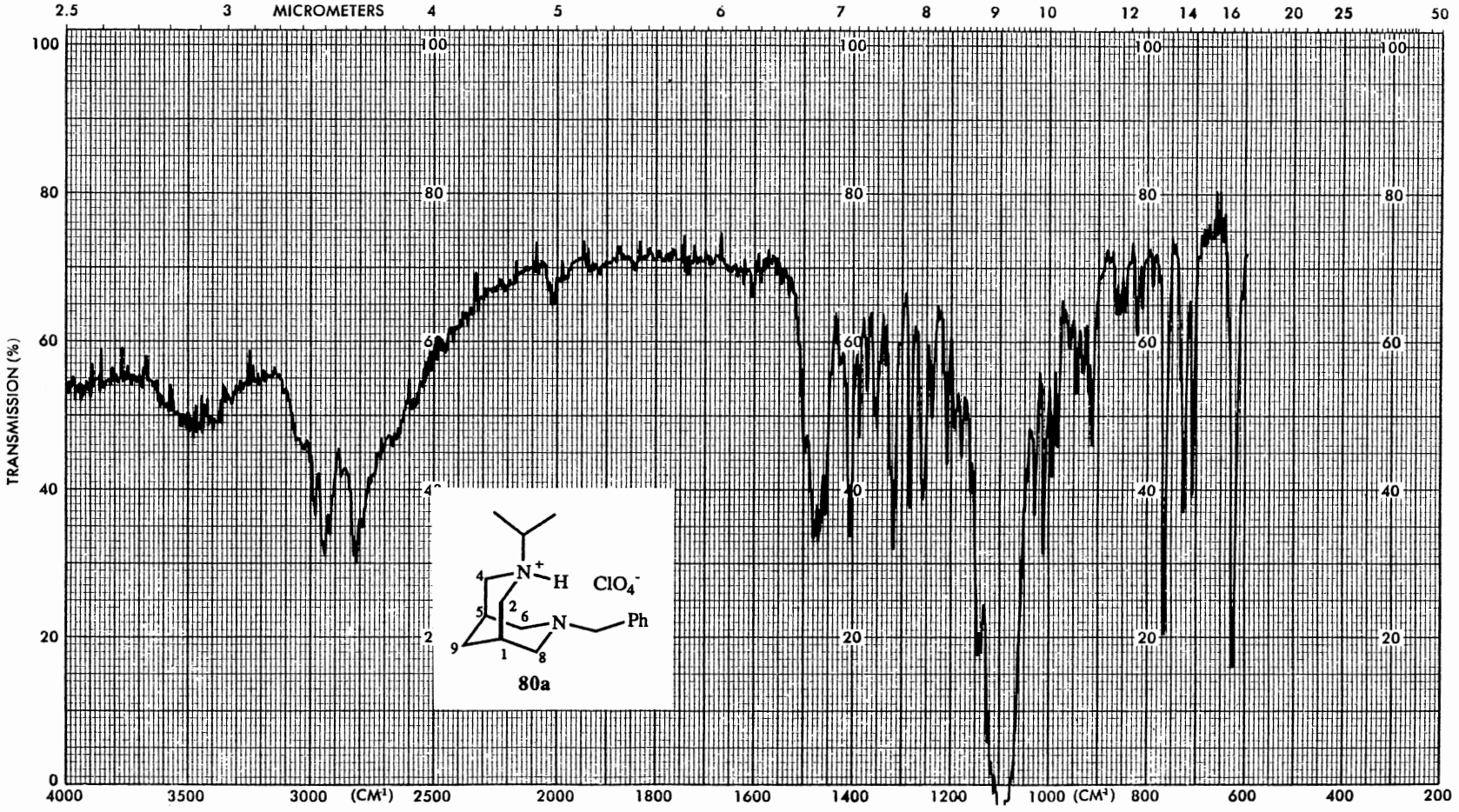
^{1}H NMR Spectrum of **79d**

Plate XXXVII



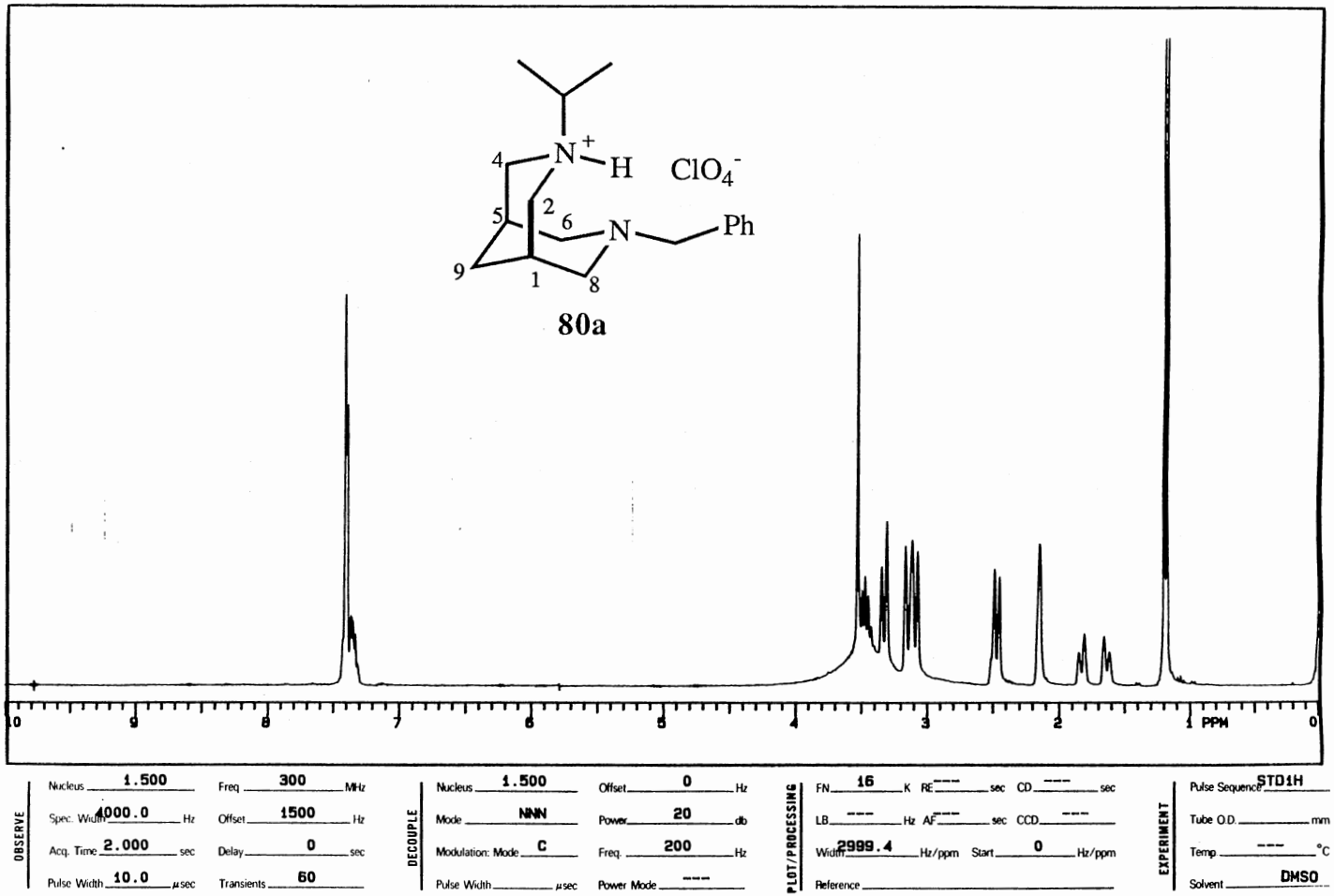
^{13}C NMR Spectrum of **79d**

Plate XXXVIII



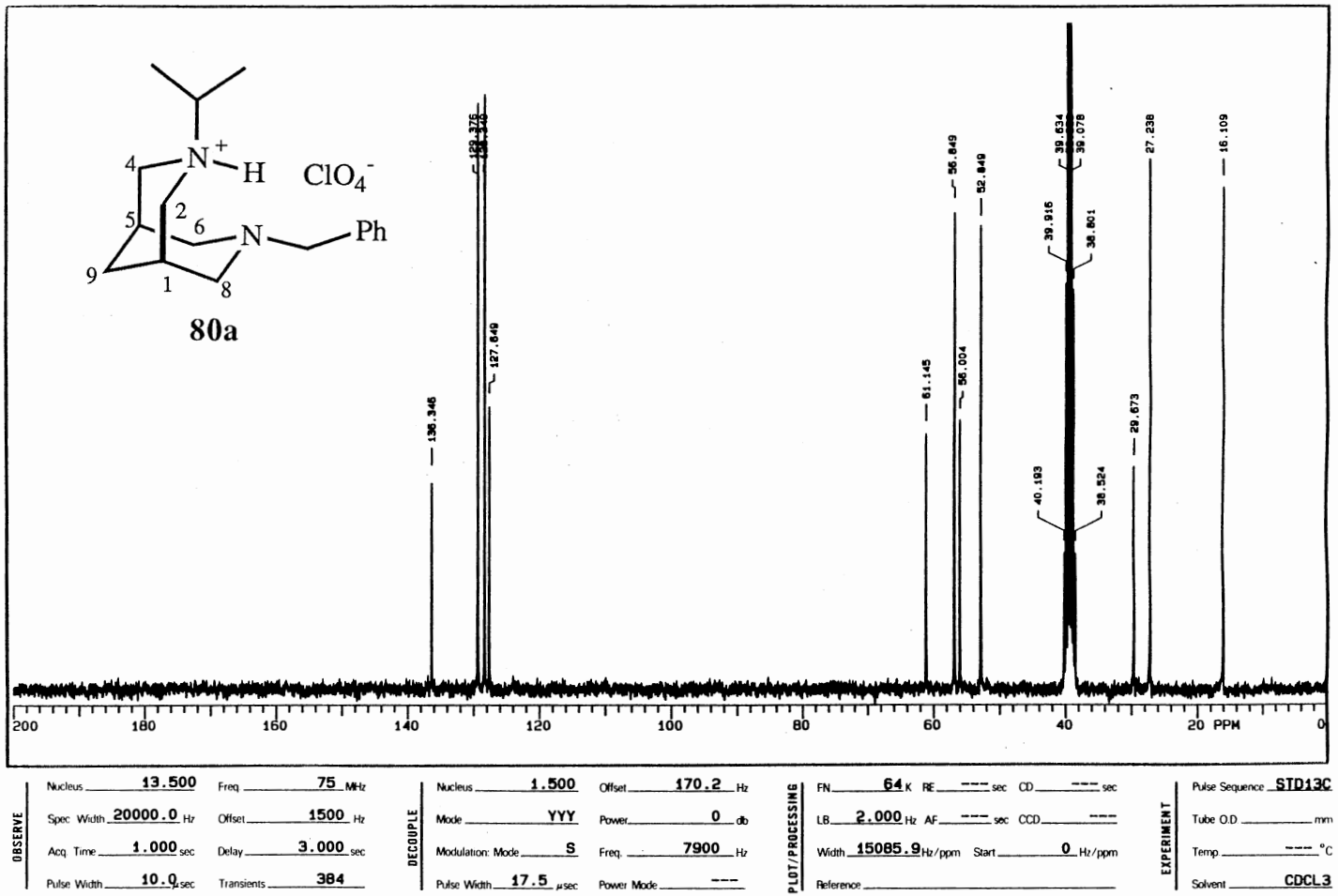
IR Spectrum of **80a**

Plate XXXIX



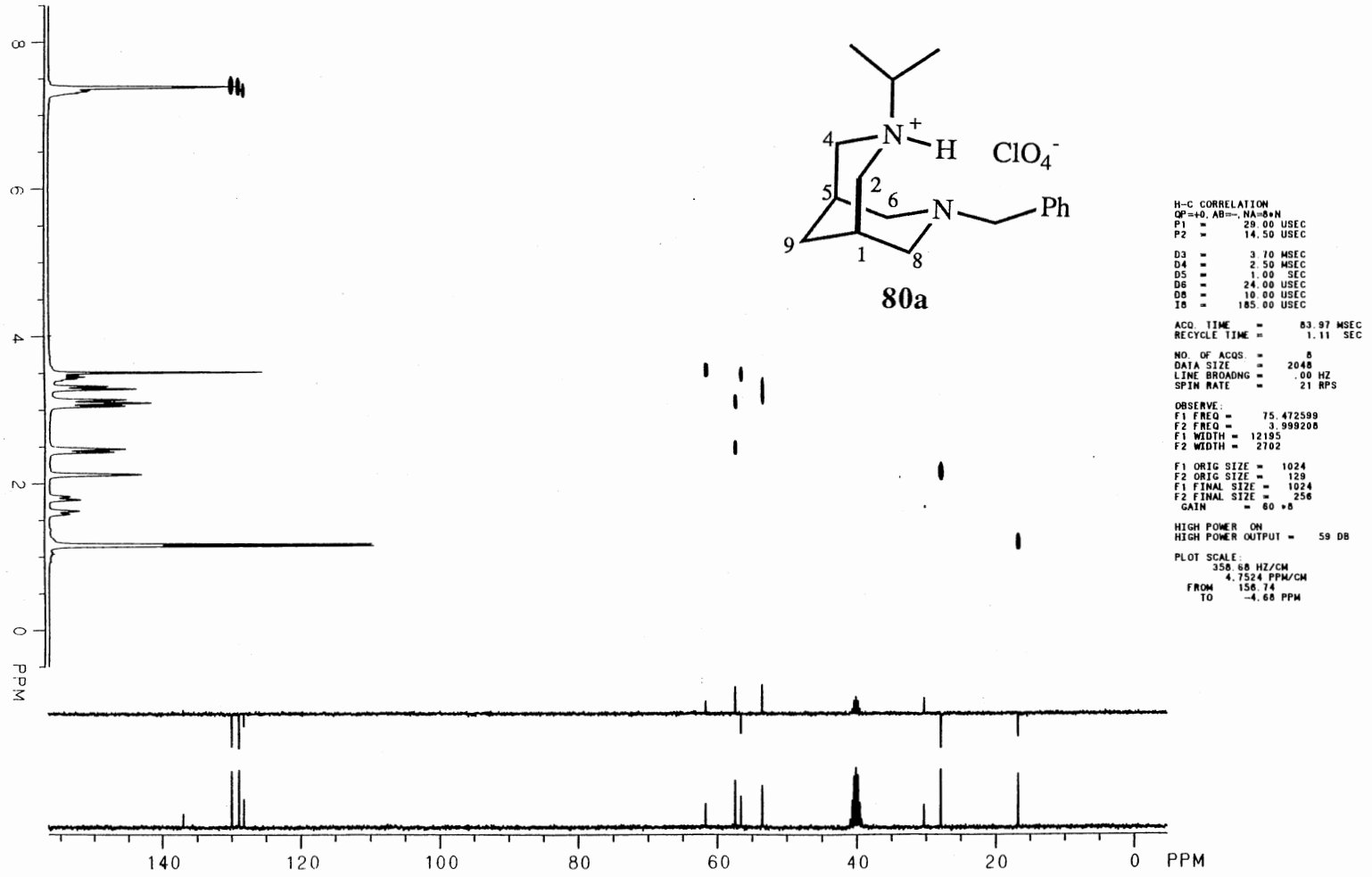
^{1}H NMR Spectrum of **80a**

Plate XL



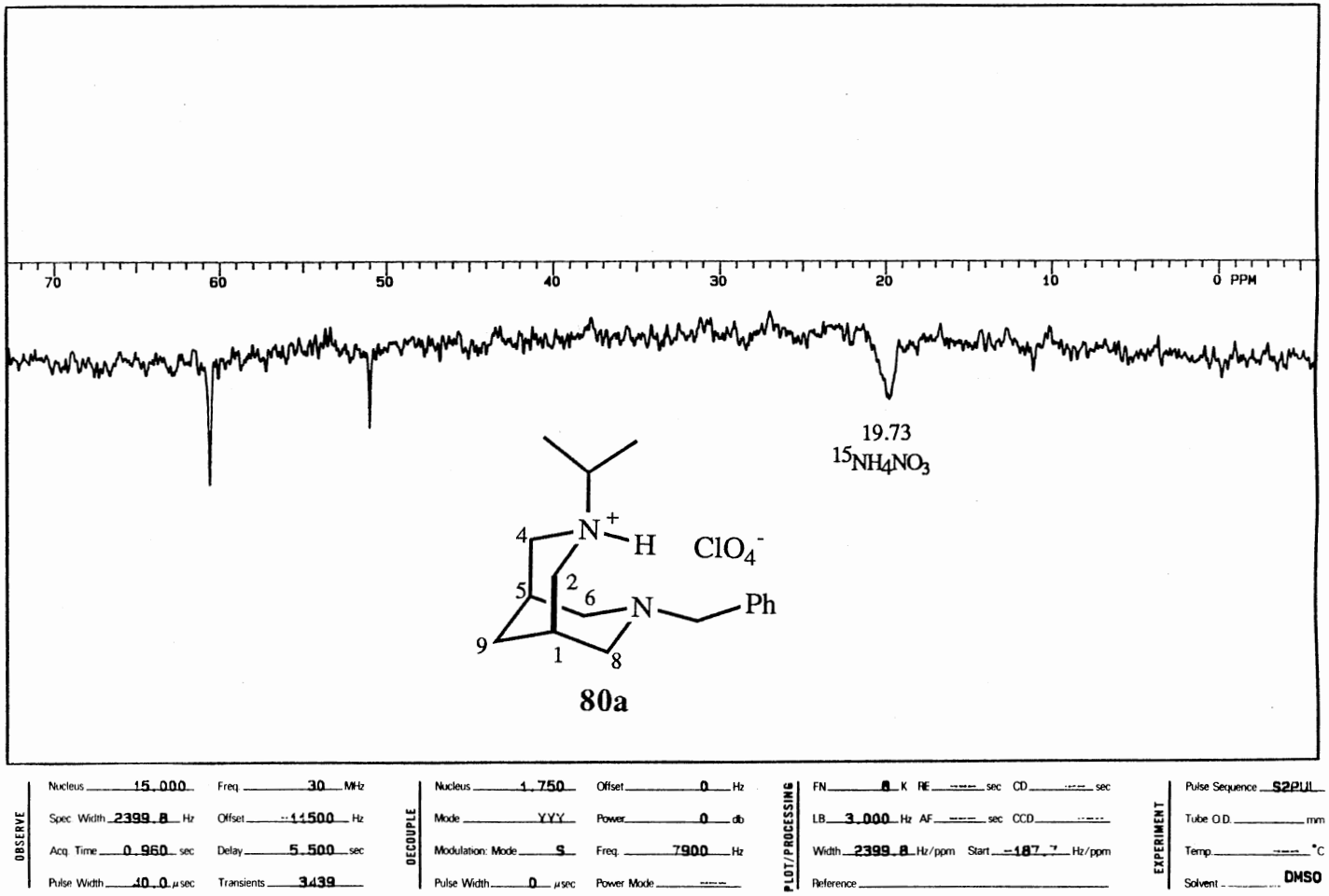
^{13}C NMR Spectrum of **80a**

Plate XLI



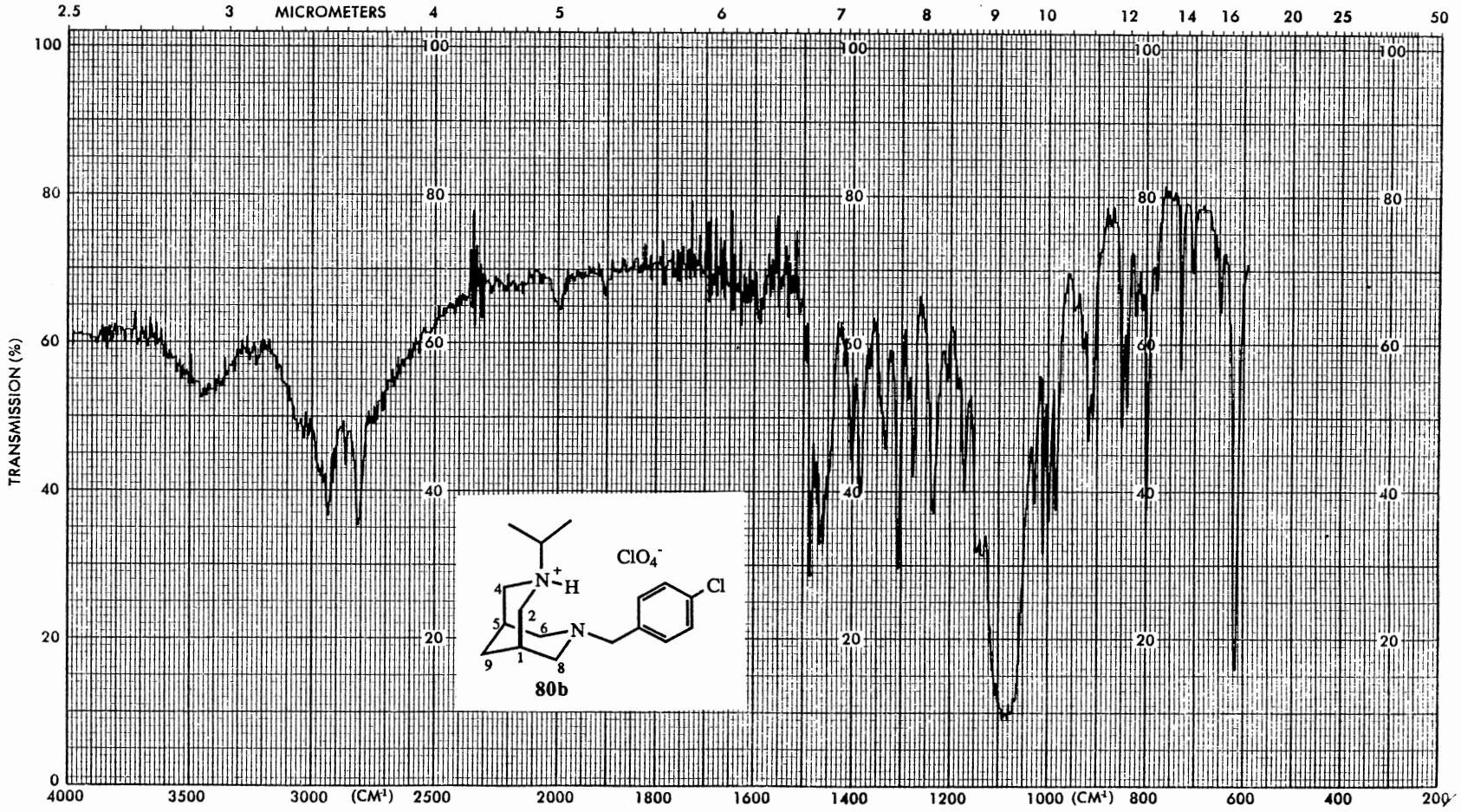
HETCOR Spectrum of **80a**

Plate XLII



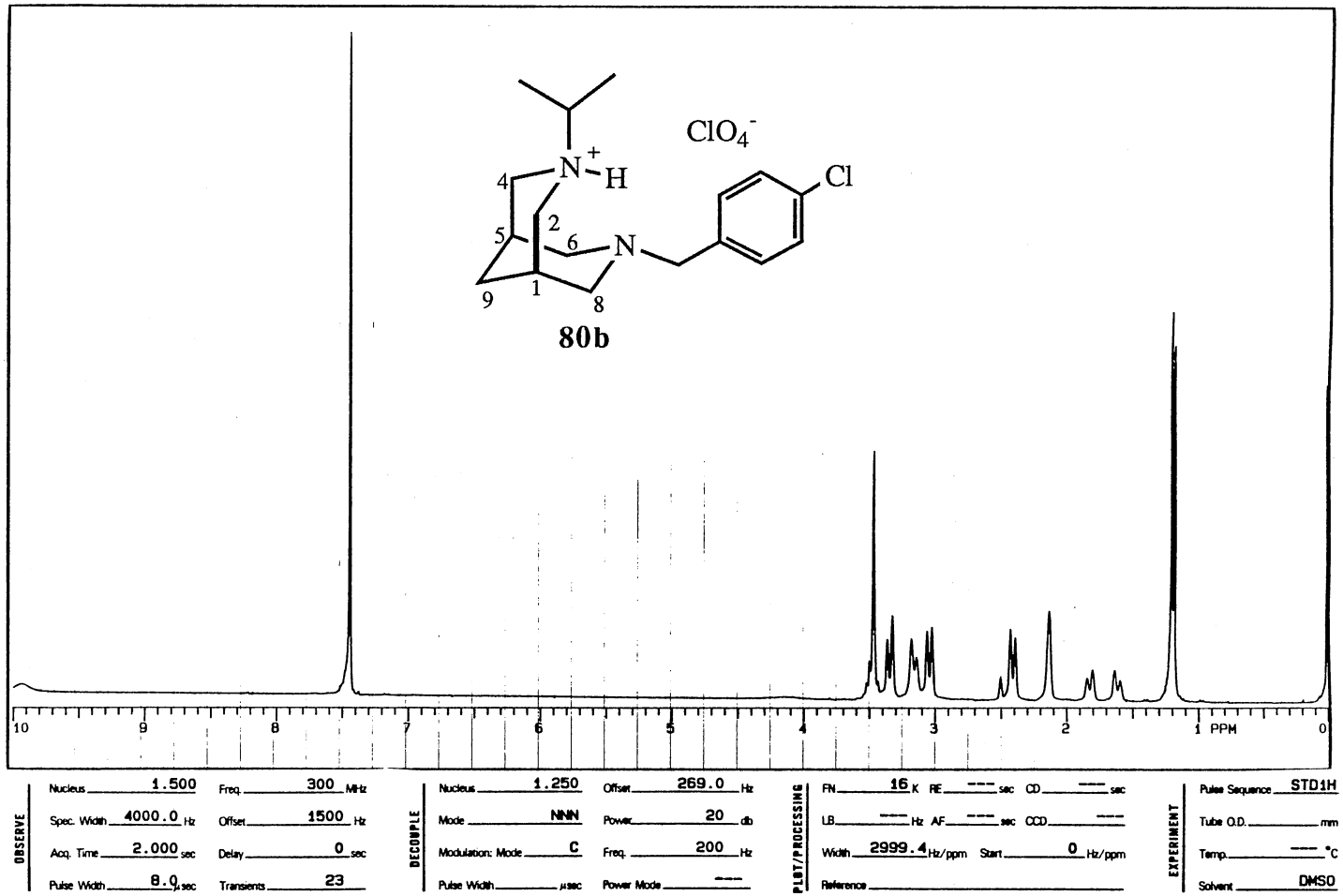
^{15}N NMR Spectrum of **80a**

Plate XLIII



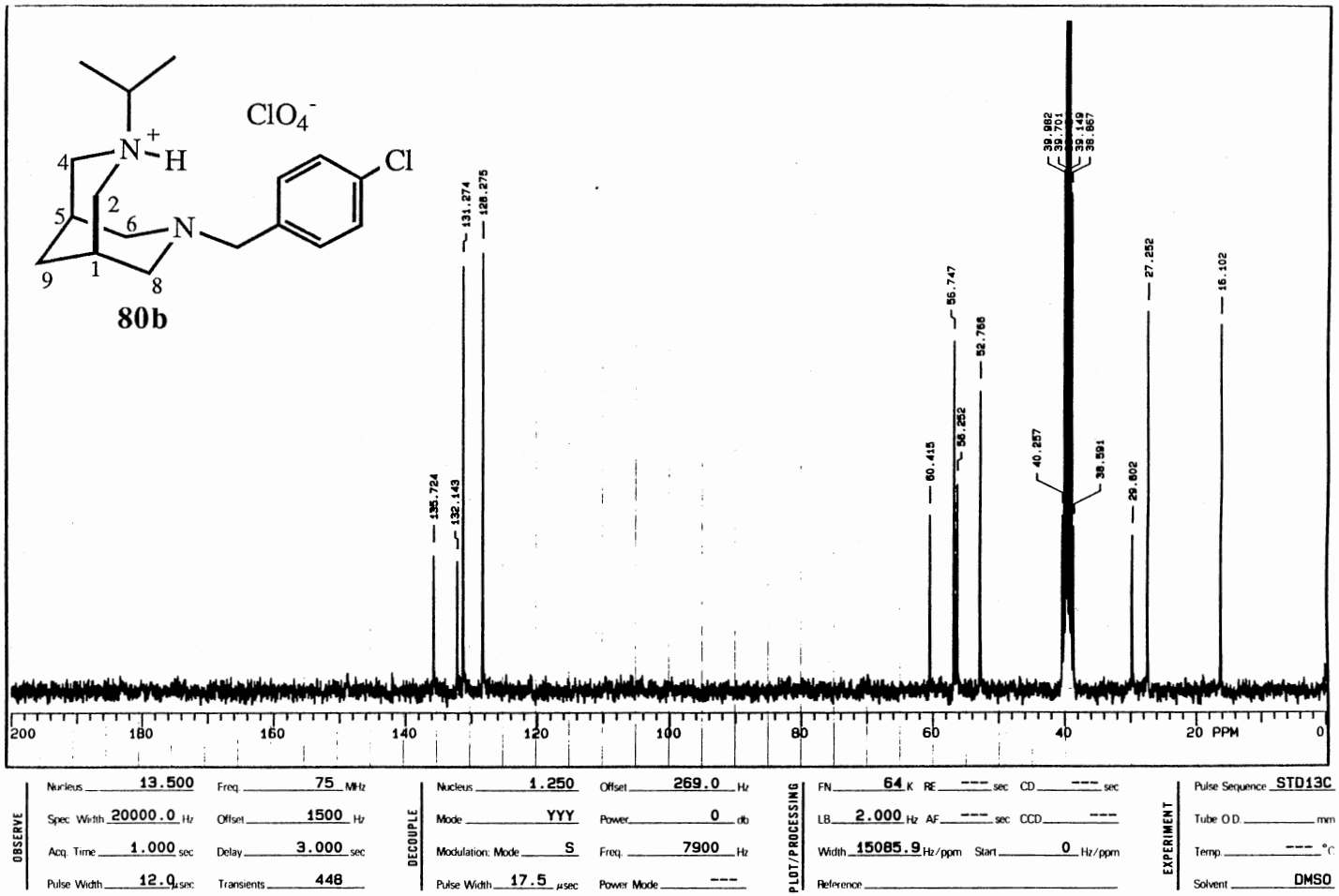
IR Spectrum of **80b**

Plate XLIV



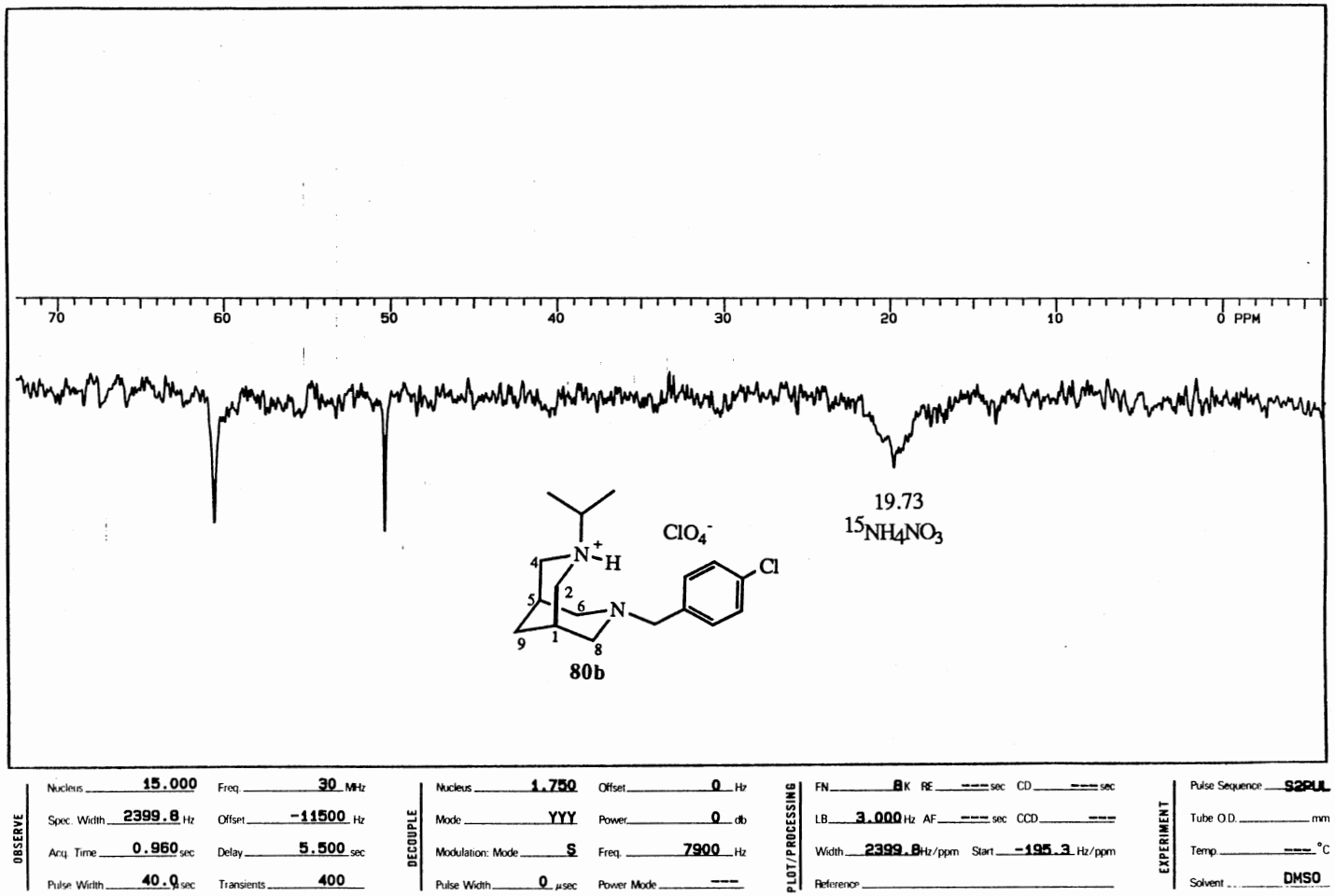
^{1}H NMR Spectrum of **80b**

Plate XLV



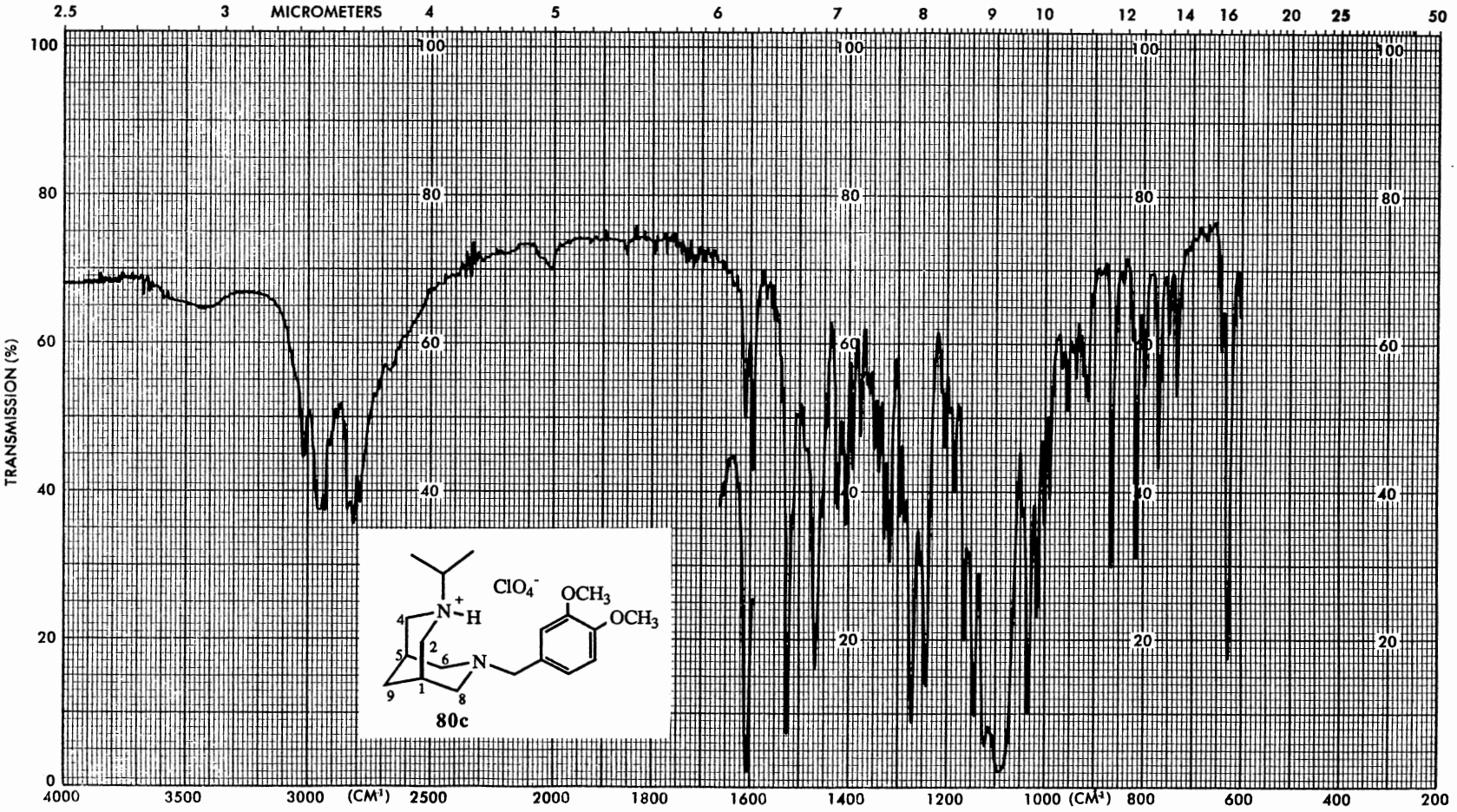
^{13}C NMR Spectrum of **80b**

Plate XLVI



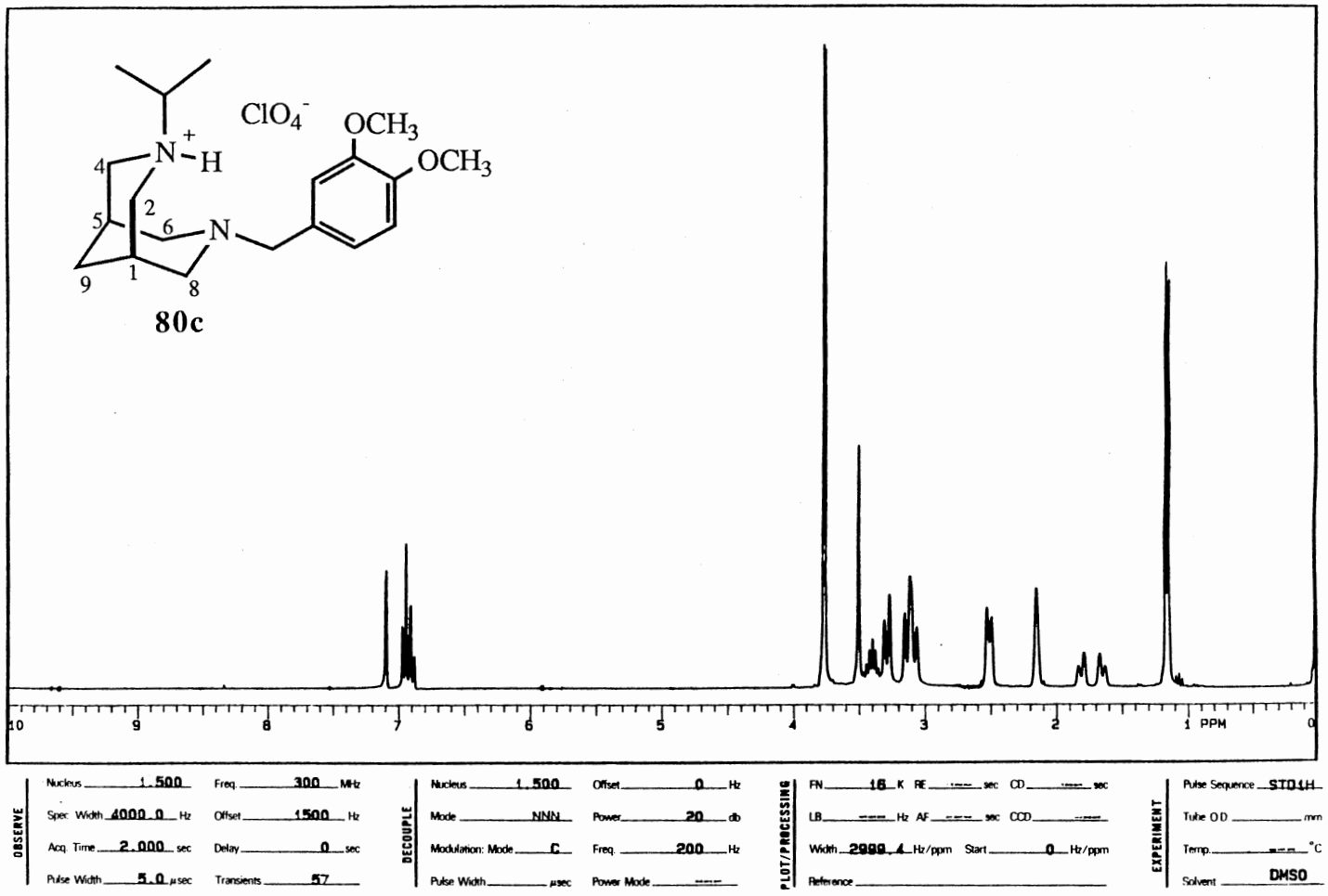
^{15}N NMR Spectrum of **80b**

Plate XLVII



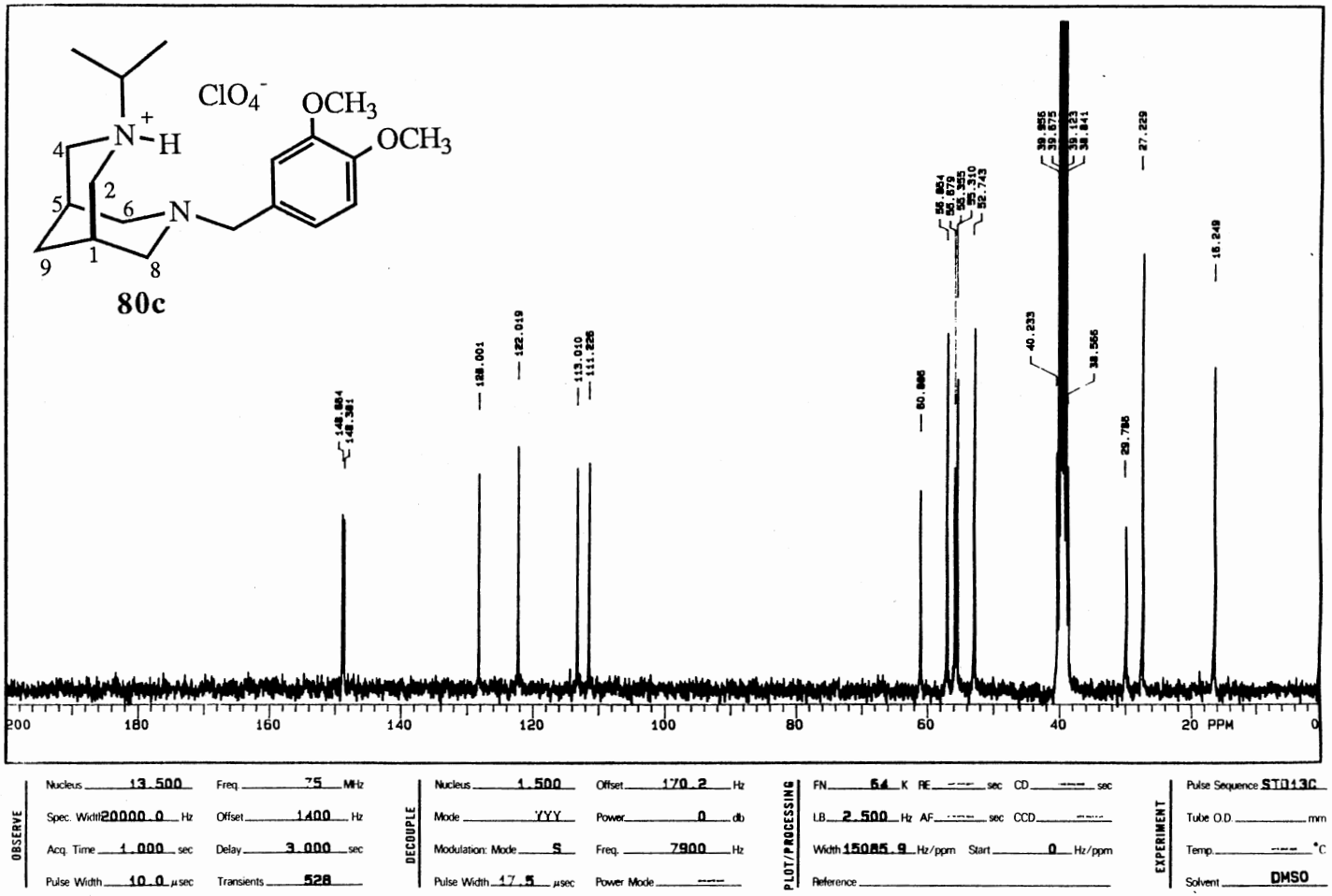
IR Spectrum of **80c**

Plate XLVIII



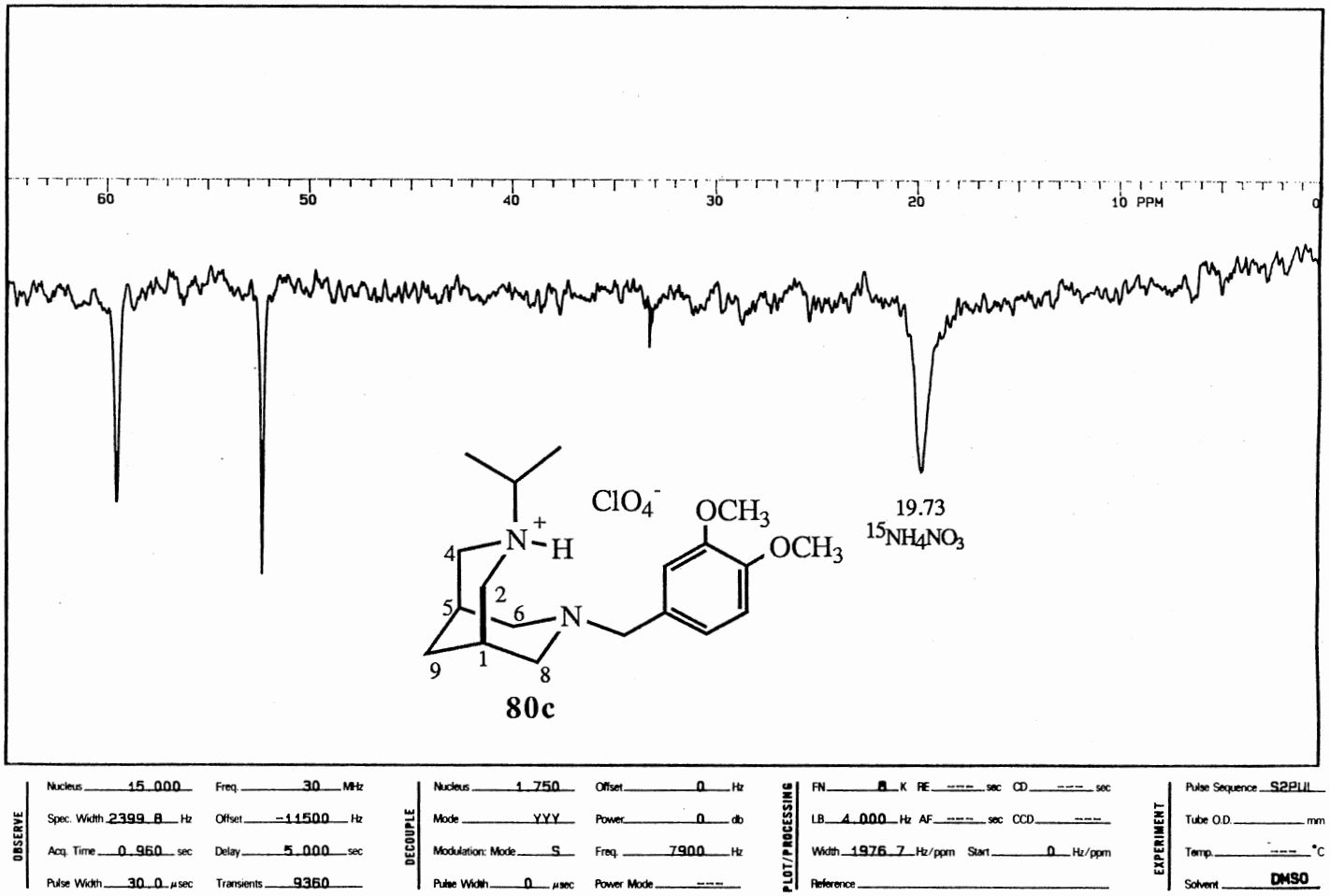
^{1}H NMR Spectrum of **80c**

Plate XLIX



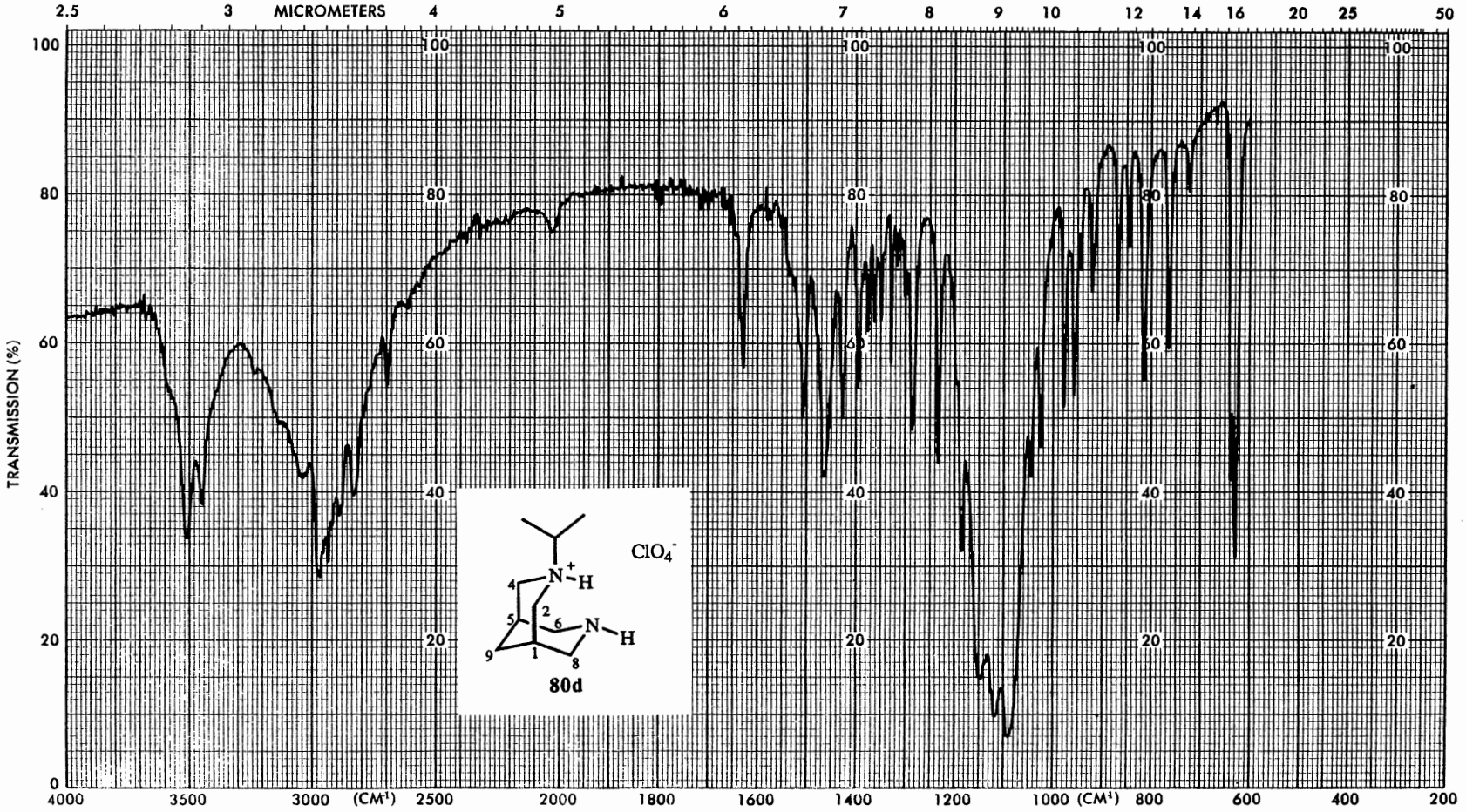
^{13}C NMR Spectrum of **80c**

Plate L



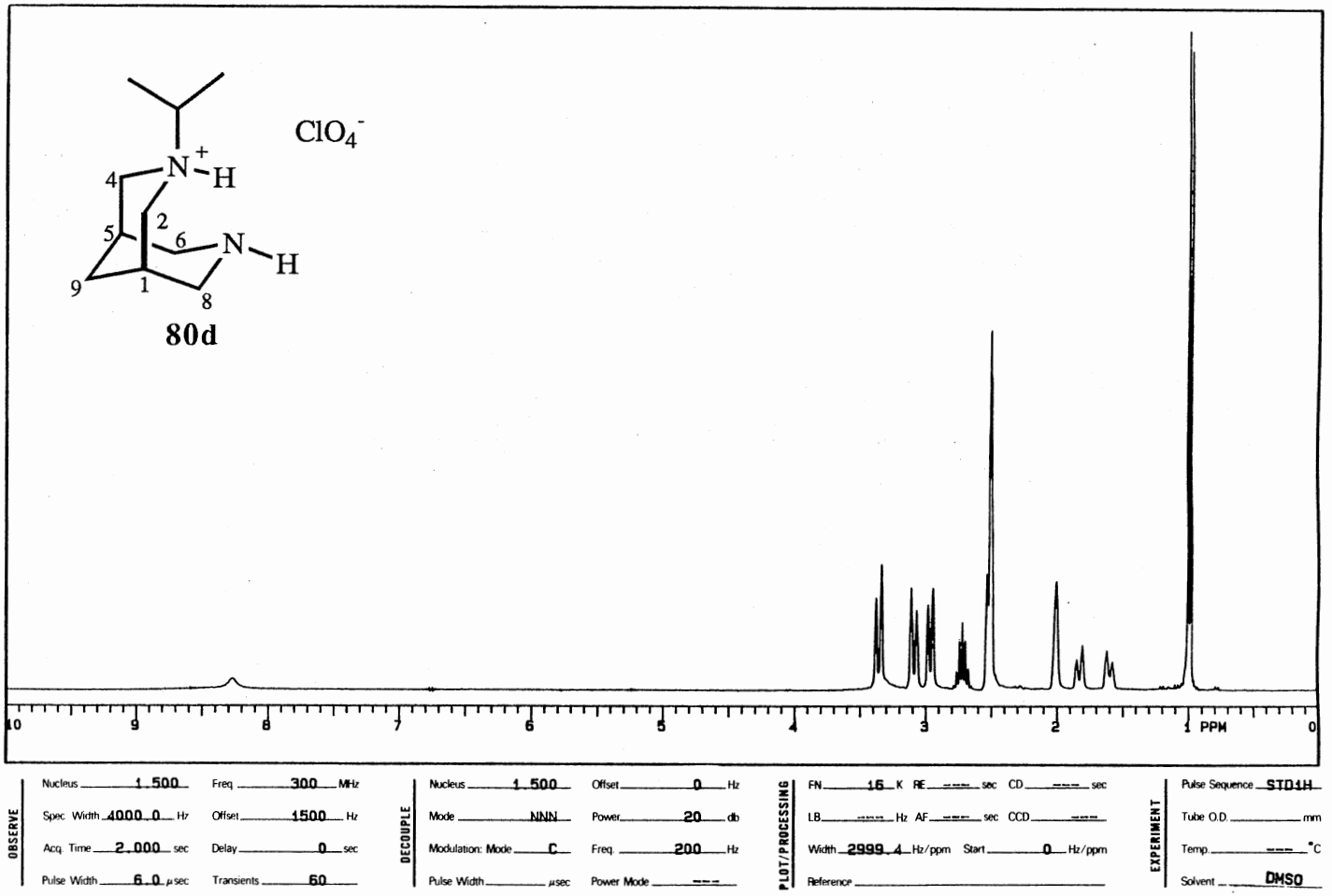
^{15}N NMR Spectrum of **80c**

Plate LI



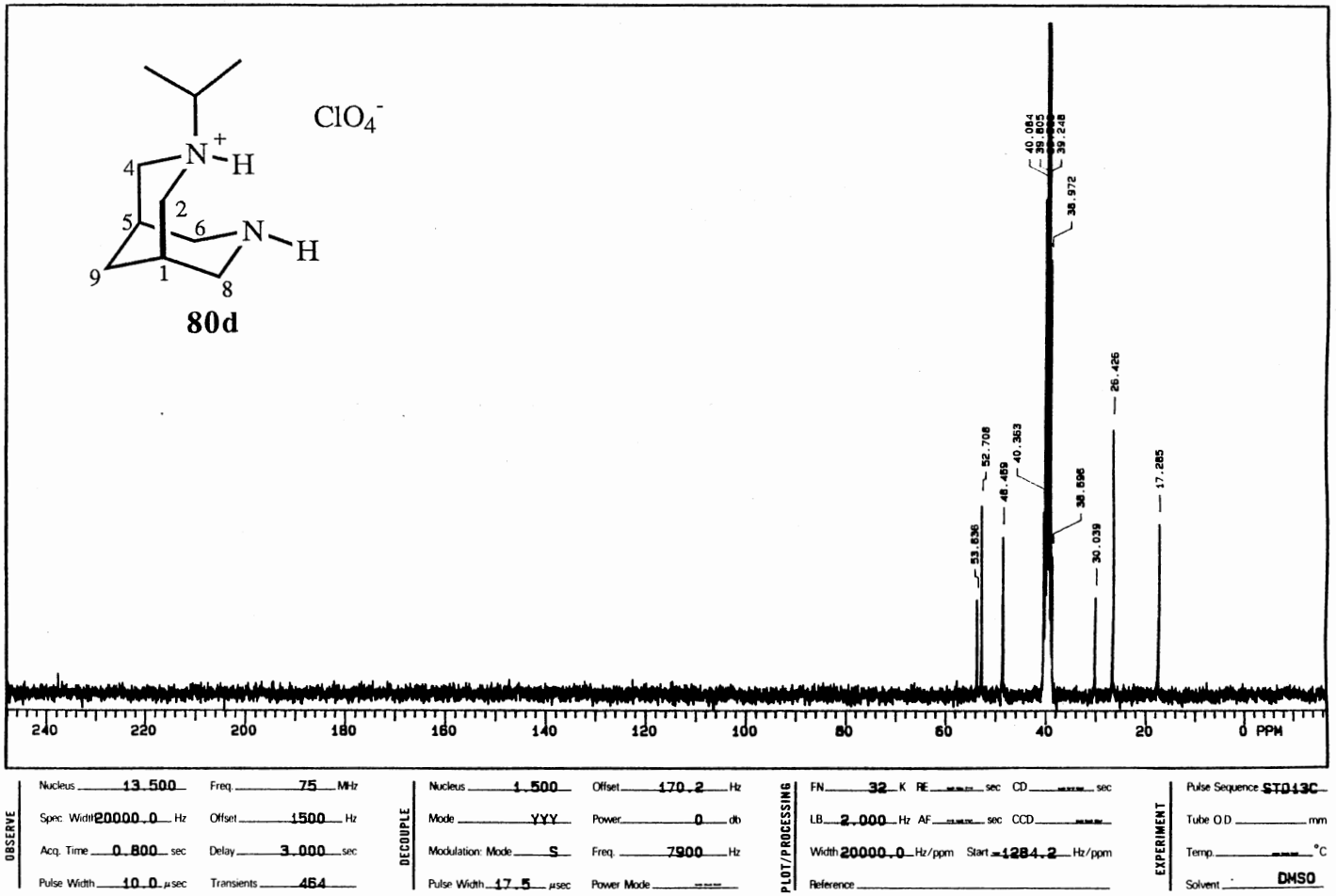
IR Spectrum of **80d**

Plate LII



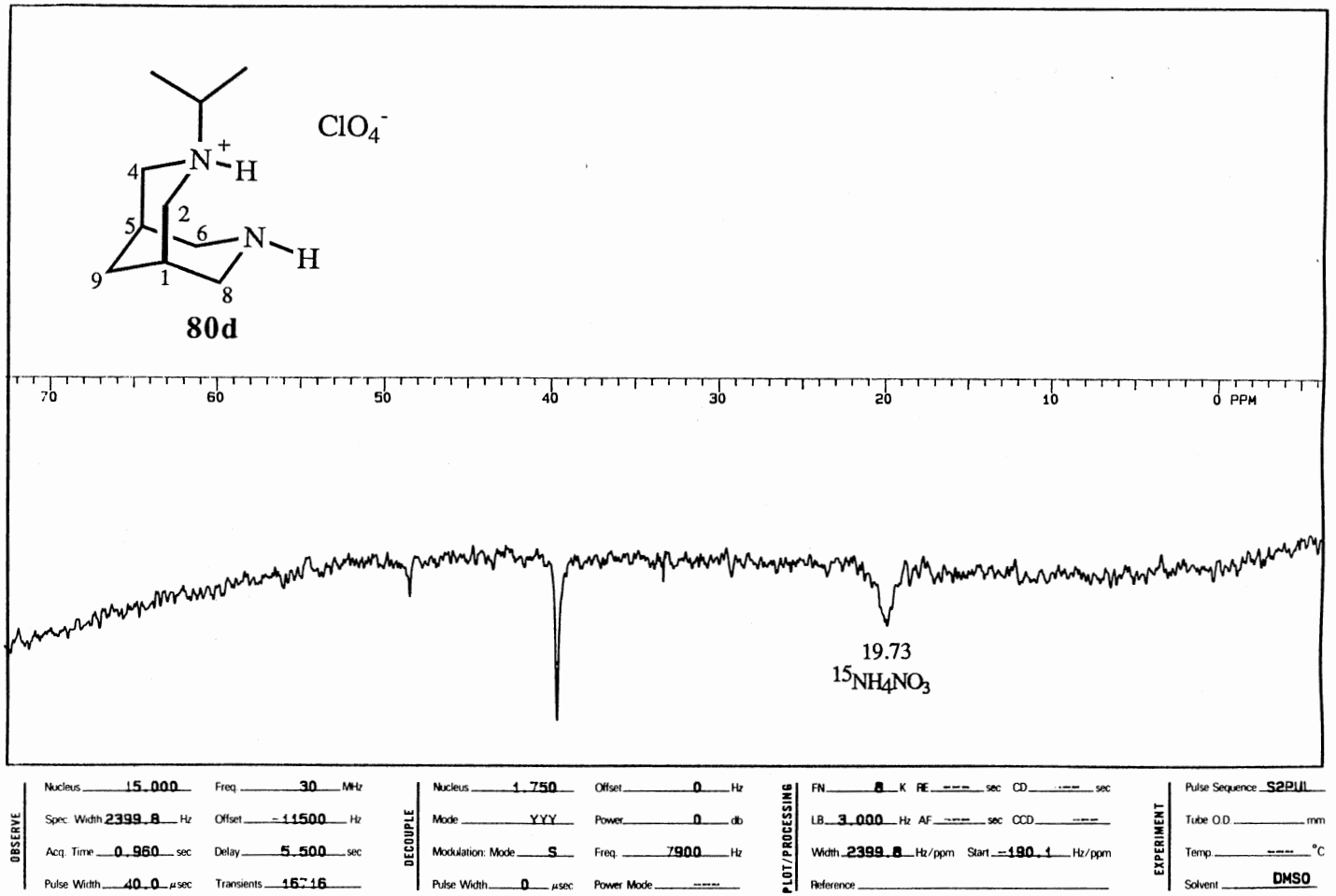
^{1}H NMR Spectrum of **80d**

Plate LIII



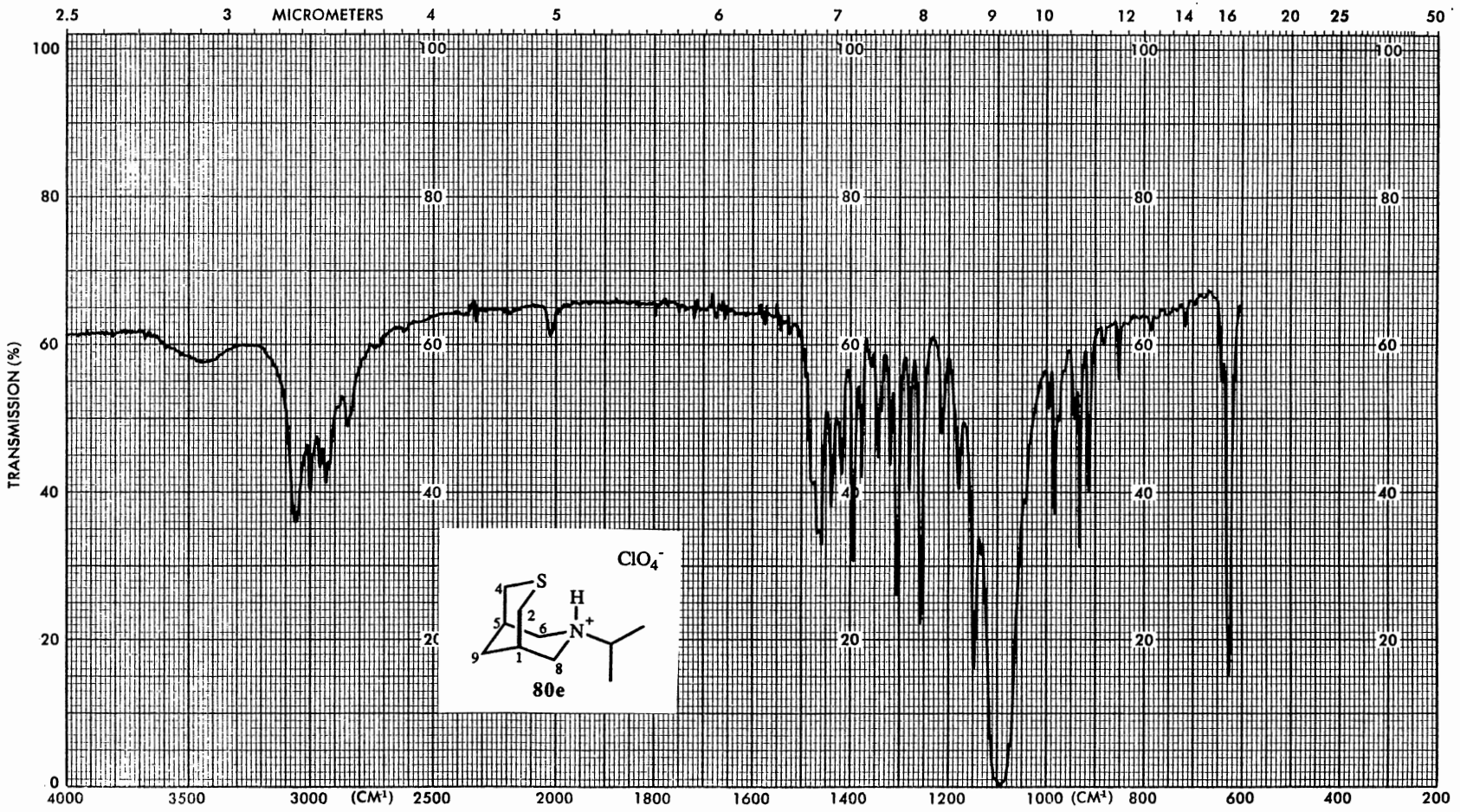
^{13}C NMR Spectrum of **80d**

Plate LIV



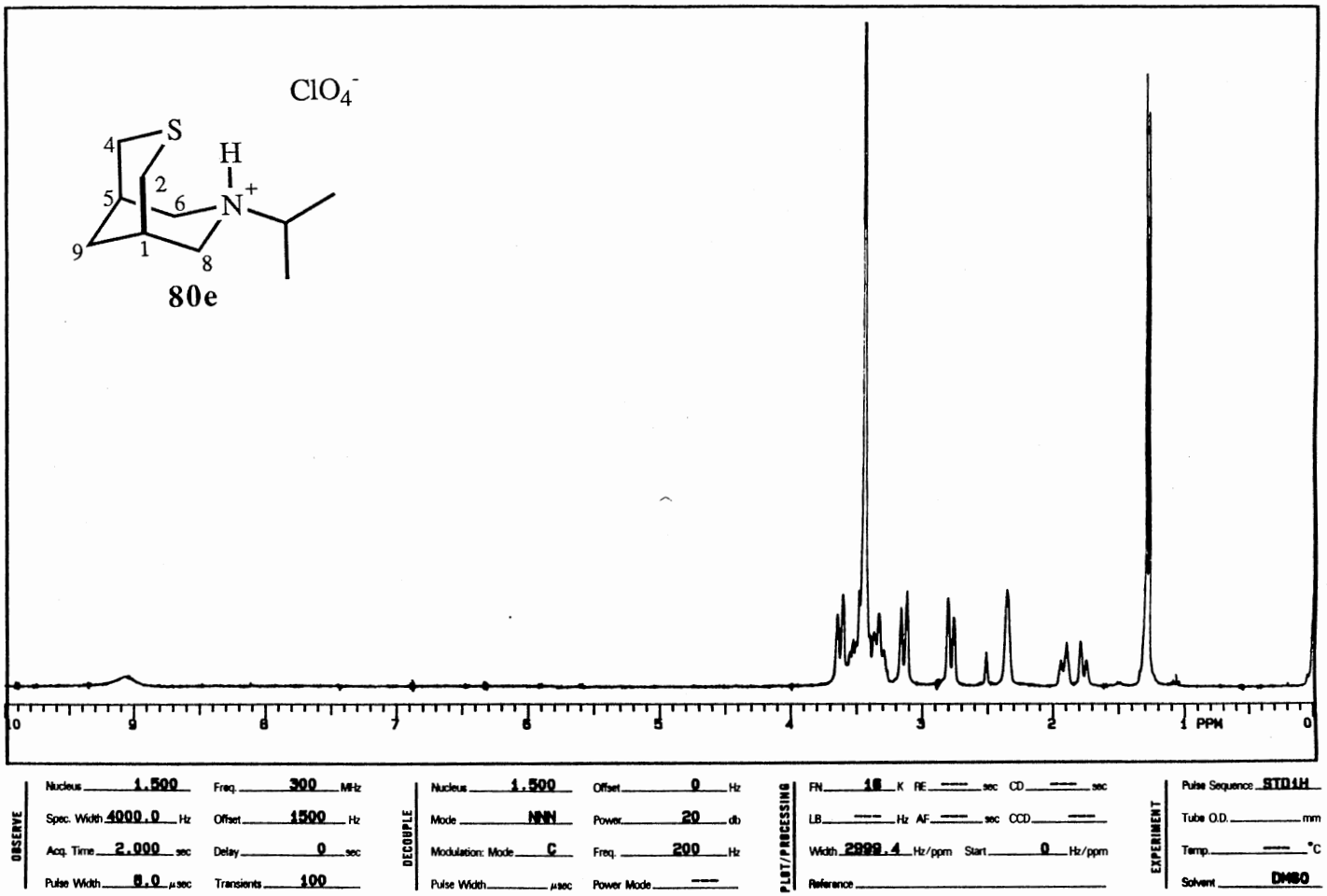
^{15}N NMR Spectrum of **80d**

Plate LV



IR Spectrum of **80e**

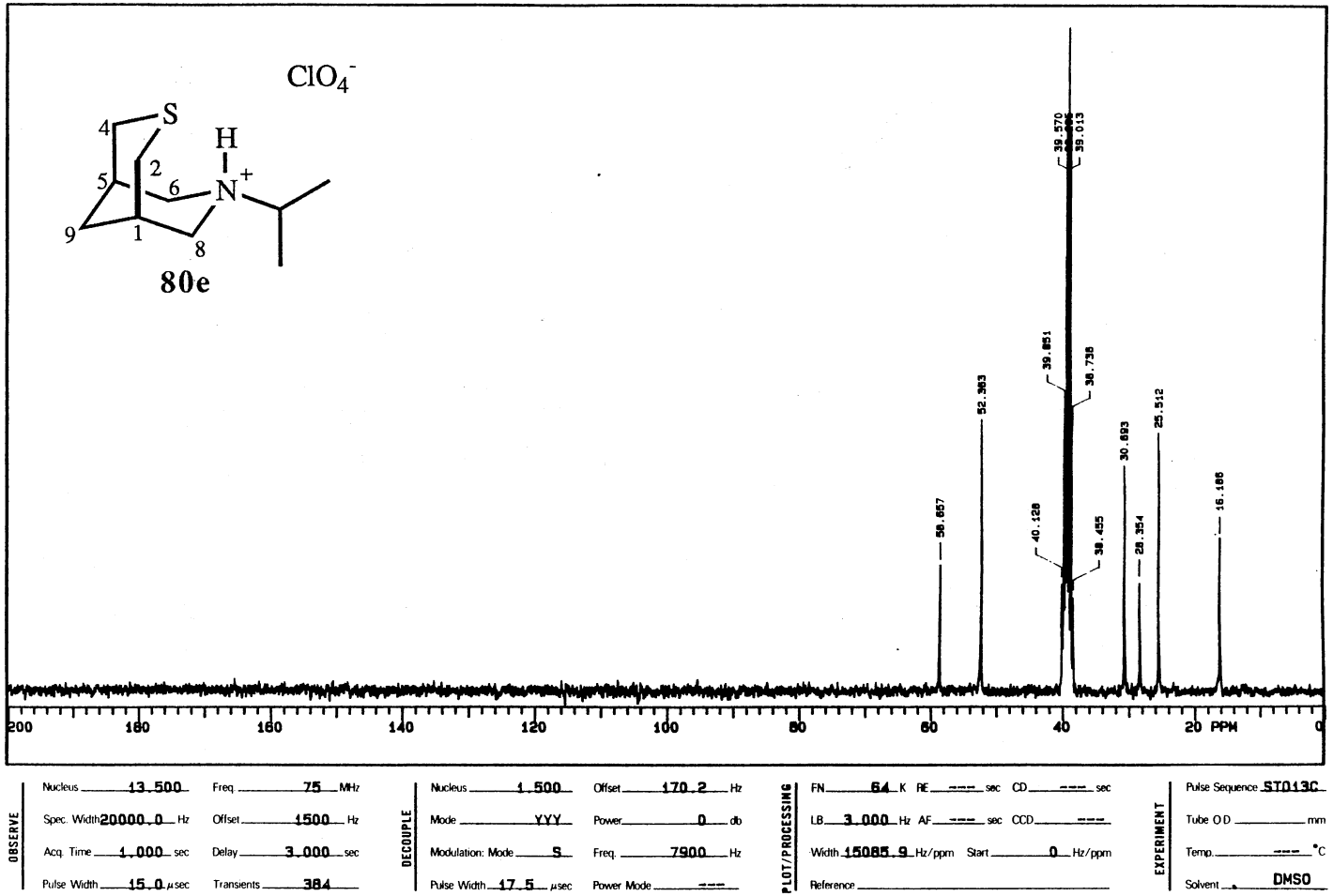
Plate LVI



80e

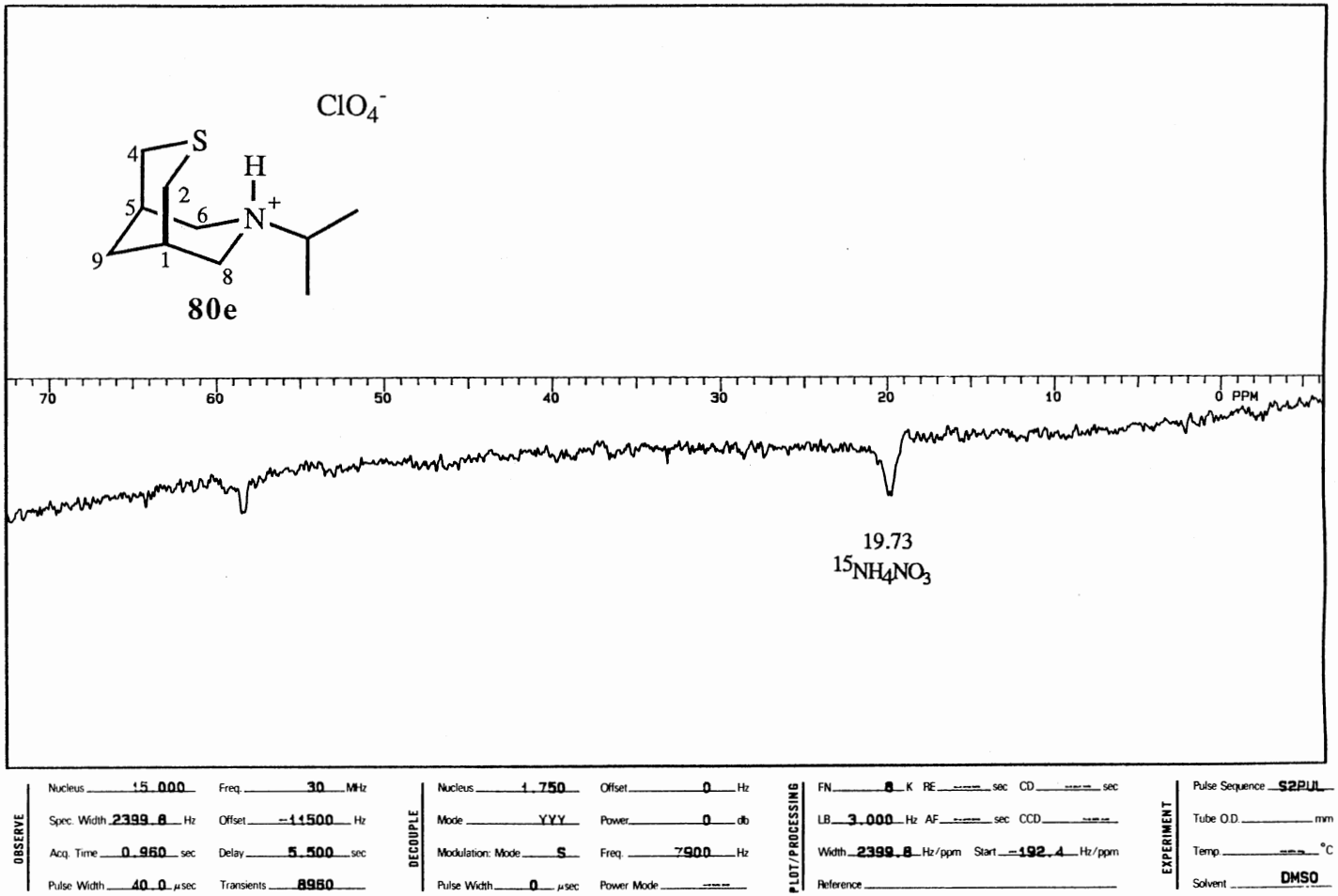
^{1}H NMR Spectrum of **80e**

Plate LVII



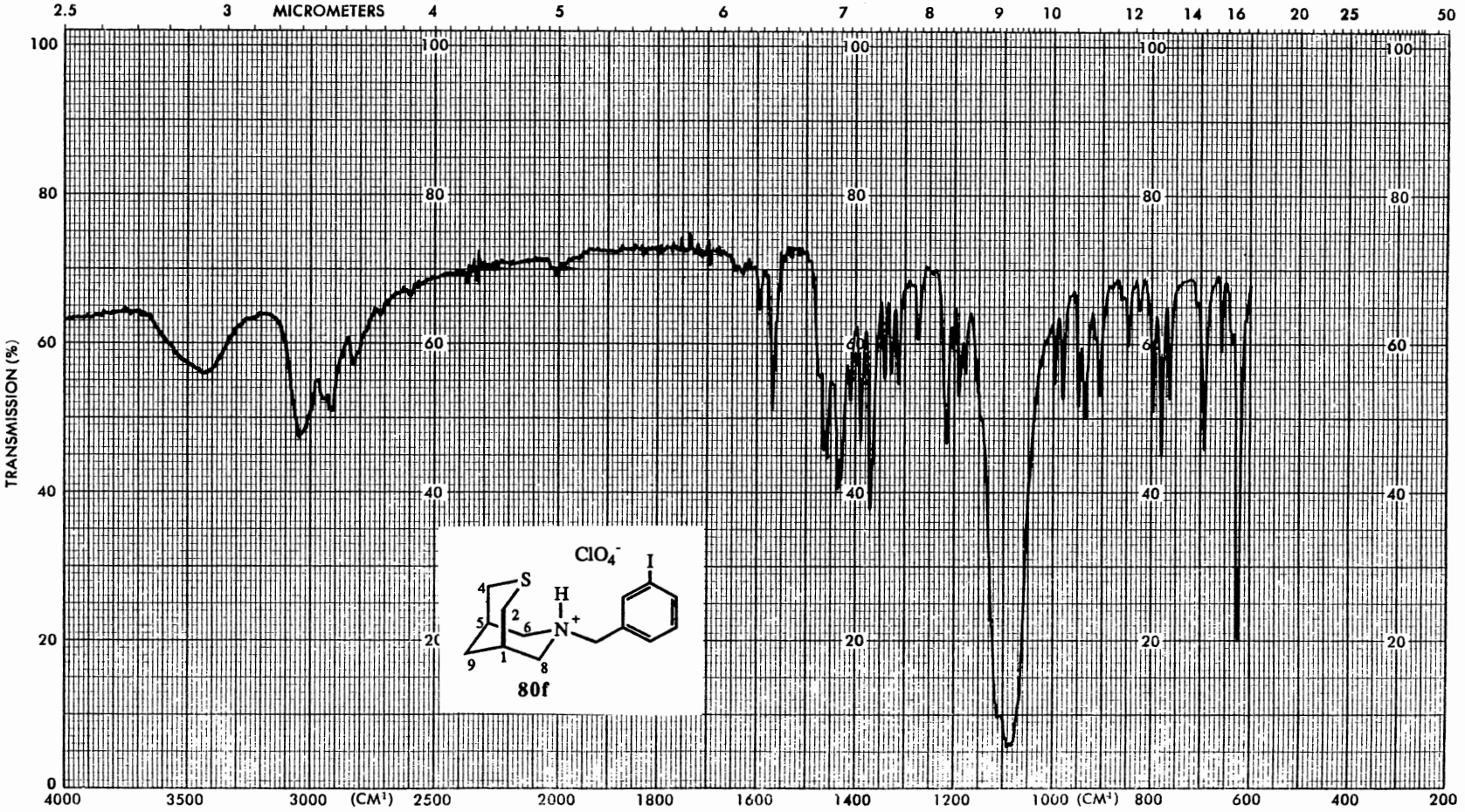
^{13}C NMR Spectrum of **80e**

Plate LVIII



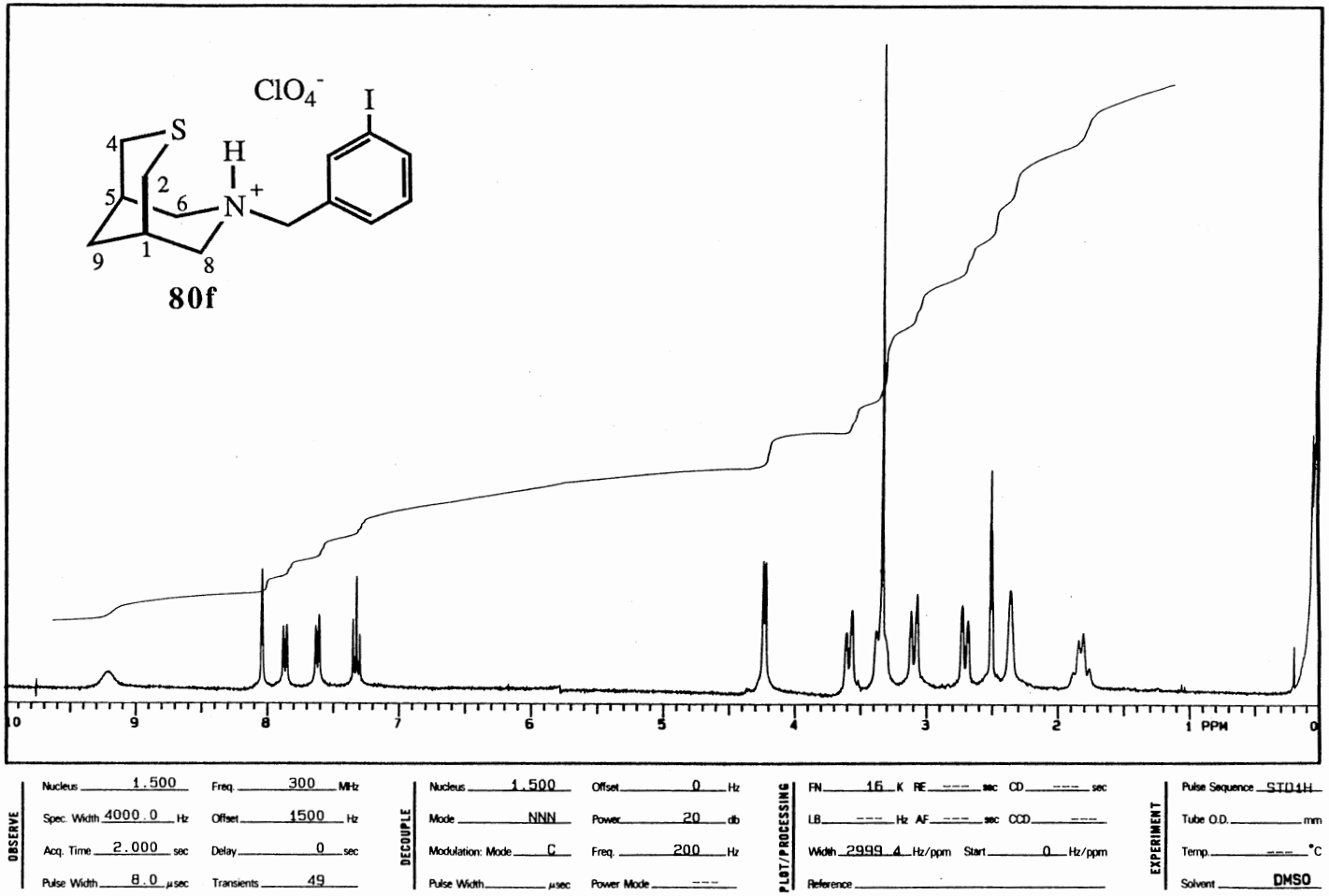
^{15}N NMR Spectrum of **80e**

Plate LIX



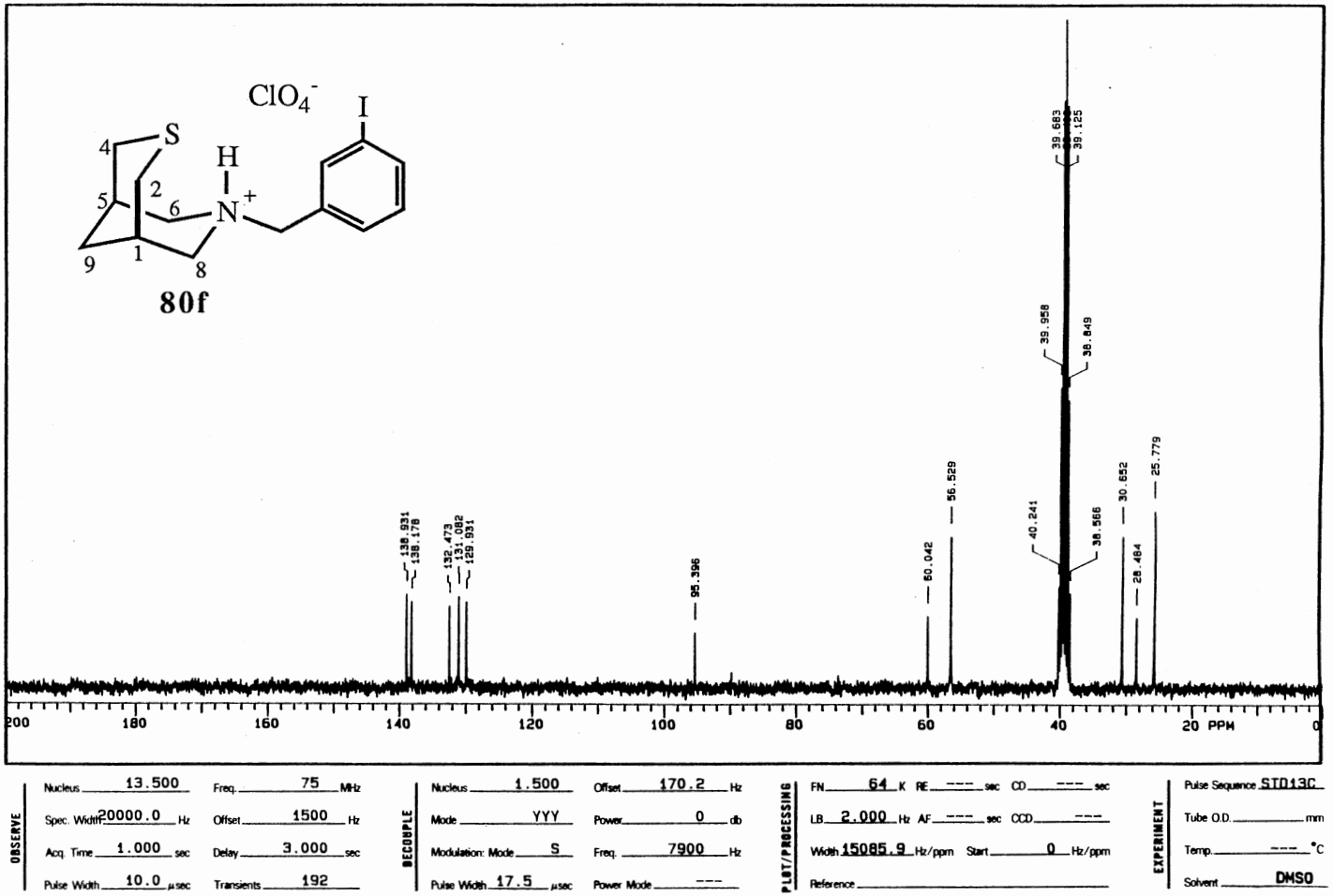
IR Spectrum of **80f**

Plate LX



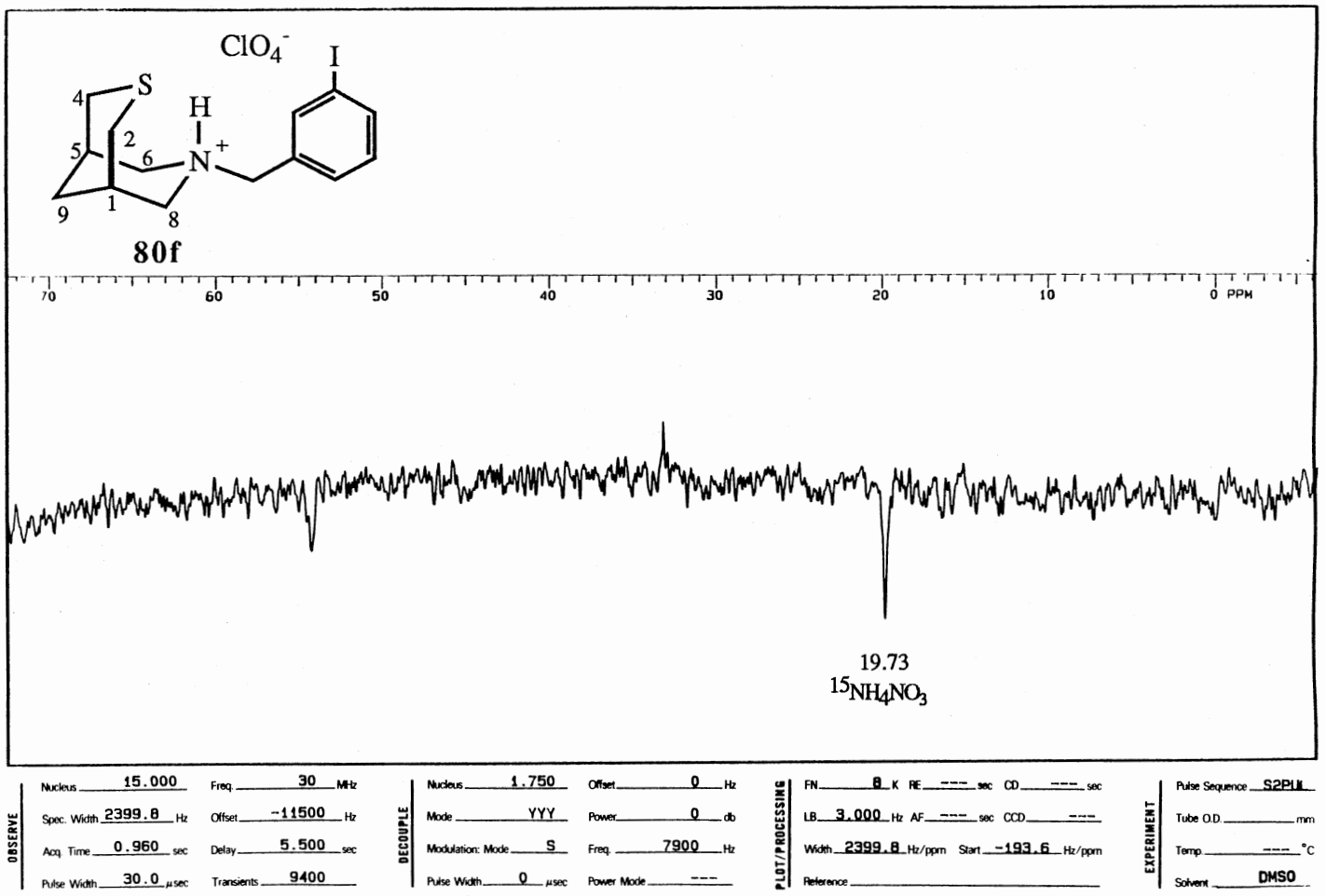
^{1}H NMR Spectrum of **80f**

Plate LXI



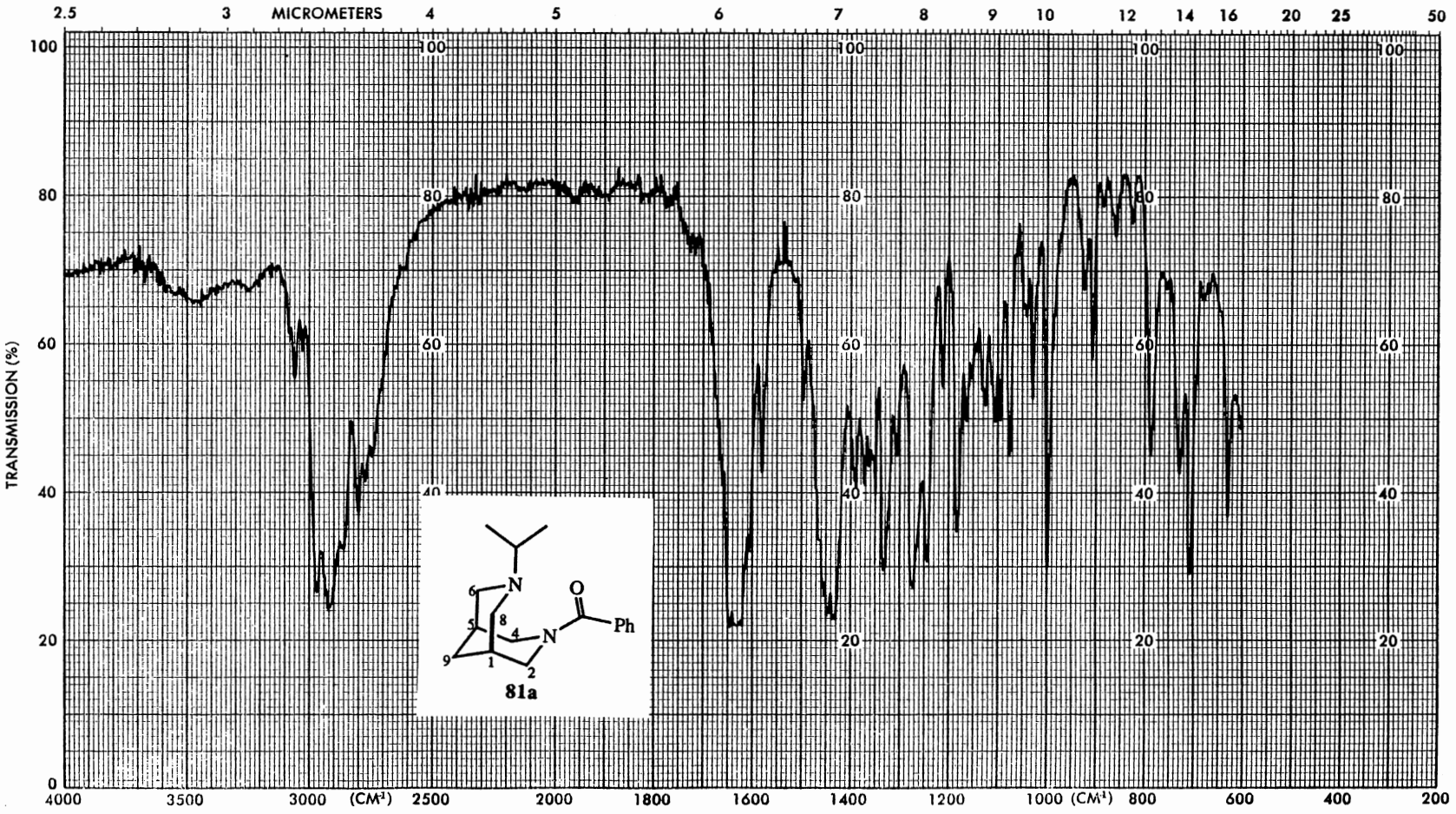
^{13}C NMR Spectrum of **80f**

Plate LXII



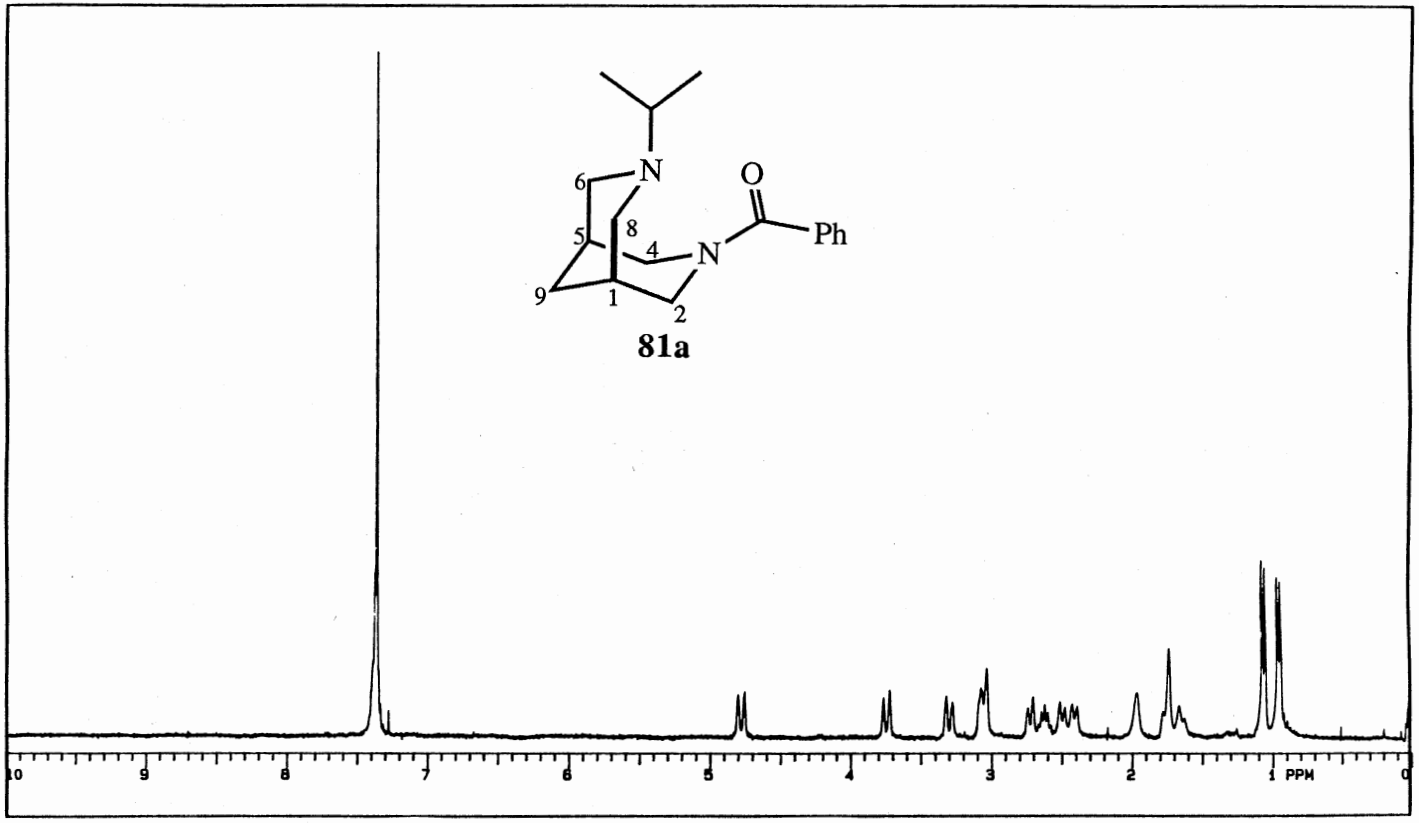
^{15}N NMR Spectrum of **80f**

Plate LXIII



IR Spectrum of **81a**

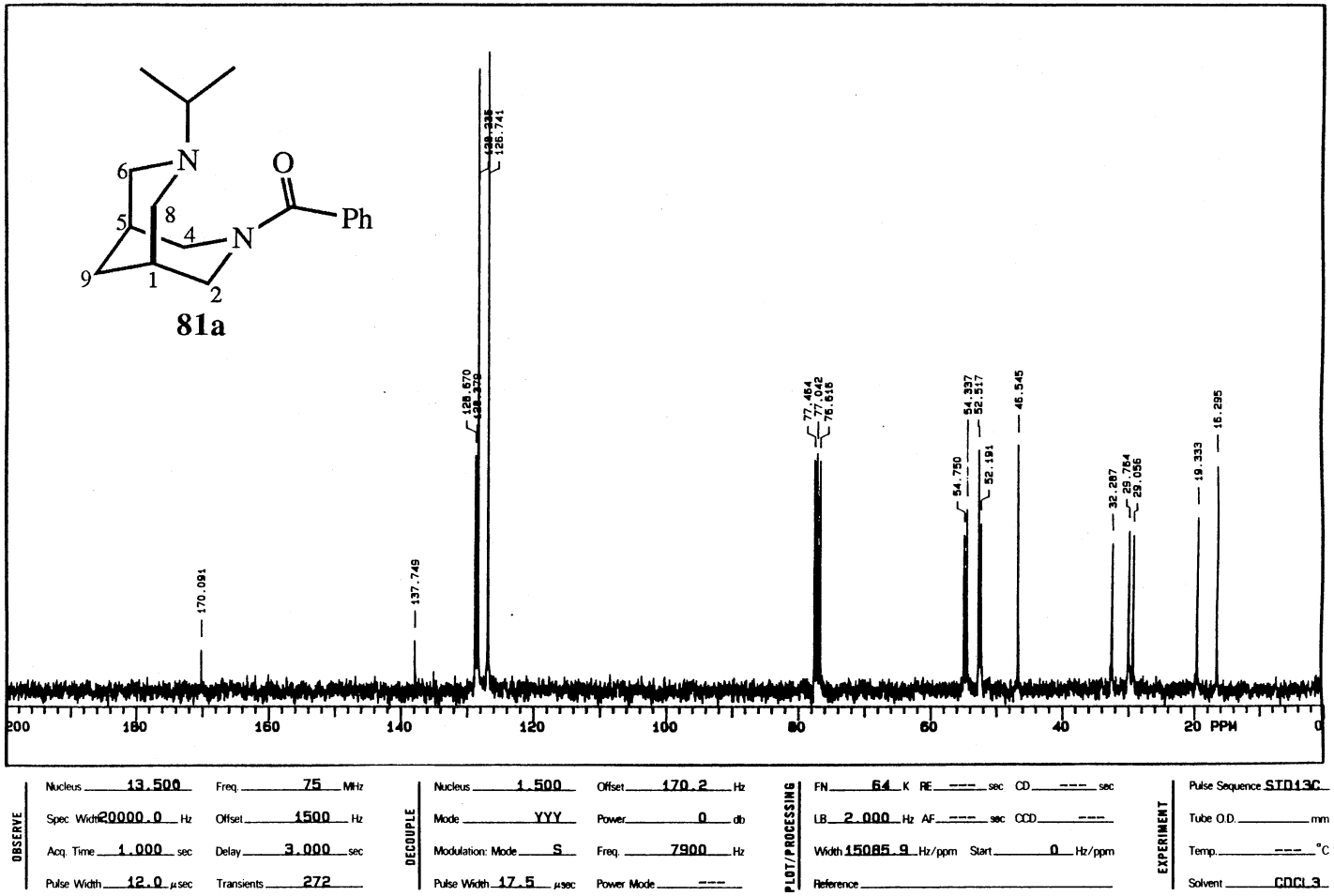
Plate LXIV



81a

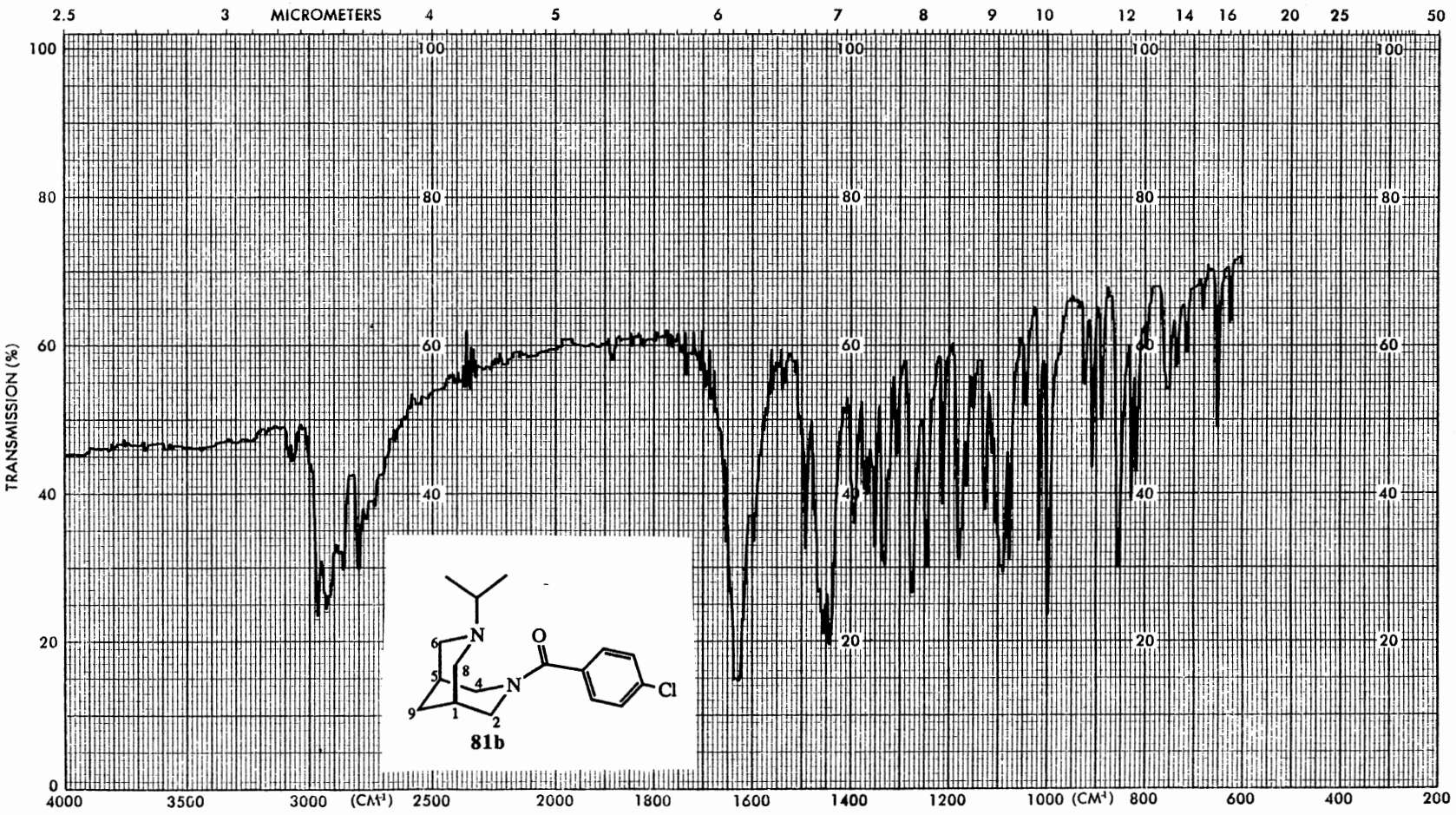
^{1}H NMR Spectrum of **81a**

Plate LXV



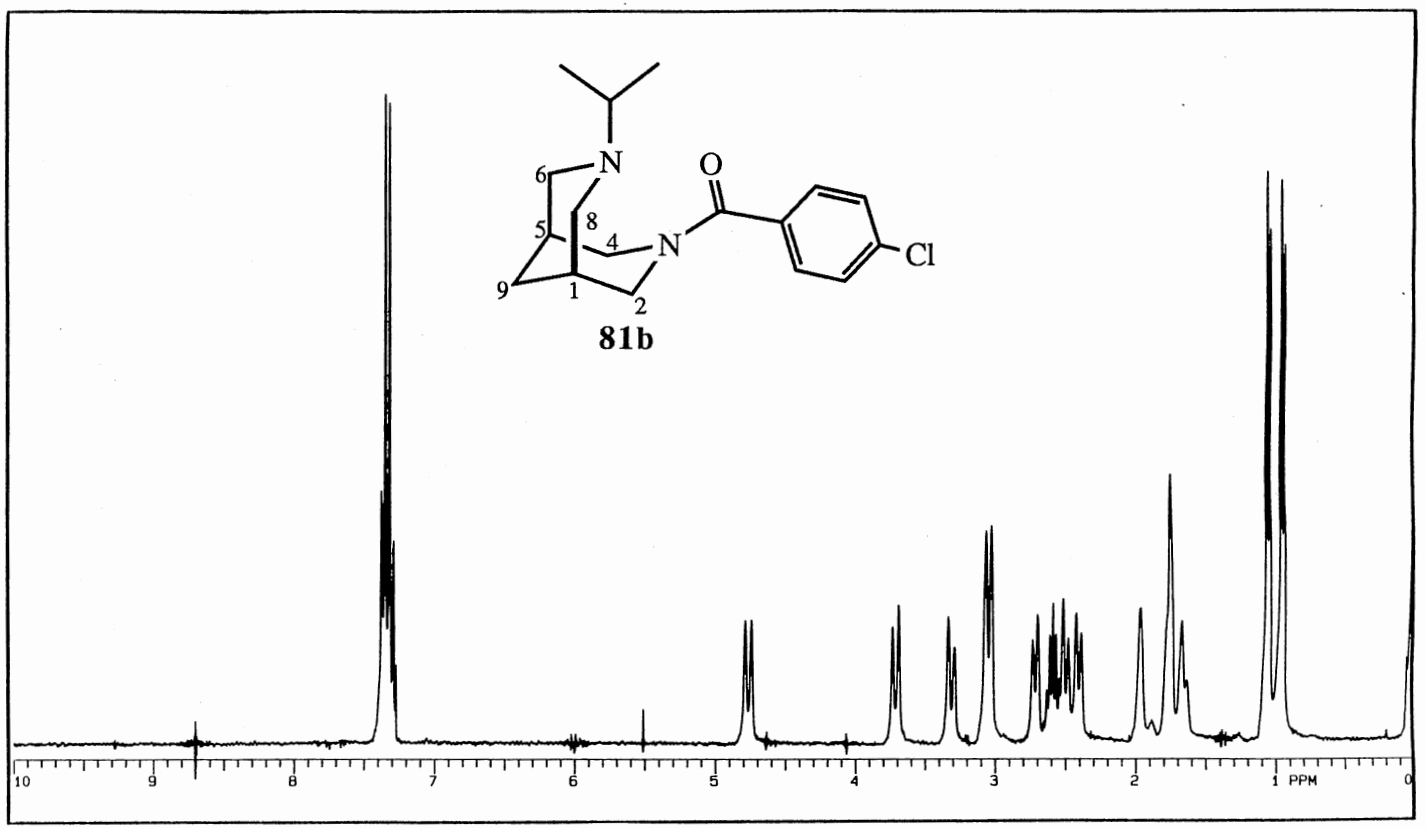
^{13}C NMR Spectrum of **81a**

Plate LXVI



IR Spectrum of **81b**

Plate LXVII



OBSERVE: Nucleus 1.500 | Freq. 300 MHz | Spec. Width 4000.0 Hz | Offset 0 Hz | Acq. Time 2.000 sec | Delay 0 sec | Pulse Width 8.0 µsec | Transients 107

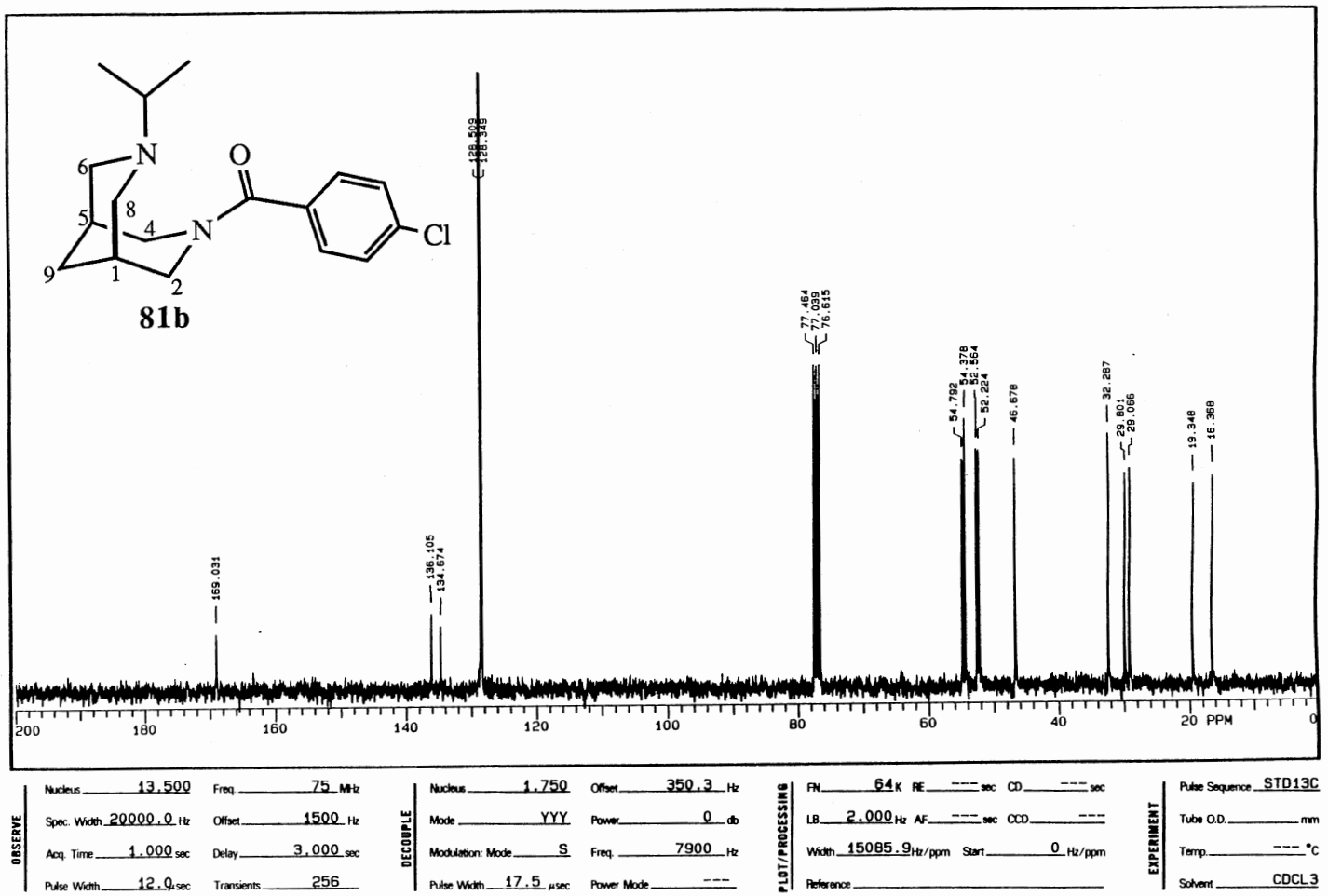
DECOUPLE: Nucleus 1.750 | Offset 350.3 Hz | Mode NNN | Power 20 db | Modulation: Mode C | Freq. 200 Hz | Pulse Width µsec | Power Mode ---

PLOT/PROCESSING: FN 16K | RE --- sec | CD --- sec | LB --- Hz | AF --- sec | CCD --- | Width 2999.4 Hz/ppm | Start 0 Hz/ppm | Reference

EXPERIMENT: Pulse Sequence STD1H | Tube O.D. mm | Temp. --- °C | Solvent CDCL3

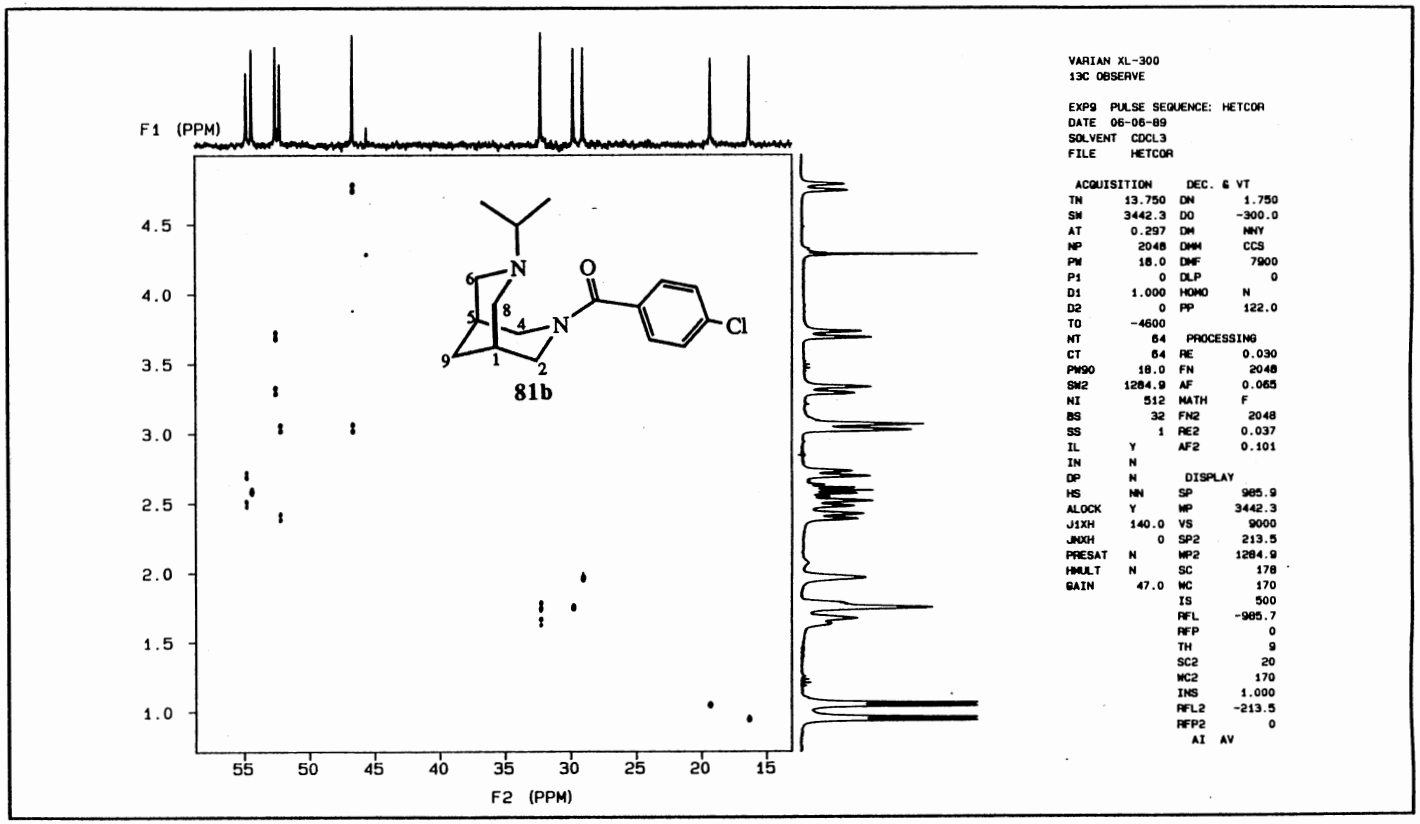
^{1}H NMR Spectrum of **81b**

Plate LXVIII



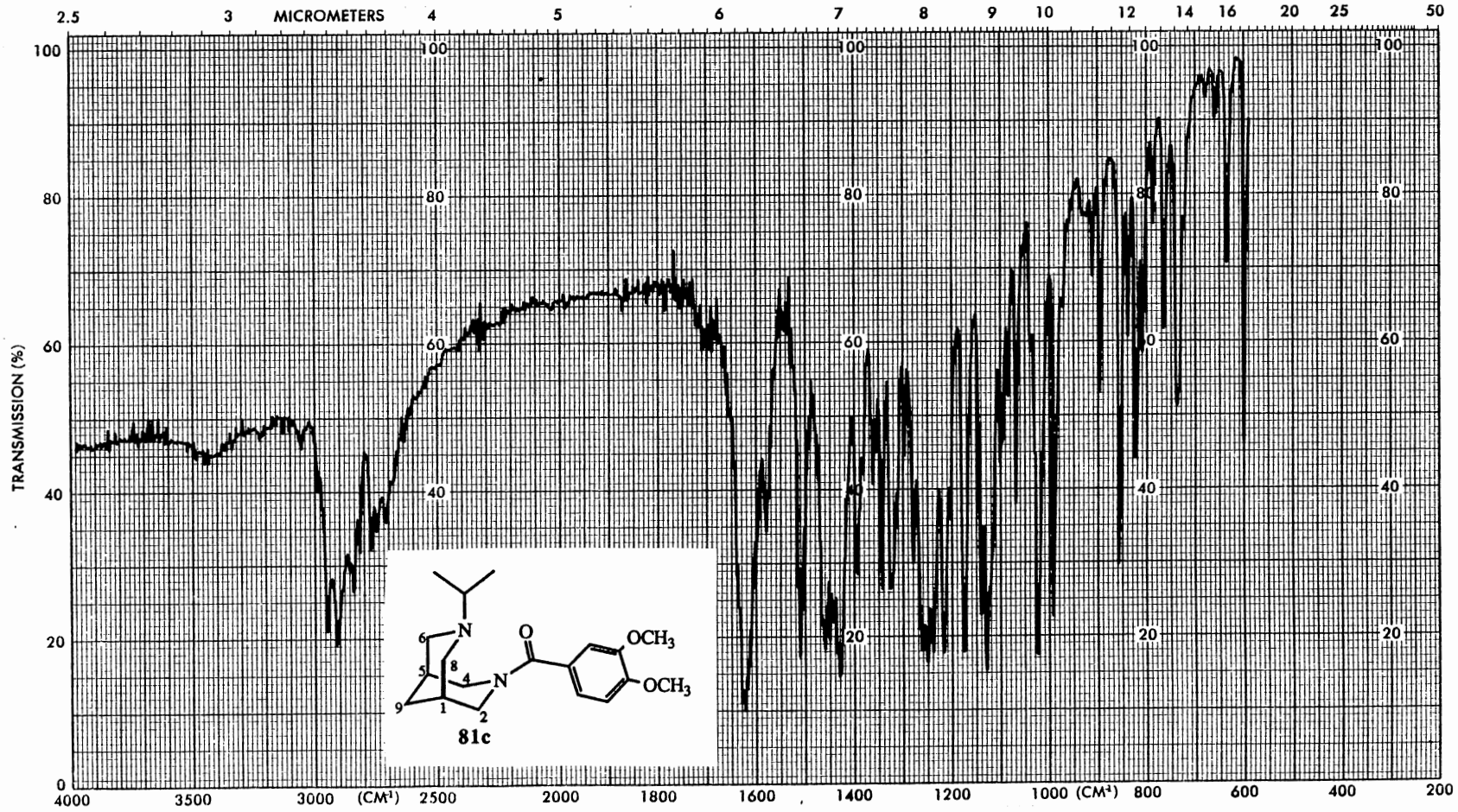
^{13}C NMR Spectrum of **81b**

Plate LXIX



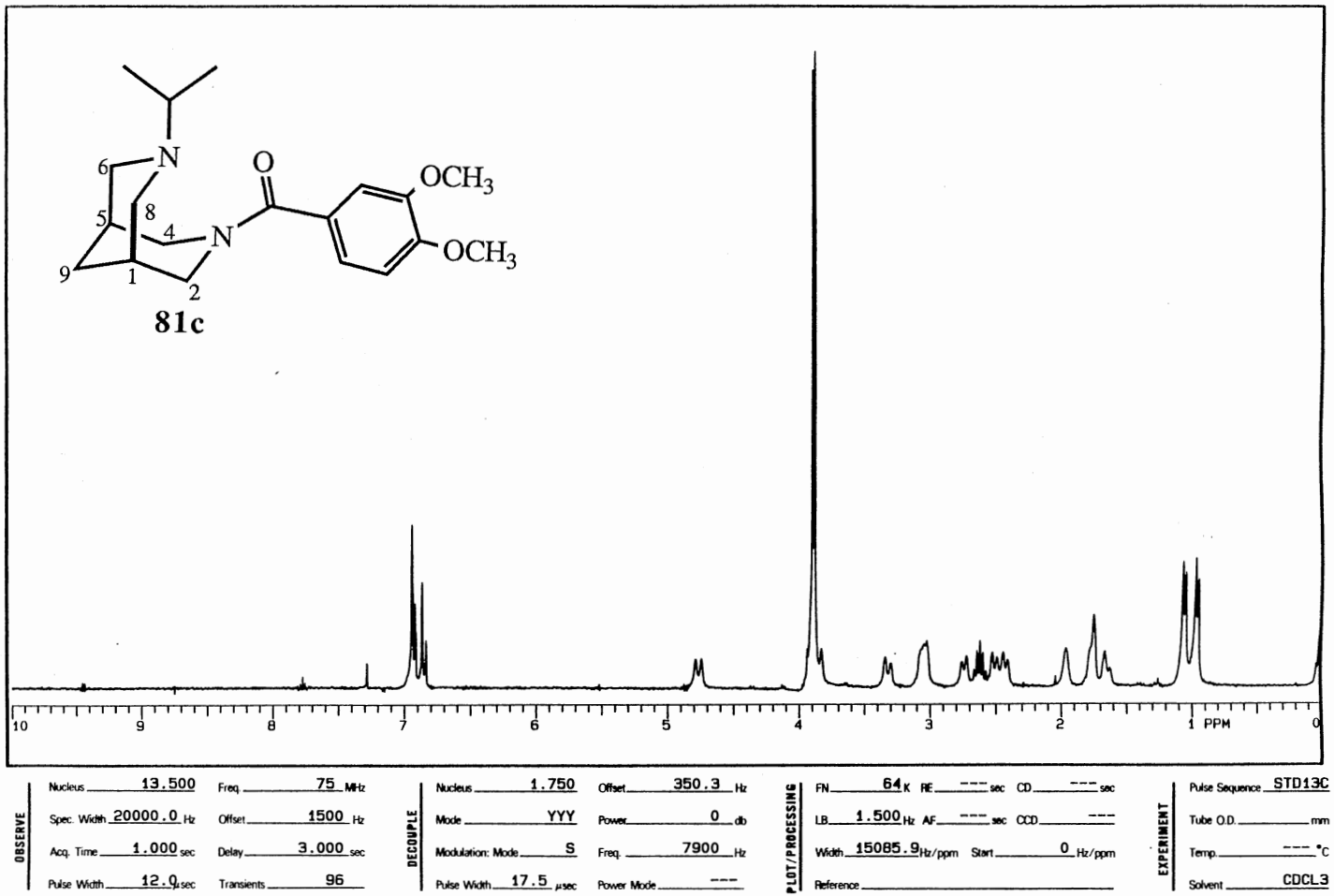
HETCOR Spectrum of **81b**

Plate LXX



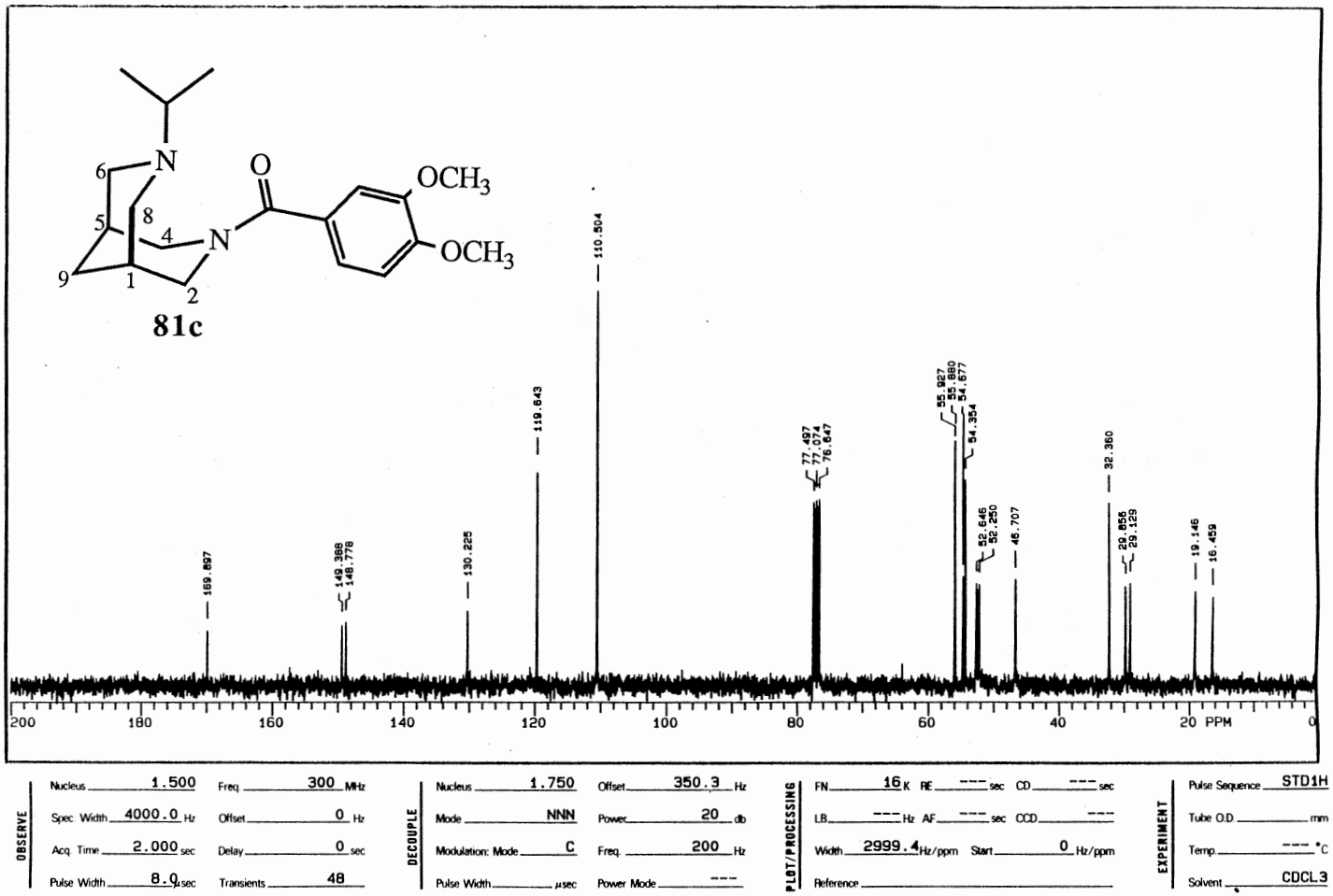
IR Spectrum of **81c**

Plate LXXI



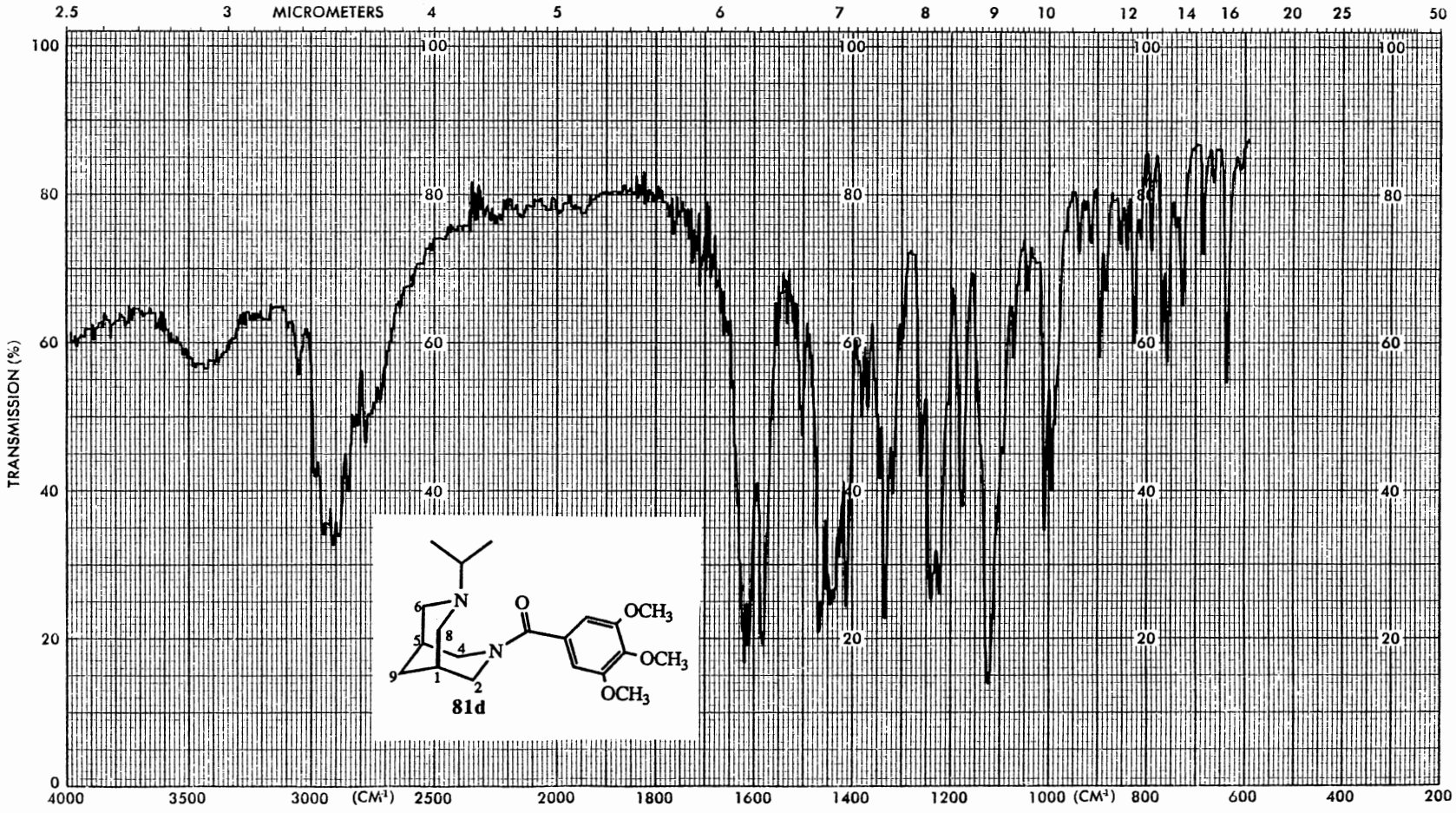
^{1}H NMR Spectrum of **81c**

Plate LXXII



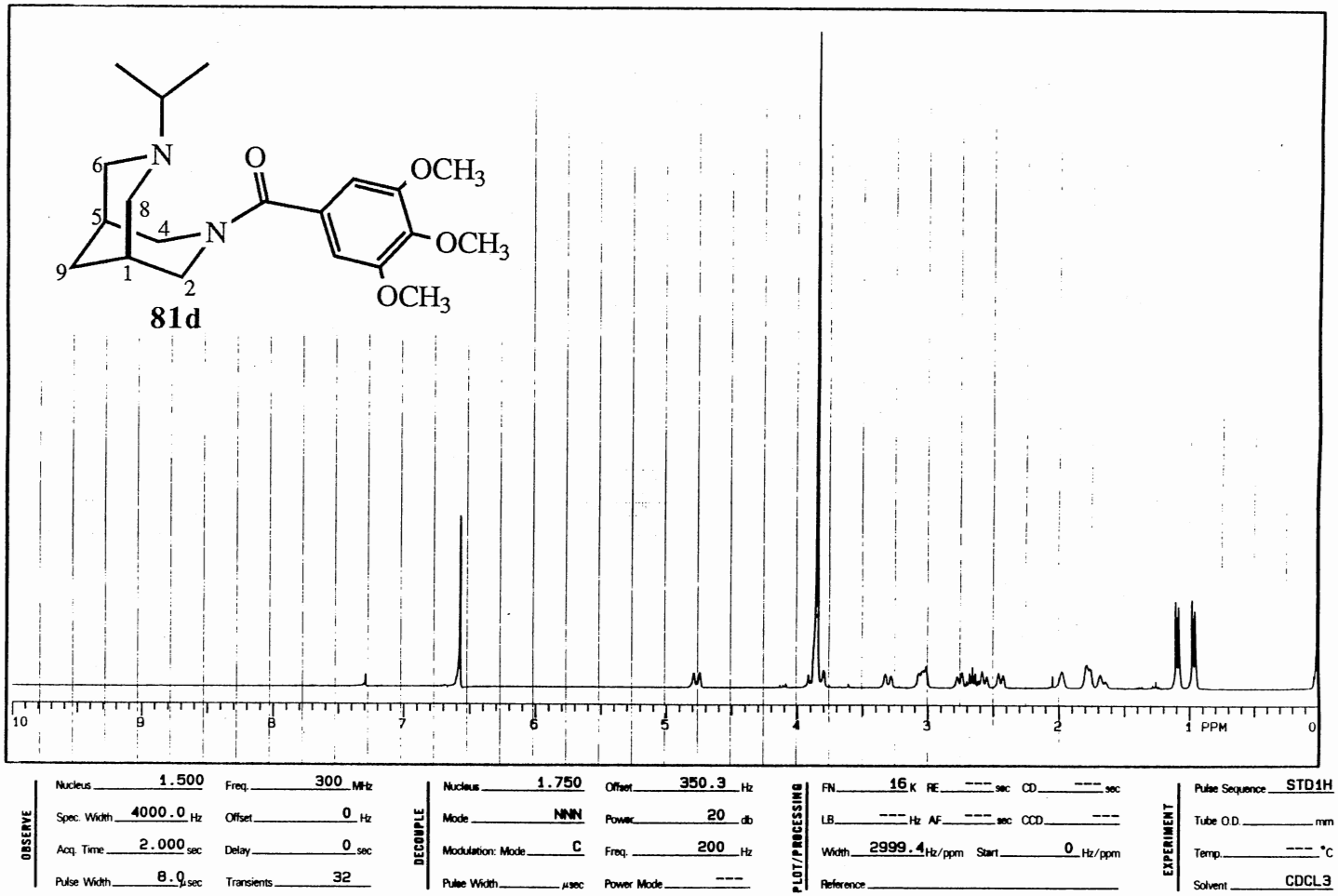
^{13}C NMR Spectrum of **81c**

Plate LXXIII



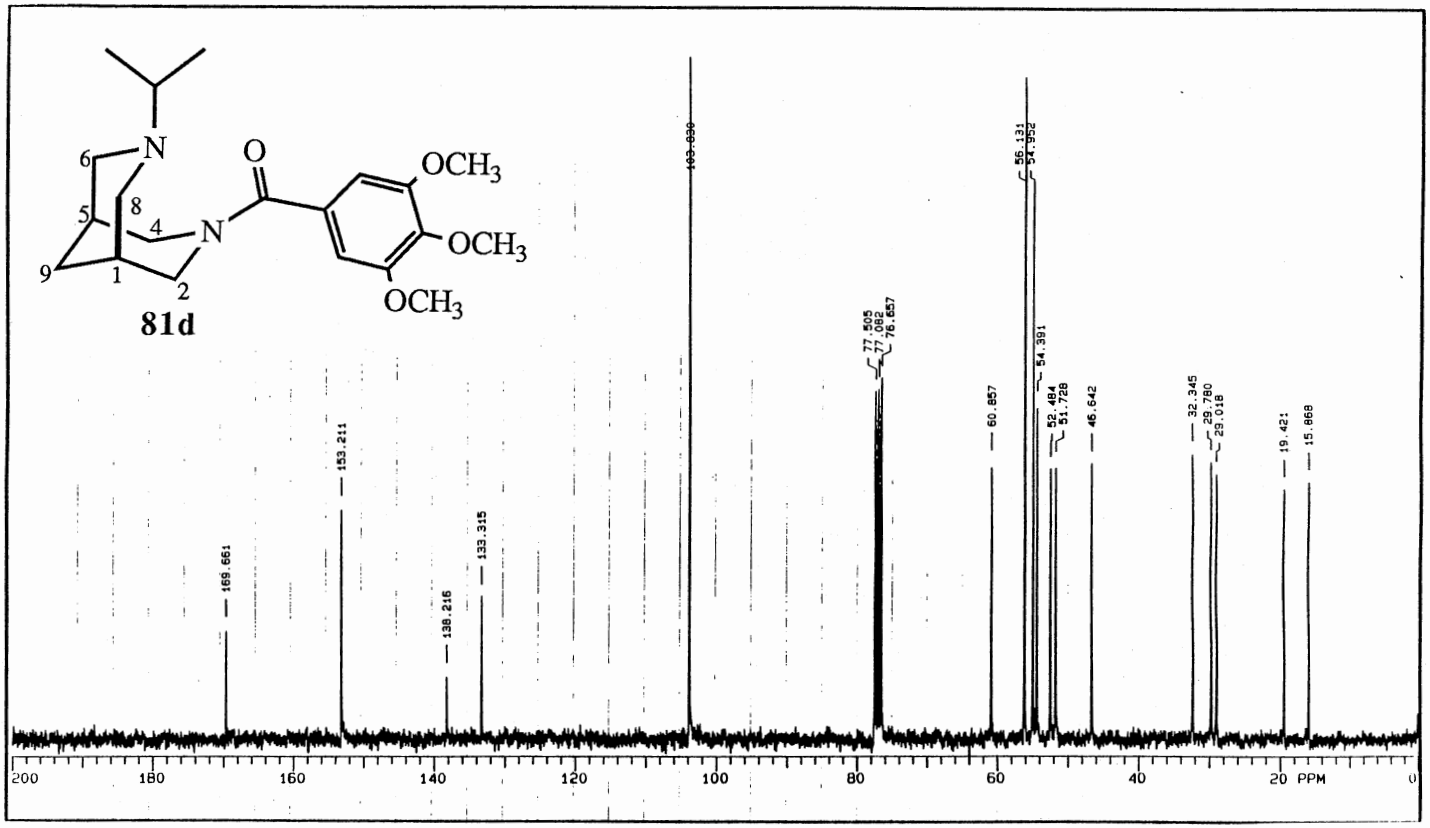
IR Spectrum of **81d**

Plate LXXIV



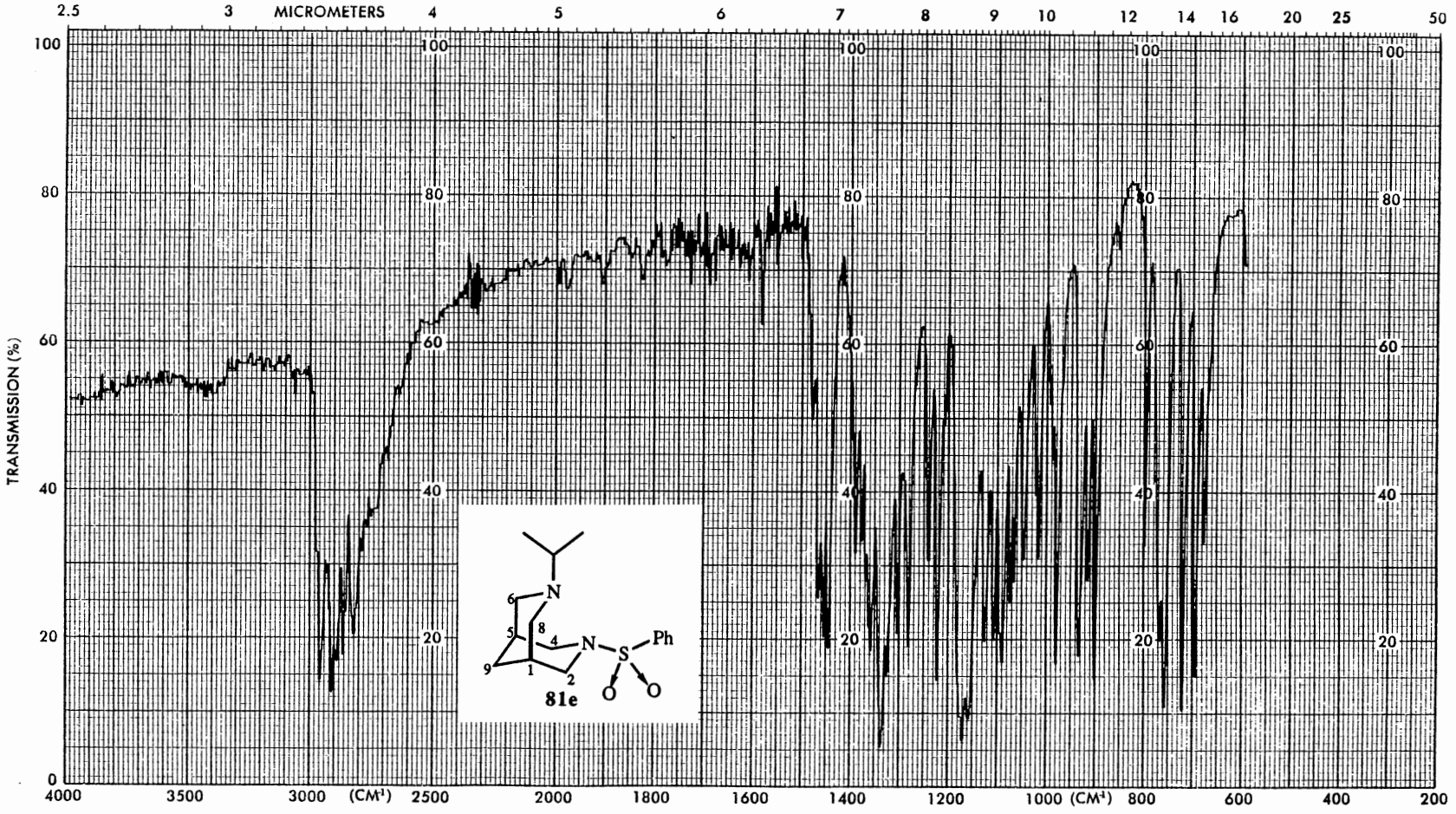
^{1}H NMR Spectrum of **81d**

Plate LXXV



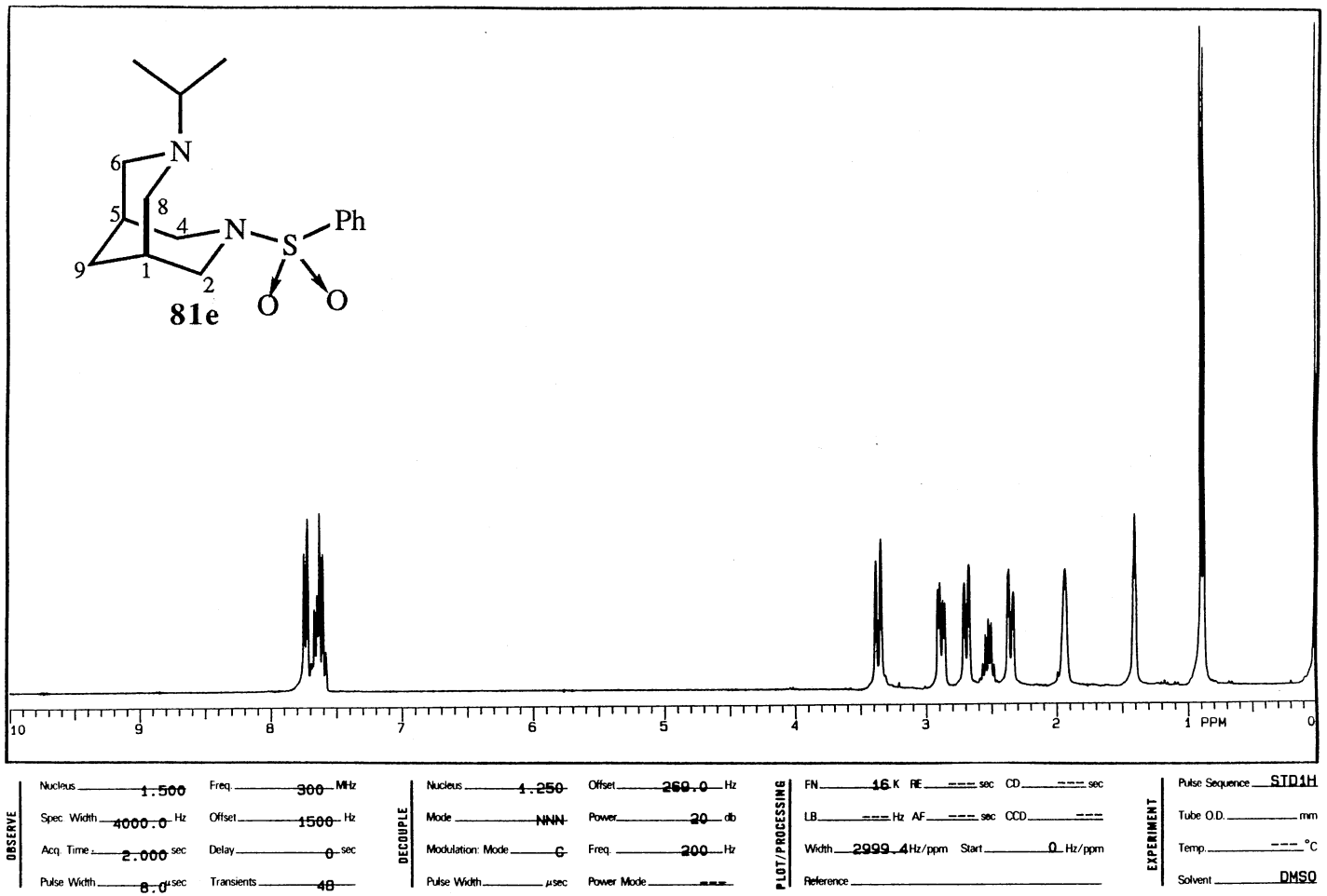
^{13}C NMR Spectrum of **81d**

Plate LXXVI



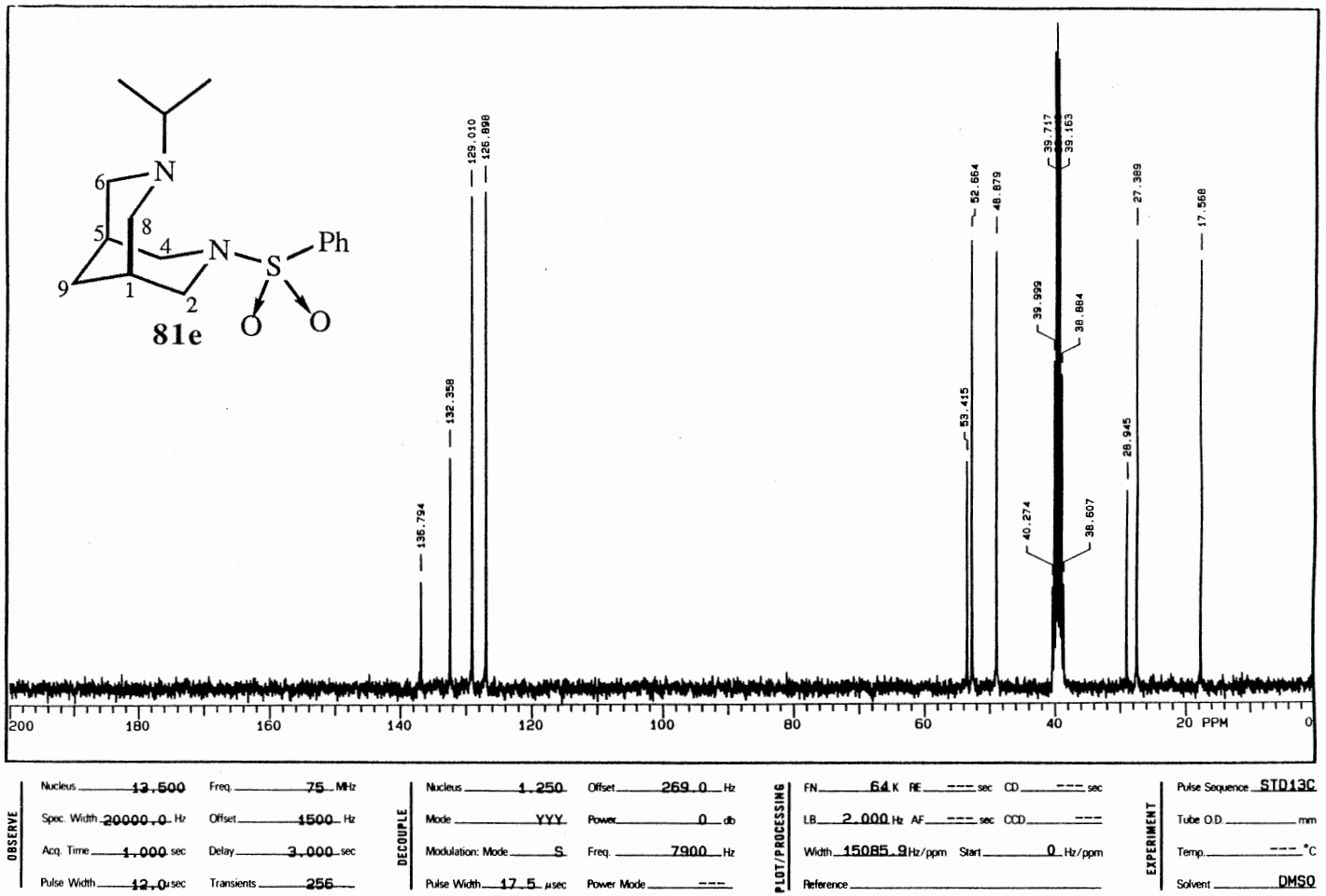
IR Spectrum of **81e**

Plate LXXVII



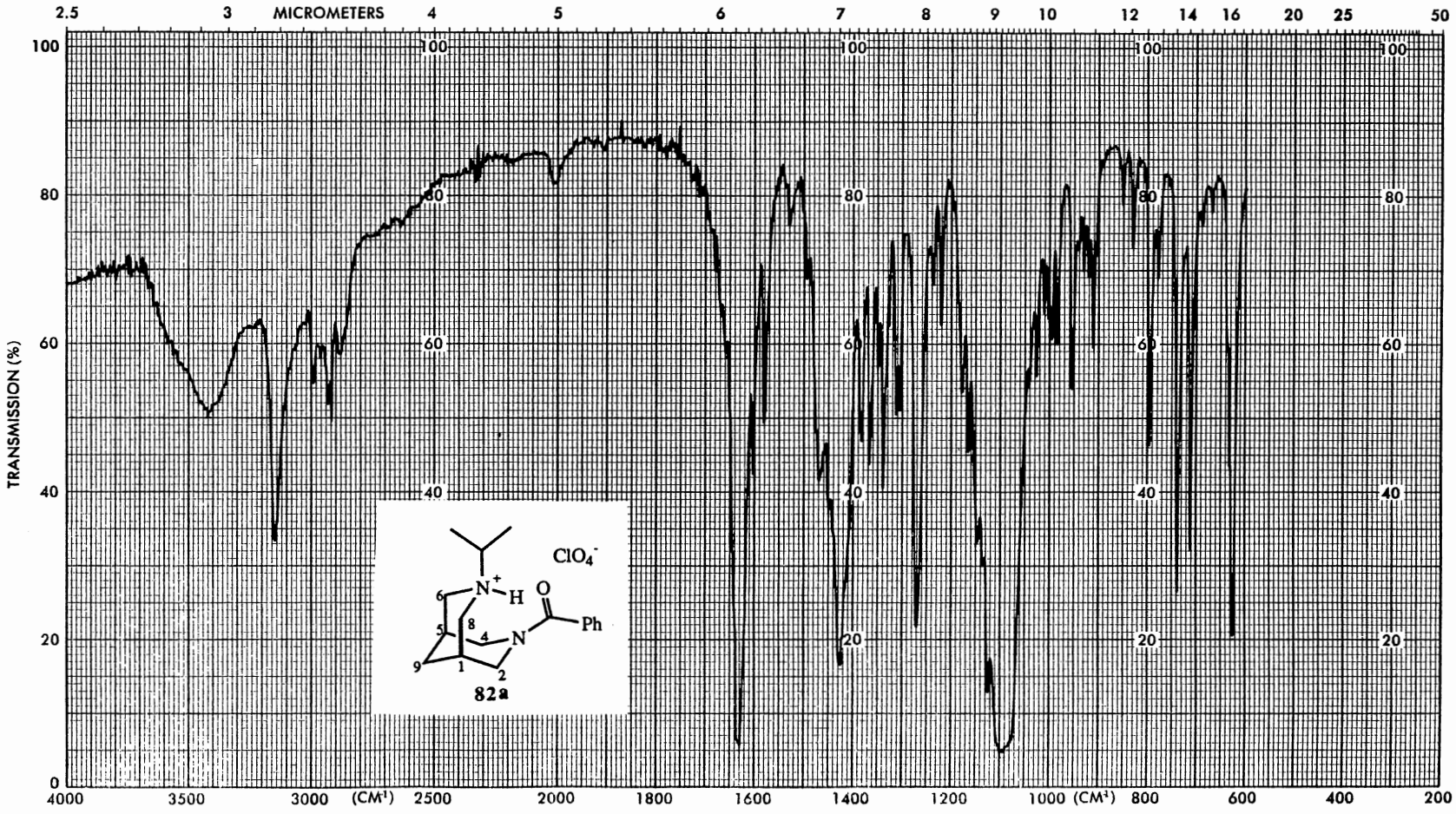
^{1}H NMR Spectrum of **81e**

Plate LXXVIII



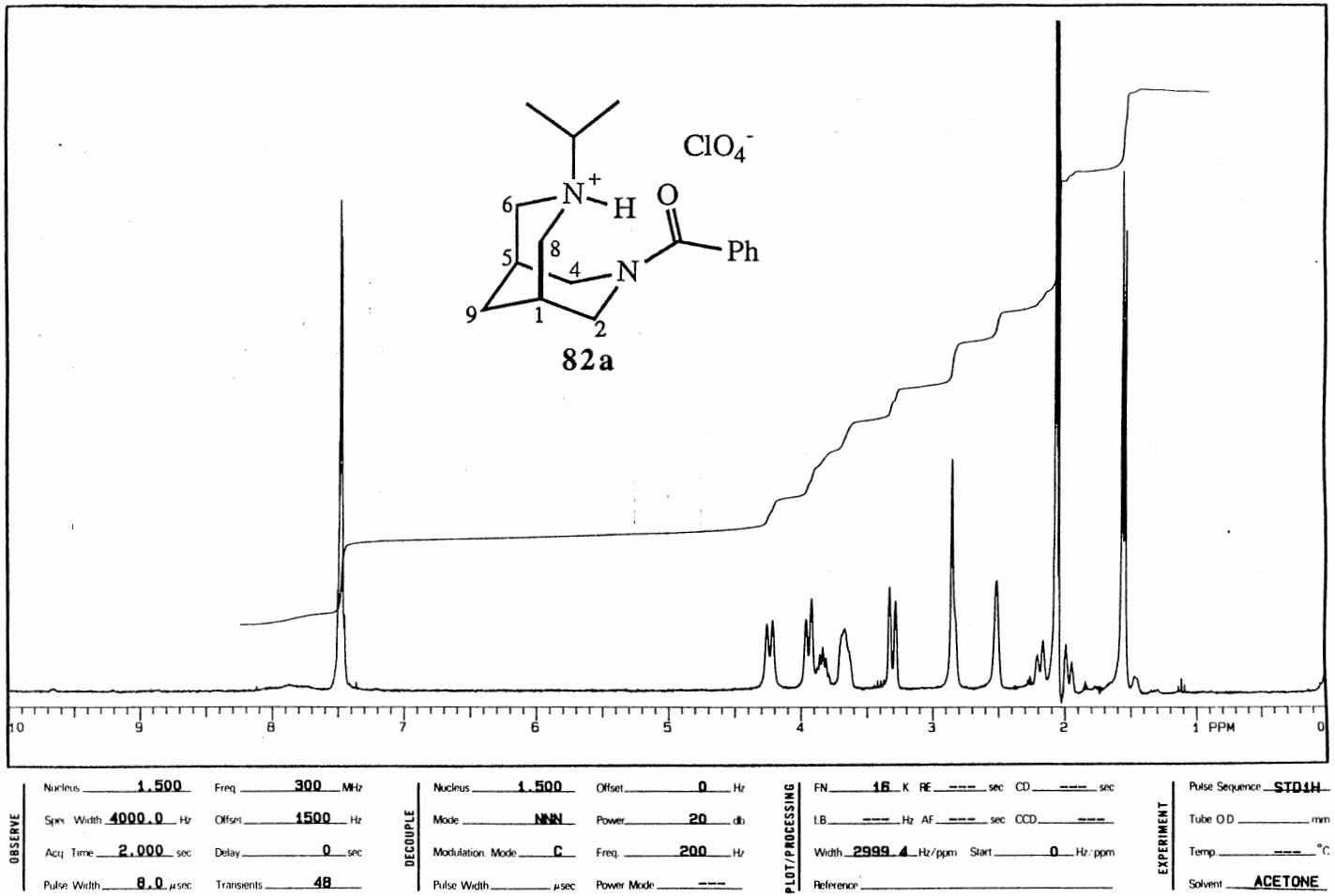
^{13}C NMR Spectrum of **81e**

Plate LXXIX



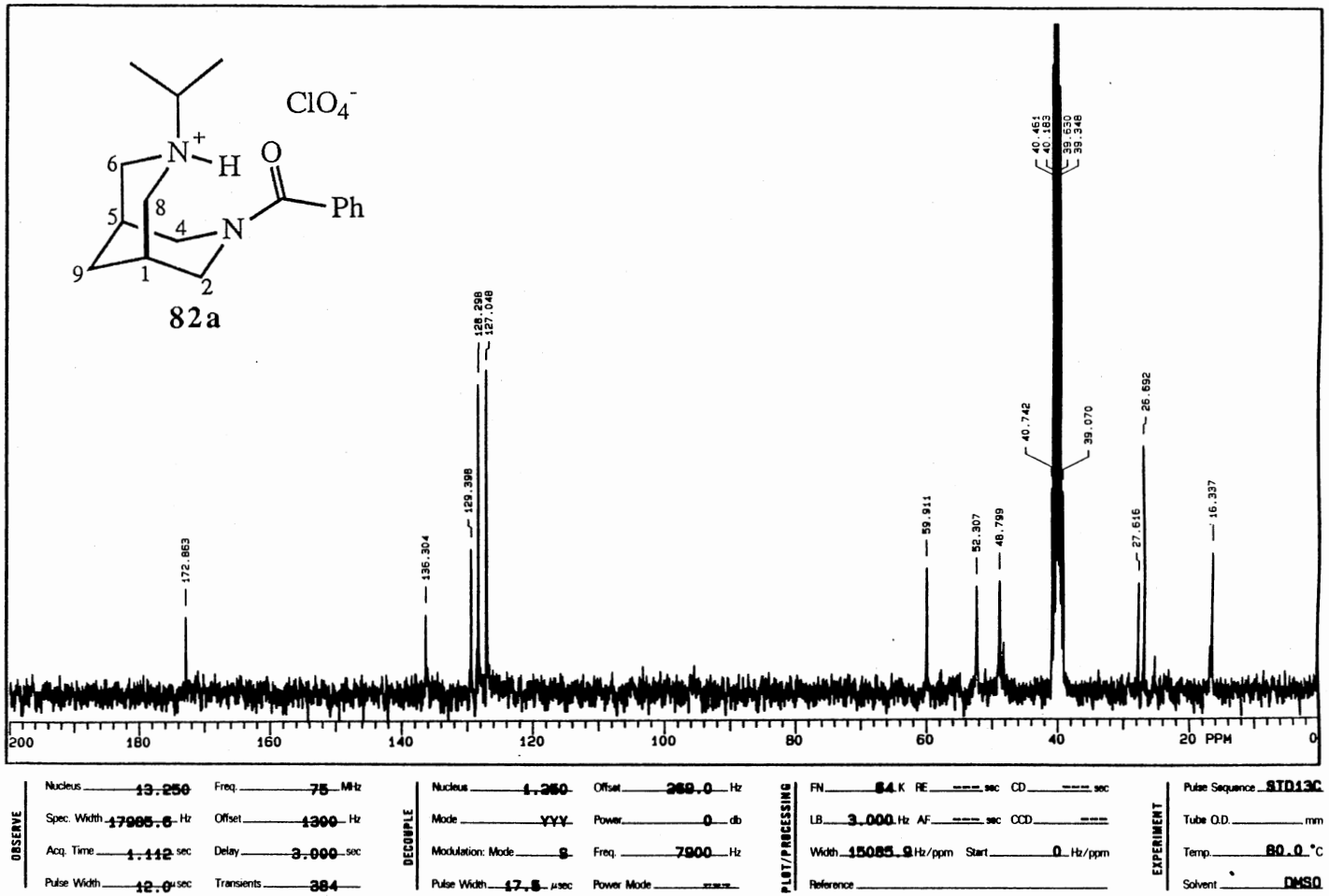
IR Spectrum of **82a**

Plate LXXX



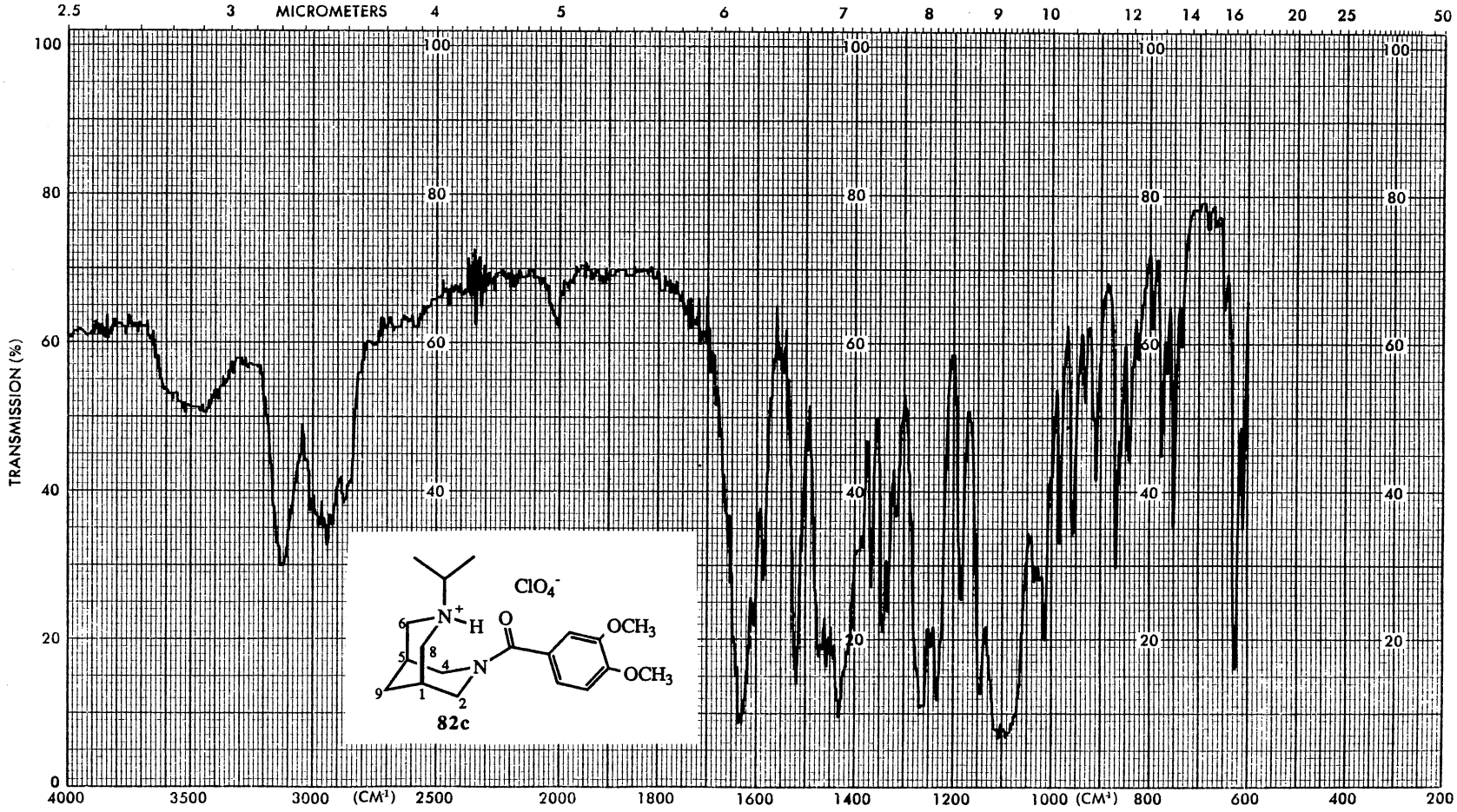
^{1}H NMR Spectrum of **82a**

Plate LXXXI



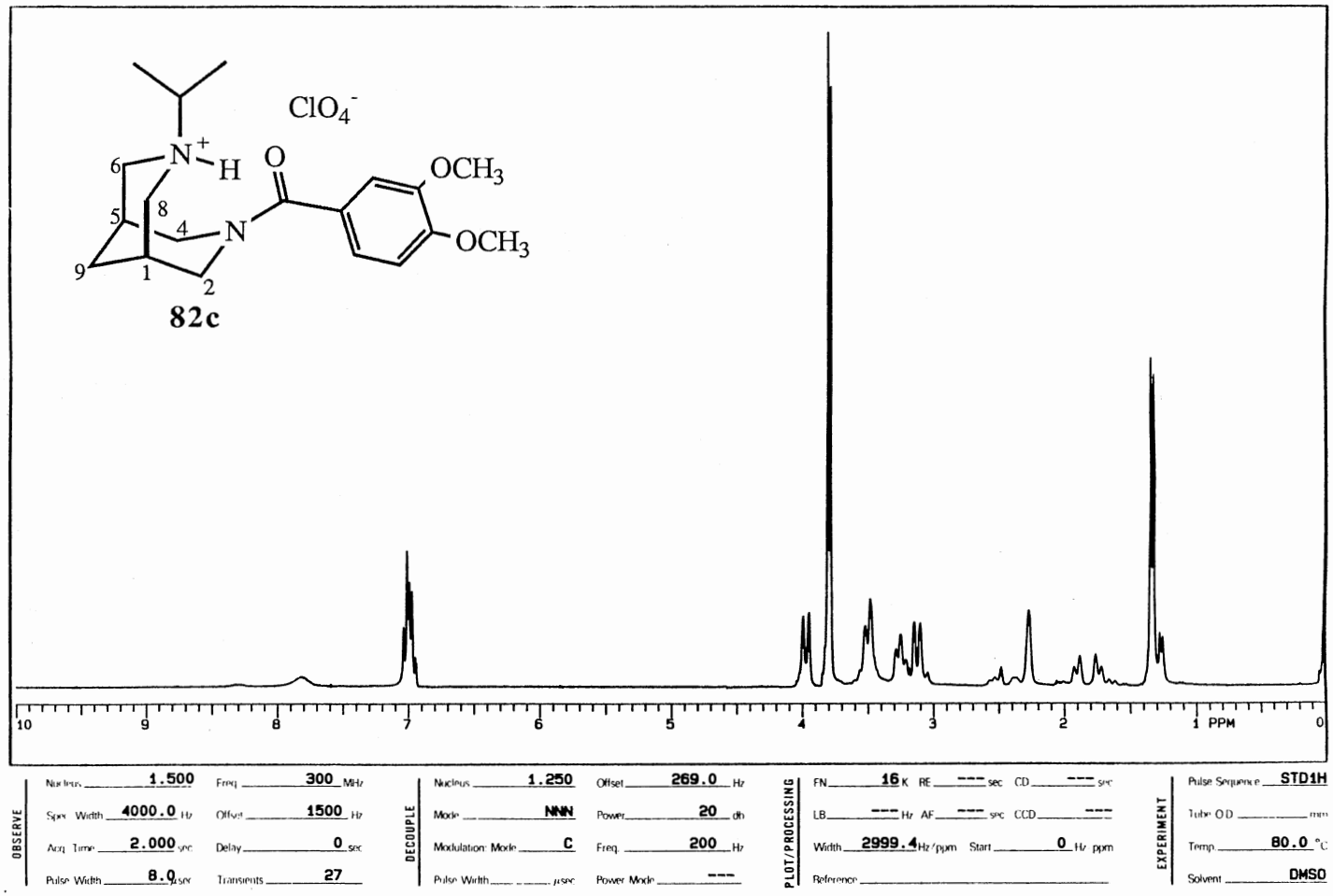
^{13}C NMR Spectrum of **82a**

Plate LXXXII



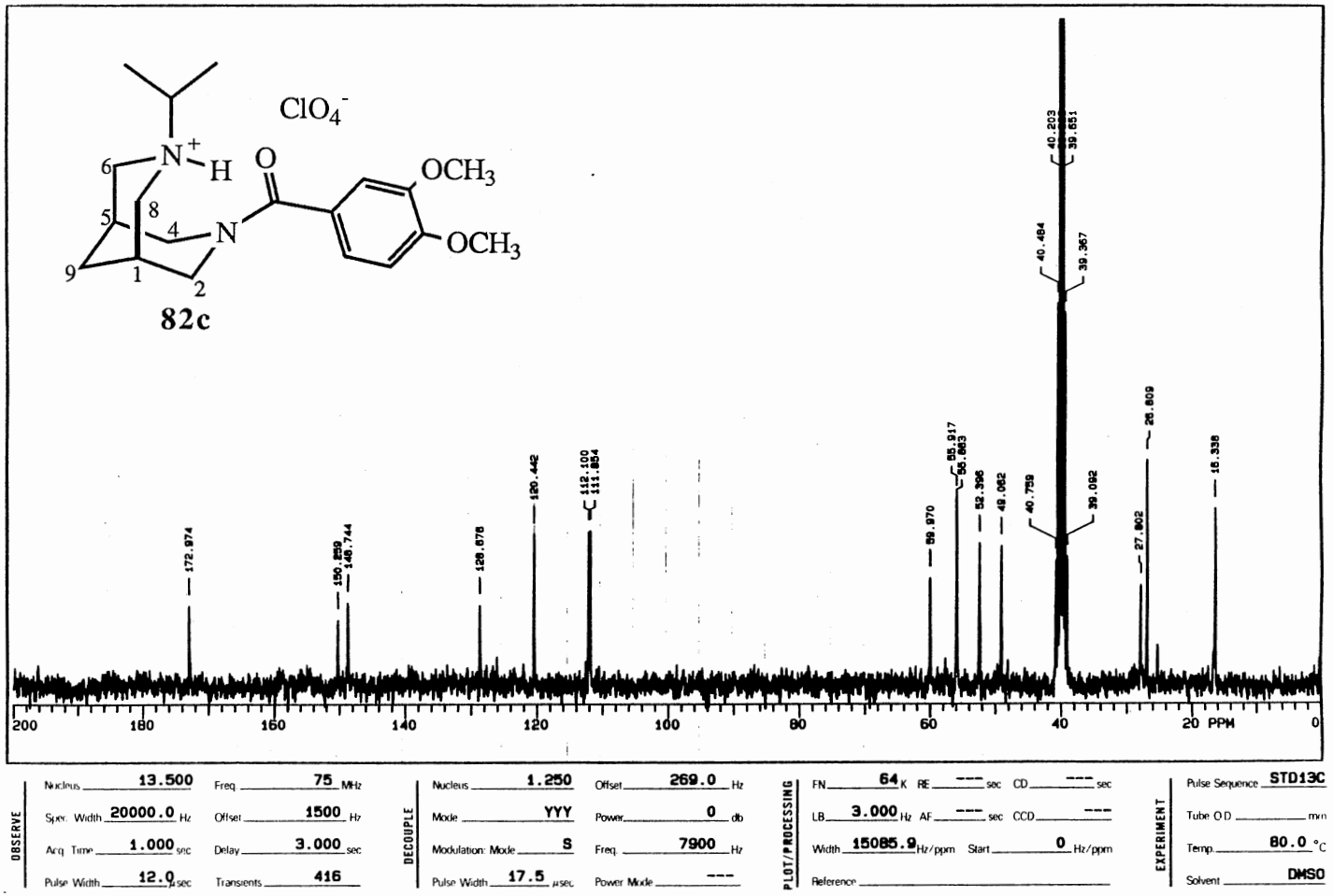
IR Spectrum of **82c**

Plate LXXXIII



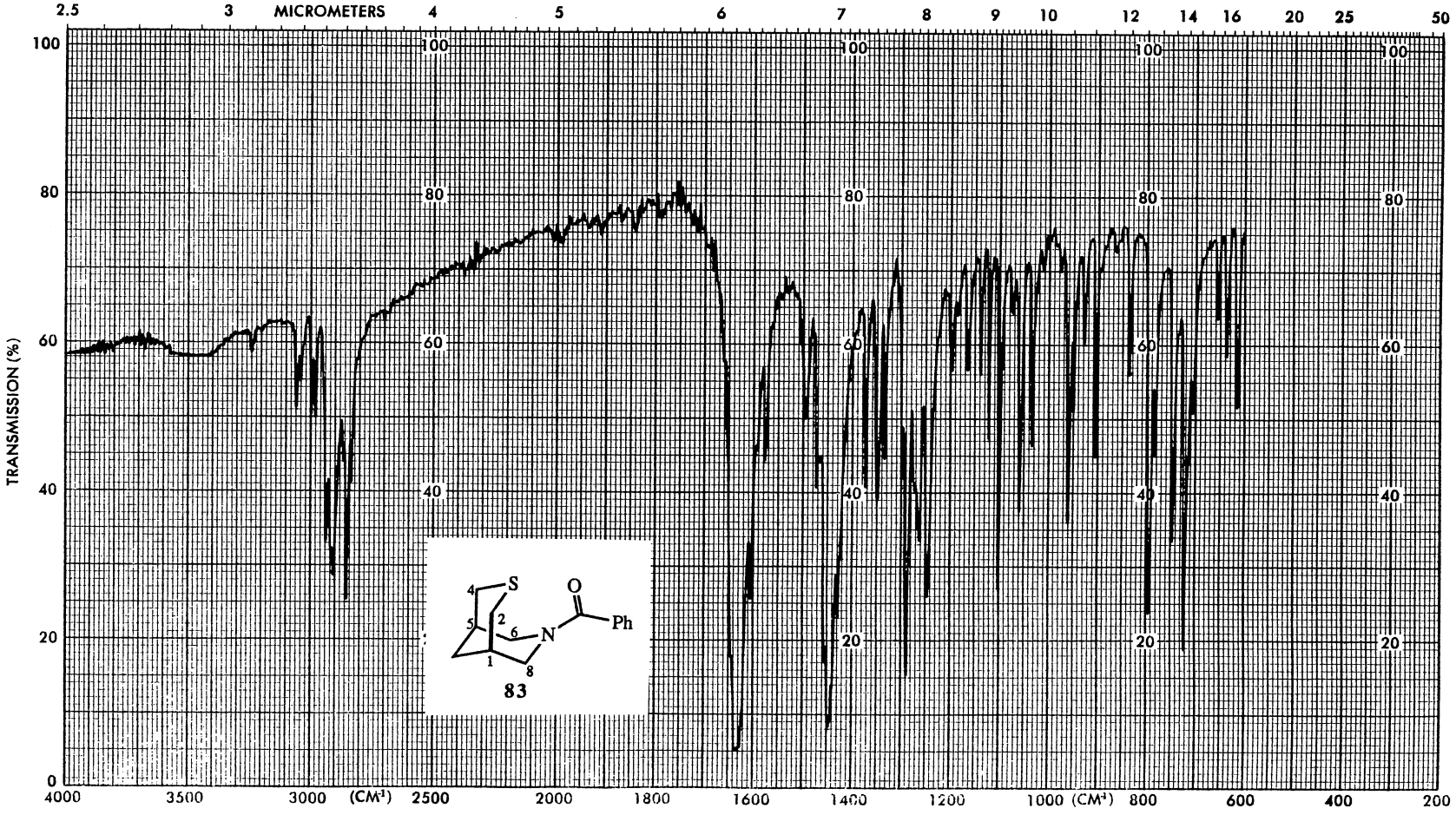
^{1}H NMR Spectrum of **82c**

Plate LXXXIV



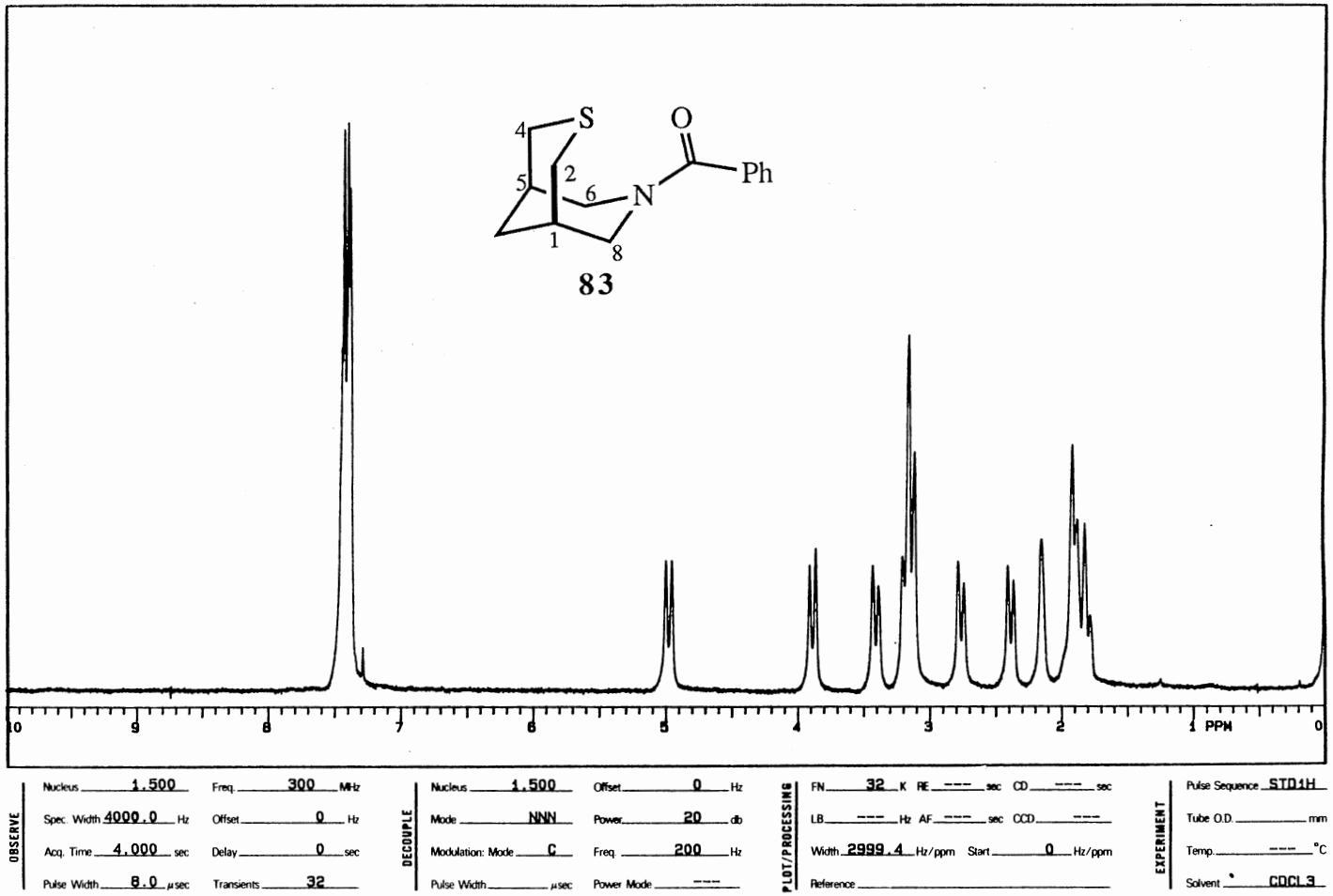
^{13}C NMR Spectrum of **82c**

Plate LXXXV



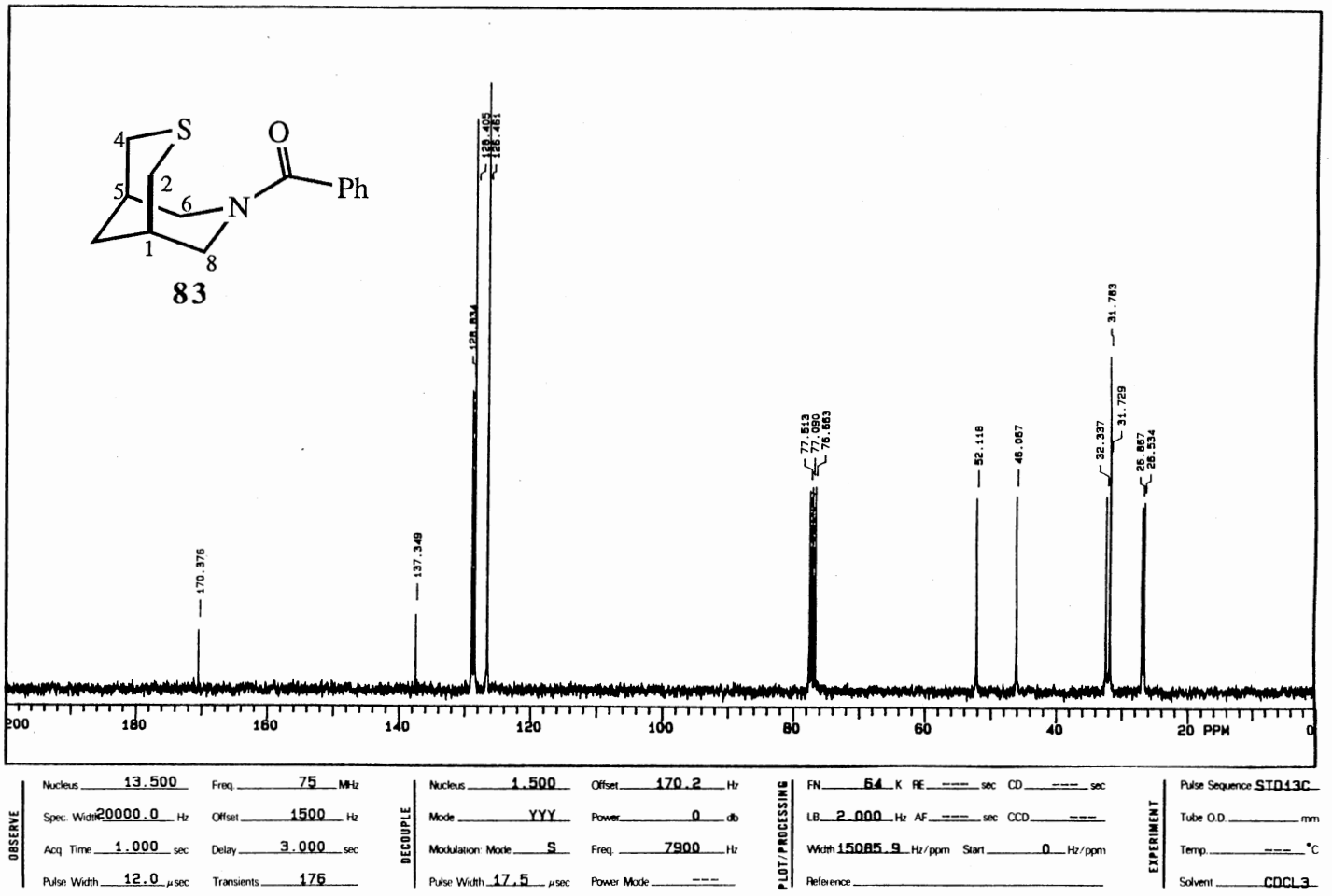
IR Spectrum of **83**

Plate LXXXVI



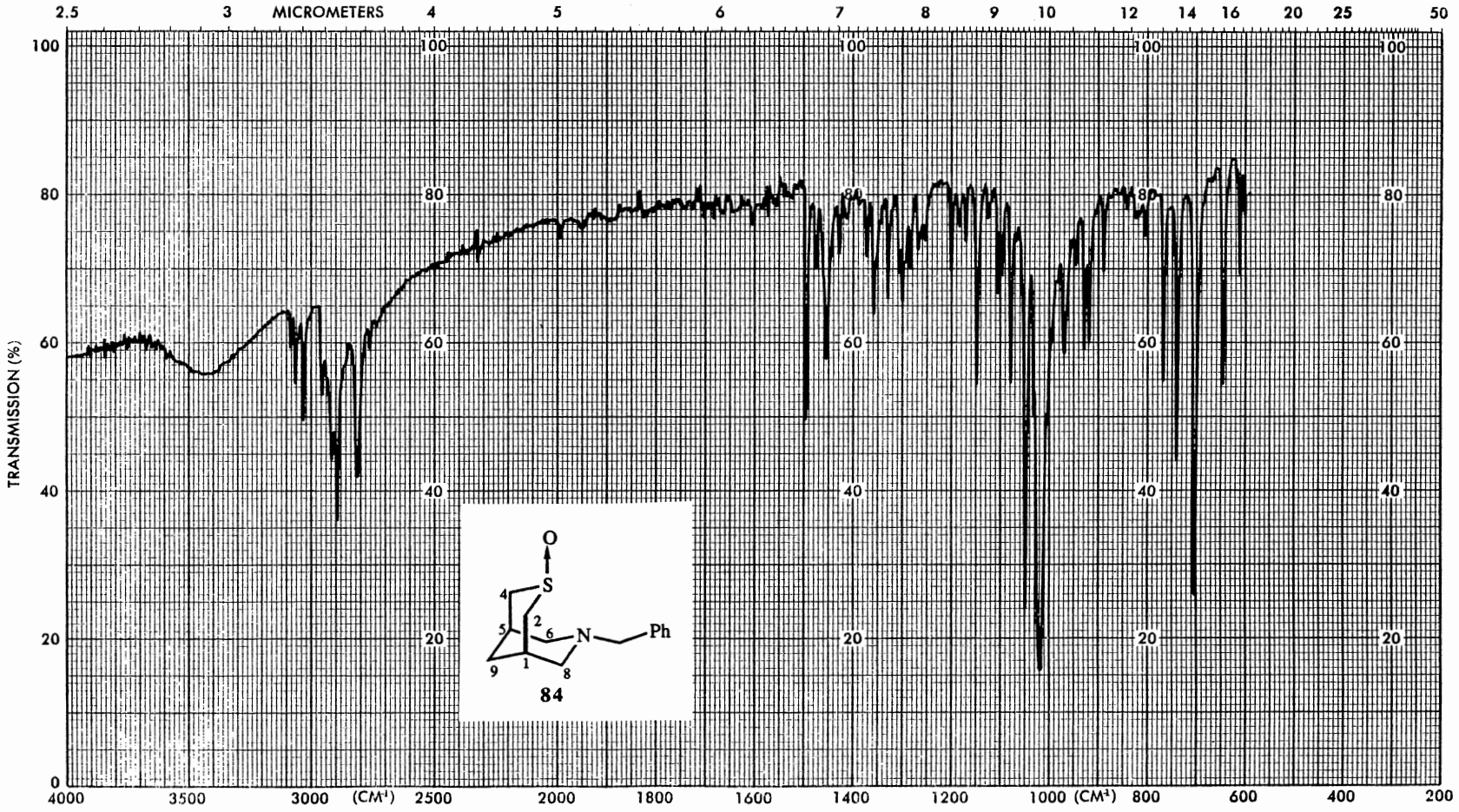
^{1}H NMR Spectrum of **83**

Plate LXXXVII



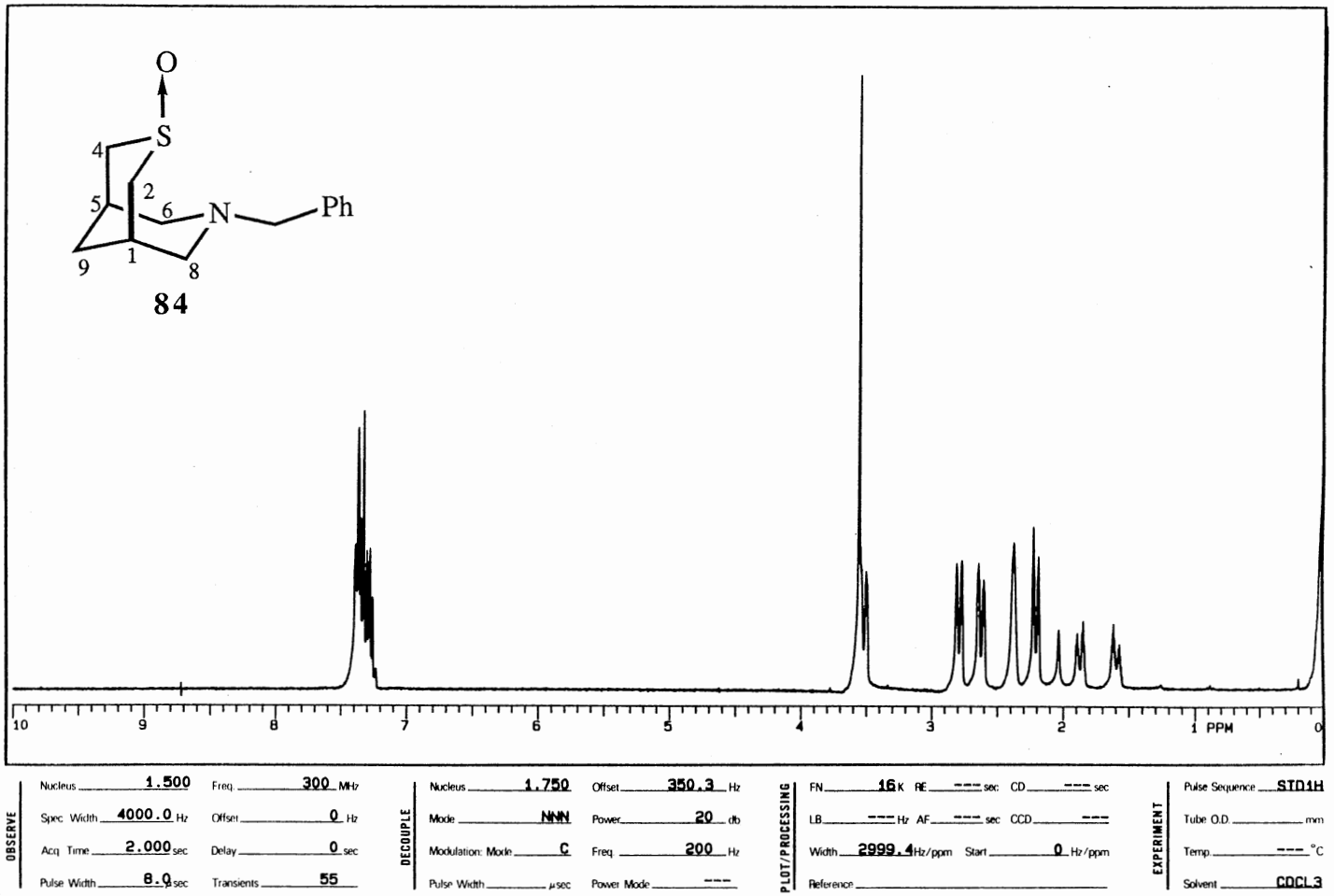
^{13}C NMR Spectrum of **83**

Plate LXXXVIII



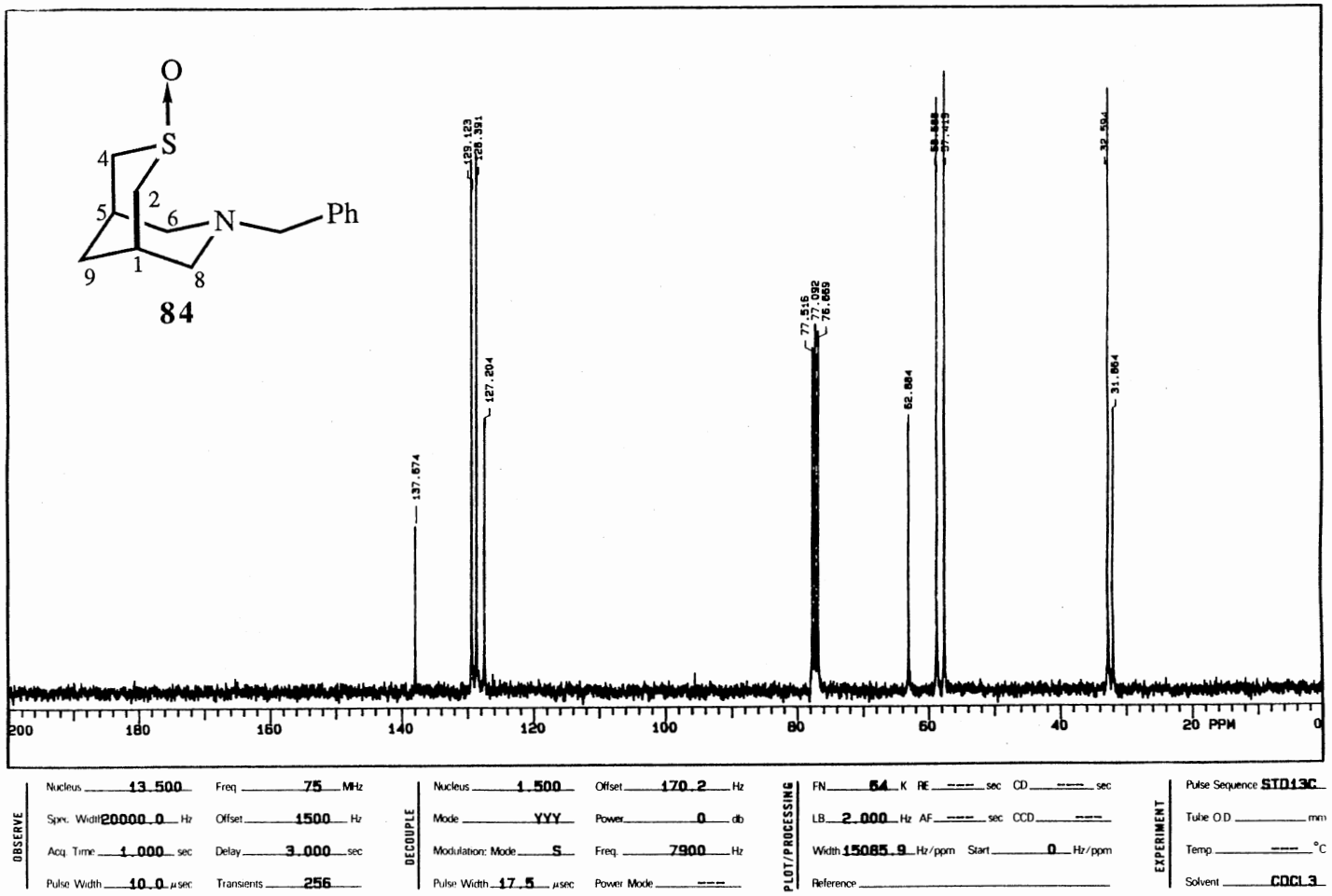
IR Spectrum of **84**

Plate LXXXIX



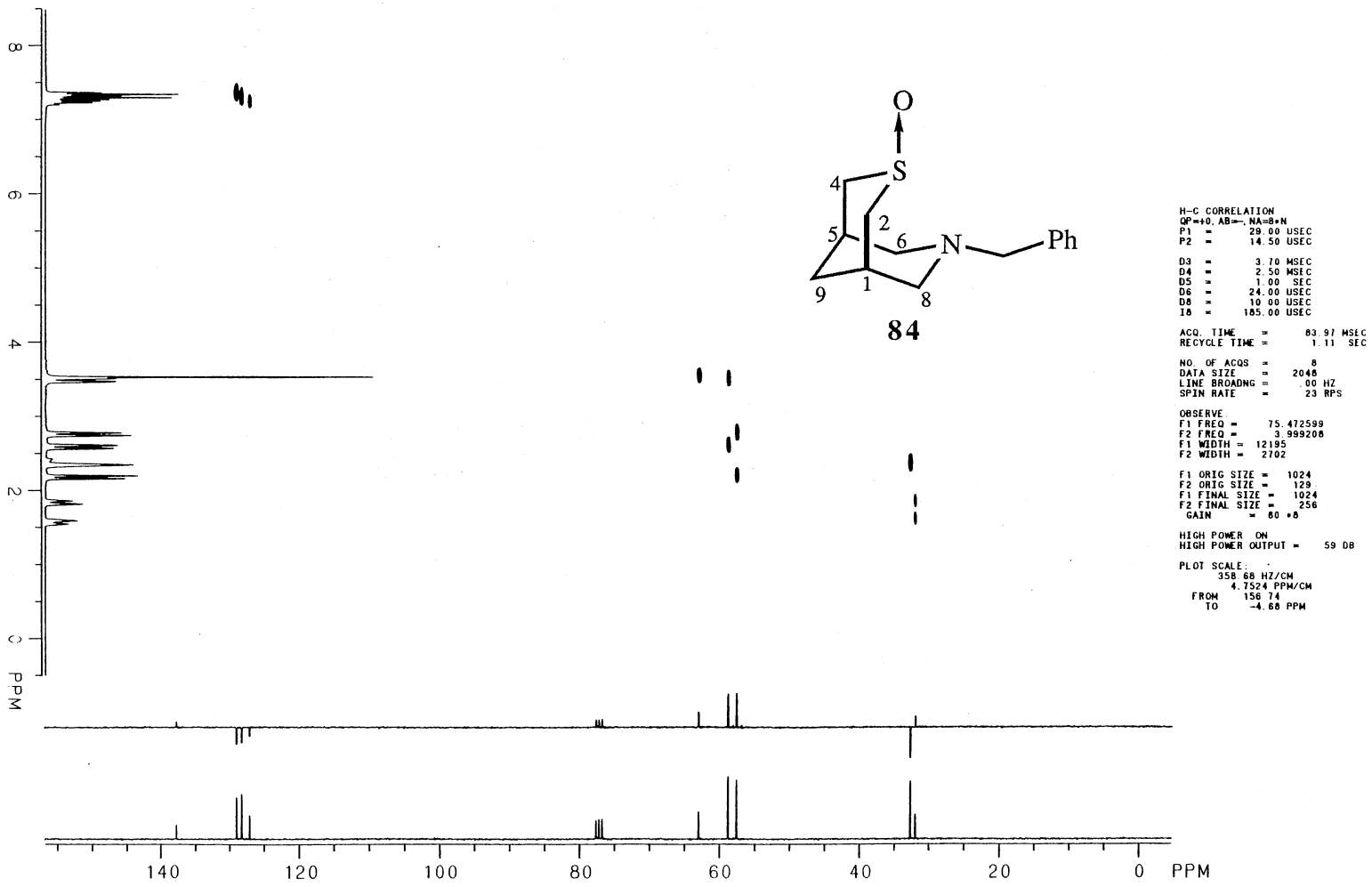
^{1}H NMR Spectrum of **84**

Plate XC



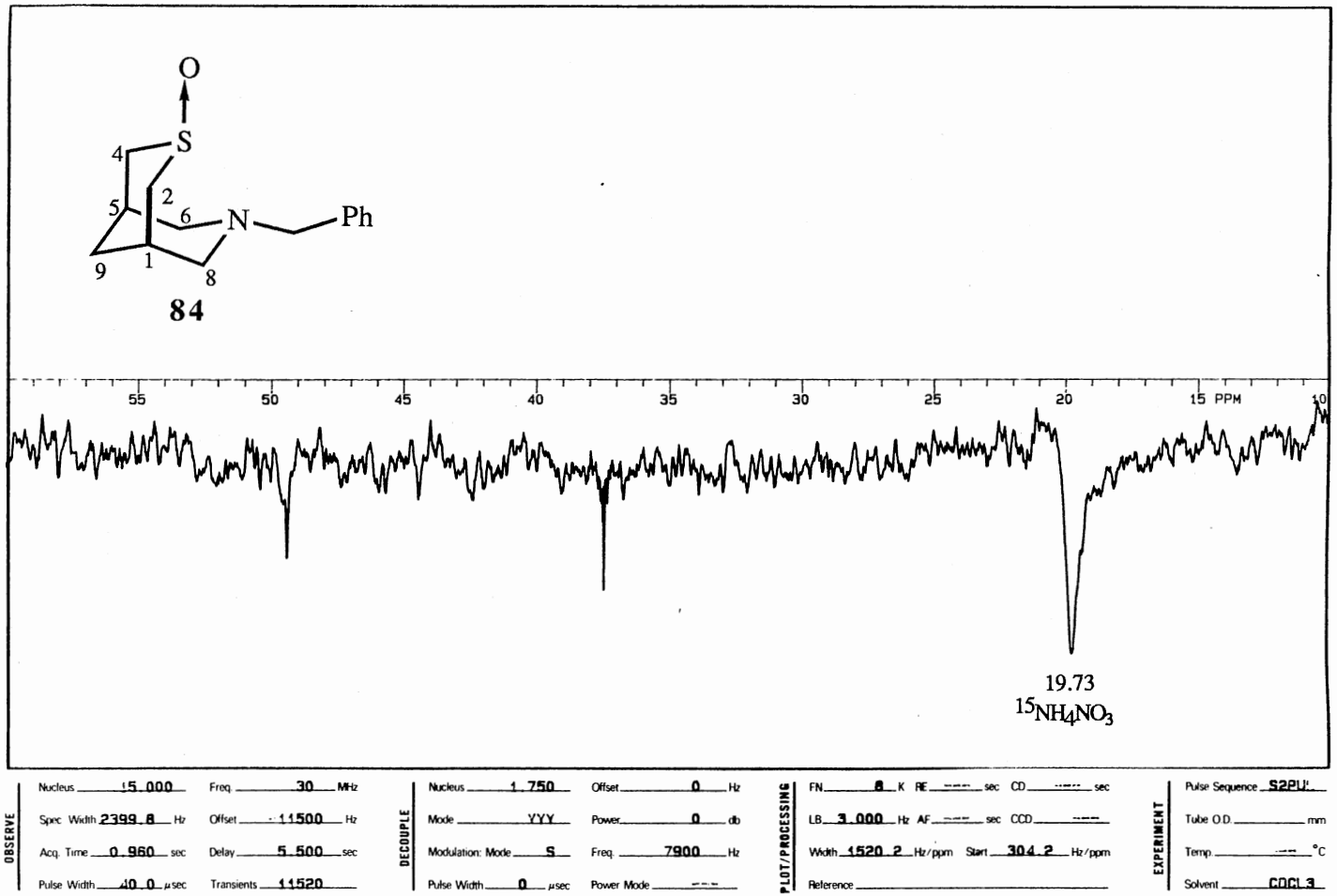
^{13}C NMR Spectrum of **84**

Plate XCI



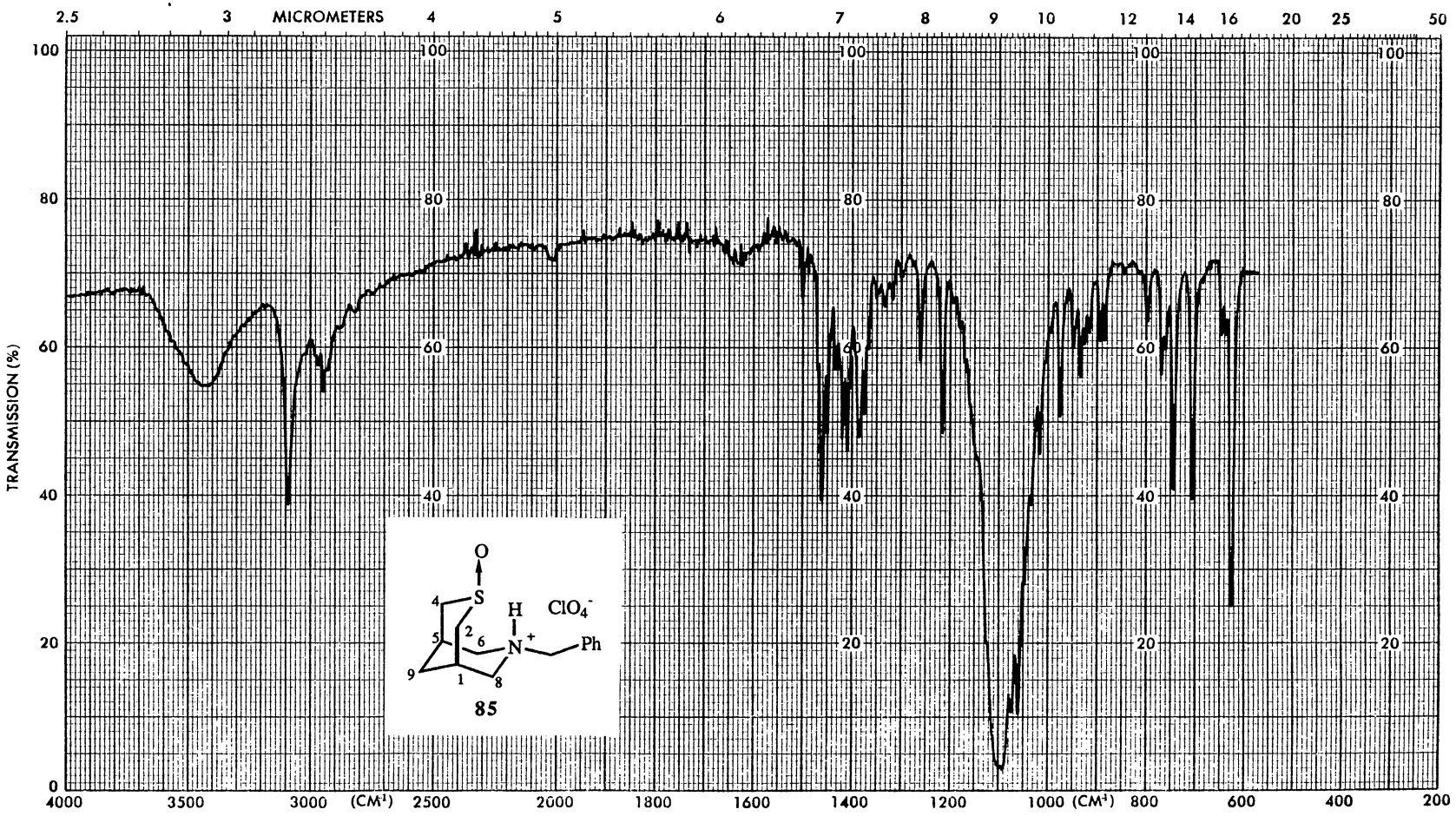
HETCOR Spectrum of **84**

Plate XCII



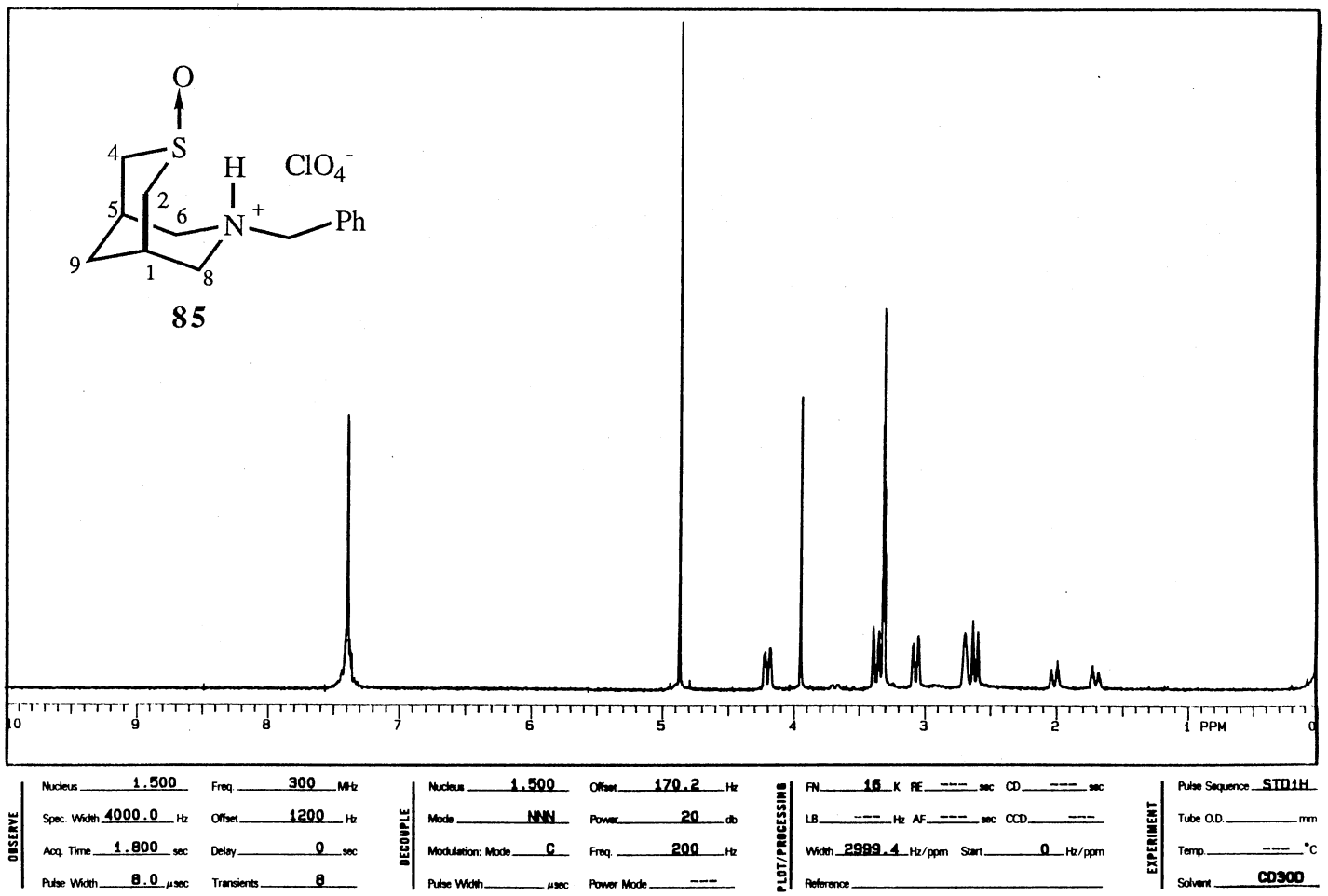
^{15}N NMR Spectrum of **84**

Plate XCIII



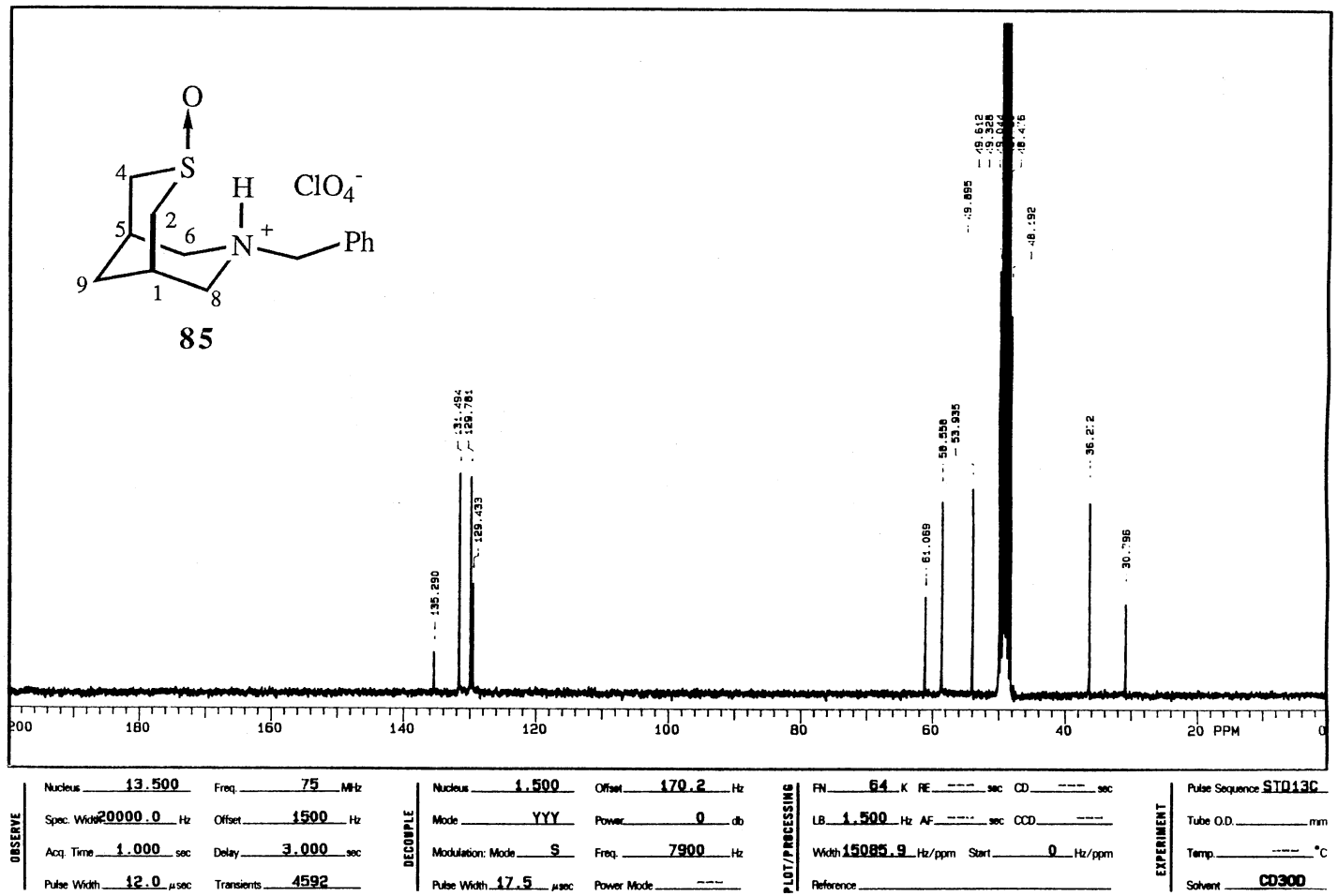
IR Spectrum of **85**

Plate XCIV



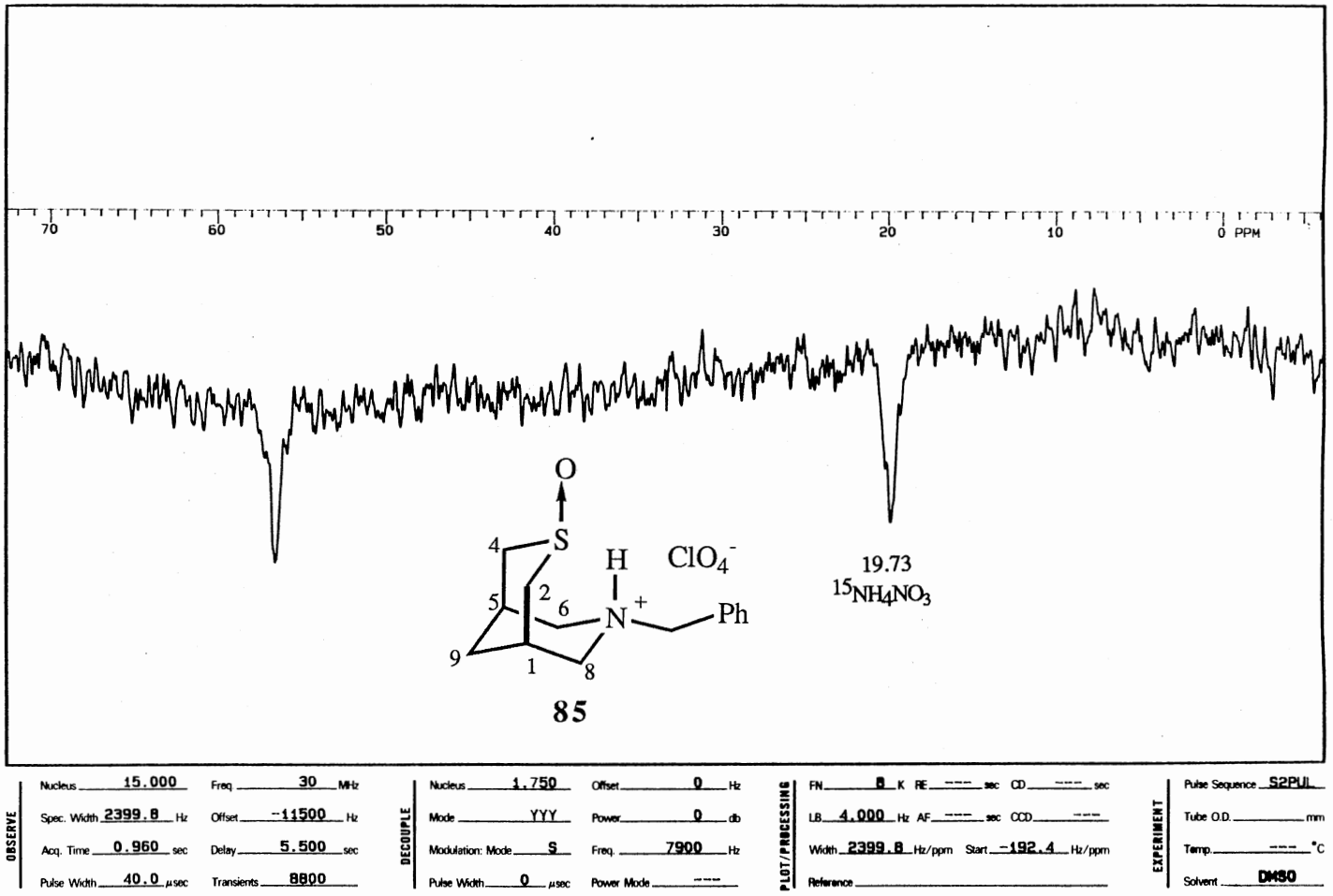
^{1}H NMR Spectrum of **85**

Plate XCV



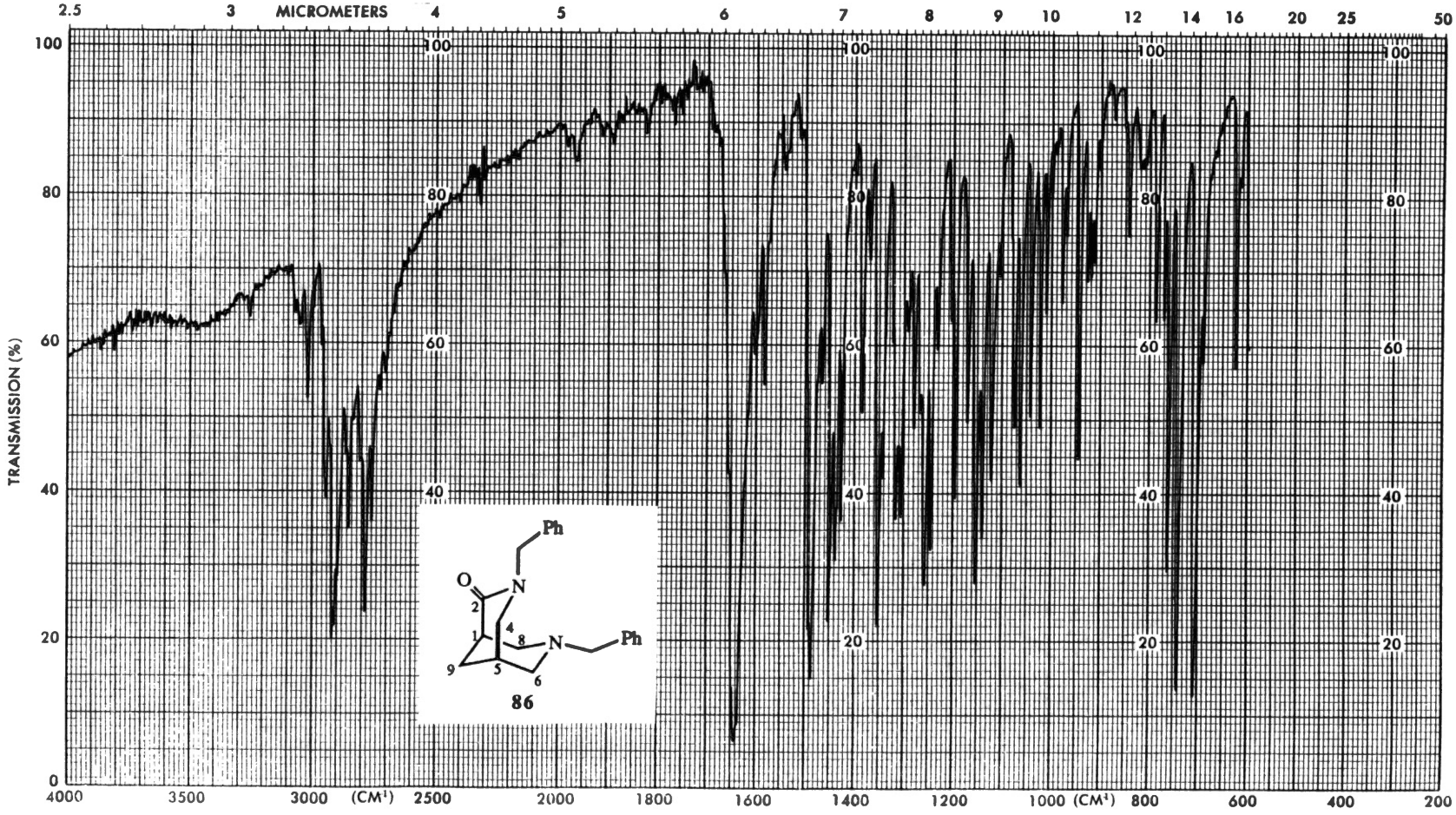
^{13}C NMR Spectrum of **85**

Plate XCVI



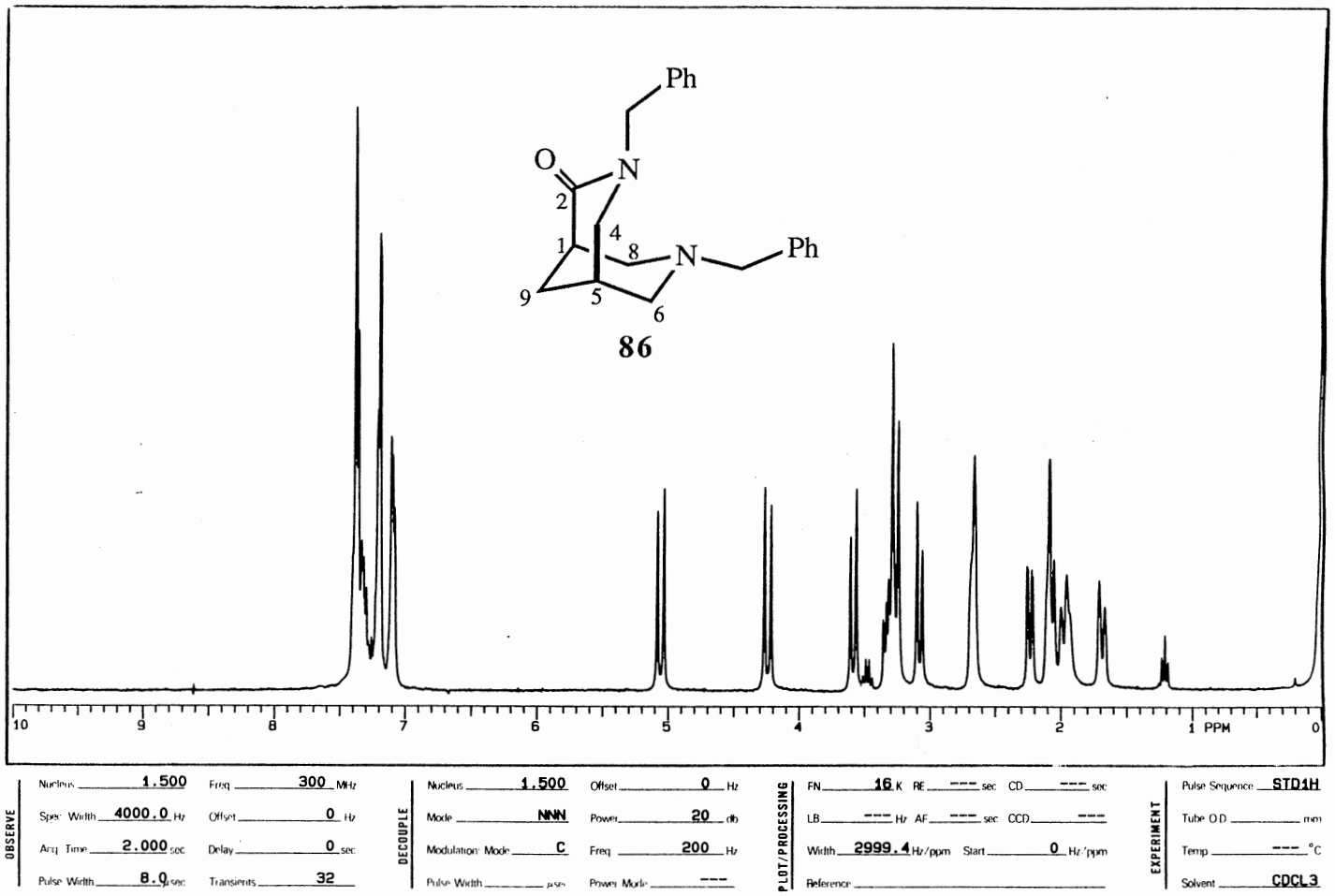
^{15}N NMR Spectrum of **85**

Plate XCVII



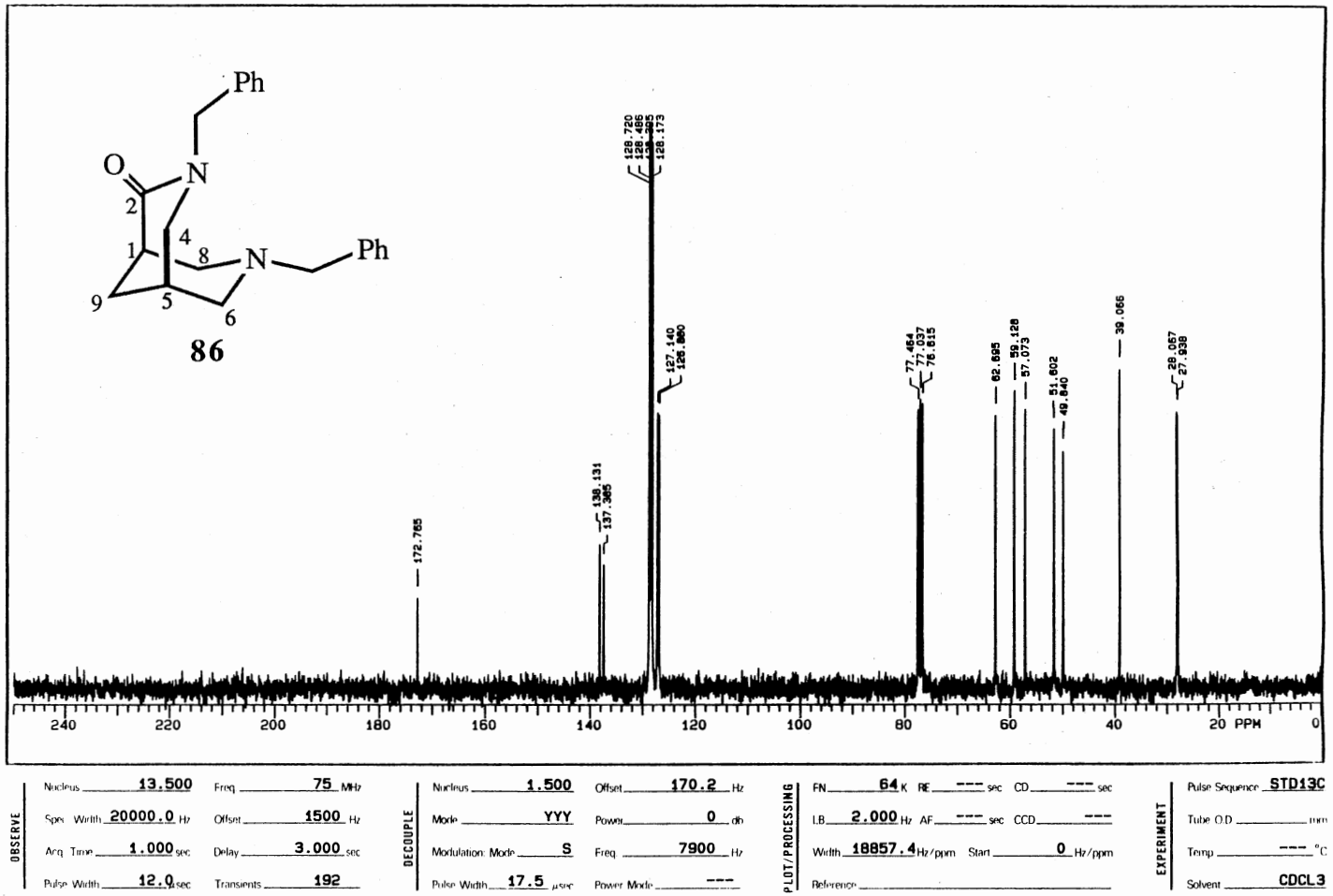
IR Spectrum of **86**

Plate XCVIII



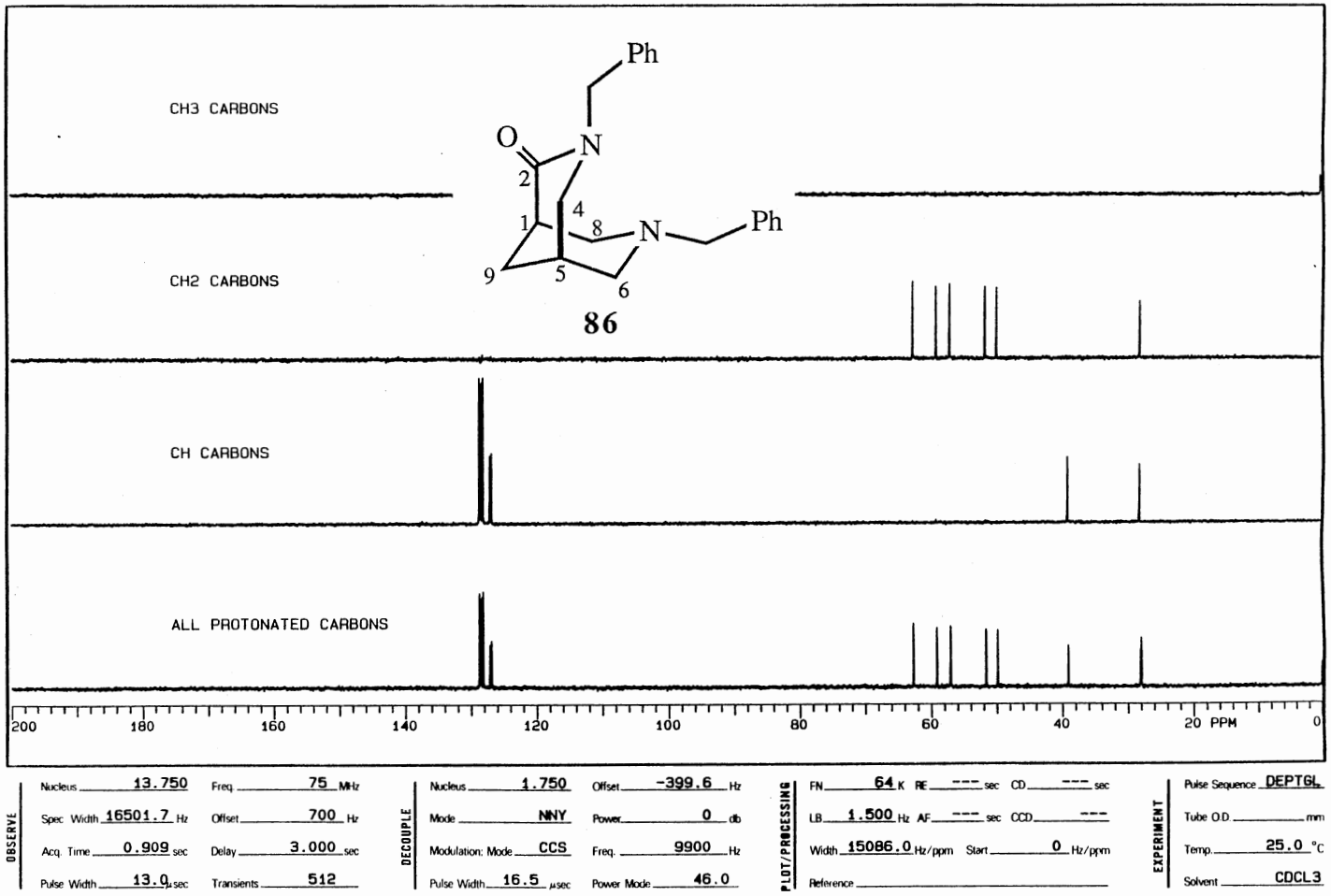
^{1}H NMR Spectrum of **86**

Plate XCIX



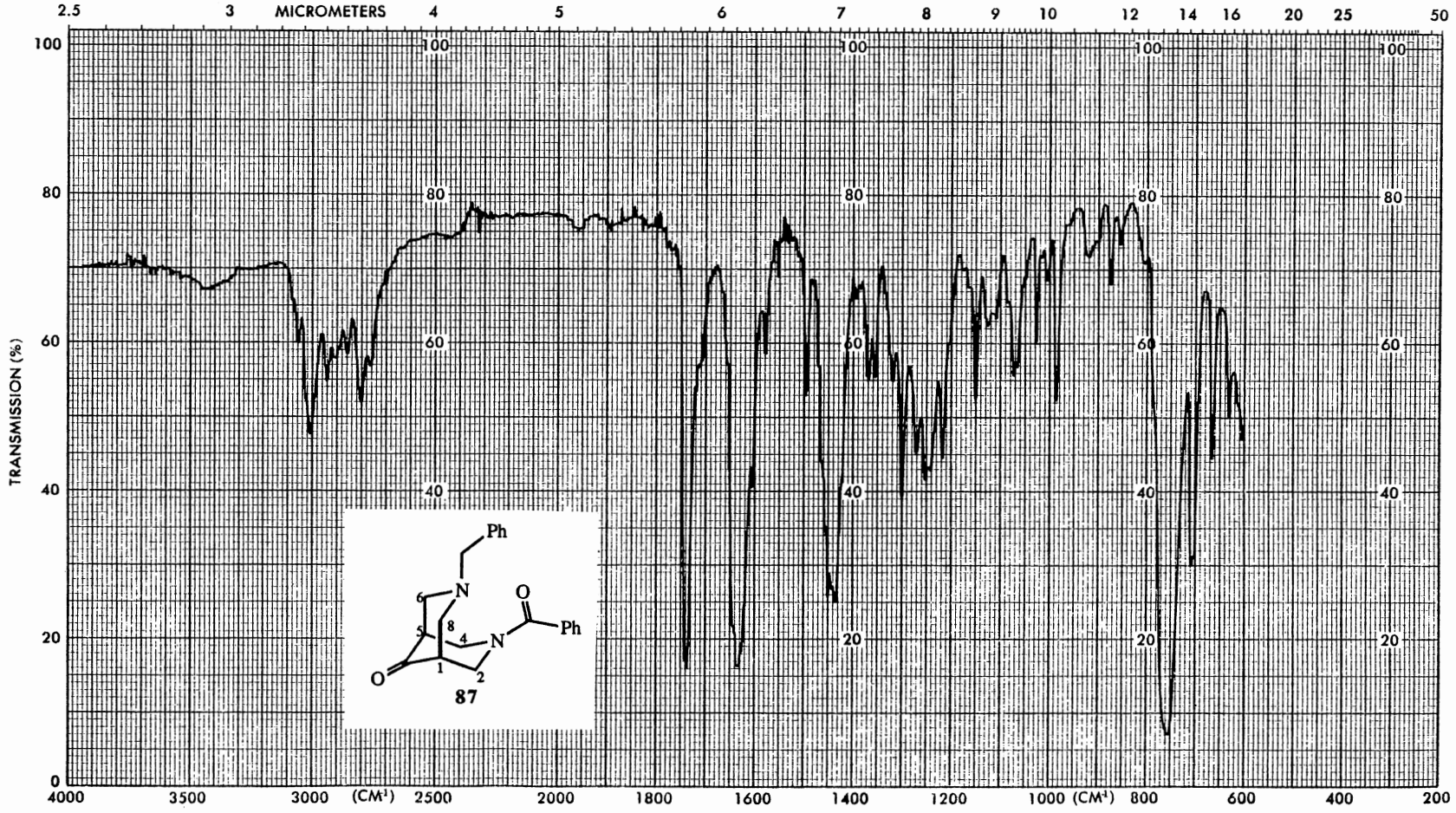
^{13}C NMR Spectrum of **86**

Plate C



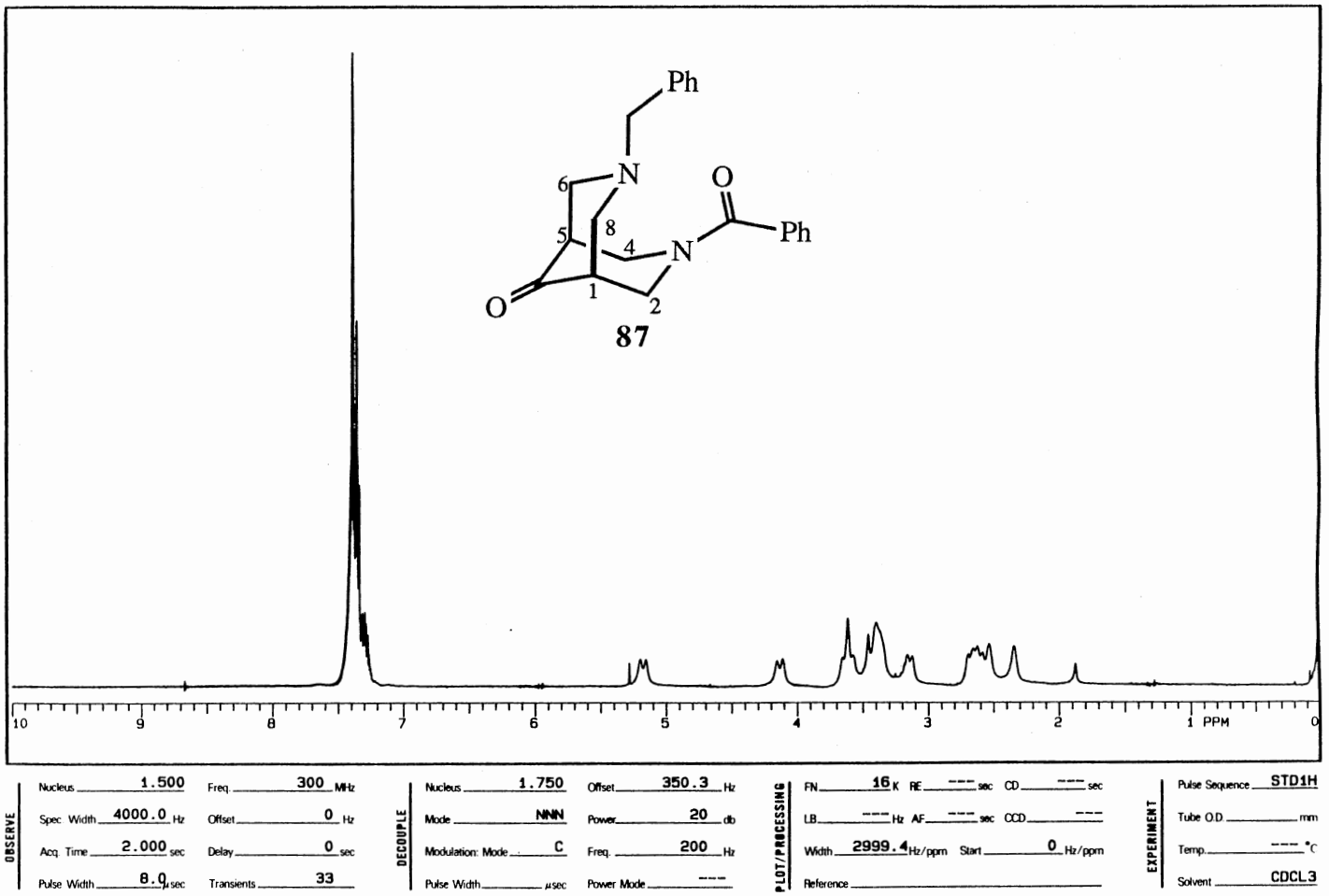
DEPT Spectrum of **86**

Plate CI



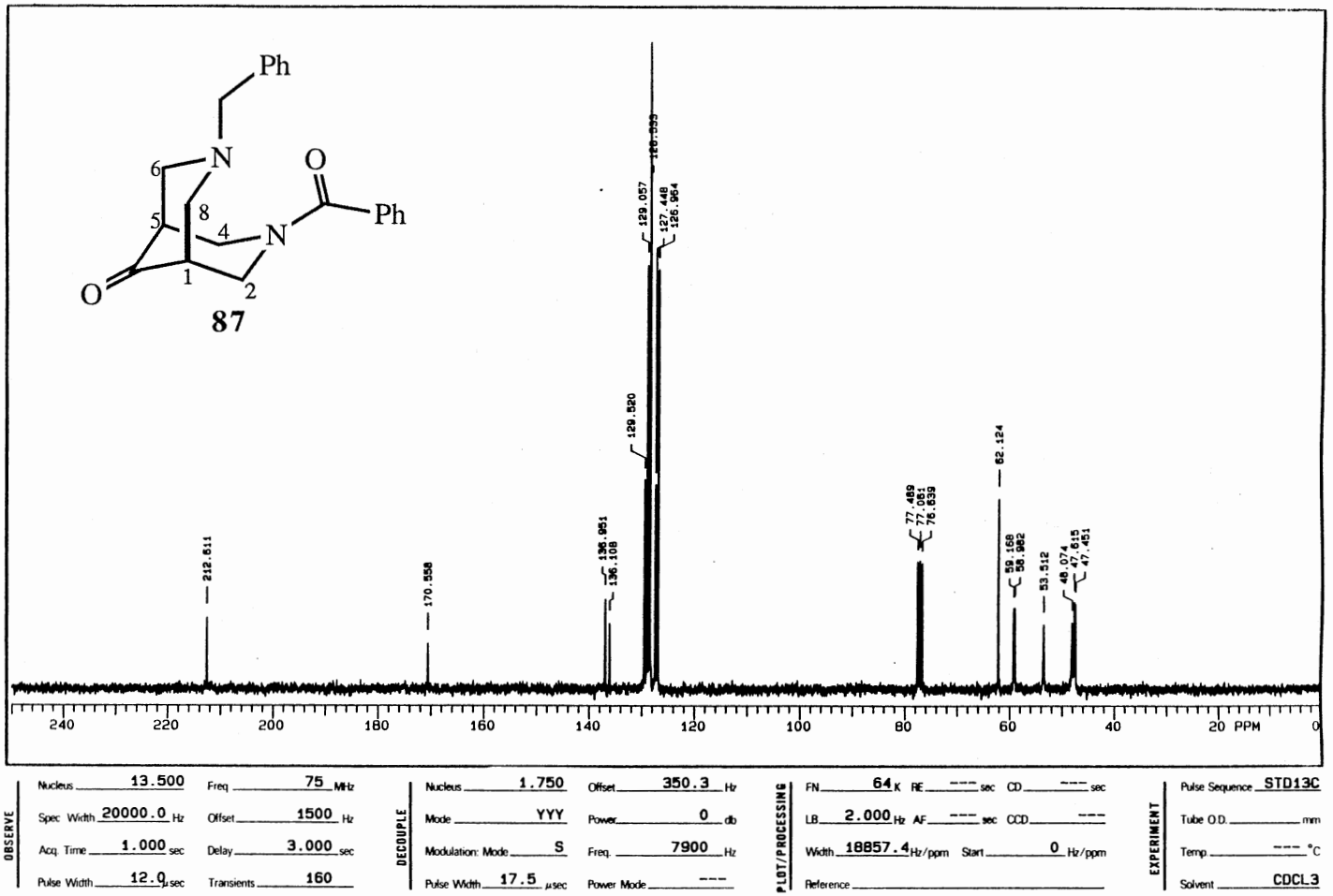
IR Spectrum of **87**

Plate CII



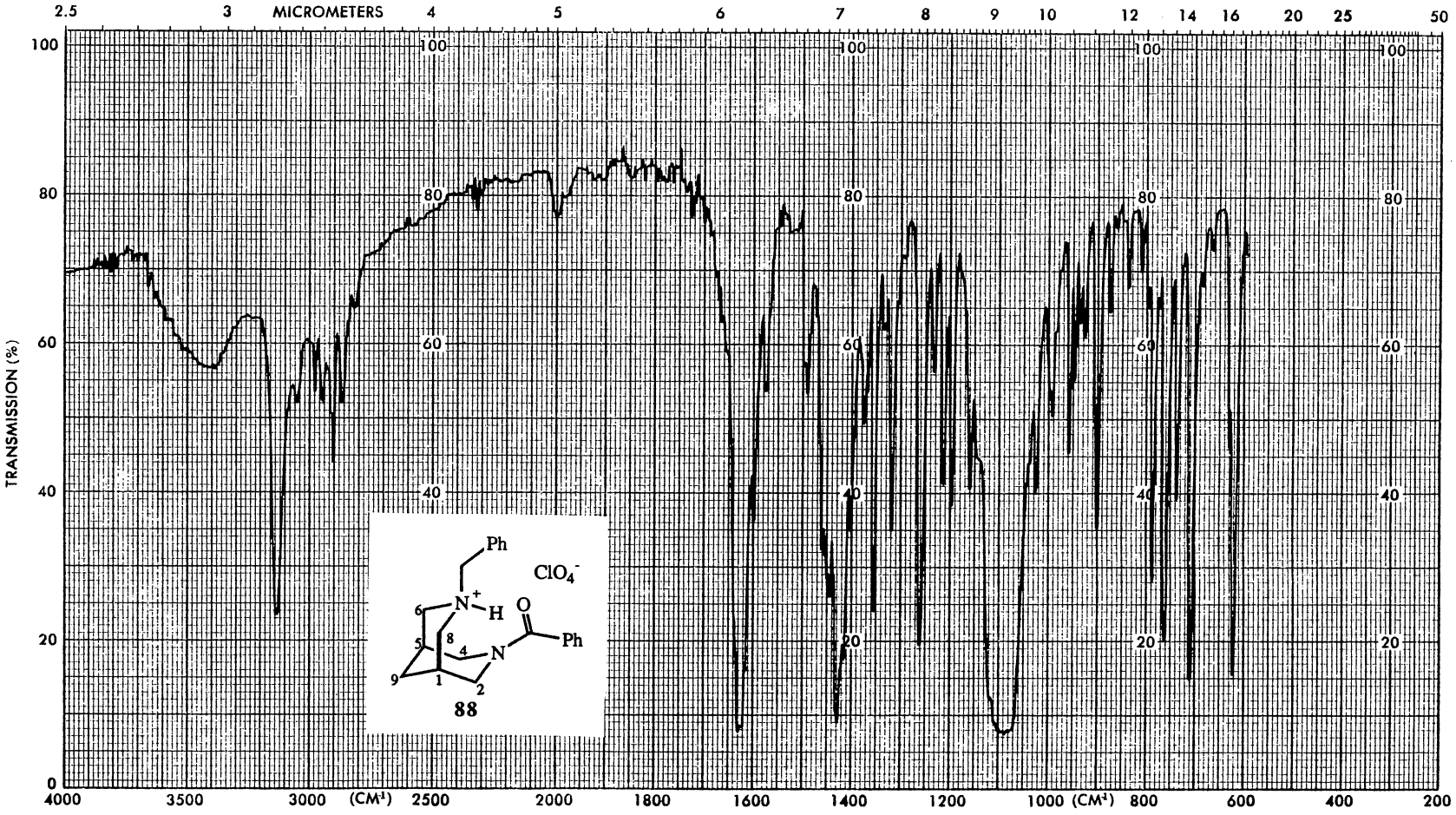
^{1}H NMR Spectrum of **87**

Plate CIII



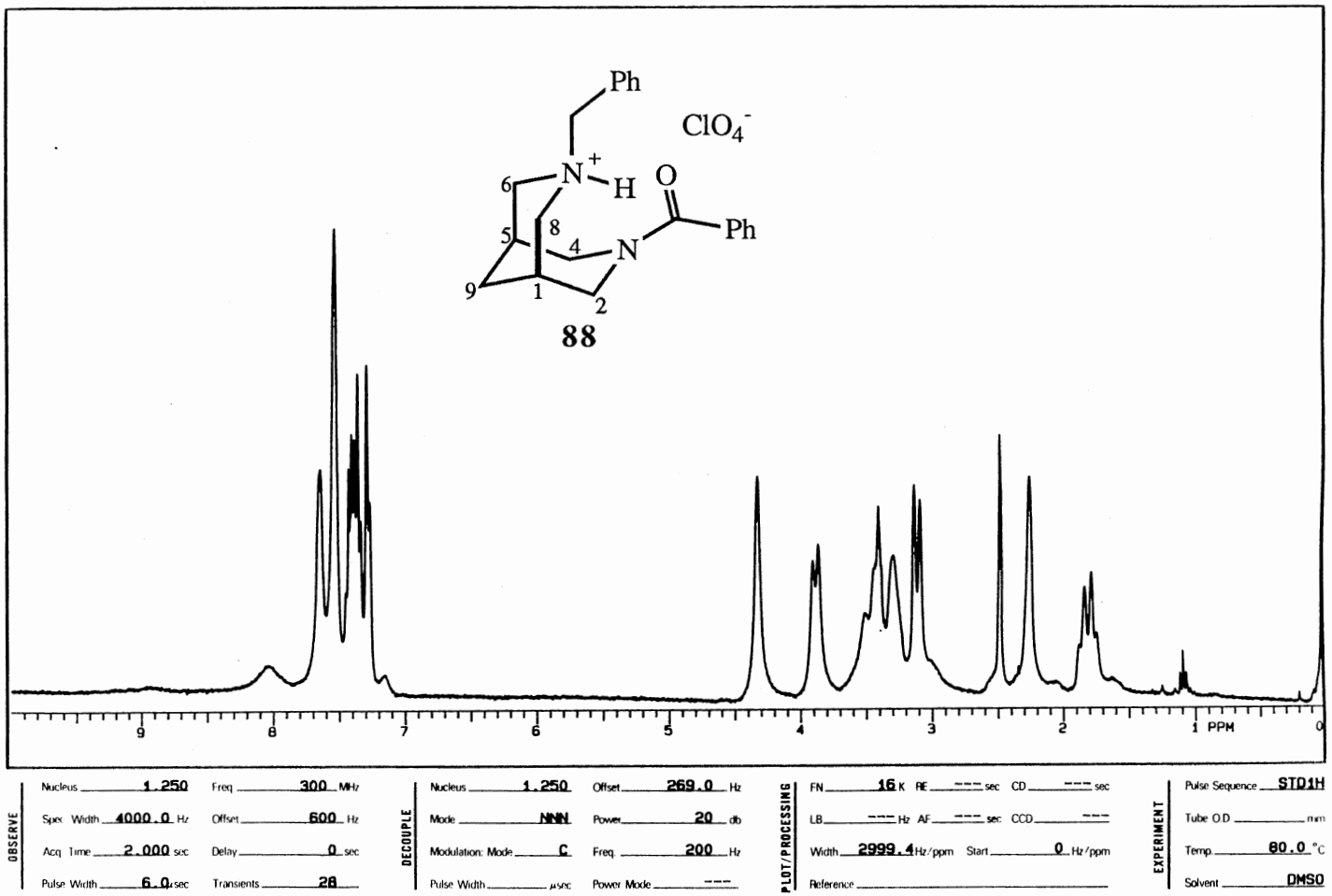
^{13}C NMR Spectrum of **87**

Plate CIV



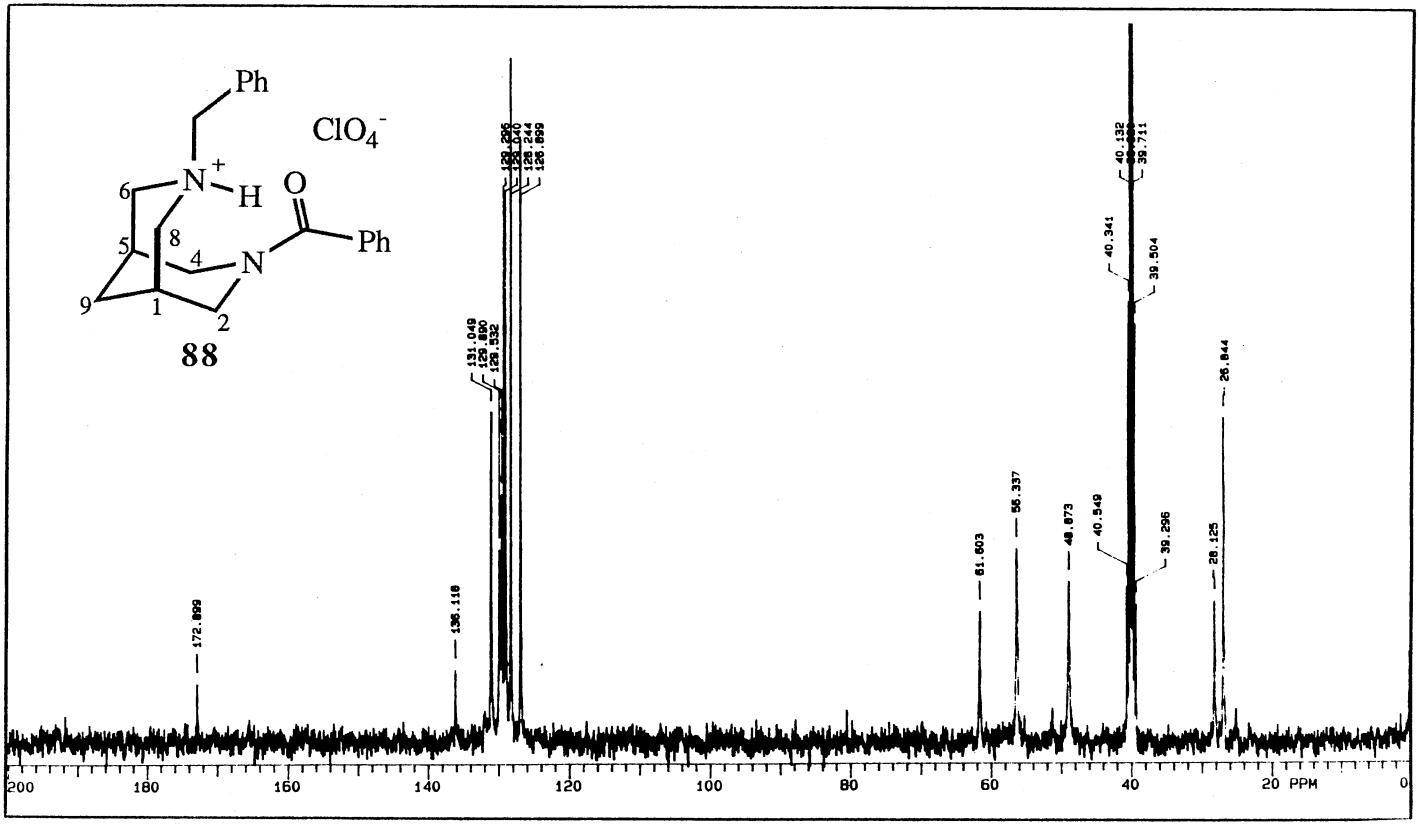
IR Spectrum of **88**

Plate CV



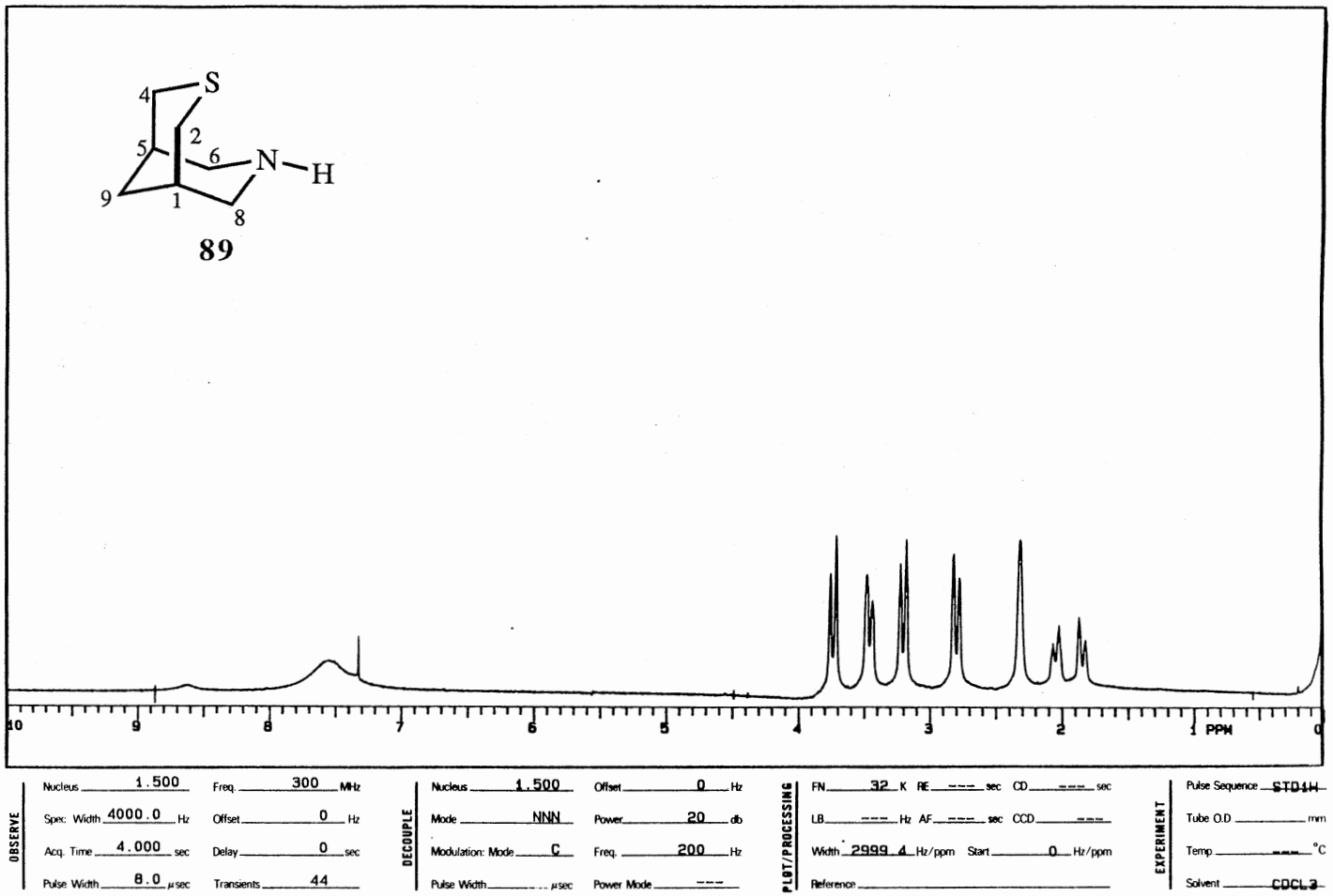
^{1}H NMR Spectrum of **88**

Plate CVI



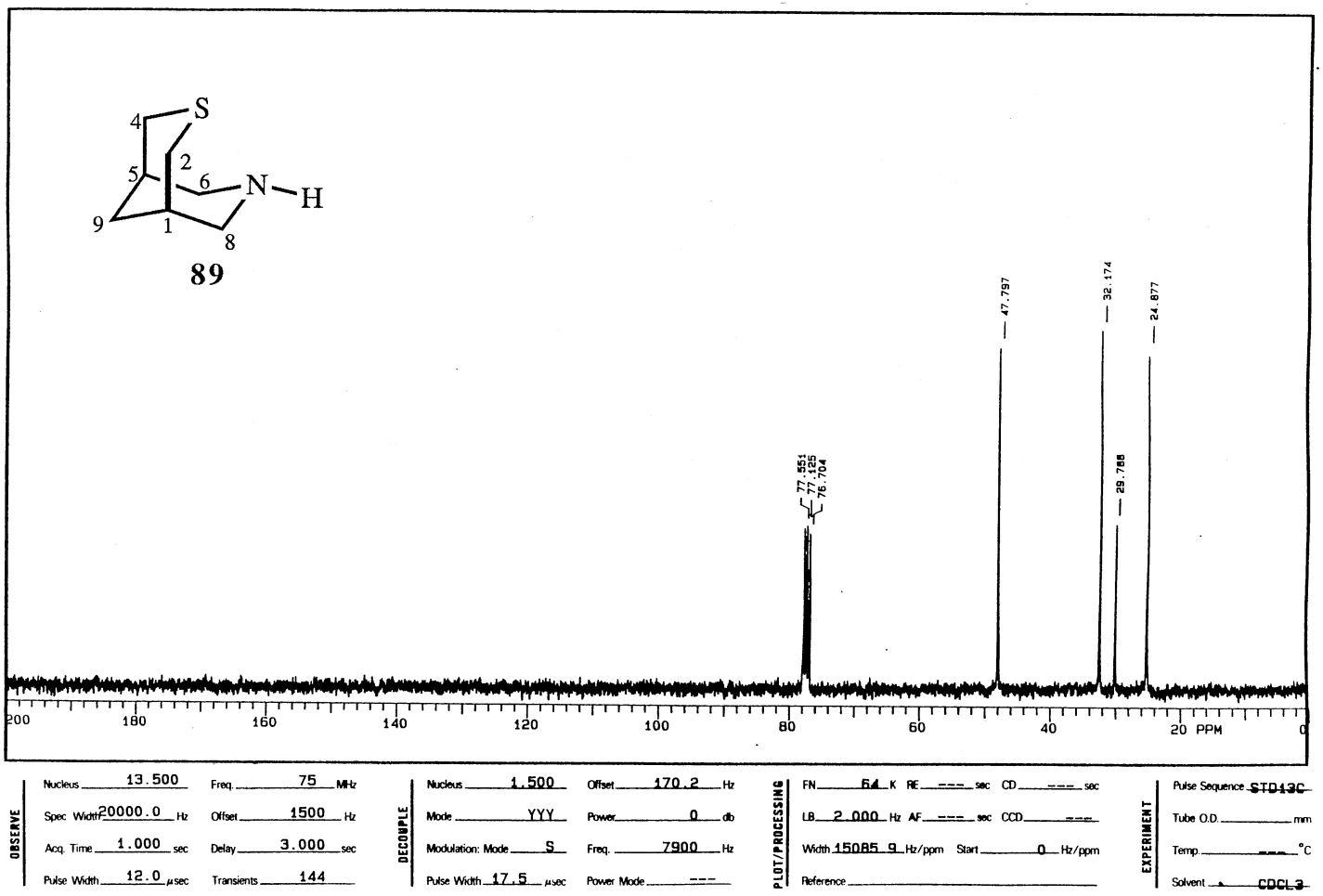
^{13}C NMR Spectrum of **88**

Plate CVII



^{1}H NMR Spectrum of **89**

Plate CVIII



^{13}C NMR Spectrum of **89**

BIBLIOGRAPHY

1. a. Adger, B. M.; O'Farrell, C. O.; Lewis, N. J.; Mitchell, M. B. *Synthesis*, **1987**, 53. b. Ram, S.; Ehrenkaufer, R. E. *Synthesis*, **1988**, 91. c. Ram, S.; Spicer, L. D. *Synth. Commun.*, **1987**, *17*, 415.

2. Al-Rawi, J. M. A.; Flamerz, S.; Khuthier, A. H. *Spectrochimica Acta*, **1985**, *41A*, 1391.

3. Arias, M. S.; Galvez, E.; Del Castillo, J. C.; Vaquero, J. J.; Chicharro, J. *J. Mol. Struct.*, **1987**, *156*, 239.

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

5. Bailey, B. R.; Berlin, K. D.; Holt, E. M. *Phosphorus and Sulfur*, **1984**, *20*, 131.

6. 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. d. Mulekar, S. V.; Berlin, K. D. *J. Org. Chem.*, **1989**, *35*, in press.

7. Bailey, B. R.; Berlin, K. D.; Holt, E. M. *Phosphorus and Sulfur*, **1984**, *20*, 131.

8. Baliah, V.; Jeyaraman, K. *Indian. J. Chem.*, **1977**, *15B*, 796.

9. Barrow, S. E.; Taylor, A. A.; Horning, E. C.; Horning, M. G. *J. Chromatogr.*, **1980**, *181*, 219.

10. Bingham, R. C.; Schleyer, P. *J. Org. Chem.*, **1971**, *36*, 1198.

11. a. Binnig, F.; Raschack, M.; Treiber, H. J. U.S. Patent 3,962,449, 1976; *Chem. Abstr.*, **1976**, *84*, 150675x. b. Binnig, F.; Friedrich, L.; Hofmann, H. P.; Kreiskott, H.; Mueller, C.; Raschack, M. U.S. Patent 4,183,935, 1980; *Chem. Abstr.*, **1979**, *90*, 121568h. c. Binnig, F.; Mueller, C. D.; Raschack, M.; von Philipsborn, G. U.S. Patent 4,556,662, 1985; *Chem. Abstr.*, **1983**, *98*, 16738f.

12. Blackburne, I. D.; Duke, R. P.; Jones, R. A. Y.; Katritzky, A. R.; Record, K. A. F. *J. Chem. Soc. Perkin Trans. 2*, **1973**, 332.

13. Blumer, J.; Strong, J. M.; Atkinson, A. J. *J. Pharmacol. Exp. Ther.*, **1973**, *186*, 31.

14. Bohlmann, F.; Schumann, D.; Arndt, C. *Tetrahedron Lett.*, **1965**, *31*, 2705.

15. Brukwicki, T.; Wiewiorowski, M. *Bull. Pol. Acad. Sci. Chem.*, **1986**, *34*, 205; *Chem. Abstr.*, **1987**, *107*, 96950m.

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

17. Darnbrough, G.; Knowles, P.; O'Connor, S. P.; Tierney, F. J. *Tetrahedron*, **1986**, *42*, 2339.

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

19. Eichelbaum, M. *Trends Pharmacol. Sci.*, **1981**, *2*, 31.

20. Eichelbaum, M.; Spannbrucker, N.; Dengler, H. J. *Eur. J. Clin. Pharmacol.*, **1979**, *16*, 189.

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

22. a. Eliel, E. L. *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962, Chapter 6. b. Eliel, E. L.; Allinger, N. C.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*, Interscience, New York, 1965, Chapter 2. c. Dale, J. *Stereochemistry and Conformational Analysis*, Verlag Chemie, New York, 1978.

23. Galvez, E.; Arias, M. S.; Bellanato, J.; Garcia-Ramos, J. V.; Florencio, F.; Smith-Verdier, P.; Garcia-Blanco, S. *J. Mol. Struct.*, **1985**, *127*, 185.

24. Gordon, A. J.; Ford, R. A. The Chemist's Companion: *A Handbook of Practical Data, Techniques and References*, John Wiley & Sons, New York, 1972.

25. Hachmeister, B.; Kehrbach, W.; Buschmann, G. U.S. Patent 4,415,577, 1983; *Chem. Abstr.*, **1982**, *97*, 39207a.

26. Hirsch, J. A.; Augustine, R. L.; Koletar, G.; Wolf, H. G. *J. Org. Chem.*, **1975**, *40*, 3547.

27. Holland, H. L. *Chem. Rev.*, **1988**, *88*, 473.

28. Holland, H. L.; Daum, U.; Riemland, E. *Tetrahedron Lett.*, **1981**, *22*, 5127.

29. Hutchinson, B. J.; Anderson, K. K.; Katritzky, A. R. *J. Am. Chem. Soc.*, **1969**, *91*, 3839.

30. Jeyaraman, R.; Avila, S. *Chem Rev.*, **1981**, *81*, 149.

31. Johnson, C. R.; Keiser, J. E. *Org. Synth.*, **1973**, Coll. Vol. *5*, 791.

32. Johnson, P. Y.; Berchtold, G. A. *J. Org. Chem.*, **1970**, *35*, 584.

33. Johnson, R. A. *J. Org. Chem.*, **1968**, *33*, 3627.

34. Jones, S. R.; Mellor, J. M. *J. Chem. Soc. Perkin Trans. 1*, **1976**, 2576.

35. Kates, R. E.; Woosley, R. L.; Harrison, D. C. *Am. J. Cardiol.*, **1984**, *53*, 248.

36. Kienzle, M. G.; Williams, P. D.; Zygmont, D.; Doherty, J. U.; Josephson, M. E. *Heart and Lung*, **1984**, *13*, 614.

37. Lambert, J. B.; Keske, R. G. *J. Org Chem.*, **1966**, *31*, 3429.

38. Levy, G. C.; Lichter, R. L. *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*, John Wiley & Sons, New York, 1979.

39. Livant, P.; Roberts, K. A.; Eggers, M. D.; Worley, S. D. *Tetrahedron*, **1981**, *37*, 1853.

40. Llama, E. F.; Trigo, G. G. *Heterocycles*, **1986**, *24*, 719.

41. Mandel, W. J., Ed. *Cardiac Arrhythmias: Their Mechanisms, Diagnosis, and Management*, J. P. Lippincott, Philadelphia, Pennsylvania, 1987.

42. Margulies, E., Ed. *Myocardial Infarction and Cardiac Death*, Academic, New York, 1983.

43. 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.

44. Morganroth, J.; Horowitz, L. N., Eds., *Sudden Cardiac Death*, Grune and Stratton, Orlando, Florida, 1973.

45. Nachtergaele, W. A.; Tavernier, D.; Anteunis, M. J. O. *Bull. Soc. Chim. Belg.* **1980**, *89*, 33.

46. Nador, K.; Kraiss, G.; Siako, K.; Paroczai, M.; Karpati, E.; Szporny, L. U.S. Patent 4,451,473, 1984; *Chem. Abstr.*, **1983**, *99*, 5654v.

47. Nowacki, E.; Wezyk, S. *Rocz. Nauk Roln.*, **1960**, *75*, 385; *Chem. Abstr.*, **1961**, *55*, 9663c.

48. Oae, S., Ed. *Organic Chemistry of Sulfur*, Plenum Press, New York, 1977.

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

50. Osina, E. L.; Mastryukov, V. S.; Vilkov, L. V.; Belikova, N. A. *J. Chem. Soc. Chem. Commun.*, **1976**, 12.

51. Pantaleo, N. S.; van der Helm, D.; Ramarajan, K.; Bailey, B. R.; Berlin, K. D. *J. Org. Chem.*, **1981**, *46*, 4199.

52. Przybylska, M.; Barnes, W. H. *Acta Cryst.*, **1953**, *6*, 377.

53. a. Quast, H.; Muller, B. *Chem Ber.*, **1980**, *113*, 2959. b. Quast, H.; Muller, B.; Peters, E. M.; Peters, K.; von Schnering, H. G. *Chem. Ber.*, **1982**, *115*, 3631. c. Quast, H.; Muller, B.; Peters, E. M.; von Schnering, H. G. *Chem. Ber.*, **1983**, *116*, 424.

54. a. Raber, D. J.; Janks, C. M.; Johnston, M. D.; Raber, N. K. *Tetrahedron Lett.*, **1980**, *21*, 677. b. Engler, E. M.; Andose, J. D.; von Schleyer, P. R., *J. Am. Chem. Soc.*, **1973**, *95*, 8005.

55. a. Reunitz, P. C.; Mokler, C. M. *J. Med. Chem.*, **1977**, *20*, 1668. b. Reunitz, P. C.; Mokler, C. M. *J. Med. Chem.*, **1979**, *22*, 1142.

56. Sadykov, A. S.; Kamayev, F. G.; Korenevsky, V. A.; Leont'ev, V. B.; Ustynyuk, Y. A. *Org. Magn. Reson.*, **1972**, *4*, 837.

57. Salva, P. S.; Hite, G. J.; Heyman, R. A.; Gianutsos, G. *J. Med. Chem.*, **1986**, *29*, 2111.

58. Sangiah, S.; Clarke, C. R.; Geno, P. W., unpublished results.

59. Scherlag, B. J.; Patterson, E.; Lazzara, R.; Bailey, B. R.; Thompson, M. D.; Berlin, K. D. *J. Electrophysiology*, **1988**, *2*, 461.

60. Senges, J.; Rudel, R.; Schmid-Wiedersheim, E. *Arch. Pharm.*, **1972**, *274*, 348.

61. Skolik, J.; Wiewiorowski, M.; Krueger, P. J. *J. Mol. Struct.*, **1970**, *5*, 461.

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

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

64. Stetter, H.; Merten, R., *Chem Ber..*, **1957**, *90*, 869.

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

66. Thompson, B. B.; *J. Pharmaceutical Sciences*, **1968**, *57*, 715.

67. Thompson, M. D.; Smith, G. S.; Berlin, K. D. *Org. Prep. Proc. Int.*, **1986**, *18*, 329.

68. Todd, D. *Org. React.*, **1948**, *4*, 378.

69. Trahanovsky, W. B. *Oxidation in Organic Chemistry*, Part D, Academic, New York, 1973.

70. Wasylishen, R. E.; Friesen, K. J. *Org. Magn. Reson.*, **1980**, *13*, 343.

71. Wiewiorowski, M.; Edwards, O. E.; Bratek-Wiewiorowska, M. D. *Can. J. Chem.*, **1967**, *45*, 1447.

72. Wink, M.; Hartmann, T.; Witte, L. *Planta Med.*, **1979**, *18*, 31.

73. Zablicky, J., Ed. *The Chemistry of Amides*, Interscience, New York, 1970.

74. Zefirov, N. S. *Russ. Chem. Rev.*, **1975**, *44*, 196.

75. Zefirov, N. S.; Rogozina, S. V. *Russ. Chem. Rev.*, **1973**, *42*, 190.

76. Zefirov, N. S.; Rogozina, S. V.; Kurkutova, E. H.; Goncharov, A. V.; Belov, N. V. *J. Chem. Soc. Chem. Commun.*, **1974**, 260.

77. Zisman, S. A.; Berlin, K. D.; Alavi, F. K.; Sangiah, S.; Clarke, C. R.; Scherlag, B. J. *J. Radiolabelled Pharmaceuticals*, **1989**, in press.

VITA

Stan A. Zisman

Candidate for the Degree of

Doctor of Philosophy

Thesis: A STUDY OF STEREOCHEMICAL AND SUBSTITUENT EFFECTS ON ANTIARRHYTHMIC ACTIVITY OF SELECTED 3-AZABICYCLO[3.3.1]-NONANES AND DERIVATIVES

Major Field: Chemistry

Biographical:

Personal Data: Born in Altus, Oklahoma, August 1, 1963, the son of Allen L. and Frances L. Zisman.

Education: Graduated from Walters Senior High School, Walters, Oklahoma, in May 1981; received Bachelor of Science Degree in Chemistry and Mathematics from Cameron University in Lawton, Oklahoma, in May, 1985; completed requirements for the Doctor of Philisophy degree at Oklahoma State University in December, 1989.

Professional Experience: Teaching Assistant, Department of Chemistry, Oklahoma State University, August, 1985, to May, 1986; Research Assistant (Water Resources Presidential Fellowship), May, 1986, to August, 1989, Department of Chemistry, Oklahoma State University.

Professional Organizations: Division of Organic Chemistry of the American Chemical Society, Phi Lambda Upsilon (President, chemistry honor fraternity), Sigma Xi Scientific Research Society, Phi Kappa Phi (national honor fraternity).