SYNTHETIC METHODOLOGY, STEREOCHEMISTRY, AND ANTIARRHYTHMIC ACTIVITY OF SELECTED 3,7-DIHETERABICYCLO[3.3.1]NONANES AND DERIVATIVES

by

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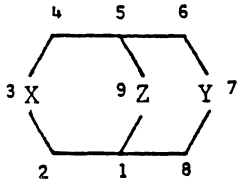
CHAPTER I

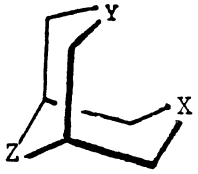
HISTORICAL

Heterocyclic and carbocyclic compounds containing the bicyclo-[3.3.1]nonane ring system **1** have been of interest due to theoretical considerations concerning the possible conformations as well as to the biological activity of certain derivatives. The basic ring system is

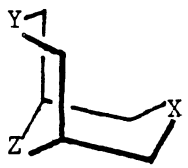


1

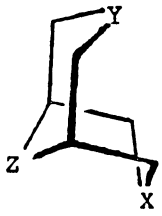
unique in that it can exist in four conformations:[46,65,115] chair-chair **1-CC**, boat-chair **1-BC**, chair-boat **1-CB** and boat-boat **1-BB**. In cases where X and Y are identical the **BC** and **CB** conformers are, of course, equivalent. Factors which determine the conformations adopted by these systems have been of considerable interest.



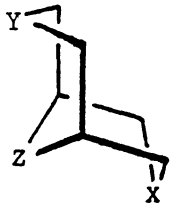
1-CC



1-BC

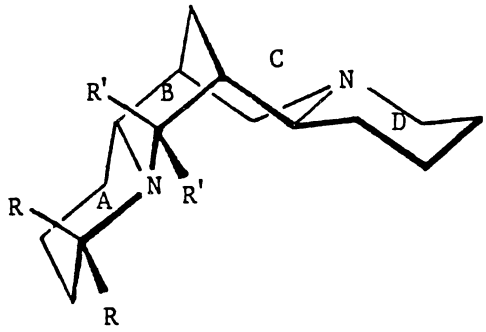


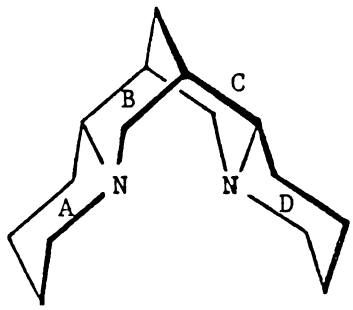
1-CB



1-BB

The primary concerns involving the biological activity of these systems have been in the analgesic and antiarrhythmic properties of the heterocyclic analogs where X and/or Y are N-R, O, S, Se while Z is CR_2.





2a R = R' = H

2b R = H, R'R' = =O

2c R R = =O, R' = H

2d

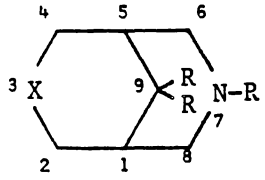
These properties may arise from the similarity of the heterocyclic systems to the B and C rings of a series of C-15 lupine alkaloids: sparteine (**2a**), aphylline (**2b**), lupanine (**2c**), and α-isosparteine (**2d**). Sparteine is known to possess biological activity as an antiarrhythmic agent; however, it is also quite toxic.[6,26,78,88,103] Interestingly, it has been postulated that **2a**, **2b**, and **2d** are side products in the biosynthesis of **2c** due to an oversupply of cadaverine, the metabolic precurser for these alkaloids.[112]

This discussion will focus on the 3-hetera-7-azabicyclo[3.3.1]nonanes with reference to other related carbocyclic and heterocyclic compounds. First, there will be an abbreviated survey of the synthetic methodologies which have been used to arrive at the 3-aza- and 3-hetera-7-azabicyclo[3.3.1]nonane systems. This will be followed by an evaluation of the stereochemical and conformational aspects of such systems as well as the biological activities found for certain derivatives of the 3-hetera-7-azabicyclo[3.3.1]nonanes, with emphasis on the antiarrhythmic properties. This last section will also include a short

synopsis on heart disease, antiarrhythmic drugs currently in use, and several of the methods used in the preliminary screening of these types of drugs.

Synthetic Routes

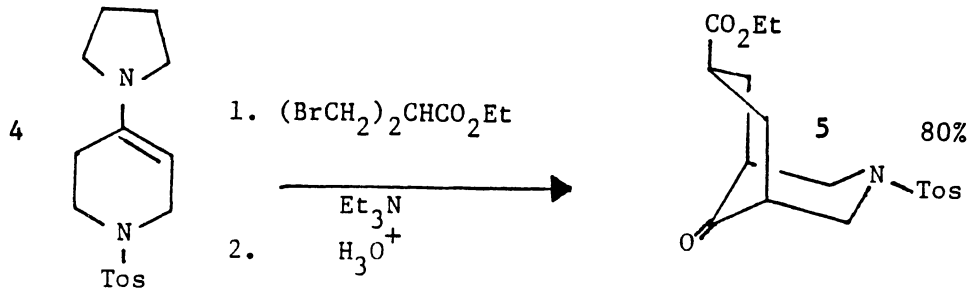
Extensive reviews have been published that cover the synthetic routes to the carbocyclic bicyclo[3.3.1]nonanes[22,65] and the analogs with heteroatoms at the 3-, 7- and 9-positions,[46,114] as well as numerous derivatives containing these ring systems. The emphasis here

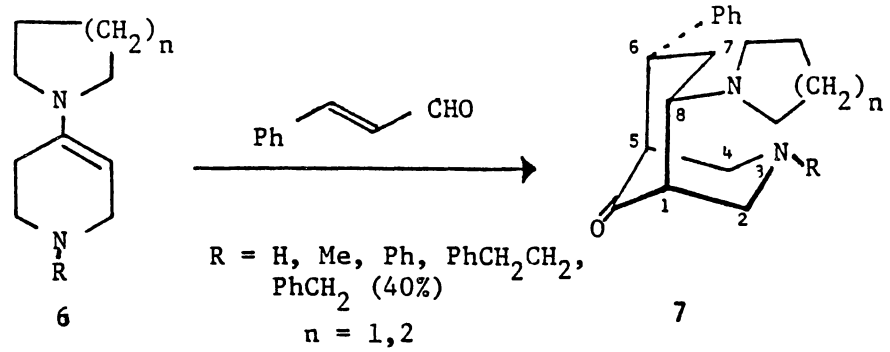


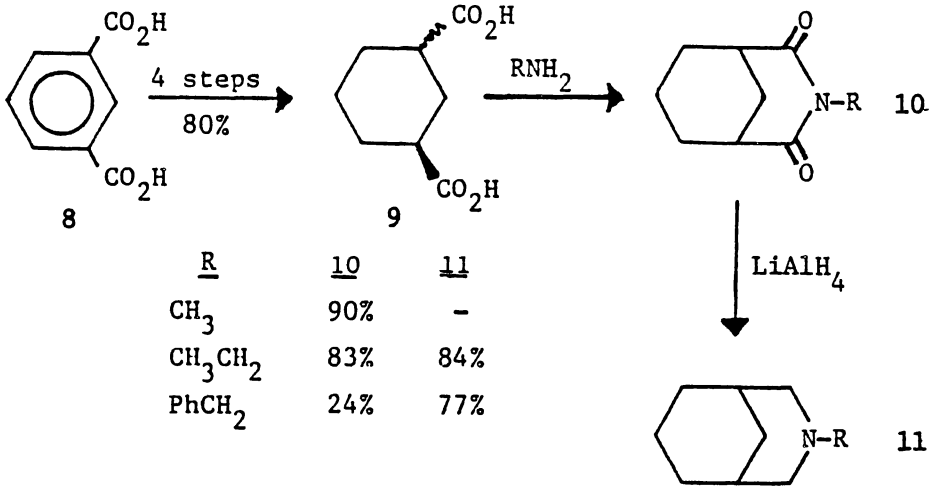
3

will be on the synthesis of compounds containing the ring system **3** where X is CR_2, NR, O, S, and Se, as well as derivatives of these compounds. The discussion is not intended to be a complete or representative survey; however, it will illustrate some of the more popular and interesting methods used in the preparation of the compounds.

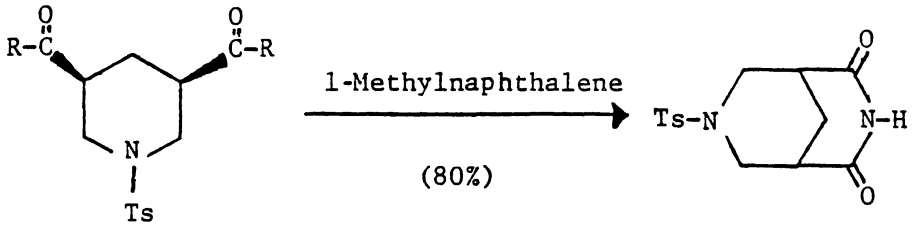
Annelation of the enamines of cyclic ketones has been employed to obtain 3-azabicyclo[3.3.1]nonan-9-ones.[46] The pyrrolidine enamine of N-tosylpiperidin-4-one (**4**), when treated with ethyl β,β-dibromoisobut-







R	10	11
CH_3	90%	-
CH_3CH_2	83%	84%
$PhCH_2$	24%	77%



12a R = Cl

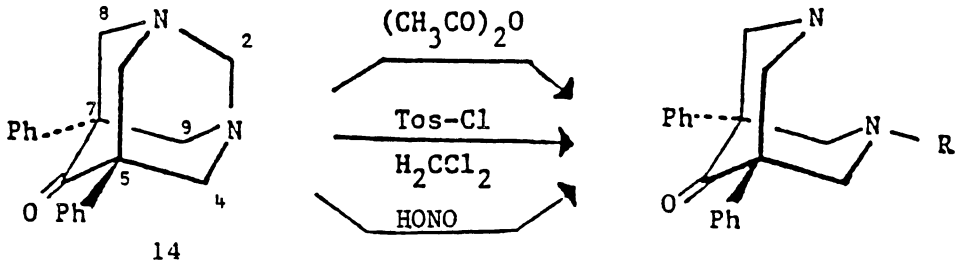
12b R = NH_2

13

yrate and triethylamine, afforded ketone **5**.[95] Interestingly, enamines **6**, when treated with cinnamaldehyde, afforded **7** with equatorial cyclic amine groups at the 8-position.[22,23] The exact nature of this rearrangement has not been established.[22,46]

Conversion of isophthalic acid (**8**) to the cis-/trans- diacid **9**, was accomplished in four high-yield steps.[87] Treatment of the diastereomeric mixture with various amines and heating afforded the diimides **10**. Reduction with $LiAlH_4$ then gave **11** in good yields. Similar treatment of the anhydride derived from cis-hexahydroisophthalic acid (**9**-cis) with dialkylaminoalkylamines afforded N-dialkylaminoalkyl derivatives of **10**.[76] Along these same lines, di-acid chloride **12a**, upon treatment with ammonia, formed the diamide **12b**.[100] Subsequent heating of **12b** induced cyclization to **13**.

Cleavage of 1,3-diazaadamantanes under acidic conditions yielded 3,7-diazabicyclo[3.3.1]nonanes.[46] For example, treatment of ketone **14**



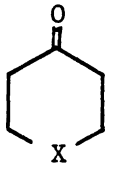
14

15

a. R = Acetyl (73%)
b. R = Tosyl (71%)
c. R = Nitroso (100%)
d. R = CH_2Ph
e. R = CH_3
f. R = $CH_3(H_2SO_4 \cdot 1/2H_2O)$

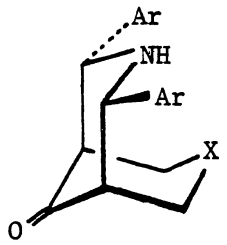
with acetic anhydride, tosyl chloride or nitrous acid produced **15a-c.**[101] In a like manner, the analogous 1,3-diazaadamantanes (with CH_2 at the 6-position) were also cleaved by benzoyl chloride or nitrous acid to afford the N,N'-dibenzoyl- and N,N'-dinitroso-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonanes.[101]

A common route to aryl-substituted 3-aza- and 3-hetera-7-azabicyclo[3.3.1]nonane ring systems (**17, 18**) is via a Mannich condensation of a cyclohexanone derivative (e.g. **16**) with an aromatic aldehyde and ammonia.[46] For example, when cyclohexanone (**16a**) was treated with benzaldehyde and ammonium acetate, the ketone **17a** was obtained along with the bisarylidene **19a.**[9] Numerous additional examples are known in the literature[46,107,108] including ketones **17b**[5], **18a,b**[47] and isomeric



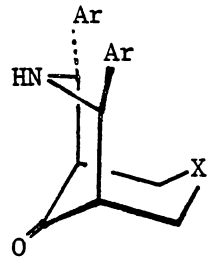
16

a. X = CH_2
b. X = O
c. X = S
d. X = Se
e. X = NCH_3
f. X = NCH_2Ph
g. X = $\overset{+}{N}(CH_3)_2$ I^-
h. X = Se ($\underline{d}_4$)



17

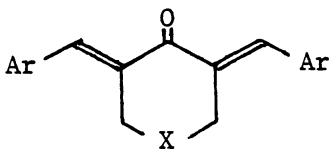
	X	Ar
a.	CH_2	Ph
b.	O	o-ClC_6H_4
c.	Se	p-ClC_6H_4
d.	NCH_2Ph	o-ClC_6H_4
e.	NCH_2Ph	Ph



18

	X	Ar
a.	S	Ph
b.	S	o-ClC_6H_4
c.	Se	p-ClC_6H_4
d.	NCH_2Ph	o-ClC_6H_4
e.	NCH_2Ph	Ph

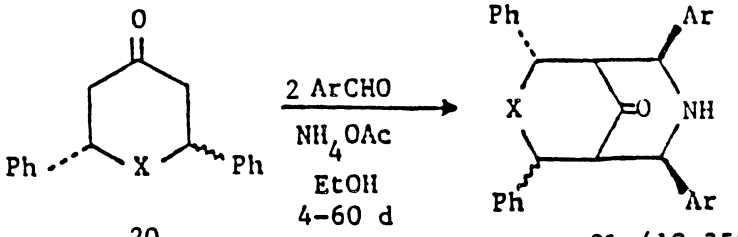
16a $\xrightarrow[NH_4OAc,\ EtOH]{2\ ArCHO}$ **17a** (40%) +



19

	X	Ar
a.	CH_2	Ph (45%)
b.	NCH_2Ph	o-ClC_6H_4
c.	NCH_2Ph	Ph

ketones **17c** and **18c**.[106] These reactions were typically performed by heating an ethanolic solution of the reactants at 60-70°C for a few minutes. The products commmonly precipitate from the reaction mixtures upon the addition of a nonpolar solvent such as ether; however, the yields are often quite modest. Tetraaryl derivatives **21** have been obtained by similar Mannich reactions from cis- or trans-2,6-diphenyl-1-heteracyclohexan-4-ones **20**.[10,12,63] Aryl-substituted bicylic ketones **23** have been obtained by the treatment of diesters **22** with formaldehyde and benzylamine.[35-37]

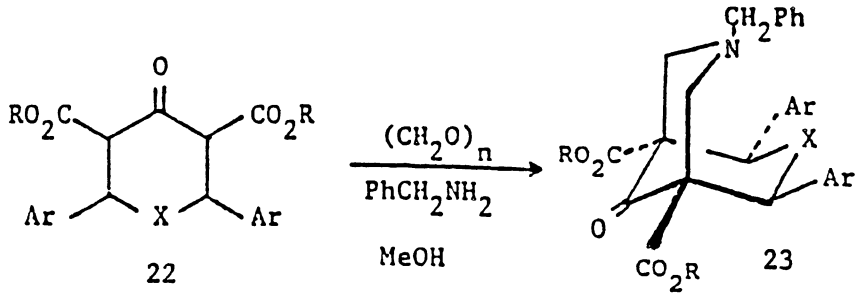


20

a. X = CH_2
b. X = S
c. X = O
d. X = NH

21 (10-35%)

a. X = CH_2, Ar = Ph
b. X = S, Ar = Ph
c. X = O, Ar = Ph
d. X = NH, Ar = p-Tolyl

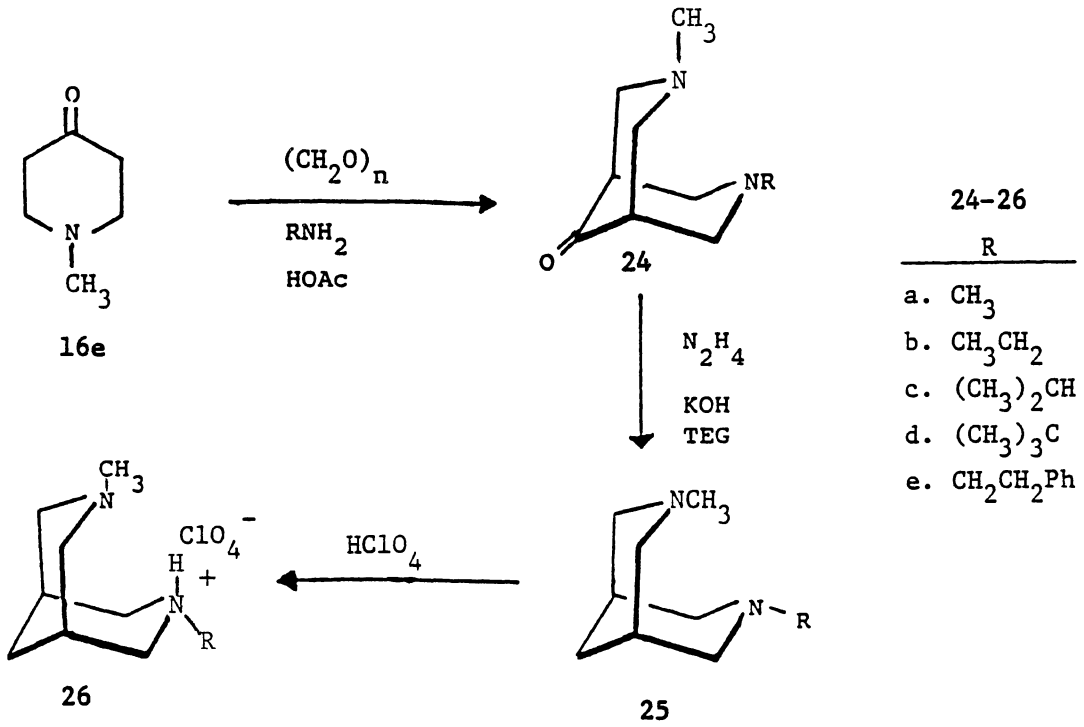


22 **23**

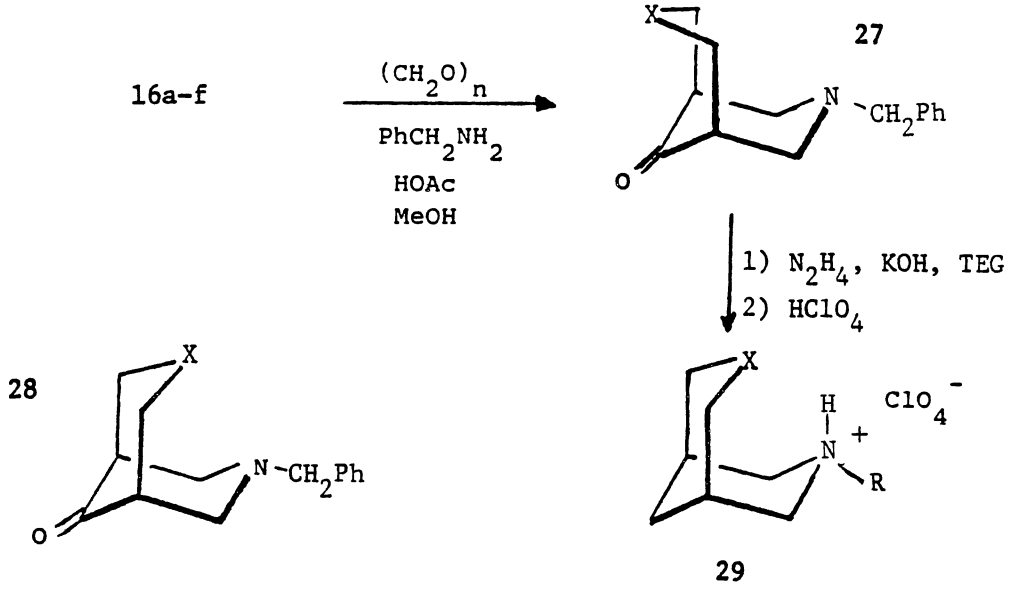
X	Ar	R	
O	C_6H_5	Et	(57%)
NH	2- pyridyl	Me	(70%)
S	2-(6'-Me-pyridyl)	Me	(37%)

Mannich condensation of N-alkylpiperidin-4-ones with alcoholic paraformaldehyde or aqueous formaldehyde, acetic acid, and various primary amines has afforded a variety of N,N'-dialkyl-3,7-diazabicyclo-[3.3.1]nonan-9-ones.[46] (In passing, it should be noted that the 3,7-diaza-bicyclic ketones system have the common name "bispidones").

Employing this route, Douglas and Ratliff[27] synthesized the N-methyl-N'-alkylbispidones **24a-d** in yields of 40-55%. Wolff-Kishner reduction of these ketones to the bispidines **25** followed by direct conversion to the hydroperchlorates **26** was accomplished in yields of 60-70%. Similarly, other workers have employed various N-alkylpiperidin-4-ones as well as other primary amines.[16,17,63,91-93] The ketones were typically isolated as crude materials via an extended aqueous workup. Occasionally, these have been further purified via distillation under reduced pressure followed by recrystallization.[16,17,27] The reduced compounds have commonly been isolated in crystalline form as



salts of perchloric, fumaric, picric, or hydrochloric acid. This general route has been extended to the synthesis of the N-benzyl-3-hetera-7-azabicyclo[3.3.1]nonan-9-ones **27a,b** and **28a,b** from the appropriate 1-heteracyclohexan-4-ones **16a-f**, paraformaldehyde and benzylamine.[5,14,15,16,92,93,107,108] Wolff-Kishner reduction followed by treatment with perchloric acid then afforded salts **29a-c**.

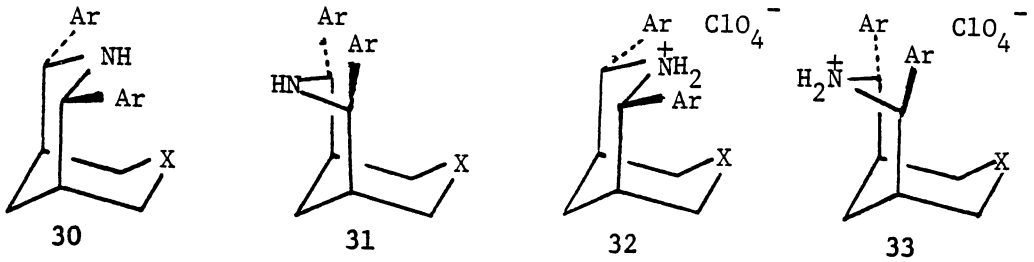


27 X
a. S (43%)
b. Se (43%)
c. NCH_3
d. NCH_2Ph

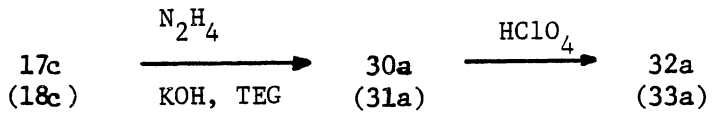
28 X
a. CH_2 (17%)
b. O (39%)
c. NCH_3 (44%)
d. NCH_2Ph (60%)

29 X	R
a. S	CH_2Ph
b. Se	CH_2Ph
c. O	CH_2Ph
d. NCH_2Ph	CH_2Ph
e. Se	CH_2CH_2Ph

Reduction of 2,4-diaryl-3-hetera-7-azabicyclo[3.3.1]nonan-9-ones under Wolff-Kishner conditions has also been reported[46]. For example, treatment of ketones **17c** and **18c** under these conditions gave rise to amines **30a** and **31a**.[106] Treatment of these amines with perchloric acid then gave the salts **32a** and **33a**, respectively.

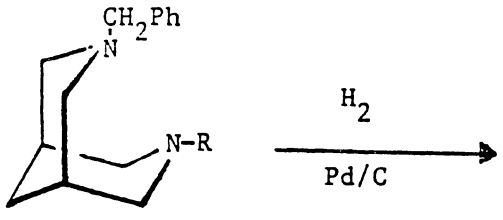


31-33		
a.	Se	p-ClC_6H_4
b.	NCH_2Ph	o-ClC_6H_4
c.	Se	Ph



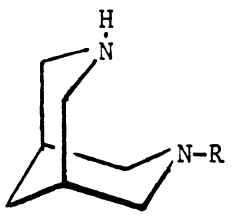
Catalytic debenzylation of N-benzyl-N'-alkylbispidines **34** has led to the N-monoalkylated bispidines **35**.[16,17,79,92,93] Treatment of the latter with sodium hydride[16,17] or methyl lithium,[79,93] followed by alkylation, has produced related N,N'-dialkylbispidines **36**. Acid chlorides and **35** have given rise to N-alkyl-N'-acylbispidines.[79]

The mechanism for the Mannich condensation is worthy of discussion. This topic as well as the variety of products formed via this reaction has been the subject of extensive reviews.[1,18,42,105,110] In its most simplistic form, the reaction effects the aminomethylation of a compound with one or more active hydrogens. These compounds may be enolizable ketones as described above, phenols, acetylenic compounds, primary or secondary amines, and mercaptans.[105,110] The generally accepted mechanism[46,105] involves the reaction of a primary or secondary amine



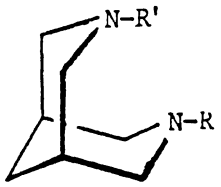
34

	R
a.	CH_3 (= 27c)
b.	$CH_3(CH_2)_3$
c.	$PhCH_2$



35

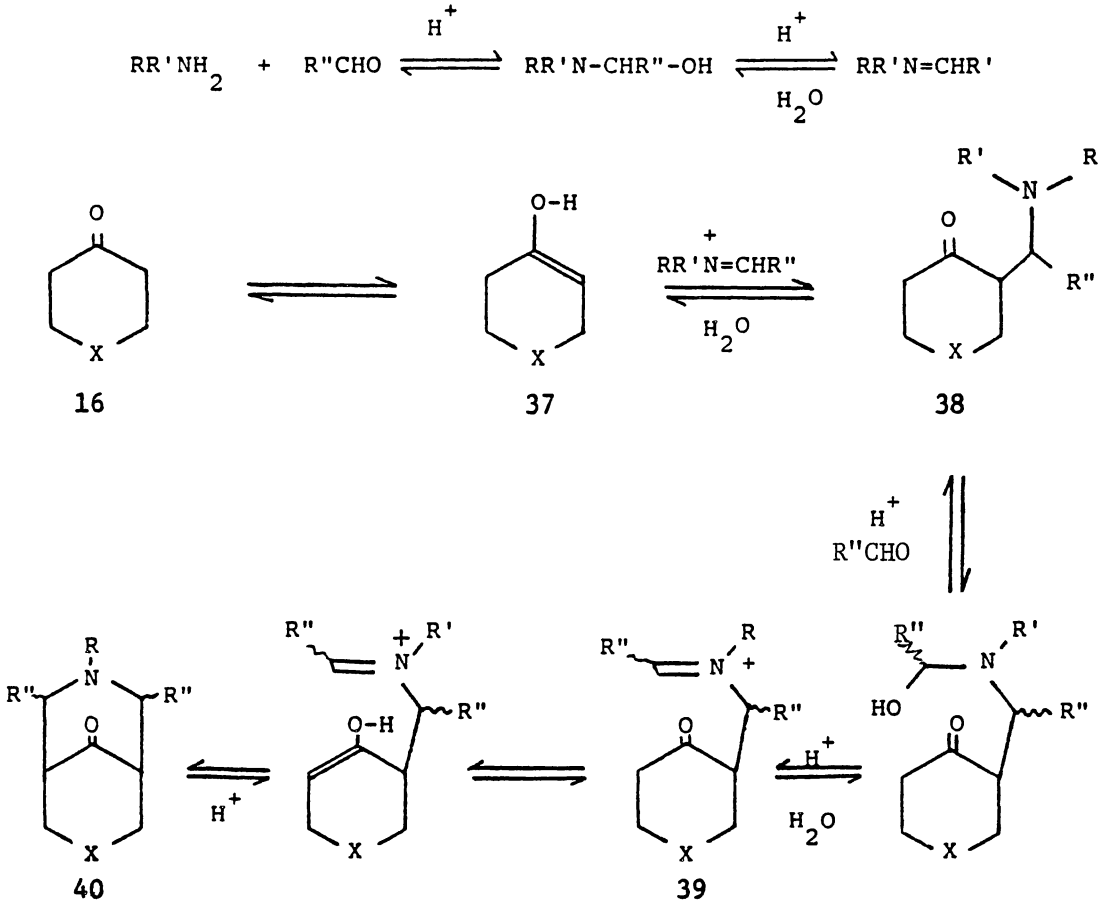
1. MeLi, or NaH
2. R''-X



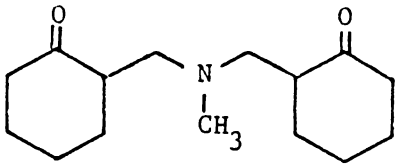
36

R	R'
a. CH_3	CH_3 (=25a)
b. $CH_3(CH_2)_3$	$CH_3(CH_2)_3$
c. $PhCH_2$	$ArCH_2$

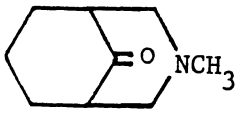
with the aldehyde to give a hydroxymethylamine[105] which, under acidic conditions, dehydrates to give an imminium ion. The imminium ion, in turn, suffers nucleophilic attack from the active hydrogen compound, e.g., the enol **37** of ketone **16** to give products collectively known as "Mannich bases" (e.g. **38**). Multiple alkylations of the active hydrogen compound are possible when there are multiple active hydrogens.[91,105] This is prevented primarily by careful selection of the reaction conditions and proper stoichiometry of the reactants.[105,110] Barring multiple alkylations of the active hydrogen compound, when a secondary amine is used, the reaction stops after the initial aminoalkylation (e.g. **38**, R,R' = alkyl). However, when a primary amine or ammonia is used, the Mannich base (**38**, R = H, R'= alkyl; R = R' = H) from the



initial aminomethylation can undergo additional condensations.[42,46] In the synthesis of the 3-hetera-7-azabicyclo[3.3.1]nonan-9-ones and 7-azabicyclo[3.3.1]nonan-9-ones, cyclization is presumed to proceed by stepwise formation of another imminium ion **39** and subsequent aminomethylation to afford **40.** Intermolecular reactions can occur to give products such as **41,** which was obtained, along with the bicyclic ketone 42 in a Mannich condensation of cyclohexanone, aqueous formaldehyde, and methylamine hydrochloride.[43] Another side reaction is deamination to give α,β-unsaturated ketones, i.e. **43.** This is reported to occur in cases where the aldehyde substituent R" can stabilize the formation of the conjugated system.[110] When aromatic



41



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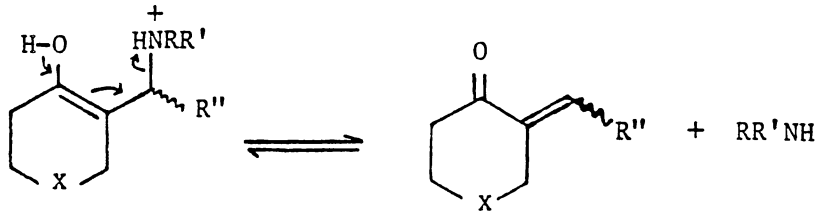


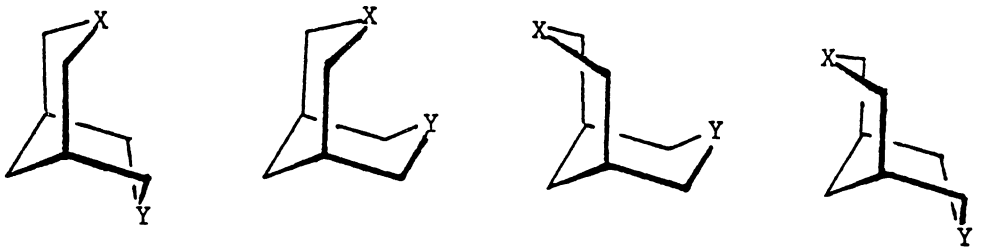
43

aldehydes and ammonium acetate are used, these are commonly the major products formed in the reaction, e.g., bisarylidene **19a.**[9] Deaminations of aminomethylated acyclic ketones obtained via the Mannich reaction have been used to synthesize acyclic vinyl and divinyl ketones as monomers for polymerization reactions.[57,58] The mechanism of the Mannich reaction to give the 3-hetera-7-azabicyclo[3.3.1]nonan-9-ones will be the subject of further discussion in next chapter.

Stereochemical and Conformational Aspects

As discussed earlier, four conformations are possible for the generalized bicyclo[3.3.1]nonane ring system where X and Y are not identical. Intramolecular steric interactions are present in all of these conformations to some degree. A survey of the conformations adopted by various carbocyclic bicyclo[3.3.1]nonanes is illustrative of many of

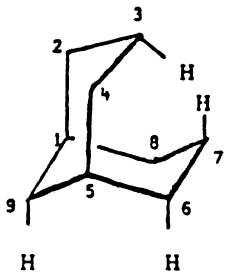
these interactions. The influence of these interactions, as well as the parameters arising from the substitution of hetero atoms into the ring system, shall be the subject of the following discussion.



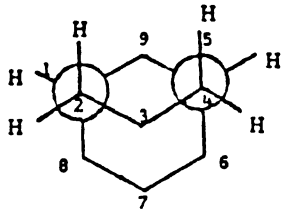
CB CC BC BB

In addition to the 1,3-diaxial interactions commonly associated with cyclohexane chairs,[68] severe transannular steric interactions between the endo protons H(3) and H(7) are present in the **CC** conformation of bicyclo[3.3.1]nonane (**44**). Furthermore, a Newman projection along the C(1)-C(2) and C(4)-C(5) bonds illustrates a gauche interaction between the C(2)-C(3)-C(4) bridge and the C(5)-C(6) and C(1)-C(8) bonds.

Bicyclo[3.3.1]nonane (**44**) has been determined to exist as a **CC** in the solid state based on crystallographic data.[22] ^{13}C NMR[71] analysis and infrared[22] data, as well as electron diffraction studies[54,55,62] have indicated that this is the predominant conformation in the gas



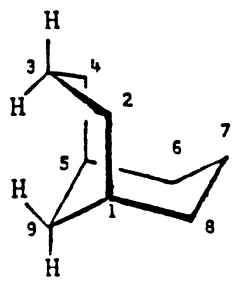
44



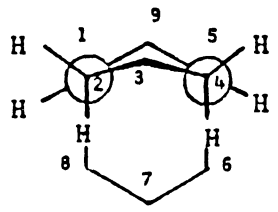
44 Newman projection

phase and in solution. If one assumes that the **CC** conformation of **44** can be treated as <u>idealized</u> cyclohexane chairs with two bonds in common, the calculated C(3)...C(7) distance would be 2.52 Å.[22] According this model, the <u>endo</u> protons H(3) and H(7) would be in the same plane as C(3) and C(7). Assuming normal C-H bond lengths (1.09 Å) and a hydrogen covalent radius of 0.32 Å,[64] the volume of space between C(3) and C(7) is too small to accomodate the <u>endo</u> protons. Experimentally, the C(3)...C(7) distance in **44** from X-ray data is 3.06 Å.[22] Moreover, the C(2)-C(1)-C(8) bond angle was found to be 113°, or slightly greater than tetrahedral.[22] Thus, it has been indicated[22] that the cyclohexane rings are flattened to minimize the <u>endo</u> H(3)...H(7) steric interaction. It was also indicated that no skewing (as seen in certain cyclohexane derivatives) was apparent; instead the planes of the three carbon bridges C(2)-C(3)-C(4) and C(6)-C(7)-C(8) are splayed outward by an angle of 18° to (rather than parallel to) the C(1)-C(9)-C(5) plane.

The **BC** conformer of bicyclo[3.3.1]nonane (**45**) also suffers from serious transannular interactions, namely between the H(3)<u>exo</u> and H(9)<u>endo</u>, in the form of cyclohexane-boat bowsprit interactions. Moreover, a Newman projection of an idealized **CB** conformer indicates the pseudo axial C-H bonds [at C(2) and C(4)] in the boat ring eclipse



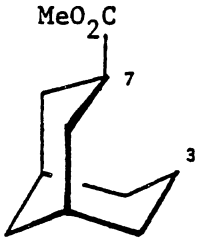
45



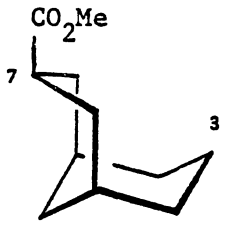
45 Newman projection

the C(1)-C(8) and C(5)-C(6) bonds in the chair ring. Electron diffraction data coupled with molecular mechanics calculations have indicated that at 65°C bicyclo[3.3.1]nonane has a **CC** ⇄ **BC** (i.e. **44** ⇄ **45**) equilibrium with only circa 5% of the population being in the **BC** form (**45**); at 400° the **BC** represents circa 25% of the population.[56] Calculations indicate that the energy difference between **44** (**CC**) and **45** (**CB**) is circa 2.3 kcal/mol with **44** being favored.

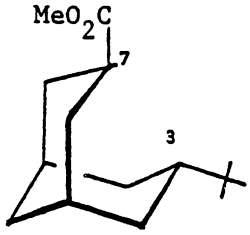
The predominant conformations of **46-50** in solution have been deduced from an analysis of ^{1}H NMR coupling constants in the presence of lanthanide shift reagents as well as by ^{13}C NMR chemical shift data.[68] Intuitively, introduction of bulky groups at the 3- or 7-exo positions should increase the **CC** ⇄ **BC** barrier, and, indeed, only the **CC** conformers



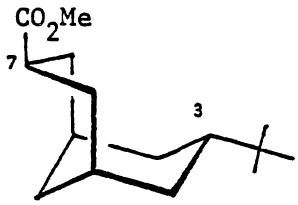
46a



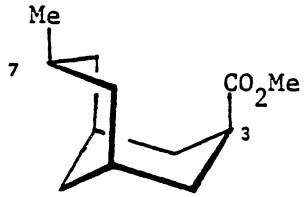
46b



47a



47b



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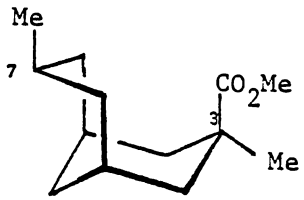

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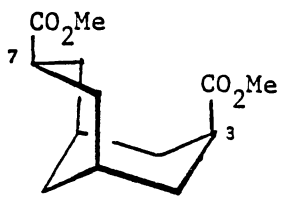
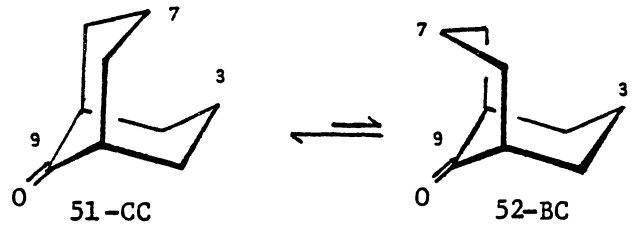


50

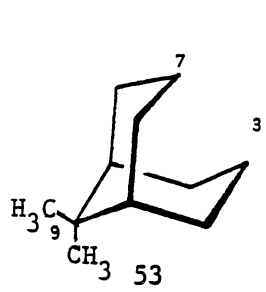
were reported. Conversely, introduction of bulky groups at the corresponding endo positions was determined to destabilize the **CC** conformer; thus, these systems (**46b, 47b**) adopt predominantly **BC** conformations in solution. It should be mentioned that, while the results of this study are internally consistent, few model compounds of known conformation are available for comparison.

Substitution of bulky groups at both 3,7-endo positions (e.g. **48-50**) was also determined to give rise to **CB** conformers, apparently with the ring possessing the less bulky substituent in the boat and with flattening of the chair ring.[68] Introduction of a carbonyl at C(9) did not alter these conclusions[42,67] although it should be expected that

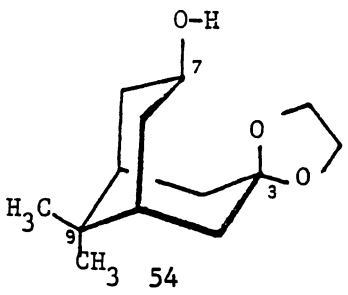


51-CC ⇌ 52-BC

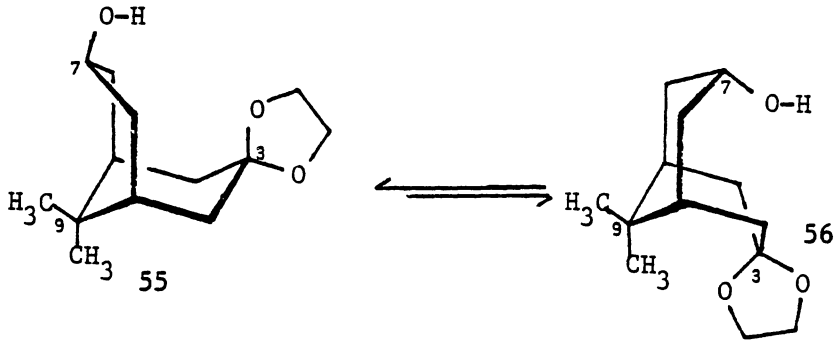
this would decrease the **CC** $\rightleftarrows$ **BB** barrier. This was ascertained to be the case in a proton NMR study on bicyclo[3.3.1]nonan-9-one (**51-52**) using lanthanide shift reagents with calculated chemical shift and coupling constant values.[74] At ambient temperature in solution, it was determined that a 78%-22% equilibrium exists between the **51** and **52**, respectively. Another study revealed that, based upon molecular mechanics calculations on molecules such as **53-55**, the introduction of geminal dimethyl groups at C(9) apparently inhibits the formation of **CB** forms, albeit the groups at the 3- and 7-positions were generally much



53



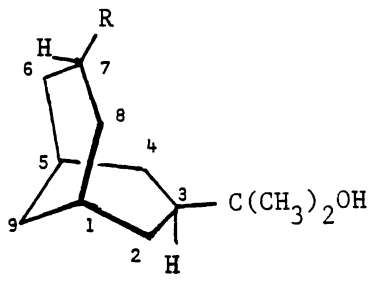
54



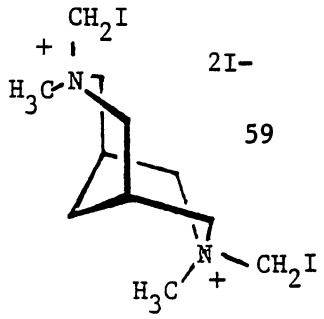
less bulky in this study.[4] The results were reinforced by ^{13}C NMR chemical shift data. In this latter effort, only compound **55** was found to exist in a **BC** form. This molecule was determined to exist in an equilibrium of **BC** $\rightleftarrows$ **CB** conformers (**55** $\rightleftarrows$ **56**) with the boat ring in each being extremely flattened. The calculated difference in energy between conformations was on the order of 1 kcal/mol with **55** being the more favored form.

The introduction of sufficiently bulky groups at both 3- and 7-endo positions could conceivably force a **BB** conformation despite the much greater transannular steric interactions. It has been pointed out that, although the **CC** and **BC** conformations in the bicyclo[3.3.1]nonane ring system are too rigid to permit twist forms, the **BB** form is more labile, allowing for the adoption of a "double twist-boat" (**DTB**) as a minimum energy conformation.[56,66] In fact, such a double twist-boat (57) has been reported.[66] The assignment of this conformation was based upon the

57 R = $HO(CH_3)_2C$
58 R = $(CH_3)_3C$



(DTB)



determination of proton NMR coupling constants in a spectrum that was so complex as to prevent simple first-order analysis. To alleviate this difficulty, varying amounts of a lanthanide shift reagent, $Eu(DPM)_3$, were employed to spread the signals over a much wider range. The measured coupling constants for the pseudo axial protons on C(2) [and thus, C(4,6,8)] were: $J_{H(2)-H(2)}$ = 12 Hz (geminal coupling), $J_{H(2)-H(3)}$ = 12 Hz (trans diaxial), $J_{H(2)-H(1)}$ = 2 Hz. The authors claimed this data could only be explained in terms of a double twist-boat conformation. The vicinal $J_{H(2)-H(3)}$ was reported to be 6.0 Hz which was the same value found for the corresponding methine and methylene protons in cis-1,4-di-t-butylcyclohexane, a compound that was presumed to prefer the twist-boat conformation.[68] The lanthanide shift reagent was determined to have no discernable influence on the conformation and geometry. Chemical shifts in the absence of $Eu(DPM)_3$ were extrapolated from the data with the shift reagent present. These, along with coupling constants found in the presence of the shift reagent, were incorporated into a computer simulation program which derived a spectrum identical to that found experimentally in the absence of $Eu(DPM)_3$.

Corrections to eliminate alpha and beta substituent effects so as to provide a more direct comparison of ^{13}C NMR chemical shift data

covalent radii with concomitant greater lone pair repulsions in **60** resulted in more severe 3,7-transannular interactions that destabilize the **CC** form.

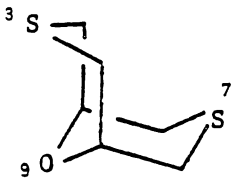
It was pointed out that lone pair repulsion should increase with increasing atomic number along the series O...O < O...S < S...S and that this trend is the opposite of the order expected if dipole-dipole repulsions were operating.[113] The S(3)...O(9) and S(3)...S(7) distances were 2.84 Å and 4.24 Å, respectively, in **60**. In **61**, the O(3)...S(7) distance was found to be 3.12 Å which was said to reflect the strong repulsions between these two atoms. The authors commented that if **60** were to exist in the **CC** form, the S(3)...S(7) distance would be 4.6 Å but that the sum of the van der Waals radii of the two sulfur atoms is 3.6-3.7 Å. They also noted that literature data show S...S nonbonded contacts in the range of 3.6-4.0 Å. Therefore, lone pair repulsion, rather than pure steric repulsions, seemed to be the destabilizing parameter. Displaying the same trend, **62**[34] and **63**[33] have been reported to exist in a **BC** (similar to **60** with the selenane ring in the boat form) and **CC** (similar to **61**), respectively.

Another interesting comparison is the ketone series **27a,b**, **28b**. Here, the conformations of solids **27a** and **27b** have been established by crystallography to be **BC** forms with the piperidine ring in the chair.[14,107] Proton NMR coupling constant data have indicated that the liquid **28b** exists as a **CC** in solution.[5] Again, this may reflect the effect of the lone pair interactions and the larger covalent radii of the S and Se atoms in **27a** and **27b** compared to that of the O atom in **28b**. It was noted that in **27b** the torsional angles C(9)-C(1)-C(2)-Se(3) and

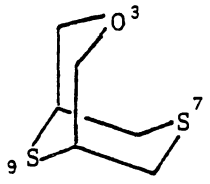
between compounds for bicyclo[3.3.1]nonane derivatives (along with average values for **CC**, **BC** and **BB** conformers) have been reported.[69] From these data, along with ^{1}H NMR shifts, **58** has also been suggested to exist as a **BB**.[71] Compound **59** was indicated to exist as a **BB**; however, no supporting evidence was presented.[27] The authors only noted that a **CC** was improbable and that endo-substitution of the iodomethyl groups was also speculative.

When a heteroatom, such as N, O, S, or Se, is introduced at the 3-, 7- or 9-position, the adoption of a **CB** (or **BC**), becomes more favorable due to the absence of bowsprit interactions found in the boat rings of bicyclo[3.3.1]nonanes. Other parameters influencing the conformation include the difference in the carbon-heteroatom bond distance and the analogous carbon-carbon bond distances which are a function of the covalent radii of the heteroatoms, nonbonding electron pair interactions, and, in the case of nitrogen, atomic inversion. These factors will be discussed in more detail in the following paragraphs.

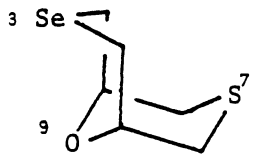
In 9-oxa-3,7-dithia- (**60**) and 3-oxa-7,9-dithiabicylo[3.3.1]nonane (**61**), X-ray crystallography revealed **CB** and **CC** conformers, respectively.[113] The authors concluded that the increase in



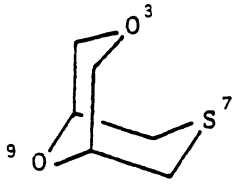
60



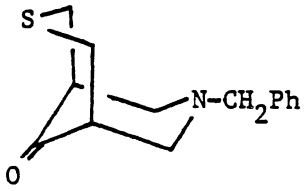
61



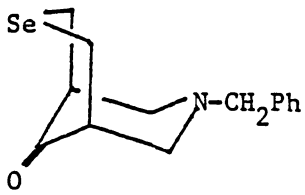
62



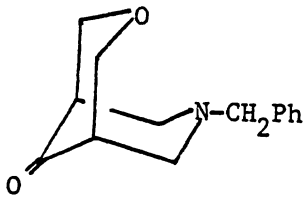
63



27a



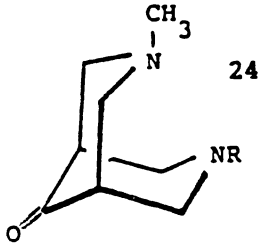
27b



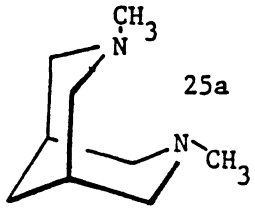
28b

C(9)-C(5)-C(4)-Se(3) were 45.5-47.2° compared to 2.6-3.9° in the analogous torsional angles of **27a**.[107] The conclusion of the authors was that this resulted from increased flattening in the selenane boat (compared to the sulfur analog) and the longer C-Se bond length (circa 1.94 Å) compared to the C-S bond (circa 1.81 Å). The Se...C(9) distance was 2.89 Å versus 2.82 Å for S...C(9) which also supported this conclusion. The C(6)-N(7)-C(8) plane in the selenium compound has a greater inward bend, i.e. it is more "puckered", than the analogous plane in the sulfur derivative, based on the comparable C(9)-C(1)-C(2)-N(3) and C(9)-C(5)-C(4)-N(3) torsional angles (67.7-68.8° versus 58.7-59.9°). However, a direct observation of an equilibrium between the **BC** and a second conformer via dynamic ^{13}C NMR analysis of **27a** at low temperatures has been reported.[13] It was observed that the four aliphatic ^{13}C NMR signals began to broaden at -85°C with the separation into four smaller peaks (37.7, 45.8, 55.3, 61.5 ppm) and four larger peaks (32.0, 47.4, 58.9, 60.3 ppm) occurring at -90°C. At -100°C, a gated off-acquisition (no NOE) spectrum of **27a** indicated an approximately 78.5:21.5 ratio of conformers with the **BC** still predominating. The identity of the second conformer (**CC, CB, BB**) was not ascertained.

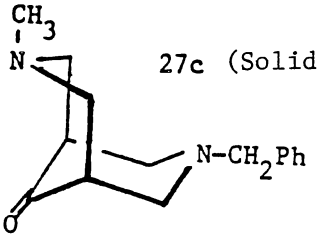
In examining a series of 3,7-diazabicyclo[3.3.1]nonanes and -9-ones (**24a,e, 25a, 28c,d**), it becomes evident that due to atomic inversion about the nitrogen, these systems may be more labile than their carbocyclic counterparts. Dipole moment measurements indicate that **25a** exists as a flattened **CC**.[27] From comparison of the solid state and solution IR spectra, ^{1}H NMR coupling constants, and ^{13}C NMR chemical shifts, it has been determined that bispidones **24a,e** and **28c,d** all exist predominantly as the **CC** conformers in solution.[32] This result for **28c** is in direct contrast to earlier work by the same group, wherein a crystal structure[94] of ketone **28c** indicated that this compound existed as a **BC** in the solid state (as in **27c**) with the methyl-substituted piperidine ring in the boat form. The discrepancy in conformation (**27c** versus **28c**) was rationalized by noting that the conformation adopted by a system in solid state is often dependent upon the packing forces involved while conformation in solution is dependent to some extent on solvation requirements.[32]



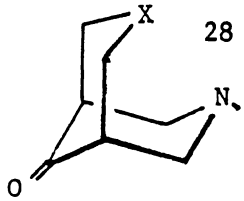
24 a. R= CH_3
e. R= CH_2CH_2Ph



25a



27c (Solid)

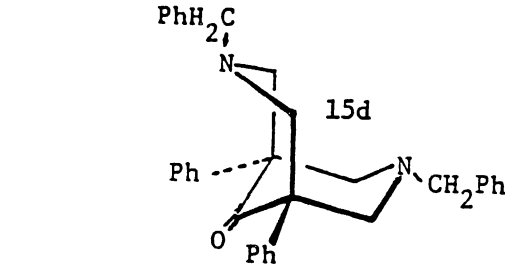


28 c. X= NCH_3
d. X= NCH_2Ph

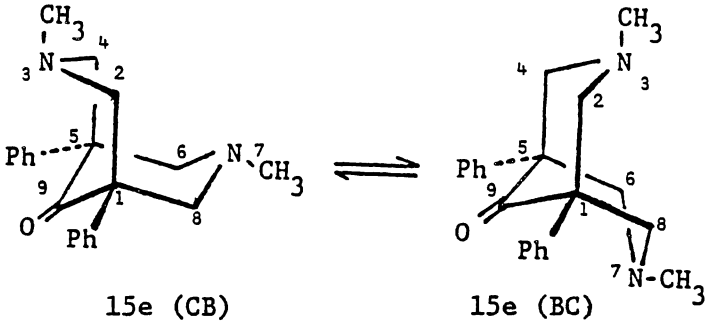
Compounds **15d**[50] and **15e**[51] have been reported to be in **BC** forms in the solid state as ascertained by crystallographic methods while a dynamic ^{13}C NMR study[102] of **15e** has indicated the observation of a rapid **CB** $\rightleftarrows$ **BC** equilibrium in solution. It was observed that, at ambient temperature the ^{1}H NMR spectrum exhibited only one AB quartet, rather than two, for the methylene protons, and that the ^{13}C NMR spectrum showed only three aliphatic signals, namely for the N-$\underline{C}H_3$, bridgehead methines C(1,5), and ring methylenes C(2,4,6,8). The authors reported that as the temperature decreased, the signal for the ring methylenes broadened and finally split into two peaks of equal intensity (coalescence temperature: $-63^{o}C$). At the slow exchange limit, the maximum chemical shift difference was 6.0 ppm. Using a simple (A $\rightleftarrows$ B) kinetic model, the calculated ΔG^{*} for this transition was determined to be 9.7 kcal/mol. As these methylene signals showed no changes below the temperature at which nitrogen inversion was presumed to be prohibited and as the C(1,5) signal remained a sharp singlet throughout the temperature range investigated, it was concluded that a **BC** $\rightleftarrows$ **CB** equilibrium was being observed. The possibility of a **DTB** $\rightleftarrows$ **DTB** equilibrium was discounted as these averaging motions are pseudorotational and, therefore, expected to have a very low energy barrier.[102] In this situation, a chemical shift difference of 6.0 ppm for C(2,6) and C(4,8) was deemed unlikely.

While the authors of the aforementioned study did not address this question, it should be pointed out that the splitting of the NMR signal for C(2,4,6,8) into two peaks of <u>equal</u> intensity at low temperatures while the peak for C(1,5) remained <u>sharp</u> is fairly strong evidence against the significant contribution of a **CC** $\rightleftarrows$ **BC** equilibrium (i.e., **15e**

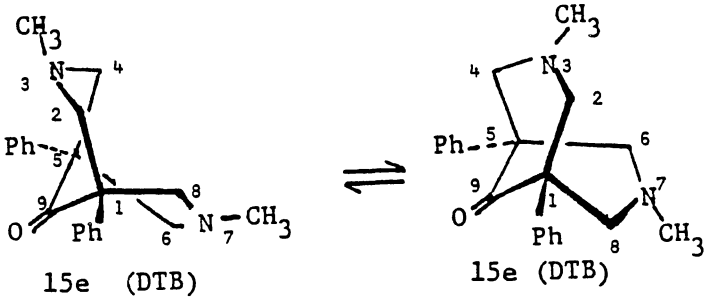
(CC) ⇌ 15e (BC). The magnetic environment of a bridgehead carbon in this system is identical in the **BC** and **CB** conformers while this is not true in the **CC** versus **BC** forms. A significant contribution from a **CC** conformer would be expected to result in splitting (or at least broadening) of the peak for C(1,5). Furthermore, a **CC** ⇌ **BC** equilibrium should not result in two peaks of equal intensity. If the chemical



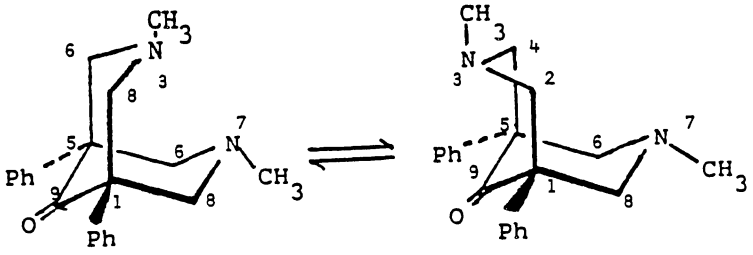
15d



15e (CB) 15e (BC)



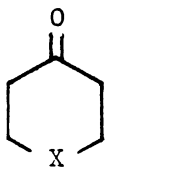
15e (DTB) 15e (DTB)



15e (CC) 15e (BC)

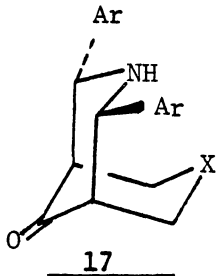
shifts of C(2,4,6,8) in the **CC** form were coincident with the shifts of C(2,4) in the boat ring or C(6,8) in the chair ring of the **BC** form, the ratio of the peak heights would be approximately 3:1 (disregarding NOE).

In bicyclo[3.3.1]nonanes with substituents at C(2,4,6,8) there exists the possibility of different configurations as well as different conformations. In a study of 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones, -9-ols, and -9-acetates (**17a, 64a,b**), it was determined by comparison of ^{13}C NMR chemical shifts that these compounds probably exist predominantly as the **CC** conformers in solution.[47] A crystal structure of **17a** has supported this conclusion.[47] A similar compound, 6,8-bis(2-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (**17b**) has also shown to be **CC** from crystallographic evidence.[5] In contrast, the 2,4-diaryl-3-thia-7-azabicyclo[3.3.1]nonan-9-one **18a** and -9-ols **65** were suggested to be largely **BC** in solution with the piperidine rings in the boat form.[47] An X-ray structure of alcohol **65** has shown this to be true



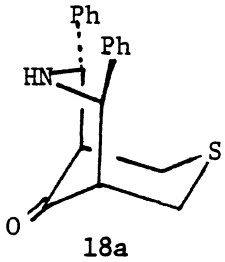
16

a. X = CH_2
b. X = O
c. X = S

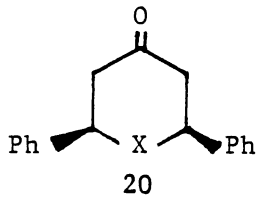


17

a. CH_2
b. O

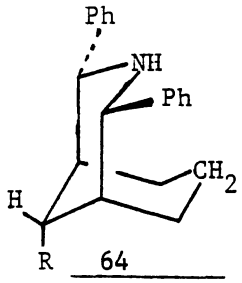


18a



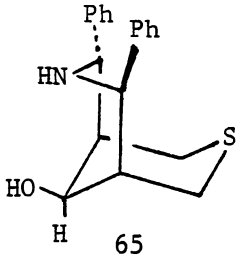
20

a. X = CH_2
b. X = S

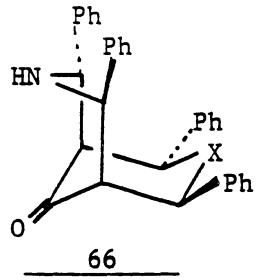


64

a. R = OH
b. R = OAc



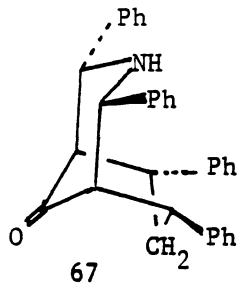
65



66

a. X = CH_2

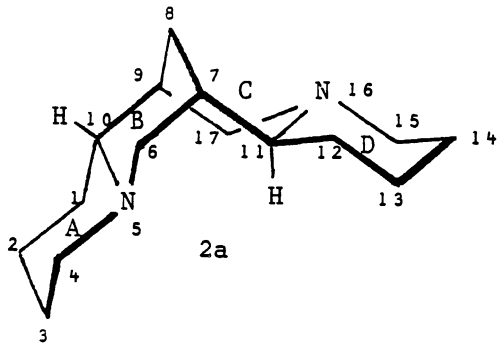
b. X = S



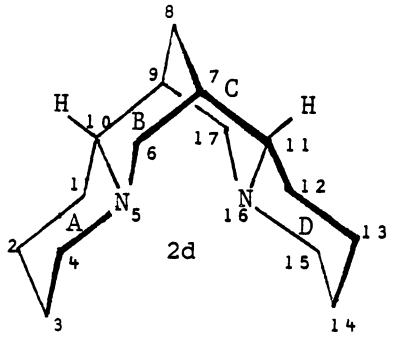
67

in the solid state.[29] Since these ketones were formed via Mannich reactions from 1-heteracyclohexan-4-ones **16a,b,c**, it was postulated that the presence of the large sulfur atom forced the formation of the piperidine boat during the Mannich condensation. Support for this idea was observed in ketone **66b** which was also obtained from a Mannich reaction, this time from cis-**20b**.[63] Again, the piperidine ring was found to be in the boat and the solid-state structure confirmed by crystallographic analysis. Isomeric tetraaryl ketones **66a** and **67a** (with boat and chair piperidine rings, respectively) have also been isolated from a Mannich reaction mixture wherein cis-**20a** was treated with benzaldehyde and ammonium acetate.[73]

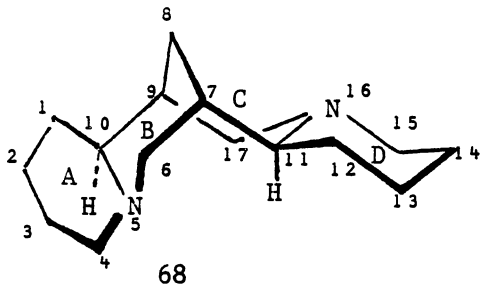
Sparteine (**2a**), as well as other C-15 lupine alkaloids, possesses in its B and C rings the bispidine ring system. Extensive IR, ^{1} NMR, ^{13}C NMR, and ^{15}N NMR investigations have demonstrated that sparteine exists in the conformation shown with the B and C rings being in a **CB** form.[19,20,30,81,87] A diastereomer, α-isosparteine (**2d**), has been determined from crystallographic evidence to exist as a **CC**.[70] β-Isosparteine (**68**), after some debate,[19,87,90] was concluded to exist as a **CB** with an axial C(1)-C(10) bond. This type of behavior was also



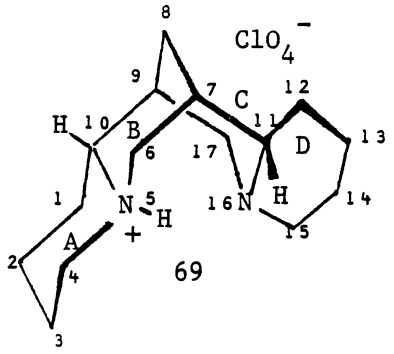
2a



2d



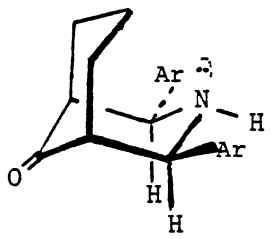
68



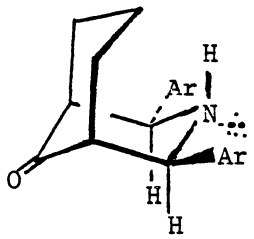
69

observed in the monohydroperchlorate of sparteine (**69**).[90] An extensive IR study of this compound indicated a **CC** conformation for the two central rings with an axial C(11)-C(12) bond.

A rather intriguing case of epimers resulting from an inversion about nitrogen in 2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one (**17a**) has been reported.[7] Ketone **17a**, as well as the relative with C(9) = CH_2, has been found by crystallographic methods to exist in a **CC** form with the phenyl rings in equatorial positions.[47] Invertomer **17a** (mp 175-176°C), with an equatorial, or <u>exo</u>, N-H bond was formed when this compound was crystrallized from polar solvents such as alcohol, dioxane, chloroform, or acetone. Invertomer **17a'** (mp 181-182°C) was formed by crystallization from nonpolar solvents such as heptane, petroleum ether,



17a

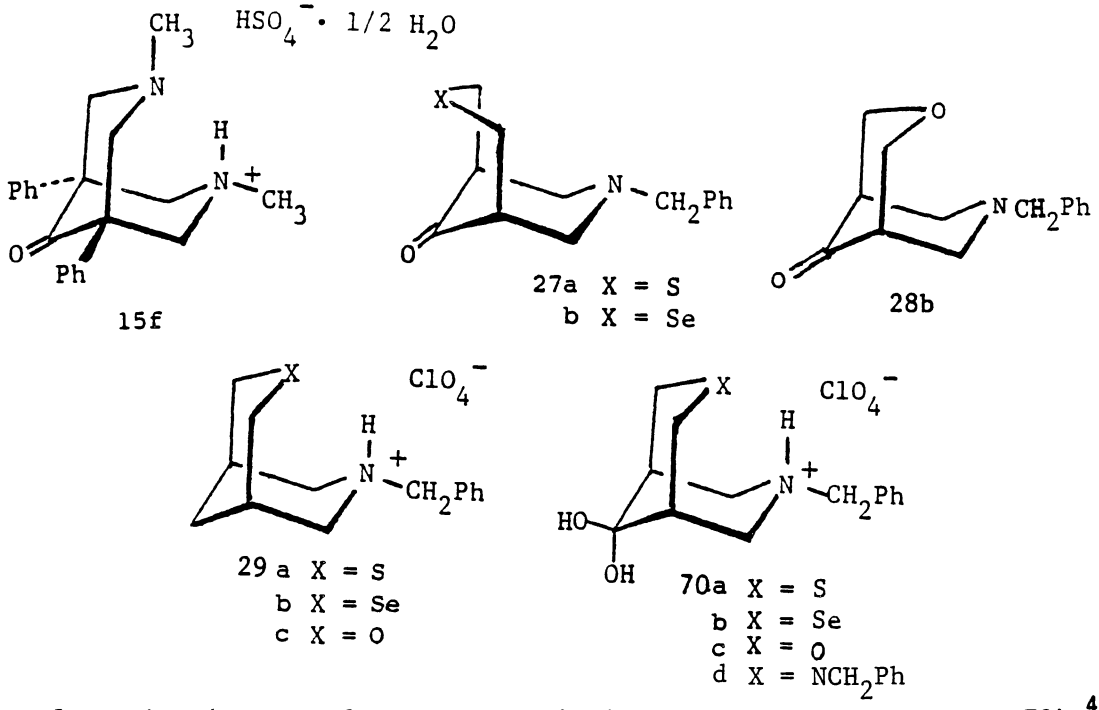


17a'

or cyclohexane. Both forms were crystallized from ether. The two invertomers were distinguished from each other by different crystalline forms and by the presence of Bohlmann bands in the solid state (KBr) IR spectrum of **17a** that are absent in the spectrum of **17a'**.

Bohlmann bands,[46,111] are C-H stretching vibrations observed in the 2700-2900 cm^{-1} region of the IR spectra of piperidine derivatives when a C-H bond alpha to nitrogen is antiperiplanar with the electron pair of nitrogen. The presence of four bands in at 2750, 2790, 2810, and 2840 cm^{-1} in the IR spectrum of **17a** indicate that there are two alpha protons trans and coplanar with the electron pair.

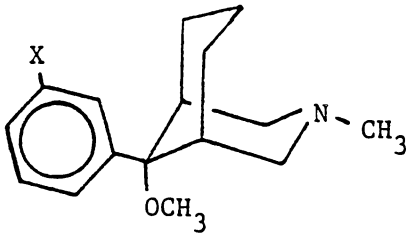
It is interesting to note that the salts of 3-hetera-7-azabicyclo-[3.3.1]nonanes typically adopt the **CC** conformation. This behavior, for example, has been observed in the 3-oxa-, 3-thia- and 3-selena- analogs of **70**, which were formed when the corresponding ketones **27a,b** and **28b** were treated with perchloric acid.[5,15,107] This conformation was indicated by spectroscopic evidence (IR, ^{1}H NMR, ^{13}C NMR, ^{15}N NMR) and confirmed in **70a** by a crystal structure. The hydroperchlorates **29**a,b,c derived from the 9-methylene analogs of ketones **27a,b** and **28b** also gave **CC** conformers as indicated by spectroscopic and crystallographic data.[5,14,107] The hemihydrated salt **15f** was reported to adopt the **CC**



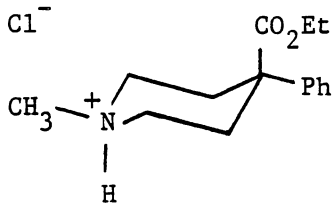
conformation (apparently retaining the keto group, in contrast to **70**).[49] As mentioned previously, it was found that sparteine monohydroperchlorate (**69**) also adopted a **CC** conformation with an axial C(11)-C(12) bond.[90] Since spectroscopic and crystallographic evidence indicated significant intramolecular hydrogen bonding between the proton at N(7) and the heteroatom at the 3-position in **29** and **70**, it was concluded that this stabilized the **CC** conformers sufficiently to overcome the 3,7-transannular crowding required for this conformation.[5,15,107] It has been suggested,[49] however, that the stabilizing parameter is the electrostatic attraction between $\overset{+}{N}$(3) and the electron pair at N(7).

Analgesic Activity

Many derivatives of the 3-azabicyclo[3.3.1]nonane possess analgesic properties.[46] For example, the citrate salt of **71a** was found to be about 3 times more potent than meperidine hydrochloride (**72**) as an analgesic with reduction of certain adverse side effects. However, the



71 a.X = H
b.X = OH



72

acute toxicity of **71a** was almost similar to that of **72.**[46] Upon addition of a hydroxyl group at the meta position of the phenyl ring (**71b**), the activity was found to be radically increased.[61] This compound was more than 400 times more active than **72** in terms of analgesic activity and 1600 times more potent than morphine hydrochloride. Despite an acute toxicity about 6.5 times higher than morphine hydrochloride, the therapeutic index (LD_{50}/ED_{50}) was determined to be about 67000 compared to 112 for morphine hydrochloride.

Heart Disease and Antiarrhythmic Agents

Coronary heart disease is the leading cause of death in the U.S. Over 38% of all deaths each year are attributed to heart disease, which is actually a wide assortment of disorders.[82] The underlying cause of many of these is atheroschlerosis, the deposition of fatty plaque along the interior walls of the arteries resulting in restriction of blood flow through these blood vessels. An estimated 98% of all patients suffering a heart attack have symptoms of atherosclerosis. Occurrence of this in a coronary artery results in a decrease in blood flow and oxygen supply to the affected portion of the myocardium, a condition known as ischemia.[82] Appreciable loss in blood flow induces angina

pectoris, or anginal pain. Complete blockage of a constricted artery, usually by a blood clot or arterial spasm, induces a myocardial infarction (MI).[45] This results in severe damage to the cardiac tissue and predominantly affects the left ventricle. The direct results of MI are the development of cardiac arrythmias and the potential failure of the heart as a pump due to ventricular fibrillation.[53]

Sudden death due to coronary heart disease represents 76% of all nontraumatic deaths in the adult population.[53] Of all deaths from atherosclerotic heart disease, 50-80% occur within 1 hour after the onset of symptoms.[28] These deaths are usually the result of ventricular fibrillation which is observed in about two-thirds of all cases.[28] During ventricular fibrillation the impulses that control the contractions of the ventricles become chaotic and all pumping action is lost. This is inevitably a fatal condition unless treatment is begun immediately.[31] This usually involves the administration of DC cardioversion to arrest the heart which can then return to its normal rhythm. It has been estimated that of sudden cardiac deaths, approximately 44% are due to MI, 34% to myocardial ischemia, and 22% to poorly understood primary cardiac-rhythm disturbances.[53]

Of cardiac arrhythmias resulting from myocardial infarction, ventricular tachycardia (literally: rapid heart beat) is by far the most serious.[24] Ventricular tachycardia (VT) is usually presaged by ventricular premature contractions, which are the most common type of cardiac arrhythmia.[24] Ventricular premature contractions (VPC) are isolated ectopic beats which may be observed in nearly every individual at some time during his or her life. An occasional occurrence is usually of no clinical significance. For example, they may be experienced in healthy

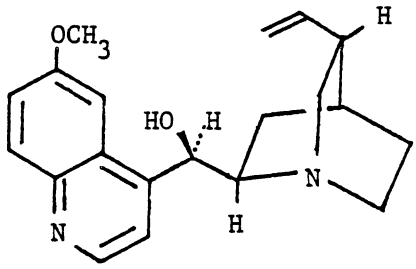
adults following excessive ingestion of coffee or tea, heavy smoking, or in times of emotional excitement. However, the frequent occurrence of this arrhythmia, particularly if it is multifocal in origin, nearly always indicates the presence of organic heart disease.[24]

The term ventricular tachycardia is used when three or more of these ectopic beats occur consecutively, typically at a rate of 150/min or greater. More specifically, VT is a rapid or accelerated heart rhythm originating in the ventricles and unrelated to atrial rhythm.[31] This is opposed to normal sinus rhythm which arises from the sinoatrial node in the right atrium. While bouts of paroxysmal VT may occur, sustained VT is particularly ominous due not only to the resultant decrease in cardiac output but also because it may degenerate into ventricular fibrillation, a potentially fatal condition.[24] To prevent this, VT is treated by DC cardioversion or by pharmacological therapy.

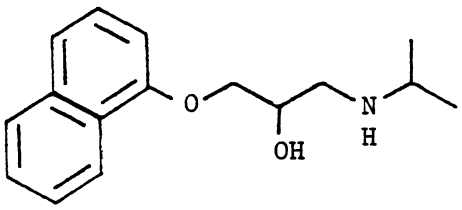
The pharmacological treatment of myocardial infarction usually involves the administration of an antiarrhythmic drug to control the arrhythmia and prevent its reoccurrence. The actual drug chosen for treatment depends on the type of cardiac arrhythmia.[31] The chemical structures of several of the more commonly prescribed agents in clinical use are given in Table I. There is great variety in the structures of compounds which exhibit antiarrhythmic activity[103] and all such cardioactive drugs exhibit a variety of undesirable side effects which limit their utility. Also, the therapeutic window, the range between the effective dose and the toxic dose, is often quite narrow in many individuals. Data on the uses of several of these compounds and some of their more pronounced detrimental effects are given in Table II.

TABLE I

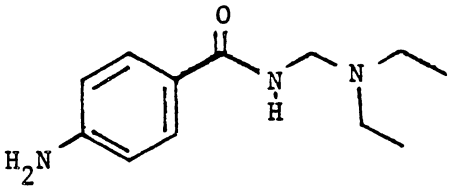
SELECTED ANTIARRHYTHMIC AGENTS IN CLINICAL USE



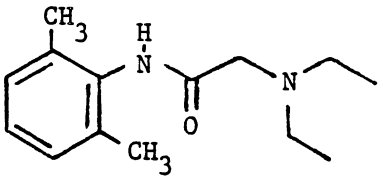
Quinidine (73)



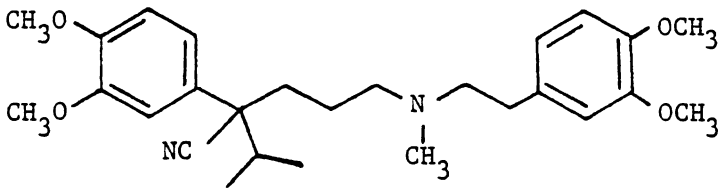
Propranolol (74)



Procainamide (75)



Lidocaine (76)



Verapamil (77)

TABLE II

PROPERTIES OF SELECTED ANTIARRHYTHMIC AGENTS IN CLINICAL USE

Drug	Treatment of	Detrimental Effects
Quinidine (73) (as sulfate, gluconate, polygalacturonate)	Ventricular tachycardia (VT) Supraventricular tachycardia Maintenance therapy after VT, atrial flutter and fibrillation.	Known to induce VT. Gastrointestinal difficulties: nausea, diarrhea, vomiting. Hypotensive effects. May induce Heart failure.[31,53]
Propranolol (74) (as hydrochloride) β-adrenoreceptor blocking agent	Catacholamine-induced arrhythmias Ventricular fibrillation (preventative agent) Angina pectoris Supraventricular tacycardia	May induce congestive heart failure, bradycardia, cardiac arrest.[31,53]
Procainamide (75) (as hydrochloride)	Ventricular tachycardia	Gastrointestinal difficulties similar to quinidine. Anorexia, giddiness. Fever and rashes in sensitive individuals.[31,53]
Lidocaine (76) (as hydrochloride)	Ventricular premature beats Myocardial infarction Ventricular tachycardia	CNS depressant: drowsiness, paresthesia muscle twitching, convulsions. Can induce VT, cardiac arrest.[31,53]
Verapamil (77) Calcium channel blocking agent	Ventricular tachycardia Supraventricular tachycardia Angina pectoris	Hypotension, vertigo, dizziness, muscle weakness, nausea, constipation. May induce VT in patients with atrial flutter, fibrillation.[2,8,82]

Of the agents given in Table I, lidocaine (76) may be the most important. It is the drug of choice in the treatment of nearly all types of ventricular tachycardia.[24] It is usually the first drug administered to patients suffering from acute myocardial infarction upon arrival at a coronary care unit.[31] It is very fast acting, having a serum half-time of only 15-20 minutes.[53] It, however, can induce cardiac arrest due to its depressant activity on the sinoatrial node.[53] While its most alarming toxic reactions involve the central nervous system, these are usually associated with excessive doses in sensitive individuals or with the presence of advanced liver disease.[31,53] As it is the current drug of choice in the treatment of MI and VT, it is used as a benchmark compound in the testing of the antiarrhythmic properties of the compounds developed in this study.

This list of antiarrhythmic agents is by no means all-inclusive. Other drugs employed in the treatment of arrhythmias and serious cardiac disorders include the digitalis glycosides,[31] diphenylhydantoin (Dilantin)[2,31,53] and disopyramide.[2,8b,53] Many others such as bretylium,[2,8c,31,53] methyl lidocaine,[53] dimethylpropranolol[53] and amiodarone[104] are still considered experimental or investigational drugs pending completion of clinical trials. Several more are undergoing preliminary testing in animal models.[40,59,77,98-100]

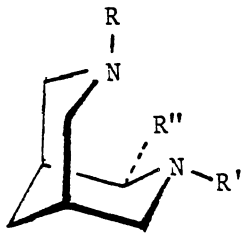
In recent years, the antiarrhythmic properties of the 3,7-diaza-, 3-thia-7-aza- and 3-selena-7-azabicyclo[3.3.1]nonanes have been investigated by a variety of screens. These tests include the mouse-chloroform fibrillation assay, wherein the effect of the drug on chloroform-induced ventricular fibrillation is determined in adult mice.[78,79] A second assay[16] involves inducing a thiobutabarbitol

narcosis in rats, subsequently followed by induction of an arrhythmia by administration of Aconitine. The relative effect of the drug is determined by the amount of Aconitine required to induce the arrhythmia in rats treated with the prospective drug. A third method involves measuring the functional refractory time after electrical stimulus in guinea pigs and measuring the effect of a prospective drug on this parameter.[17] The above three assays offer the advantage of being relatively inexpensive and permiting a large number of experiments with limited quantities of each compound. A fourth method, considered to be more definitive,[53] involves surgical induction of a myocardial infarction in dogs followed by induction of a ventricular tachycardia by cardiac pacing.[84-86] The effectiveness of a prospective agent is then determined by its ability to control ventricular tachycardia. This method is preferable in that the cardiovascular physiology of the dog model is very similar to that of man, as are the induced MI and VT.[45] Since this was the testing methodology used in the current study, it will be discussed in greater detail in Chapter III.

The antiarrhythmic properties of several N,N'-dialkyl-3,7-diazabicyclo[3.3.1]nonanes have been examined. Based upon data from mouse-chloroform fibrillation assays wherein each compound was tested in 8-12 mice, Ruenitz and Mokler[78] reported that although the salts of amines **34a-c, 78, 79** (Table III) were reasonably potent, their toxicity was high with therapeutic indices for all the compounds in the study being in the 0.87-1.46 range. Correlation of octanol/water partitioning of these compounds indicated that activity increased with lipophilicity. In a separate study[79] the same authors found that several N-alkyl-

TABLE III

ANTIARRHYTHMIC PROPERTIES OF N,N'-DIALKYLBISPIDINES[a,b]



	R	R'	R"	ED_{50}[c]	LD_{50}[d]	LD_{50}/ED_{50}
34a[e]	CH_3	$C_6H_5CH_2$	H	154	189	1.23
34b[f]	$CH_3(CH_2)_3$	$C_6H_5CH_2$	H	159	198	1.25
34c[f]	$C_6H_5CH_2$	$C_6H_5CH_2$	H	160	199	1.24
78[g]	CH_3	CH_3	$(CH_3)_2CH$	191	279	1.46
79[f]	CH_3	$(C_6H_5)_2CH$	H	259	225	0.87
2a[h]	Spartiene			150	134	0.89
74[f]	Propranolol			100	406	4.06
80	Disopyramide[i]			60	504	8.40

a. SOURCE: reference 78.
b. As determined by the mouse-chloroform fibrillation assay in adult CF_1 mice.
c. Effective dose (μmol/kg, i.p.) to reduce heart rate below 200 beats per min in 50% of sample (8-18 mice per compound).
d. Lethal dose (μmol/kg, i.p.) required to shorten survival time to less than 2 h.
e. Monomesylate
f. Monohydrochloride
g. Monohydrobromide
h. Sulfate
i. Disopyramide (**80**):

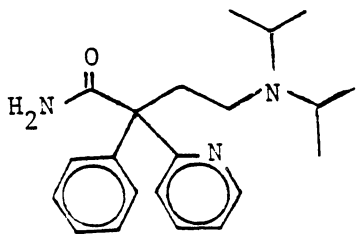
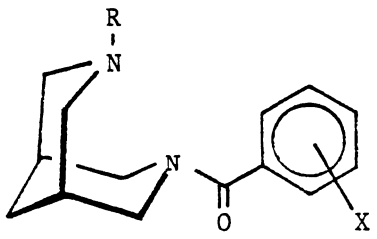


TABLE IV

ANTIARRHYTHMIC PROPERTIES OF BENZAMIDES 80-84[a,b]



	X	R	ED_{50}[c]	LD_{50}[d]	LD_{50}/ED_{50}
80	4-Cl	CH_3	49	535	10.89
81	H	CH_3	85	621	7.29
82	4-CH_3O	CH_3	78	463	5.93
83	4-CH_3O	$CH_3(CH_2)_3$	106	488	4.60
84	H	$CH_3(CH_2)_3$	242	500	2.07
80	Disopyramide		60	504	8.40

a. SOURCE: reference 79.
b. As determined by the mouse-chloroform fibrillation assay in adult CF_1 mice.
c. Effective dose (μmol/kg, i.p.) to reduce heart rate below 200 beats per min in 50% of sample (8-12 mice per compound).
d. Lethal dose (μmol/kg, i.p.) required to shorten survival time to less than 2 h (6-10 mice per compound).

bispidinebenzamides 80-84 (Table IV) were more potent and less toxic (having therapeutic indices in the range of 2-10) than the N,N'-dialkylbispidines.

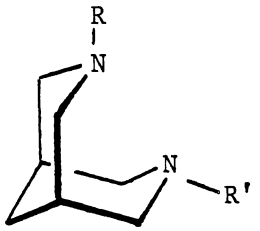
Similar bispidines have been examined by Binnig and coworkers.[16] Amines **34c** and **86** (Table V) were more potent than lidocaine (**76**) as determined by left auricle refractory period prolongation in guinea pigs. In a separate study,[17] **88-91** (Table VI) were found to be more active and with lower toxicity than quinidine (**73**) as determined by prolongation of arrhythmia induction by Aconitine in laboratory rats.

Nador and coworkers[60] have determined the antiarrhythmic properties of a series of N,N'-dialkylbispidines with either an aryl ether or aryl ester group at the 9-position (Table VII). All tested compounds were found to be 5-58 times more active than lidocaine in restoring normal sinus rhythm in rats suffering from Aconitine-induced arrhythmias.

Studies by Scherlag and coworkers[14,84,107] demonstrated the antiarrhythmic properties of several 3-thia- and 3-selena-7-azabicyclo[3.3.1]-nonanes. 3-Thia-7-azabicyclo[3.3.1]nonane hydroperchlorate (**29a**, Table VIII) was found to prevent the induction of sustained ventricular tachycardia (SVT) in 8 of 10 dogs that had surgically-induced myocardial infarctions.[84] Moreover, in the animals that did exhibit SVT, the heart rate was dramatically slowed by an average of 29% relative to control experiments. Lidocaine (**76**), in contrast, permitted induction of SVT in all 10 dogs tested with reduction of the rate of the SVT by only an average of 11% relative to the control. Lidocaine generally showed a hypotensive effect during the SVT while **29a** was found to increase blood pressure 10-15% during the SVT. This latter activity is desirable since

TABLE V

ANTIARRHYTHMIC PROPERTIES OF BISPIDINES **34c** and **86**[a,b]



	R	R'	Antiarrhythmic effect, ED_{25}[c]	Inotropic effect, ED_{25}[d]	I/A[e]
34c	$C_6H_5CH_2$	$C_6H_5CH_2$	0.034	0.07	2.0
86	$C_6H_5CH_2CH_2$	$(CH_3)_2CH$	0.13	0.26	2.0
76	Lidocaine		0.47	0.48	1.0
87	N-Propylajmaline[f]		0.0037	0.0015	0.4

a. SOURCE: reference 16.
b. As determined by refractory period elongation of left auricle of guinea pigs (18-30 experiments per compound).
c. Effective dose to produce 25% extension of refractory period (mg/kg).
d. Effective dose to lower contractile force by 25% (mg/kg).
e. Inotropic (contractile force lowering) effect/antiarrhythmic effect relative to lidocaine (**76**).
f. N-Propylajmaline (**87**):

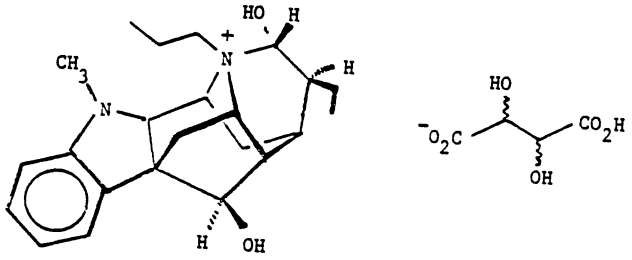
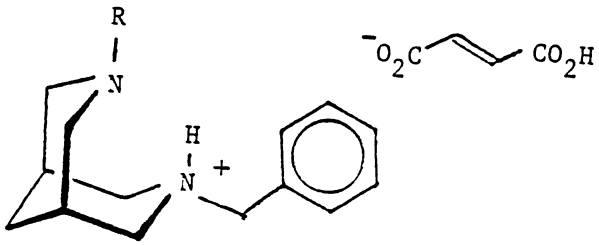


TABLE VI

ANTIARRHYTHMIC PROPERTIES OF N-ALKYL-N'-BENZYLBISPIDINES[a,b]

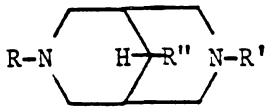


	R	ED_{50}[c]	Max. effect dose[d]	Max. effect Δ%[e]	Toxic Dose[f]	Q[g]
88	$3,4\text{-}Cl_2C_6H_5CH_2$	15.6	215	283	464	29.7
89	$(C_6H_5)_2CH$	20.4	215	205	464	22.8
90	$4\text{-}FC_6H_4CH_2$	20.2	100	240	215	10.6
91	$3\text{-}ClC_6H_4CH_2$	16.6	46.4	123	100	6.0
73	Quinidine	42.7	215	133	464	10.7

a. SOURCE: reference 17.
b. As measured by prolongation of arrhythmia induction by Aconitine (at 0.005 mg/kg-min) in Spraque-Dawley rats treated with thiobutabarbitol.
c. Effective dose for the increase by 50% in the duration of Aconitine infusion (mg/kg).
d. Maximum tolerated dose to achieve maximum effect (mg/kg).
e. Percentage by which Aconitine infusion increased by at maximum dose.
f. Dose at which first toxic effects (cyanosis or ECG change) appear.
g. Toxic dose/ED_{50}.

TABLE VII

ANTIARRHYTHMIC PROPERTIES OF 9-SUBSTITUTED BISPIDINES[a,b]

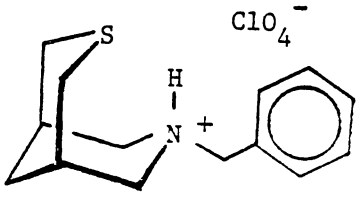


	R	R'	R''	ED_{50}[c]	LD_{50}[d]	T.I.[e]	R.I.[f]
92[h]	CH_3	CH_3	2-Napthyl-CO_2	0.11	17.0	154	58
93	CH_3	CH_3	C_6H_5-CO_2	0.08	9.0	112	39
94[h]	CH_3	CH_3	4-ClC_6H_4-O	0.9	52.0	58	21
95	CH_3	CH_3	9-Xanthenyl-CO_2	0.27	14.0	52	16
96[i]	CH_3	CH_3CH_2	4-ClC_6H_4-CO_2	0.6	26.0	43	15
97[h]	CH_3	CH_3	C_6H_5-O	1.15	39.0	34	12
98[h]	CH_3	CH_3CH_2	4-ClC_6H_4-O	1.25	41.0	33	12
99[i]	CH_3CH_2	CH_3CH_2	4-ClC_6H_4-CO_2	0.4	11.0	28	10
100[h]	CH_3	CH_3	4-ClC_6H_4-CO_2	0.25	5.0	20	7
76	Lidocaine			10.	28.5	2.9	1

a. Adapted from reference 60.
b. As determined by the dosage required to restore normal sinus rhythm (NSR) for Aconitine-induced arrhythmia in rats.
c. Effective dosage to restore NSR in 50% of tested rats (mg/kg).
d. Dose causing mortality in 50% of tested rats (mg/kg).
e. Therapeutic index: LD_{50}/ED_{50}.
f. Relative index: T.I.(compound)/T.I.(lidocaine).
g. Methane sulfonate.
h. Fumarate.
i. Dihydrochloride.

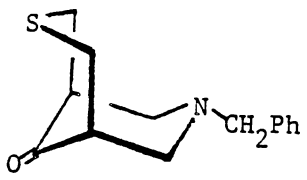
TABLE VIII

ANTIARRHYTHMIC PROPERTIES OF **29a**[a,b]

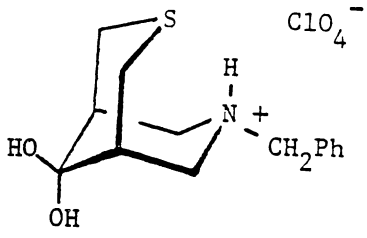


	N[c]	Inducible[d]	Avg. Rate of SVT[e]
Control[f]	10	8	352
29a[g]		3	250
Control[f]	10	8	336
Lidocaine[g] **76**		10	298

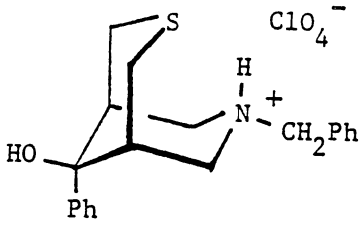
a. SOURCE: reference 84.
b. As determined by inhibition/reduction of sustained ventricular tachycardia in 24-h infarcted dog heart.
c. Number of dogs tested.
d. Number of dogs wherein sustained ventricular tachycardia (SVT) could be induced via cardiac pacing after surgical indiction of myocardial infarction.
e. Average rate (beats/min) of induced SVT.
f. No antiarrhythmic drug present.
g. 3-6 mg/kg, i.p.



27a



70a



101

mean blood pressure commonly drops during SVT, often to dangerously low levels.[53]

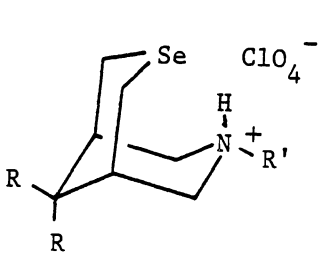
Ketone **27a** showed little antiarrhythmic effect while its hydrated salt **70a** was found to have activity similar to but not as good as **29a**.[14] The phenyl alcohol **101** showed an overall depressive effect on myocardial conduction in infarcted as well as normal tissue.

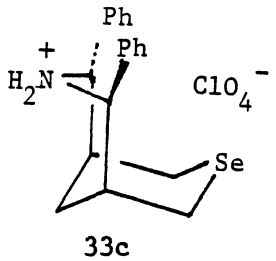
The antiarrhythmic and hemodynamic properties[107] of several 3-selena-7-azabicyclo[3.3.1]nonane derivatives are given in Table IX. The 7-benzyl- and 7-phenethyl- derivatives **29b** and **29e** demonstrated activity similar to **29a**. In preliminary studies on one dog, **29e** prevented the induction of the SVT at both 3 and 6 mg/kg doses. In a separate experiment, **29b** reduced the rate of the SVT by 27% at 3 mg/kg. Lidocaine, in the same animal, only showed an 11% reduction in the rate of the SVT at 4 mg/kg. Compounds **33c** and **70b** showed only modest reductions in the rate of the SVT at 3 mg/kg. However, **33a** showed improved activity at 6 mg/kg.[107]

Although it is difficult to compare activities of compounds assayed by different methods, and provided that all the compounds discussed, as well as those mentioned in the appropriate references, are operating by the same physiological mechanism, some generalized observations can be

TABLE IX

ANTIARRHYTHMIC PROPERTIES OF 3-SELENA-7-AZA-BICYCLO[3.3.1]NONANE HYDROPERCHLORATES[a,b]





33c

			Control[c]		Dosage			
					3 mg/kg		6 mg/kg	
	R	R'	SVT[d]	BP[e]	SVT[d]	BP[e]	SVT[d]	BP[e]
29b[f]	H	$C_6H_5CH_2$	450	50	330 (27%)	100		
76[f]	Lidocaine[h]		450	50	375 (16%)	50		
29e[g]	H	$C_6H_5CH_2CH_2$	330	70	240[i] (27%)	-	270[i] (18%)	-
33c[g]			330	70	300 (9%)	70	280 (15%)	75
70b[g]	OH	$C_6H_5CH_2$	330	70	300 (9%)	85	310 (6%)	70

a. SOURCE: reference 107.
b. As determined by inhibition/reduction in rate of sustained ventricular tachycardia in 24 h infarcted dog heart.
c. No antiarrhythmic drug present.
d. Rate of sustained ventricular tachycardia (percent decrease relative to control) (beats/min).
e. Mean blood pressure during SVT (mm Hg).
f. Dog A.
g. Dog B.
h. Dosage: 4 mg/kg.
i. Nonsustained ventricular tachycardia.

made from review of the information discussed in this section. The presence of an N-methyl, N-benzyl, N-phenethyl, or N-aryloyl group is generally associated with good activity. As indicated by the work of Ruenitz and Mokler,[79] several N-benzoyl derivatives show excellent activity. Although the number of directly comparable compounds is limited, the N-benzoyl derivatives demonstrated better activity than the corresponding benzyl analogues, e.g., **81** versus **34a** and **84** versus **34b** (see Tables III and IV).

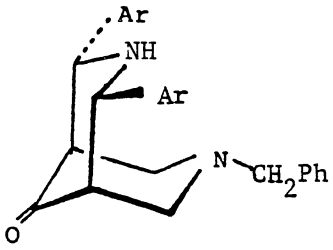
Ruenitz and Mokler[78] commented on the correlation of activity with lipophilicity. The presence of lipophillic groups at the 9-position appears to be associated with good activity. The data presented by Scherlag and coworkers [14,85,107] indicated that compounds with a methylene group at the 9-position had better activity than those with protic groups at this position, although the number of derivatives evaluated was small. Furthermore, comparing the data in Tables III and VII, the presence of bulky but relatively nonpolar aryl moieties at the 9-position may enhance the activity over a methylene group, although, again, a direct comparison is not possible with the data at hand.

CHAPTER II

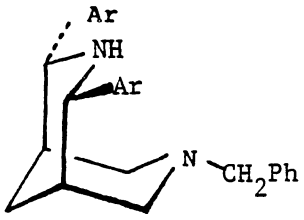
RESULTS AND DISCUSSION

The major accomplishment of this research has been the development of synthetic procedures to obtain several new and novel 3-hetera-7-aza-bicyclo[3.3.1]nonane derivatives. Several of the compounds have displayed excellent antiarrhythmic properties as determined by electro-cardiological analysis of 24-hour infarcted-heart dogs. As discussed in the previous chapter, such dogs are considered[53] excellent models of the human cardiovascular system for the testing of antiarrhythmic drugs.

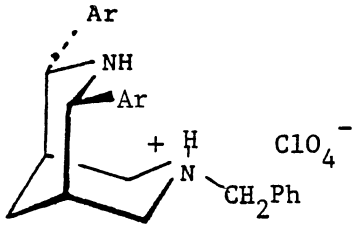
Isomeric ketones **17d, 18d,** the reduced analogs **30b, 31b** as well as



17d

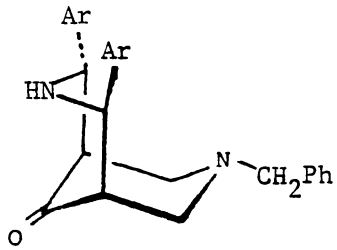


30b

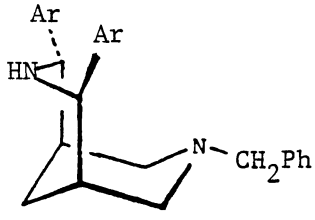


32b

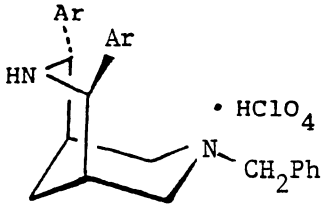
Ar = o-ClC_6H_4



18d



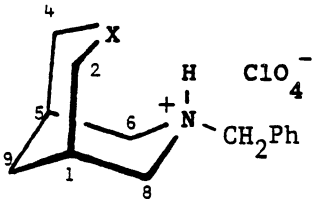
31b



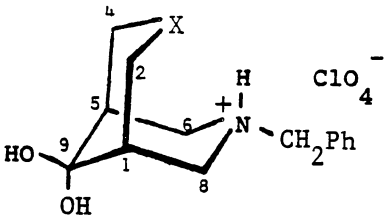
33b

the monohydroperchlorates **32b, 33b** were prepared. As shall be discussed, isomeric ketones such as **17d** and **18d**, obtained via a Mannich reaction, are rare in the chemical literature. Salts **32b** and **33b** were submitted to Dr. B. J. Scherlag (Veterans Administration Hospital, Oklahoma City, OK) for biological testing in dog models.

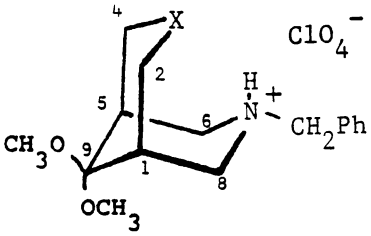
In addition, synthetic procedures were developed for the preparation of the 9,9-diol (hydrated ketone) **70d**, the dimethyl ketal derivatives **102a,b** and the 9-methylene analog **29d**. Since hydroperchlorate **29a** [see Table VIII (page 44)] is known to possess significant antiarrhythmic properties by the above assay,[14,84] and since **29d** as the amine or as the hydrochloride [see compound **34c**, Tables III (page 38), V (page 41)] has been shown to also have good activity by other screening methods,[16,78] it seemed desirable to compare the effects of the nonpolar ketal group with those of the derivatives with the methylene group at the 9-position. This also provided an opportunity to make a direct comparison of **29a** and **29d** in terms of the relative effects of the thiane ring versus the piperidine ring, thus affording information about the optimum structural characteristics for good biological activity.



29 a X = S
b X = Se
d X = NCH_2Ph



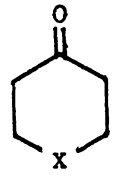
70a X = S
b X = Se
d X = NCH_2Ph



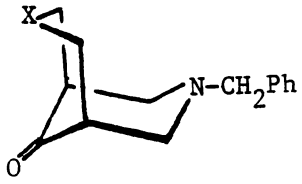
102 a X = S
b X = NCH_2Ph

Although the diols **70a,b** have not been found to be as active as the 9-methylene analogs **29a,b**,[14,107] it was felt that a screening of diol **70d** would help establish whether this trend held true for the diaza analogs as well.

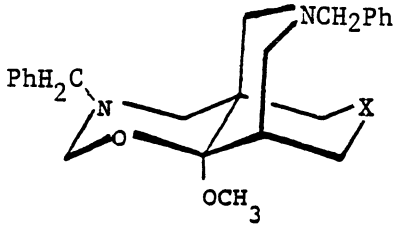
It was also possible to isolate the novel tricyclic ketals **103a,b** and spiral ketones **104a,b** as well as the bicyclic ketones **27a,b** from reaction mixtures realized from the Mannich condensations of ketones **16c,d** with benzylamine and paraformaldehyde. While compounds containing 1,3-oxazine rings have been obtained via Mannich reactions with precursors possessing phenolic groups,[75] ketals **103** are apparently the first case of oxazine ring systems being derived from simple ketones. Possible mechanisms to explain the formation of the products of these reaction will be discussed. As the tricyclic ketals **103a,b** do possess



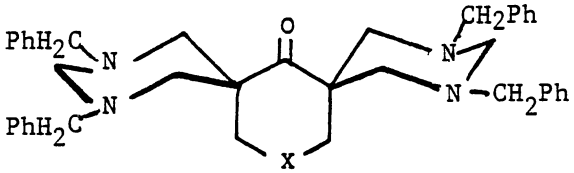
16c X = S
d X = Se



27a X = S
b X = Se



103 a X = S
b X = Se
c X = S · 2HClO4
d X = O
e X = CH2

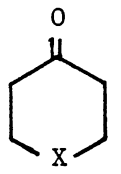


104 a X = S
b X = Se

the 3-hetera-7-azabicyclo[3.3.1]nonane ring system as a structural moiety, it was thought that these compounds might display antiarrhythmic activity. Therefore, dihydroperchlorate **103c** was also submitted to Dr. Scherlag for antiarrhythmic screening.

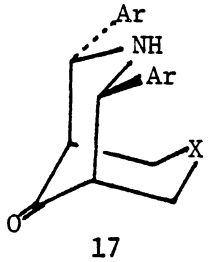
Synthetic Procedures

As discussed in the previous chapter, cyclic ketones such as 1-heteracyclohexan-4-ones **16**, as well as the aryl substituted analog **20b**, have been employed in Mannich condensations with aromatic aldehydes and ammonium acetate to arrive at aryl-substituted 3-hetera-7-azabicyclo-[3.3.1]nonan-9-ones **17a,b**, **18a**, and **66b**. It is interesting to note that these reactions are recorded as giving only products with cis-aryl substituents on the piperidine ring. Depending on the 1-heteracyclohex-



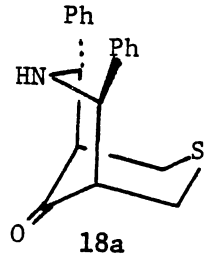
16

a. X = CH_2
b. X = O
c. X = S
d. X = Se

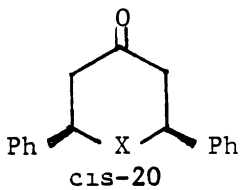


17

	X	Ar
a.	CH_2	Ph
b.	O	o-ClC_6H_4

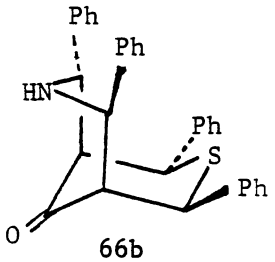


18a



cis-20

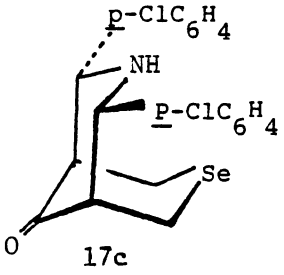
a. X = CH_2
b. X = O



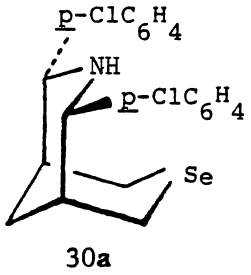
66b

an-4-one precursor, the configurations (chair or boat piperidine ring) of the products with of these reactions are those shown.

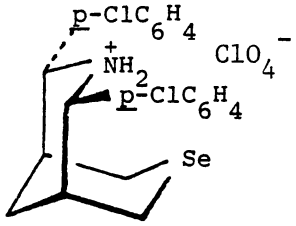
Reports in the literature about the isolation of both types of products from the same reaction mixture are very rare. Concurrent with the present study, Thompson[106] synthesized the isomeric ketones **17c** and **18c** from reaction of 4-selenanone (**16d**), p-chlorobenzaldehyde and ammonium acetate. These ketones were then reduced to the isomeric



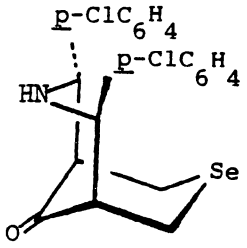
17c



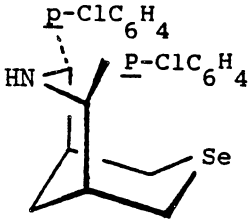
30a



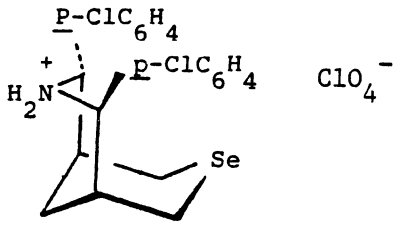
32a



18c



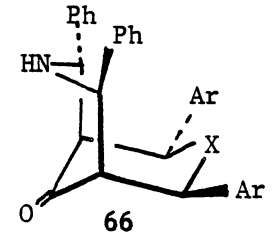
31a



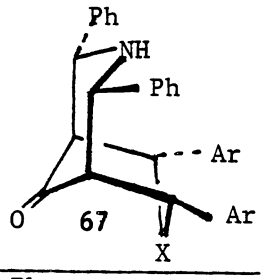
33a

amines **30a** and **31a**, which were converted to the hydroperchlorates **32a**, **33a**. Quast and co-workers[73] have recently reported obtaining the isomeric ketones **66a** and **67a** from a Mannich reaction involving cis-diphenylcyclohexanone, benzaldehyde and ammonium acetate, as well as the amines **105**, **106** from reduction of these ketones. Another incidence of isomeric ketones (however, not from the same reaction) was reported[71] by the same authors. When cis-diphenylpiperidin-4-one was treated with p-tolualdehyde and ammonium acetate in ethanol, ketone **66c**

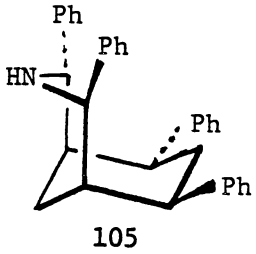
(mp 252-254°C) was the only product isolated. In contrast, a similar reaction of bis(p-tolyl)piperidin-4-one with benzaldehyde and ammonium acetate afforded ketone **67c** (apparently as a mixture, mp 192-209°C). Mass spectral data on the two products indicated they were isomeric, however, no additional spectral evidence was presented for **67c.** Initial indications[73] were that the overall conformation was **CC** in both isomers with the phenyl groups in axial positions in **66c** (as in structure **66c'**), while in **67c** the p-methylphenyl groups were in the axial positions (as in **67c'**). Subsequent work[72] by the same authors indicated that they now favor conformers **66c** and **67c.**



66



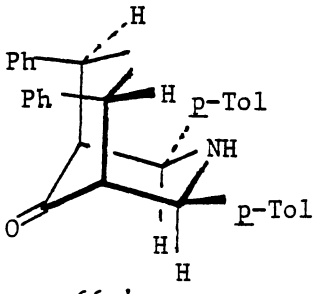
67



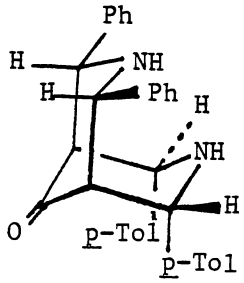
105

a. X = CH_2, Ar = Ph

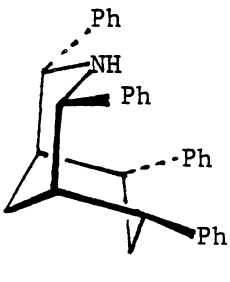
c. X = NH, Ar = p-Tol



66c'

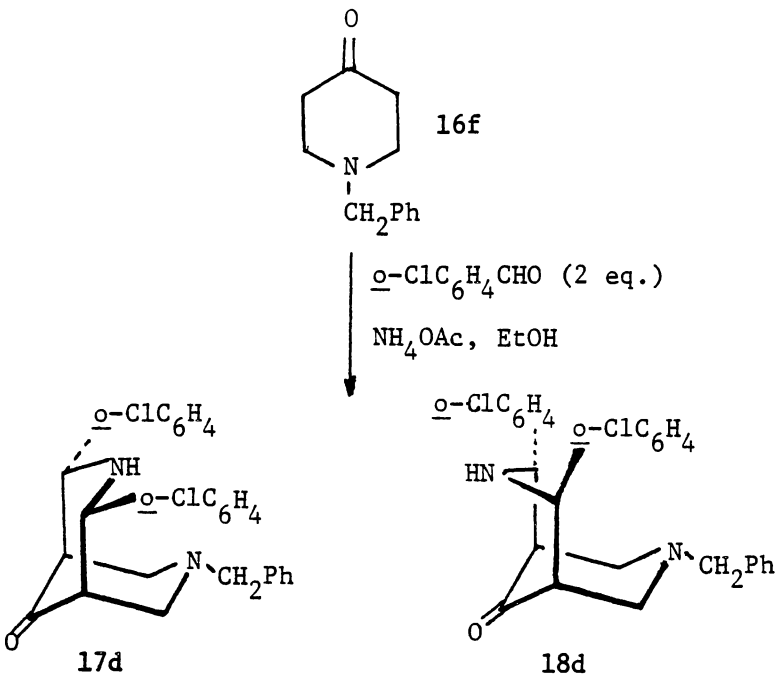


67c'



106

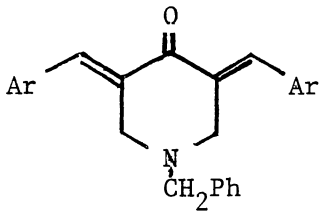
In the present study, the isomeric ketones **17d** and **18d** have been prepared by the Mannich reaction of 1-benzylpiperidin-4-one (**16f**), o-chlorobenzaldehyde, and ammonium acetate. These products initially formed when an ethanolic solution of the reactants was warmed to 70°C



over fifteen minutes, followed by cooling to room temperature. Ketone **18d** precipitated from the reaction mixture and could be filtered directly. Dilution of the mother liquor with ether, followed by standing at -10°C for several hours, afforded additional **18d**. Removal of the solvent gave a yellow-orange oil which was treated with ether. Upon standing at -10°C, ketone **17d** precipitated from this solution. Both products were recrystallized from 2-propanol/chloroform (3:1). By this method pure isomers **18d** (long needles, mp 184.0-184.5°C) and **17d** (short needles, mp 209.5-210.0°C) were isolated in low yields of 16% and 4%, respectively.

Subsequently, specific conditions to give predominantly either isomer were developed. For example, if the reaction mixture was allowed to stir at room temperature for 5 days, 17d and 18d were isolated in respective yields of 2% and 30%. If, however, the reaction was carried out in boiling ethanol over 1.3 h , the yield of **18d** was only 4% while

that of **17d** was 16%. Also isolated from the high temperature reaction was the 3,5-bisarylidenylpiperidin-4-one **19b** in a yield of 2%. The yield of this latter product relative to the bicyclic compounds usually increased if longer reaction timers were permitted.

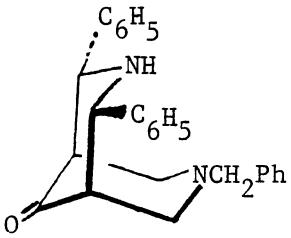


19

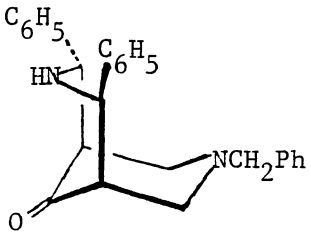
a. Ar = o-ClC_6H_4

b. Ar = Ph

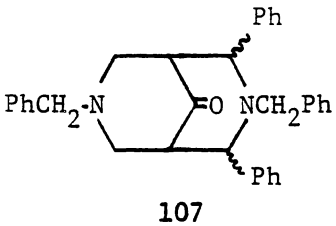
Several attempts to prepare the 2,4-diphenyl analogs **17e** and **18e** were unsuccessful under either set of conditions. When the reaction was attempted at room temperature for 11 days, the only isolatable product was the bright yellow ketone **19c**, obtained in a yield of 38% after column chromatography. The high temperature reaction also afforded this product in a yield of 60% after column chromatography. Along these same lines, an early attempt at the synthesis of ketone **107** by treatment of ketone **16f** with benzaldehyde, benzylamine, and acetic acid in boiling



17e



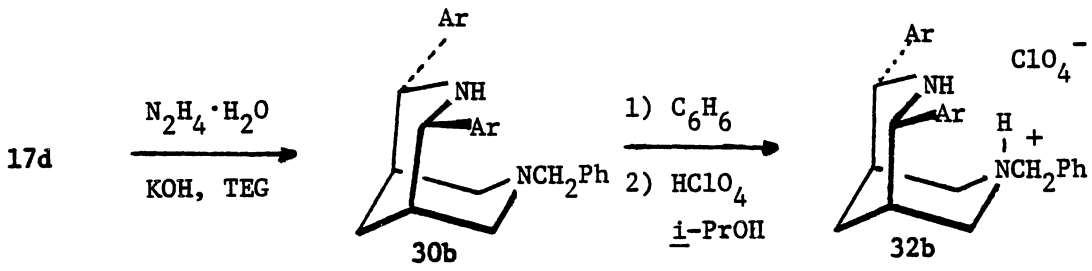
18e



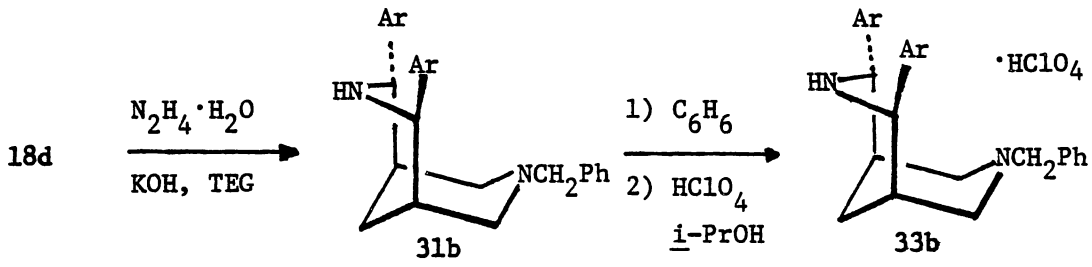
107

methanol afforded **19c** in a yield of 96%.

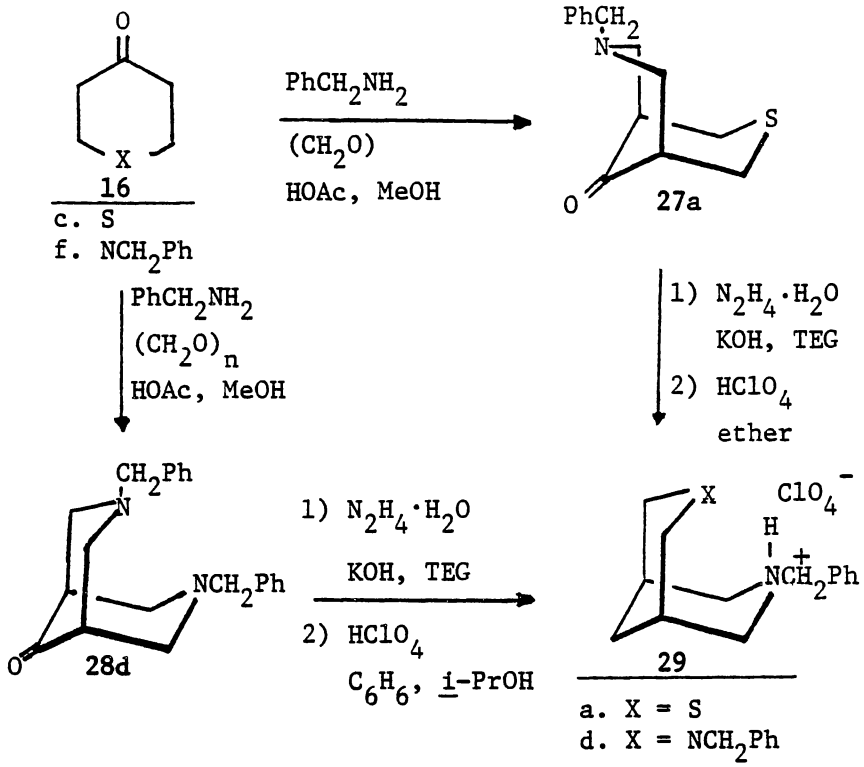
Ketone **17d** was reduced under Wolff-Kishner conditions (Huang Minlon modification[44]) to give the diamine **30b** in a yield of 61% as cubic crystals (mp 149-151°C). This diamine was in turn treated with perchloric acid to give **32b** as the monohydroperchlorate [74%, mp 260-262°C (dec)]. In a similar manner, ketone **18d** was reduced to afford the diamine **31b** in a yield of 69% as white plate-like cystals (mp 136.4-137.0 °C) followed by conversion to the monohydroperchlorate **33b** [81%, mp 246-247°C (dec)].



Ar = o-ClC_6H_4 TEG = Triethylene glycol



Hydroperchlorates **29a,d** were prepared by the following reaction scheme. Ketone **16f** was treated in a Mannich condensation with paraformaldehyde, benzylamine and acetic acid to afford **28d.** The latter has been prepared by two somewhat different procedures given in the literature. The first, by Binnig and coworkers,[16] employed two equivalents of paraformaldehyde in a reaction held at reflux for 3.5 h.

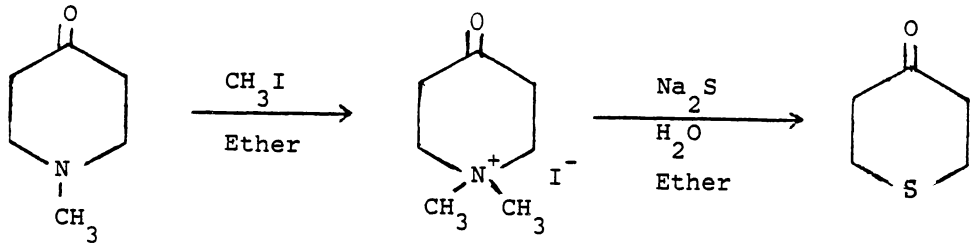


These authors report that, after an aqueous workup, the crude product was distilled twice at 185°C under vacuum followed by recrystallization (hexanes) to afford the pure ketone **28d** in a yield of 60%. In our hands the yield was significantly lower (32%). Following the aqueous workup the crude product was obtained as an orange oil in a yield of ~80%. Preliminary distillation at either 1 mm Hg or at 10^{-6} mm Hg (diffusion pump) resulted in substantial decomposition of the product, although the second distillation generally proceeded without mishap. After dissolution in Skelly B, **28c** precipitated in spectroscopically pure form upon standing at -10°C.

Smissman and Ruenitz[92] report a procedure wherein the reaction was

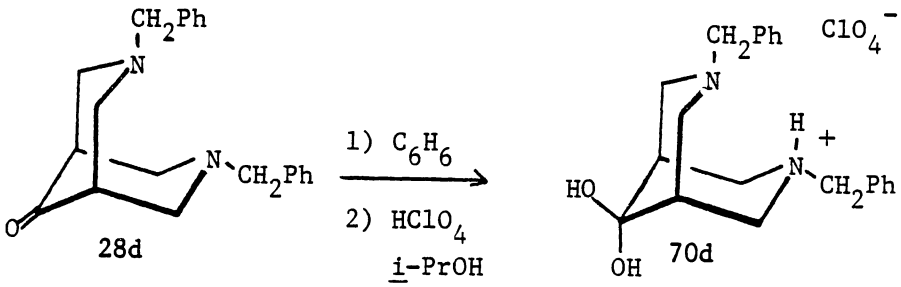
performed at room temperature over 30 days with an excess of paraformaldehyde (8 equivalents) being employed. A variation in this second procedure was actually employed in our work and was found to be more practical than either literature method. The reaction was carried out at reflux for 24 hours followed by the standard aqueous workup. The crude ketone was then digested in Skelly B for 30 minutes. Decantation of the supernatant from the orange-brown residue, followed by removal of the solvent, provided the ketone as a spectroscopically pure white oil, which did not solidify upon standing. The yield for this variation was 85%, and the product in this form proved quite satisfactory for use in subsequent reactions.

N-Benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one (**27a**) was prepared from **16c** by the method of Bailey and coworkers[14]. This reaction will be discussed later in more detail. Ketone **16c** is commercially available (Aldrich Chemical Co., Milwaukee, WI); however, it is relatively expensive. It was found to be more economical to prepare[48] it from 1-methylpiperidin-4-one (**16e**) via the methyl iodide salt **16g**. Treatment of the quaternary ammonium salt with aqueous sodium sulfide afforded **16d** in moderately large quantities, albeit in relatively low yields (32-53%).



16e 16g 16c

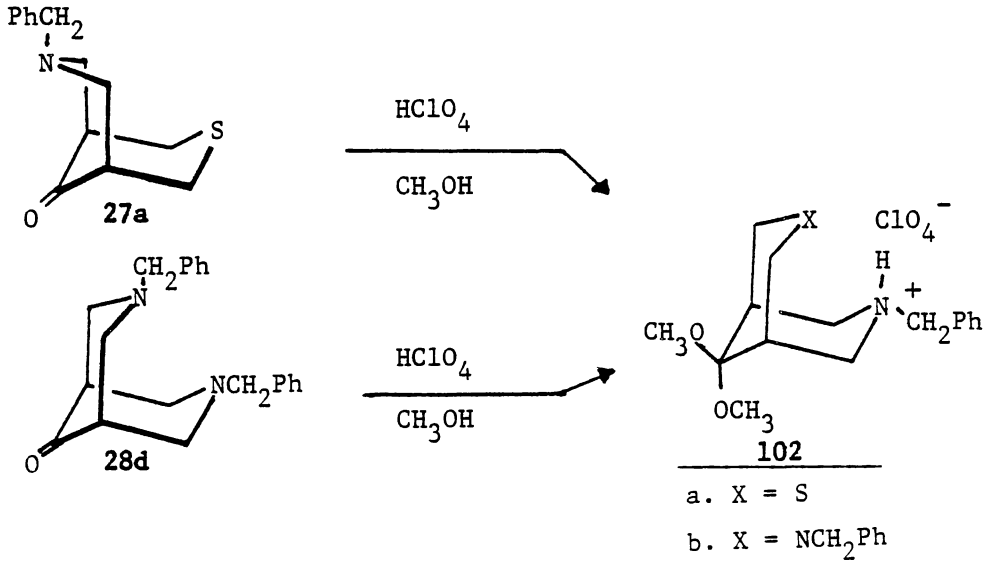
Heterocyclic bicyclo[3.3.1]nonan-9-ones ketones have been reported to give geminal diols on treatment with strong acid.[5,15,41,107] These diols are, of course, the result of the acid catalyzed addition of H_2O across the carbonyl double bond. Diol **70d** was obtained by treatment of ketone **28d** in benzene or ether with 60% perchloric acid. The most satisfactory procedure involved slow addition of the acid, as a 2-propanol solution, to a benzene solution containing the ketone. Upon vigorous agitation the diol salt precipitated as a white powder. Careful addition of the acid directly to either a benzene or ether solution resulted in the formation of a gummy orange semisolid which proved difficult to purify. Recrystallization of the crude diol from isopropyl alcohol was straightforward while recrystallization from methanol afforded the dimethoxy ketal **102a** in low yield.

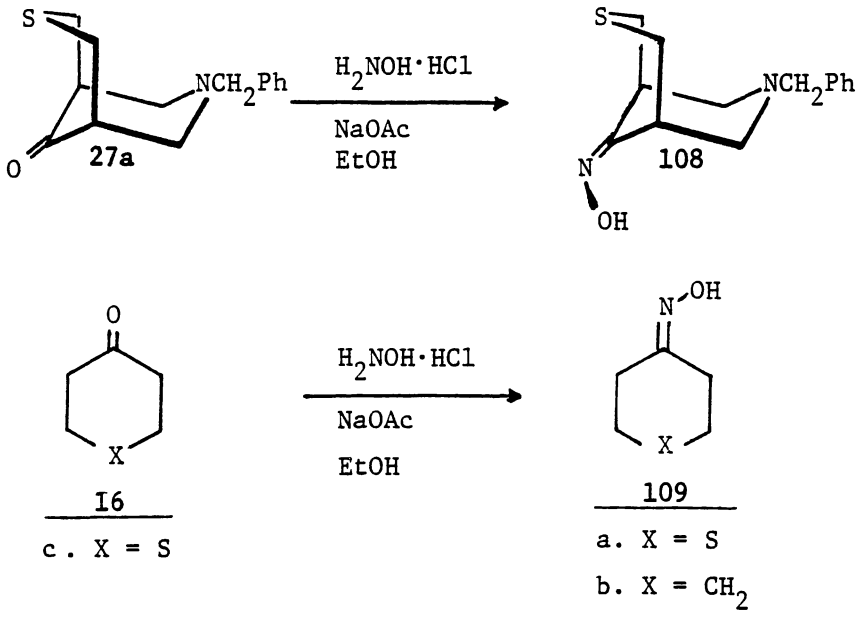


A derivative of bicyclic ketone **27a** was also synthesized. The oxime **108** was prepared by treatment of the ketone with hydroxylamine hydrochloride and sodium acetate in ethanol. Other than the hydrazones prepared in situ as intermediates in Wolff-Kishner reductions, derivatives of heterocyclic bicyclo[3.3.1]nonan-9-ones are relatively uncommon.[3,10,71] By the same method the oxime (**109a**) of tetrahydro-thiapyran-4-one, was also prepared for comparison of the NMR spectra.

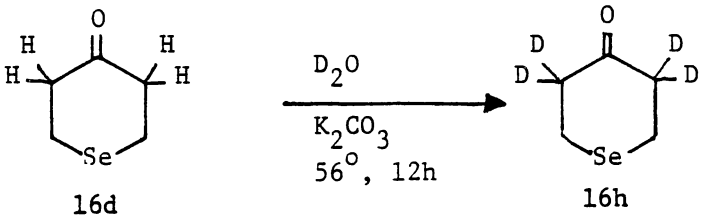
Hydroperchlorate **29d** was obtained by a procedure similar to that described in the literature[16,92] wherein ketone **28d** was treated with hydrazine hydrate and potassium hydroxide in triethylene glycol (TEG). The crude amine obtained from this Wolff-Kishner reduction was not isolated in pure form but treated as crude material with perchloric acid to afford **29d** as white crystals (mp 220-221°C). The salt described in the literature preparation[92] was not pure [mp 210-217°C (dec)], nor was it well characterized.[91] Hydroperchlorate **29a** was prepared from by a similar literature method.[14]

Ketone **28d** was treated in with perchloric acid in boiling methanol to afford the dimethoxy ketal **102b.** If the water was removed from the reaction mixture via the use of Molecular Sieve 3A in a Soxhlet extractor, the reaction was found to proceed in a yield of 69%. While this process was recognized as being inherently dangerous due to potential formation of explosive methyl perchlorate,[83] when the reaction was performed without the drying agent the yield was substantially reduced. Conversion of ketone **27a** to ketal **102a** was accomplished in a similar way.



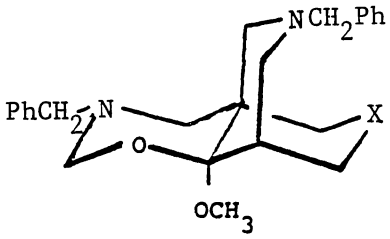


As will be discussed later, it proved desirable to obtain the tetradeuterated ketone **16h.** This compound was obtained by treating ketone **16d** with K_2CO_3 in D_2O. When the reaction mixture was heated to 100°C substantial decomposition of the starting material occurred as noted by the deposition of red elemental selenium along the walls of the flask. Performance of the reaction at 57°C proved satisfactory, although some decomposition was noted at this temperature.

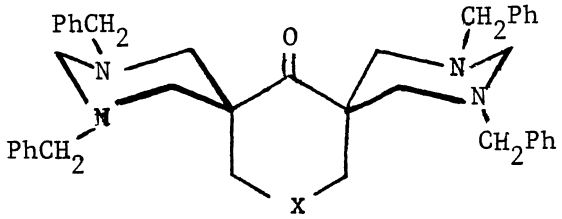


16c X = S
d X = Se

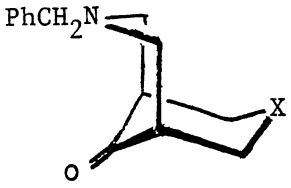
$PhCH_2NH_2$
HOAc
CH_2O
MeOH



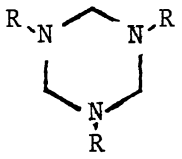
103 a X = S
b X = Se



104 a. X = S
b. X = Se



27 a X = S
b X = Se



110 a R = $PhCH_2$
b R = CH_3
c R = C_2H_5

repeat the synthesis of the selenium-containing ketone **27b**, we initially (and rather inadvertantly) found that if ketone **16d** was treated with an excess of benzylamine and acetic acid (1.4 equivalents of each) the only product isolated was the novel tricyclic ketal 103a in a yield of 22% (relative to the amount of benzylamine). The structure of this rather complex molecule was deduced by a combination of spectroscopic techniques and then confirmed by a crystal structure.

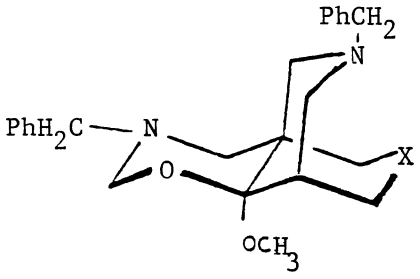
the sulfur analog **27a** by a similar procedure. While attempting to repeat the synthesis of the selenium-containing ketone **27b**, we initially (and rather inadvertantly) found that, if ketone **16d** was treated with an excess of benzylamine and acetic acid (1.4 equivalents each) the only product isolated was the novel tricyclic ketal **103b** in a yield of 22% (relative to the amount of benzylamine). The structure of this rather complex molecule was deduced by a combination of spectroscopic techniques and then confirmed by a crystal structure.

Subsequently, it was found the a third product could be isolated from this reaction mixture. In a reaction where **16d** was treated with benzylamine and acetic acid (2 equivalents each) along with an excess of paraformaldehyde in methanol, the precipitation of a white solid from the reaction mixture was noted. This was filtered and recrystallized (2-propanol) to afford the spiro ketone **104b** in a yield of 1.7%. Removal of the solvent from the reaction mixture, followed by partitioning of the reaction mixture between equal amounts of ether and water, permitted the separation of the tricyclic ketal **103b** from the bicyclic ketone **27b**. The bulky ketals apparently are poorly soluble in water under the mildly acidic (pH 6.0-6.5) conditions of the extraction. Ketal **104b** then crystallized from the ether layer upon standing. The bicylic ketone **27b** was then isolated from the aqueous phase by the method described by Thompson.[107] Repetition of the reaction under the original conditions described by Thompson afforded the tricyclic ketal **103b** in a yield of 14.3% while the 3-selena-7-azabicyclo[3.3.1]nonan-9-one **27b** was isolated in a yield of 28.5% (crude).

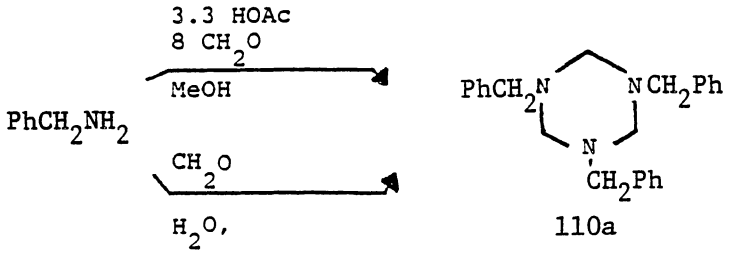
In similar reactions the sulfur analogs of these products (**27a, 103a, 104a**) were obtained. Under the original conditions of the

reaction,[14] treatment of **16c** with benzylamine (1 equivalent), acetic acid (1.5 eqivalents), and paraformaldehyde (8 equivalents) in methanol afforded the tricyclic ketal **103a** and the bicyclic ketone **27a** in a yield of 5.9% (relative to benzylamine) and 33.7%, respectively. If the reaction was carried out with two equivalents of benzylamine and a slight excess acetic acid, the yields of ketal **103a** increased but were quite variable. In one experiment **103a** was isolated in a yield of 45% (as the only product isolated in pure form), however, typical yields for this product were 12-35%. Maximum yield for spiro compound **104a** was obtained when a methanolic solution of ketone **16c** and benzylamine (2 equivalents) was added dropwise to a boiling suspension of paraformaldehyde and acetic acid (2.2 equivalents). In this reaction the spiro ketone **104b** was obtained in a yield of 8.6%, while ketal **103a** and bicyclic ketone **27a** were obtained in yields of 10% and 48%, respectively.

Attempted preparations of analogous ketals 103d,e were not successful under the conditions described. While there was evidence that the ketals are formed, separation by fractional crystallization or by preparative thin layer chromatography was not achieved. However, ^{13}C NMR spectra of the crude ether extracts (obtained during the workup)



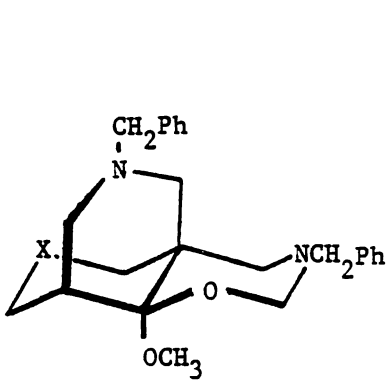
103 d X = O
e X = CH_2



110a

were found to have peaks in the range of 90-100 ppm. From our own experience, peaks in this range are due to carbons singly-bonded to two oxygens, i.e., ketals and geminal diols. The primary impurity of these mixtures (in fact, the primary constituent) was the hexahydrotriazine **110a.** Other evidence for the formation of **110a** in these reaction mixtures was obtained in a reaction where, under essentially the same conditions as the above Mannich reactions but in the absence of a ketone substrate, **110a** was obtained in pure form in a yield of 57.3%. Hexahydrotriazine **110a** was also prepared by a procedure similar to that described in the literature[34a] from benzylamine and aqueous formaldehyde in yields of 93%. Repetition of this latter reaction employing methanol as a cosolvent afforded **110a** in a slightly improved yield of 95%.

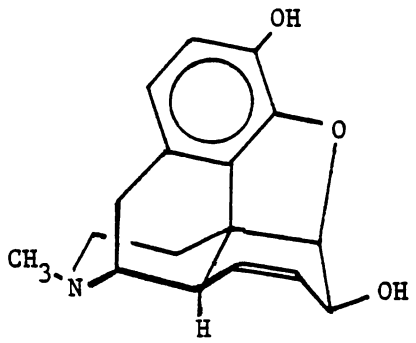
It interesting to note the similarity of the ring junctures in tricyclic ketals **103a,b** with those of the central three rings of morphine. This is most effectively visualized in **109'**, the enantiomer of **109.** Not withstanding the different conformation of the cyclohexene rings of morphine (as compared to the piperidine and 1,3-oxazine rings of **109'**) and the difference in heteroatom content and placement, it can



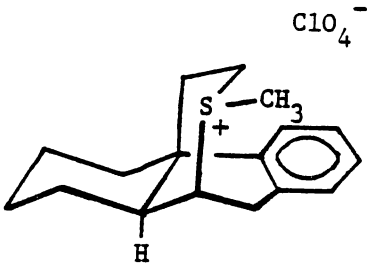
109'

a. X = S

b. X = Se



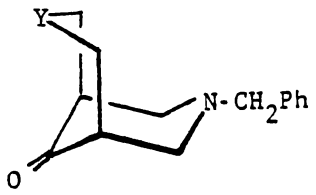
Morphine



be seen that the central ring junctures are quite analogous. This three-ring juncture is also observed in a few opiate isosteres (see sulfonium salt above) examined for analgesic activity.[61]

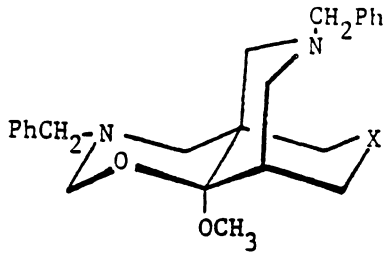
Mechanistic Considerations

The formation of the novel tricyclic ketals **103a,b** and spiro ketones **104a,b** can be explained in terms of essentially two different mechanistic pathways, which, for convenience, we will call the stepwise iminium ion route (A) and the nucleophilic displacement route (B). As shall be discussed, both pathways are initiated by an aminoalkylation, but differ in the processes required to achieve the cyclization.



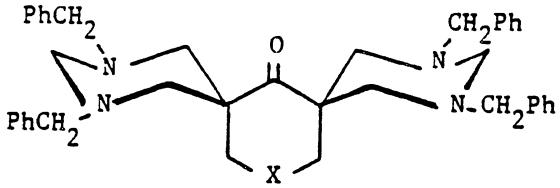
27

a X = S
b X = Se



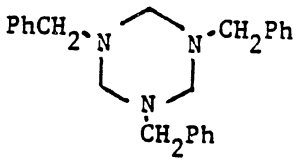
103

a X = S
b X = Se



104

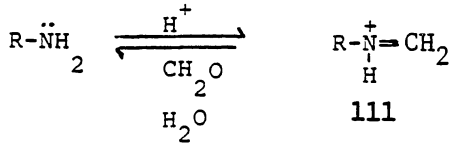
a X = S
b X = Se



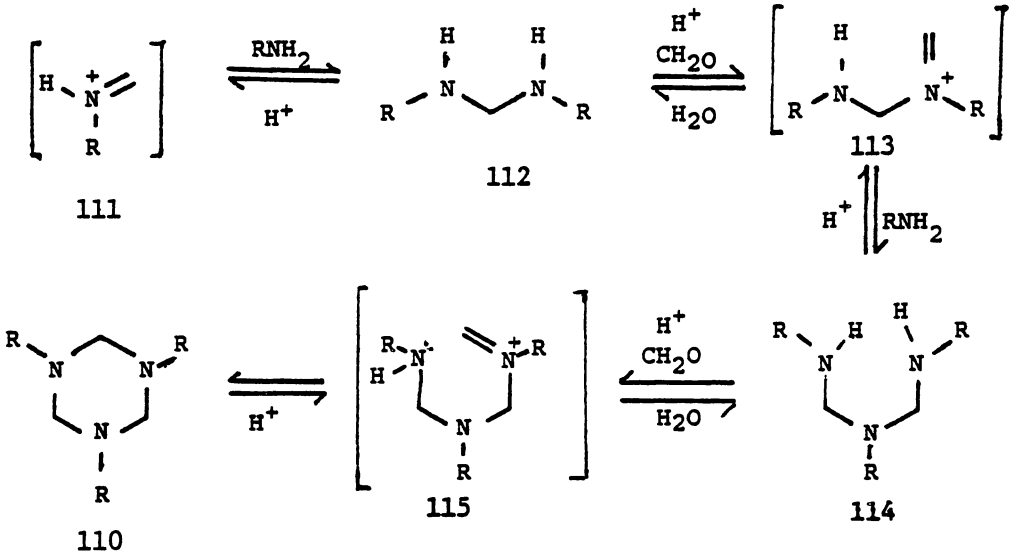
110a

The mechanism commonly cited[105,110] in the literature for the Mannich reaction involves the initial generation of **111** (Scheme I). Formation of hexahydrotriazine **110a** can be easily envisioned simply by the sequential reaction of this species with additional amine, and formaldehyde (Scheme II). Cyclic triamines and diamines (such as **110, 112, 114**) are known to be formed via the Mannich reaction under basic conditions, but are reportedly unstable under acidic conditions,[105,110] affording the reversible reactions to iminium ions **111, 113,** and **115.**

Scheme I (R = Benzyl)



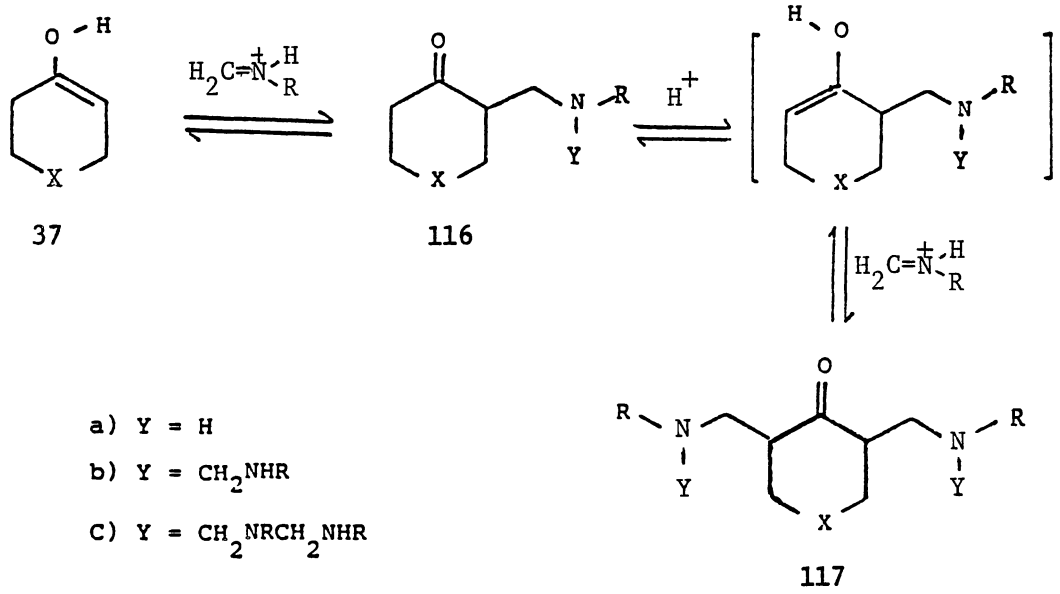
Scheme II (R = Benzyl)



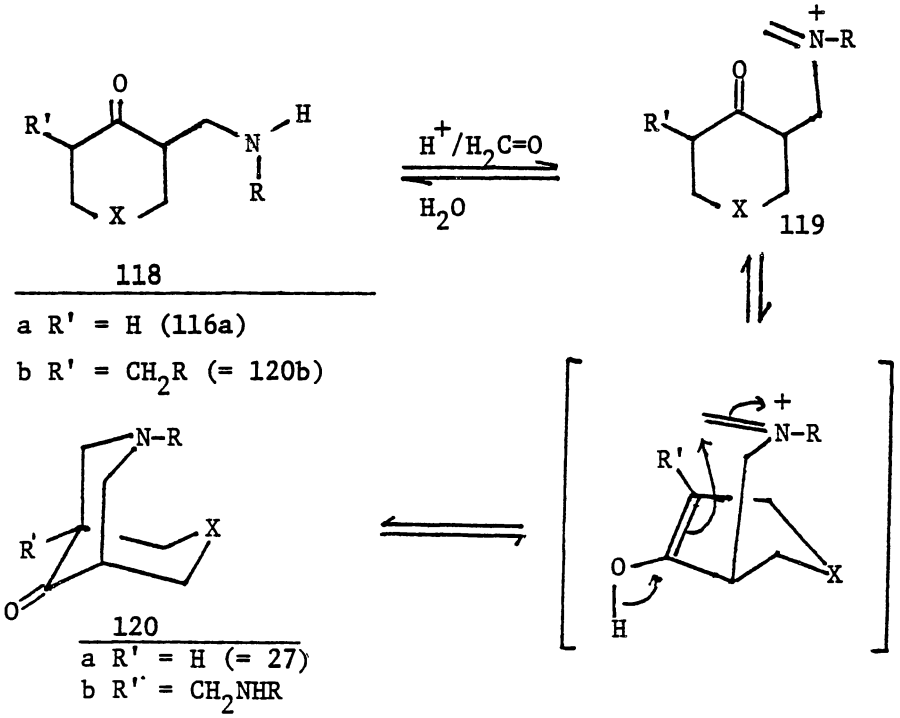
However, the reaction conditions for our experiments were only mildly acidic (pH 6.0-7.0). The mild acidity may be the major factor that permitted the isolation of **110a**. Presumably, all three iminium species are present to some extent at equilibrium. The crucial question here is which species (**111, 113, 115**) is the principle alkylating species and by what pathway does it lead to the cyclized products. As shall be shown, the products found in our work can be conceived as being formed by either route A or B.

Presuming the literature mechanism[46,71] is correct, alkylation of enol 37 by **111** will generate monoalkylated intermediate **116a** (Scheme III). Cyclization to afford the bicyclic ketone **27** (Scheme IV-A) proceeds by the route shown in Scheme V-A. Attack on **118a** (identical to **116a**) by formaldehyde and subsequent dehydration affords the iminium ion **119**. Cyclization then ensues by a second Mannich-type aminoalkylation to give **120a** (identical to **27**).

Scheme III (R = benzyl)

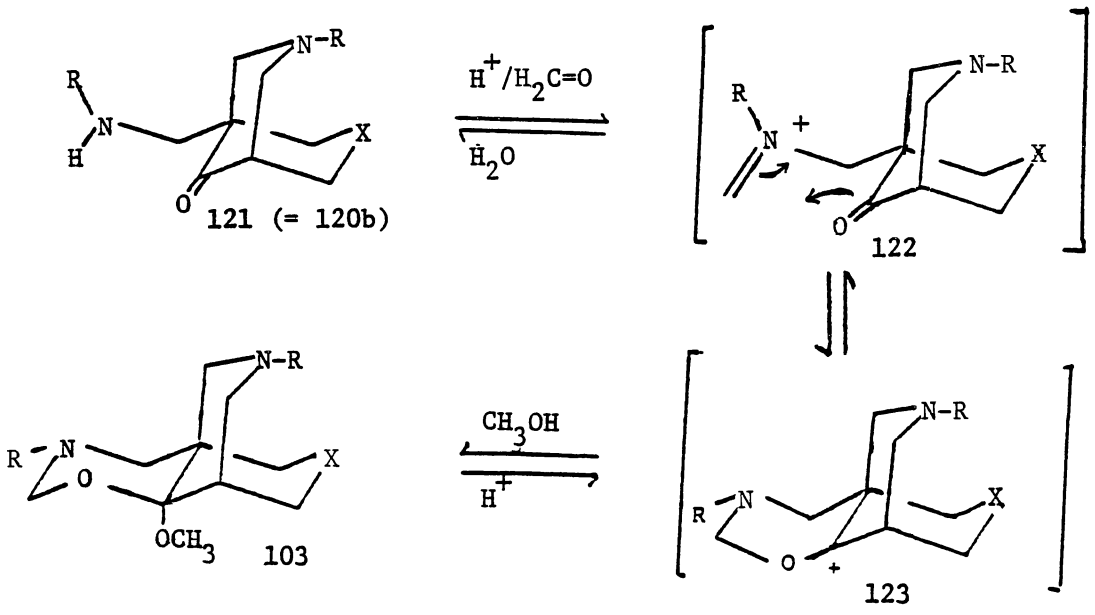


Scheme IV - A (R = benzyl)



The presence of the 3-hetera-7-azabicyclo[3.3.1]nonane moiety with a quaternary carbon in the ketals **103** suggests that these compounds arise from dialkylated ketone **117a** (Scheme III). A stepwise cyclization similar to that described previously affords the substituted 3-hetera-7-azabicyclo[3.3.1]nonan-9-one **120b** (Scheme IV-A, **118b** to **120b**). The formation of the 1,3-oxazine ring can then be envisioned (Scheme V-A) from **121** (identical to **120b**) via the formation of iminium ion **122.** Subsequent nucleophilic attack by the oxygen affords a carbocation (**123,** stabilized by electron delocalization from oxygen), which is trapped by methanol to give the ketal functionality as in **103.**

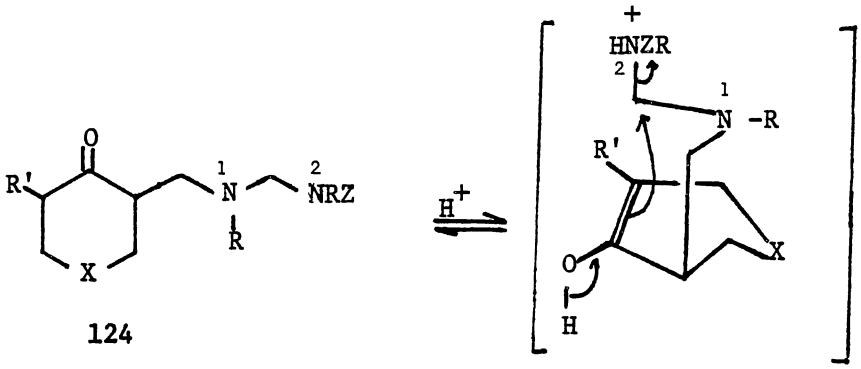
Scheme V-A (R = Benzyl)



If one presumes that the initial alkylating species in Scheme III (page 68) is **113** or **115** an alternative mechanistic pathway is possible. By this route, the formation of bicylic ketones **27** (Scheme IV-B) arises

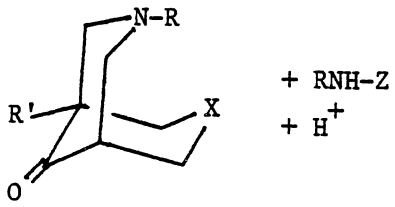
from **124a** or **124b**. Protonation at N(2) followed by nucleophilic displacement of RZNH by the transition state enol generates the bicyclic ketone **120a** (identical to **27**). Cyclization of **124c,d** by a similar route affords the substituted analogs **120c,d** The 1,3-oxazine ring can then be envisioned as being formed (Scheme V-B) from **125** or **125** via protonation [at N(2)] and subsequent nucleophilic displacement of RZNH to give carbocation **123**. As before, entrapment by methanol affords **109**.

Scheme IV-B (R = Benzyl)



124

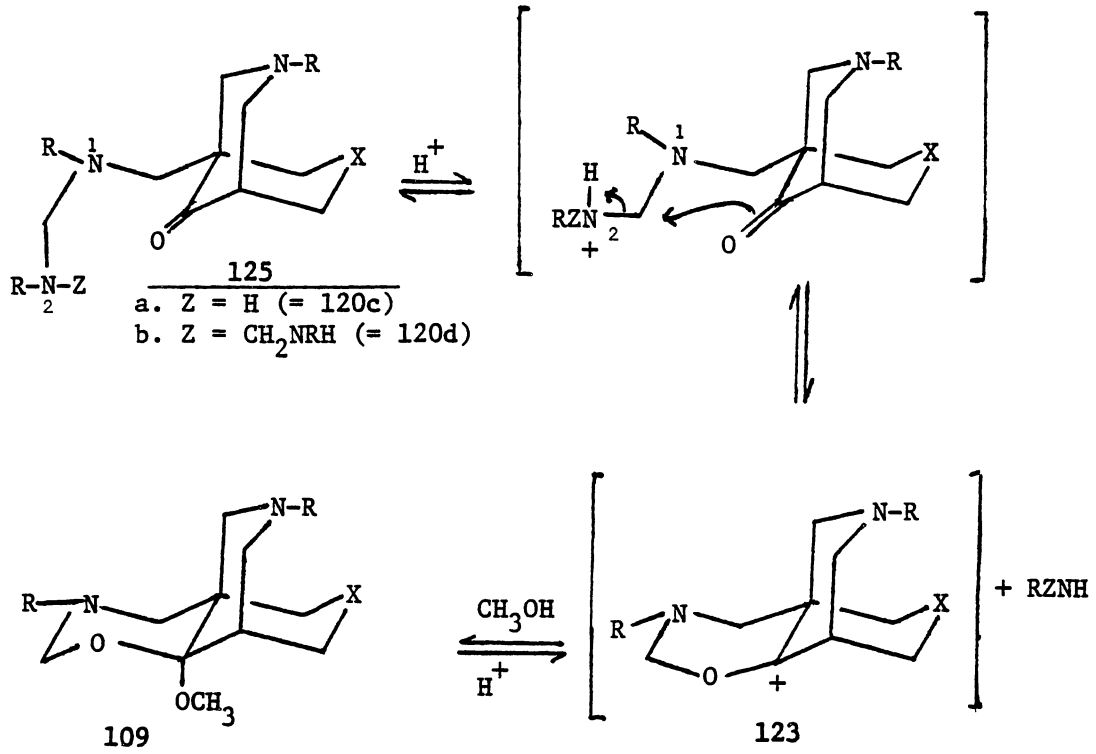
a. R' = H, Z = H (= **116b**, Scheme III)
b. R' = H, Z = CH_2NRH (= **116c**)
c. R' = CH_2NR-Z, Z = H (= **117b**)
d. R' = CH_2NR-Z, Z = CH_2NHR (= **117c**)



120

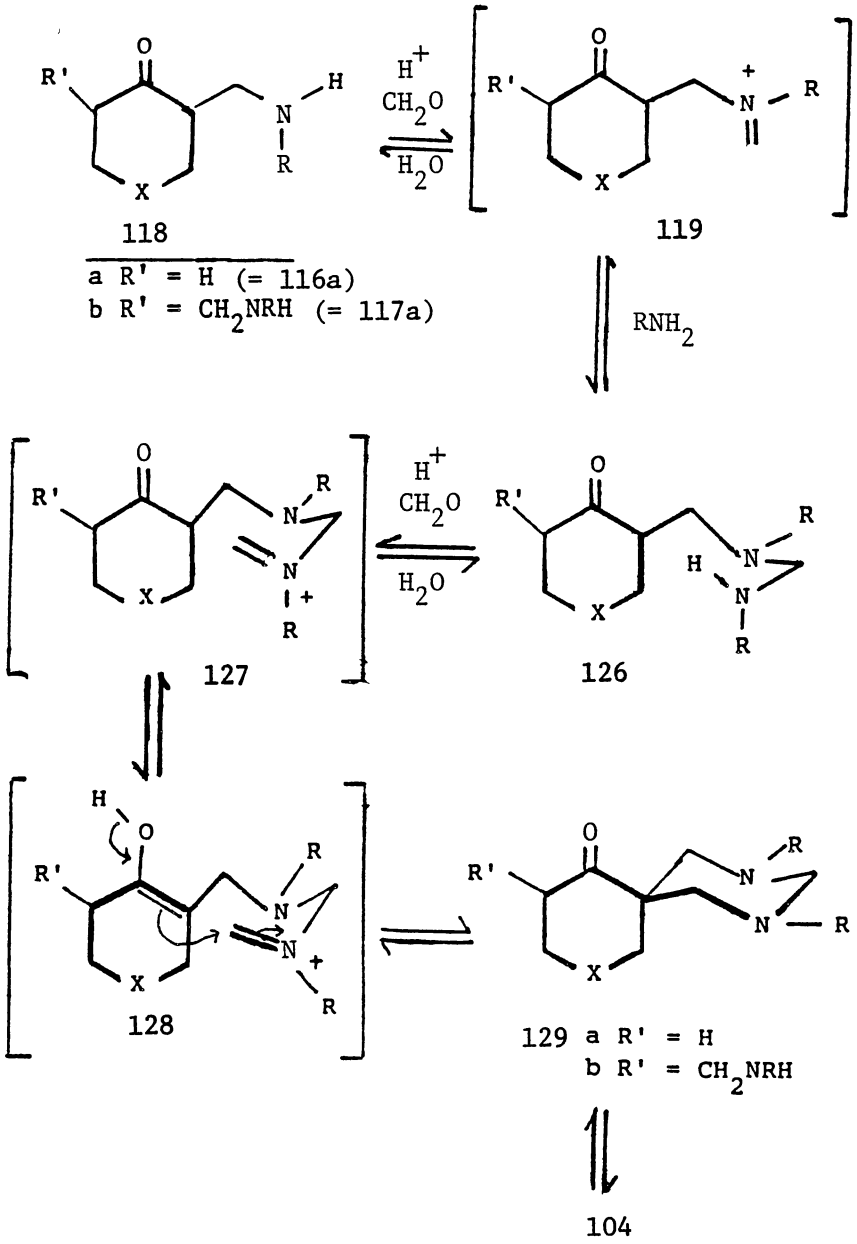
a. R' = H (= **27**)
c. R' = CH_2NRCH_2NRH
d. R' = $CH_2NRCH_2NRCH_2NRH$

Scheme V-B (R = Benzyl)



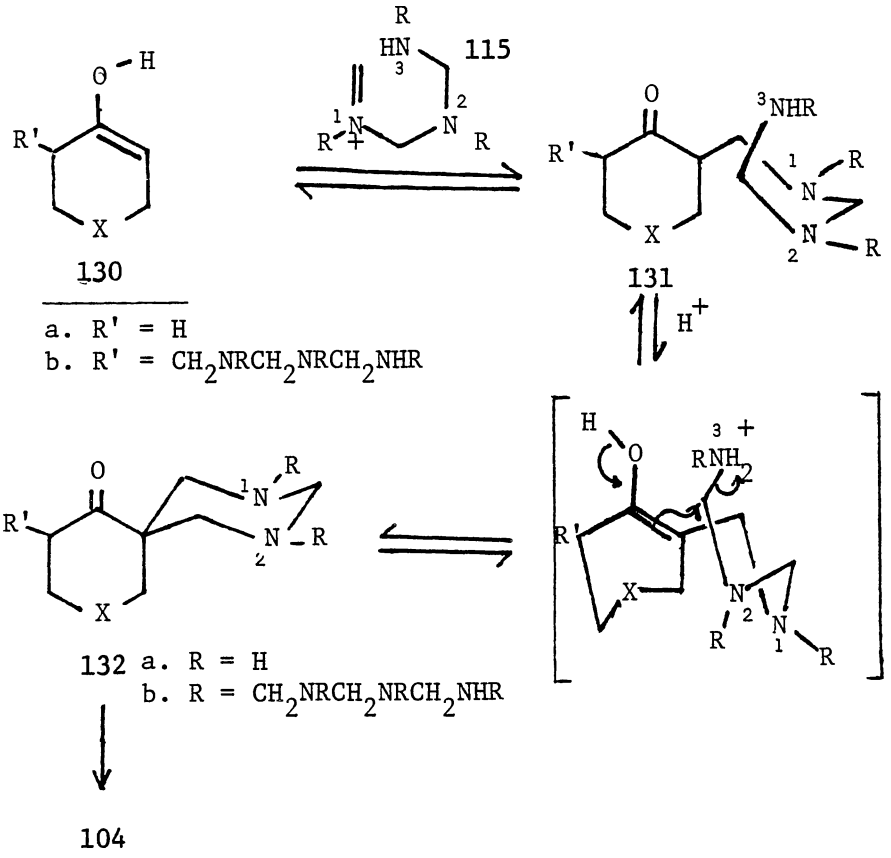
Formation of the hexahydropyrimidine rings in **104** can be envisioned by either mechanistic route. By the stepwise imminium route (Scheme VI-A), the formation of the hexahydropyrimidine ring from **118** (identical to **116a** and **117a** from Scheme III) can be visualized as occurring by formation of imminium ion **119** and subsequent attack by RNH_2 to afford diamine **126.** Cyclization then ensues by formation of **127** followed by aminoalkylation of the enol **128.** The second hexahydropyrimidine ring could arise from **118b** by two such ring formations or by aminomethylation of 129a to afford **129b** and subsequent ring formation. Envisioned in this manner, the reaction pathway in Scheme VI-A would be competitive with the reaction pathway described in Scheme IV-A (and ultimately with that is Scheme V-A).

Scheme VI-A

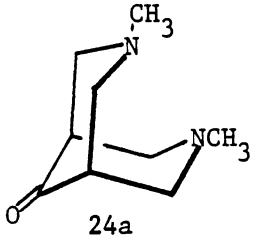


The nucleophilic displacement pathway to form the hexahydropyrimidine rings (Scheme VI-B) would be competitive with the routes described in Scheme IV-B. However, to achieve cyclization by this mechanism the

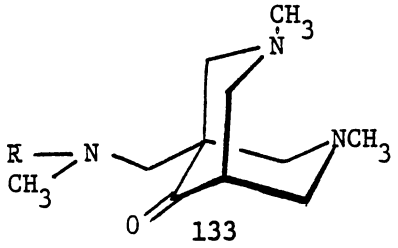
initial alkylating species (Scheme III) should be **115**. The resulting intermediate **130** (Scheme VI-B) would then be protonated [at N(3)] with cyclization occurring by displacement of R-NH_2. As before, the formation of the second hexahydropyrimidine ring could be the result of the formation of two such rings from **130b** or by the sequential aminomethylation of **132a** to afford **132b** followed by cyclization.



We have no evidence that conclusively favors either mechanism for the cyclization to afford the products observed in these reactions. However, we do note that Smissman and Ruenitz[91] have reported the isolation of **24a** and **133a** from a reaction mixture derived from the treatment of N-methylpiperidin-4-one with methylamine, acetic acid and



24a

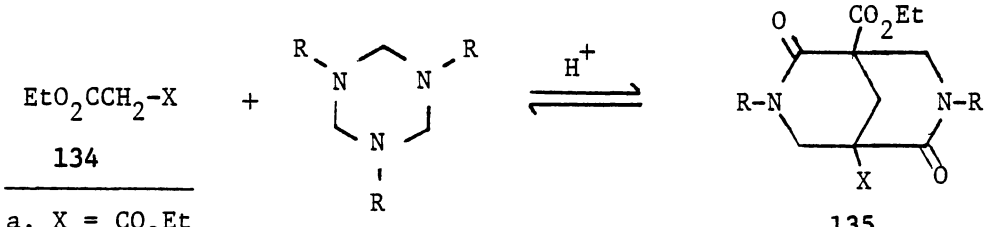


133

a. R = H
b. R = o-$O_2NC_6H_4S$

paraformaldehyde. The product mixture by GC-MS analysis consisted of **24a** (58%) and **133a** (42%). Separation was achieved by treatment of the mixture with o-nitrophenylsulfenyl chloride which gave both **24a** and **133b**. An aqueous mixture of these latter compounds was separated by extraction (chloroform). Treatment of **133b** with ethereal HCl then afforded pure **133a**.

Moreover, it has been reported that diaminomethylene derivatives are the initially formed products in the Mannich reaction of secondary amines with formaldehyde.[105] Subsequent cleavage by acid then led to the formation of iminium ions. Furthermore, 1,3,5-trialkylhexahydro-1,3,5-triazines **110** have been treated with **134** under acidic



134

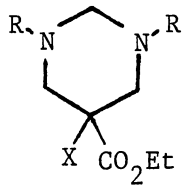
a. X = CO_2Et
b. X = CN

110

a. R = CH_2Ph
b. R = CH_3
c. R = CH_3CH_2

135

X = CO_2Et, CN
R = CH_2Ph, CH_3, CH_3CH_2



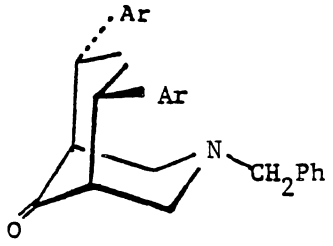
a. X = CN
b. X = CO_2Et

136

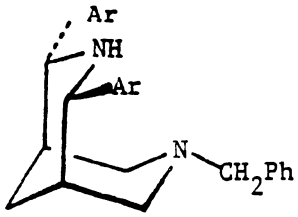
conditions to afford 3,7-diazabicyclo[3.3.1]nonan-2,6-diones **135.**[25] The authors reported that the reaction proceeds with either stoichiometric or catalytic amounts of acid and that the initially formed intermediate is the hexahydropyrimidine **136.**

Structural and Conformational Analysis

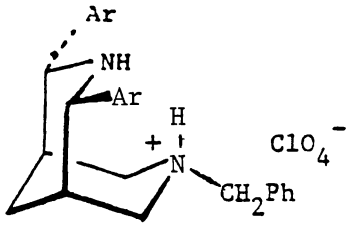
The determinations of the identity and conformations of ketones **17d,18d,** diamines **30b, 31b** and hydroperchlorates **32b, 33b** were based upon the comparison of their ^{13}C, ^{1}H and ^{15}N NMR spectra as well as upon X-ray crystal structures for **18d, 32b** and **33b.** Since each ketone isomer **17d** and **18d** had only four aliphatic signals in the ^{13}C NMR spectrum, a <u>trans</u> arrangement of the <u>o</u>-chlorophenyl substituents relative to each



17d

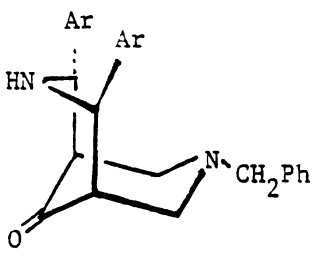


30b

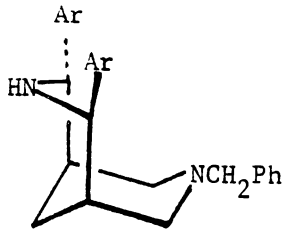


32b

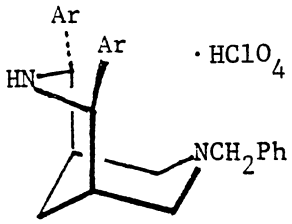
Ar = <u>o</u>-ClC_6H_4



18d



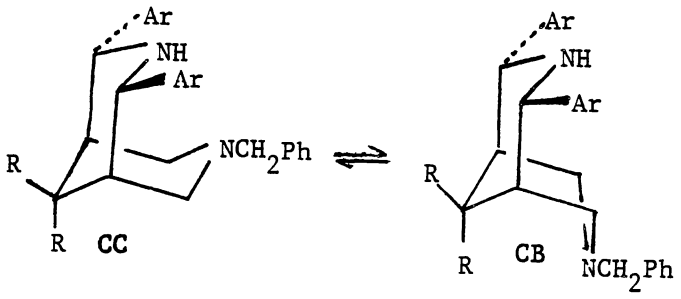
31b

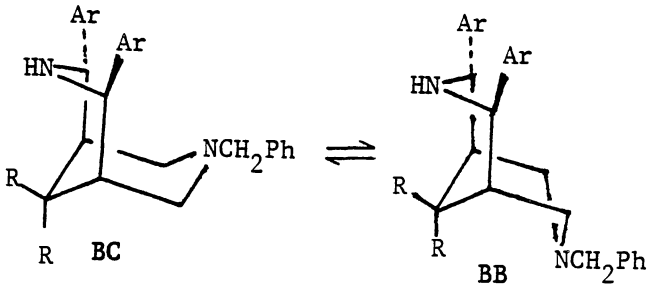


33b

Ar = o-ClC_6H_4

other for either isomer was precluded. Thus, the configurational and conformational possibilities for these compounds were :

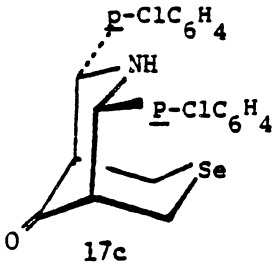




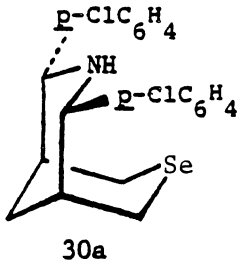
R,R = O or R = H

The crystallographic analysis of **18d** indicated that this ketone possessed the structure and conformation indicated for the **BC** form in the solid state. Since the configuration about the aryl-substituted

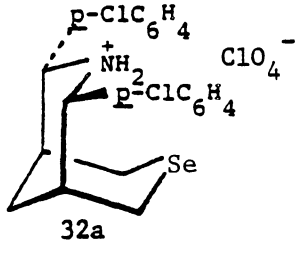
evidence suggests that the predominant conformations of **17d** and **30b** are **CC**. The arguments for this conclusion follow. Ketones **17c, 18c, 66a** and **67a**; the analogous amines **30a, 31a, 105** and **106**; and the hydroperchlorates **32a, 33a** served as the primary model isomeric systems in this study.[73,106] The aliphatic ^{13}C spectral data for the ketones are summarized in Table X while that for the amines are summarized in Table XI. Table XII lists the aliphatic ^{13}C NMR data for hydroperchlorates **33** and **34**.



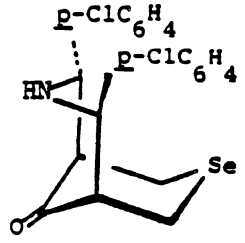
17c



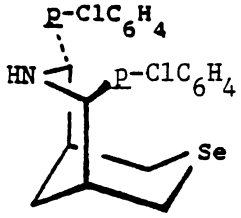
30a



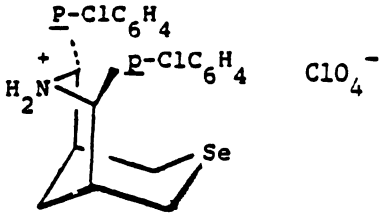
32a



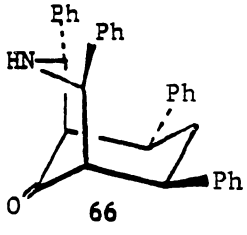
18c



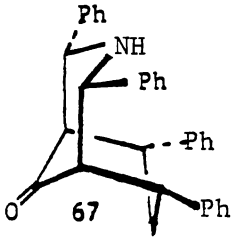
31a



33a



66

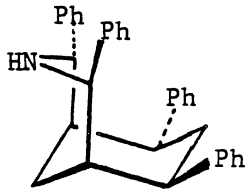


67

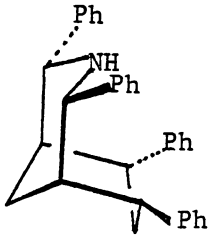
ring is locked, this **BC** conformation was also presumed to be the predominant species in solution. The significant contribution of the **BB** conformer was dismissed from consideration as the benzyl group on N(7) was probably not bulky enough to force this conformation. Since a trans arrangement of the o-chlorophenyl substituents had already been precluded, the structure for **18d** mandated that the aryl-substituted ring in the isomeric ketone **17d** be in a chair conformation. Determination of the exact conformation of **17d** (**CC** or **CB**) by way of crystallographic examination was not possible as suitable crystals could not be obtained. The determination of the predominant conformation of this ketone in solution via NMR analysis will be discussed later.

Given the established configurations of ketones **17d** and **18d**, the structures of isomeric amines **30b** and **31b**, obtained via Wolff-Kishner reduction of the respective ketones, were examined. While epimerization of C(2,4) might be conceivable under the strongly alkaline and hot (195^{o}C) conditions of the reduction, this was not found to be the case. Crystal structures of the salts (**32b**, **33b**) derived from **30b** and **31b** indicated that the relative stereochemistry of the aryl-substituted piperidine rings remained unchanged from that found for the ketones. The crystal structure of hydroperchlorate **32b** (derived from **30b**) indicated chair conformations for both rings in this salt. Hydroperchlorate **33b**, derived from amine **31b**, was found to adopt the **BC** conformation with the aryl-substituted ring in the boat form.

After consideration of the crystal structures of ketone **18d** and salt **33b**, the **BC** conformation of amine **31b** could be assigned with some degree of confidence. The question remained as to the conformations (**BC** or **CC**) of ketone **17d** and amine **30b**. A review of the spectroscopic

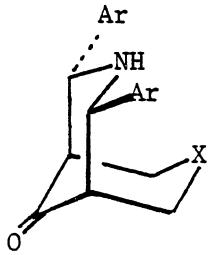


105



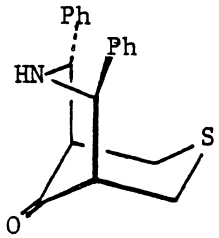
106

Carbon-13 NMR spectroscopy has been used quite effectively in the conformational analysis of several 3-hetera-7-aza- and 7-azabicyclo-[3.3.1]nonane systems.[14,46,47] Berlin and co-workers[14] noted that, in a series of 3-hetera-7-azabicyclo[3.3.1]nonan-9-ones, the ^{13}C NMR shifts for the carbonyl carbons [C(9)] in systems where both rings were in the chair form were usually downfield of those in systems where one ring was in the boat form. For example, the carbonyl peak (217.2 ppm) in ketone **17a**[47] was observed downfield of carbonyl peaks in **18a** (212.7 ppm)[47] and

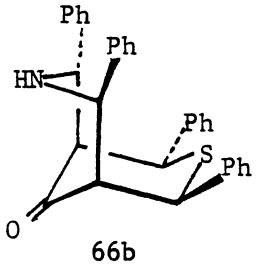


17

a. X = CH_2, Ar = Ph
b. X = O, Ar = o-ClC_6H_4



18a



66b

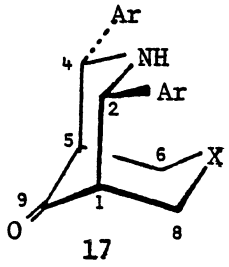
66b (211.5 ppm).[5] This trend may not be diagnostic in all cases, however. The carbonyl carbon in **66a** (with the piperidine ring in the boat) had a chemical shift of 212.6 ppm (Table X) while the analogous

carbon in isomer **67** (with the cyclohexane ring in the boat) occurred at 215.3 ppm. The shift for C=O in ketone **17c** (presumed to be **CC**, see Table X) was reported as occurring slightly upfield (by 0.5 ppm) of that for isomeric ketone **18c** (presumed to be **CB**). Moreover, the shift of this carbon in **17b** (known to be **CC** from a crystal structure[5]) was reported at 209.7 ppm. The trend was certainly not diagnostically conclusive in ketones **17d** and **18d** synthesized in this project. The difference in the positions (212.0, 212.2 ppm) of the C=O was quite small, which might suggest that these are **BC** and **CB** conformers. However, as the chemical shift of the carbonyl is apparently not a sound criterion for the assignment of conformations in these systems, a **CC** cannot be ruled out.

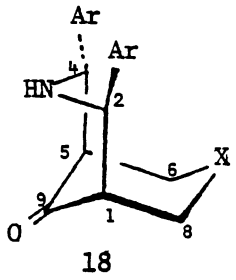
In amines **31b** and **30b**, however, a significant difference exists in the ^{13}C NMR shifts for C(9) (see Table XI). The shift for this carbon in **30b** was found to be 11.3 ppm downfield of that in **31b**. This suggested that these carbons are in quite different magnetic environments, and since **31b** is presumed to be **BC**, this was considered strong evidence for a **CC** conformation for **30b**. This trend was also observed in the ^{13}C NMR spectra of the hydroperchlorates **32b** and **33b** derived from these amines (see Table XII) where the shift for C(9) in the **CC** salt **32b** occurred downfield of that in the **BC** salt **33b**. Reinforcement for this conclusion could be seen in the reported shifts for this carbon in isomeric amines **30a**, **31a** and **105**, **106** (see Table XI). The chemical shift[106] for C(9) in CC isomer **30a** was downfield of that in **BC** isomer **31a** by 8.1 ppm while the difference in **BC** and **CB** isomers **105** and **106** was only 0.8 ppm (see Table X). Similarly, C(9) for the **CC** salt **32a** (see Table XII) was also downfield by 5.5 ppm from that for the **BC**

TABLE X

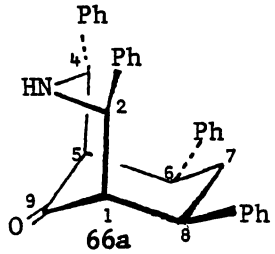
^{13}C NMR[a] CHEMICAL SHIFTS[b] OF ISOMERIC 2,4-DIARYL-7-HETERA-3-AZABICYCLO[3.3.1]NONAN-9-ONES



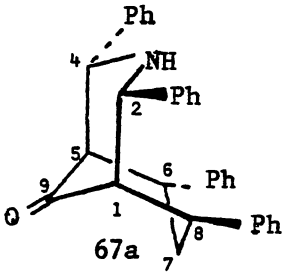
17



18



66a



67a

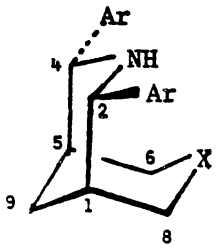
17, 18		
	X	Ar
c.	Se	$\underline{p}$-ClC_6H_4
d.	NCH_2Ph	$\underline{o}$-ClC_6H_4

	C(1,5)	C(2,4)	C(6,8)	C(9)	other
17c[c,d]	51.5	63.8	20.9	212.9	
18c[c,d]	53.9	63.4	29.0	213.4	
17d	50.9	62.1	55.5	212.2	62.5 ($\underline{CH}_2C_6H_5$)
18d	55.2	59.0	58.8	212.0	61.0 ($\underline{CH}_2C_6H_5$)
66a[e]	60.4[f]	59.7[f]	46.2	212.6	24.2 [C(7)]
67a[e]	60.5	63.8	41.2	215.3	38.4 [C(7)]

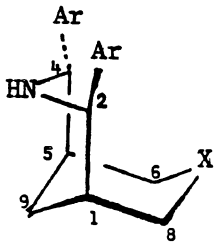
a. Aliphatic and carbonyl regions only.
b. Downfield from $(CH_3)_4Si$ in ppm ($DCCl_3$).
c. Reference 106.
d. Position numbers changed from systematic numbering to aid comparison.
e. Reference 73.
f. Assignment may be reversed.

TABLE XI

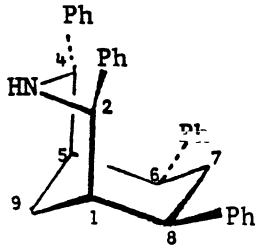
^{13}C NMR[a] CHEMICAL SHIFTS[b] OF ISOMERIC 2,4-DIARYL-7-HETERA-3-AZABICYCLO[3.3.1]NONANES



30

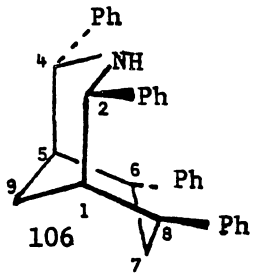


31



105

30, 31		
	X	Ar
a.	Se	p-ClC_6H_4
b.	NCH_2Ph	o-ClC_6H_4



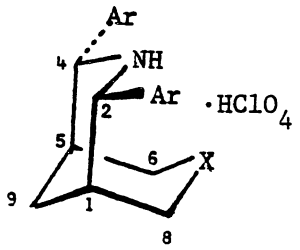
106

	C(1,5)	C(2,4)	C(6,8)	C(9)	other
30a[c,d]	30.4	64.0	17.7	35.0	
31a[c,d]	33.8	60.9	25.1	26.9	
30b	31.5	61.6	54.9	35.9	64.3 ($\underline{CH_2}C_6H_5$)
31b	36.1	56.1	58.8	24.6	62.9 ($\underline{CH_2}C_6H_5$)
105[e]	42.5	55.9	45.7	28.5	24.5 [C(7)]
106[e]	38.2	64.3	41.5	30.3	36.1 [C(7)]

a. Aliphatic region only.
b. Downfield from $(CH_3)_4Si$ in ppm ($DCCl_3$).
c. Reference 106.
d. Position numbers changed from systematic numbering to aid comparison.
e. Reference 73.

TABLE XII

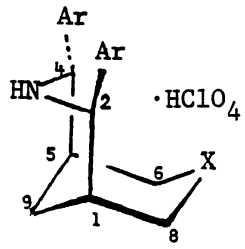
^{13}C NMR[a] CHEMICAL SHIFTS[b] OF ISOMERIC 2,4-DIARYL-7-HETERA-3-AZA-BICYCLO[3.3.1]NONANE HYDROPERCHLORATES



30

32, 33

	X	Ar
a.	Se	p-ClC_6H_4
b.	NCH_2Ph	o-ClC_6H_4

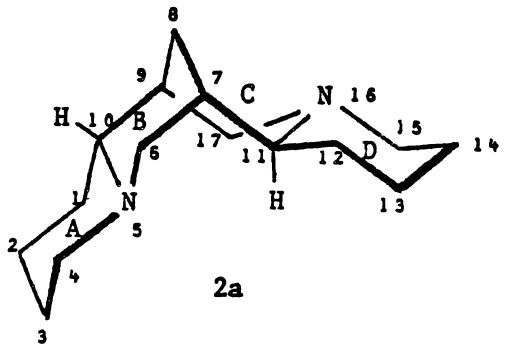


31

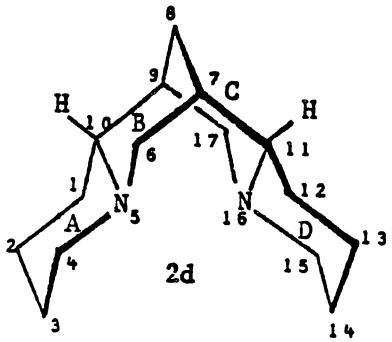
	C(1,5)	C(2,4)	C(6,8)	C(9)	other
32a[c,d]	29.7	63.7	17.7	32.0	
33a[c,d]	31.1	60.6	23.5	26.5	
32b	29.8	60.8	53.0	31.4	60.3 ($\underline{C}H_2C_6H_5$)
33b	33.7	56.9	55.9	24.5	60.9 ($\underline{C}H_2C_6H_5$)

a. Aliphatic region only.
b. Downfield from $(CH_3)_4Si$ in ppm (DMSO-$\underline{d}_6$).
c. Reference 106.
d. Position numbers changed from systematic numbering to aid comparison.

salt **33a**. Spartiene (**2a**) and α-isospartiene (**2e**) are also isomeric systems with the two center rings in **BC** and **CC** conformations, respectively. The shift for the bridge carbon C(8) in **BC** spartiene is reported[20] to be upfield of that in **CC** α-isospartiene by 9.1 ppm. Furthermore, the relative ^{13}C NMR shifts of this carbon in **2a** (**BC**, 27.6 ppm) and **2e** (**CC**, 36.7 ppm) were quite similar to those observed in the isomeric bispidines **30b** (**CC**, 35.9 ppm) and **31b** (**CB**, 24.6 ppm).



2a

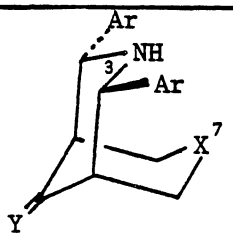


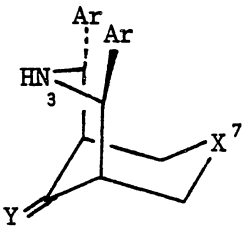
2d

Additional evidence could observed in the ^{15}N NMR spectra of isomeric ketones **17c, 18c** and isomeric amines **30b, 31b**. The ^{15}N NMR spectral data are given in Table XIII. It was noted that upon reduction of **BC 18d** to amine **BC 31b**, the peak for N(3) was shifted upfield by 7.7 ppm. The greater steric interactions between a methylene group at C(9), as opposed to a carbonyl, with N(3) could account for this upfield shift. In addition, the position of N(7) was only shifted upfield by 0.2 ppm. This was not unexpected as N(7) in the chair ring suffers no transannular steric interaction with the group at C(9), while N(3) in the boat ring does suffer this type of interaction. Upon reduction of

TABLE XIII

$^{15}N^{a}$ NMR CHEMICAL SHIFTS[b] OF ISOMERIC 3-HETERA-7-AZA-BICYCLO[3.3.1]NONANE DERIVATIVES





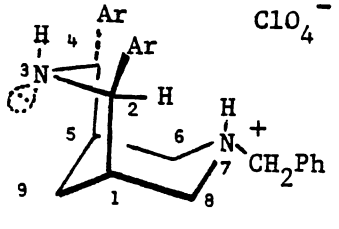
	X	Y	Ar			X	Y	Ar	
17d.	NCH_2Ph	O	o-ClC_6H_4		18d.	NCH_2Ph	O	o-ClC_6H_4	
30b.	NCH_2Ph	H_2	o-ClC_6H_4		31b.	NCH_2Ph	H_2	o-ClC_6H_4	
32b.	NCH_2Ph	H_2	o-ClC_6H_4	($HClO_4$)	33b.	NCH_2Ph	H_2	o-ClC_6H_4	($HClO_4$)
17c.	Se	O	p-ClC_6H_4		18c.	Se	O	p-ClC_6H_4	
30a.	Se	H_2	p-ClC_6H_4		31a.	Se	H_2	p-ClC_6H_4	
32a.	Se	H_2	p-ClC_6H_4	($HClO_4$)	33a.	Se	H_2	p-ClC_6H_4	($HClO_4$)

	N(3)	N(7)		N(3)	N(7)
17d	54.4	46.9	**18d**	58.2	38.3
30b	53.8	47.4	**31b**	50.5	38.1
32b	52.6[c]	50.5[c]	**33b**	54.6	38.3
17c[d,e]	44.2	-	**18c**[d,e]	62.8	-
30a[d,e]	50.5	-	**31a**[d,e]	55.4	-
32a[d,e]	49.6	-	**33a**[d,e]	57.7	-

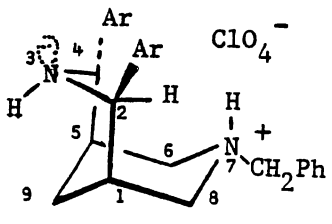
a. In ppm downfield from NH_3(l) using 8.0 M $^{15}NH_4NO_3$ (19.73 ppm) as a secondary reference. Samples run at ambient temperature.
b. Amines **17**, **18**, **30**, and **31** run in $DCCl_3$. Salts **32**, **33** run in DMSO-d_6.
c. Assignments may be reversed.
d. Reference 106.
e. Position numbers changed from systematic numbering to aid comparison.

17d to **30b**, however, both N(3) and N(7) experienced only small changes in chemical shift (0.6 ppm upfield and 0.5 ppm downfield, respectively). Thus, these nitrogens apparently experienced only small changes in their magnetic environment. This was thought to be rather strong evidence that: (1) there was no substantial change in the conformation of the ring system upon reduction; and (2) nitrogens N(3) and N(7) suffer no significant transannular steric interaction with the group at C(9). A **CC** conformation for ketone **17d** and amine **31b** best explained these observations.

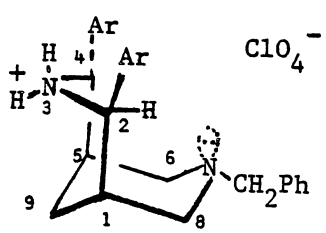
A rather surprising observation was made in the ^{15}N NMR spectrum of hydroperchlorate **33b**. The crystal structure for this compound clearly indicated that the tertiary nitrogen N(7) was protonated in the solid state. The ^{15}N NMR spectrum, however, affords a chemical shift for N(7) that is identical to that for N(7) in ketone **18d** and almost identical (only 0.2 ppm downfield) to that observed for this nitrogen in the amine precurser **31b**. On the other hand, the peak for N(3) is shifted downfield by 4.1 ppm upon protonation (50.5 ppm in amine **31b** versus 54.6 ppm in salt **33b**). This suggests that, in solution, secondary nitrogen N(3) is protonated while N(7) exists in an unprotonated state. For



33b



33b'



33b''

Ar = o-ClC_6H_4

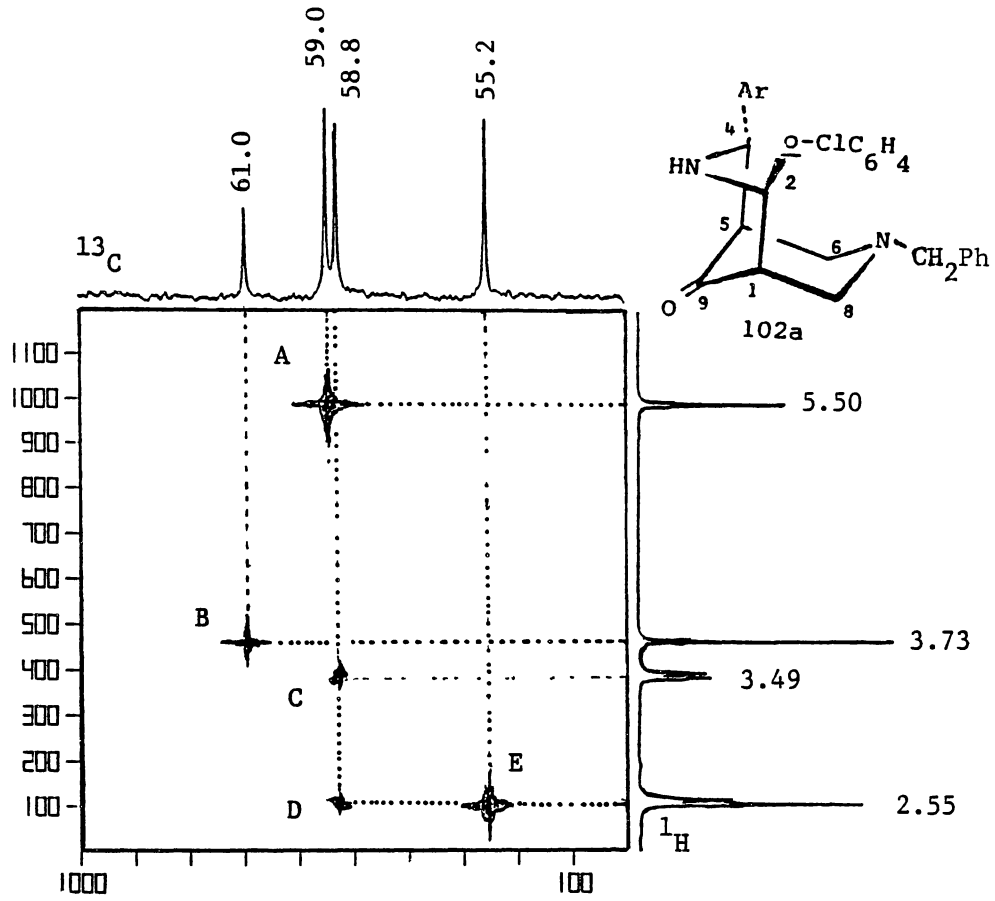
comparison, N(3) is shifted downfield by 3.3 ppm upon protonation in going from the selenium analog **31a** to **33a.**

Additional evidence that protonation had occurred in solution at the secondary nitrogen rather than at the tertiary nitrogen in salt **33b** was the observation of coupling between an amino proton H(3) and the vicinal protons H(2,4) in the proton NMR. In addition to peaks readily assignable to other aliphatic and aromatic protons, this spectrum exhibited a large doublet (2 H, J = 8.3 Hz) at δ 5.00, which was assigned to H(2,4); and two broad singlets (1 H each) at δ 8.10 and δ 9.84, assigned to the amino protons. Selective decoupling of the signal at δ8.10 resulted in the collapse of the signal at δ 5.00 to a singlet, but no detectable change in the broad singlet at δ 9.84. Irradiation of the broad singlet at δ 9.84 resulted in no detectable change in the peaks at δ8.10 and δ 5.00.

Two possible structures that are consistent with the data observed in the ^{1}H NMR spectrum are **33b'** and **33b"**. The size of the coupling constant at δ 5.00 is suggestive of an axial N-H bond. However, as previously mentioned, the crystal structure of this salt clearly shows that H(3) is in an equatorial position with protonation to give the salt having occurred at N(7) (as in structure **33b**). It would seem unlikely an axial N-H bond (as in **33b'**) would predominate in solution (in spite of atomic inversion at nitrogen) when an equatorial N-H bond is observed in the solid state, therefore structure **33b'** did not seem tenable. In contrast, structure **33b"** fits the observations in the ^{1}H NMR and ^{15}N NMR spectra quite well. The difference in structure in solution (**33b"**) compared to that found in the solid state (**33b**) might arise from the enhanced solvation of the positive charge by the polar solvent (DMSO)

that is possible when the charge is at the peripheral nitrogen [N(3)] (i.e. **33b"**). We have no explanation as to why tautomer **33b** is the observed species in the solid state, other than to note that in this tautomer, the positive charge is more effectively "masked" in the cavity between the rings of the molecule and this might be a factor in the packing forces operating in the solid state.

Two-dimensional heteronuclear-correlated (HETCOR) $\delta(^{13}C)$-$\delta(^{1}H)$ NMR spectra[35] were obtained for the aliphatic carbons and protons in **17d, 18d, 30b, 31b, 32b** and **33b.** These HETCOR NMR spectra supply direct information regarding the connectivities of protons and carbons, thereby making peak assignments in the ^{13}C and ^{1}H NMR spectra much more certain. The HETCOR spectrum **18d** (Figure 1) will serve as an example. The ^{13}C NMR spectrum of the region of interest (52-65 ppm) is plotted along the horizontal axis of the HETCOR spectrum while the appropriate region (δ2.1-6.0) of the proton spectrum is plotted along the vertical axis. A vertical line taken from a peak on the HETCOR spectrum established which peak in the carbon spectrum correlates with a given peak in the HETCOR while a horizontal line established the correlation to a peak in the proton spectrum. Thus, in the HETCOR spectrum of **18d,** the peak labelled "A" correlates with the carbon peak at 59.0 ppm and with the proton peak at δ5.50. This indicates that the proton from which the signal at δ5.50 arises is bonded to the carbon giving the peak at 59.0 ppm. In a similar fashion, the overlapping singlet and doublet at δ2.55 in the proton spectrum were easily determined to arise from the axial (upfield) protons connected to the carbons responsible for the ^{13}C signals at 58.8 [C(6,8)] and 55.2 ppm [C(1,5)].



HETCOR Peak	^{13}C (ppm)	^1H (δ)	Position Assignment
A	59.0	5.50	2,4
B	61.0	3.73	$PhCH_2$
C	58.8	3.49	6,8 (eq)
D	58.8	2.55	6,8 (ax)
E	55.2	2.55	1,5

Figure 1. HETCOR NMR Spectrum of 18d

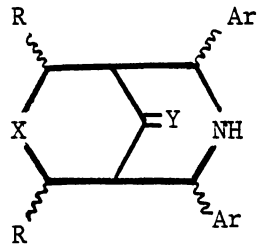
Proton NMR has been effectively employed to determine the conformational preferences of heterocyclic[46] and carbocylic[66,74] bicyclo-[3.3.1]nonane derivatives, usually by examination of the coupling constants. Unfortunately, compounds **17d, 18d, 30b, 31b, 32b** and **33b** all afforded proton spectra characterized by relatively broad peaks for all ring protons. This broadening effectively obscured most vicinal coupling constants. However, the geminal couplings were usually quite pronounced, typically on the order of 10-12 Hz.

One interesting aspect of the proton spectra for **17d, 18d, 30b** and **31b** was the observation that the signals for the amino protons in **18d** and **31b** were upfield relative to those in **17d** and **30b** (δ 1.61 and 1.18 versus 4.70 and 4.44, see Table XIV). Moreover, these peaks in amines (**30b** and **31b**) with a 9-methylene group, were upfield of those in the ketones (**17d** and **18d**) from which they were derived. This is likely a manifestation of the greater steric interaction between the group at the 9-position and the N-H in the structures with the aryl-substituted piperidine ring in the boat configuration (as opposed to when this ring is in the chair), as well as the greater transannular interaction of the 9-methylene protons with the N-H group over that of the ketone. This trend may be of some diagnostic use in determining the configurations of stereochemically-fixed piperidine rings in 3-hetera-7-aza- or 7-azabicyclo[3.3.1]nonane derivatives as it could also be observed in the shifts of ketone isomers **17c, 18c,** amine isomers **30a, 31a,** and in other systems (Table XIV).

Ketone **28d** has been reported to exist predominantly in the **CC** conformation in solution.[32] Our data did not afford complete agreement

TABLE XIV

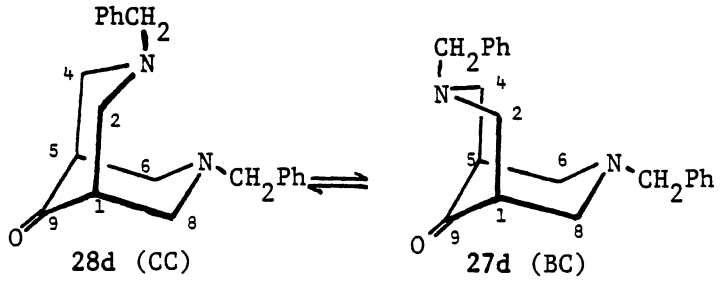
^{1}H NMR CHEMICAL SHIFTS[a] FOR N-H IN SELECTED 3-HETERA-7-AZA-BICYCLO[3.3.1]NONANE DERIVATIVES



	X	Y	R	Ar	Boat ring N-H (δ)	Chair ring N-H (δ)
17b[b]	O	O	H	o-ClC_6H_4		2.31
17c[c]	Se	O	H	p-ClC_6H_4	-	3.12
17d	$NCH_2C_6H_5$	O	H	o-ClC_6H_4	-	4.70
18c[c]	Se	O	H	p-ClC_6H_4	1.70	-
18d	$NCH_2C_6H_5$	O	H	o-ClC_6H_4	1.61	-
30a[c]	Se	H_2	H	p-ClC_6H_4	-	2.59
30b	$NCH_2C_6H_5$	H_2	H	o-ClC_6H_4	-	4.40
31b	$NCH_2C_6H_5$	H_2	H	o-ClC_6H_4	1.18	-
31a[c]	Se	H_2	H	p-ClC_6H_4	1.74	-
66b[d]	S	O	C_6H_5	C_6H_5	1.50	-
137[e]	NH	H_2	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	1.04	1.70

a. In ppm downfield from $(CH_3)_4Si$. All samples run in $DCCl_3$.
b. Reference 5.
c. Reference 106.
d. Reference 63.
e. Reference 73.

with this conclusion. The ^{13}C NMR spectrum of **28d** had only three aliphatic peaks (46.7, 58.0 and 61.1 ppm, see Table XV) assignable to the bridgehead [C(1,5)], ring methylenes [C(2,4,6,8)] and benzylic carbons. The ^{15}N NMR spectrum exhibited only one peak (39.2 ppm). However, there was nonequivalence visible in the upfield signal of the ^{1}H NMR. This signal (at δ 2.76 and 2.78) was two doublets [J = 10.5 and 10.7 Hz, 4 H, assigned to H(2,4,6,8)ax]. The downfield signal at δ 3.00 (4 H) was a broadened doublet (J = 10.7 Hz) with no fine structure. The upfield signals did not display the classic symmetry of an AB quartet. Rather, the relative peak heights of the two upfield doublets suggested that the overall spin system for the peaks at δ 2.76, 2.78 and 3.00 consisted of two separate upfield AB quartets with the downfield signals being nearly coincident. This might indicate the substantial contribution of a **BC** conformer. As discussed in the first chapter, labile 3,7-diazabicyclo[3.3.1]nonan-9-ones often exhibit **BC** $\rightleftarrows$ **CB** or **CC** $\rightleftarrows$ **CB** equilibria in solution.

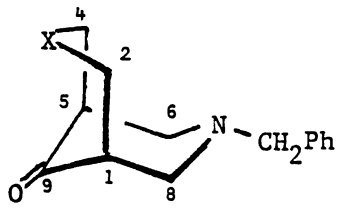


28d (CC) 27d (BC)

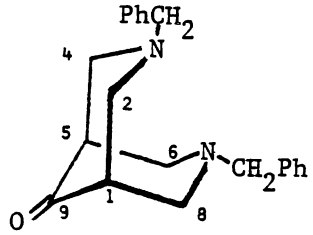
Ketones **27a,b** are known to exist in the **BC** conformation in the solid state and predominantly as the **BC** in solution.[13,14,107] HETCOR NMR spectra of these compounds exhibited a rather interesting anomaly. While the carbons alpha to selenium or sulfur [C(2,4)] afford the most

TABLE XV

^{13}C AND ^{1}H NMR CHEMICAL SHIFTS OF 7-BENZYL-3-HETERA-7-AZABICYCLO[3.3.1]NONAN-9-ONES[a,b]



27a. X = S
b. X = Se

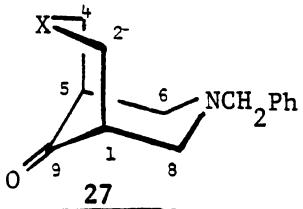


28d

	27a	27b	28d
C(1,5)	47.1 ppm	46.2 ppm	46.7 ppm
C(2,4)	34.8	25.5	58.0[c]
C(6,8)	58.4	59.0	58.0[c]
C(9)	212.8	213.9	214.0
$C_6H_5\underline{C}H_2$	61.4	61.5	61.1
H(1,5)	2.80	2.73	2.52
H(2,4)ax	3.12	3.23	2.76[d]
H(2,4)eq	3.23	3.23	3.00
H(6,8)ax	2.71	2.71	2.78[d]
H(6,8)eq	3.08	3.10	3.00
$C_6H_5\underline{C}H_2$	3.57	3.58	3.53

a. All samples run in $DCCl_3$. See Chapter III for coupling constants.
b. Proton spectrum correlated with carbon spectrum in 27a,b via HETCOR NMR spectrum.
c. One peak for C(2,4,6,8)
d. Assignment may be reversed.

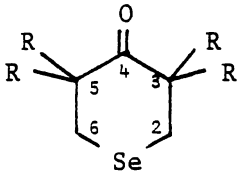
upfield peaks in the ^{13}C NMR spectra of these compounds, the protons (both axial and equatorial) alpha to S or Se [H(2,4)ax and H(2,4)eq] are downfield of the protons alpha to nitrogen [H(6,8)ax and H(6,8)eq] in the ^{1}H spectrum. These observations in the ^{1}H NMR spectra are the opposite of what simple electronegativity or electron-cloud polarization arguments would predict. As a simple experiment to gather information concerning the ^{1}H and ^{13}C NMR shielding/deshielding characteristics of the selenium atom, the tetradeuterated species **16h** was synthesized from **16d.** The ^{1}H and fully-decoupled ^{13}C NMR spectra of the deuterated compound **16h** were then compared with the spectra of **16d.** Upon deuteration, the downfield ^{13}C peak (43.6 ppm) became a multiplet, thus assuring that the upfield signal (19.2 ppm) could be assigned to the carbons alpha to selenium [C(2,6)]. The proton spectrum, on the other hand, indicated the loss of the upfield triplet (δ2.88) upon deuteration and the collapse of the downfield triplet (δ3.00) to a singlet. Thus, H(2,6) were determined to be downfield of H(3,5). We currently have no rationalization for the dichtonomous behavior observed in the proton and carbon-13 NMR spectra.



27

a. X = S

b. X = Se

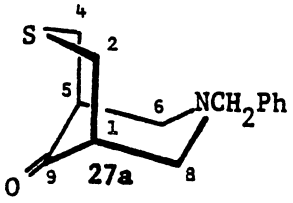


16

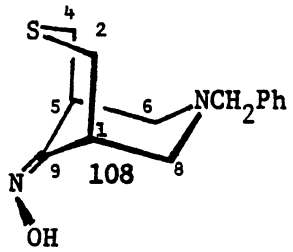
c. R = H

h. R = D

The aliphatic ^{13}C NMR data for oxime **108** are presented in Table XVI. Substitution of the carbonyl with the ketoxime functionality introduced an element of asymmetry into the ring system as could be easily seen by the increase in the number of aliphatic peaks (seven) in the ^{13}C NMR spectrum of the oxime as compared to the number of such peaks (four) present in the spectrum of the ketone precursor **27a**. ^{13}C NMR spectral data for ketones **16a,c** and their oxime derivatives **109a,b** are given for comparison. Relative to the ^{13}C NMR shifts for the bicyclic-ring carbons of ketone **27a**, nearly all carbons in the bicyclic ring of oxime **108** were shifted upfield. Carbons <u>syn</u> to the



27a

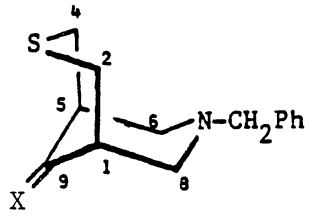


108

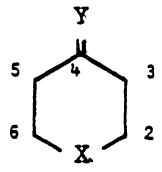
hydroxyl group [C(1,2,8)] were shifted <u>upfield</u> to a greater extent than those <u>anti</u> to this group [C(4,5,6)]. For example, C(1) was shifted upfield by 17.3 ppm while C(5) was only shifted upfield by 10.4 ppm. This effect was also visible, although to a lesser degree, at the ring methylenes. The same trend was observed in comparing the shifts of monocyclic ketones **16a,c** those of their oxime derivatives **109a,b**. The general upfield shift in the oximes was thought to be primarily due to the loss of the inductive and, to some extent, the anisotropic shielding effects of the carbonyl. The greater steric interactions between the hydroxyl group and the <u>syn</u> atoms of the molecule may be invoked to

TABLE XVI

^{13}C NMR[a] CHEMICAL SHIFTS[b] OF N-BENZYL-3-THIA-7-AZABICYCLO-[3.3.1]NONAN-9-ONE OXIME (108) AND RELATED OXIMES



27a. X = O
108. X = NOH

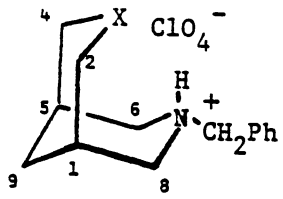


16a. X = CH_2, Y = O
16c. X = S, Y = O
109a. X = S, Y = NOH
109b. X = CH_2, Y = NOH

	syn to OH			anti to OH				
	C(2)	C(1)	C(8)	C(4)	C(5)	C(6)	C(9)	$PhCH_2$
108	34.8	47.1	58.4	34.8	47.1	58.4	212.8	61.3
108	32.5	29.9	58.4	34.1	36.7	58.5	160.9	61.7

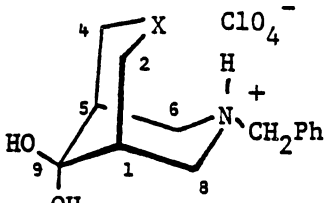
	C(2)	C(3)	C(6)	C(5)	C(4)
16c	30.0	44.0	30.0	44.0	205.8
109a	29.7	26.7	28.2	33.8	157.9
16a[c]	26.8	40.7	26.8	40.7	211.3
109b[d]	26.1	27.5	26.3	32.3	159.4

a. Aliphatic region only.
b. Downfield from $(CH_3)_4Si$ in ppm ($DCCl_3$).
c. Reference 89.
d. Reference 21.



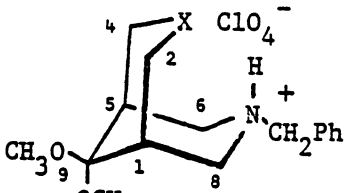
29

a. X = S
b. X = Se
d. X = NCH_2Ph



70

a. X = S
b. X = Se
d. X = NCH_2Ph



102

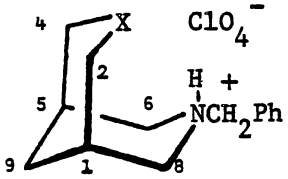
a. X = S
b X = NCH_2Ph

explain the greater upfield shifts of these atoms. The ^{15}N NMR spectrum of oxime **108** indicated that the benzylic nitrogen also experienced a slight upfield shift of relative to the ketone (36.3 versus 37.4 ppm, respectively).

From spectroscopic and X-ray data, it was concluded that salts **29d**, **70d**, and **102a,b** adopt a **CC** conformation in the solid state as well as in solution. As discussed in the first chapter, the salts of 3-hetera-7-azabicyclo[3.3.1]nonane derivatives exist primarily in this conformation in the absence of structural features that fix the stereochemistry in a boat form. The two-fold structural symmetry in the diaza ring systems was quite obvious upon examination of the ^{13}C NMR spectra (see Table XVII). Salt **29d** possessed, in its ^{13}C NMR spectrum, only four aliphatic peaks which were assigned to the bridge methylene [C(9)], bridgehead methines [C(1,5)], ring methylenes [C(2,4,6,8)] and benzylic carbons. Similarly, the spectrum of diol **70b** afforded only four aliphatic carbon peaks while that of ketal **102b** afforded a very similar spectrum but with the addition of the signal for the methoxy groups. The ^{15}N NMR spectra of the 3,7-diaza-salts **29d**, **70d**, **102b** all exhibited only one peak with shifts in the 52.5-54.6 ppm range which were quite similar to those exhibited by the 3-thia-7-aza- and

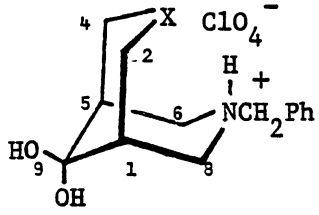
TABLE XVII

^{13}C NMR[a] CHEMICAL SHIFTS[b] OF N-BENZYL-3-HETERA-7-AZABICYCLO-[3.3.1]NONANE HYDROPERCHLORATE DERIVATIVES



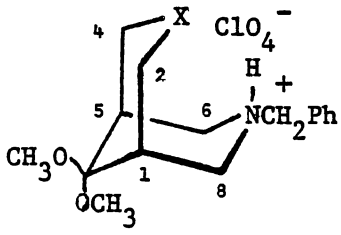
29

a. X = S
b. X = Se
c. X = NCH_2Ph



70

a. X = S
b. X = Se
c. X = NCH_2Ph



102

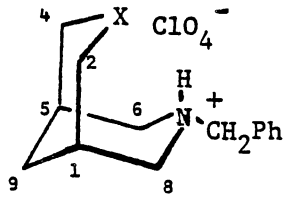
a. X = S
b. X = NCH_2Ph

	C(1,5)	C(2,4)	C(6,8)	C(9)	$\underline{C}H_3O$	Ph$\underline{C}H_2$
29a	24.9	29.9	58.5	27.7	-	63.1
29d	27.4	----	54.2 ---	29.5	-	60.4
70a[e]	37.3	29.0	54.7	88.5	-	57.9
70d	33.2	----	53.8 ---	89.2	-	59.6
102a	33.0	----	53.8 ---	95.6	46.9	59.6
102b	32.2	28.8	54.5	95.1	46.5[c] 47.0[d]	60.2

a. Aliphatic region only.
b. Downfield from $(CH_3)_4Si$ in ppm (DMSO-$\underline{d}_6$).
c. Sulfur side (assignment uncertain).
d. Nitrogen side (assignment uncertain).
e. Reference 14.

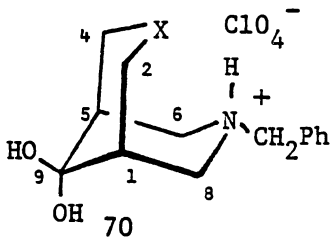
TABLE XVIII

^{15}N NMR CHEMICAL SHIFTS[a] OF N-BENZYL-3-HETERA-7-AZABICYCLO-[3.3.1]NONANE HYDROPERCHLORATE DERIVATIVES



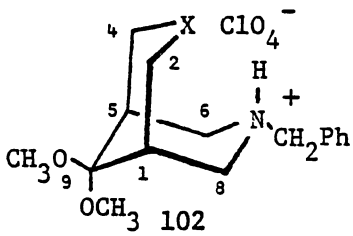
29

a. X = S
b. X = Se
d. X = NCH_2Ph



70

a. X = S
b. X = Se
d. X = NCH_2Ph



102

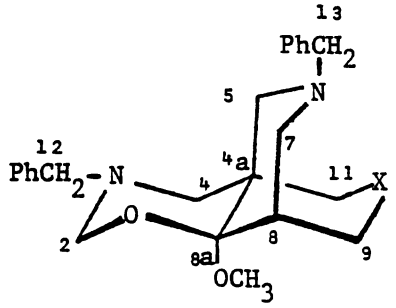
a. X = S
b X = NCH_2Ph

	$\delta(^{15}N)$	
29a[b]	54.2	[N(7)]
29b[c]	51.6	[N(7)]
29d	54.6	[N(3,7)]
70a[b]	54.0	[N(7)]
70b[c]	51.6	[N(7)]
70d	52.9	[N(3,7)]
102b	52.5	[N(3,7)]
102a	53.5	[N(7)]

a. Downfield from NH_3(l) in ppm. All samples run in DMSO-d_6 using $^{15}NH_4NO_3$ (19.73 ppm) as a secondary reference.
b. Shifts for **29a** and **70b** from reference 14.
c. Shifts for **29b** and **70b** from reference 107.

3-selena-7-aza- salts **29a,b,d** and **70a,b** (see Table XVIII). These data were in agreement with what was expected for such compounds with the **CC** conformation. A crystal structure of ketal **102b** confirmed this conclusion for the solid state. The 3-thia-7-aza- ketal **102a** also was determined to be in this conformation based upon the analysis of the ^{13}C NMR spectral data. The analogous diol **70d** and 9-methylene derivative **29b** have previously been proven to exist as **CC** conformers in the solid state as well as in solution.[14,15]

The structures of the tricyclic ketals **103a,b** and hydroperchlorate **103c** were elucidated from the fully decoupled and off-resonance ^{13}C NMR and the ^{1}H NMR spectra. $\delta(^{1}H)$-$\delta(^{13}C)$ HETCOR NMR spectra proved to be indespensible in the interpretation and complete assignment of the ^{13}C and ^{1}H NMR spectra. These HETCOR spectra are shown in Figures 2 and 3. The ^{13}C NMR data for **103a,b,c** are given in Table XIX while the ^{1}H NMR data for these tricyclic ketals are given in Table XX.



103

a. X = S

b. X = Se

c. X = S $\cdot 2HClO_4$

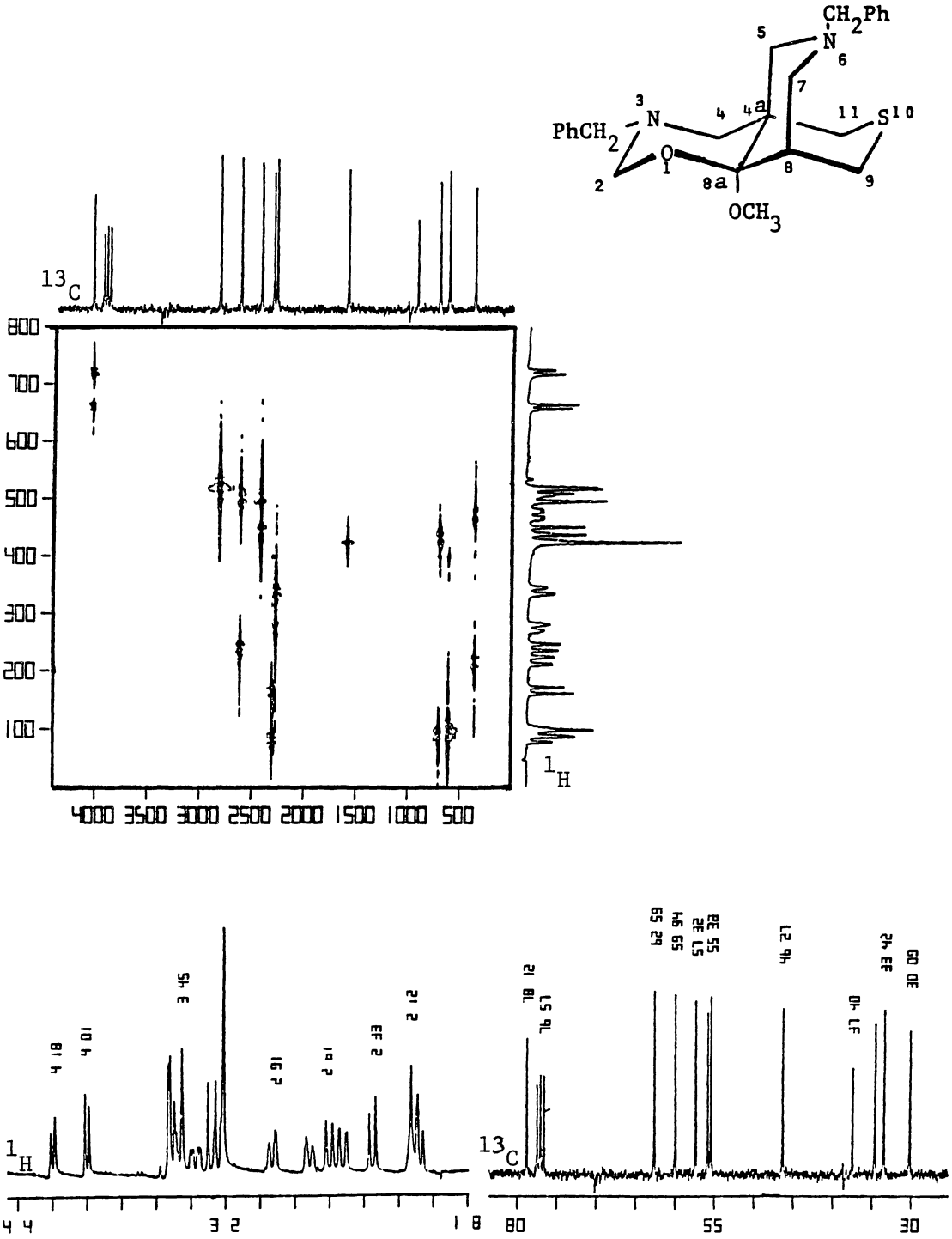


Figure 2. HETCOR NMR spectrum of **103a**.

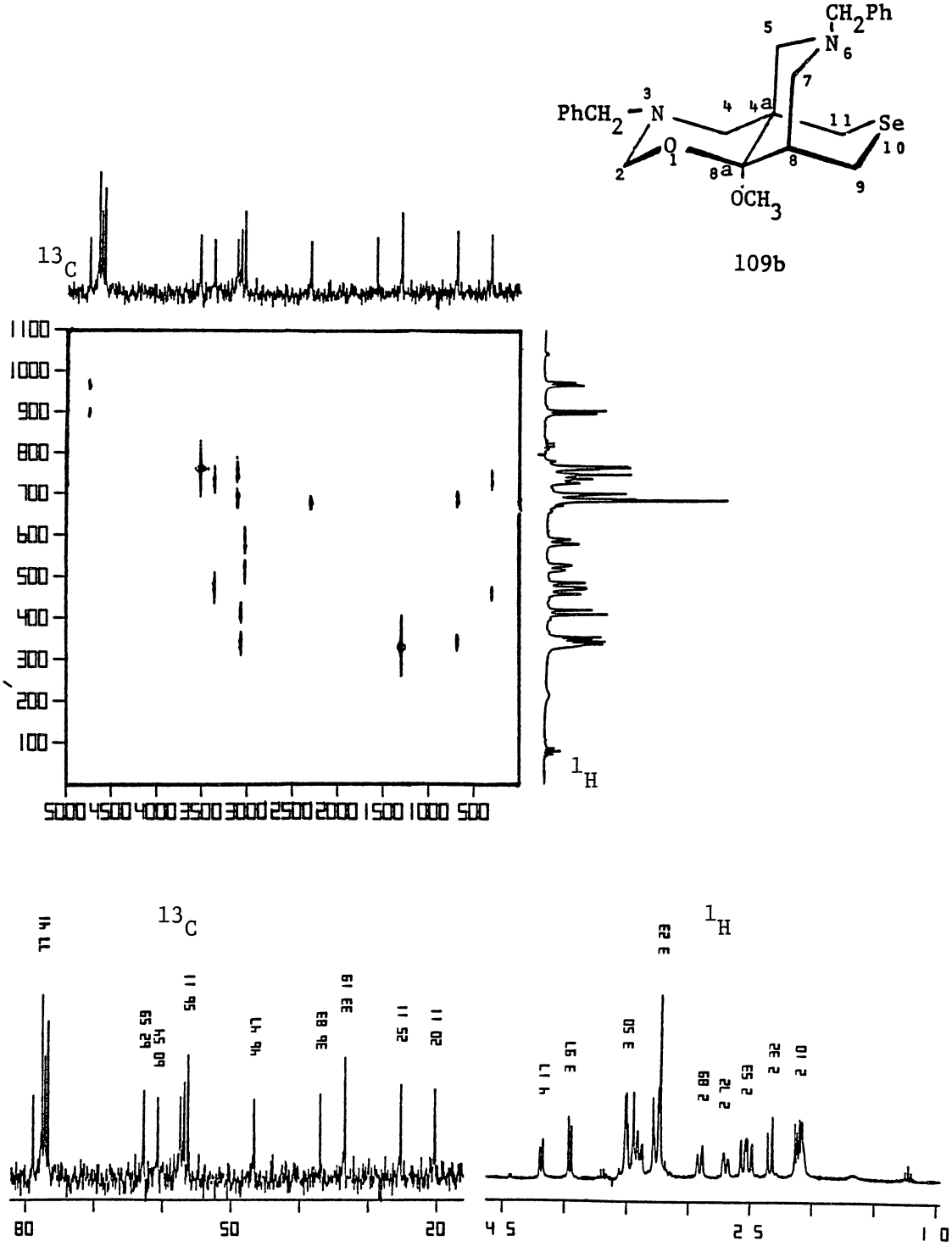
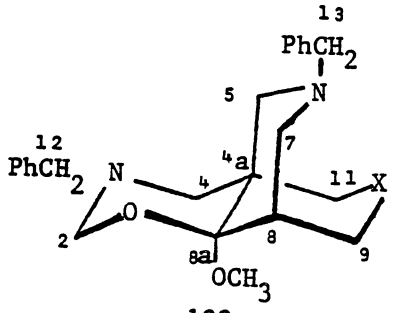


Figure 3. HETCOR NMR spectrum of **103b.**

TABLE XIX

^{13}C NMR CHEMICAL SHIFTS[a,b] FOR **103a,b,c**



103

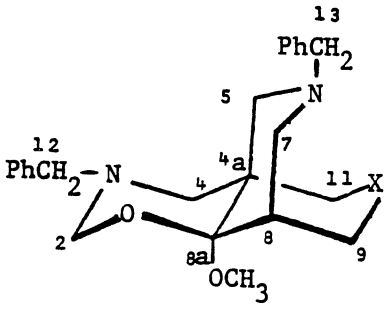
a. X = S
b. X = Se
c. X = S $\cdot 2HClO_4$

	103a	**103b**	**103c**
C(2)	78.8 (t)	78.8 (t)	78.0 (t)
C(4)	55.4 (t)	56.1 (t)	52.3 (t)
C(4a)	37.8 (s)	36.8 (s)	37.4 (s)
C(5)	55.8 (t)	56.7 (t)	55.4 (t)
C(7)	34.6 (t)	25.1 (t)	31.8 (t)
C(8)	33.3 (d)	33.2 (d)	31.3 (d)
C(8a)	96.9 (s)	97.6 (s)	93.7 (s)
C(9)	30.0 (t)	20.1 (t)	28.3 (t)
C(11)	34.6 (t)	25.1 (t)	31.8 (t)
C(12)	59.9 (t)	60.5 (t)	56.2 (t)
C(13)	62.6 (t)	62.6 (t)	60.2 (t)
CH_3O	46.3 (q)	46.5 (q)	46.4 (t)

a. In ppm from $(CH_3)_4Si$. **103a,b** run in $DCCl_3$. **103c** run in $DMSOd_6$. Aliphatic carbons only.
b. Letters in parentheses indicate off-resonance multiplicities: s=singlet, d=doublet, t=triplet, q=quartet.

TABLE XX

^{1}H NMR CHEMICAL SHIFTS[a] OF **103a,b,c**



103

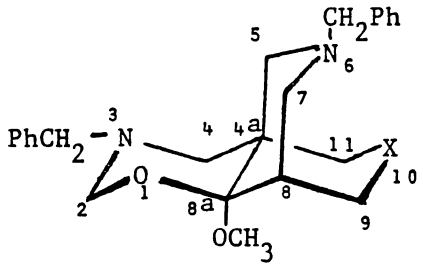
a. X = S
b. X = Se
c. X = S $\cdot 2HClO_4$

	103a	**103b**	**103c**
H(2)ax	4.01	3.97	4.00
H(2)eq	4.21	4.21	4.24
H(4)ax	2.72	2.72	2.17
H(4)eq	2.94	2.93	2.35
H(5)ax	2.12	2.11	3.32
H(5)eq	2.36	2.37	3.57
H(7)ax	3.28	3.29	3.46
H(7)eq	3.49	3.51	3.79
H(8)	2.14	2.09	2.64
H(9)ax	2.54	2.53	2.76
H(9)eq	3.38	3.47	3.22
H(11)ax	2.08	2.13	2.43
H(11)eq	3.25	3.29	3.00
H(12)	2.61	2.58	4.19
H(12)	3.46	3.44	4.24
H(13)	3.54	3.53	4.40
H(13)	-	-	4.54
CH_3O	3.22	3.25	3.18

a. Proton NMR assignments as based on HETCOR spectrum. **103a,b** run in $DCCl_3$. **103c** run in $DMSO\underline{d}_6$.

As this was a rather involved procedure, the selenium ketal **102b** will serve as an example of the methodology used in making the ^{1}H and ^{13}C NMR assignments. The off-resonance singlet at 97.7 ppm had a chemical shift quite similar to that observed in other ketals (e.g., see positions for C(9) in ketals **102a,b**, Table XVII). Thus, this peak was assigned to C(8a). The off-resonance quartet at 46.5 ppm was assigned to the methoxy carbon while the singlet at 36.8 ppm and the doublet at 33.2 ppm were assigned to C(4a) and C(8), respectively. All remaining aliphatic peaks were triplets in the off-resonance spectrum (i.e. methylenes). The downfield peak at 78.7 ppm was presumed to be that of C(2), as this carbon is bonded with the electron-withdrawing oxygen and nitrogen.

The upfield peaks at 20.1 and 25.1 ppm were assigned to the carbons alpha to selenium [C(7,9)] due to the tendency of selenium to shield attached carbons and thus result in upfield chemical shifts. The HETCOR spectrum (Figure 3) indicated that the ^{13}C peak at 20.1 ppm correlated with an AB quartet with an upfield doublet at δ 2.53 and a downfield doublet that was part of the complex pattern centered at δ 3.50. Careful comparison of the coupling constant (^{2}J = 11 Hz) of the upfield doublet with various peaks in the downfield multiplet permitted an exact assignment for the shift (δ3.47) of the downfield doublet. A similar treatment of the proton AB quartet associated with the ^{13}C peak at 25.1 ppm permitted assignment of the ^{1}H signals at δ2.13 and δ3.29 to the protons attached to this carbon. It was presumed that the axial protons of a given methylene group would be upfield of the equatorial proton. Examination of a model (ball and stick) indicates that H(11)ax is gauche to both C(8a) and C(4) while H(9)ax is gauche to only C(8a). It could



a. X = S

b. X = Se

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therefore be expected that H(11)ax would be upfield of H(9)ax. A similar argument can be made for H(11)eq [gauche to both C(4) and C(5)] and H(9)eq [gauche to C(7)]. The ^{1}H shift of the axial proton (δ2.13) correlated with the 25.1 ppm carbon-13 signal is at higher field of that for the axial proton (δ 2.53) correlated with the ^{13}C NMR signal at 20.1 ppm. The same was found to be true in the case of the equatorial protons associated with these carbons (δ3.29 and δ3.47, respectively). Thus the upfield axial proton was assigned to H(11)ax, the upfield equatorial proton signal to H(11)eq and the carbon peak at 25.11 ppm to C(11). This meant that the ^{1}H signals at δ2.53 and 3.47 were assignable to H(9)ax and H(9)eq, respectively, with the carbon peak at 20.1 being assigned to C(9).

The five remaining methylene carbons ^{13}C peaks (56.1, 57.3, 56.7, 60.5, 62.6 ppm) were all assigned to carbons alpha to nitrogen [C(4,5,7,12,13)]. The two benzylic methylenes [C(12,13)] could be assigned to the two downfield peaks (60.5, 62.6 ppm) due to the anisotropic deshielding from the aromatic rings these carbons would experience. The HETCOR spectrum indicated that the benzylic protons

associated with the 60.5 ppm carbon were diastereotopic, giving an AB quartet with the upfield doublet at δ 2.58 and the downfield doublet at δ3.44. The coupling constant for each doublet was 11 Hz. The benzylic protons associated with the 62.6 ppm carbon signal are apparently identical or very nearly so. A small (4 Hz) splitting of this peak (δ 3.53) is observable in the proton spectrum but the HETCOR spectrum indicates no other ^{1}H NMR peaks coupled to this proton signal. As the molecular structure is inherently chiral, this <u>may</u> be the separate signals for what should be diastereotopic protons. It is not apparent from examining a model (ball and stick) which set of benzylic protons should exhibit the greatest degree of nonequivalence. The peak at 60.5 ppm was tentatively assigned to C(12) as the nitrogen adjacent to this carbon experiences two upfield-shifting γ-<u>gauche</u> interactions with C(9) and C(11) which might result in an upfield shift for this carbon. However, this assignment is debatable.

The carbon-13 peaks at 56.1, 56.7 and 57.3 ppm remain to be assigned. The upfield signal was assigned to C(4) as this carbon has <u>gauche</u> interactions with two C-O bonds while both C(5) and C(7) are <u>gauche</u> to one C-C and one C-O bond. The greater shielding of the <u>gauche</u> interactions with the two C-O bonds could result in a greater upfield shift than the the <u>gauche</u> interaction induced by a C-C and C-O bond. The assignments for C(5) and C(7) were then made on similar criteria as the assignments of C(9) and C(11). As the relative stereochemistry about C(8a) (i.e., the orientation of the methoxy group relative to the thiane ring or the piperidine ring) could not be deduced from the NMR analysis for either **103a** or **103b**, these ketals were submitted for crystallographic analysis.

Single Crystal X-ray Diffraction Crystallography

Ketone **18d**, isomeric salts **32b**, **33b**, dimethoxy ketal **102b**, and tricyclic ketal **103b** were submitted to Dr. Elizabeth M. Holt (Dept. of Chemistry, Oklahoma State University) for crystallographic analysis while tricyclic ketal **103a** was submitted to Dr. Dick van der Helm (Dept. of Chemistry, University of Oklahoma) for similar analysis. Crystal data for these compounds are given in Tables XXI and XXII.

Ketone **18d** existed in a boat-chair conformation in the solid state with the N-benzyl-substituted piperidine ring assuming the chair form. The stereochemically-fixed o-chlorophenyl-substituted piperidine ring was in the boat form with the aryl groups in equatorial positions. The proton at N(3) was also in an equatorial position and was not involved in hydrogen bonding. Bond distances and bond angles are given in Tables XXIII and XXIV.

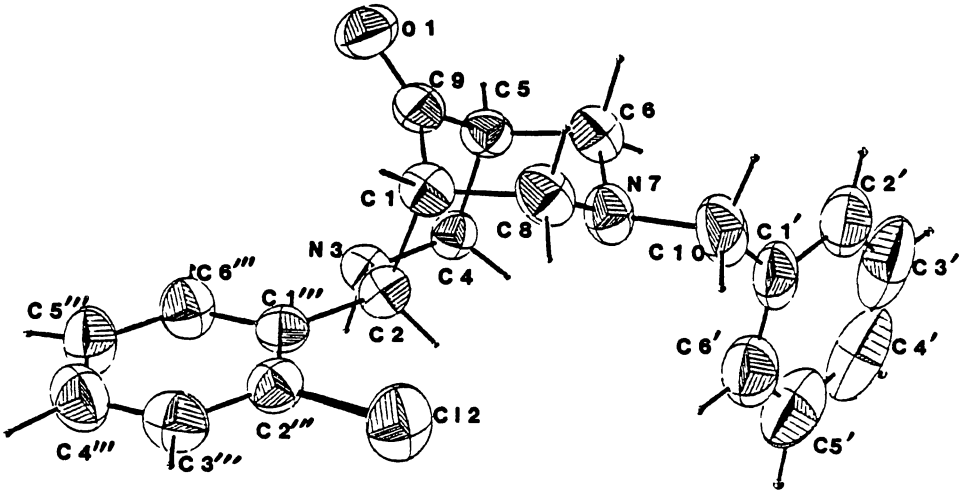


Figure 4. Perspective drawing of **18d**.

TABLE XXI

CRYSTAL DATA FOR **18d**, **32b** AND **33b**

	18d	**32b**[a]	**33b**
Formula	$C_{26}H_{24}Cl_2N_2O$	$C_{26}H_{27}Cl_3N_2O_4$	$C_{26}H_{27}Cl_3N_2O_4$
MWT	451.4	537.87	537.87
a	11.452(3) Å		14.654(10) Å
b	9.951(4) Å		13.036(6) Å
c	113.097(4) Å		13.512(9) Å
	99.05°		90.0°
	66.27(2)°		98.48(5)°
	68.44(2)°		90.0°
Cell Volume	1143 (6) $Å^3$		2552.7(27) $Å^3$
F(000)	472		1120
μMoK_α	3.025 cm^{-1}		3.930 cm^{-1}
λMoK_α	0.71069 Å		0.71069 Å
Calcd. Density	1.311 g/cm^3		1.399 g/cm^3
Z	2		4
Obs. Reflections	3036		1544
R/Rw	4.7%/ -		8.8%/11.0%
Space Group	P_1		$P2_1/n$

a. Analysis of crystal data still in progress.

TABLE XXII

CRYSTAL DATA FOR **102b, 103a** and **103b**

	102b	**103a**[a]	**103b**
Formula	$C_{27}H_{31}ClN_2O_6$	$C_{24}H_{30}N_2O_2S$	$C_{24}H_{30}N_2O_2Se$
MWT	467.0	410.6	457.5
a	15.026(3) Å	17.395(6) Å	17.155(7) Å
b	10.568(3) Å	7.596(3) Å	7.600 Å
c	14.774(6) Å	16.959(7) Å	17.633(7) Å
	90.0°	90.0°	90.0°
	97.97(2)°	106.87(2)°	106.48(3)°
	90.0°	90.0°	90.0°
Cell Volume	2323.3(12) $Å^3$	2144.39 $Å^3$	2204.5(16) $Å^3$
F(000)	992		952
μMoK_α	2.01 cm^{-1}		17.05 cm^{-1}
λMoK_α	0.71069 Å		0.71069 Å
Calcd. Density	1.335 g/cm^3		1.378 g/cm^3
Z	4	4	4
Obs. Reflections	2123	4406	1500
R/Rw	7.6%/ -	4.57%/4.19%	7.3%/9.2%
Space Group	$P2_1/n$		$P2_1/C$

a. Analysis of crystal data still in progress.

TABLE XXIII

SELECTED BOND DISTANCES (Å) FOR KETONE **18d** AND ISOMERIC HYDROPERCHLORATES **32b, 33b**[a]

BOND	**18d**	**32b**	**33b**
C(1)-C(2)	1.565 (6)	1.59 (2)	1.57 (2)
C(2)-N(3)	1.509 (3)	1.48 (2)	1.49 (1)
C(2)-ArC[b]	1.534 (6)	1.50 (2)	1.53 (2)
N(3)-C(4)	1.488 (5)	1.47 (2)	1.49 (1)
C(4)-C(5)	1.558 (5)	1.56 (2)	1.55 (1)
C(4)-ArC[c]	1.557 (4)		1.50 (2)
C(5)-C(6)	1.540 (6)	1.49 (2)	1.52 (2)
C(6)-N(7)	1.480 (4)	1.52 (2)	1.52 (1)
N(7)-C(8)	1.497 (6)	1.52 (2)	1.51 (1)
N(7)-C(10)	1.474 (6)	1.48 (2)	1.54 (1)
C(8)-C(1)	1.538 (6)	1.50 (2)	1.49 (1)
C(9)-C(1)	1.530 (4)	1.53 (2)	1.55 (2)
C(9)-C(5)	1.561 (6)	1.56 (2)	1.50 (2)
C(10)-ArC[d]	1.552 (7)	1.53 (2)	1.46 (2)
C(9)-O(1)	1.209 (5)		

a. Values in parentheses are estimated standard deviations (E.S.D.).
b. ArC = C(1"') in **18d**, C(23) in **32b**, C(17) in **33b**.
c. ArC = C(1") in **18d**, C(17) in **32b**, C(23) in **33b**.
d. ArC = C(1') in **18d**, C(11) in **32b**, C(11) in **33b**.

TABLE XXIV

SELECTED BOND ANGLES (°) FOR KETONE **18d** AND ISOMERIC HYDROPERCHLORATES **32b**, **33b**[a]

	18d	**32b**	**33b**
C(2)-C(1)-C(9)	105.1 (2)	106 (1)	107.9 (9)
C(8)-C(1)-C(9)	107.6 (3)	112 (1)	110.6 (9)
C(8)-C(1)-C(2)	113.8 (3)	115 (1)	116.2 (9)
C(1)-C(2)-N(3)	109.3 (2)	107 (1)	109.9 (8)
C(1)-C(2)-Arc[b]	109.4 (3)	113 (1)	110.7 (9)
Arc[b]-C(2)-N(3)	111.0 (3)	112 (1)	109.9 (9)
C(2)-N(3)-C(4)	115.4 (3)	111 (1)	113.8 (8)
N(3)-C(4)-C(5)	106.0 (3)	108 (1)	107.8 (8)
N(3)-C(4)-Arc[c]	111.0 (3)		108.4 (8)
Arc[c]-C(4)-C(5)	113.8 (2)		114.2 (9)
C(4)-C(5)-C(6)	112.2 (3)	116 (1)	112.2 (8)
C(4)-C(5)-C(9)	108.6 (3)	106 (1)	112.2 (8)
C(6)-C(5)-C(9)	106.1 (3)	109 (1)	109.3 (9)
C(5)-C(6)-N(7)	108.2 (3)	113 (1)	111.1 (9)
C(6)-N(7)-C(8)	113.1 (3)	111 (1)	112.0 (8)
C(6)-N(7)-C(10)	110.7 (4)	110 (1)	110.0 (8)
C(8)-N(7)-C(10)	111.4 (3)	112 (1)	109.9 (8)
N(7)-C(8)-C(1)	110.5 (3)	111 (1)	112.8 (9)
C(1)-C(9)-C(5)	112.4 (3)	107 (1)	106.1 (9)

TABLE XXIV continued

O(1)-C(9)-C(1)	122.5 (4)		
O(1)-C(9)-C(5)	125.1 (3)		
N(7)-C(10)-ArC[d]	110.9 (4)	112 (1)	115.0 (9)

a. Values in parentheses are estimated standard deviations (E.S.D.).
b. ArC = C(1"') in **18d**, C(23) in **32b**, C(17) in **33b**.
c. ArC = C(1") in **18d**, C(17) in **32b**, C(23) in **33b**.
d. ArC = C(1') in **18d**, C(11) in **32b**, C(11) in **33b**.

Hydroperchlorate **33b** also existed in the boat-chair conformation with the bis(o-chlorophenyl)-substituted piperidine ring in the boat form. Like ketone **18d**, the o-chlorophenyl substituents were in equatorial positions. The nitrogen [N(7)] in the N-benzyl-substituted ring is clearly protonated with the proton in an axial or endo position. The nitrogen in the diaryl-substituted ring is secondary with the proton on this nitrogen [N(3)] in an equatorial position. Tables XXIII and XXIV list selected bond distances and bond angles for this salt.

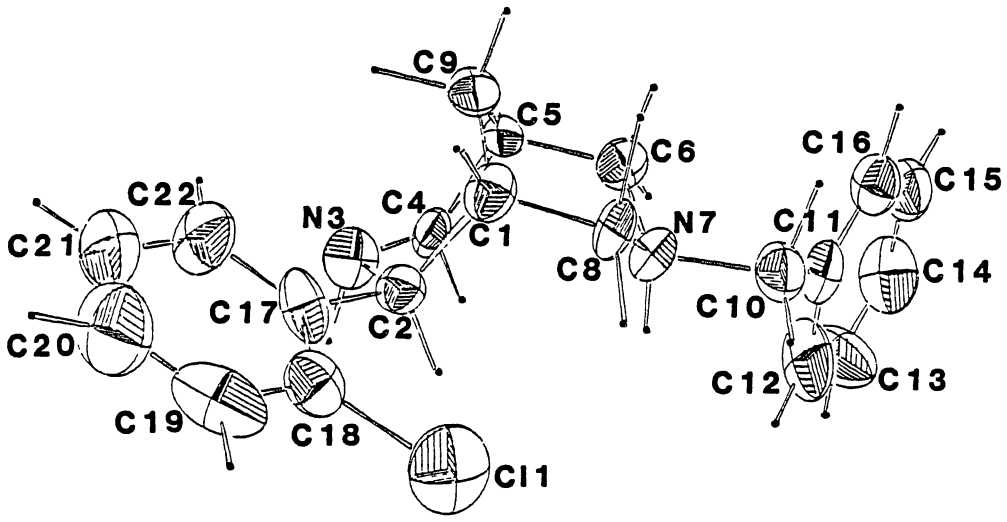


Figure 5. Perspective drawing of **33b**.

Isomeric hydroperchlorate **32b**, in contrast to **33b**, existed in a chair-chair conformation. The bis(o-chlorophenyl)-substituted piperidine ring in this molecule was in the chair form with the aryl groups in equatorial positions. The tertiary nitrogen N(7) was protonated with intramolecular hydrogen bonding occuring between the proton and the free electron pair of the secondary nitrogen N(3).

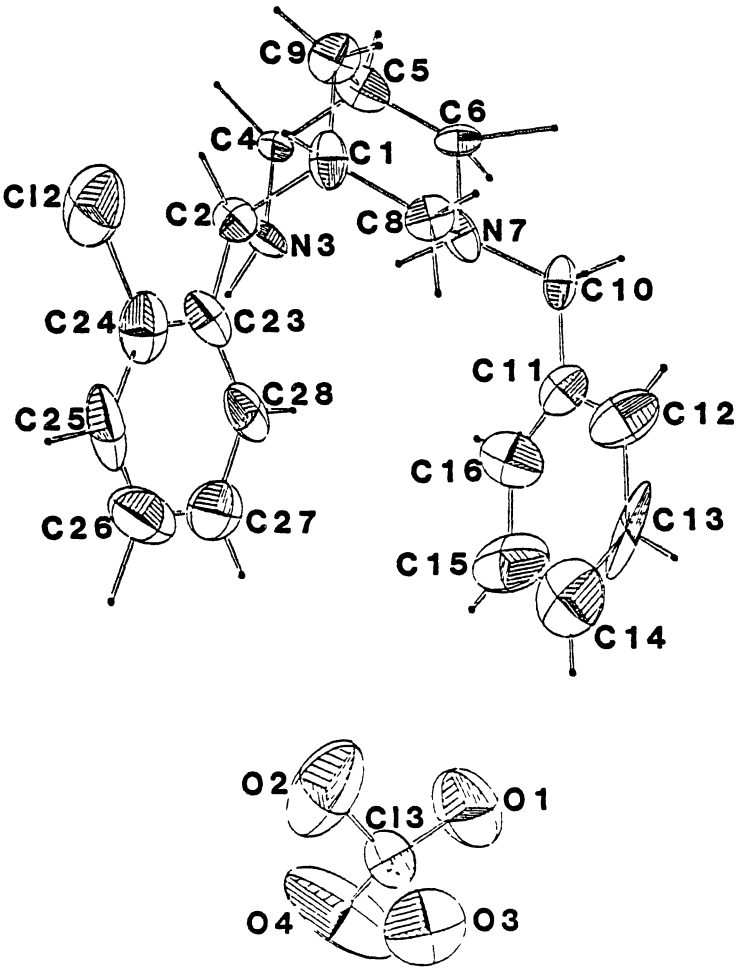


Figure 6. Perspective drawing of **32b**.

The 9,9-dimethoxy-ketal **102b** was found to be in the chair-chair conformation with N(3) clearly bonded to the proton of $HClO_4$. Intramolecular hydrogen-bonding between this proton and the unshared pair at N(7) was quite evident upon consideration of the N(3)-H and N(3)-H... N(7) interatomic distances of 1.02 Å and 1.82 Å. The sum of the van der Waals radii[64] of nitrogen (1.5 A) and hydrogen (1.2 A) is considerably larger than the observed N-H...N interatomic distance. While a hydrogen bond might normally be expected to be linear, steric considerations make this impossible in this system as is evidenced by the N(3)-H ...N(7) bonding angle of 138.8°. Similar nonlinear intramolecular hydrogen bonding behavior has been reported in related systems **29a** and **29b** where the N-H...X bonding angles were 128.8° and 119.0°,

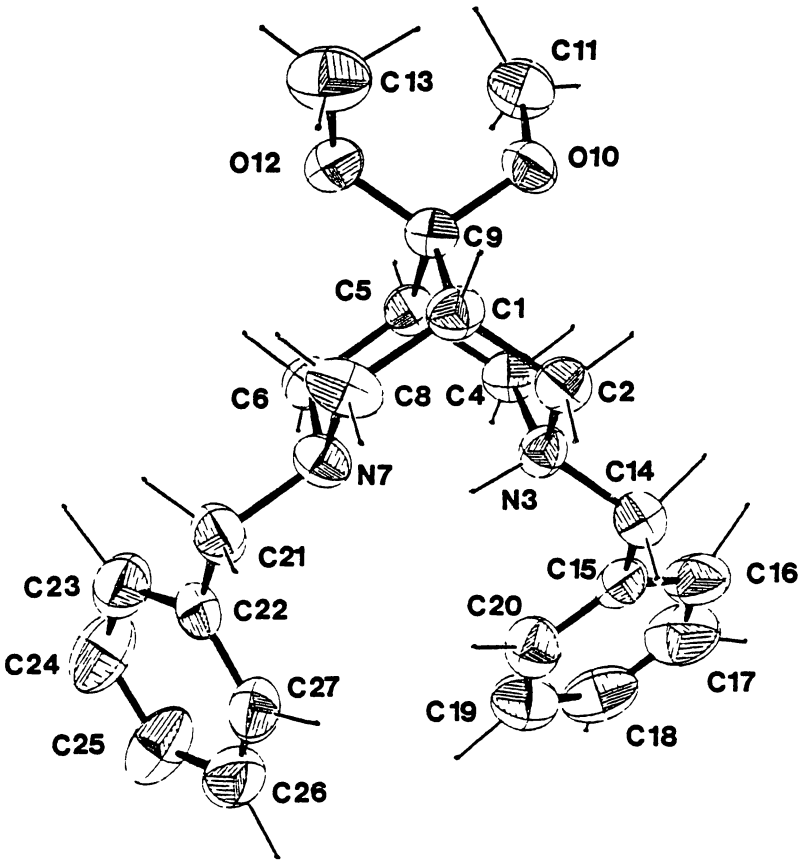
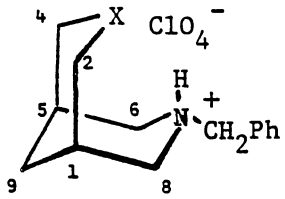


Figure 7. Perspective drawing of **102b**.



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a. X = S
b. X = Se

respectively.[107] The bicyclic ring system displayed no internal crystallographic symmetry elements. Despite the existence of one nitrogen as a quaternary cation while the other is uncharged with the unshared pair involved in a hydrogen bond, C-N bond distances for the two piperidine rings both averaged 1.51 Å while the bond angles about the nitrogen were similar.

Upon examination of the perspective drawing (Figure 4), the methoxy groups can be seen to be bent to the opposite sides of bridging carbon C(9). The benzyl groups, however, are twisted to the same side of the bicyclic ring system. Relief from crowding is achieved by twisting about the C(21)-C(22) and C(14)-C(15) bonds. The perchlorate anion is well removed from the bicyclic ring system. No intermolecular hydrogen bonding is present as all O...H distances are in excess of 2.36 Å.

TABLE XXV

SELECTED BOND DISTANCES (Å) FOR KETAL **102b**[a]

C(1)-C(2)	1.518 (9)
C(2)-N(3)	1.513 (8)
N(3)-C(4)	1.499 (8)
N(3)-C(14)	1.492 (8)
C(4)-C(5)	1.527 (9)
C(5)-C(6)	1.522 (9)
C(6)-N(7)	1.474 (9)
N(7)-C(8)	1.546 (9)
N(7)-C(21)	1.472 (8)
C(8)-C(1)	1.517 (9)
C(9)-C(1)	1.531 (9)
C(9)-C(5)	1.538 (9)
C(9)-O(10)	1.412 (8)
C(9)-O(12)	1.405 (8)
O(10)-C(11)	1.417 (9)
O(12)-C(13)	1.454 (9)

a. Values in parentheses are estimated standard deviations (E.S.D.).

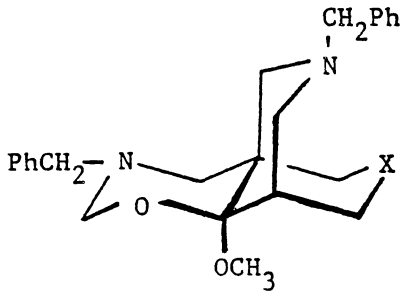
TABLE XXVI

SELECTED BOND AND DIHEDRAL ANGLES (°) FOR KETAL **102b**[a]

Bond Angles (°)			
C(2)-C(1)-C(9)	110.0 (5)	C(6)-N(7)-C(21)	112.5 (5)
C(8)-C(1)-C(9)	109.5 (5)	C(8)-N(7)-C(21)	107.0 (5)
C(8)-C(1)-C(2)	113.8 (5)	N(7)-C(8)-C(1)	108.9 (5)
C(1)-C(2)-N(3)	110.6 (5)	C(1)-C(9)-C(5)	105.7 (5)
C(2)-N(3)-C(14)	110.6 (5)	C(1)-C(9)-O(10)	106.1 (5)
C(2)-N(3)-C(4)	111.0 (5)	C(1)-C(9)-O(12)	114.2 (5)
C(4)-N(3)-C(14)	113.2 (5)	C(5)-C(9)-O(10)	113.3 (5)
N(3)-C(4)-C(5)	110.5 (4)	C(5)-C(9)-O(12)	106.0 (5)
C(4)-C(5)-C(6)	112.4 (5)	O(10)-C(9)-O(12)	111.5 (5)
C(4)-C(5)-C(9)	109.4 (5)	C(9)-O(10)-C(11)	115.5 (5)
C(6)-C(5)-C(9)	110.4 (5)	C(9)-O(12)-C(13)	116.7 (6)
C(5)-C(6)-N(7)	110.6 (5)	N(3)-C(14)-C(15)	113.2 (6)
C(6)-N(7)-C(8)	109.2 (5)	N(7)-C(21)-C(22)	112.7 (5)
Dihedral Angles (°)			
C(1)-C(2)-N(3)-C(4)	59.6 (6)	C(5)-C(6)-N(7)-C(8)	55.7 (6)
C(2)-N(3)-C(4)-C(5)	58.4 (6)	C(6)-N(7)-C(8)-C(1)	55.2 (6)
N(3)-C(4)-C(5)-C(6)	61.4 (7)	N(7)-C(8)-C(1)-C(2)	63.4 (7)
C(4)-C(5)-C(6)-C(7)	62.1 (7)	C(8)-C(1)-C(2)-N(3)	60.7 (7)

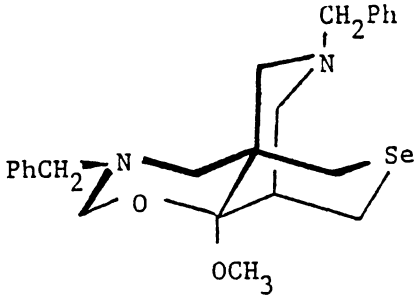
a. Values in parentheses are estimated standard deviations (E.S.D.).

Tricyclic ketals **103a,b** were submitted for X-ray diffraction analysis to establish the conformations of the 1,3-oxazine, piperidine, and 1-thiacyclohexane (or 1-selenacyclohexane) rings as well as the relative stereochemistry at C(8a) in each molecule. As can be seen in the perspective drawings (Figures 8 and 9) of these molecules, both consist of three fused heterocyclic six-membered rings with the C(4a)-C(8a) bond common to all three rings. In ketal **103a** the thiane ring is fused to the 1,3-oxazine ring with a <u>trans</u> ring juncture about the C(4a)-C(8a) bond , while the piperidine ring is fused with a <u>cis</u> ring juncture about the same bond. The thiane and piperidine rings were fused with two common bonds [C(4a)-C(8a) and C(8)-C(8a)] to afford, for this end of the molecule, a ring system similar to the **CC** conformer of the <u>N</u>-alkyl-3-thia-7-azabicyclo[3.3.1]nonane ring system. The selenium derivative **103b** was also arranged in a similar manner. In both ring systems the piperidine ring was <u>trans</u> to the methoxy group while the thiane (or selenane) ring was <u>cis</u> to this group. While the relative stereochemistry in both systems was identical, the perspective drawing of the selenium derivative **103b** is actually that of the enantiomeric molecule **103b'** found in crystal analysis.



103

a. X = S
b. X = Se



103b'

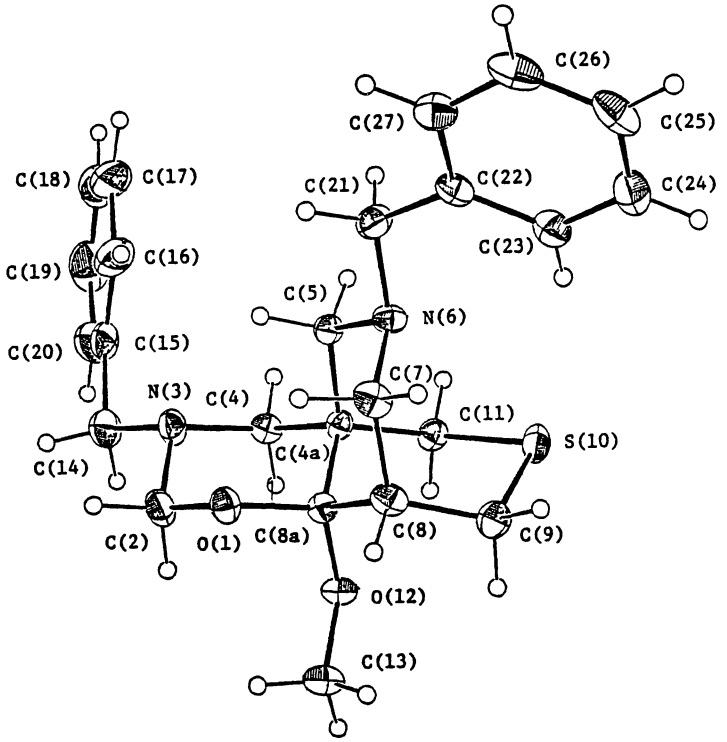


Figure 8. Perspective drawing of **103a.**

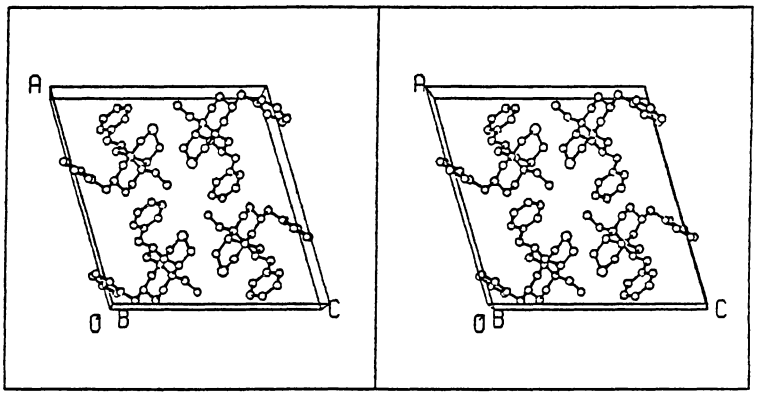


Figure 9. Stereo drawing of **103a.**

Examination of the torsional angles (see Table XXVIII) about sulfur in **103a** indicated that the C(9)-S(10)-C(11) plane of the thiane ring is flattened relative to the C(4a)-C(11)-C(9)-C(8) plane while the C(4a)-C(8a)-C(8) plane is somewhat puckered. The C-C-S-C torsional angles averaged 39.6° while the two C-C-C-C torsional angles for this ring were both 70.6°. A similar examination of the torsional angles about selenium in **103b** indicated that the Se atom induced greater flattening of the selenane ring compared to that of the thiane ring in **103a.** The C-C-Se-C torsional angles averaged 33.2° while the two C-C-C-C torsional angles (∿69.7°) for the selenane ring were similar to that seen in the sulfur analog.

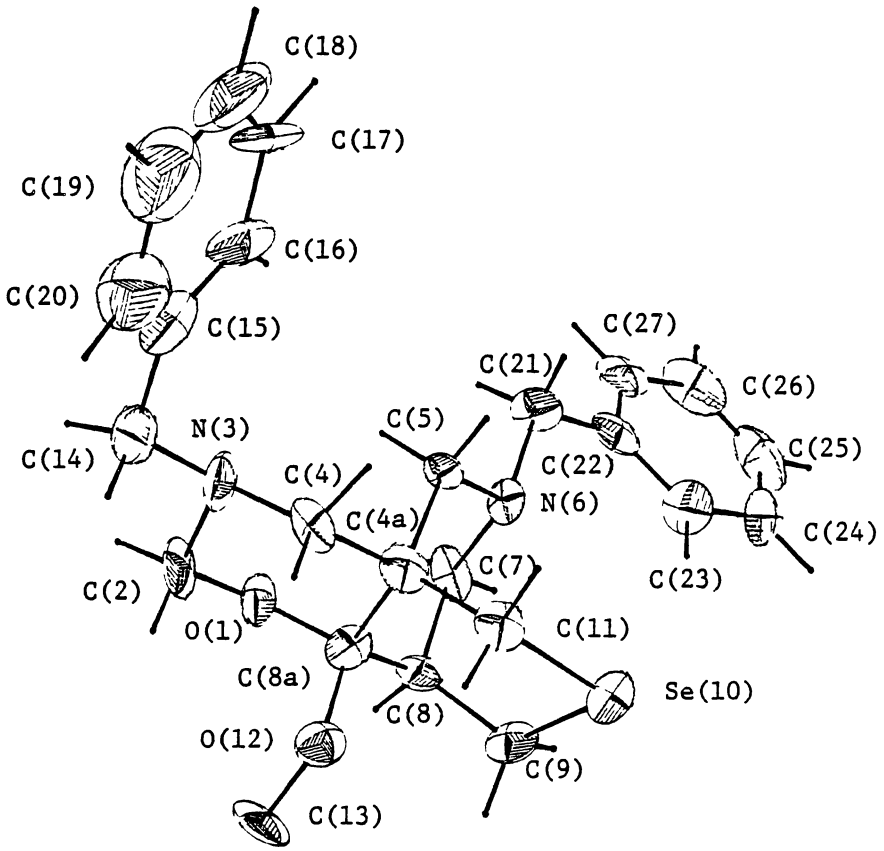


Figure 10. Perspective drawing of **103b.**

TABLE XXVII

SELECTED BOND DISTANCES (Å) IN 3,6-DIBENZYLHEXAHYDRO-8a-METHOXY-5H-4a,8-(METHANOHETEROMETHANO)-2H-PYRIDO[3,4-e]-1,3-OXAZINES **103a,b**

Bond	**103a**[a] (S)	**103b**[b] (Se)	Bond	**103a**[a] (S)	**103b**[b] (Se)
O(1)-C(8a)	1.427	1.40 (1)	N(6)-C(7)	1.460	1.45 (2)
O(1)-C(2)	1.427	1.41 (2)	C(7)-C(8)	1.528	1.53 (2)
C(2)-N(3)	1.454	1.45 (2)	C(8)-C(8a)	1.527	1.50 (2)
N(3)-C(14)[d]	1.466	1.44 (2)	C(8)-C(9)	1.540	1.52 (2)
N(3)-C(4)	1.473	1.46 (2)	C(8a)-O(12)	1.416	1.44 (1)
C(4)-C(4a)	1.534	1.57 (2)	C(9)-X(10)[c]	1.824	1.96 (2)
C(4a)-C(5)	1.538	1.57 (2)	X(10)-C(11)[c]	1.819	1.95 (1)
C(4a)-C(11)	1.532	1.53 (2)	O(12)-C(13)	1.433	1.45 (1)
C(4a)-C(8a)	1.540	1.55 (2)	C(14)-C(15)[d]	1.509	1.53 (3)
C(5)-N(6)	1.459	1.43 (2)	C(21)-C(22)[d]	1.509	1.52 (2)
N(6)-C(21)[d]	1.450	1.46 (2)			

a. Range of estimated standard deviations (E.S.D) in **103a** = 0.1-0.4.
b. Values in parentheses indicate E.S.D for **103b**.
c. X(10) = S(10) in **103a** and Se(10) in **103b**.
d. C(14) and C(21) in the perspective drawing are identical to C(13) and C(12), respectively, in the structural and conformational analysis sections.

TABLE XXVIII

SELECTED BOND AND DIHEDRAL ANGLES IN 3,6-DIBENZYLHEXAHYDRO-8a-METHOXY-5H-4a,8-(METHANOHETEROMETHANO)-2H-PYRIDO[3,4-e]-1,3-OXAZINES **103a,b**

	103a[a] (S)	**103b**[b] (Se)	
Selected Bond Angles (°)			
C(8a)-O(1)-C(2)	112.7	114	(1)
O(1)-C(2)-N(3)	110.8	110	(1)
C(2)-N(3)-C(4)	109.0	109	(1)
C(2)-N(3)-C(14)[c]		112	(1)
C(4)-N(3)-C(14)	110.8	109	(1)
N(3)-C(4)-C(4a)	110.1	110	(1)
C(4)-C(4a)-C(5)	108.5	108	(1)
C(4)-C(4a)-C(8)	108.0	108	(1)
C(4)-C(4a)-C(11)	107.5	108	(1)
C(5)-C(4a)-C(8a)	109.2	107	(1)
C(5)-C(4a)-C(11)	112.6	113	(1)
C(8a)-C(4a)-C(11)	110.9	113	(1)
C(4a)-C(5)-N(6)	114.1	114	(1)
C(5)-N(6)-C(7)	110.7	110	(1)
C(5)-N(6)-C(21)[c]	109.9	109	(1)
C(7)-N(6)-C(21)[c]	111.6	113	(1)
N(6)-C(7)-C(8)	109.4	113	(1)
C(7)-C(8)-C(8a)	110.3	108	(1)
C(7)-C(8)-C(9)	115.2	113	(1)
C(8a)-C(8)-C(9)	109.9	114	(1)

Table XXVIII continued

O(1)-C(8a)-C(4a)	109.8	111 (1)
O(1)-C(8a)-C(8)	107.5	108 (1)
O(1)-C(8a)-O(12)	110.5	111 (1)
C(4a)-C(8a)-C(8)	109.3	111 (1)
C(4a)-C(8a)-O(12)	107.0	105 (1)
C(8)-C(8a)-O(12)	112.7	111 (1)
C(8)-C(9)-X(10)[d]	116.2	116.2 (10)
C(9)-X(10)-C(11)[d]	100.9	98.7 (6)
X(10)-C(11)-C(4a)	115.9	116.2 (9)
C(8a)-O(12)-C(13)	115.4	116 (1)
N(3)-C(14)[a]-C(15)	111.8	114 (1)
N(6)-C(21)-C(22)	114.1	111 (1)

Selected Dihedral Angles (°)

1,3-Oxazine ring:

C(8a)-O(1)-C(2)-N(3)	62.0 (2)	62.9 (16)
O(1)- C(2)-N(3)-C(4)	61.3 (2)	62.9 (15)
C(2)-N(3)-C(4)-C(4a)	59.4 (2)	59.5 (16)
N(3)-C(4)-C(4a)-C(8a)	55.8 (2)	53.0 (15)
C(4)-C(4a)-C(8a)-O(1)	54.1 (2)	50.1 (14)
C(4a)-C(8a)-O(1)-C(2)	58.1 (2)	56.6 (16)

Piperidine ring:

C(8a)-C(4a)-C(5)-N(6)	54.8 (2)	55.0 (13)
C(4a)-C(5)-N(6)-C(7)	56.2 (2)	57.2 (13)
C(5)-N(6)-C(7)-C(8)	57.3 (2)	58.7 (13)
N(6)-C(7)-C(8)-C(8a)	59.1 (2)	59.6 (13)
C(7)-C(8)-C(8a)-C(4a)	57.1 (2)	57.9 (14)

C(8)-C(8a)-C(4a)-C(5)	54.0 (2)	54.6 (12)

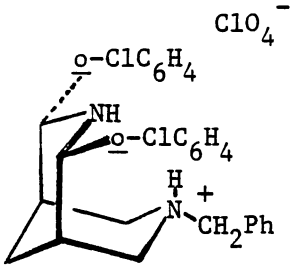
TABLE XXVIII continued

<u>1-Heteracyclohexane ring:</u>		
C(8a)-C(8)-C(9)-X(10)[d]	58.1 (2)	53.6 (16)
C(8)-C(9)-X(10)-C(11)[d]	40.1 (2)	33.5 (12)
C(9)-X(10)-C(11)-C(4a)[d]	39.1 (2)	34.8 (12)
X(10)-C(11)-C(4a)-C(8a)[d]	56.6 (2)	54.7 (14)
C(11)-C(4a)-C(8a)-C(8)	70.6 (2)	69.9 (14)
C(4a)-C(8a)-C(8)-C(9)	70.6 (2)	69.6 (16)

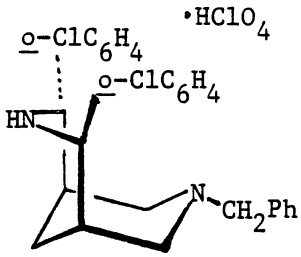
a. Estimated standard deviation (E.S.D.) for **103a** was 0.1-0.4.
b. Values in parentheses indicate E.S.D. for each angle in **103a,b.**
c. C(14) and C(21) in the perspective drawing are identical to C(13) and C(12), respectively, in the structural and conformational analysis sections.
d. X(10) = S(10) in **103a** or Se(10) in **103b.**

Antiarrhythmic Properties

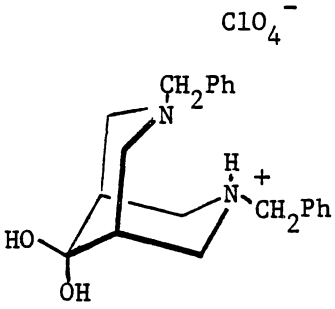
The antiarrhythmic properties of several 3-thia-7-aza- and 3,7-diazabicyclo[3.3.1]nonane hydroperchlorates were assessed in 24-hour infarcted-heart mongrel dogs by Dr. Benjamin J. Scherlag of the Veterans Administration Hospital in Oklahoma City, Oklahoma. The compounds tested were salts **32b, 33b, 70d, 102a,b,** and **103c.**



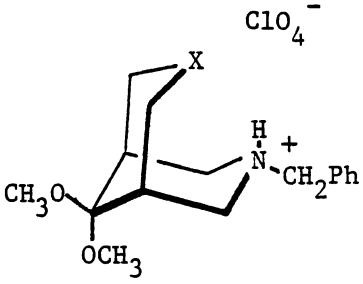
32b



33b

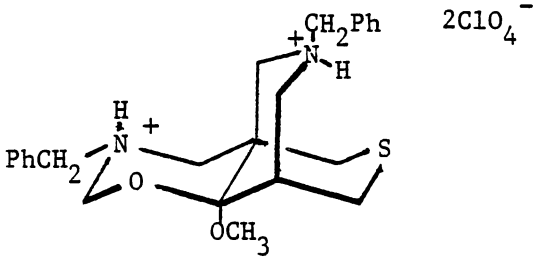


70d



102

a. X = S
b. X = NCH_2Ph



103c

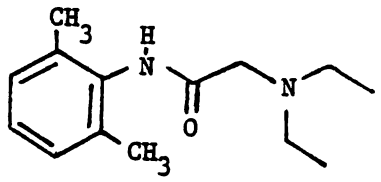
Dogs have been used extensively as models for humans in the testing of cardioactive drugs due to the great similarities in the biochemistry and physiology of the cardiovascular system of dogs and humans.[53] A commonly used dog model employed for the assessment of potential antiarrhythmic agents is the 24-hour infarcted-heart dog. As this was

the model used in the testing of the compounds developed in this study, a short description[86,87] of the preparation of these dogs is in order.

Mongrel dogs of weights between 12 and 25 kg were anesthesized (sodium pentobarbitol, 30 mg/kg, i.v.) and connected to a respirator.[85,86] A thoracotaomy was performed in the fourth intercostal space. The left atrium was reflected to expose the left anterior descending coronary artery. A two-stage ligation of this artery was performed in which the artery was constricted for a period of thirty minutes before finally closing it completely and permanently. This procedure induces a myocardial infarction quite similar to that seen in humans.[53] The thoracotomy was then repaired and the dog allowed to recover for 24 hours. After this time the dog was reanesthesized the chest cavity was reopened at the site of the first thoracotomy. A series of electrogram and pacing electrodes were then set in place. A multipolar composite electrode was placed on the epicardium over the infarcted zone and a similar composite electrode was positioned on the posterior wall to record from normal tissue. A common carotid artery was exposed in the neck and a cathode electrode slowly advanced to the aortic root to monitor His-bundle activity. Blood pressure was monitored at a second carotid artery exposed for this purpose. A stainless-steel pacing electrode was inserted into the right ventricular myocardium.

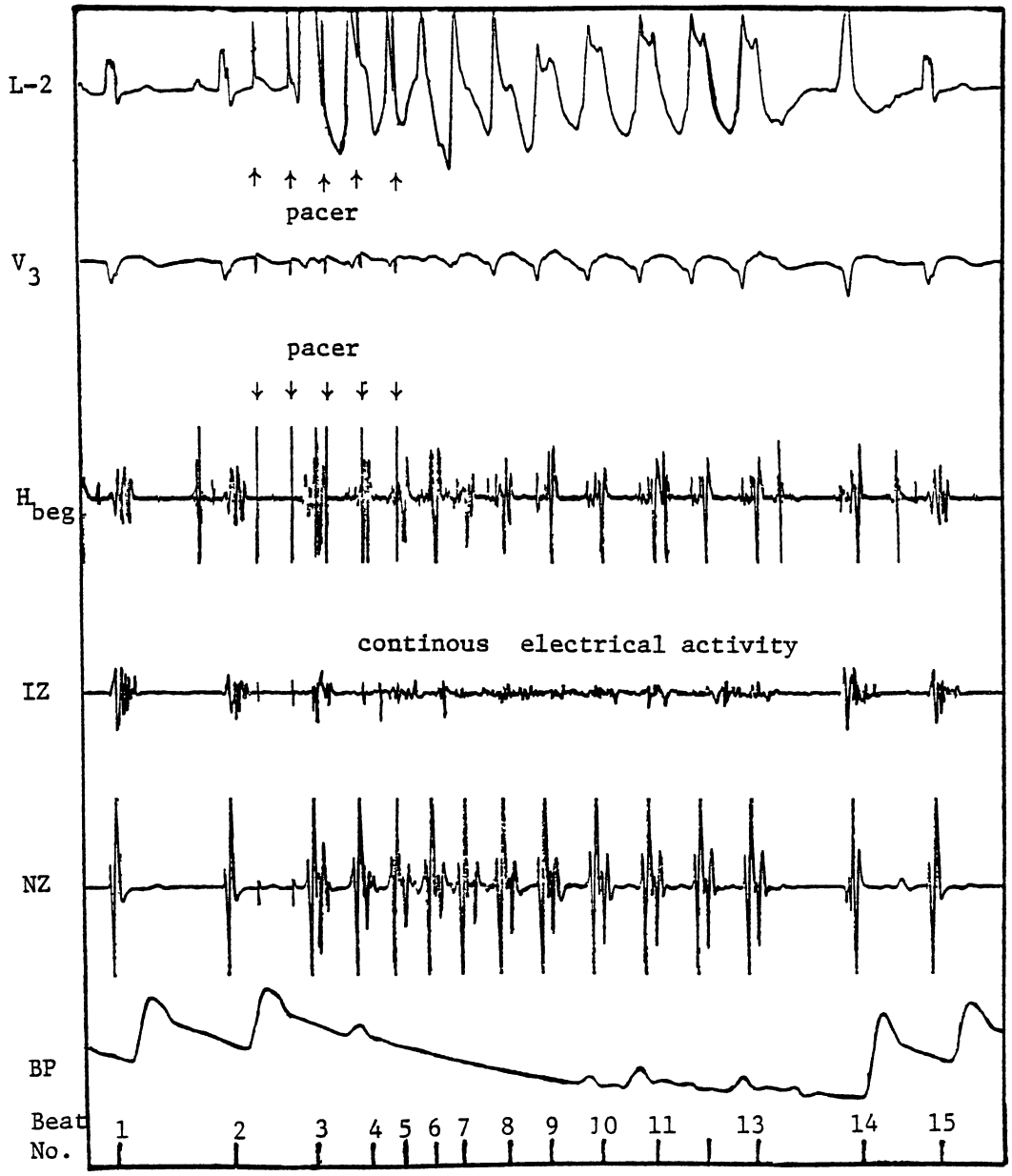
The experimental procedure [14,107] for the determination of antiarrhythmic activity involved the induction by ventricular pacing of sustained ventricular tachycardia (SVT) in the test animal. This was accomplished by subjecting the heart to 3-5 electrical pulses (2-10 V) of 2 ms duration at a rate corresponding to 240-420 beats per minute

(bpm). The rate of the resultant SVT in an animal that had been previously treated with a prospective antiarrhthmic agent was compared directly with the SVT rate obtained in the same animal in the absence of any antiarrhythmic agent; the latter experiment serving as a control. The prospective agents were tested at doses of three and six mg/kg with the activity of lidocaine (**76**) at these doses serving as a benchmark for the comparison of the antiarrhythmic properties. Lidocaine is currently the drug of choice in the treatment of SVT.



76

A portion of the electrogram obtained from one experiment is shown in Figure 11. In this experiment salt **102b** was administered at a dose of 6 mg/kg. A normal sinus rhythm was observable in the top trace (L-2) for the first two beats on the left of the electrogram. Associated with this were bursts of electrical activity observable in the third, fourth and fifth traces [for the His-bundle (H_{beg}), infarcted zone (IZ) and normal zone (NZ) of the myocardium, respectively]. Ventricular pacing (arrows) at a rate of 390 bpm induced ventricular tachycardia (VT, beats 3-13) characterized by the irregular wave form observed in L-2 as well as the continuous electrical activity observed for the IZ trace. The effect of salt **102b** was apparent in the nonsustained nature of the VT. After only eleven beats the heart returned to its normal sinus rhythm (beats 14, 15), while in a control experiment (no antiarrhythmic agent



L-2 : Limb electrode
V_3 : Chest wall electrode
H_{beg}: His-bundle electrogram
IZ: Infarcted zone electrogram
NZ: Normal zone electrogram
BP: Blood pressure

Figure Electrogram recorded for 24-hour infarcted dog after administration of salt 102b.

present), pacing at 360 bpm induced a sustained VT with a rate of 390 bpm.

The effect of the VT on the measured blood pressure could be seen in the lower trace (BP). The blood pressure drops almost continually throughout the VT, but returns to the normal pattern as the heart recovers from the VT.

If one were to establish a hierarchy of desirable properties for a prospective antiarrhythmic agent, the relative order could be the ability to: (1) entirely prevent the induction of any VT; (2) prevent the induction of sustained VT; and (3) substantially reduce the rate of sustained VT. Undesirable characteristics would include increasing the rate of the observed SVT as compared to that observed in the absence of the drug (the proarrhythmic effect) and, of course, the drug having no observable effect on the SVT. Another important factor in the determination of the utility of any prospective drug is the toxicity of the compound. As the goal of the present study was to synthesize and make preliminary assessments of the antiarrhythmic properties, no toxicity data was acquired. However, this type of data must eventually be acquired if the development of the more active of these compounds is to be pursued.

As observed in Figure 11, blood pressure drops quite markedly during a VT episode. As blood pressure can drop to dangerously low levels during SVT,[53] a desirable secondary characteristic of an antiarrhythmic compound might be the ability to elevate the mean blood pressure during the SVT.

The observed antiarrhythmic properties of **32b, 33b, 70d, 102a,b** and **103c** as determined by the above assay are summarized on Table XXIX. As

TABLE XXIX

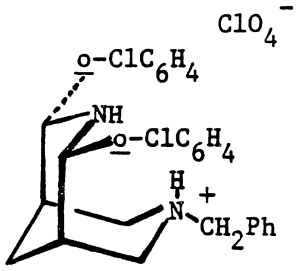
ANTIARRHYTHMIC PROPERTIES OF **32b, 33b, 70d, 102a, 102b, 103c**[a]

	Control			Dosage 3 mg/kg					Dosage 6 mg/kg				
	P.R.[b]	SVT[c]	BP[d]	P.R.[b]	SVT[c]	$\%\Delta_{SVT}$[e]	BP[d]	$\%\Delta_{BP}$[f]	P.R.[b]	SVT[c]	$\%\Delta_{SVT}$[e]	BP[d]	$\%\Delta_{BP}$[f]
32b	390	330	80	390	330	NE[g]	90	+12.5	390	330	NE[g]	86	+7.5
76				390	360	PA[h]			390	330	NE[g]		
33b	390	NSVT[i]	95	390	330	PA[h]	103	+8.4	390	390	PA[h]	104	+9.5
103c				390	330	PA[h]	98	+3.2	390	330	PA[h]	101	+6.3
76				390	NI[j]	-	-	-	360	270	-30.8		
33b	390	390-420	70	390	340	-15.4	83	+18.5	390	390	NE[g]	82	+17.5
76				390	390	NE[g]			360	270	-11.0		
70d	390	390	102	390	330	-15.4	99	-2.9	360	300	-23.0	90	-11.8
76				390	330	-15.4			330	210	-46.2		
102a	390	390	120	390	NSVT	-	133	+10.8	390	NSVT	-	130	+8.3
76				390	330	-15.4			360 390	330 390	-15.4 NE[g]		

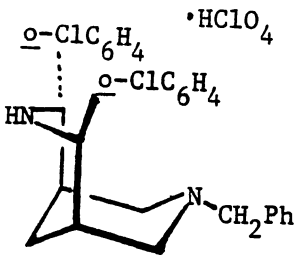
TABLE XXIX continued

102a	330	270	70	360	NSVT[i]	-	90	+29	390	240	-11.1	95	+36
76				360	270	NE[g]			360	240	-11.1		
102a	360	390	90	390	NSVT[i]	-	99	+10	360 390	NSVT[i] 390	- NE[g]	99	+10
102b				390	210	-46.2	92	+2.2	360 390	NSVT[i] NSVT[i]	- -	85	+5.5
76				330	300	-9.1			300	270			
102b		330	107		270	-18.2	120	+12.1		240	-27.3	125	+16.8

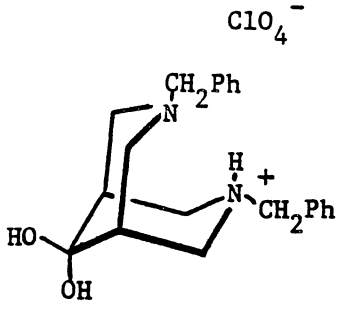
a. Each division represents experiments on one dog.
b. Pacing Rate (beats/min).
c. Rate of sustained ventricular tachycardia (beats/min).
d. Mean blood pressure during ventricular tachycardia (VT) episode (mm Hg).
e. Percent change in rate of SVT relative to control experiment.
f. Percent change in mean blood pressure during VT episode.
g. No effect.
h. Proarrhythmic effect.
i. Nonsustained VT.
j. VT not inducible.
k. Multiple VT forms.



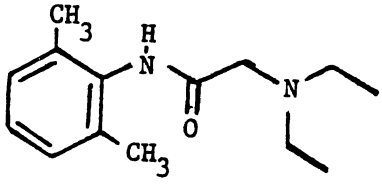
32b



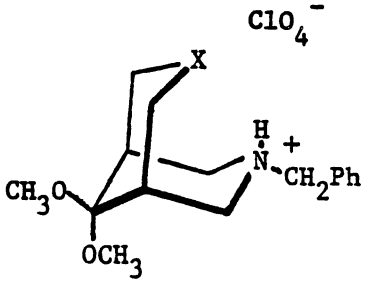
33b



70d

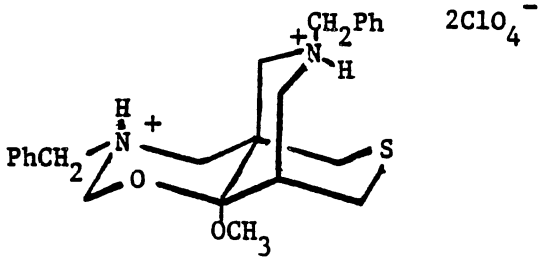


76



102

a. X = S
b. X = NCH_2Ph



103c

discussed in the first chapter, hydroperchlorate **29a** has previously been found to possess excellent antiarrhythmic properties.[14,85] This compound has been found to inhibit the induction of ventricular tachycardia in a majority of animals tested. While none of the

compounds developed in the current study displayed this type of activity, several exhibited otherwise excellent properties. Ketal **102a** was found in one animal to inhibit the induction of sustained ventricular tachycardia (SVT) at a dose of 6 mg/kg. At the lower dose (3 mg/kg), it reduced the rate of SVT by 46.2%. In contrast, lidocaine (**75**) in the same animal only permitted a reduction in the rate of the SVT at the higher (10%) and lower doses (9.1%). In another dog, ketal **102b** was found to decrease the SVT rate by 27.3% at the higher dosage and 18.2% at the lower dosage. In this respect ketal **102b** was similar in effect to **28d.** (In animals where SVT was inducible, **28d** has been determined to reduce the SVT rate by aproximately 30%).[85] Ketal **102b** was found to enhance the mean blood pressure during VT at both dosage levels in the second animal while having only slight effects in the first.

The related ketal **102a** was determined to have properties similar to those of **102b.** Ketal **102a** was found to inhibit the induction of SVT in three animals at the lower dosage. At the higher dosage in two animals, the induction was also inhibited. However, in an animal where both ketals **102a,b** (6 mg/kg) were tested, **102a** was found to exhibit a proarrhythmic effect at high rates (390 bpm) of ventricular pacing. At lower rates (300, 330 and 360 bpm) of cardiac stimulation the compound was quite effective. Ketal **102a** was more effective than lidocaine in all animals at both dosage levels. It was also found to elevate the mean blood pressure in all animals at both dosages.

Diol **70d** was found to be as effective as lidocaine (**75**) at 3 mg/kg in one animal, both compounds reducing the SVT rates by 15.4% as compared to the control experiment. However, at the higher dosage

lidocaine was more effective. Diol **70d** was found to have a negative effect on the mean blood pressure at the higher dosage but essentially no effect at the lower dosage.

Tricyclic ketal **103c** was determined to be proarrhythmic at both dosages in experiments on one dog. Lidocaine (76) was quite effective at both dosages in this animal.

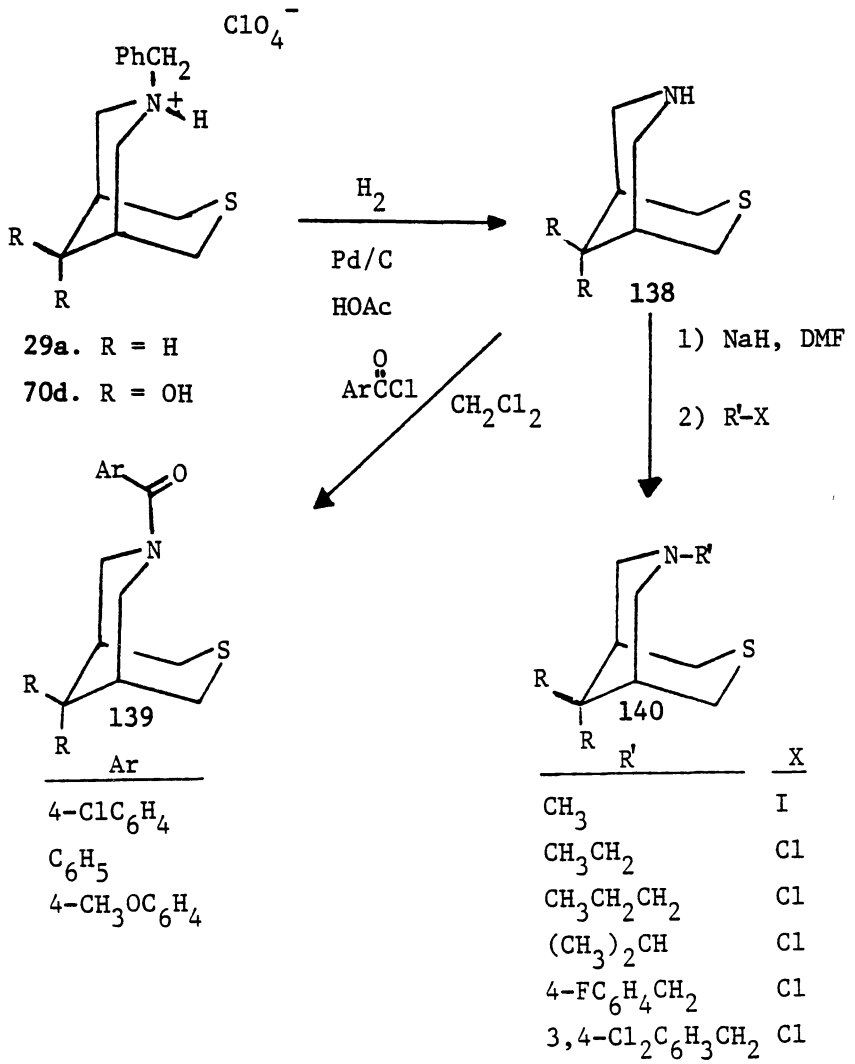
The isomeric salts **32b** and **33b** were found to give rather ambivalent results. At the lower dosage in one animal isomer **33b** was found to have relatively weak-to-moderate antiarrhythmic activity, causing an approximately 15.9% reduction in the rate of SVT. At this dosage in this animal lidocaine (76) was found to have no effect. At the higher dosage **33b** was found to have no effect in this dog. In another dog this compound was found to be proarrhythmic at both dosages. Isomer **32b** was found to have no effect in one dog at either dosage. In other experiments, **32b** was found to have only very weak activity. These negative results were not entirely conclusive, however, as lidocaine was also relatively ineffective in these dogs.

As several of these compounds showed promise as potential antiarrhythmic agents, experiments to examine the antiarrhythmic properties are continuing. To summarize the results to date, ketal **102b** exhibited execellent properties, being more effective than lidocaine and nearly as effective as **28a**. Related ketal **102a** was generally more effective than lidocaine, but did display proarrhythmic properties at high rates of ventricular stimulation. Diol **70d** was more effective than lidocaine, but not as effective as those compounds with the more nonpolar ketal group at the 9-position. Tricyclic ketal **103a**, which might be regarded as a 5-dialkylaminomethyl-derivative of **102a**,

exhibited proarrhythmic effects at both dosage levels. Given the data acquired to date, isomers **33b** and **32b** do not show promise as antiarrhythmic agents, however, the data was not conclusive in this regard.

Suggestions for Future Work

As noted in the first chapter, work by Ruenitz and Mokler[62] has suggested that N-alkylbispidinebenzamides may show generally better antiarrhythmic activity than the N-benzyl derivatives. Since N-benzyl-3-thia-7-azabicyclo[3.3.1]nonane hydroperchlorate **29a** has a



Ar
4-ClC$_6$H$_4$
C$_6$H$_5$
4-CH$_3$OC$_6$H$_4$

R'	X
CH$_3$	I
CH$_3$CH$_2$	Cl
CH$_3$CH$_2$CH$_2$	Cl
(CH$_3$)$_2$CH	Cl
4-FC$_6$H$_4$CH$_2$	Cl
3,4-Cl$_2$C$_6$H$_3$CH$_2$	Cl

good track record in the animal studies to date, it might be worthwhile to test benzamide derivatives of this compound. The most likely route to these compounds involves the catalytic debenzylation of hydroperchlorates **29a** or **70d** with palladium on charcoal in acetic acid to afford, after treatment with base, the amines **137.** Ruenitz and Mokler[94] have indicated that N-alkyl-N'-benzylbispidines and the 9-keto derivatives can be treated under similar conditions to obtain N-monoalkylbispidines and related bispidones. Amines **138** then can be converted to aryl amides **139** by treatment with the appropriate acid halide. Several N-alkylbispidinebenzamides possessing these aryl groups have been shown to have marked antiarrhythmic properties (see pages 37-40), therefore, it might be most profitable to select the arylamide groups associated with the best activity as the initial target compounds.

Amines **138** can also be converted to other N-alkyl derivatives **140,** which may also have good activity. Work by Binnig and coworkers[17] has indicated that N-benzylbispidines with these N-alkyl-substituents also show some activity.

CHAPTER III

EXPERIMENTAL SECTION

General Information

All Mannich reactions and Wolff-Kishner reductions were performed under an atmosphere of nitrogen with magnetic stirring. Solvents were removed with a rotary evaporator connected to an aspirator. The following reagents were obtained from commercial sources and used without further purification: acetic acid (DuPont), deuterium oxide (100 atom %, Aldrich), formaldehyde (37%, Fisher), hydrazine hydrate (85%, Fisher), hydroxylamine hydrochloride (96%, Fisher), paraformaldehyde (Eastman), perchloric acid (60%, Baker), potassium carbonate (anhydrous, Baker), potassium hydroxide (pellets, 85%, Fisher), sodium acetate trihydrate (Mallinckrodt), and sodium sulfide (60%, Curtin). The following required distillation prior to use: benzaldehyde (Eastman, bp 26-27°C/1 mm Hg), benzylamine (Eastman, 35-36°C/0.1 mm Hg), N-benzylpiperidin-4-one (**16f**, Lancaster, bp 111-112°C/0.3 mm Hg), o-chlorobenzaldehyde (bp 39-40°C/0.1 mm Hg), methyl iodide (Lancaster, bp 35-36°C), and N-methylpiperidin-4-one (**16e**, Lancaster, bp 49-50°C/0.3 mm Hg). Tetrahydrothiapyran-4-one (**16c**, mp 61-62°C, lit [48]) was prepared by from **16e** by known methods[48] and was sublimed (45°C/0.5 mm Hg) before use. 4-Selenanone (**16d**, mp 55-56°C), previously prepared[106,109] in our laboratory, was sublimed (43°C/0.1 mm Hg) prior

to use. Hydroperchlorate **29a** was prepared by known methods[14] from **27a**. All solvents were reagent grade. Silica gel (Davison Chemical "Davisil 62") and alumina (neutral, Merck) were employed for chromatographic separations. All solvents were reagent grade. In the Mannich reactions, ethanol and methanol were heated at reflux under a stream of N_2 for 0.5-1.0 h prior to use. "RT" refers to room temperature.

Melting points were acquired on a Thomas Hoover capillary apparatus and were uncorrected. Infrared spectra were obtained with a Perkin-Elmer 681 IR spectrophotometer. High resolution mass spectral data were acquired with a CEC Model 21-110B HR spectrometer while unit-mass spectral data was obtained with an LKB-2091 GC-MS spectrometer. ^{13}C NMR spectra were acquired at 25.20 MHz on a Varian XL-100(15) NMR spectrometer with a Nicolet TT-100 PFT accessory, or at 75.43 MHz on a Varian XL-300 NMR spectrometer. ^{1}H, ^{15}N, ^{77}Se NMR spectra were obtained on the XL-300 operating at 299.94, 30.41, 57.22 MHz, respectively. ^{1}H and ^{13}C NMR data are reported in parts per million (ppm) downfield from $(CH_3)_4Si$. ^{15}N NMR data are reported in ppm downfield from NH_3 (ℓ, 25°C, 0 ppm) using $^{15}NH_4NO_3$ (8.0 M, 19.73 ppm) or formamide (neat, 112.4 ppm) as external secondary standards. ^{77}Se NMR data are reported in ppm downfield from $(CH_3)Se$ (0 ppm)using $(C_6H_5)_2Se_2$ (481 ppm) as an external secondary standard. Elemental analyses were obtained from Galbraith Laboratories, Inc., Knoxville, Tennessee.

3,3,5,5-Tetradeutero-4-selenanone (16h)

A jacketed, two-necked flask was fitted with a condenser and a heating mantle. This flask was charged with freshly sublimed 4-selenanone[106,109] (**16g**, 0.2500 g, 1.533 mmol), anhydrous K_2CO_3 (0.9322

g, 6.743 mmol) and D_2O (5 mL). The mixture was heated at 56° for 12 h with boiling acetone in the jacket to maintain this temperature. As the reaction proceeded, some decomposition of the starting material (as indicated by the deposition of red elemental selenium on the walls of the flask) was noted. The reaction mixture was cooled to RT and dry NaCl (0.5 g) was added. The mixture was then extracted ($DCCl_3$, 3 x 10 mL), dried (K_2CO_3), filtered, and evaporated (aspirator with drying tube containing Mol. Sieve 3A) to afford a yellow oil that solidified upon standing. Sublimation (50°C/0.01 mmHg) then afforded the tetradeuterated ketone **16h** (95 mg, 37%): mp 54-55°C; IR (melt) 2910 (C-H), 2100, 2090 (C-D), 1700 (C=O); ^1H NMR ($DCCl_3$) δ 3.00; ^{13}C NMR ($DCCl_3$) (<u>fully-decoupled</u>) ppm 19.2 [s, C(2,6)], 43.6 [m, C(3,5)], 211.1 [C(4)]. Mass spectral m/e calcd. for $C_5H_4D_4O^{78}Se$: 167.9990 (M^+). Found: 167.9990. Integration of the ^1H NMR spectrum indicated greater than 90% deuteration.

Upon deuteration the triplet at δ 2.88 in the ^1H NMR spectrum of the starting material (**16d**) was lost while the triplet at δ 3.00 collapsed to a singlet. This requires a correction in the ^1H NMR assignments given in the literature.[109] The correct ^1H NMR assigments should be: δ 2.88 [t, J = 6.1 Hz, 4 H, H(3,5)], 3.00 [t, J = 6.1 Hz, 4 H, H(2,6)]. An earlier attempt to prepare this compound under the same conditions, but at 100°C, resulted in severe decompositon of the ketone with no recovery of **16d** or **16h**.

7-Benzyl-2,4-bis(2-chlorophenyl)-3,7-diazabicyclo[3.3.1]nonan-9-ones 17d, 18d

Method A. A three-necked, 50-mL round-bottomed flask was fitted with a condenser, an addition funnel, a thermometer, and a heating mantle. This flask was charged with ammonium acetate (2.31 g, 30.0 mmol) and ethanol (10 mL), and the flask was flushed with N_2. The slurry was warmed to 40°C with stirring until all NH_4OAc dissolved, then the solution was cooled to RT. A solution of 2-chlorobenzaldehyde (5.67 g, 40.3 mmol), ketone **16f** (3.78 g, 20.0 mmol), and ethanol (15 ml) was added in one portion. The resulting solution was slowly warmed to 70°C over 30 min. Upon cooling to RT, a white precipitate (solid A) formed which was filtered and washed with anhy ethyl ether (20 mL). These washings were combined with the original filtrate and this solution was cooled at -10°C for 1 h giving a second solid precipitate (solid B) which was also filtered and set aside. Evaporation of the filtrate afforded an oily orange solid which was dissolved in ether (10 mL). Upon standing for 1 h at -10°C, a third white solid (solid C) precipitated. This too was filtered and set aside. Upon standing for 24 h, a fourth white solid (solid D) was precipitated, which was also filtered and set aside. Upon standing for 22 days at -10°C, a small amount of a fifth solid (solid E) precipitated.

Solid A was recrystallized (2-propanol/$HCCl_3$, 3:1, 40 mL) to afford pure ketone **18d** (1.06 g) as long white needles: mp 184-185°C; IR (KBr) cm^{-1} 3340 (N-H), 1733 (C=O); ^1H NMR ($DCCl_3$) δ 1.61 [s, 1 H, N-H], 2.54, 2.56 [overlapping d, J = 12 Hz, and br s, 4 H, H(1,5) and H(6,8)ax], 3.49 [d, J = 12 Hz, 2 H, H(6,8)eq], 3.73 [s, 2 H, $PhCH_2$], 5.50 [br s, 2 H, H(2,4)], 7.14-7.80 [m, 13 H, ArH]; ^{13}C NMR ($DCCl_3$) ppm 55.2 [d,

C(1,5)], 58.8 [t, C(6,8)], 59.0 [d, C(2,4)], 61.0 [t, Ph$\underline{C}H_2$], 127.4, 127.5, 128.3_8, 128.4_3, 128.6, 129.1_6, 129.2_1, 132.2, 138.4, 142.6 [Ar$\underline{C}$], 212.0 [s, C(9)]; ^{15}N NMR ($DCCl_3$) ppm 38.3 [N(7)], 58.2 [N(3)]. Anal. of **18d** calcd. for $C_{26}H_{24}Cl_2N_2O$: C, 69.18; H, 5.36; Cl, 15.71; N, 6.21. Found: C, 69.31, H, 5.20; Cl, 15.83; N, 6.18.

Solids B, C and E were combined and recrystallized (2-propanol/$HCCl_3$, 3:1, 15 mL) to afford additional ketone **18d** (0.50 g, 17.3% total), mp 184-185°C. Solid D was also recrystallized from an identical solvent system (15 mL) to afford ketone **17d** (0.36 g, 4.0%) as short white needles: mp 207-208°C; IR (KBr) cm^{-1} 3270 (N-H), 1717 (C=O); ^{1}H NMR ($DCCl_3$) δ 2.54 [d, J = 12 Hz, 2 H, H(6,8)ax], 2.76 [br s, 2 H, H(1,5)], 3.12 [d, J = 12 Hz, 2 H, H(6,8)eq], 3.32 [s, 2 H, Ph$\underline{C}H_2$], 4.70 [br s, 1 H, N-$\underline{H}$], 4.80 [br s, 2 H, H(2,4)], 7.15-7.60 [m,Ar$\underline{H}$]; ^{13}C NMR ($DCCl_3$) ppm 50.9 [d, C(1,5)], 55.5 [t, C(6,8)], 62.1 [d, C(2,4)], 62.5 [t, Ph$\underline{C}H_2$], 126.6, 127.4, 128.4, 128.6, 129.8, 129.8, 129.9, 132.3, 136.6, 137.2 [Ar$\underline{C}$], 212.2 [s, C(9)]; ^{15}N NMR ($DCCl_3$) ppm 46.9 [N(7)], 54.4 [N(3)]. Anal. of **17d** calcd. for $C_{26}H_{24}Cl_2N_2O$: C, 69.18; H, 5.36; Cl, 15.71; N, 6.21. Found: C, 69.33; H, 5.53; Cl, 15.97; N, 6.09.

Method B: reaction performed at RT. A one-necked, 50-mL round-bottom flask was fitted with a condenser. The flask was charged with 95% ethanol (50 mL) and the apparatus flushed was with N_2. Ketone **16f** (4.73 g, 25.0 mmol), 2-chlorobenzaldehyde (7.03 g, 50.0 mmol), and ammonium acetate (5.78 g, 75.0 mmol) were added to the flask. The apparatus was flushed with N_2 and the mixture was allowed to stir at RT. The NH_4OAC slowly dissolved over 1 h and the formation of a small amount of white precipitate was noted shortly thereafter. Continued stirring at RT for 5 d gave additional white precipitate while the supernatant

slowly developed a bright red-orange color. The precipitate (solid A) was filtered and washed with ethyl ether (50 mL); the washings were combined with the original filtrate. This solution was cooled at -10°C for 2 d, thus precipitating additional white solid (solid B) which was filtered and washed with ether. The filtrate was evaporated (aspirator) to give an orange gum. Ethyl ether (100 mL) was added and the mixture heated on a steam bath until a third, almost white solid separated from the orange supernatant. This was filtered, washed with ether and recrystallized (2-propanol/$HCCl_3$, 3:1, 10 mL) to afford **17d** (0.1983 g, 1.8%) as tiny needles, mp 207-209°C.

Solid A was recrystallized (2-propanol/$HCCl_3$, 3:1, 110 mL) to afford **18d** (3.14 g) as long white needles, mp 184.0-184.5°C. Solid B was recrystallized in the same solvent system (15 mL) to give additional **18d** (0.40 g, 31.3% total), mp 184-185°C. The IR, ^1H and ^{13}C NMR spectra for these products were identical to that given previously.

Method C: reaction performed in boiling ethanol. A three- necked, 25-mL round-bottomed flask was fitted with a condenser, an addition funnel, and a heating mantle. This flask was charged with ammonium acetate (1.16 g, 15.0 mmol) and ethanol (10 mL) and the flask flushed with N_2. The slurry was heated to reflux and the NH_4OAc allowed to dissolve. The resulting solution cooled to RT and then treated in one portion with a solution of 1-benzylpiperidin-4-one (1.89 g, 10.0 mmol), o-chlorobenzaldehyde (2.81 g, 20.0 mmol) and ethanol (10 mL). This solution was heated at reflux for 1.3 h. Upon cooling to RT, a yellow white solid precipitated from the reaction mixture. This solid was filtered, washed with ether, and recrystallized (2-propanol/$HCCl_3$, 3:1, 10 mL) to afford **18d** (0.1871 g, 4.1%) mp 184-185°C.

to afford **19c** (0.74 g), mp 170.5-171.7°C. Thin layer chramatography (silica gel, hexane/ethyl acetate, 19:1) of the brown filtrate previously set aside revealed the presence of unreacted benzaldehyde (R_f 0.53), **18c** (R_f 0.35) and dark polymeric materials (at the baseline). No other easily eluted materials were present in other than trace quantities. The brown filtrate was evaporated and placed onto a silica gel column. Amine **19c** was eluted (hexane/ethyl acetate, 6:1) as a yellow band. Evaporation, followed by air drying resulted in additional **19c** (0.35 g, 60% total). The IR spectrum of this compound was identical that described elsewhere (see attempted preparation of **107**).

N,N'-Dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one (28d)

Method A. Following a procedure similar to that reported[16] for this compound, a three-necked, 50-mL round-bottomed flask was fitted with a dropping funnel (60 mL), a condenser and a heating mantle. This flask was charged with benzylamine (2.68 g, 25.0 mmol), glacial acetic acid (1.54 g, 25.8 mmol) and methanol (25 mL). Paraformaldehyde (1.58 g, 52.5 mmol) was added, the apparatus was flushed with N_2 and the mixture was brought to reflux with stirring. After 15 min, a solution of 1-benzylpiperidin-4-one (**16f**, 4.73 g, 25.0 mmol) and glacial acetic acid (1.50 g, 25.0 mmol) in methanol (18 mL) was added dropwise over 0.5 h. The resulting orange solution was then heated at reflux for an additional 9.5 h. Upon cooling to RT, the solvent was evaporated from the reaction mixture to leave an orange oil. Water (50 mL) and KOH pellets (85%, 3.30 g, 50.0 mmole) were added and the resulting oily, orange suspension was extracted (CH_2Cl_2, 3 x 50 mL). The organic

The filtrate of the original reaction mixture was diluted with ether (20 mL) and allowed to stand at -10°C for 3 h. No additional solid was observed to precipitate. The solvent was evaporated and ether (20 mL) was added to the resulting orange oil. Warming on a steam bath for a few minutes resulted in the precipitation of a white solid. Filtration of this solid, washing with cyclohexane, and recrystallization (2-propanol/$HCCl_3$, 3:1, 30 mL) afforded **17d** (0.7300 g, 16.2%) mp 209.5-210°C.

The remaining portion or the original reaction mixture was evaportated and partitioned between ether (30 mL) and water (30 mL). The red-orange ether layer was dried (Na_2SO_4), filtered, an evaporated to afford an orange-red oil that solidified. Addition of cyclohexane (30 mL) followed by heating on a steam bath, resulted in the dissolution of a red impurity from the now yellow solid. This solid was filtered and recrystallized (2-propanol/$HCCl_3$, 3:1, 10 mL) to afford **19b** (88.3 mg, 2.0%): mp 171-172°C, IR (KBr) cm^{-1} 1665 (C=O); ^1H NMR ($DCCl_3$) δ 3.63 [s, 2H. $PhC\underline{H}_2$], 3.71 [s, 4H, ring CH_2], 7.06-7.50 [m, 12 H], 8.10 [s, 1H]; ^{13}C NMR ($DCCl_3$) 53.5 [t, ring CH_2], 60.0 [t, $PhC\underline{H}_2$], 126.3, 127.2, 128.2, 128.9, 129.8, 129.9, 130.2, 133.5, 134.4, 135.0, 137.2, 187.2 [s, $\underline{C}$=O]. Mass spectral m/e calcd. for $C_{26}H_{21}Cl_2NO$: (M^+) 433.0994. Found: 433.1003. Anal. calcd. for $C_{26}H_{21}Cl_2NO$: C, 71.89; H, 4.87; N, 3.22; Cl, 16.32. Found: C, 71.79; H, 5.13; N, 3.06; Cl, 16.45. The spectral properties of the bicyclic products **17d** and **18d** were identical to those given previously.

Attempted Preparation of 7-Benzyl-2,4-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-ones 17e, 18e

By method B. Employing the apparatus and procedure described, N-benzyl-piperidin-4-one (**16f**, 1.50 g, 7.93 mmol) was treated with benzaldehyde (1.68 g, 15.9 mmol), ammonium acetate (1.83 g, 23.7 mmol) in ethanol (20 mL total). The reaction mixture was allowed to stir for 21 d during which a red-brown color developed. No solid precipitate was noted to form in the reaction mixture, nor was any formed during the workup described. Finally the reaction mixture was evaporated to an orange oil. This was dissolved in CH_2Cl_2 (5 mL) and absorbed onto silica gel. After evaporation of the solvent, this mixture was placed on a silica gel chromatography column. Elution with hexane/ethyl acetate (9:1) afforded the separation of a yellow band (R_f 0.61, same solvent system) from a dark brown band which remained at the top of the column. Evaporation of the solvent afforded a yellow solid (1.09 g, 38%), mp 169-170°C, that afforded an IR spectrum identical with that of **19c**, (see procedure for the attempted preparation of **107**).

By method C. Employing the apparatus and procedure described, N-benzylpiperidin-4-one (0.95 g, 5.0 mmol) was treated with benzaldehyde (1.06 g, 10.0 mmol), ammonium acetate (0.58 g, 7.5 mmol) in ethanol (10 mL total). The reaction mixture was heated at reflux for 4 h, during which the reaction mixture turned to a tan-brown color. After cooling to RT the reaction mixture was diluted with ether and permitted to stand for 3 d at RT. No solid precipitate was observed. Evaporation of the solvent afforded a oily yellow solid. This was washed with ether and filtered. The solid was recrystallized (2-propanol/$HCCl_3$, 3:1, 30 mL)

extracts were combined and dried ($MgSO_4$, overnight). Filtration of the drying agent, followed by removal of the solvent, afforded another orange oil (6.41 g) which was vacuum distilled (8 x 10^{-7} mm Hg, diffusion pump). At 106-108°C, a colorless oil (0.36 g) was collected, the ^{13}C NMR of which was identical to that of the starting material **16f**. A second fraction (bp 180-205°C) was collected as a yellow oil but with substantial decompositon of the residue. Redistillation (180-185°C, 1.0 x 10^{-6} mm Hg) of this second fraction again afforded a yellow oil, however, no significant decomposition was noted in this second distillation. The distillate from the second distillation was dissolved in hot Skelly B (80 mL). Upon cooling to -10°C, ketone **28d** (2.53 g, 31.6%) was precipitated as a white solid, mp 61-63°C (lit.[16] 70-71°C). The compound was used in the next step without further purification. Spectroscopic data for this compound were: IR (KBr) cm^{-1} 2963, 2822, 1738, 1721, 748, 703; ^1H NMR ($DCCl_3$) δ 2.52 [br s, 2 H, H(1,5)], 2.76, 2.78 [two d, J = 10.5, J = 10.7 Hz, 4 H, H(2,4,6,8)ax], 3.00 [br d, J = 10.7 Hz, 4 H, H(2,4,6,8)eq], 3.53 [s, 4 H, $PhC\underline{H}_2$], 7.23-7.30 [m, 10 H, $Ar\underline{H}$]; ^{13}C NMR ($DCCl_3$) ppm 46.7 [d, C(1,5)], 58.0 [t, C(2,4,6,8)], 61.1 [t, $Ph\underline{C}H_2$], 126.9 [d, $\underline{p}$-$Ar\underline{C}$], 128.0 [d, $\underline{o}$- or $\underline{m}$-$Ar\underline{C}$], 128.5 [d, $\underline{m}$- or $\underline{o}$-$Ar\underline{C}$] 138.0 [s, $\underline{i}$-$Ar\underline{C}$], 214.0 [s, C(9)]; ^{15}N NMR ($DCCl_3$) ppm 39.2 [N(3,7)].

Method B. In a modification of the previous procedure, a solution of 1-benzylpiperidin-4-one (**16f**, 4.73 g, 25.0 mmol) and glacial acetic acid (1.50 g, 25.0 mmol) in methanol (25 mL) was added as before to a boiling mixture of paraformaldehyde (6.00 g, 200 mmol), glacial acetic acid (1.62 g, 27.0 mmol), benzylamine (2.68 g, 25.0 mmol), and methanol (100 mL). The mixture was permitted to heat at reflux for 24 h and the

aqueous workup was as outlined above (Method A). Instead of the distillation described, the crude oil from the workup was digested in Skelly B (300 mL) on a steam bath for 0.5 h. The hot supernatant was decanted from the yellow residue and evaporated (aspirator followed by vacuum pump, RT, 0.02 mm Hg, 20 min). This afforded ketone **28d** (6.84 g, 85.4%) as a white oil that did not solidify after 3 d at -10°C. The ^{1}H and ^{13}C NMR spectra of this oil were virtually identical to that described above and the material proved to be satisfactory for use in the next steps.

N,N'-Dibenzyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (29d)

Following a procedure similar to those in the literature,[16,92] a jacketed, two-necked, 70-mL flask was fitted with a lower take-off condenser and a receiving flask, a thermometer, a condenser on the jacket and a heating mantle. This flask was charged with ketone **28d** (oil, 2.00 g, 6.24 mmol), hydrazine hydrate (85%, 1.10 g, 18.7 mmol), KOH pellets (85%, 2.06 g, 31.2 mmol), and triethylene glycol (25 mL). The apparatus was flushed with N_2 and the mixture was heated at 120°C for 0.5 h using tetralin (bp 207°C) in the jacket. The reaction mixture was then allowed to heat at reflux for 5 h. The temperature slowly increased to 207°C with removal of the volatile distillates and with the evolution of N_2. After cooling to RT, the reaction mixture was poured, along with the distillate, into cool water (30 mL). The resulting white suspension was extracted (ethyl ether, 4 x 30 mL), and the combined extracts were washed successively with NaOH solution (10%, 30 mL), H_2O (30 mL), and NaCl solution (saturated, 30 mL). After drying (Na_2SO_4,

overnight), the solution was filtered and evaporated to give the crude reduced amine as a yellow oil (1.34 g, 70.1%). This oil was dissolved in C_6H_6 (20 mL) and treated dropwise over 15 min with a solution of $HClO_4$ (60%, 2.20 g, 13.1 mmol) in 2-propanol (5 mL) to give a dark solution. This solution was stirred (magnetic) for 1 h after which it was concentrated (~5 mL). Addition of ethyl ether (20 mL) precipitated the salt as a dark brown solid. Filtration and recrystallization (aqueous ethanol, 20 mL, decolorizing carbon) afforded a first crop of **29d** (0.6522 g) white crystals; mp 221-222°C (lit.[92] 210-217°C, orange crystals). Concentration of the mother liquor to 7 mL gave a second crop (0.1257 g, 43.7% total), again as white crystals (mp 220-222°C). The spectral data for **29d** were: IR (KBr) cm^{-1} 2960, 2841 (C-H), 2800-2600 ($\overset{+}{N}$-H), 1100, 1080 (Cl-O); ^1H NMR (DMSO-d_6) δ 1.72 [br s, 2 H, H(9)], 2.14 [br s, 2 H, H(1,5)], 2.77 [d, J = 13 Hz, 4 H, H(2,4,6,8)ax], 3.13 [d, J = 13 Hz, 4 H, H(2,4,6,8)eq], 3.43 [br s, 1 H, $\overset{+}{N}$-H], 3.86 [s, 4 H, $PhCH_2$], 7.30-7.48 [m, 10 H, ArH]; ^{13}C NMR (DMSO-d_6) ppm 27.4 [d, C(1,5)], 29.5 [t, C(9)], 56.9 [t, C(2,4,6,8)], 60.4 [t, $PhCH_2$], 128.2 [d, p-ArC], 128.4 [d, o- or m-ArC], 129.6 [d, m- or o-ArC], 133.3 [s, i-ArC]; ^{15}NMR (DMSO-d_6) ppm 54.6 [N(3,7)]. Anal. calcd. for $C_{21}H_{27}ClN_2O_4$: C, 61.99; H, 6.69; Cl, 8.71; N, 6.88. Found: C, 61.92; H, 6.84; Cl, 8.71, N, 6.82.

7-Benzyl-2,4-bis(2-chlorophenyl)-3,7-diazabicyclo[3.3.1]nonane (30b)

A two-necked, 200-mL jacketed flask was fitted with a thermometer, a lower take-off condenser with receiving flask , a heating mantle, and a condenser on the jacket. This flask was charged with ketone **17d**

(1.87 g, 4.15 mmol) and triethylene glycol (75 mL) and the jacket charged with tetralin. The apparatus was flushed with N_2 and the mixture heated to 110°C with stirring to dissolve the ketone. Hydrazine hydrate (85%, 1.22 g, 20.7 mmol) was added in one portion and the resulting solution heated at 110-120°C for 1 h. Potassium hydroxide pellets (85%, 8.8 g) were then added and the resulting mixture heated to 195°C over 4 h with the distillation of volatiles and the evolution of N_2. After cooling to RT, the solution was poured into H_2O (50 mL) and the resulting suspension was extracted with ether (7 x 50 mL). The combined ether extracts were washed with NaOH solution (10%, 100 mL) and dried (K_2CO_3, overnight). Filtration followed by evaporation (aspirator) of the filtrate gave a yellow oil which was dissolved in warm ethanol (50 mL). Trituration with ethyl ether afforded, upon cooling, white cubic crystals which were filtered, washed with ether, and dried to give amine **30b** (1.11 g, 61%): mp 149-151°C; IR (KBr) cm^{-1} 3250 (N-H); ^1H NMR ($DCCl_3$) δ 2.04 [br s, 2 H, H(1,5)], 2.06 [d, J = 10 Hz, 1 H, H(9)], 2.17 [d, J = 10 Hz, 2 H, H(6,8)ax], 2.29 [d, J = 10 Hz, 1 H, H(9)], 2.82 [d, J = 10 Hz, 2 H, H(6,8)eq], 3.10 [s, 2 H, PhC<u>H</u>$_2$], 4.44 [br s, 1 H, N-<u>H</u>], 4.68 [br s, 2 H, H(2,4)], 7.08-7.44 [m, 13 H, Ar<u>H</u>]; ^{13}C NMR ($DCCl_3$) ppm 31.5 [d, C(1,5)], 35.9 [t, C(9)], 54.9 [t, C(6,8)], 61.6 [d, C(2,4)], 64.3 [t, Ph<u>C</u>H$_2$], 126.5, 127.3, 127.5, 128.2, 129.3, 129.8, 132.3, 138.0, 140.2 [Ar<u>C</u>]; ^{15}N NMR ($DCCl_3$) ppm 47.4 [N(7)], 53.8 [N(3)]. Anal. calcd. for $C_{26}H_{26}Cl_2N_2$: C, 71.39; H, 6.00; Cl, 16.21; N, 6.40. Found: C, 71.48; H, 6.04; Cl, 16.00; N, 6.65.

7-Benzyl-2,4-bis(2-chlorophenyl)-3,7-diazabicyclo[3.3.1]nonane 31b

A two-necked, jacketed flask was fitted with a thermometer, a lower take-off condenser, a heating mantle, and a condenser on the jacket. The flask was charged with ketone **18d** (0.80 g, 1.8 mmol) and triethylene glycol (50 mL), and the jacket charged with tetralin (bp 207°C). The apparatus was flushed with N_2 and warmed to 110 C with stirring to dissolve the ketone. To this solution was added in one portion hydrazine hydrate (85%, 0.52 g, 10.4 mmol), and the resulting solution was stirred at 110°C for 1 h. Potassium hydroxide pellets (85%, 5.00 g) were then added and the mixture heated to 195°C over 4.5 h with the continuous distillation of volatiles and until N_2 evolution ceased. Upon cooling to RT, the tan solution was poured into H_2O (50 mL) and the resulting suspension was extracted with ethyl ether (5 x 30 mL). The combined ether extracts were washed with NaOH solution (10%, 50 mL) and dried (Na_2SO_4, overnight). Filtration followed by evaporation (aspirator) of the filtrate afforded a yellow oil which was dissolved in hot ethanol (25 mL). Upon cooling, the product precipitated as white plates, which were filtered and dried to a afford amine **31b** (0.54 g, 69%): mp 136.4-137.0°C; IR (KBr) cm^{-1} 3300 (N-H); ^1H NMR ($DCCl_3$) δ 1.07 [dt, J = 12.3, 2.7 Hz, 1 H, H(9)endo], 1.18 [br s, 1 H, N-H], 1.83 [br s, 2 H, H(1,5)], 2.09 [d, J = 10 Hz, 2 H, H(6,8)ax], 2.35 [d, J = 12.3 Hz, 1 H, H(9)exo], 3.08 [d, J = 10 Hz, 2 H, H(6,8)ax], 3.50 [s, 2 H, $PhCH_2$], 4.77 [d, J = 2.5 Hz, 2 H, H(2,4)], 7.09-7.92 [m, 13 H, ArH]; ^{13}C NMR ($DCCl_3$) ppm 24.6 [t, C(9)], 36.1 [d, C(1,5)], 56.1 [d, C(2,4)], 58.8 [t, C(6,8)], 62.8 [t, $PhCH_2$], 126.8, 127.0, 127.5, 128.0, 128.1, 129.1, 129.3, 132.4, 139.2, 145.7 [ArC]; ^{15}N NMR ($DCCl_3$) ppm 38.2

[N(7)], 50.5 [N(3)]. Anal. calcd. for $C_{26}H_{26}N_2Cl_2$: C, 71.39; H, 6.00; N, 6.40; Cl, 16.21. Found: C, 71.17; H, 6.25, N, 6.32, Cl, 16.15.

7-Benzyl-2,4-bis(2-chlorophenyl)-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate 32b

In a one-necked, 100-mL round-bottomed flask, a solution of amine **30b** (0.4957 g, 1.14 mmol) in C_6H_6 (20 mL) was treated dropwise over 15 min with $HClO_4$ (60%, 0.5 mL) with vigorous stirring. This resulted in the precipitation of a white solid. The flask was fitted with a condenser and heated on a steam bath for an additional 5 min, followed by cooling to RT. The solution was filtered and the cloudy filtrate set aside. Recrystallization of this solid (CH_3OH, 30 mL) afforded the monoperchlorate **32b** (0.1050 g) as white crystals, mp 264.0-264.5°C (dec). The cloudy benzene filtrate was evaporated to about 2 mL and the resulting oil was dissolved in hot CH_3OH (30 mL). Upon cooling to RT, additional product precipitated as a white powder. This was filtered and recrystallized (CH_3OH, 65 mL) to afford additonal **32b** (0.3575 g, 74% total) again as white crystals, mp 260-262°C (dec). The spectroscopic data were as follows: IR (KBr) cm^{-1} 3300 (N-H), 2850-2700 ($\overset{+}{N}$-H), 1090 (Cl-O); ^1H NMR (DMSO-d_6) δ 2.19 [d, J = 12 Hz, 1 H, H(9)], 2.35 [d, J = 12 Hz, 1 H, H(9)], 2.38 [br s, 2 H, H(1,5)], 3.02 [br s, 4 H, H(6,8)ax and eq], 4.08 [br s, 2 H, PhCH_2], 4.88 [br s, 2 H, H(2,4), 5.63 [br s, 1 H, N-H], 7.36-7.72 [m, 13 H, ArH], 10.13 [br s, 1 H, $\overset{+}{N}$-H]; ^{13}C NMR (DMSO-d_6) ppm 29.8 [d, C(1,5)], 31.4 [t, C(9)], 53.0 [t, C(6,8)], 60.3 [t, PhCH_2], 60.8 [d, C(2,4)], 127.3, 127.4, 128.9, 129.3, 129.9, 130.8, 131.2, 131.3, 136.3, 142.0, [ArC]; ^{15}N NMR (DMSO-d_6) ppm 50.0 [N(7],

52.6 [N(3)]. Anal. calcd. for $C_{26}H_{27}Cl_3N_2O_4$: C, 58.05; H, 5.07; Cl, 19.73; N, 5.21. Found: C, 58.07; H, 5.08; Cl, 19.66; N, 5.27.

7-Benzyl-2,4-bis(2-chlorophenyl)-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate 33b

In a one-necked, 100-mL round-bottomed flask, a solution of amine **31b** (0.80 g, 1.83 mmol) in C_6H_6 (30 mL) was treated dropwise slowly with a solution of $HClO_4$ (60%, 1.50 g, 8.96 mmol) in 2-propanol (5 mL) resulting in the formation of a white powdery precipitate. The flask was fitted with a condenser and the mixture heated warmed on a steam bath for 15 min. After cooling to RT, the precipitate was filtered and recrystallized in a minimum amount of 70% acetone to afford the monohydroperchlorate **33b** (0.80g, 81%) as fine white crystals: mp 246-247°C (dec); IR (KBr) cm^{-1} 3330 (N-H), 2900-2600 ($\overset{+}{N}$-H), 1110 (Cl-O); ^1H NMR (DMSO-d_6) δ 1.70 [d, J = 14 Hz, 1 H, H(9)endo], 2.33 [d, J = 11 Hz, 2 H, H(6,8)ax], 2.38 [br s, 2 H, H(1,5)], 2.51 [overlapping d, J = 14 Hz, H(9)exo and br s, DMSO-d_5], 2.85 [d, J = 11 Hz, 2 H, H(6,8)eq], 3.70 [s, 2 H, PhCH_2], 5.00 [d, J = 8 Hz, H(2,4)], 7.32-7.94 [m, 13 H, ArH], 8.10 [br s, 1 H, N-H], 9.84 [br s, 1 H, $\overset{+}{N}$-H]; ^{13}C NMR (DMSO-d_6) ppm 24.5 [t, C(9)], 33.7 [d, C(1,5)], 55.9 [t, C(6,8)], 56.9 [d, C(2,4)], 60.9 [t, C(10)], 127.6-130.9 [ArC], 132.6, 135.5, 137.1 [ArC]; ^{15}NMR (DMSO-d_6) ppm 38.3 [N(7)], 54.6 [N(3)]. Anal. calcd. for $C_{26}H_{27}Cl_3N_2O_4$: C, 58.06; H, 5.06; Cl, 19.78; N, 5.21. Found: C, 58.16; H, 5.20, Cl, 19.65; N, 5.16.

3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9,9-diol Hydroperchlorate (70d)

In a 50-mL Erlenmeyer flask, a vigorously stirred (magnetic) solution of ketone **28d** (1.00 g, 3.12 mmol) in C_6H_6 (20 mL) was treated dropwise with a solution of $HClO_4$ (60%, 1.56 g, 9.32 mmol) in 2-propanol (5 mL) over 15 min, thus precipitating the salt as a white powder. The mixture was stirred for an additional 1 h. The solid was filtered and recrystallized (2-propanol/H_2O, 11:1) to afford, after drying (Abderhalden, 82°C, 0.2 mm Hg, P_2O_5, 24 h) diol **70d** (0.51 g, 37%): mp 209.5-210.8°C; ^1H NMR (DMSO-d_6) δ 1.96 [s, 2 H, H(1,5)], 3.05 [s, 8 H, H(2,4,6,8)], 3.89 [s, 4 H, PhCH_2], 6.22 [s, 2 H, O-H], 7.36-7.56 [m, 10 H, ArH], 9.88 [s, 1 H, $\overset{+}{N}$-H]; ^{13}C NMR (DMSO-d_6) ppm 38.54 [d, C(1,5)], 54.3 [t, C(2,4,6,8)], 59.7 [t, PhCH_2], 89.2 [s, C(9)], 128.1, 128.1, 128.4, 130.0 [ArC]; ^{15}N NMR (DMSO-d_6) ppm 52.9 [N(3,7)]. Anal. calcd. for $C_{21}H_{27}N_2Cl$: N, 6.38; Cl, 8.08. Found: N, 6.56; Cl, 8.55.

7-Benzyl-9,9-dimethoxy-3-thia-7-azabicyclo[3.3.1]nonane Hydroperchlorate (102a)

Caution: The use of shields, protective goggles and gloves is very strongly recommended when performing this experiment. The formation of explosive methyl perchlorate is a likely side reaction in this experiment. No difficulty was noted in when the reaction was performed as described, but this may have been fortuitous. A one-necked, 100-mL round bottomed flask was fitted with a Soxhlet containing 3A molecular sieves (30 g), a condenser, a heating mantle, a magnetic stirrer, and a heating mantle. The effective cycling volume of the Soxhlet was approximately 15 mL. The flask was charged with a

solution of ketone **27a** (1.00 g, 4.04 mmol) in methanol (20 mL) and benzene (20 mL). To this solution was added $HClO_4$ (60%, 2.03 g, 12.1 mmol) in one portion. The apparatus was flushed with N_2 and the pale yellow solution was heated at reflux with stirring and cycling through the Soxhlet for 24 h. The solution was cooled to RT and concentrated to about 5 mL. Ethyl ether (20 mL) was added, thus precipitating the salt as a powder. This was filtered, washed with ether (5 mL), and dissolved in hot methanol (20 mL, decolorizing carbon). Trituration with ether (25 mL), followed by standing for 24 h, afforded **102a** (0.7345 g, 46.2%) as small white crystals: mp 193-194°C (dec); IR (KBr) cm^{-1} 2800-2600 ($\overset{+}{N}$-H), 1090 (Cl-O); ^1H NMR (DMSO-d_6) δ 2.58 [br s, 2 H, H(1,5)], 2.75 [d, J = 14 Hz, 2 H, H(2,4)ax], 3.15-3.18 [m, 8 H, H(2,4)eq, CH_3O], 3.38 (dd or br t, J = 12 Hz, 2 H, H(6,8)ax], 3.60 [d, J = 12 Hz, H(6,8)eq], 4.33 [d, J = 5 Hz, 2 H, $PhCH_2$], 7.49-7.62 [m, 5 H, ArH], 9.28 [br s, 1 H, $\overset{+}{N}$-H]; ^{13}C NMR (DMSO-d_6) ppm 28.8 [t, C(2,4)], 32.2 [d, C(1,5)], 46.6 [q, CH_3O], 47.0 [q, CH_3O], 54.5 [t, C(6,8)], 60.2 [t, $PhCH_2$], 95.1 [s, C(9)], 129.0 [d, o- or m-ArC], 129.5 [s, i-ArC], 130.1 [d, p-ArC], 130.2 [d, m- or o-ArC]; ^{15}N NMR (DMSO-d_6) ppm 53.5 [N(7)]. Anal. calcd. for $C_{26}H_{24}ClNO_6S$: C, 48.79; H, 6.14; Cl, 9.00; N, 3.56; S, 8.14. Found: C, 48.73; H, 6.09; Cl, 9.39; N, 3.54; S, 8.40.

N,N'-Dibenzyl-9,9-dimethoxy-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (102b)

Caution: The use of shields, protective goggles and gloves is very strongly recommended when performing this reaction. The formation of explosive methyl perchlorate is a likely side reaction in this

experiment. No difficulty was noted in when the experiment was performed as described, but this may have been fortuitous. A one-necked, 100-mL round bottomed flask was equipped with a Soxhlet containing 3A molecular sieve (30 g), a condenser with N_2 inlet, a magnetic stirrer and a heating mantle. The effective cycling volume of the Soxhlet was approximately 20 mL. The flask was charged with a solution of ketone **28d** (1.00 g, 3.12 mmol) in CH_3OH (25 mL) and C_6H_6 (25 mL) to which was added $HClO_4$ (60%, 1.50 g, 8.96 mmol) in one portion. The apparatus was flushed with N_2 and the colorless solution was heated to reflux with cycling through the Soxhlet. After 24 h, the now pale yellow solution was cooled to RT and concentrated to about 5 mL. Upon standing for a few minutes, a product precipitated as a white solid which was filtered, washed with C_6H_6 (10 mL), and recrystallized (CH_3OH, 80 mL) to afford the monoperchlorate **102b** (0.9103 g) as small white crystals, mp 223.6-224.0°C (dec). The mother liquor was concentrated to approximately 10 mL. Upon cooling at -10°C overnight, a second crop of **102b** was obtained (89.4 mg, 68.6% total), mp 219-220°C (dec). The spectral data were as follows: IR (KBr) cm^{-1} 2800-2600 ($\overset{+}{N}$-H), 1100 (Cl-O); ^1H NMR (DMSO-d_6) δ 2.35 [br s, 2 H, H(1,5)], 2.90 [d, J = 13 Hz, 4 H, H(2,4,6,8)ax], 3.08 [d,J = 13, 4 H, H(2,4,6,8)eq], 3.14 [s, 6 H, CH_3O], 3.88 [s, 4 H, $PhCH_2$], 7.38-7.54 [m, 10 H, ArH], 9.84 [br s, 1 H, $\overset{+}{N}$-H]; ^{13}C-NMR (DMSO-d_6) ppm 33.0 [d, C(1,5)], 47.0 [q, CH_3O], 53.8 [t, C(2,4,6,8)], 59.6 [t, $PhCH_2$], 95.4 [s, C(9)], 128.2 [d, p-ArC], 128.4 [d, o- or m-ArC], 129.6 [d, m- or o-ArC], 133.5 [s, i-ArC]; ^{15}N NMR (DMSO-d_6) ppm 52.9 [N(3,7)]. Anal. calcd. for $C_{23}H_{31}ClN_2O_6$: C, 59.16: H, 6.69; Cl, 7.59; N, 6.00. Found: C, 58.98; H, 6.81; Cl, 7.86; N, 6.28.

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one (27a), 3,6-Dibenzylhexahydro-8a-methoxy-5H-4a,8-(methanothiomethano)-2H-pyrido[3,4-e]-1,3-oxazine (103a) and 2,4,10,12-Tetrabenzyl-2,4,10,12-tetraaza-15-thiadispiro-[5.1.5.3]hexadecan-7-one (104a)

Method A: 2.0 equivalents benzylamine. A three-necked, 50 mL round-bottomed flask was fitted with a condenser and a heating mantle. This flask was charged with paraformaldehyde (1.20 g, 40.0 mmol), benzylamine (1.07 g, 10.0 mmol), glacial acetic acid (0.66 g, 11.0 mmol), and methanol (20 mL). The apparatus was flushed with N_2 and the mixture boiled at reflux with stirring for 15 min. To the mixture was added in one portion a solution of ketone **16c** (0.58 g, 5.0 mmol) in methanol (10 mL) and the resulting mixture heated at reflux for 9 h during which the paraformaldehyde slowly dissolved and the solution turned yellow. After cooling to RT, the solution was allowed to stir an additional 10 h. Removal of the solvent afforded a yellow oil which was partitioned between ether (50 mL) and water (50 mL). The layers were separated and the pale yellow ether layer was allowed to stand for 24 h at -10°C. A white crystalline solid precipitated from this ether solution. This was filtered and set aside. The filtrate was concentrated to half of the previous volume and allowed to stand for 3 h. A second crop of the white solid was precipitated. This was filtered, combined with the first crop, and recrystallized (95% ethanol, 30 mL) to afford **103a** (0.93 g, 45%) as white needles: mp 147.2-148.8°C.

The aqueous phase was cooled in an ice bath and made alkaline by the addition of NaOH pellets (0.50 g, 12 mmol) and extracted with ether

(4 x 50 mL). The combined ether extracts from this last step were dried (Na_2SO_4, overnight), and were evaporated to afford a yellow oil. This oil was digested in boiling Skelly B for 30 min. The supernatant was decanted from the brown residue and evaporated to afford a yellow oil (0.50 g) that did not solidify. Although this oil was not characterized, later experiments have indicated that this oil was most likely usually crude **27b**.

Method B: Dropwise Addition. A three necked, 50 mL round-bottomed flask was fitted with a dropping addition funnel, a condenser, and a heating mantle. The flask was charged with a slurry of paraformaldehyde (1.20 g, 40.0 mmol) in methanol (20 mL) and was heated at reflux under N_2 for 15 min. To this boiling mixture was added dropwise over 3.5 h a solution of ketone **16b** (0.58 g, 5.0 mmol), benzylamine (1.07 g, 10.0 mmol), glacial acetic acid (0.66 g, 11.0 mmol) in methanol (10 mL). During the addition the paraformaldehyde slowly dissolved and the solution turned to an orange-red color. The solution was heated at reflux for an additional 3.5 h, then allowed to stir at RT for 48 h. A white solid precipitated from the now pink solution. This solid was filtered, washed with methanol (5 mL) and recrystallized (2-propanol, 30 mL) to afford **104a** (0.2610 g, 8.5% relative to the amount of benzylamine used) as white needles: mp 172.5-173.5°C. The reaction mixture filtrate was evaporated to an orange-red oil which was partitioned between ether (50 mL) and water (50 mL). The ether layer was treated as before to afford after recrystallization (ethanol, 25 mL) **103a** (0.2119 g, 11%), mp 146.5-148.0°C; the ^{13}C NMR spectrum of which was identical to that given previously. The pink aqueous suspenson was made alkaline by the addition of NaOH pellets (0.50 g, 12.5 mmol) to

give a yellow suspension. This suspension was extracted with ether (4 x 50 mL) and the combined ether extracts were dried (Na_2SO_4, overnight). The dry ethereal solution was filtered and evaporated (aspirator) and the resulting yellow oil was digested in boiling Skelly B (200 mL) for 30 min. The hot supernatant was decanted from the brown residue and evaporated (aspirator followed by vaccuum pump) to leave a pale yellow oil (0.59 g, ~47%). The ^{13}C NMR ($DCCl_3$) of this oil indicated that it was mostly ketone **27a** with a small amount of **103a** present as an impurity.

Method C: 1.0 Equivalent Benzylamine. The general procedure and ratio of reagents described by Bailey and coworkers[14] was repeated. However, the relatively large scale employed here required some modifications in the procedure. A three-neck, 1000 mL round-bottomed flask was fitted with a condenser, a power stirrer, and a heating mantle. This flask was charged with benzylamine (21.43 g, 0.2000 mol), paraformaldehyde (48.04 g, 1.600 mol), acetic acid (18.02 g, 0.3000) and methanol (750 mL). The apparatus was thoroughly flushed with N_2, and the mixture heated to reflux with stirring. Ketone **16c** (23.24 g, 0.2000 mol) was then added in one portion. As before, the solution immediately developed a yellow color, changing to red as the reaction proceeded and the paraformaldehyde slowly dissolved. On cooling to RT, no solid precipitate was noted. The workup of the reaction mixture was as described previously. The red oil, afforded by removal of the solvent, was suspended in water (1500 mL), and this suspension washed with ether (4x400 mL). The aqueous layer was set aside. The combined ether layers were partially dried (K_2CO_3, 1 h, vigorous stirring) and filtered. Standing at RT for 3 d resulted in the formation of white crystals in

the ether solution. These were treated as before to afford **103a** (2.43 g, 5.92%), mp 147-149°C.

The aqueous phase was extracted with H_2CCl_2 (5 x 400 mL) and the combined organic extracts dried ($MgSO_4$, overnight). Filtration followed by evaportion afforded a brown oil, which was digested in boiling Skelly B (1000 mL) for thirty minutes. The hot supernatant was decanted from the brown residue and evaporated to afford afford a yellow oil. The residue was treated twice more in this manner, then once with 500 mL of Skelly B, each time combining the supernatant with the oil (22.5 g) from the previous digestion process. The resulting oil solidified on standing and was sublimed (104°C/0.04 mmHg) to afford **28a** (16.69 g, 33.73%), mp 92-93°C (lit[14] 90-91°C) and a residual yellow oil that did not sublime. In a previous experiment, it was found that this residual oil consists primarily of **27a**. Further efforts at sublimation (90-150°C, 5 x 10^{15} mmHg, diffusion pump) of the oily residue in this earlier experiment failed to give significant quantities of **27a**. However, a ^{13}C NMR of this earlier oil indicated that it consists primarily of **27a**.

Analytical Data. The ^{13}C NMR, ^{15}N NMR and IR spectral data for **28d** have been previously reported[14]. A HETCOR NMR spectrum of this compound has permitted a greater resolution of the ^{1}H NMR spectrum ($DCCl_3$) in the aliphatic region: δ 2.71 [dd, ^{2}J = 11.2 Hz, ^{3}J = 5.0 Hz, 2 H, H(6,8)ax], 2.80 [m, 2 H, H(1,5)], 3.08 [dd, ^{2}J = 11.2 Hz, ^{3}J = 1.3 Hz, 2 H, H(6,8)eq], 3.12 [dd, ^{2}J = 13.5 Hz, ^{3}J = 7.3 Hz, 2 H, H(2,4)ax], 3.23 [dd, ^{2}J = 13.5 Hz, ^{3}J = 4.0 Hz, 2 H, H(2,4)eq], 3.57 [s, 2 H, H(10)], 7.26-7.34 [m, 5 H, ArH].

The spectral data for **103b** were: IR (KBr) cm^{-1} 3030, 2940, 2830, 1365, 1358, 1104, 1067, 740, 704; ^{1}H NMR ($DCCl_3$) δ 2.08 [d, J = 12 Hz, 1 H, H(5)ax], 2.13 [br s, 1 H, H(8)], 2.37 [d, J = 12 Hz, 1 H, H(5)eq], 2.54 [dd, J = 12, 2 Hz, 1 H, H(9)ax], 2.62 [d, J = 11 Hz, 1 H, PhC$\underline{H}_2$], 2.74 [d, J = 10 Hz, 1 H, H(4)ax], 2.95 [d, J = 10 Hz, 1 H, H(4)eq], 3.22 [s, 3 H, C$\underline{H}_3$O], 3.25 [d, J = 1 H, H(11)eq], 3.31 [d, J = 13 Hz, 1 H, H(7)ax], 3.39 [dd, J = 12, 2 Hz, 1 H, H(9)eq], 3.49 [d, J = 11 Hz, 1 H, PhC$\underline{H}_2$], 3.50 [d, J = 13 Hz, 1 H, H(7)eq], 3.55 [d, J = 13 Hz, 2 H, PhC$\underline{H}_2$], 4.02 [d, J = 8 Hz, 1 H, H(2)ax], 4.18 [d, J = 8 Hz 1 H, H(2)eq], 7.22-7.38 [m, 8 H, Ar$\underline{H}$], 7.58 [d, J = 8 Hz, 2 H, Ar$\underline{H}$]; ^{13}C NMR ($DCCl_3$) ppm 30.1 [t, C(9)], 33.4 [d, C(8)], 34.6 [t, C(11)], 37.4 [s, C(4a)], 46.3 [q, $\underline{C}H_3O$], 55.4 [t, C(4)], 55.8 [t, C(5)], 57.3 [t, C(7)], 59.9 [t, Ph$\underline{C}H_2$], 62.6 [t, Ph$\underline{C}H_2$], 78.7 [t, C(2)], 96.9 [s, C(8a)], 126.5 [d, $\underline{p}$-Ar$\underline{C}$], 127.1 [d, $\underline{p}$-Ar$\underline{C}$], 128.2, 128.3, 128.3, 128.5 [$\underline{o}$- and $\underline{m}$-Ar$\underline{C}$], 137.5 [s, $\underline{i}$-Ar$\underline{C}$], 139.7 [s, $\underline{i}$-Ar$\underline{C}$]; ^{15}N NMR ($DCCl_3$) ppm 46.4 [N(3)], 35.92 [N(3)]. Anal. of **103a** calcd. for $C_{24}H_{30}N_2O_2S$: C, 70.21; H, 7.37; N, 6.82; S, 7.81. Found: C, 69.99; H, 7.51; N, 6.64; S, 7.97.

The spectral data for **104b** were: IR (KBr) cm^{-1} 3065, 3030, 2950, 2920, 2895, 2830, 2800, 1680 (C=O), 1500, 1457, 1097, 748, 736, 703; ^{1}H NMR ($DCCl_3$) δ 2.17 [d, J = 10.8 Hz, 4 H, H(1,5,9,13)ax], 2.50 [d, J = 8.8 Hz, 2 H, H(3,11)ax], 2.77 [d, J = 10.8 Hz, 4 H, H(1,5,9,13)eq], 3.15 [s, 4 H, H(14,16)], 3.33 [d, J = 13.0 Hz, 4 H, PhC$\underline{H}_2$], 3.49 [d, J = 13.0 Hz, 4 H, PhC$\underline{H}_2$], 3.62 [d, J = 8.8 Hz, 2 H, H(3,11)], 7.20-7.30 [m, 20 H, Ar$\underline{H}$]; ^{13}C NMR ($DCCl_3$) ppm 36.4 [t, C(14,16)], 51.3 [s, C(6,8)], 57.6 [t, C(1,5,9,13)], 59.6 [t, Ph$\underline{C}H_2$], 76.6 [t, C(3,11)], 127.1 [d, $\underline{p}$-Ar$\underline{C}$], 128.2 [d, $\underline{o}$- or $\underline{m}$-Ar$\underline{C}$], 128.6 [d, $\underline{m}$- or $\underline{o}$-Ar$\underline{C}$], 137.8 [s, $\underline{i}$-Ar$\underline{C}$], 211.7 [s, C(7)]; ^{15}N NMR ($DCCl_3$) ppm 43.1 [N(2,4,10,12)]. Anal.

of **104a** calcd. for $C_{39}H_{44}N_4SO$: C, 75.94; H, 7.19; N, 9.08; S, 5.20. Found: C, 75.73; H, 7.33; N, 9.10; S, 5.20.

7-Benzyl-3-selena-7-azabicyclo[3.3.1]nonan-9-one (27b), 3,6-Dibenzylhexahydro-8a-methoxy-5H-4a,8-(methanoselenomethano)-2H-pyrido-[3,4-e]-1,3-oxazine (103b) and 2,4,10,12-tetrabenzyl-2,4,10,12-tetraaza-15-selena-dispiro[5.3.5.1]hexadecan-7-one (104b)

Method A: 1.4 equivalents benzylamine. A three-necked, 50-mL round-bottomed flask was equipped with a condenser and heating mantle. The flask was charged with benzylamine (0.67 g, 6.2 mmol), glacial acetic acid (0.38 g, 6.3 mmol), paraformaldehyde (1.50 g, 50.0 mmol), and methanol (30 mL). The apparatus was flushed with N_2 and the mixture heated to reflux with stirring. After 0.5 h, the mixture was cooled to RT and 4-selenanone[106] (**16d**, 0.75 g, 4.6 mmol) was added in one portion. The mixture was again heated at reflux for 5 h during which all solids dissolved and the resulting solution turned yellow. The solution was then cooled to RT and allowed to stir overnight. Evaporation of the solvent resulted in a yellow oil, which was partitioned between water (50 mL) and ethyl ether (50 mL).

The layers were separated and the ether layer was allowed to stand for two days at RT during which a white solid precipitate formed in this solution. This was filtered and recrystallized (95% ethanol, 25 mL) to afford **103b** (0.25 g) as white needles: mp 160.0-160.5°C.

The aqueous layer was cooled (ice bath) and was made alkaline by the addition of KOH pellets (85%, 1.20 g, 21.4 mmol). The resulting

suspension was extracted (ether, 5 x 40 mL) and the combined extracts were dried (K_2CO_3, overnight). Filtration, followed by evaporation (aspirator), afforded a yellow oil which was digested in Skelly B (50 mL) for 0.5 h on a steam bath. The hot supernatant was decanted and evaporated to give another yellow oil. This was dissolved in hot 95% ethanol (10 mL) which, upon cooling, precipitated additional **103b** (67.0 mg, 22% total), mp 159-160°C.

Method B: 2.0 equivalents benzylamine. Using the apparatus and procedure described for Method A, ketone **16d** (0.83 g, 5.0 mmmol) was treated with benzylamine (1.07 g, 10.0 mmol), glacial acetic acid (0.62 g, 10.3 mmol), paraformaldehyde (1.20 g, 40.0 mmol), and methanol (25 mL). The apparatus was flushed with N_2 and the mixture heated at reflux with stirring for 15 min. Ketone **16d** (0.83 g, 5.0 mmol) was then added in one portion and the mixture heated at reflux. The supernatant turned yellow upon addition of 4-selenanone. Continued heating resulted in the slow dissolution of the paraformaldehyde and the development of a brilliant pink color in the supernatant. After 3 h the formation of a white precipitate was noted. After 5 h the reaction mixture was cooled to RT and stirred an additional 13 h. The white solid was filtered from the reaction mixture, washed with methanol (5 mL) and recrystallized (95% 2-propanol, 20 mL) to give **104b** (57.6 mg, 1.9%) as white crystals: mp 165-166°C.

The reaction mixture filtrate was evaporated to leave a pink oil which was partitioned between ethyl ether (50 mL) and water (50 mL). The colorless ether layer was separated and treated as before to afford after recrystallization **103b** (0.2030 g, 8.8%), mp 159-160°C.

The pink aqueous suspension from the partitioning was made alkaline by the addition of KOH pellets (85%, 2.00 g, 30.3 mmol) to give an oily yellow suspension. Ether extraction (5 x 40 mL), drying (K_2CO_3, overnight), and Skelly B digestion as previously described resulted in a yellow oil. This was dissolved in hot 95% ethanol (30 mL), decolorized with carbon, and evaporated to 10 mL. Upon standing at -10^C for 1 d white needles precipitated. These were filtered and air dried to afford ketone **27b** (0.38 g, 25.8%), mp 91-92^{o}C.

Method C: 1.0 equivalent of benzylamine. The reaction was repeated using the conditions and ratios of reagents described in the earlier of work by Thompson and coworkers.[106,107] Using the apparatus described above ketone **16d** (0.58 g, 3.7 mmol) was treated with benzyamine (0.40 g, 3.7 mmol), acetic acid (0.23 g, 3.8 mmol), and paraformaldehyde (0.90 g, 29.9 mmol) in methanol (25 mL). The mixture was heated at reflux for 5 h, and was stirred at RT for an additional 1 h. No precipitate formation was noted from the red solution. After removal of the solvent, the resulting red oil was partitioned between ether (30 mL) and water (30 mL). The ether layer was treated as described above to afford, after recrystallization, ketal **103b**(0.1001 g, 11.8% relative to the amount of benzylamine) mp 161-162^{o}C. The aqueous layer was cooled to 0^{o}C and was made alkaline by the addition of KOH pellets (85%, 0.70 g, 12.5 mmol) and the resulting suspension extracted with ether (6 x 30 mL). The combined ether extracts were dried (K_2CO_3). Filtration, followed by evaporation afforded a yellow oil, the spectrum of which was essentially identical to **27b** (0.24 g, 22% relative to 4-selenanone, **16d**).

Analytical Data. The IR, ^{13}C NMR, ^{15}N NMR, and ^{77}Se NMR spectra **27b** have been previously reported.[106,107] The ^{1}H NMR ($DCCl_3$) assignments have been modified in light of a HETCOR NMR spectrum: δ 2.71 [d, J = 9 Hz, 2 H, H(6,8)ax], 2.73 [br s, 2 H, H(1,5)], 3.10 [d, J = 9 Hz, 2 H, H(6,8)eq], 3.23 [m, 4 H, H(2,4)], 3.58 [s, 2 H, PhC$\underline{H}_2$], 7.24-7.32 [m, 5 H, Ar$\underline{H}$].

The spectroscopic data for **103b** were: IR (KBr) cm^{-1} 2840, 1370, 1362, 1108, 1062, 1055, 762, 706; ^{1}H NMR ($DCCl_3$) δ 2.09 [br s, 1 H, H(8)], 2.11 [d, J = 11 Hz, 1 H, H(5)ax], 2.13 [d, J = 12 Hz, 1 H, H(11)ax], 2.37 [d, J = 11 Hz, 1 H, H(5)eq], 2.53 [d, J = 11 Hz, 1 H, H(9)ax], 2.58 [d, J = 11 Hz, 1 H, PhC$\underline{H}_2$], 2.72 [d, J = 11 Hz, 1 H, H(4)ax], 2.93 [d, J = 11 Hz, 1 H, H(4)eq], 3.25 [s, 3 H, C$\underline{H}_3$O], 3.29 [d, J = 12 Hz, 1 H, H(11)eq], 3.29 [d, J = 14 Hz, 1 H, H(7)ax], 3.44 [d, J = 11 Hz, 1 H, PhC$\underline{H}_2$], 3.47 [d, J = 11 Hz, 1 H, H(9)eq], 3.51 [d, J = 14 Hz, 1 H, H(7)eq], 3.53 [d, J = 4 Hz, 2 H, PhC$\underline{H}_2$], 3.97 [d, J = 8 Hz, 1 H, H(2)ax], 4.21 [d, J = 8 Hz, 1 H, H(2)ax], 7.26-7.64 [m, 10 H, Ar$\underline{H}$]; ^{13}C NMR ($DCCl_3$) ppm 20.1 [t, C(9)], 25.1 [t, C(11)], 33.2 [d, C(8)], 36.8 [s, C(4a)], 46.5 [q, CH_3O], 56.1 [t, C(4)], 56.7 [t, C(5)], 57.3 [t, C(7)], 60.5 [t, Ph$\underline{C}H_2$], 62.6 [t, Ph$\underline{C}H_2$], 78.7 [t, C(2)], 97.7 [s, C(8a)], 126.5 (d), 127.1 (d), 128.1 (d), 128.3 (d), 128.4_7 (d), 128.5_7 (d), 137.4 (s), 139.6 (s) [Ar$\underline{C}$]; ^{15}N NMR ($DCCl_3$) ppm 36.2 [N(12)], 47.0 [N(3)]; ^{77}Se NMR ppm 126.6 [Se(8)]. Anal. calcd. for $C_{24}H_{30}N_2O_2Se$: C, 63.01; H, 6.61; N, 6.12; Se, 17.26. Found: C, 62.88; H, 6.83; N, 6.02; Se, 16.91.

The spectral data for **104b** were: IR (KBr) cm^{-1} 3062, 3032, 2910, 2820, 2792, 1675, 1494, 1453, 1086, 1068, 741, 729, 697; ^{1}H NMR ($DCCl_3$) δ 2.27 [d, J = 11.2 Hz, 4 H, H(1,5,9,13)ax], 2.55 [d, J = 8.1 Hz, 2 H,

H(3,11)ax], 2.77 [d, J = 11.2 Hz, 4 H, H(1,5,9,13)eq], 3.17 [s, 4 H, H(14,16)], 3.34 [d, J = 13.5 Hz, 4 H, PhC$\underline{H}_2$], 3.50 [d, J = 13.5 Hz, 4 H, PhC$\underline{H}_2$], 3.54 [d, J = 8.1 Hz, 2 H, H(3,11)eq], 7.20-7.30 [m, 20 H, Ar$\underline{H}$]; ^{13}C NMR ($DCCl_3$) ppm 26.7 [t, C(14,15)], 51.1 [s, C(6,8)], 58.4 [t, C(1,5,9,13)], 59.6 [t, PhC$\underline{H}_2$], 126.9 [d, $\underline{p}$-Ar$\underline{C}$], 128.0 [d, $\underline{o}$- or $\underline{m}$-Ar$\underline{C}$], 128.5 [d, $\underline{m}$- or $\underline{o}$-Ar$\underline{C}$], 137.7 [s, $\underline{i}$-Ar$\underline{C}$], 211.8 [s, C(7)]; ^{15}N NMR ($DCCl_3$) ppm 43.6; ^{77}Se NMR ($DCCl_3$) ppm 51.4.

<u>3,6-Dibenzylhexahydro-8a-methoxy-5H-4a,8-(methanothiomethano)-2H-pyrido[3,4-e]-1,3-oxazine dihydroperchlorate (103c)</u>

A 125-mL Ehrlenmeyer flask was charged with a solution of ketal **103a** (1.00 g, 2.44 mmol) in benzene (20 mL). To this solution was added dropwise over 15 min a solution of $HClO_4$ (60%, 1.00 g, 5.97 mmol) in 2-propanol (5 mL) with vigorous stirring (magnetic). This precipitated the salt as a white powdery solid. Additional 2-propanol (10 mL) was added as necessary to prevent caking of the precipitate. The mixture was stirred an additional 1 h at RT. The salt was filtered, recrystallized (ethanol, 25 mL), and dried (Abderhalden, P_2O_5, 77°C, vacuum pump, 12 h) to afford **103c** (0.60 g, 40%) as white crystals: mp 160-162°C (dec); IR (KBr) cm^{-1} 2760-2845 (N-H), 1080 (Cl-O); ^{1} NMR (DMSO-$\underline{d}_6$) δ 2.17 [d, J = 11.7 Hz, 1 H, H(4)ax], 2.35 [d, J = 11.7 Hz, 1 H, H(4)eq], 2.43 [d, J = 13.0 Hz, 1 H, H(11)ax], 2.64 [br s, 1 H, H(8)], 2.76 [d, J = 13.6 Hz, 1 H, H(9)ax], 3.00 [d, J = 13.0 Hz, H(11)eq], 3.18 [s, 3 H, C$\underline{H}_3$O], 3.22 [m, 2 H, H(9)eq and PhC$\underline{H}_2$], 3.32 [d, J = 13.6 Hz, 1 H, H(5)ax], 3.46 [d, J = 12.0 Hz, H(7)ax], 3.57 [d, J = 13.6 Hz, 1 H, H(5)eq], 3.79 [d, J = 12.0 Hz, H(7)eq], 4.00 [d, J =

7.3 Hz, 1 H, H(2)ax], 4.19 [d, J = 12.0 Hz, 1 H, PhC$\underline{H}_2$], 4.24 [d, J = 7.3 Hz, 1 H, H(2)eq], 4.40 [dd, J = 12.6, 5.9 Hz, PhC$\underline{H}_2$], 4.54 [dd, J = 12.6, 3.9 Hz, 1 H, PhC$\underline{H}_2$], 7.25-7.39 [m, 5 H, Ar$\underline{H}$], 7.49-7.64 [m, 5 H, Ar$\underline{H}$], 9.53 [br s, 1 H, N-$\underline{H}$]; ^{13}C NMR (DMSO-$\underline{d}_6$) ppm 28.3 [t, C(9)], 31.3 [d, C(8)], 31.8 [t, C(11)], 37.4 [s, C(4a)], 46.4 [q, $\underline{C}H_3O$], 52.3 [t, C(4)], 54.2 [t, C(7)], 55.4 [t, C(5)], 56.2 [t, PhC$\underline{H}_2$], 60.2 [t, PhC$\underline{H}_2$], 78.0 [t, C(2)], 93.8 [s, C(8a)], 127.1, 128.3, 129.1, 129.7, 130.6, 137.0 [Ar$\underline{C}$]. Anal. Calcd. for $C_{24}H_{30}N_2O_2S$ 2 $HClO_4$: C, 47.14; H, 5.27; Cl, 11.59; N, 4.58; S, 5.24. Found: C, 47.22; H, 5.14; Cl, 11.38; N, 4.44; S, 5.47.

Attempted Preparation of 3,7-Dibenzyl-2,4-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (107)

A three-necked, 100-mL round-bottomed flask was fitted with a condenser and a heating mantle. This flask was charge with a solution of benzaldehyde (5.40 g, 49.9 mmol), benzylamine (1.08 g, 10.1 mmol), acetic acid (0.92 g, 15.3 mmol) and methanol (50 mL). The apparatus was flushed with N_2 and the solution brought to a boil. Ketone **16f** (0.96 g, 5 mmol) was then added in one portion and resulting solution boiled for 9 h. The initially colorless solution developed an intense yellow color as the reaction proceded. Upon cooling to RT, a yellow solid precipitated from the reaction mixture, which was filtered. This yellow solid was dissolved in a minimum amount of hot ethanol and triturated with water to afford, upon cooling to RT, **107** (3.50 g, 96%): mp 152.8-153.4°C; IR (KBr) cm^{-1} 3060, 3030, 2750, 1642, 1623; ^{13}C NMR ($DCCl_3$) ppm 54.4 [C(2)], 61.4 [PhC$\underline{H}_2$], 127.4, 128.3, 128.5, 129.0,

130.4, 133.3, 135.2, 136.6, 137.3, 187.8 [C(4)]. Mass spectral m/e calcd. for $C_{26}H_{23}NO$: 365. Found: 365.

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one oxime (108)

A 50-mL round-bottomed flask was fitted with a condenser and a heating mantle. This flask was charged with ketone **27a** (1.05 g, 4.26 mmol), $NH_2OH.HCl$ (0.62 g, 8.57 mmol), NaOAc . 3 H_2O (1.47 g, 10.8 mmol) and ethanol (25 mL). The apparatus was flushed with N_2 and the mixture heated at reflux for 4 hr. The reaction mixture was cooled to RT and the unreacted NaOAc filtered. The filtrate was evaporated to leave a white solid, which was suspended in water (50 mL). Extraction with ether (3 x 50 mL), followed by drying (K_2CO_3, overnight), filtration, and evaporation afforded a white solid. This was recrystallized (95% ethanol, 30 mL) to yield the oxime **108a** (0.71 g, 64%): mp 128.4-129.2°C; IR (KBr) cm^{-1} 3275 (O-H), 2926, 2790, 752, 697; ^1H NMR ($DCCl_3$) δ 2.26 [dd, J = 11.5, 4.2 Hz, 1 H, H(8)ax], 2.32 [dd, J = 11.0, 4.3 Hz, 1 H, H(6)ax], 2.83 [br s, 1 H, H(1)], 2.89 [br t, J = ~11 Hz, 2 H, H(6,8)eq], 3.04 [m, 4 H, H(2,4)], 3.52 [s, 2 H, $PhC\underline{H}_2$], 3.88 [br s, 1 H, H(5)], 7.24-7.30 [m, 5 H, Ar$\underline{H}$], 9.28 [br s, 1 H, O$\underline{H}$]; ^{13}C NMR ($DCCl_3$) ppm 29.9 [d, C(1)], 32.5 [t, C(2)], 34.1 [t, C(4)], 36.7 [d, C(5)], 57.2 [t, C(8)], 58.5 [t, C(6)], 61.7 [t, $PhC\underline{H}_2$], 126.9 [d, $\underline{p}$-Ar$\underline{C}$], 128.1 [d, $\underline{o}$-Ar$\underline{C}$ or $\underline{m}$-Ar$\underline{C}$], 128.6 [d, $\underline{m}$-Ar$\underline{C}$ or $\underline{o}$-Ar$\underline{C}$], 138.2 [$\underline{i}$-Ar$\underline{C}$], 160.9 [s, C(9)]; ^{15}N NMR ($DCCl_3$) ppm 36.3 [N(7), oxime N not observed]. Mass spectral m/e calcd. for $C_{14}H_{18}N_2O$: 262.1136 (M^+). Found: 262.1140. Analysis calcd. for $C_{14}H_{18}N_2OS$: C, 64.09; H, 6.92; N, 10.68; S, 11.94. Found: C, 64.26; H, 6.94; N, 10.60; S, 12.22.

Tetrahydrothiapyran-4-one oxime (109a)

Employing the same procedure as described above ketone **16d** (0.50 g, 2.02 mmol) was treated with $NH_2OH.HCl$ (0.30 g, 4.43 mmol) and NaOAc $3H_2O$ (0.70 g, 5.05 mmol) in ethanol (25 mL). After heating at reflux for 4 h, the reaction mixture was filtered, evaporated and extracted [water (30 mL), ether (3 x 30 mL)]. Recrystallization from 95% ethanol afforded oxime **109a** (0.32 g, 56%), mp 79.5-80.0°C (lit.[101] 84-86°C) ^1H NMR ($DCCl_3$) δ 2.57 [m, 2 H, H(3)], 2.75 [m, 4 H, H(2,6)], 2.87 [m, 2 H], 9.01 [br s, NH]; ^{13}C NMR ($DCCl_3$) ppm 26.7 [t, C(2)], 28.3 [t, C(6)], 29.7 [t, C(3)], 33.84 [t, C(5)], 205.9 [s, C(4)].

1,3,5-Tribenzylhexahydro-1,3,5-triazine (110a)

Method A. A three-necked, 100-mL round-bottomed flask was fitted with a condenser and an addition funnel (20 mL). The flask was charged with benzylamine (10.72 g, 0.1000 mol) and the apparatus was flushed with N_2. Formaldehyde (37%, aq.) 12.17 g, 0.15 mol) was added in a dropwise manner over 30 min. An exothermic reaction ensues, and the product separated (upper layer) from the reaction mixture as a viscous oil. Upon completion of the addition the reaction mixture was heated at reflux for an additional 3 h to ensure completion. After cooling to RT, the mixture was diluted with NaCl solution (sat'd, 50 mL), extracted (ether, 5 x 50 mL), and the combined extracts dried (K_2CO_3, 5 h). This oil was passed through a column [neutral alumina, hexane/ethyl acetate (5:1)] afforded the triamine (R_f 0.64) as the first band. Evaporation of the solvent gave **110a** as a colorless oil (11.09 g, 93.1%) that solidified on standing: mp 43.5-45.5°C (lit.[34a] 46°C); IR (film) 3058, 3024, 2905, 2804, 1600, 1570, 740, 700; ^1H NMR ($DCCl_3$) δ 3.40 (s, 6 H,

ring $C\underline{H}_2$), 3.63 (s, 6 H, $PhC\underline{H}_2$), 7.17-7.32 (m, Ar$\underline{H}$); ^{13}C NMR ($DCCl_3$) ppm 56.9 (t, $PhC\underline{H}_2$), 73.6 (t, ring $\underline{C}H_2$), 126.7 (d, $\underline{p}$-Ar$\underline{C}$), 127.9 (d, $\underline{o}$ or $\underline{m}$-Ar$\underline{C}$), 128.6 (d, $\underline{m}$- or $\underline{o}$-ArC), 138.2 (s, $\underline{i}$-Ar$\underline{C}$); ^{15}N NMR ($DCCl_3$) ppm 49.2. Mass spectral m/e calcd. for $C_{24}H_{27}N_3$: 357 (M^+). Found: 357.

A ^{13}C NMR spectrum ($DCCl_3$of the crude oil prior to chromatography indicated that the only significant impurity was the linear triamine $RNH-CH_2-NR-CH_2NHR$ (where R = $PhCH_2$): $\delta(^{13}C)$ ppm 55.1 ($Ph\underline{C}H_2NH-$), 70.8 (other $Ph\underline{C}H_2$), 84.7 ($N\underline{C}H_2N$). Repetition of the reaction under identical conditions, but with methanol as a solvent, resulted in a slightly improved yield of 95%.

Method B. (Conditions similar to those in the preparation of **27,103,104**). a three-necked, 50-mL round-bottomed flask was fitted with a condenser and a heating mantle. The flask was charged with benzylamine (6.42 g, 60.0 mmol), paraformaldehyde (7.21 g, 240 mmol), acetic acid (3.96 g, 66.0. mmol) and methanol (360 mL). The apparatus was flushed with N_2, and mixture was heated at reflux for 12 h. The reaction was then cooled to RT and unreacted paraformaldehyde was filtered. Removal of the solvent afforded an oil to which was added water (250 mL) and NaOH pellets (3.00g, 75 mmol). Extraction (CH_2Cl_2, 4 x 250 mL), subsequent drying (K_2CO_3, 8 h), filtration, and evaporation afforded an almost colorless oil. This oil was treated as before (Method A) to afford 110a (4.10 g, 57.3 %), mp 45-46°C. The IR and ^{13}C were identical to that reported in Method A.

PLATE I. IR Spectrum of 16h

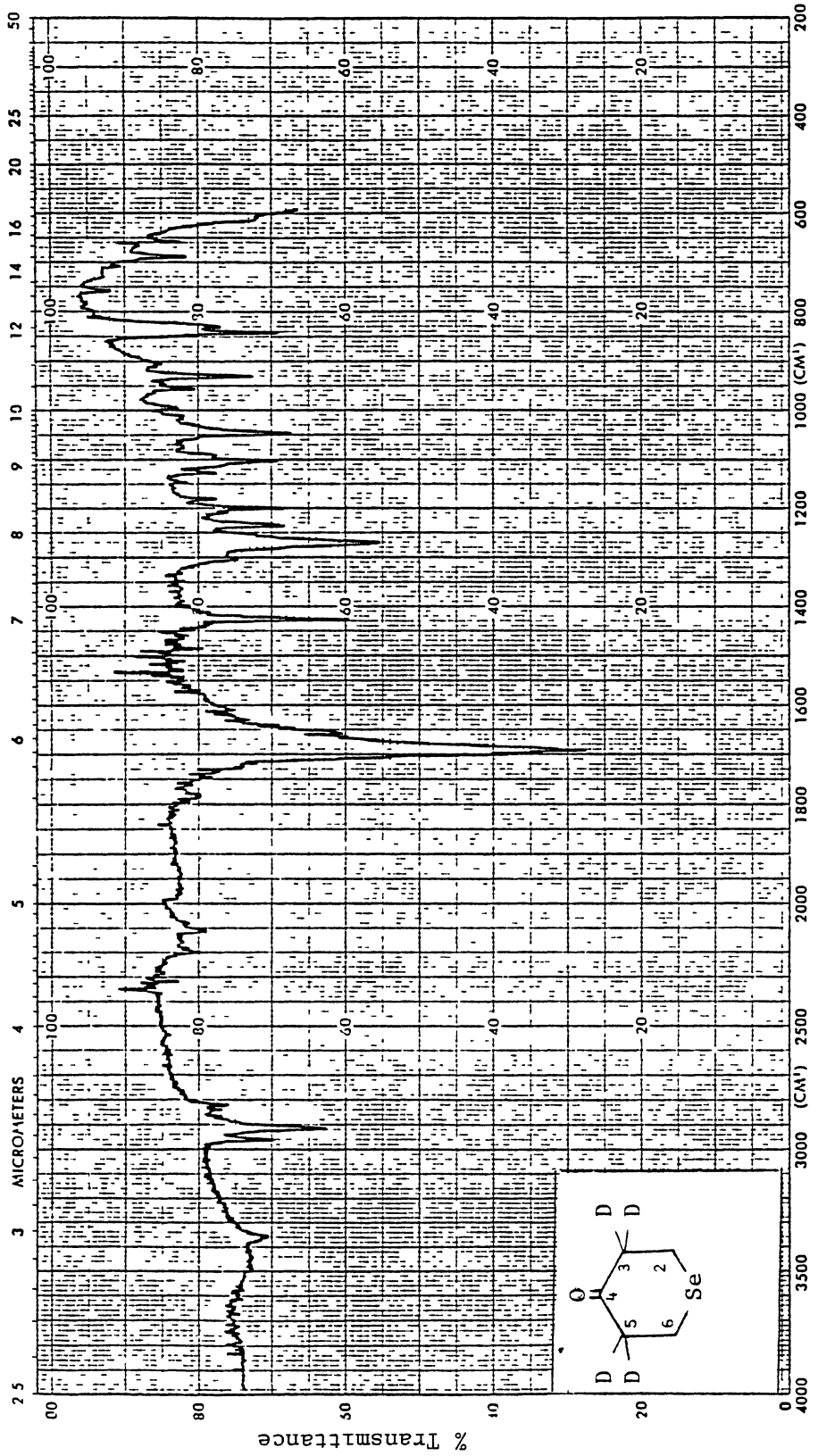
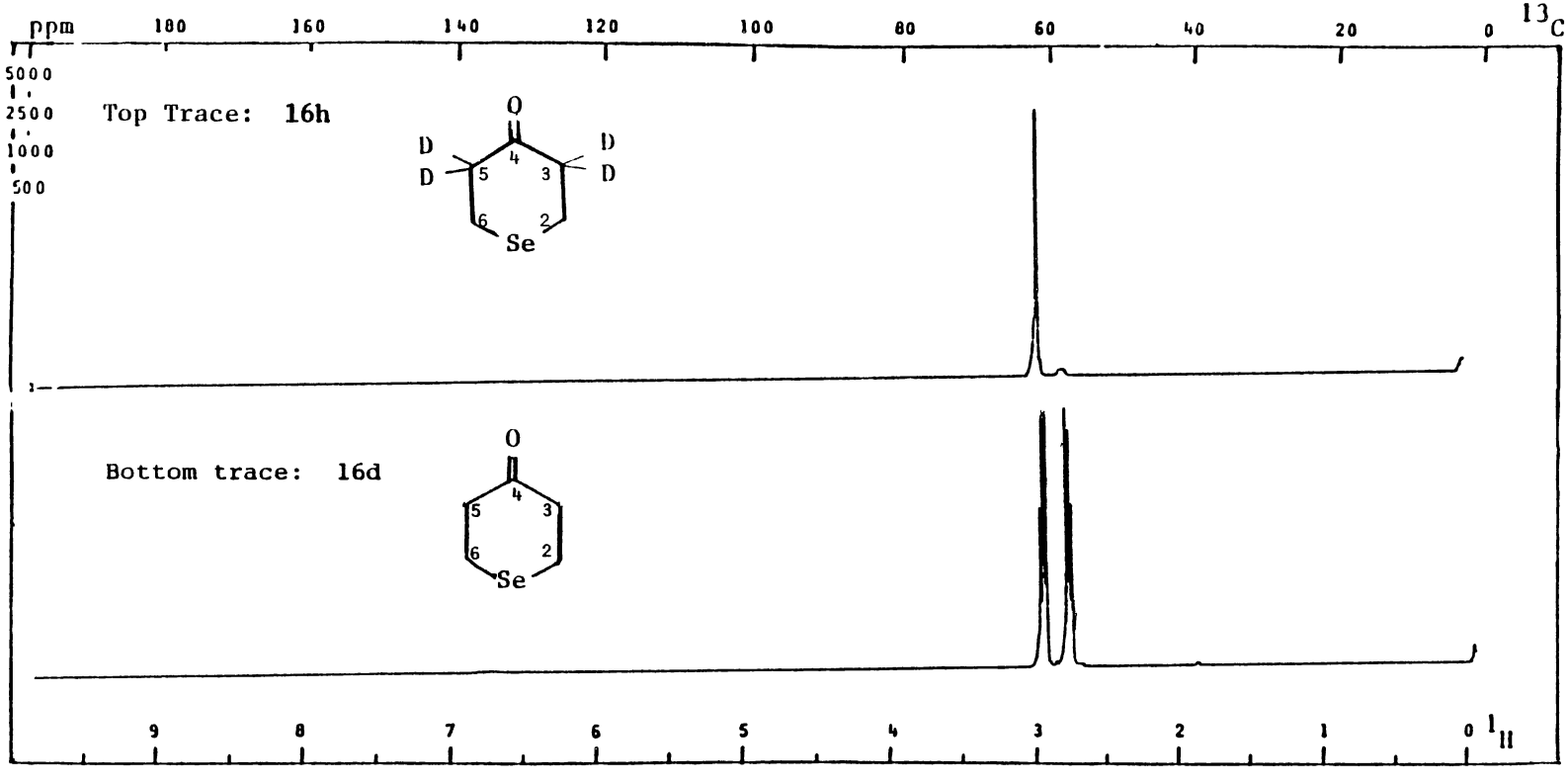


Plate II. ^{1}H NMR Spectrum of **16d** and **16h**

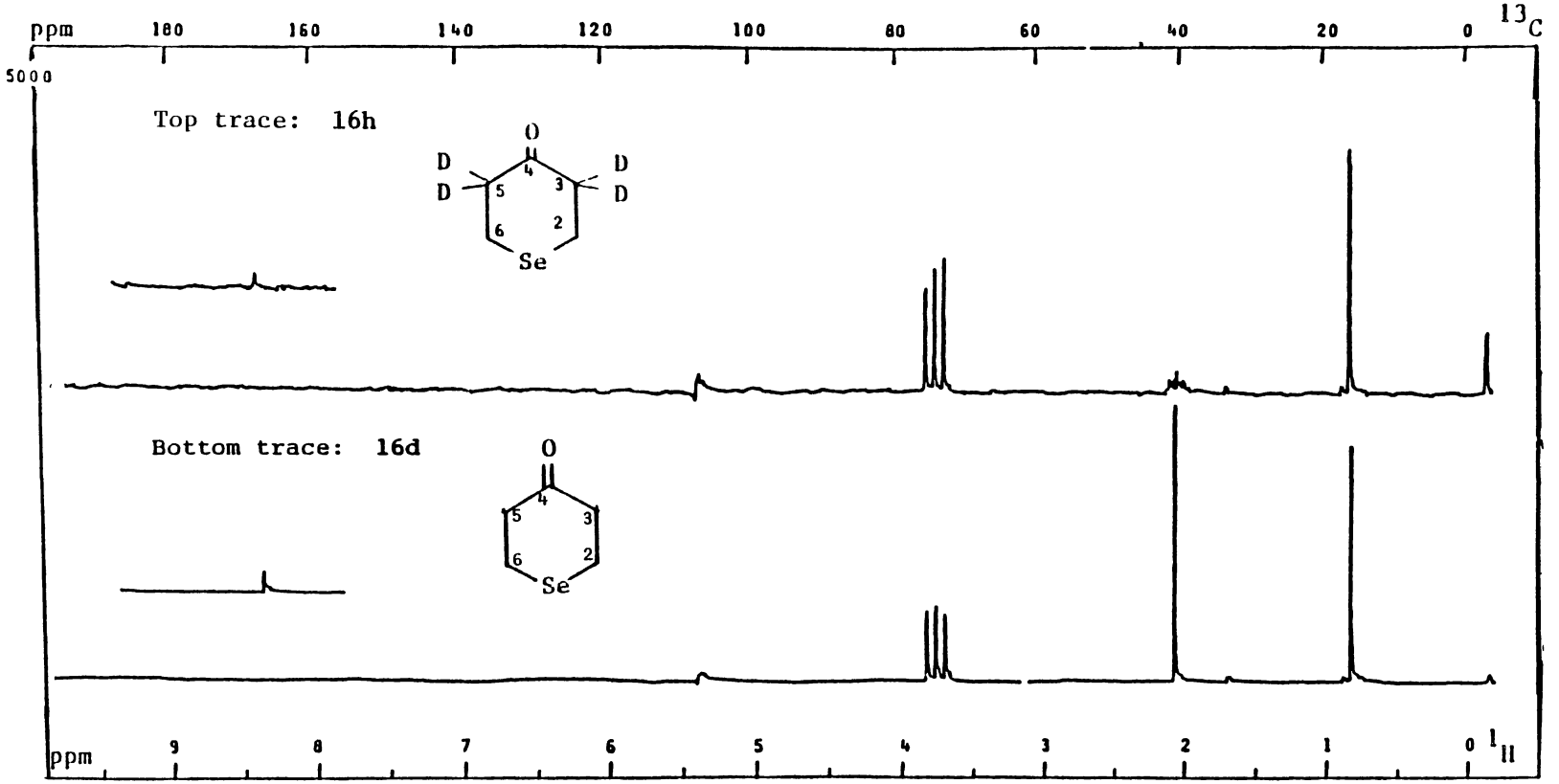


PFT x CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 3000 Hz; T: amb °C; NT: 4

Size: 8 K; PW/RF: 10.00 µs/dB; TO: 0 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: .5 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): W/dB; NBW: Hz; LB: 0.500 Hz.

Plate III. ^{13}C NMR spectra of 16d and 16h



PFT x CW _ ; Solvent: $DCCl_3$; SF: 25.2 MHz; WC: 5000 Hz; T: amb. °C; NT: 1488/1636

Size: 8 K; PW/RF: 20.0 μs/dB; TO: 35101 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 20.00 s.

DC: Y N ; Gated Off: A or D ; DO: 45316 Hz; RF(Power): 119 W/dB; NBW: Hz; LB: 1.00 Hz.

Plate IV. IR Spectrum of 17d

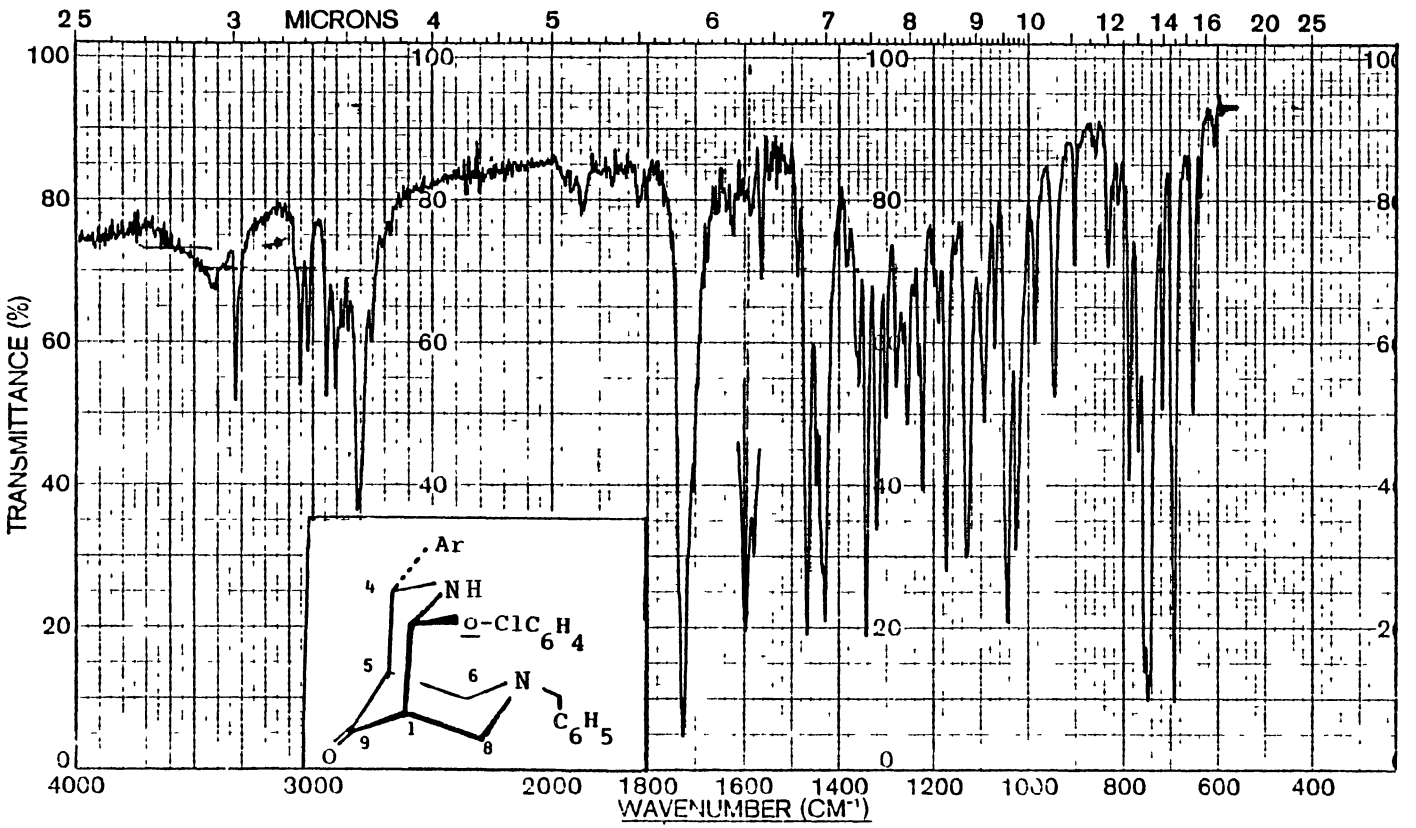
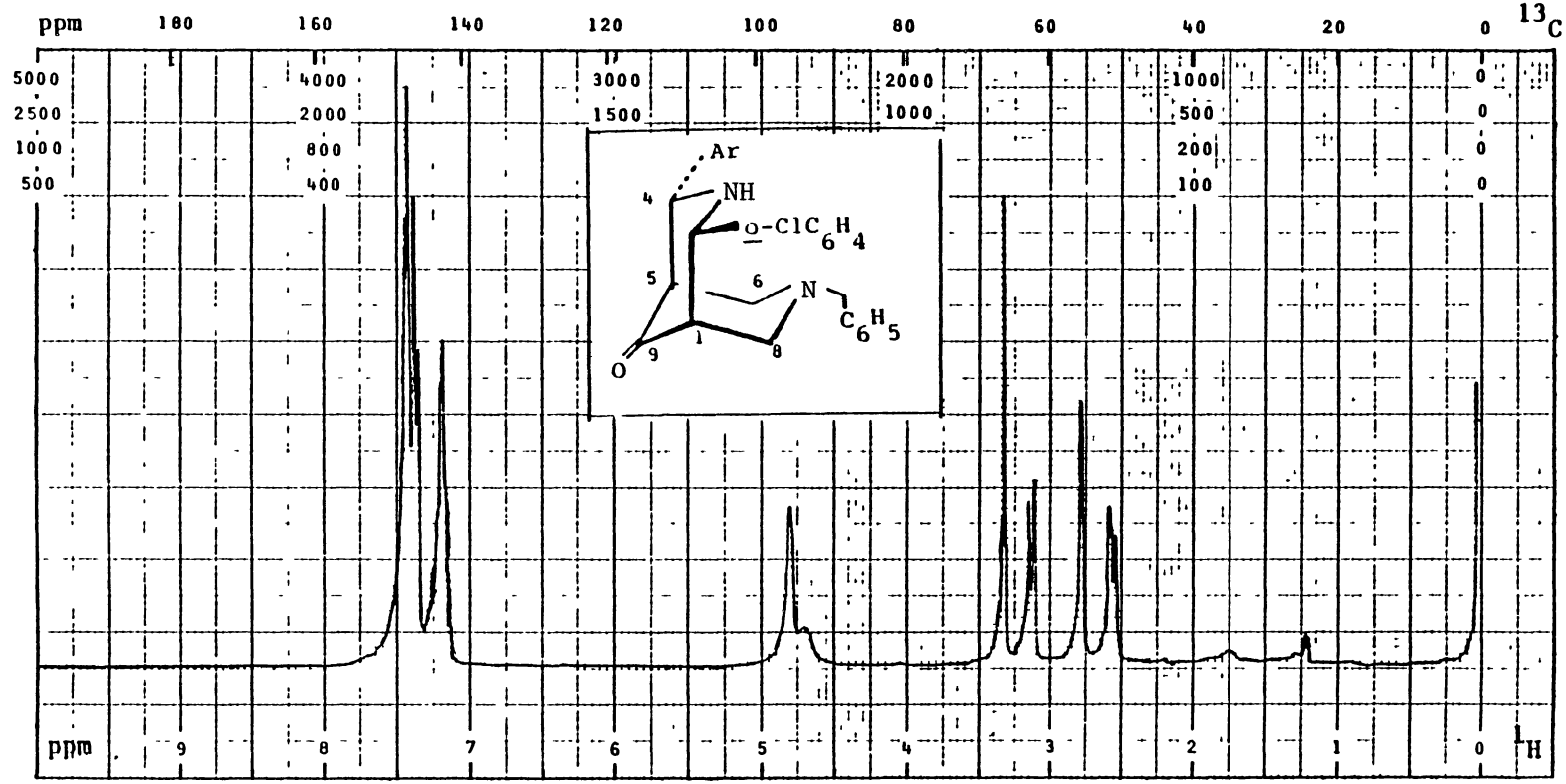


Plate V. ^{1}H NMR Spectrum of 17d

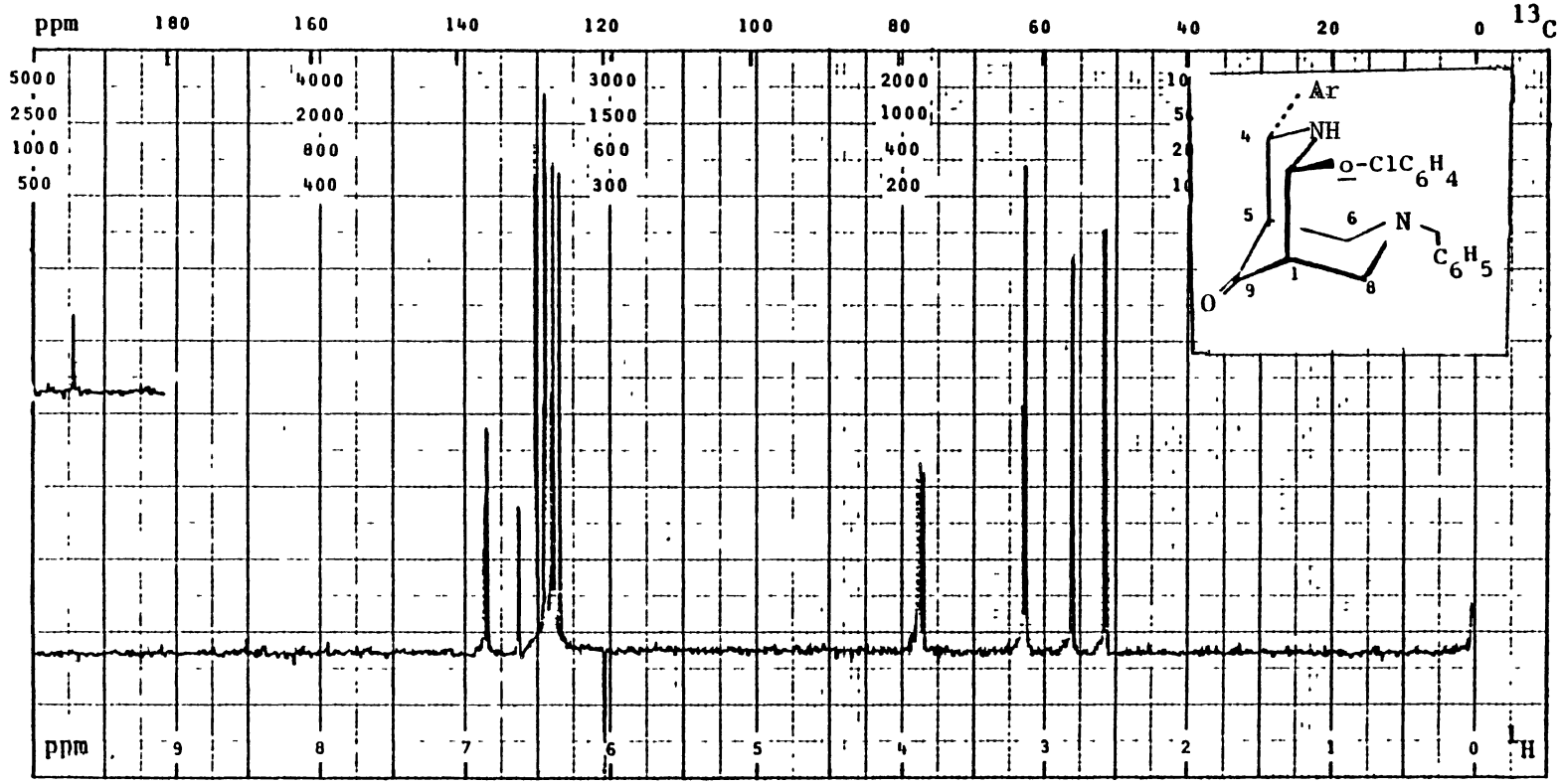


PFT x CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 3000 Hz; T: amb. °C; NT: 8 .

Size: 8 K; PW/RF: 5 µs/dB; SO: 100 Hz; FB: Hz; Lock: $DCCl_3$; Delay: 0.5 s.

DC: ; Gated Off: ; Offset: 0 Hz; RF: 20 W/dB; NBW: Hz; LB: - .

Plate VI. ^{13}C NMR Spectrum of 17d

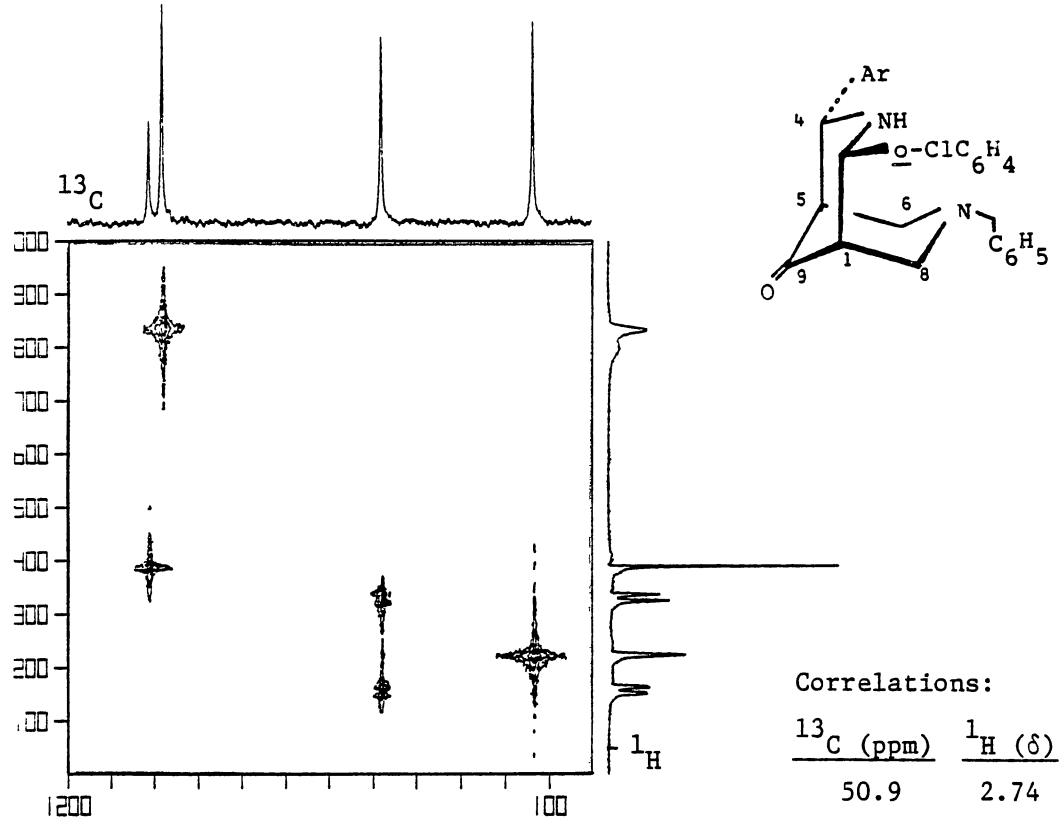


PFT x CW _ ; Solvent: $DCCl_3$; SF: 75429 MHz; WC: 15085 Hz; T: amb. °C; NT: 240 .

Size: 20 K; PW/RF: 14 µs/dB; SO: 1500 Hz; FB: Hz; Lock: $DCCl_3$; Delay: 4.0 s.

DC: Y ; Gated Off: ; Offset: 0 Hz; RF: 20 W/dB; NBW: Hz; LB: 1.0 .

Plate VII. HETCOR NMR Spectrum of **17d**



Correlations:

^{13}C (ppm)	^{1}H (δ)
50.9	2.74
55.5	2.54
55.5	3.08
62.1	4.77
62.5	3.29

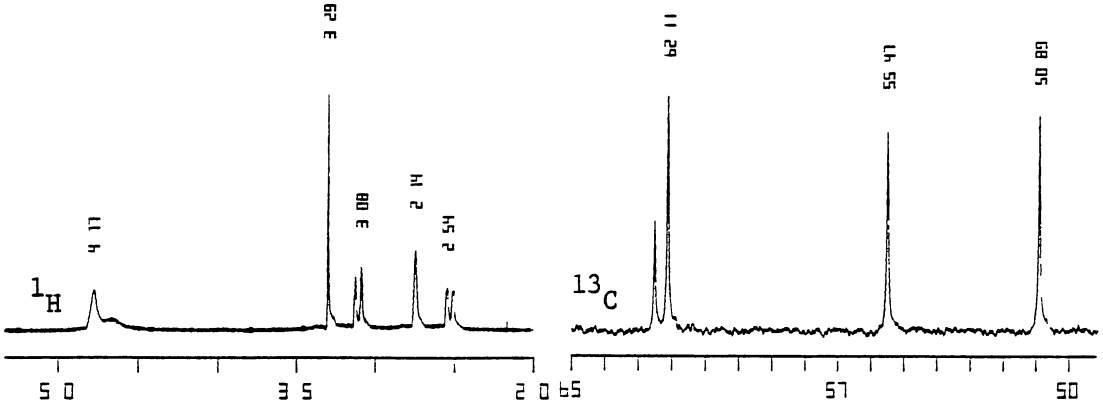
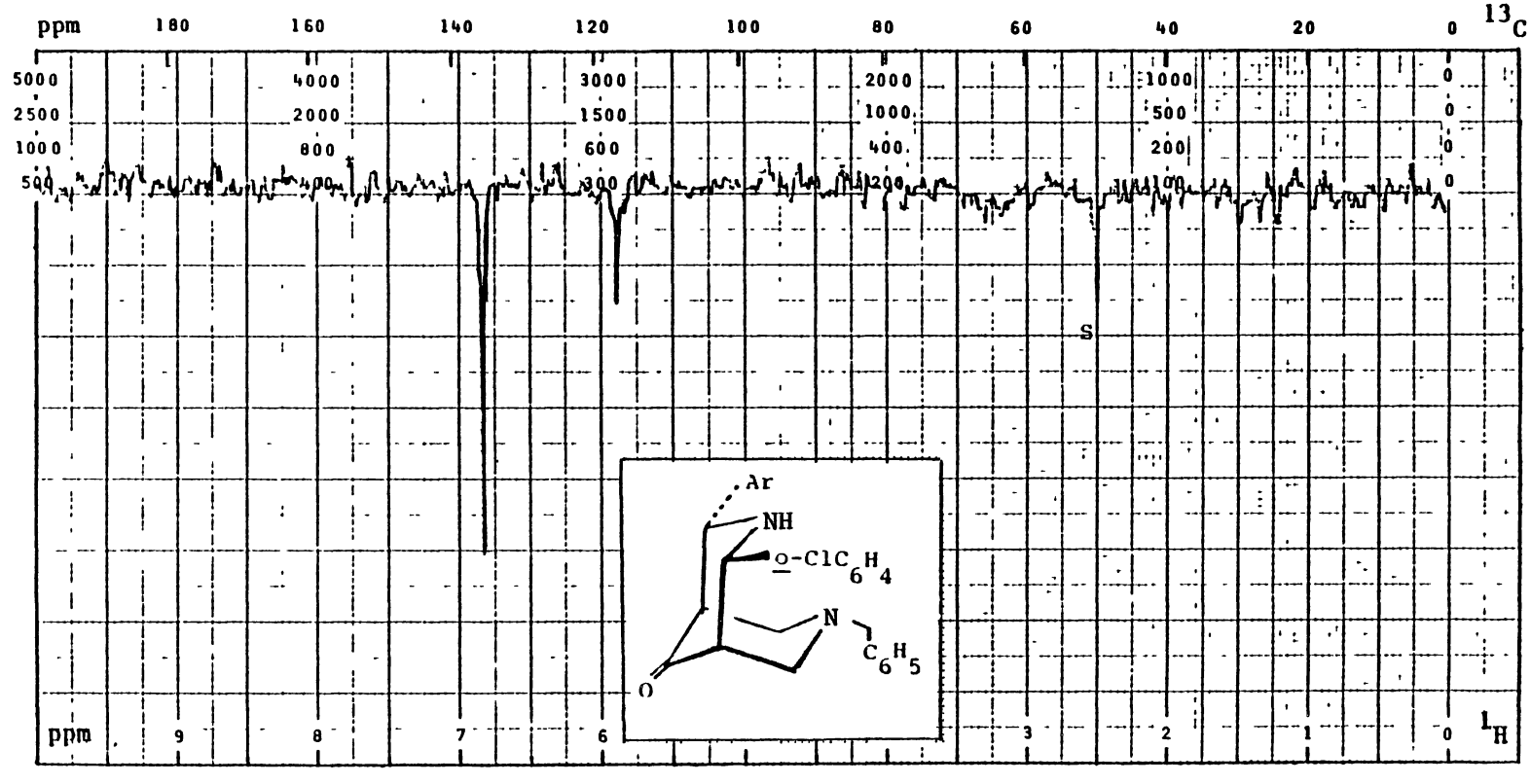


Plate VIII. ^{15}N NMR Spectrum of **17d**



PFT^x_ CW _ ; Solvent: $DCCl_3$; SF: 3040 MHz; WC: 2432 Hz; T: amb. °C; NT: 6000 .

Size: 12 K; PW/RF: 40 µs/dB; SO: 600 Hz; FB: Hz; Lock: $DCCl_3$; Delay: 8 s.

DC: Y ; Gated Off: ; Offset: 0 Hz; RF: 0 W/dB; NBW: Hz; LB: 2.0 .

Plate IX. IR Spectrum of **18d**

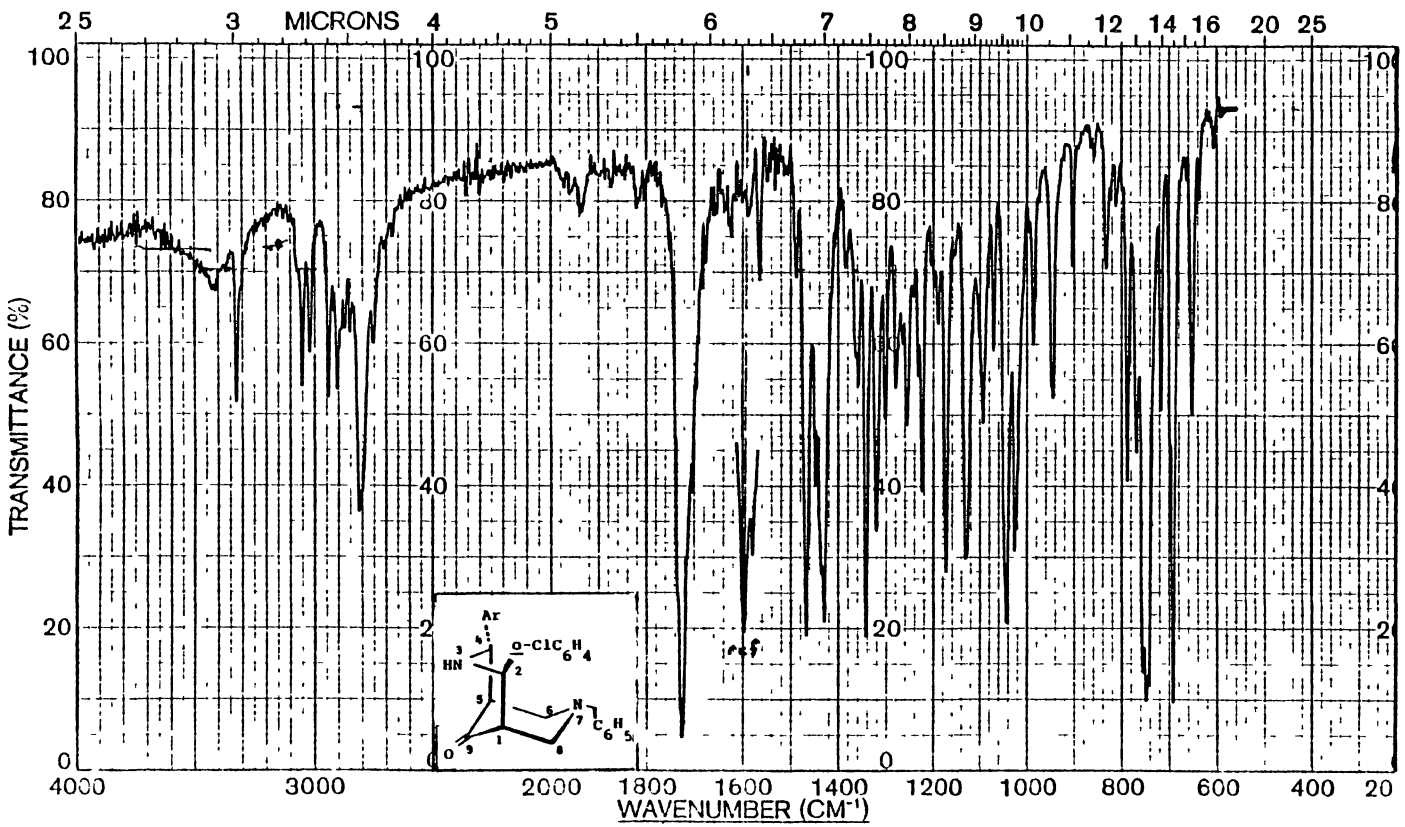
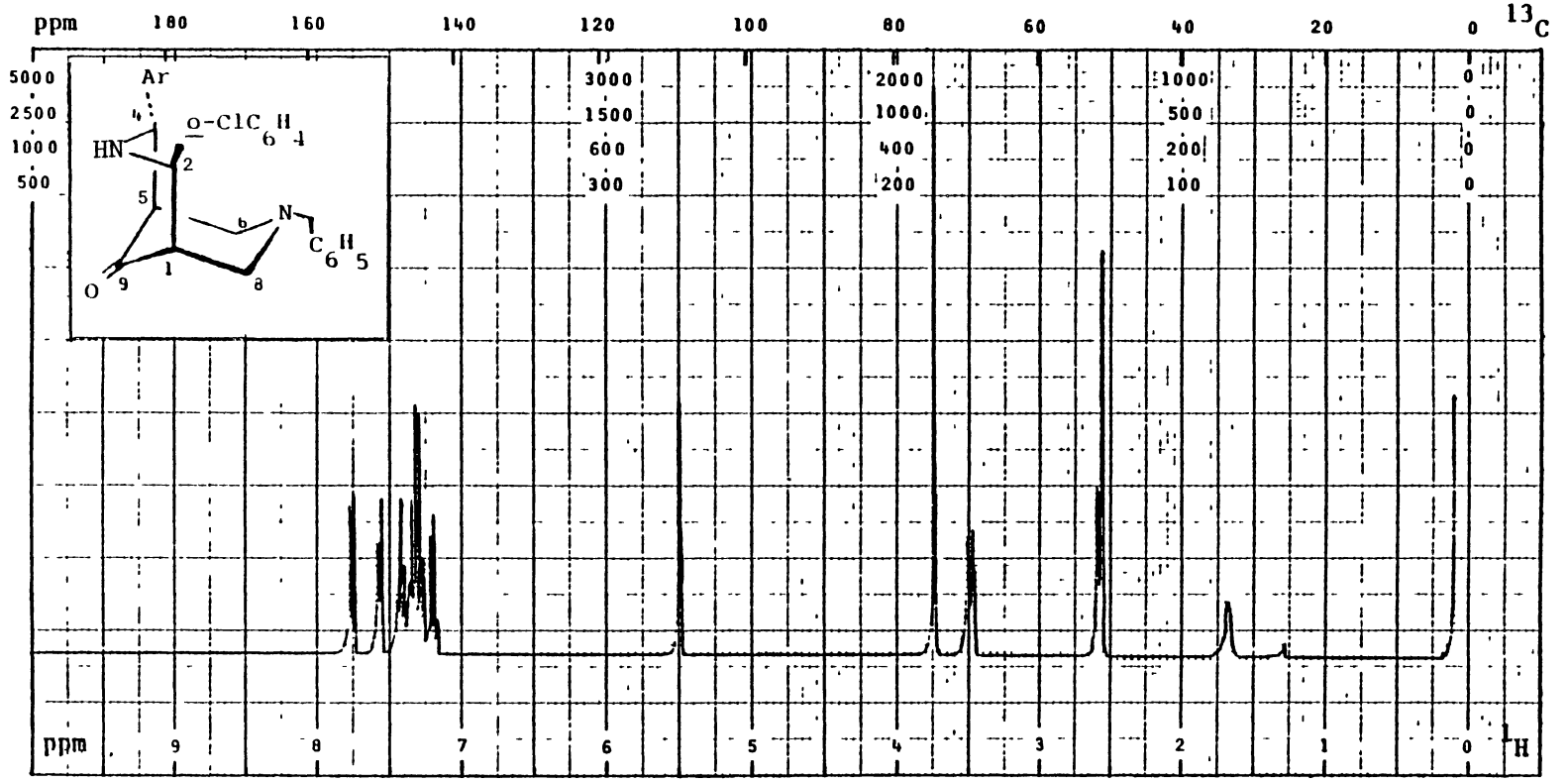


Plate X. ^{1}H NMR Spectrum of **18d**

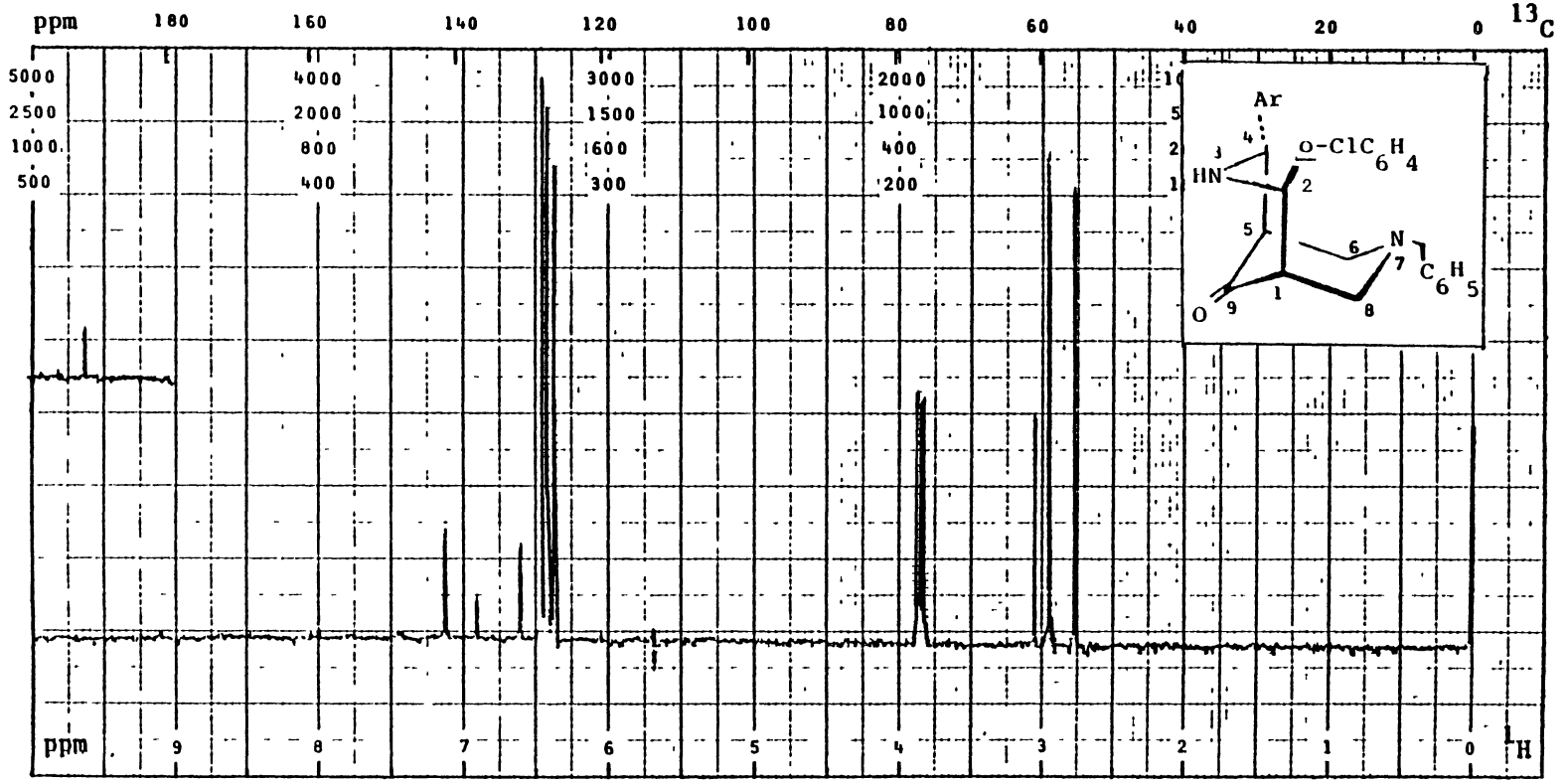


PFT x CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 3000 Hz; T: amb. °C; NT:8

Size: 8 K; PW/RF: 10 μs/dB; SO: Hz; FB: Hz; Lock: $DCCl_3$; Delay: 0.2 s.

DC: ; Gated Off: ; Offset: 0 Hz; RF: 20 W/dB; NBW: Hz; LB: _

Plate XI. ^{13}C NMR Spectrum of **18d**

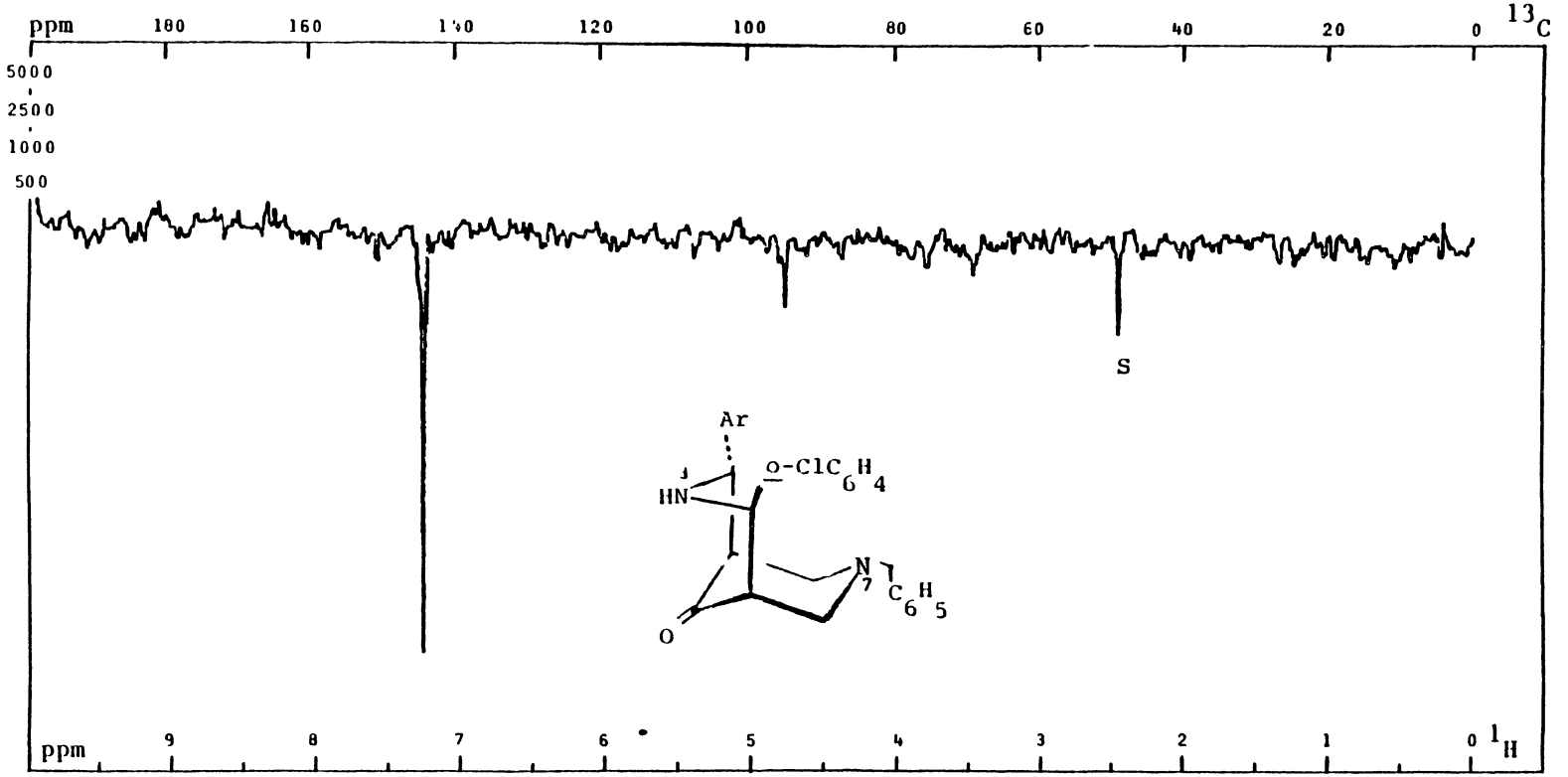


PFT x CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085 Hz; T: amb. °C; NT: 800

Size: 20 K; PW/RF: 12 μs/dB; SO: 1000 Hz; FB: Hz; Lock: $DCCl_3$; Delay: 1 s.

DC: ; Gated Off: ; Offset: 0 Hz; RF: 20 W/dB; NBW: Hz; LB: 2

Plate XII. ^{15}N NMR Spectrum of **18d**



PFT x CW _ ; Solvent: $DCCl_3$; SF: 30.046 MHz; WC: 2128 Hz; T: amb. °C; NT: 25000

Size: 12 K; PW/RF: 40 µs/dB; SO: -11600 Hz; FB: Hz; Lock: $DCCl_3$; Delay: 8.0 s.

DC: N ; Gated Off: A ; Offset: 0 Hz; RF: 0 W/dB; NBW: Hz; LB: 1

Plate XIII. IR Spectrum of **19b**

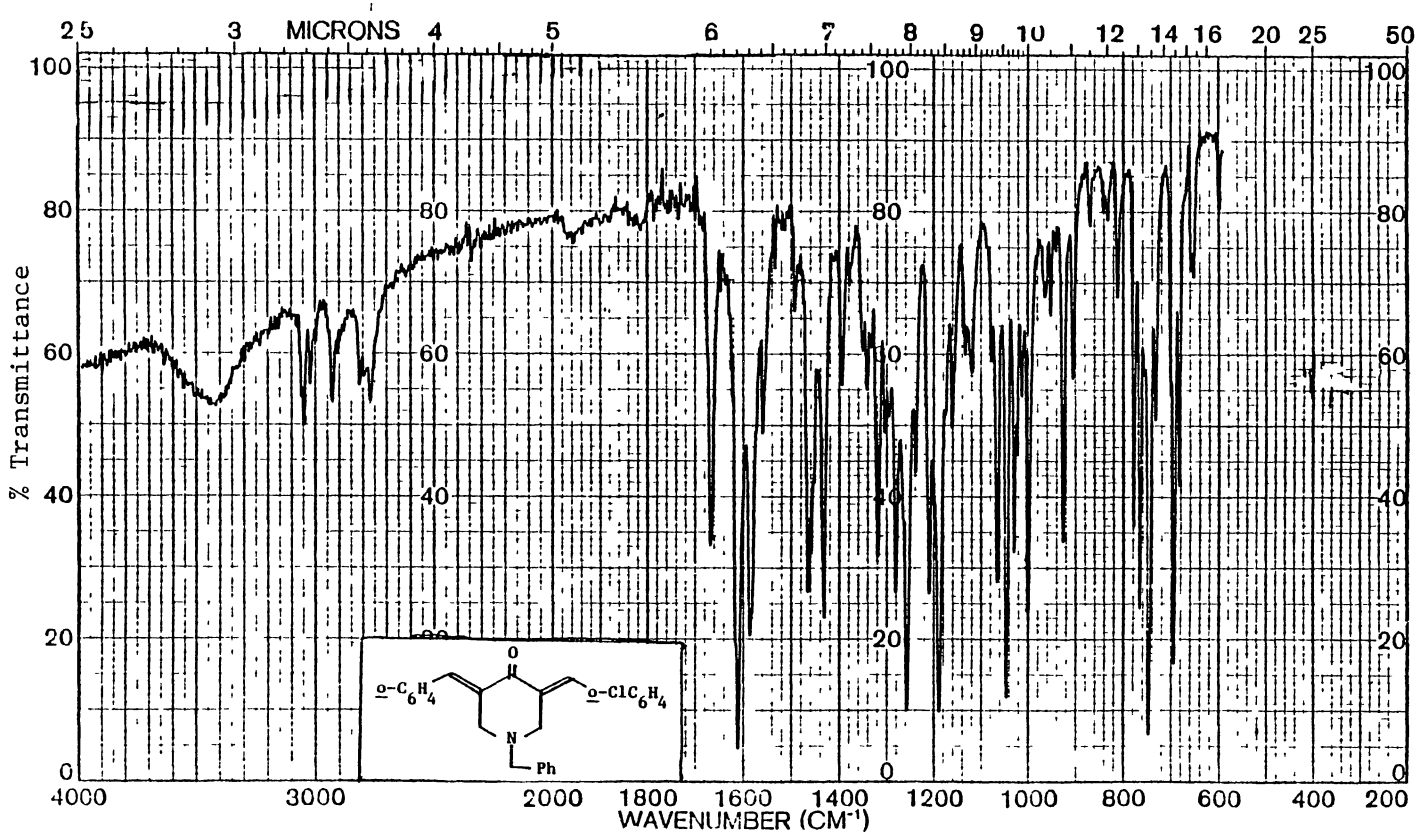
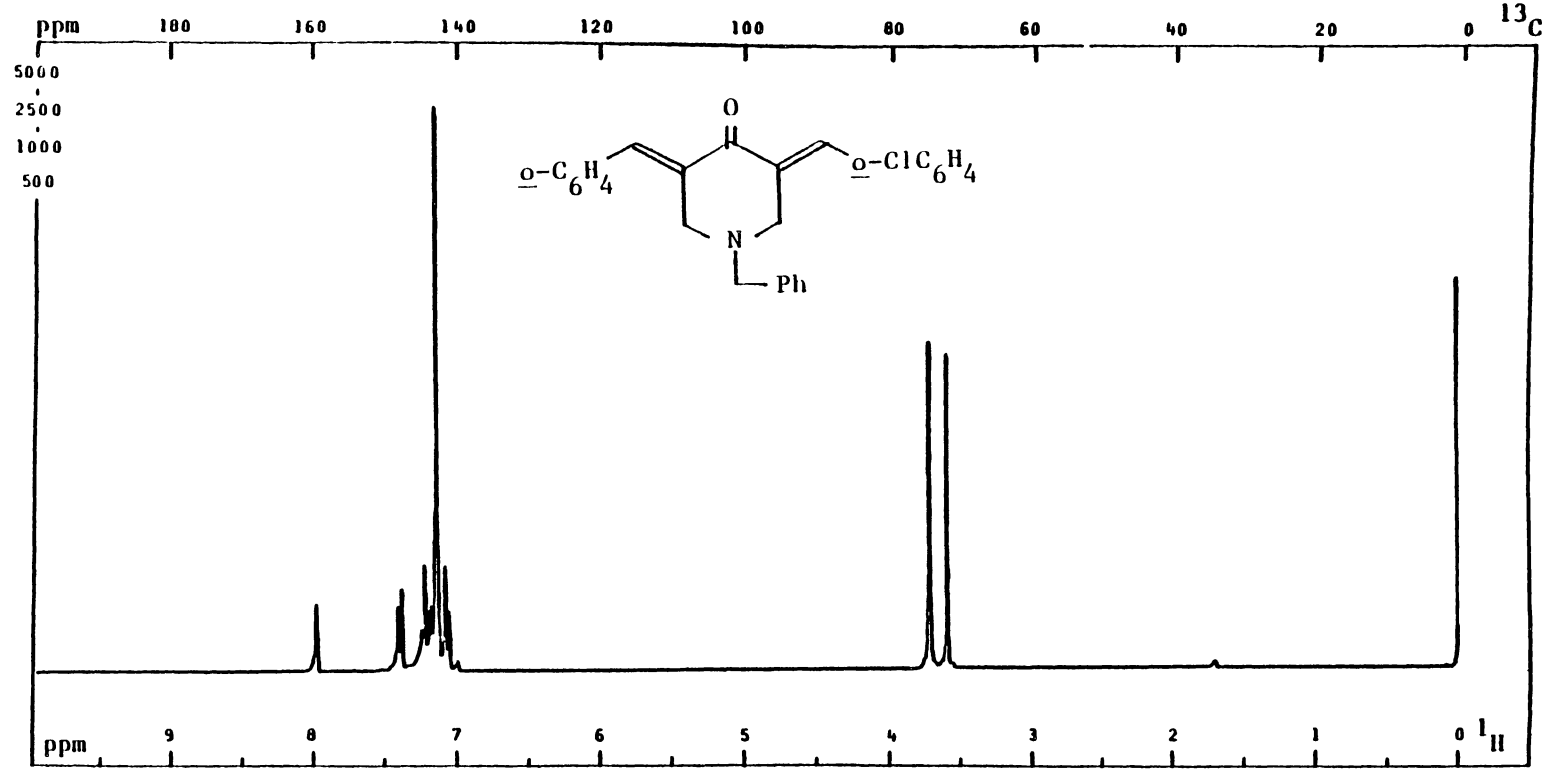


Plate XIV. ^{1}H NMR Spectrum of **19b**

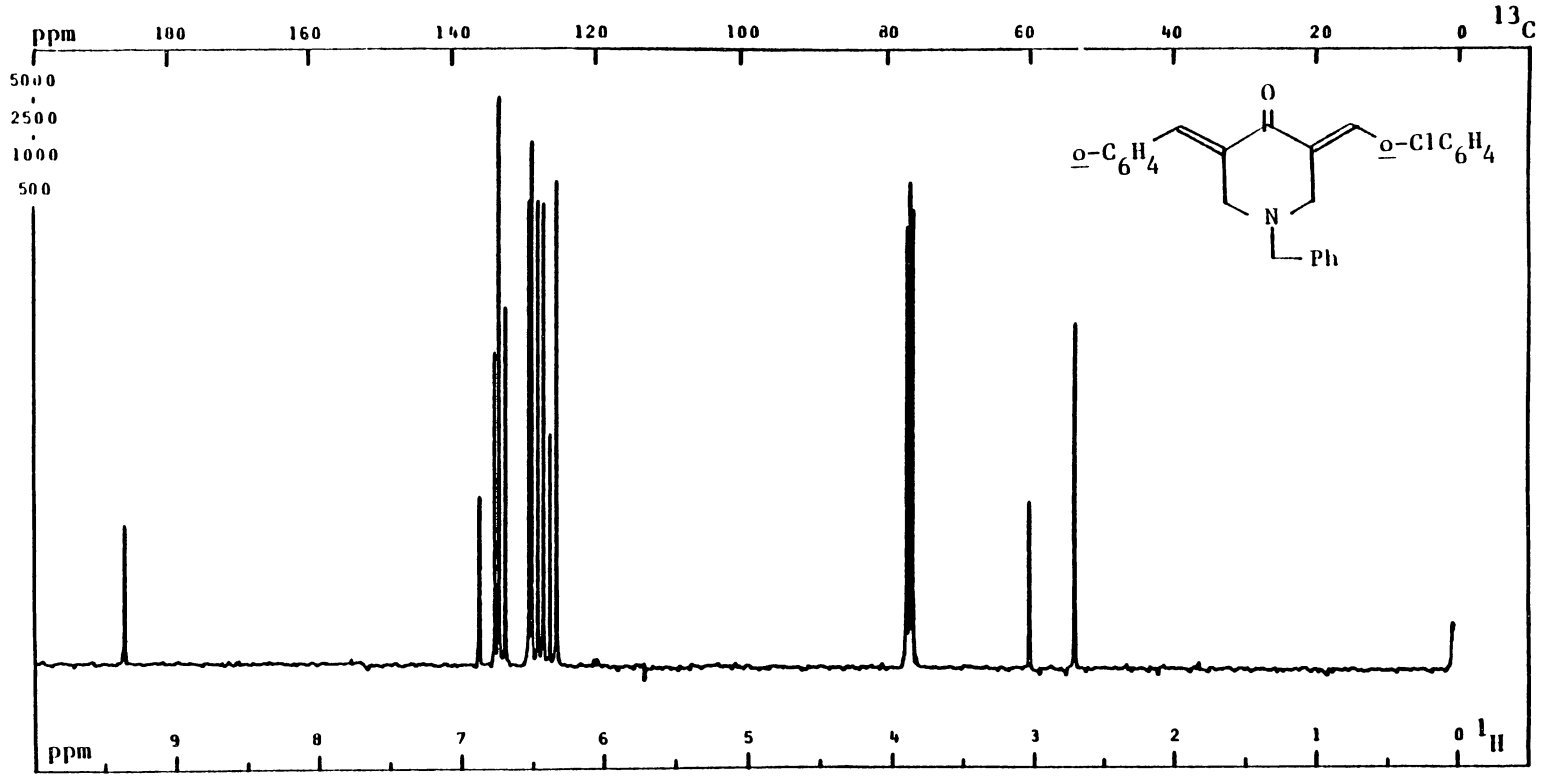


PFT _x CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 3000 Hz; T: amb °C; NT: 16

Size: 12 K; PW/RF: 8.0 μs/dB; TO: 0 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 0.50 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 16 W/dB; NBW: Hz; LB: 0 Hz.

Plate XV. ^{13}C NMR Spectrum of 19b



PFT x CW _ ; Solvent: $DCCl_3$; SF: 75.43 MHz; WC: 15000 Hz; T: amb °C; NT: 1000 .

Size: 20 K; PW/RF: 12.0 µs/dB; SO: 1000 Hz; FB: Hz; Lock: $DCCl_3$; Delay: 4.00 s.

DC: on ; Gated Off: ; Offset: 0 Hz; RF: W/dB; NBW: Hz; LB: 1.500 .

Plate XVI. IR Spectrum of **19c**

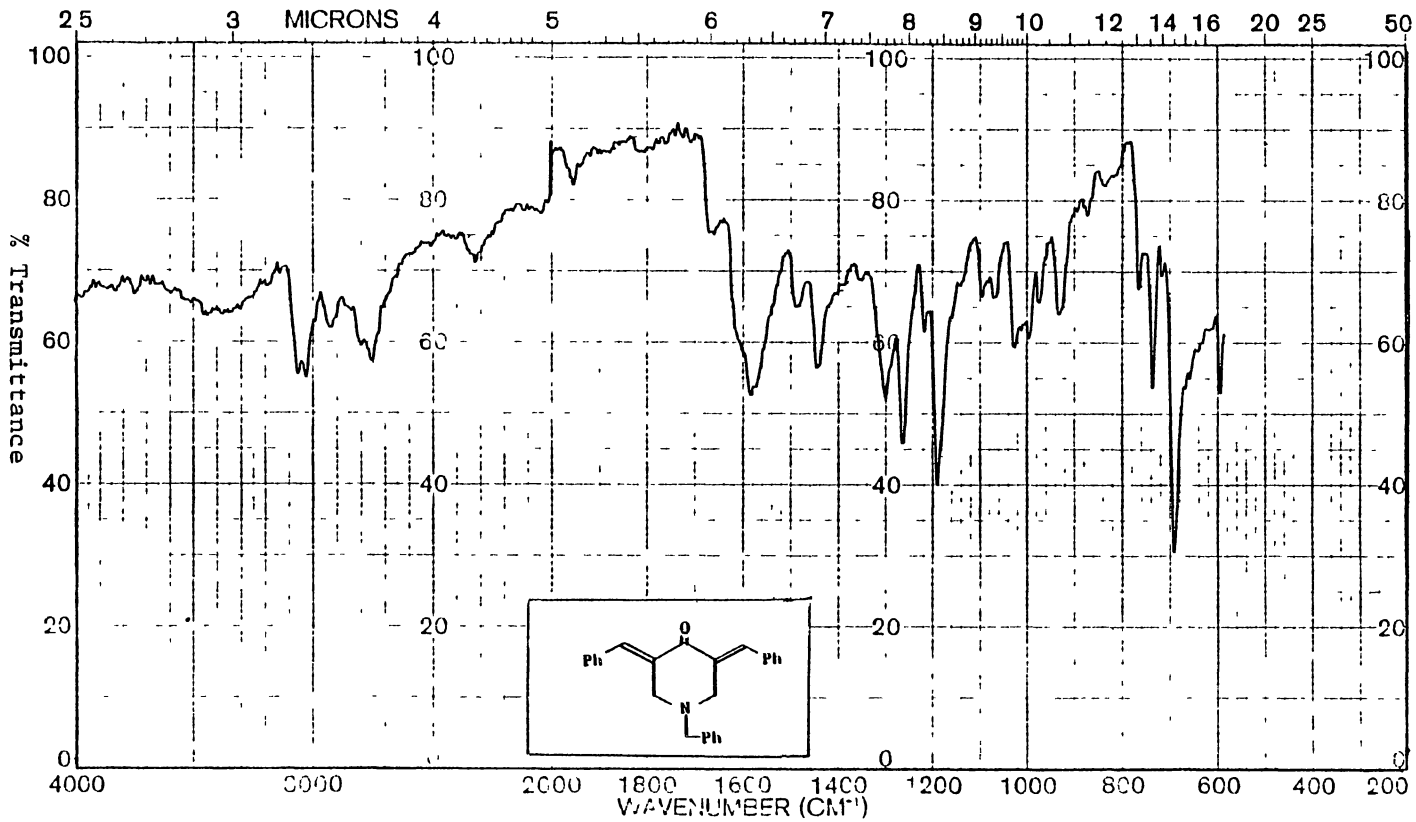
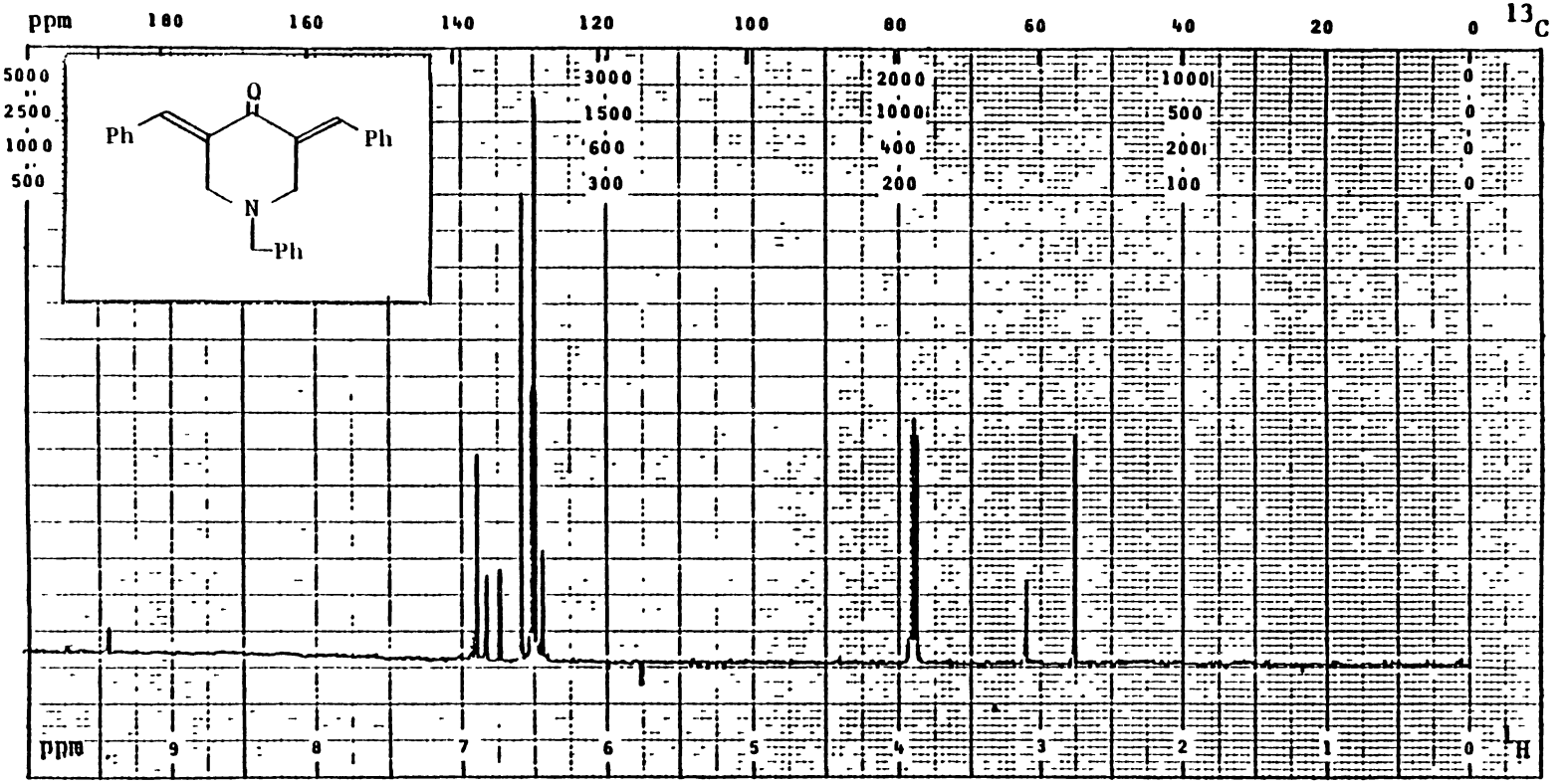


Plate XVII. ^{13}C NMR Spectrum of 19c



PFT x CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: Hz; T: amb. °C; NT: .

Size: 20 K; PW/RF: 12 μs/dB; SO: 1000 Hz; FB: Hz; Lock: $DCCl_3$; Delay: 4.0 s.

DC: On ; Gated Off: ; Offset: 0 Hz; RF: W/dB; NBW: Hz; LB: 1.00 .

Plate XVIII. IR Spectrum of **27a**

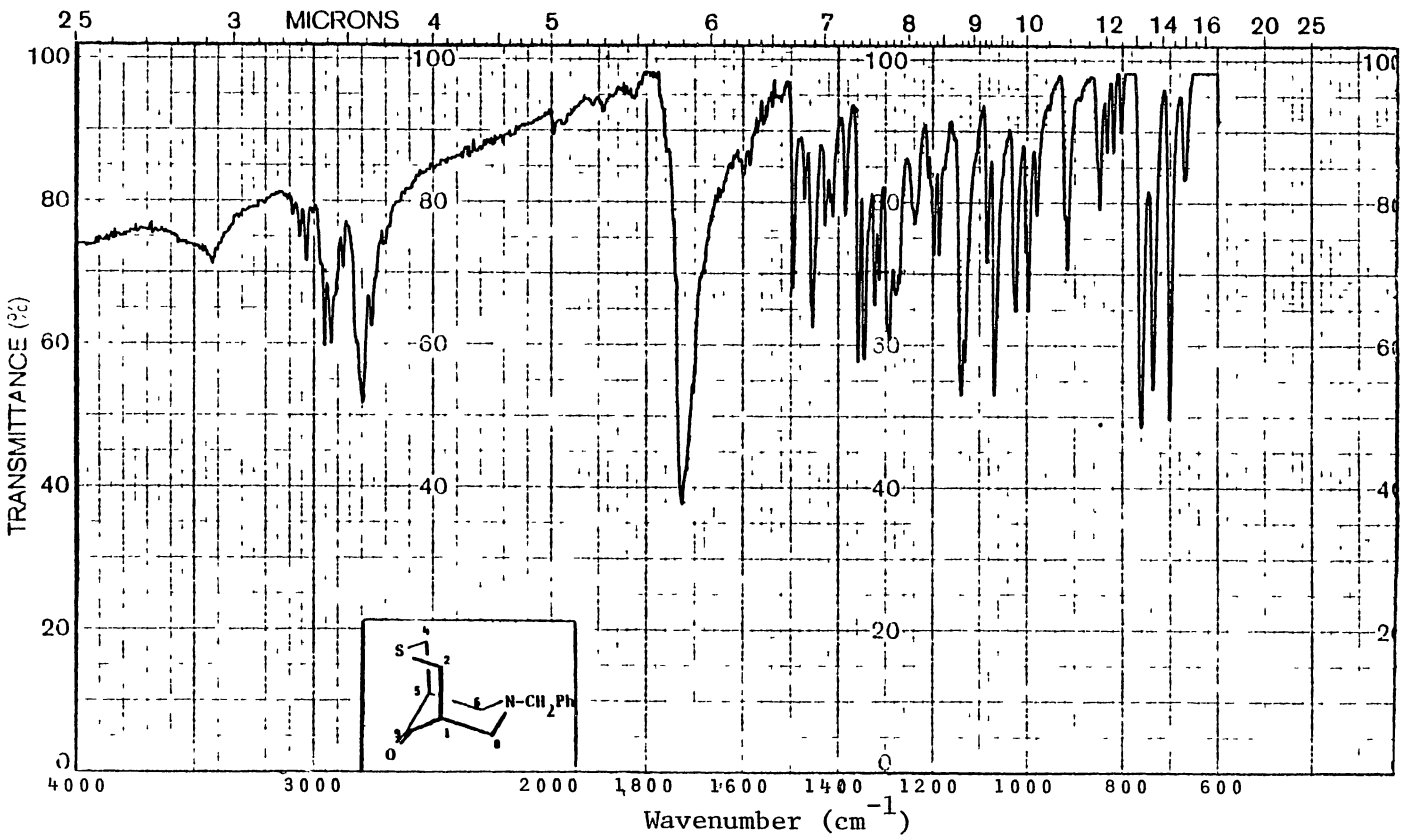
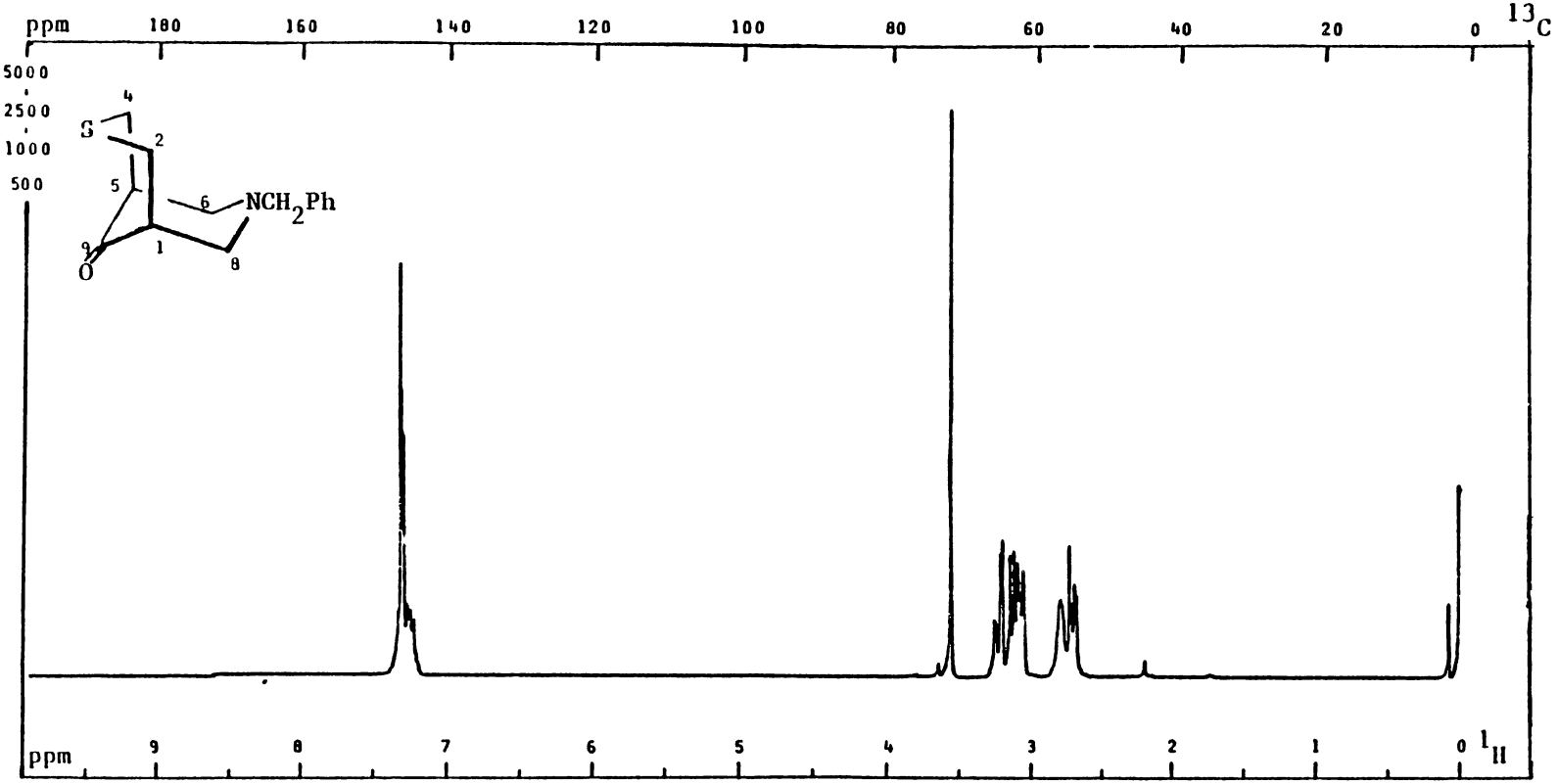


Plate XIX. ^{1}H NMR Spectrum of 27a

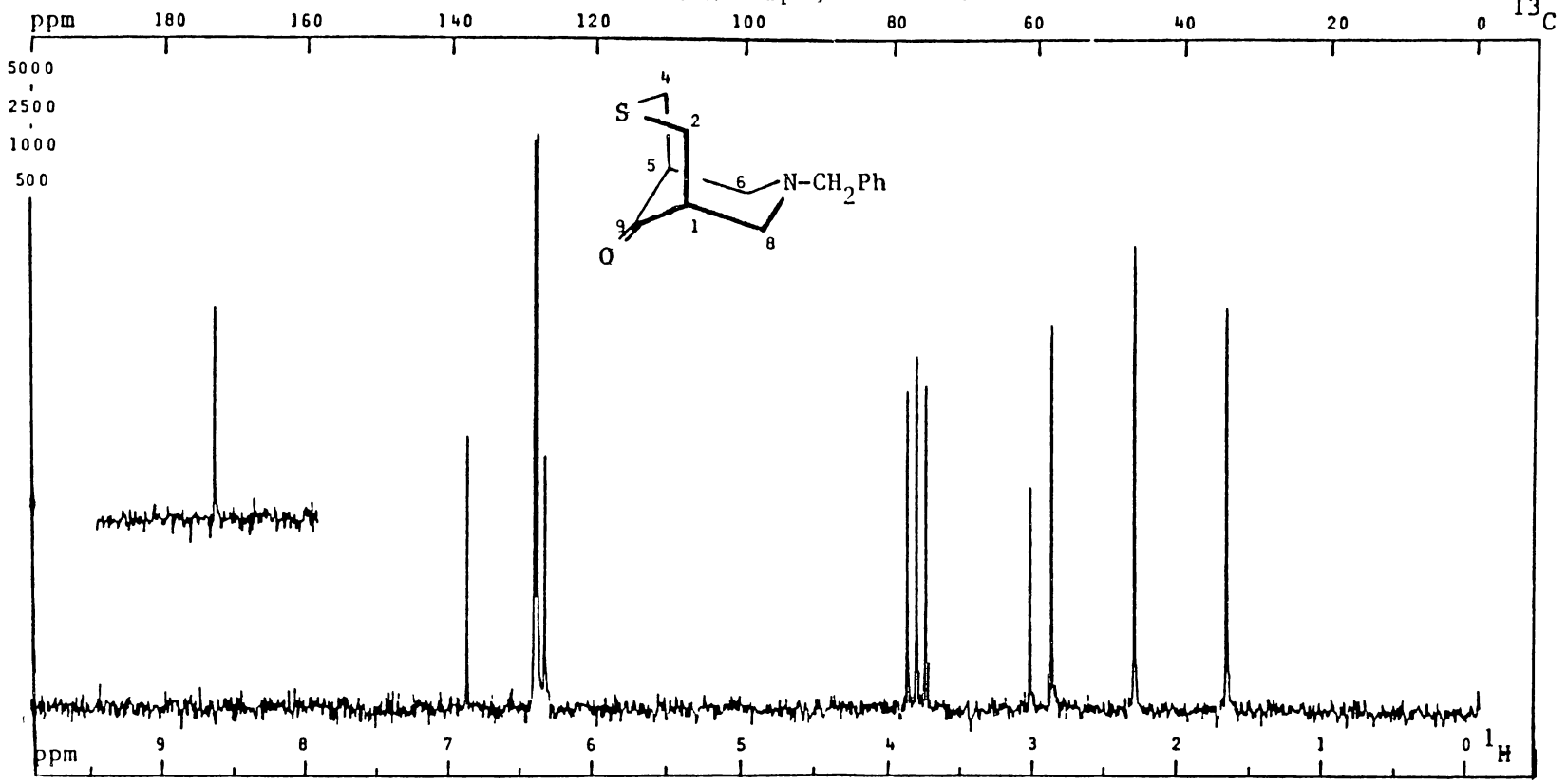


PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 3000 Hz; T: amb. °C; NT: 16 .

Size: 8 K; PW/RF: 10 µs/dB; TO: 0 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 0.5 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 17 W/dB; NBW: Hz; LB: 0.5 Hz.

Plate XX. ^{13}C NMR Spectrum of **27a**



PFT x CW _ ; Solvent:$DCCl_3$; SF: 75.429 MHz; WC: 15086 Hz; T: amb. °C; NT:40 .

Size: 16 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: Hz; Lock:$DCCl_3$; D1,D5: 4.0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 2 Hz.

Plate XXI. **HETCOR NMR Spectrum of 27a**

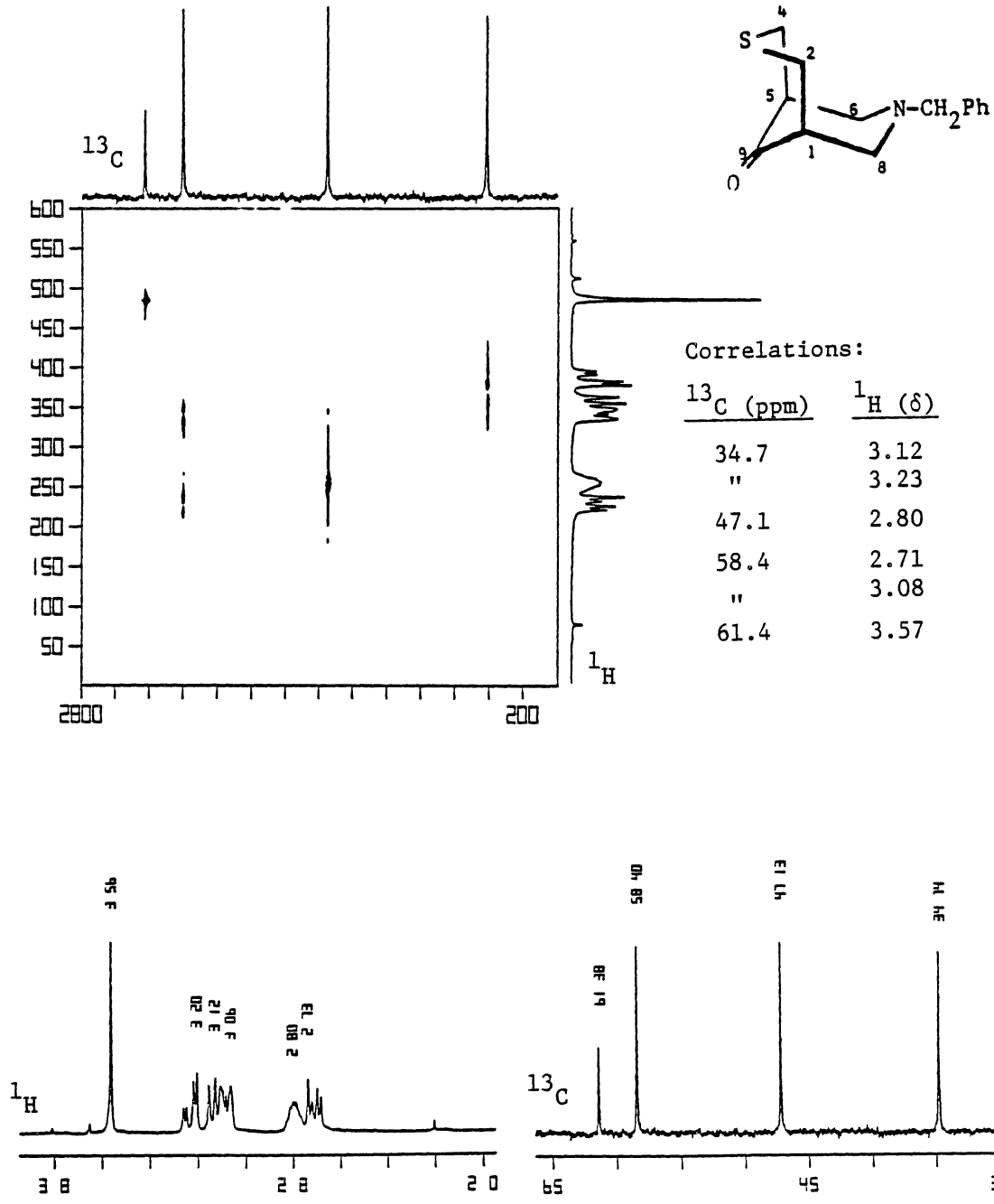


Plate XXII. IR Spectrum of **27b**

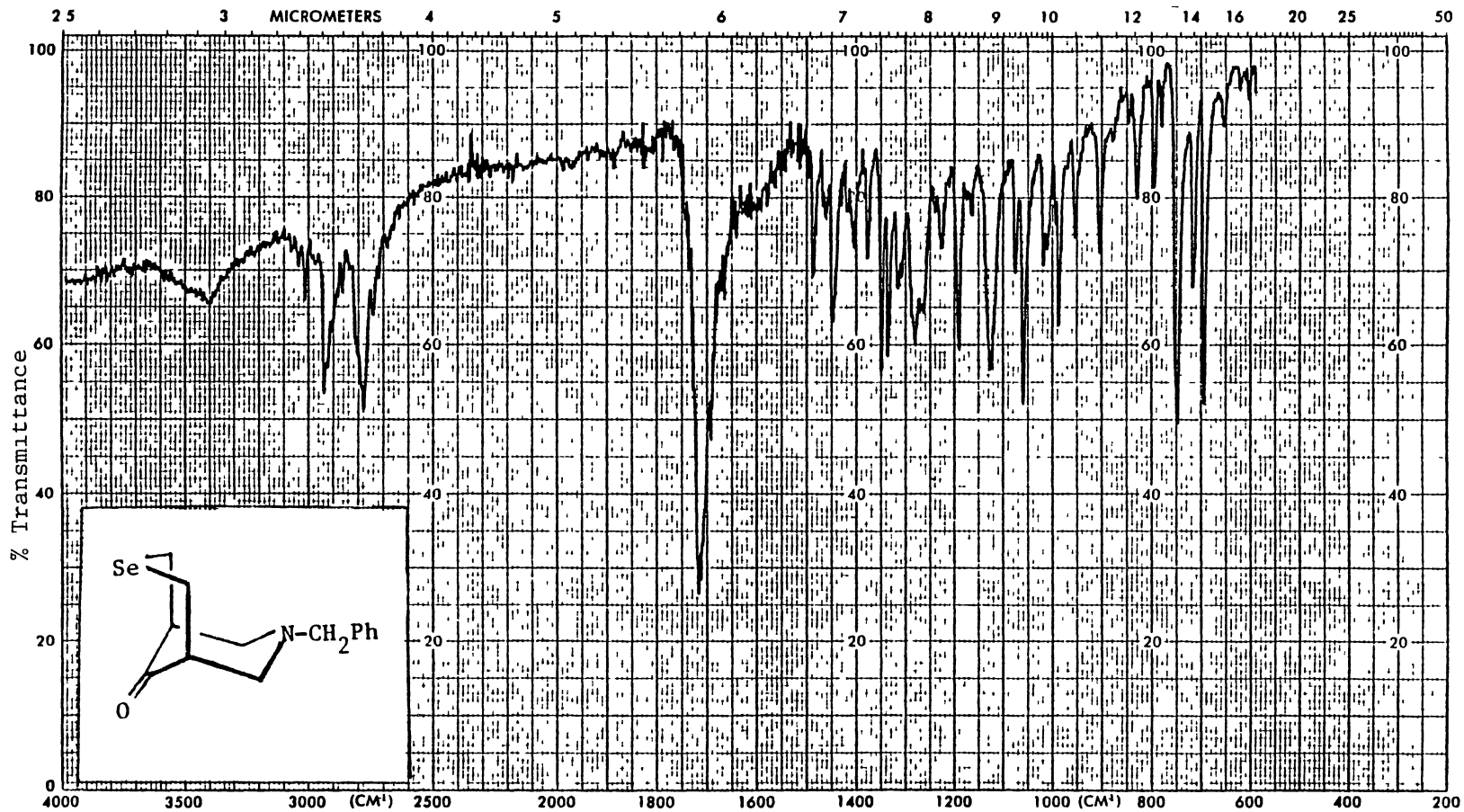
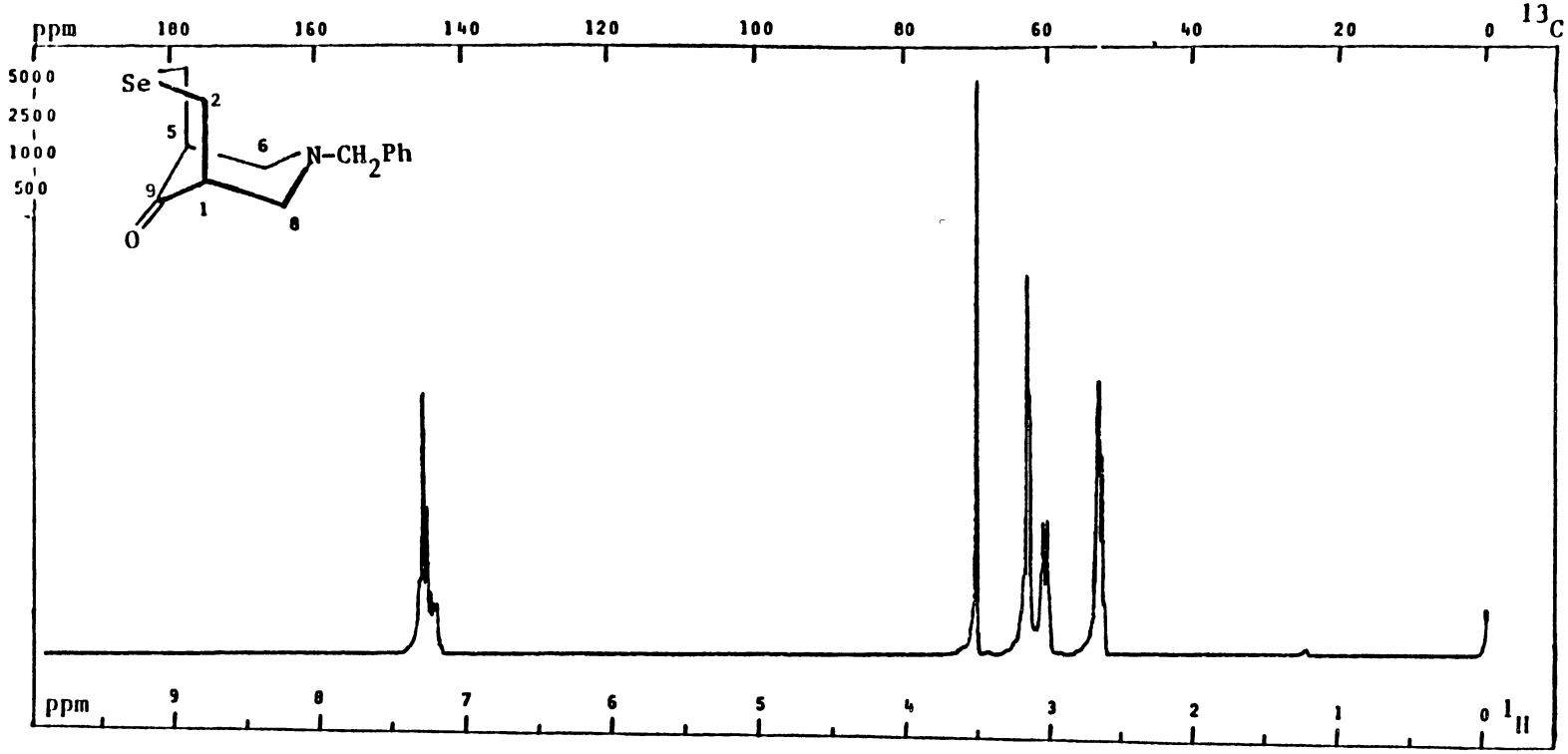


Plate XXIII. ^{1}H NMR Spectrum of 27b

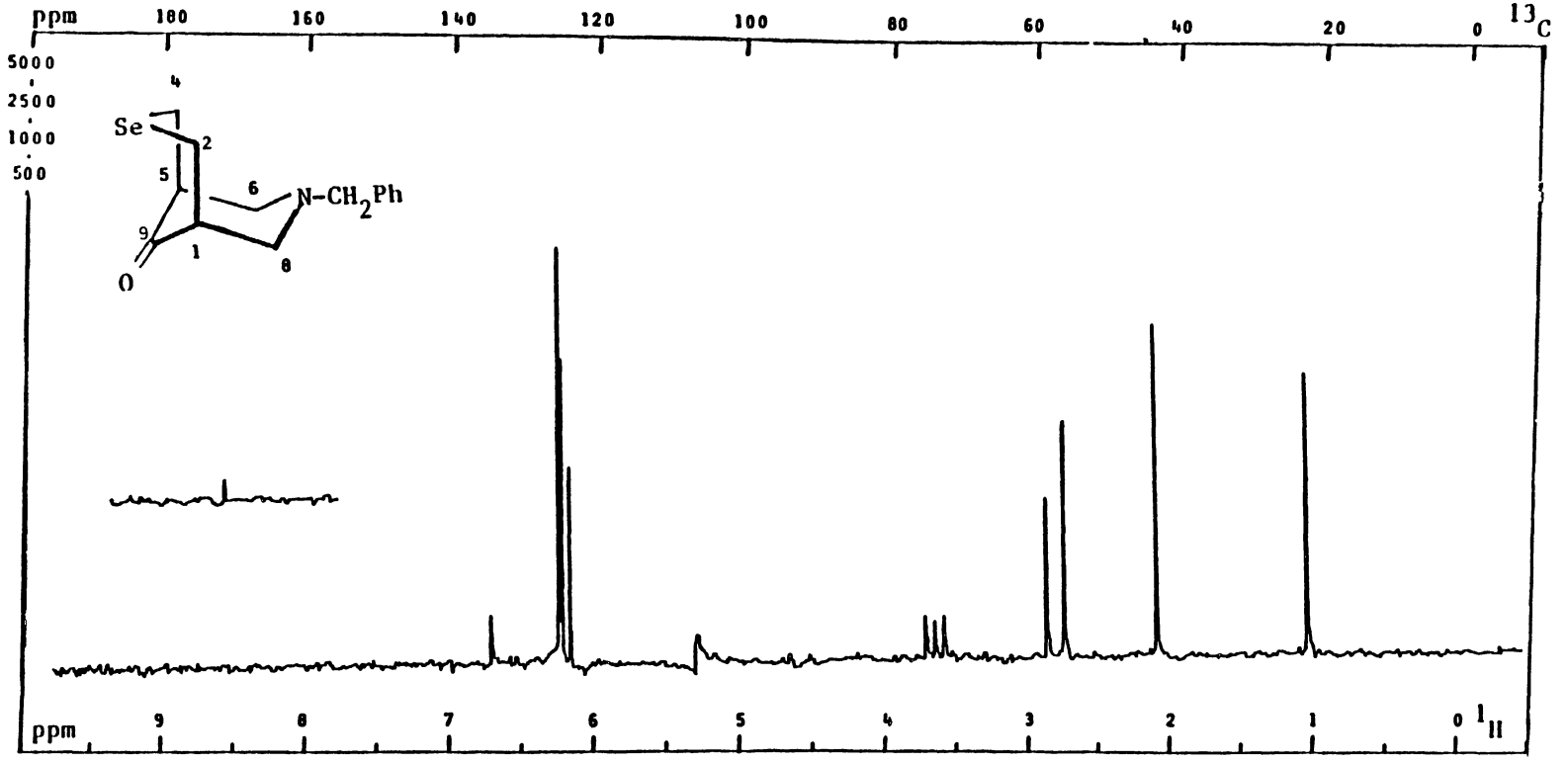


PFT x CW _ ; Solvent:$DCCl_3$; SF:299.944 MHz; WC:3000 Hz; T:amb. °C; NT: 16 .

Size:8 K; PW/RF: 10 µs/dB; TO: 0 Hz; FB: Hz; Lock:$DCCl_3$; D1,D5: 0.5 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 17 W/dB; NBW: Hz; LB: 0.5 Hz.

Plate XXIV. ^{13}C NMR Spectrum of 27b

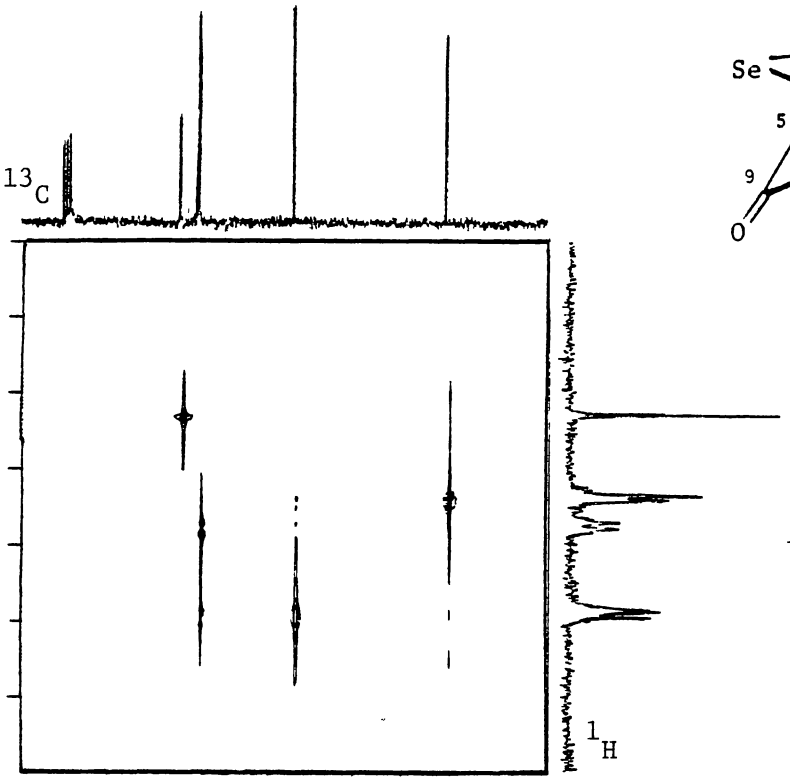


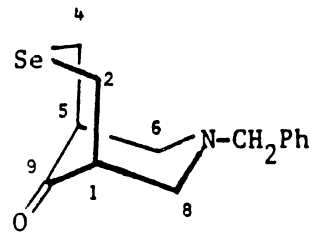
PFT x CW _ ; Solvent: $DCCl_3$; SF: 25.20 MHz; WC: 5000 Hz; T: amb. °C; NT: 1600 .

Size: 8 K; PW/RF: 20 µs/dB; TO: 35101 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 4.0 s.

DC: Y, N ; Gated Off: A or D ; DO: 45316 Hz; RF(Power): 119 W/dB; NBW: Hz; LB: 1.0 Hz.

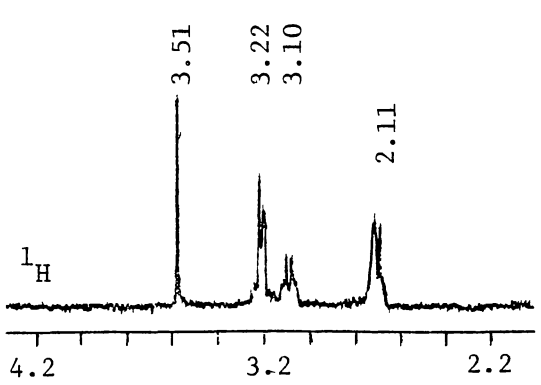
Plate XXV. HETCOR NMR Spectrum of **27b**





Correlations:

^{13}C (ppm)	^{1}H (δ)
25.5	3.22
46.2	2.11
59.0	2.11
59.0	3.10
61.5	3.51



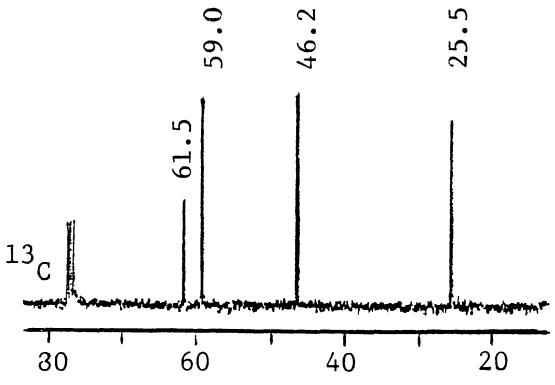


Plate XXVI. IR Spectrum of **28d**

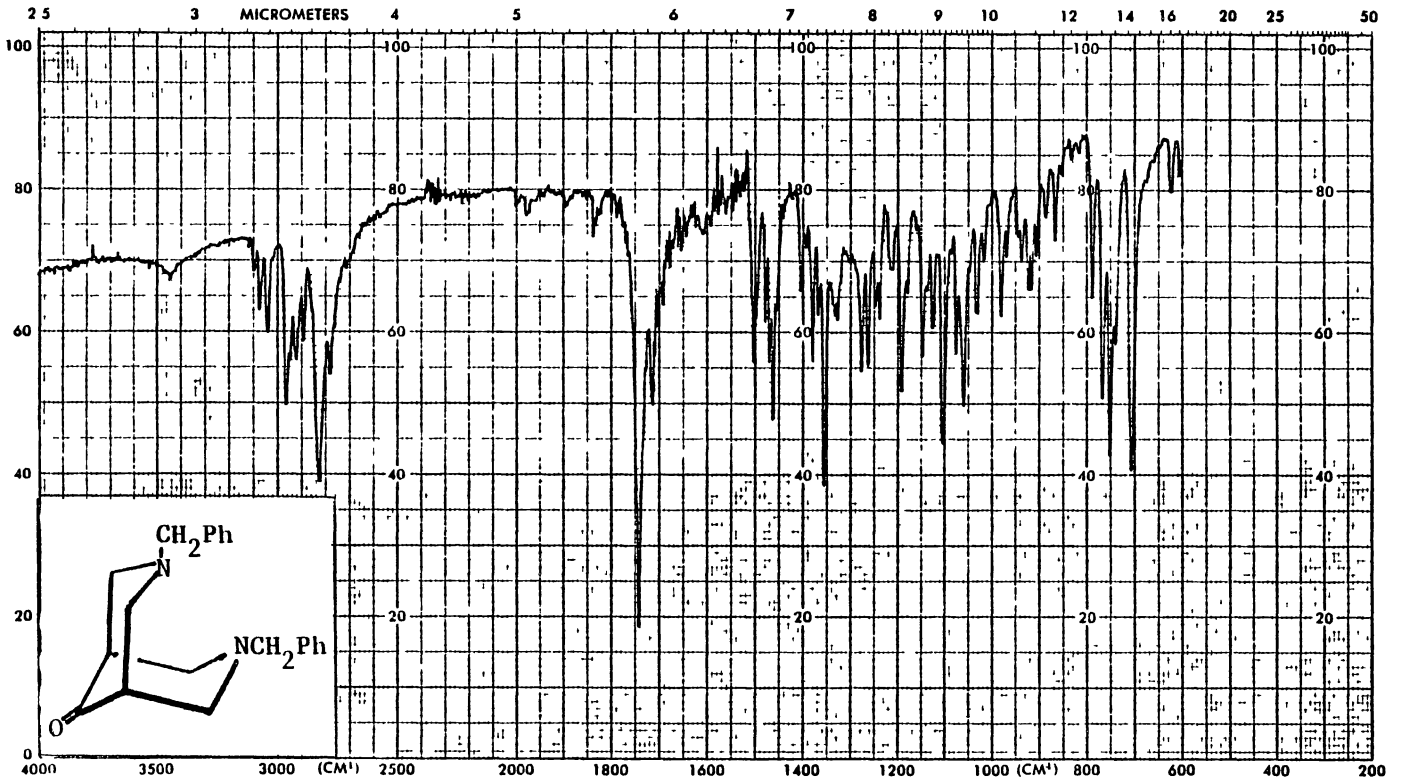
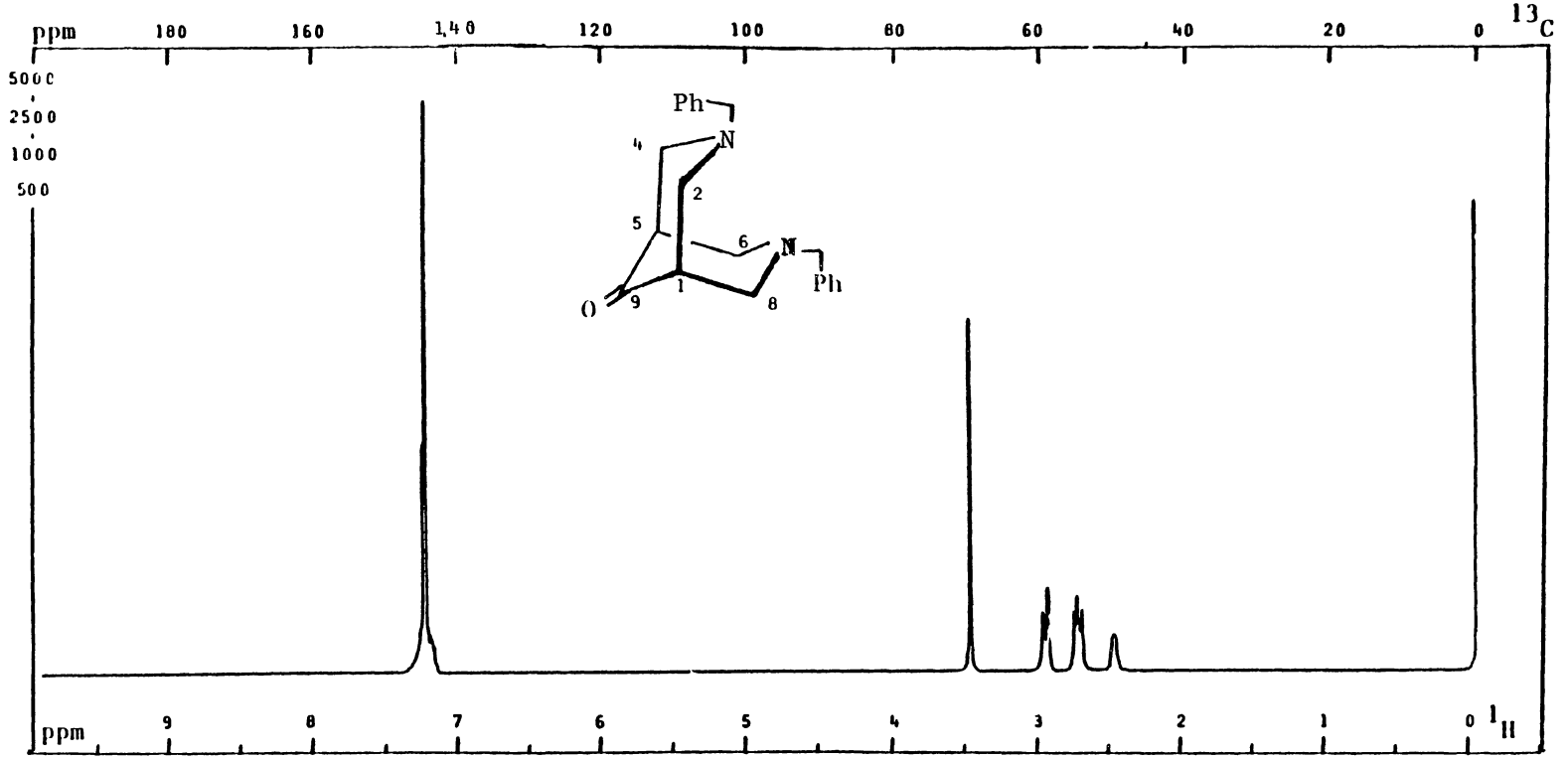


Plate XXVII. ^{1}H NMR Spectrum of 28d

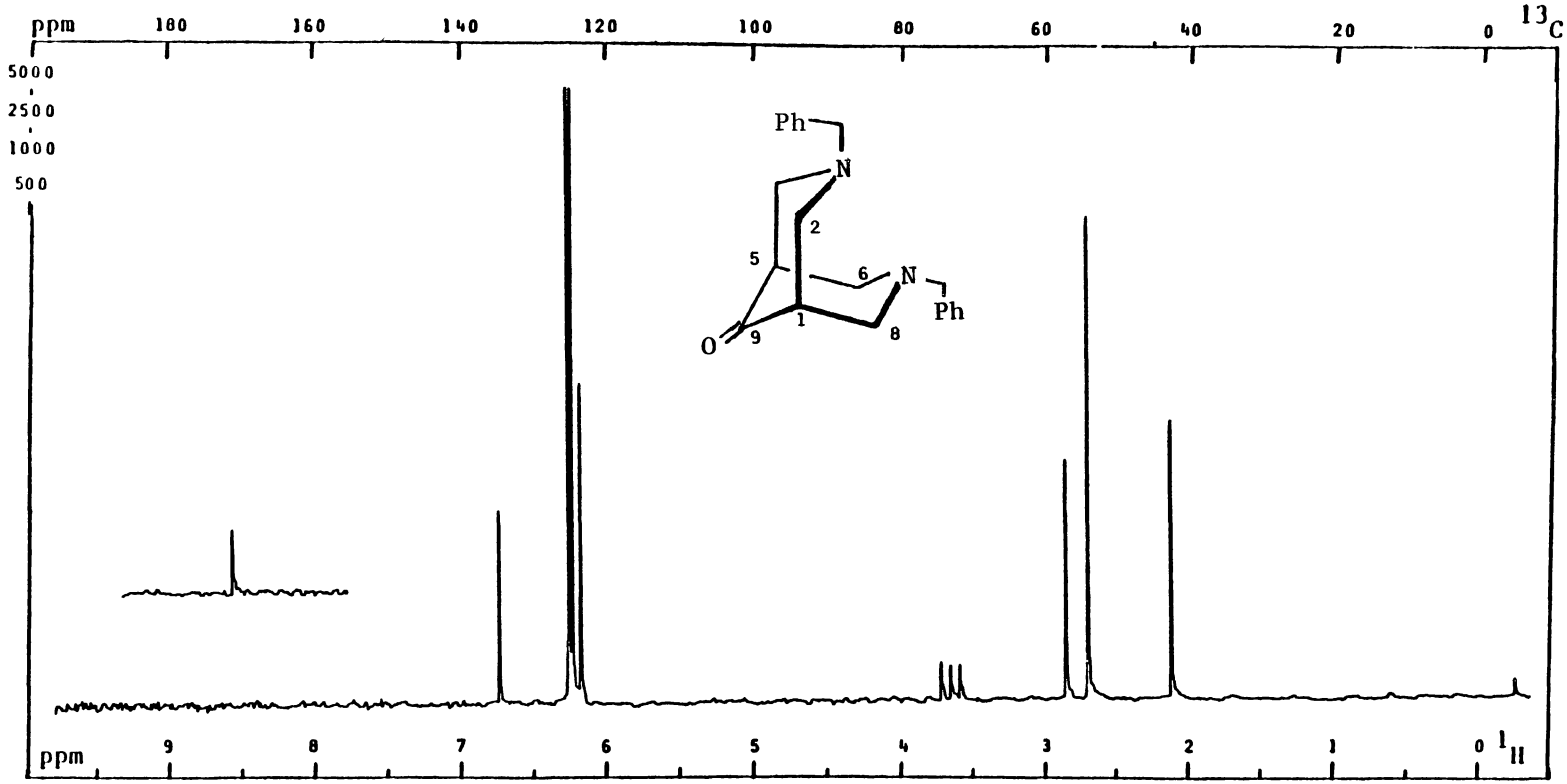


PFT x CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 3000 Hz; T: amb. °C; NT: 16 .

Size: 8 K; PW/RF: 2.0 μs/dB; TO: 0 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: Hz; LB: - Hz.

Plate XVIII. ^{13}C NMR Spectrum of 28d

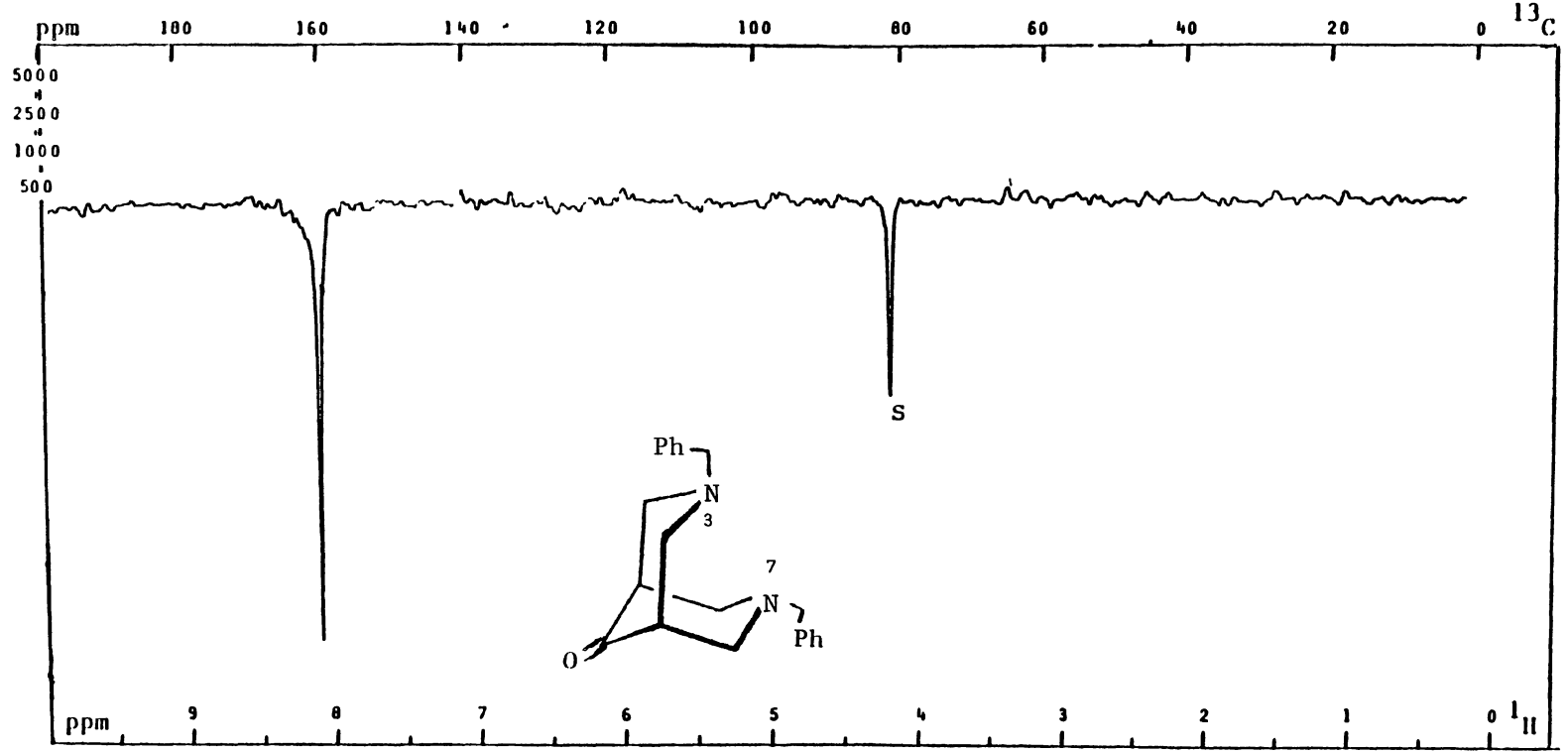


PFT X CW _ ; Solvent: $DCCl_3$; SF: 25.2 MHz; WC: 5000 Hz; T: amb. °C; NT: 500 .

Size: 16 K; PW/RF: μs/dB; TO: 35101 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 4.0 s.

DC: Y, N ; Gated Off: A or D ; DO: 45316 Hz; RF(Power): 119 W/dB; NBW: Hz; LB: 1.5 Hz.

PLATE XXIX. ^{15}N NMR Spectrum of **62c**



PFT x CW _ ; Solvent: $DCCl_3$; SF: 30.406 MHz; WC: 1520.3 Hz; T: amb. °C; NT: 8724

Size: 12 K; PW/RF: 40 μs/dB; TO: -11600 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 25 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: Hz; LB: 2.0 Hz.

Plate XXX. IR Spectrum of **29d**

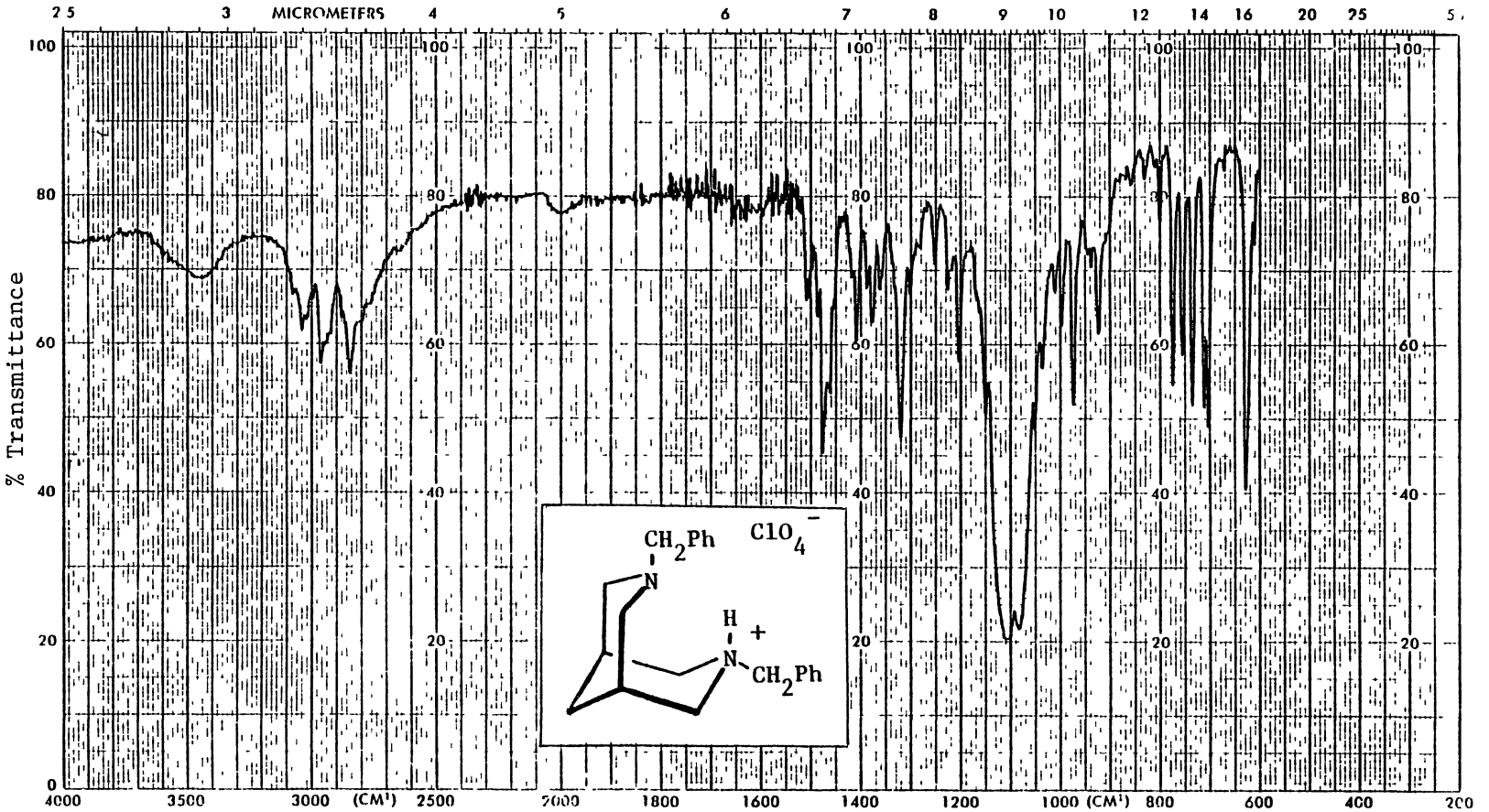
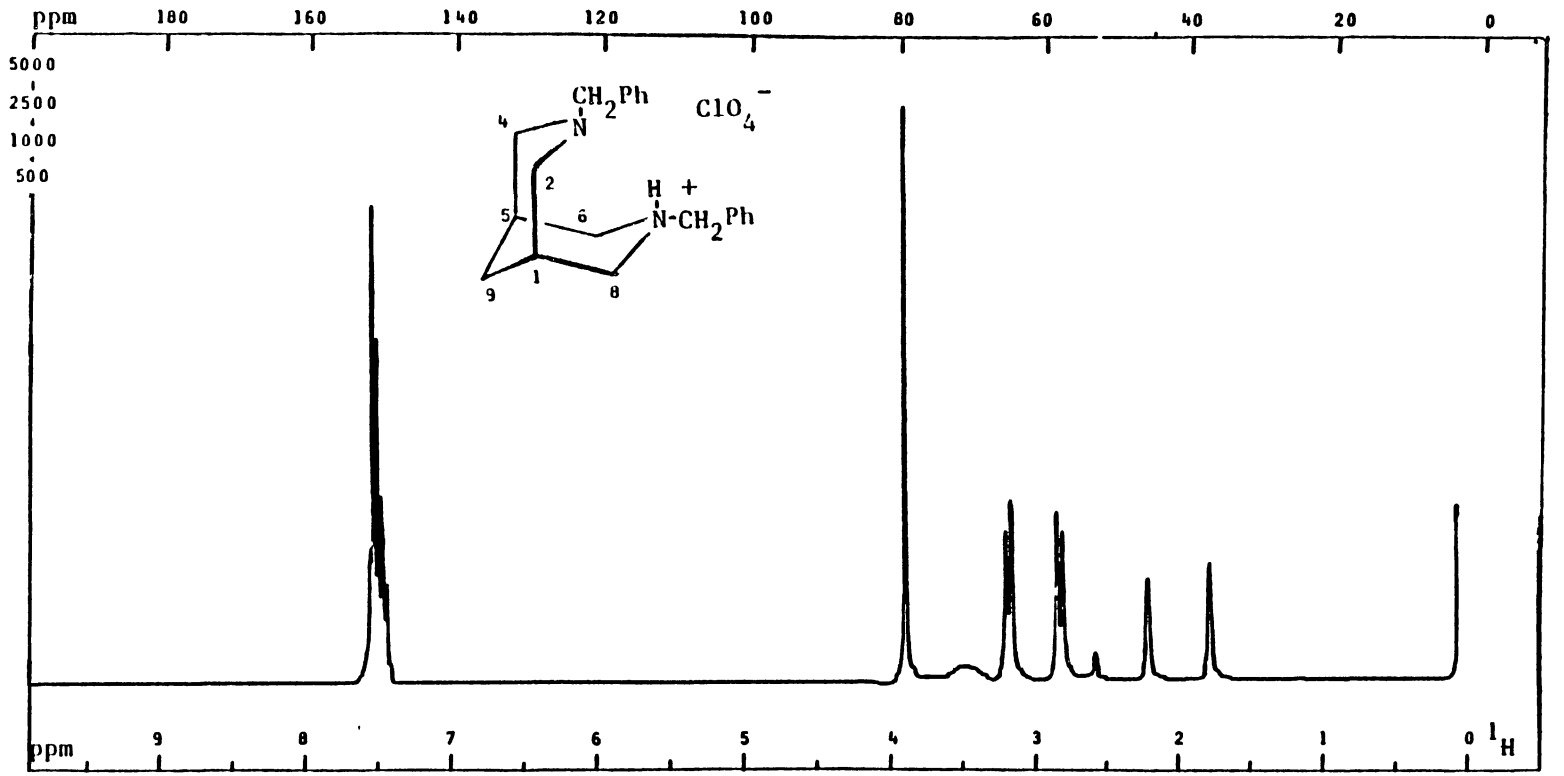


Plate XXXI. ^{1}H NMR Spectrum of **29d**

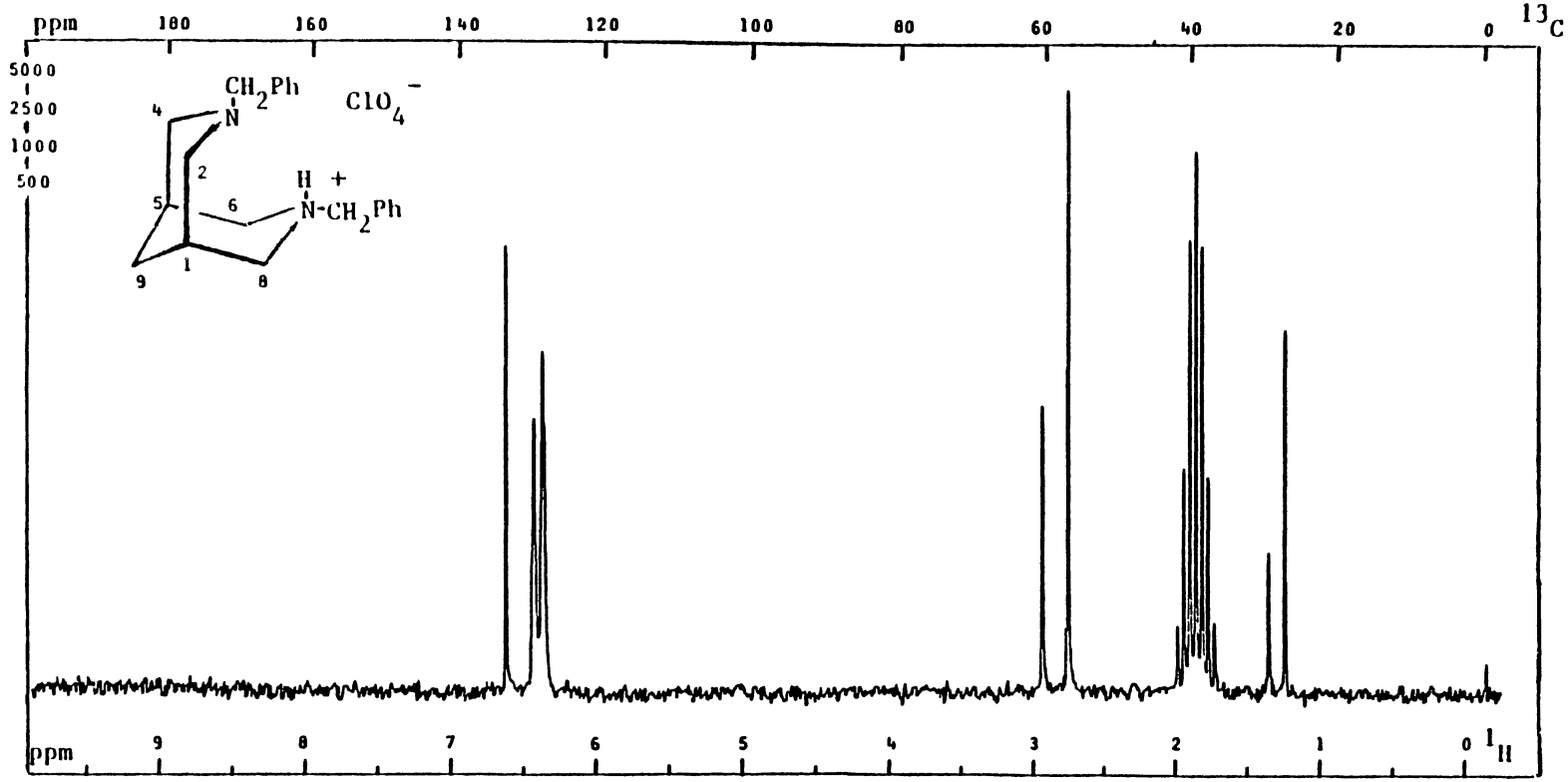


PFT x CW _ ; Solvent: DMSO-d_6 ; SF: 299.944 MHz; WC: 3000 Hz; T: amb. °C; NT: 16 .

Size: 8 K; PW/RF: 4.0 µs/dB; TO: 1500 Hz; FB: Hz; Lock:DMSO-d_6; D1,D5: 0.5 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: Hz; LB: - Hz.

Plate XXXII. ^{13}C NMR Spectrum of 29d

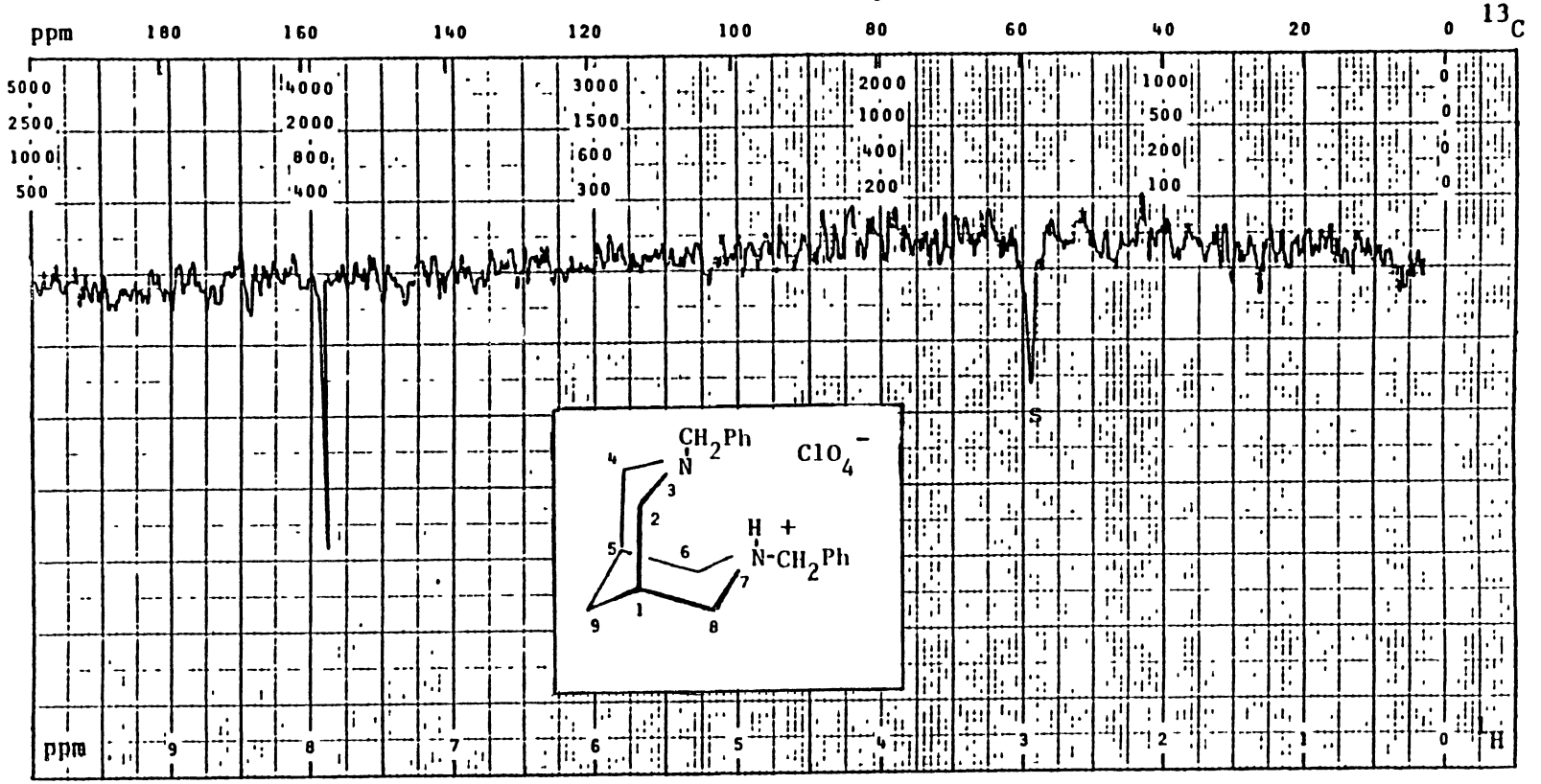


PFT $\underline{x}$ CW _ ; Solvent: DMSO-d_6 ; SF: 25.20 MHz; WC: 5000 Hz; T: amb. °C; NT: 3540 .

Size: 8 K; PW/RF: 20 µs/dB; TO: 35101 Hz; FB: Hz; Lock: DMSO-d_6; D1,D5: 4.0 s.

DC: $\underline{Y}$, N ; Gated Off: A or D ; DO: 45316 Hz; RF(Power): 119 W/dB; NBW: Hz; LB: 1.5 Hz.

Plate XXXIII. ^{15}N NMR Spectrum of 29d



PFT x CW _ ; Solvent: DMSO-d_6 ; SF: 30.406 MHz; WC: 2432.05 Hz; T: amb. °C; NT: 6000 .

Size: 12 K; PW/RF: 40 µs/dB; TO: -11600 Hz; FB: Hz; Lock: DMSO-d_6; D1,D5 : 25 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: Hz; LB: 2.0 Hz.

Plate XXXIV. IR Spectrum of 30b

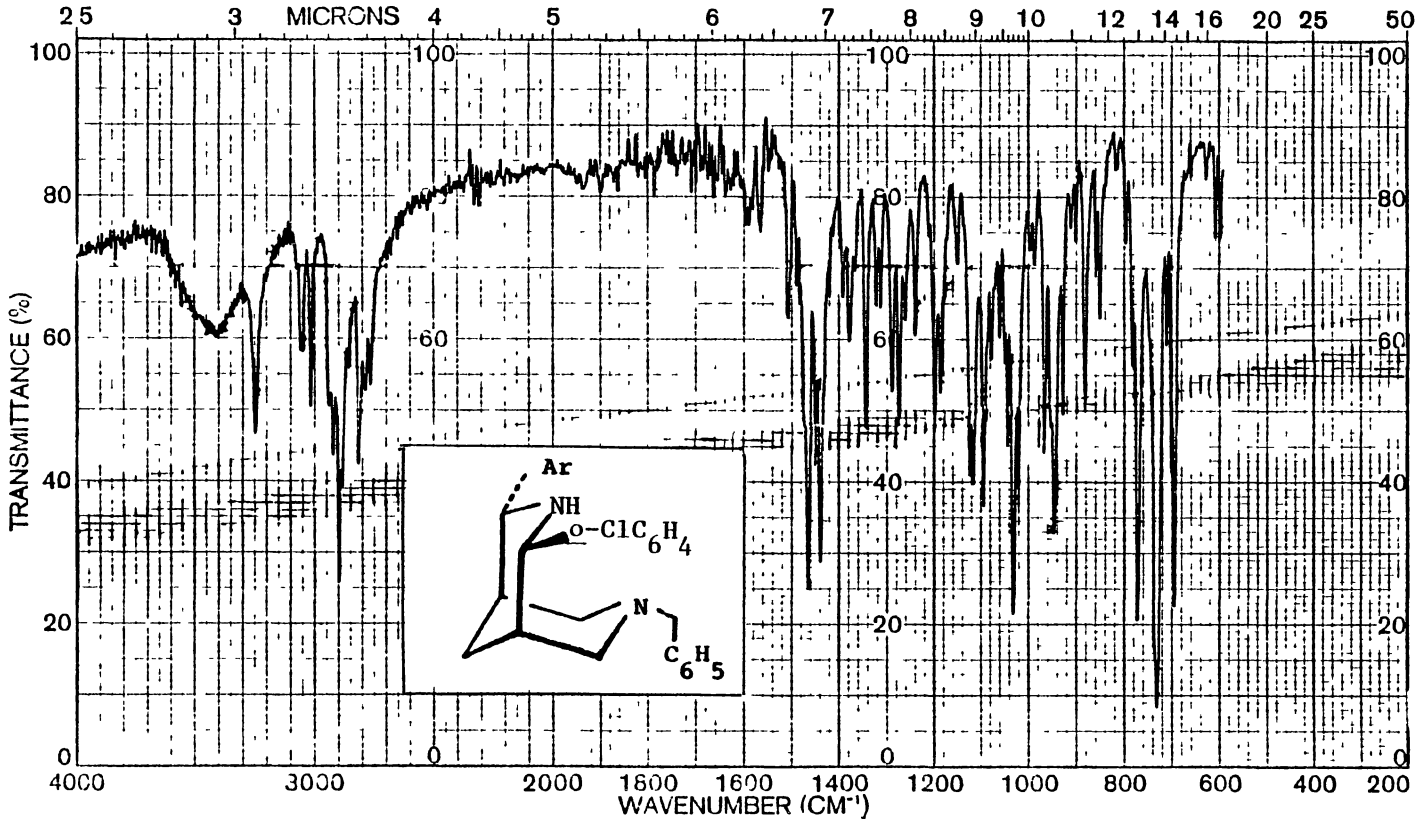
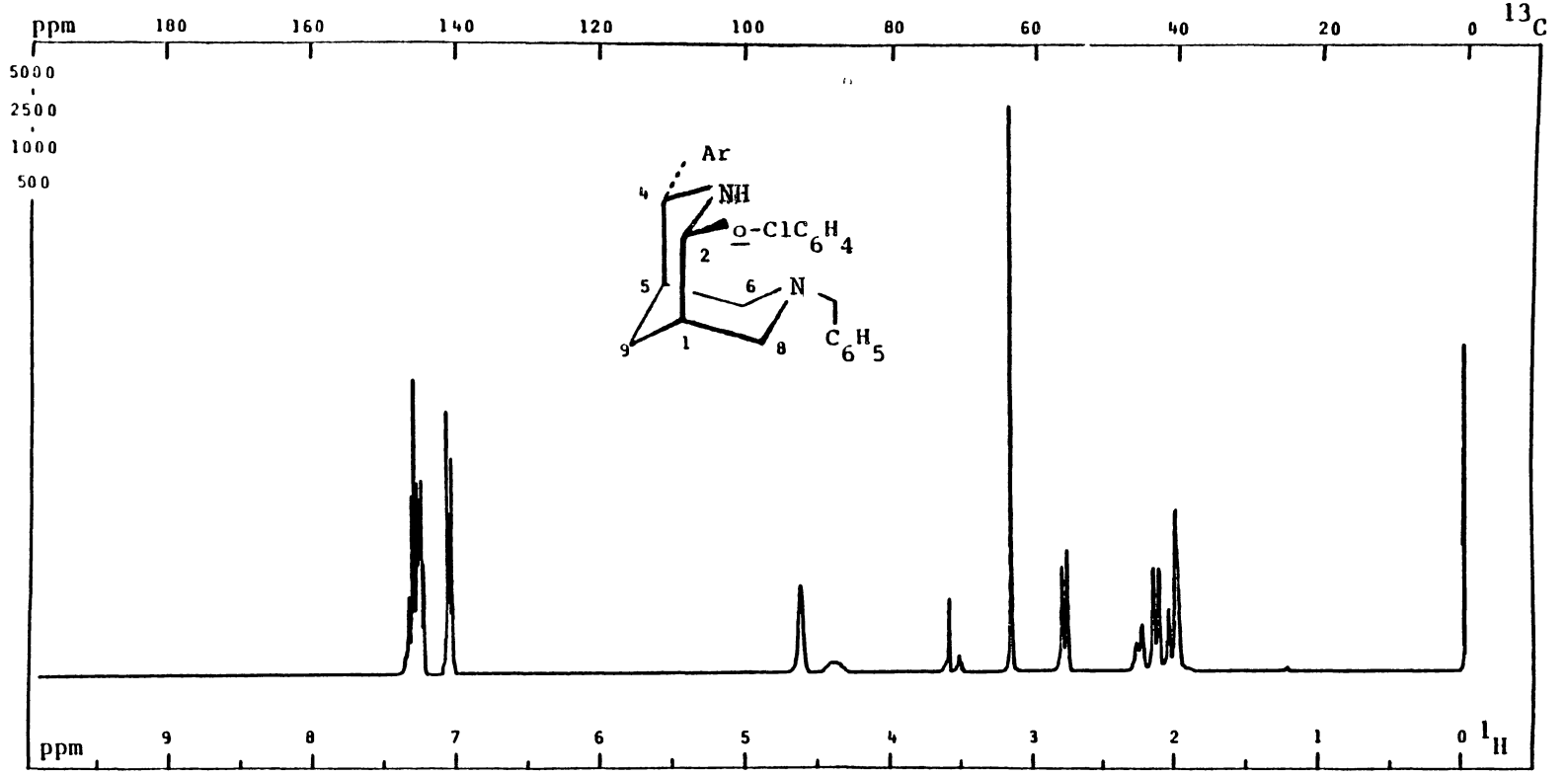


Plate XXXV. ^{1}H NMR Spectrum of 30b

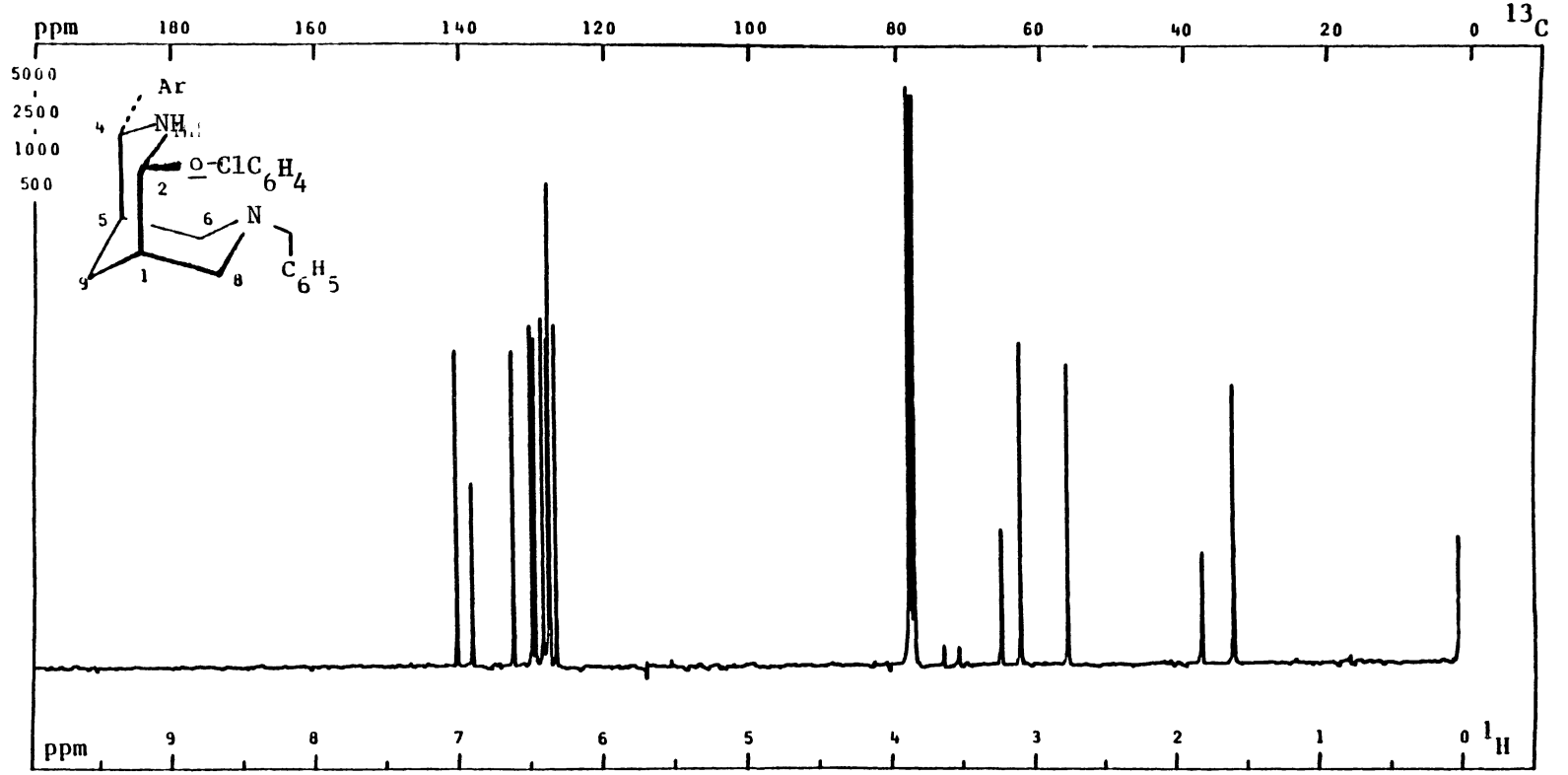


PFT x CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 3000 Hz; T:amb. °C; NT: 20 .

Size: 8 K; PW/RF:6 μs/dB; TO: 0 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 0.5 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 16 W/dB; NBW: Hz; LB: 1.5 Hz.

Plate XXXVI. ^{13}C NMR Spectrum of 30b

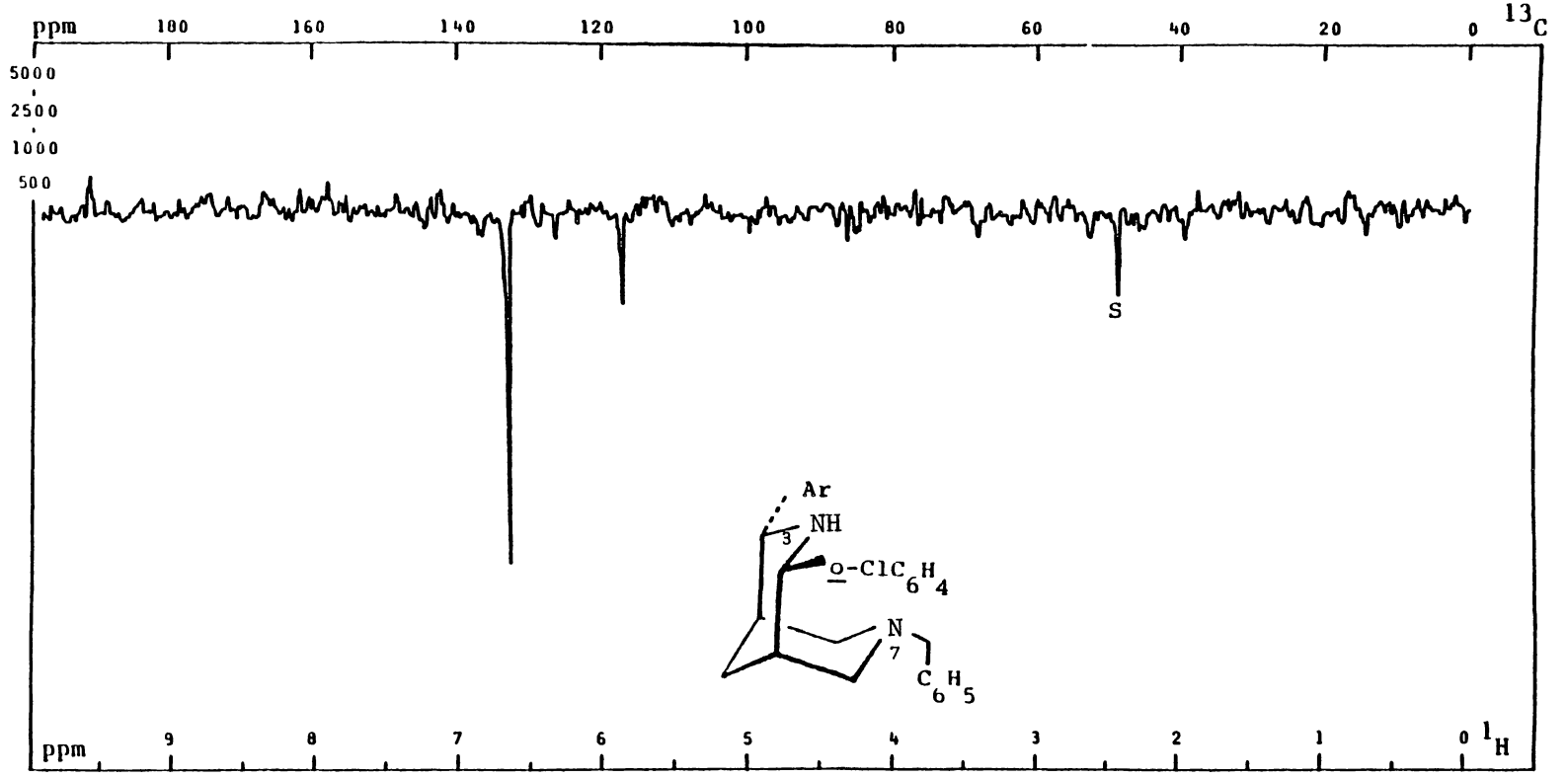


PFT x CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085 Hz; T: amb. °C; NT: 492 .

Size: 32 K; PW/RF: 10 µs/dB; TO: 1000 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 8 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 2 Hz.

Plate XXXVII. ^{15}N NMR of 30b



PFT x CW _ ; Solvent: $DCCl_3$; SF:30.406 MHz; WC: 2432.5 Hz; T: amb. °C; NT:6000 .

Size: 12 K; PW/RF: 40 µs/dB; TO: -11600 Hz; FB: Hz; Lock:$DCCl_3$;D1,D5: 8 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: Hz; LB: 2.0 Hz.

Plate XXXVIII. IR Spectrum of **31b**

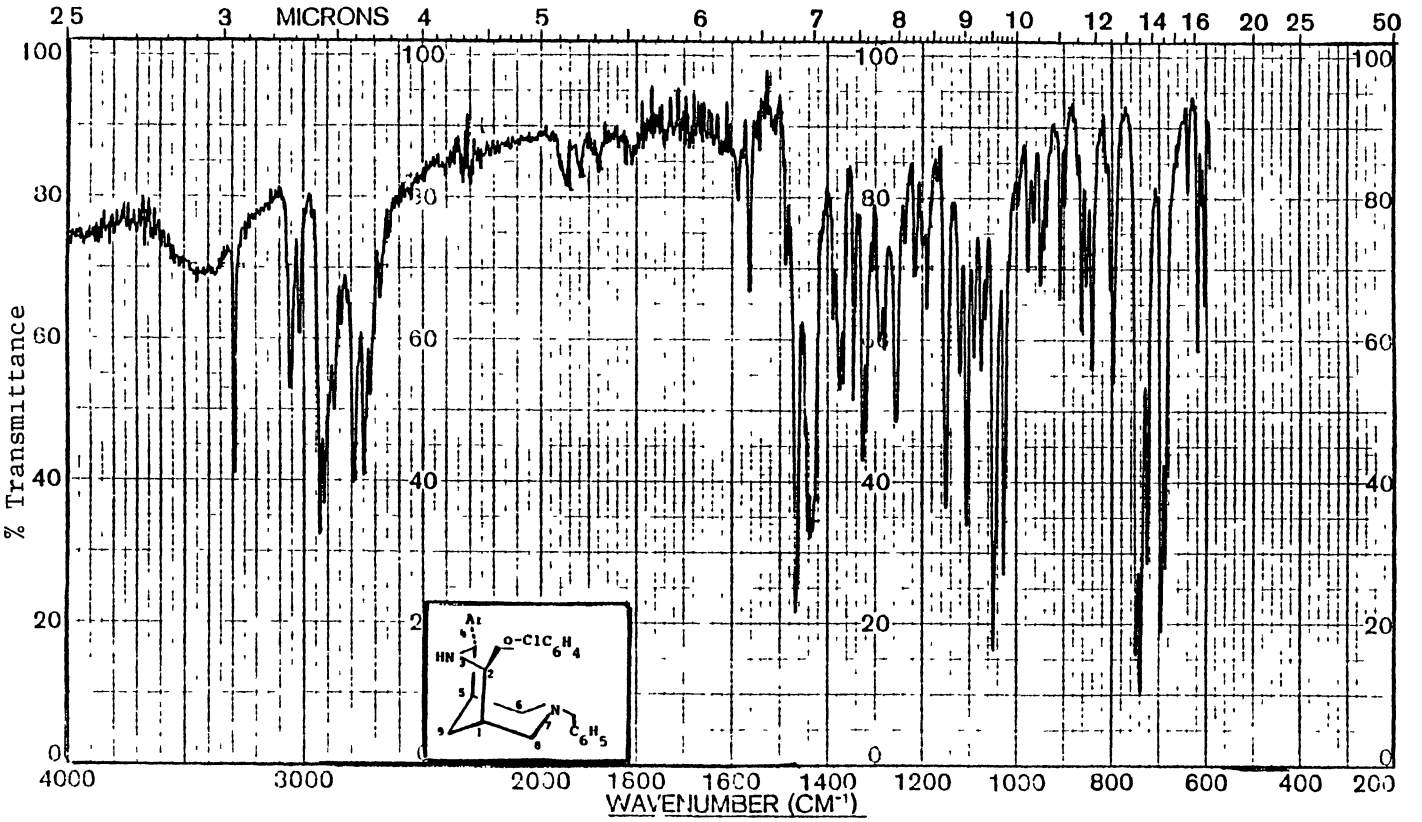
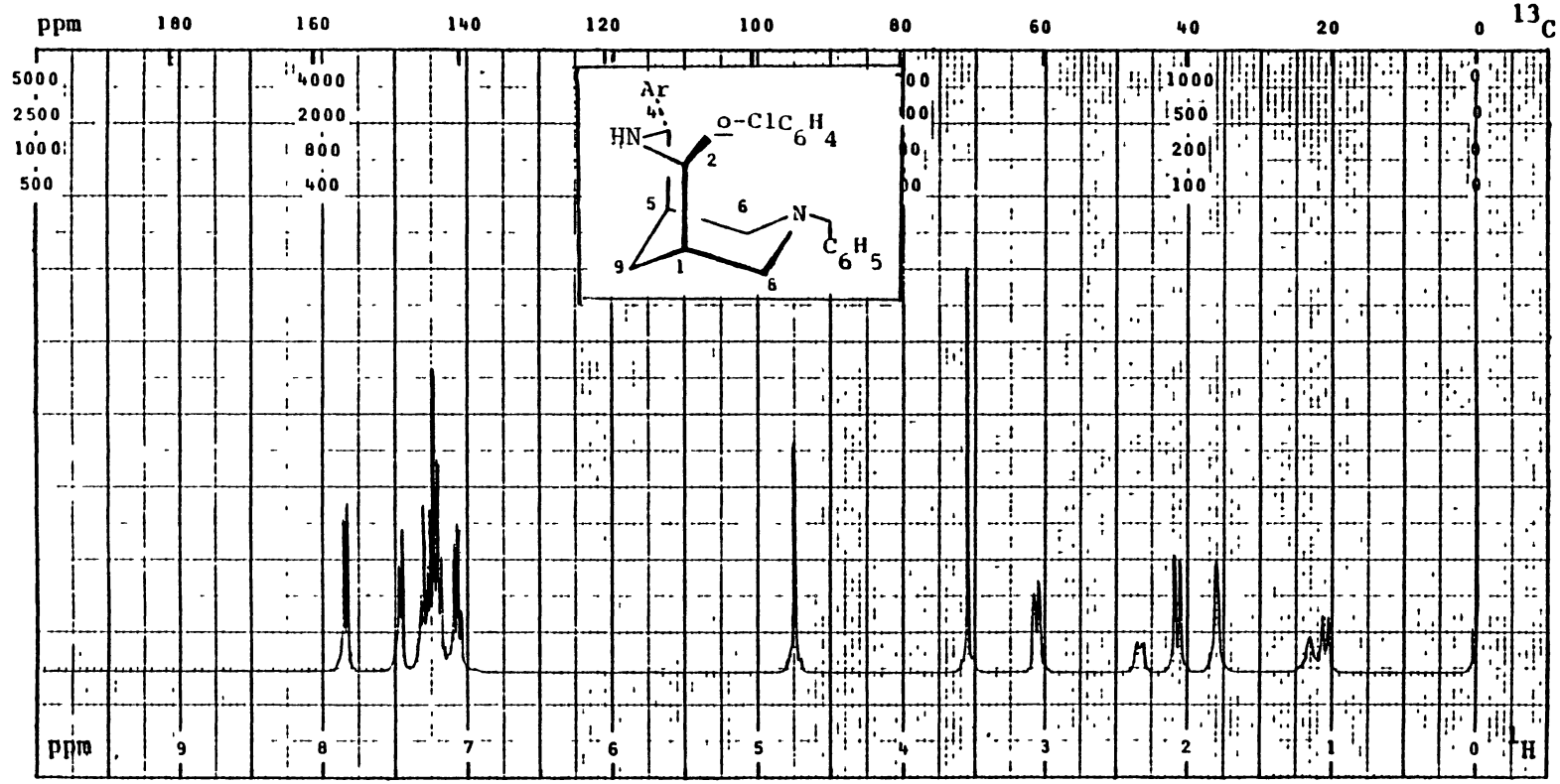


Plate XXXIX. ^{1}H NMR Spectrum of 31b

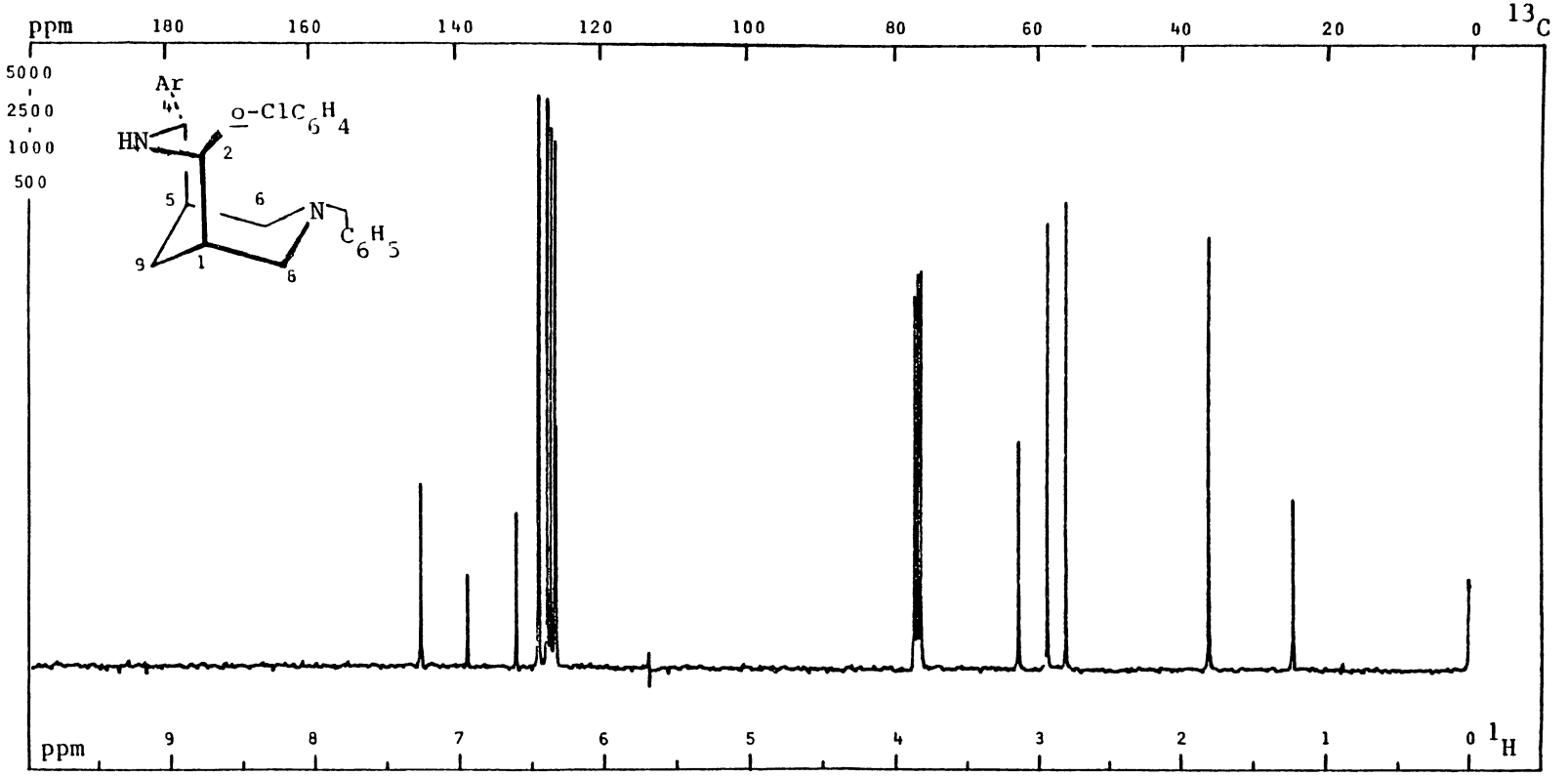


PFT x CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 3000 Hz; T: amb. °C; NT: 8

Size: 12 K; PW/RF: 7 µs/dB; SO: 0 Hz; FB: Hz; Lock: $DCCl_3$; Delay: 0 s.

DC: N ; Gated Off: ; Offset: 0 Hz; RF: 15 W/dB; NBW: Hz; LB: -

Plate XL. ^{13}C NMR Spectrum of 31b

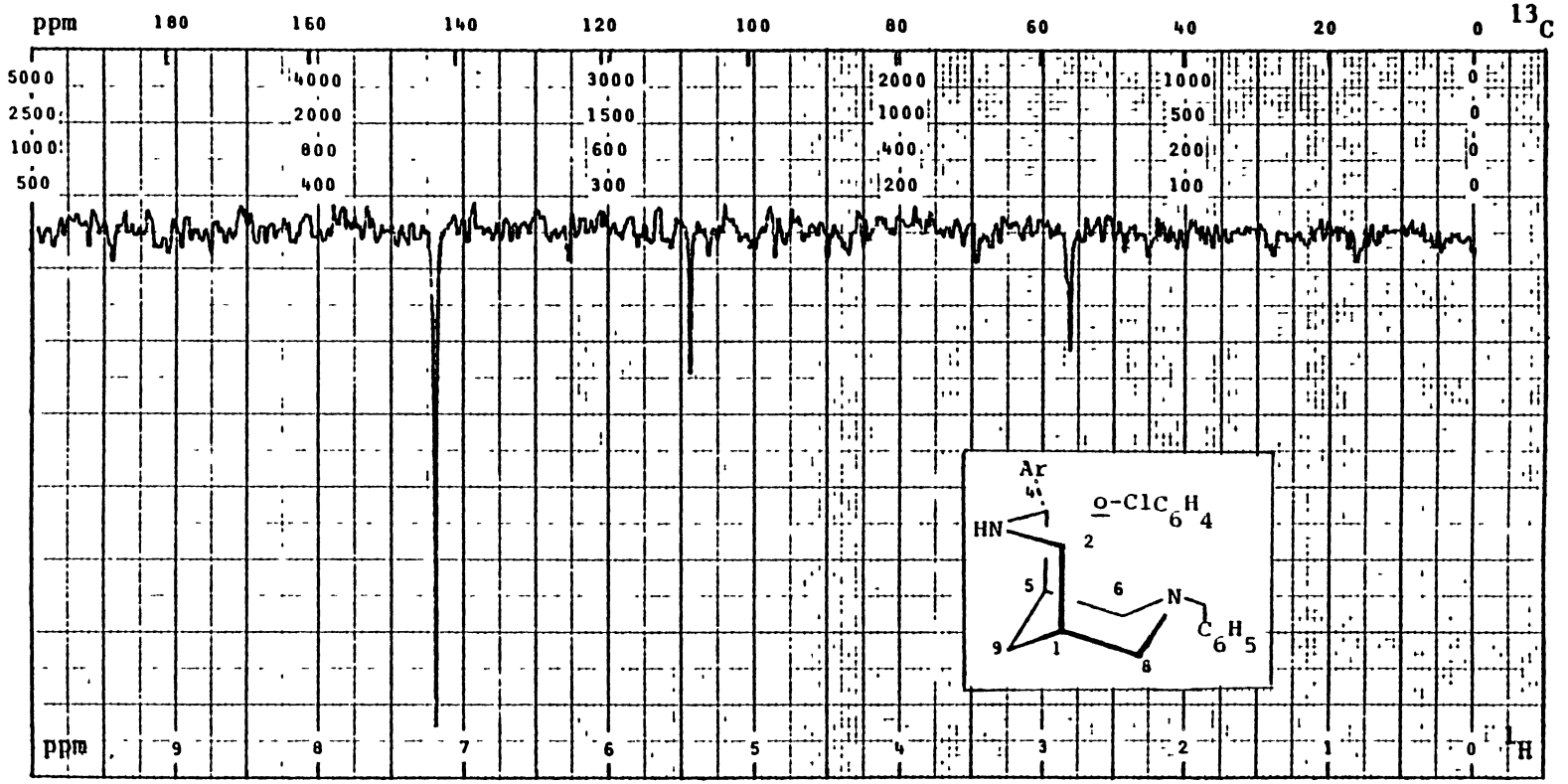


PFT x CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085 Hz: T: amb. °C; NT:1000

Size: 20 K; PW/RF: 12 μs/dB; SO: 0 Hz; FB: Hz; Lock: $DCCl_3$; Delay: 4 s.

DC: Y ; Gated Off: ; Offset: 0 Hz; RF: 20 W/dB; NBW: Hz; LB: 1.5

Plate XLI. ^{15}N NMR Spectrum of 31b



PFTx_ CW _ ; Solvent: $DCCl_3$; SF: 30406 MHz; WC: 2128 Hz; T:amb. °C; NT: 6000 .

Size: 12 K; PW/RF: 40 μs/dB; SO: -11600 Hz; FB: Hz; Lock: $DCCl_3$; Delay: 8 s.

DC: Y ; Gated Off: ; Offset: 0 Hz; RF: 0 W/dB; NBW: Hz; LB: 2.0 .

Plate XLII. IR Spectrum of **32b**

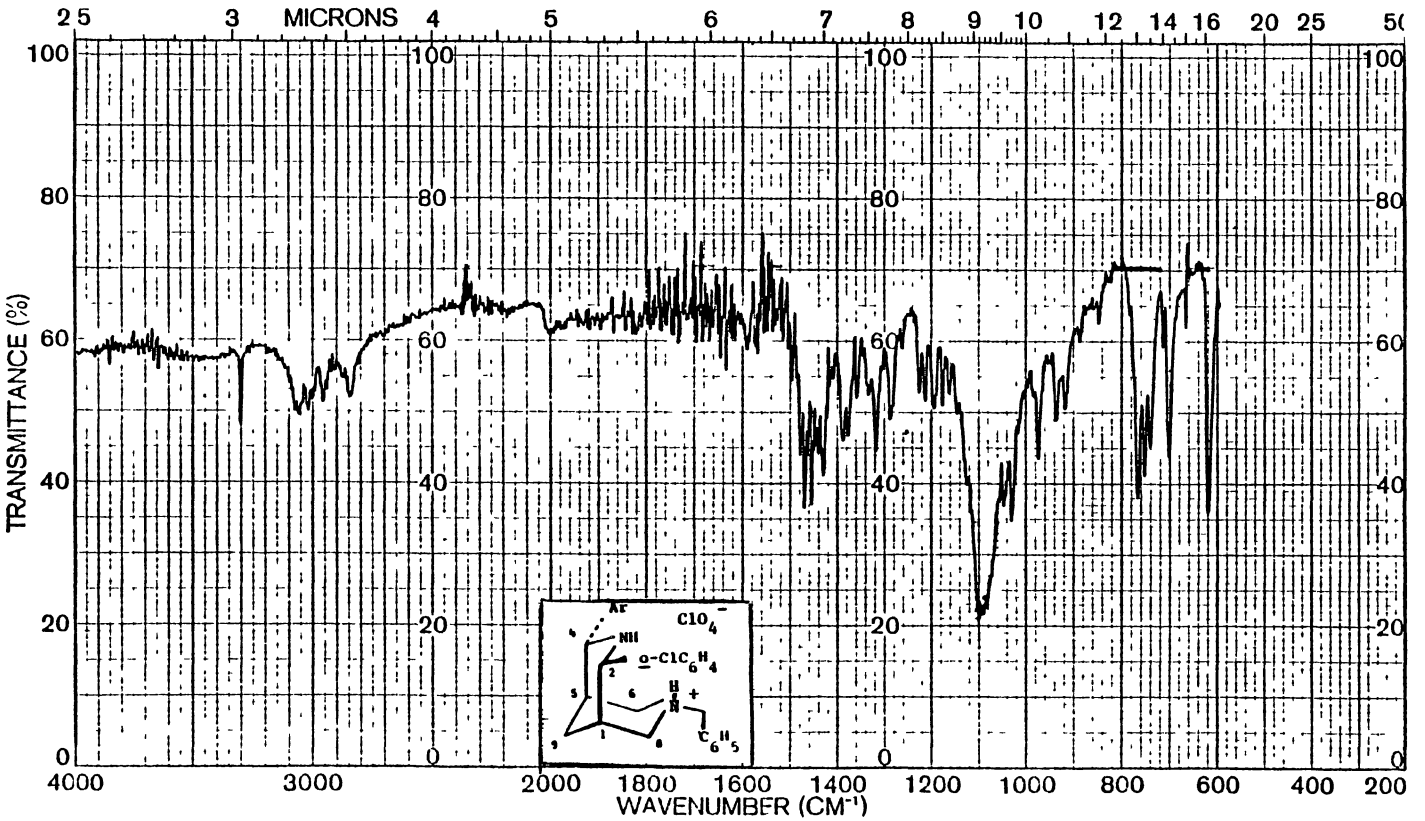
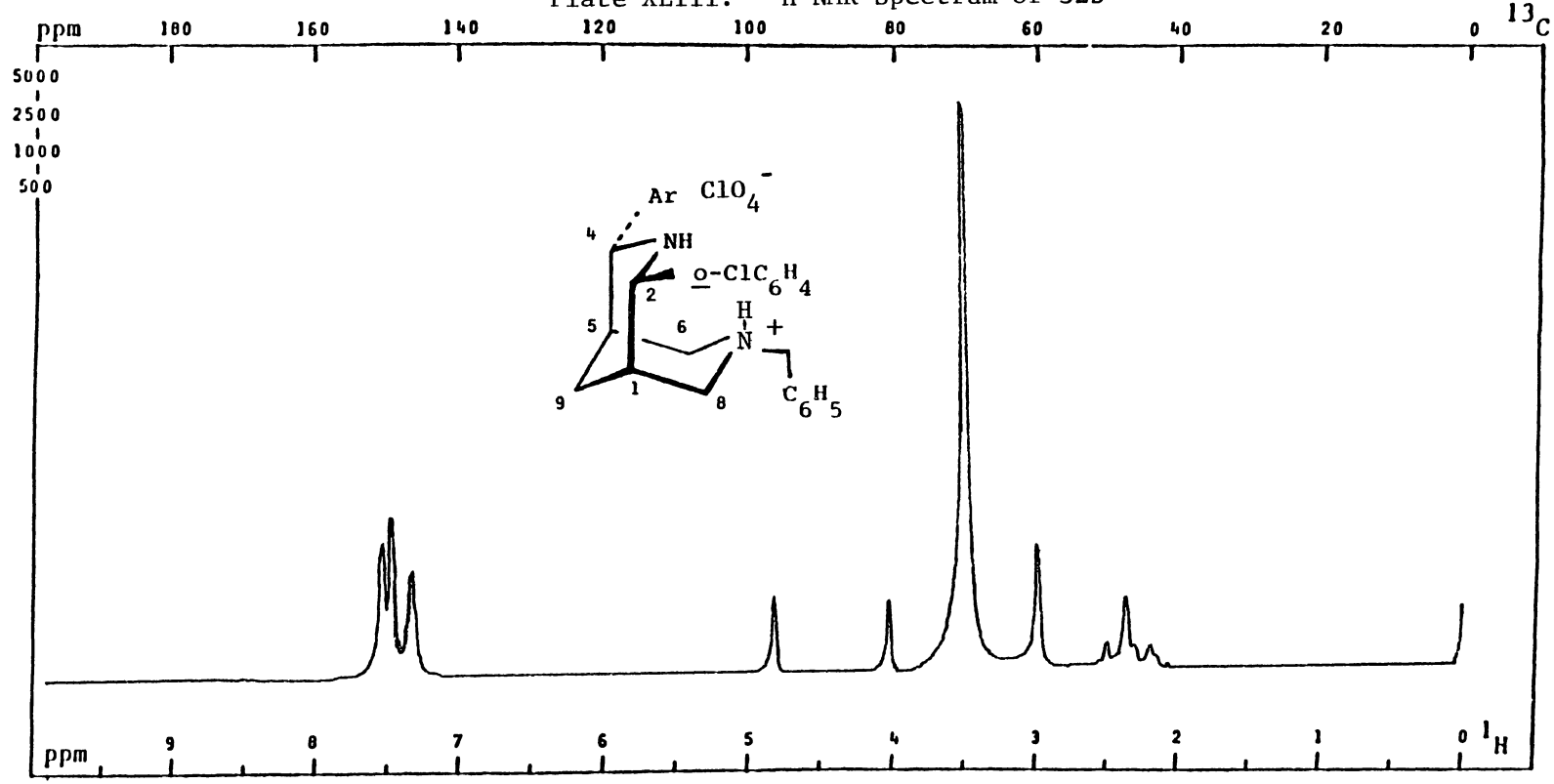


Plate XLIII. ^{1}H NMR Spectrum of 32b

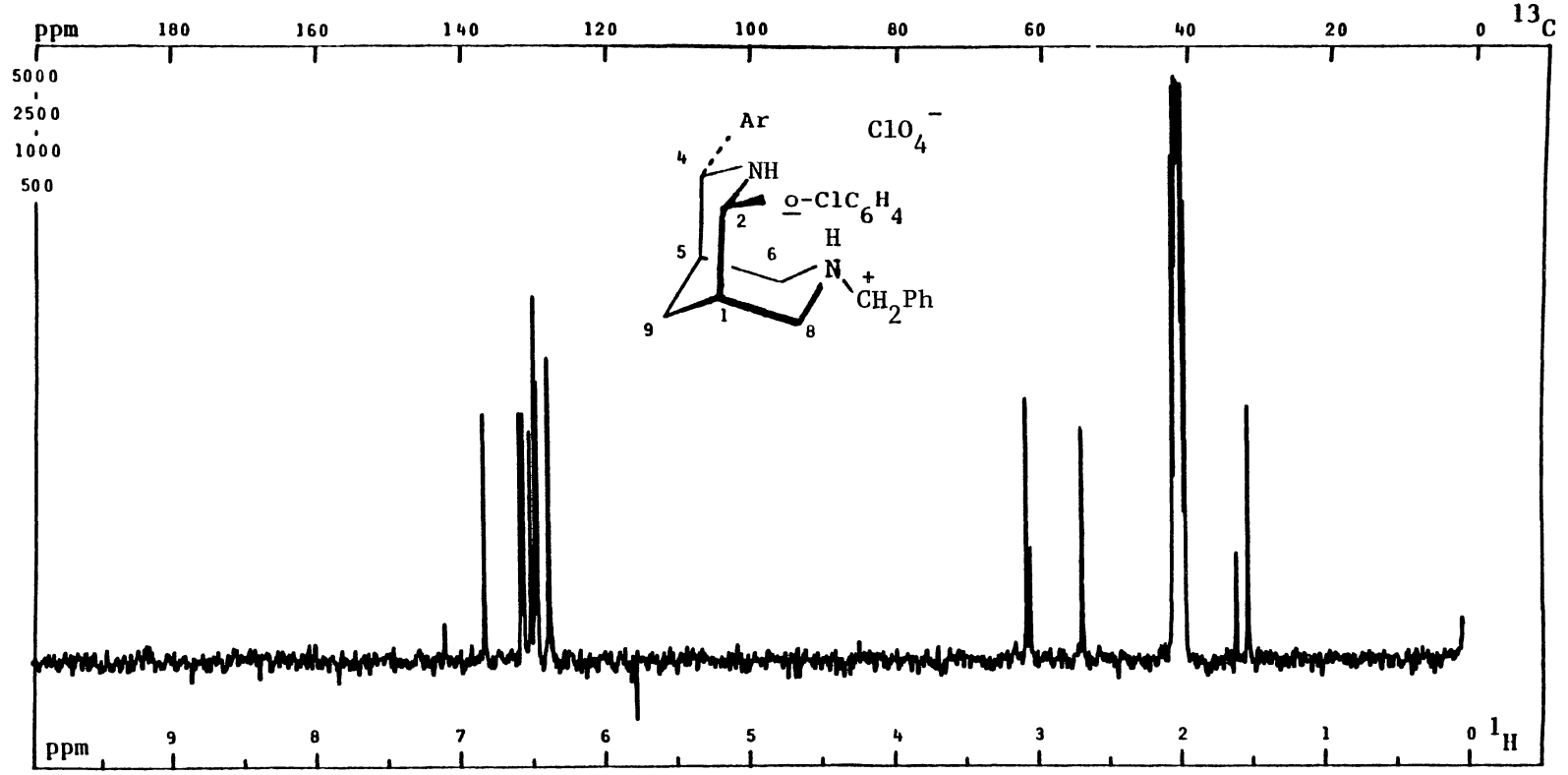


PFT X CW _ ; Solvent: DMSO-d_6 ; SF: 299.944 MHz; WC: 3000 Hz; T: amb. °C; NT: 4 .

Size: 12 K; PW/RF: 5. µs/dB; TO: 1500 Hz; FB: Hz; Lock: DMSO-d_6; D1,D5: 0.50 s.

DC: Y, N ; Gated Off: A or D ; DO: 750 Hz; RF(Power): W/dB; NBW: Hz; LB: 1.0 Hz.

Plate XLIV. ^{13}C NMR Spectrum of 32b



PFT x CW _ ; Solvent: DMSO-d_6 ; SF: 75.43 MHz; WC: 15085 Hz; T: amb °C; NT: 120 .

Size: 12 K; PW/RF: 12 μs/dB; TO: 1000 Hz; FB: Hz; Lock: DMSO-d_6; D1,D5: 4 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 2.5 Hz.

Plate XLV. HETCOR NMR Spectrum of 32b

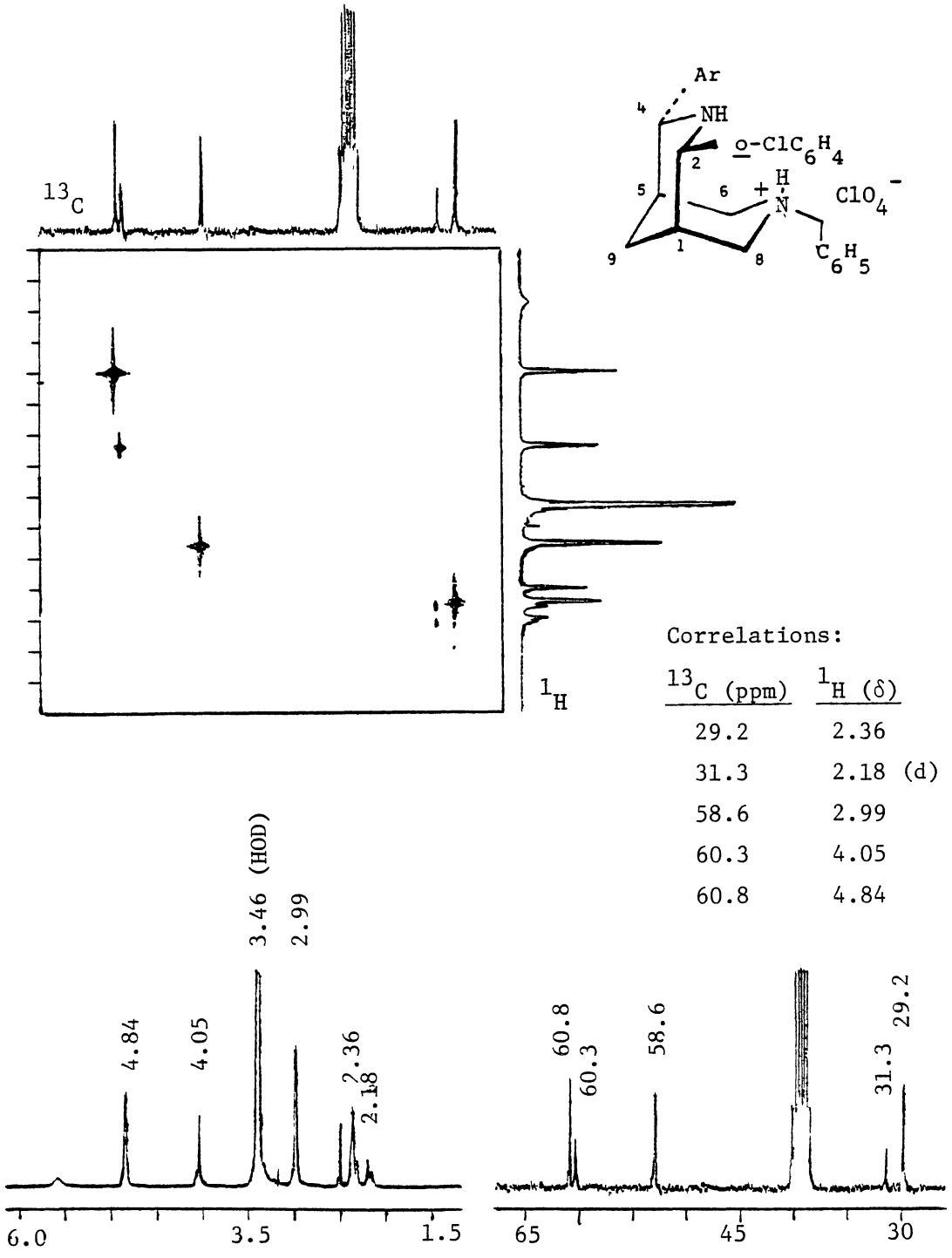
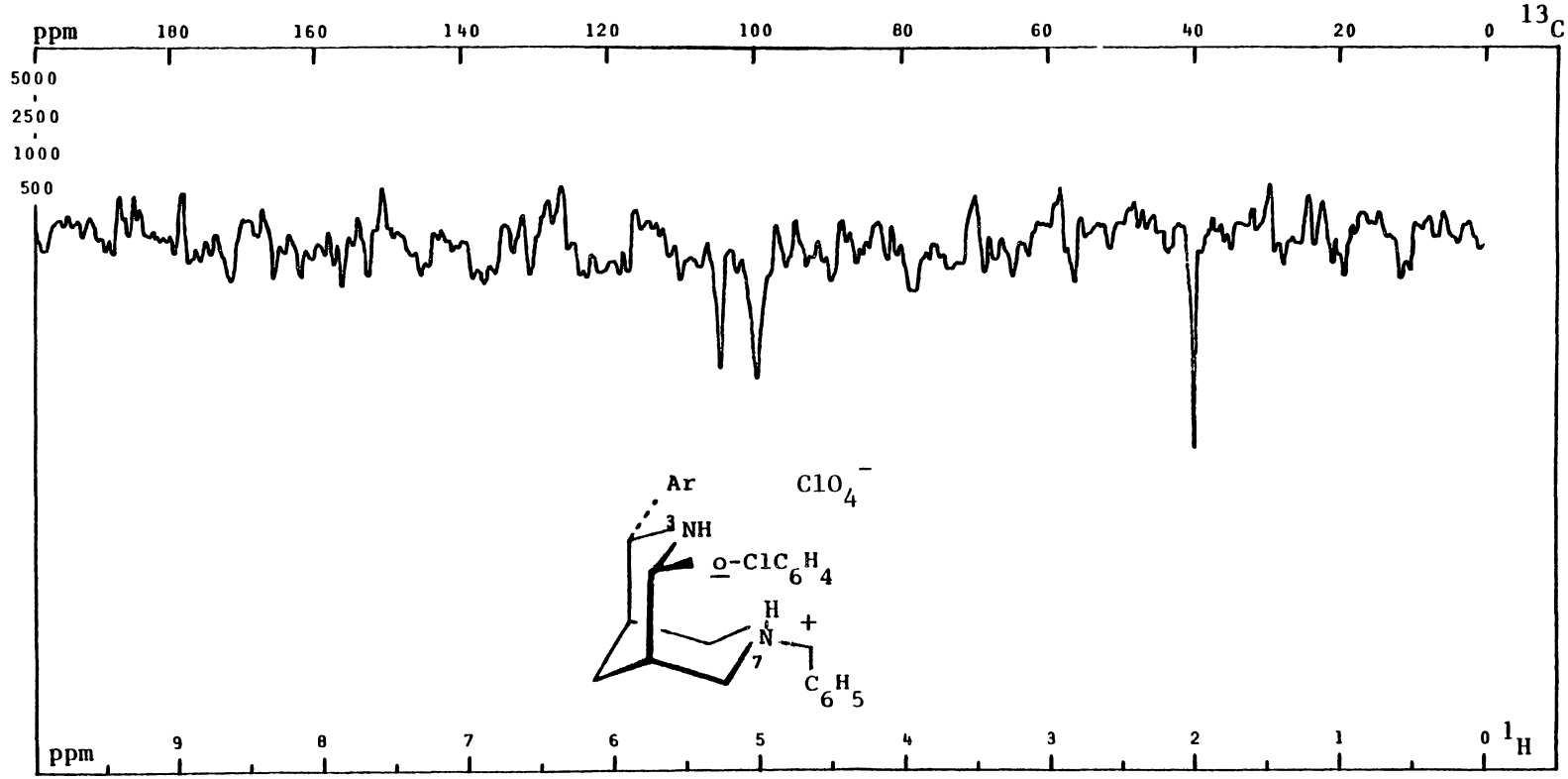


Plate XLVI. ^{15}N NMR Spectrum of **32b**



PFT X CW _ ; Solvent: DMSO-d_6 ; SF: 30.406 MHz; WC: 3040 Hz; T: amb. °C; NT: 6000 .

Size: 12 K; PW/RF: 40.0 μs/dB; SO: -11600 Hz; FB: Hz; Lock: DMSO-d_6; Delay: 8.00 s.

DC: N ; Gated Off: N ; Offset: 0 Hz; RF: 0 W/dB; NBW: Hz; LB: 8.00 .

Plate XLVII. IR Spectrum of 33b

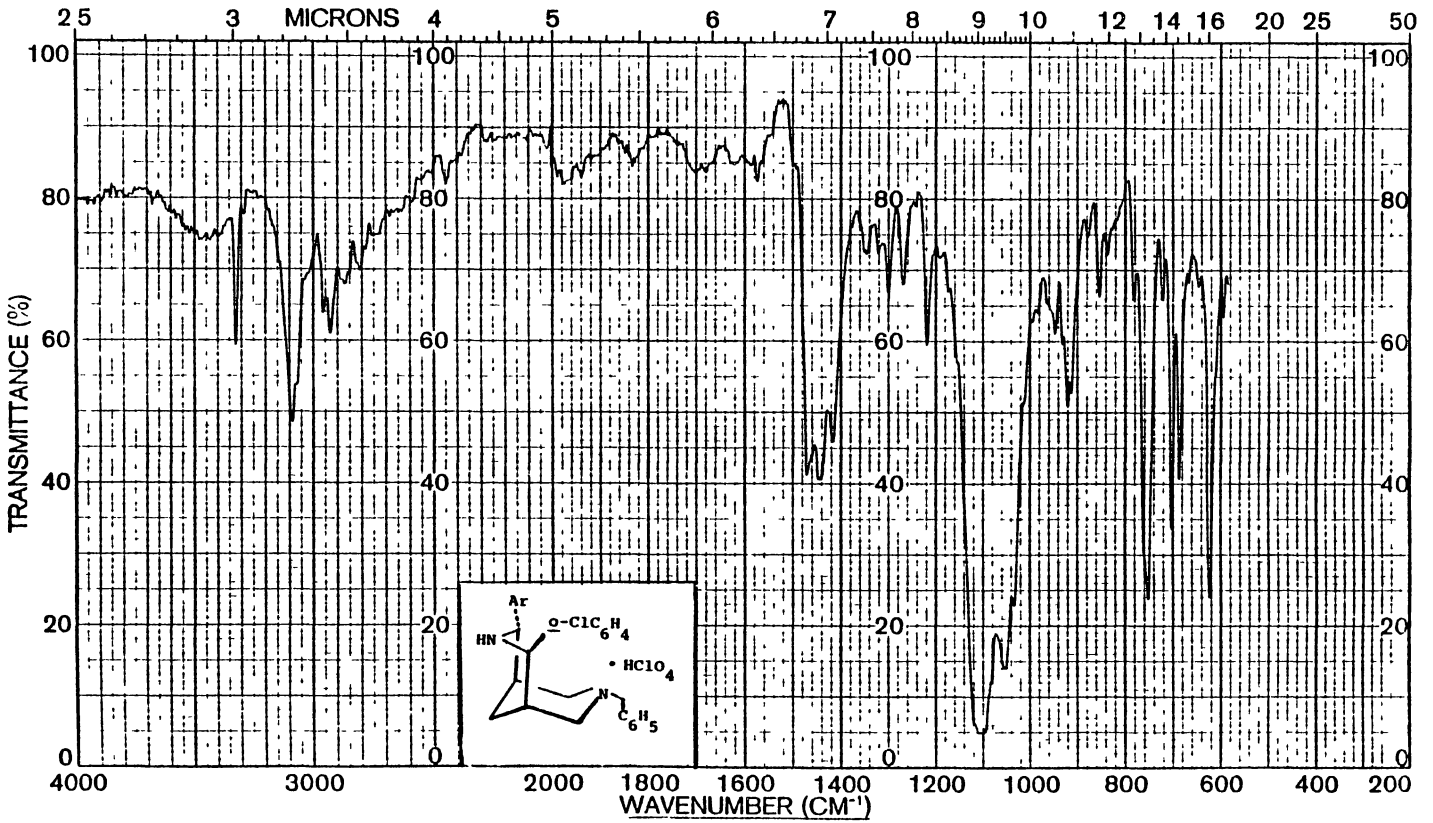
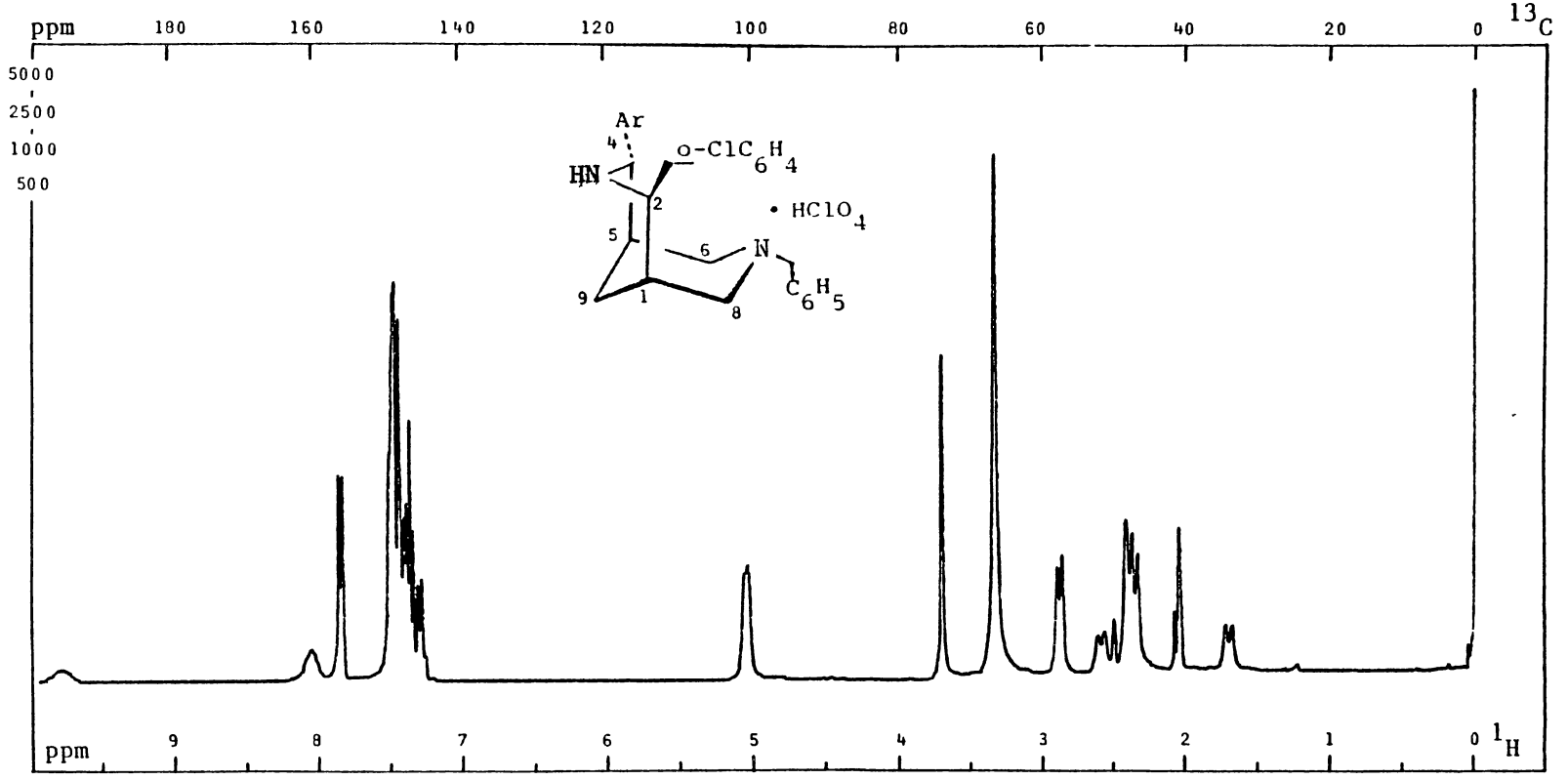


Plate XLVIII. ^{1}H NMR Spectrum of 33b

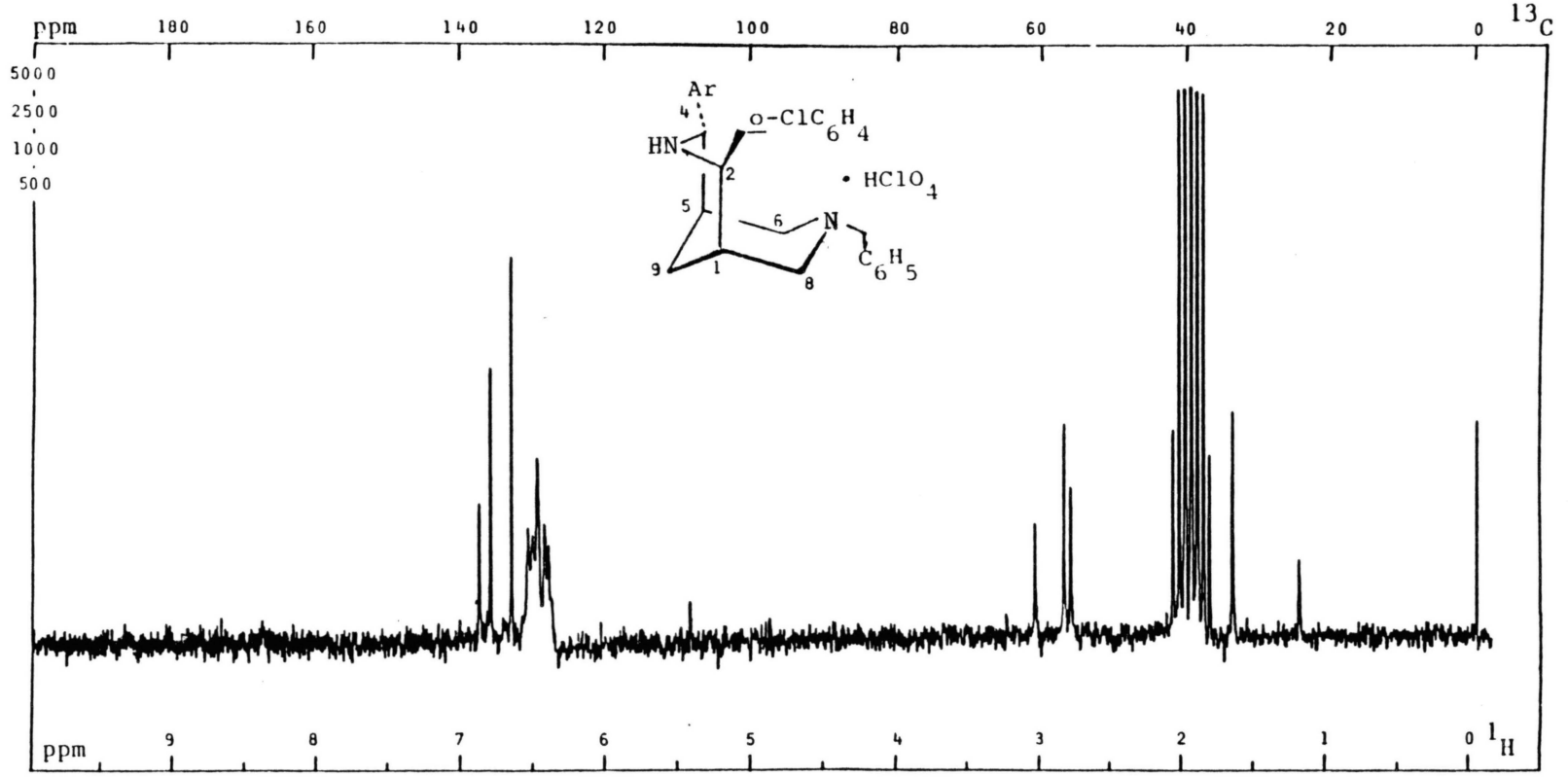


PFT x CW _ ; Solvent: DMSO-d_6 ; SF: 299.944 MHz; WC: 3000 Hz; T: amb. °C; NT: 8 .

Size: 12 K; PW/RF: 5 µs/dB; SO: 15000 Hz; FB: Hz; Lock: DMSO-d_6 ; Delay: 0.5 s.

DC: N ; Gated Off: ; Offset: 0 Hz; RF: 15 W/dB; NBW: Hz; LB: - .

Plate XLIX. ^{13}C NMR Spectrum of 33b

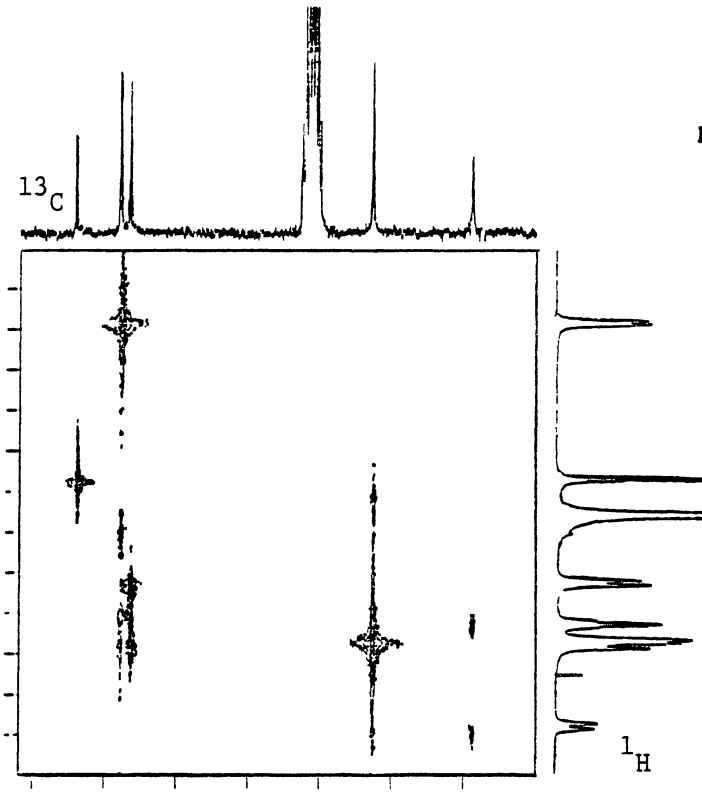


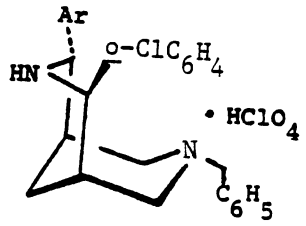
PFT X CW _ ; Solvent: DMSO-d_6 ; SF: 25.20 MHz; WC: 5000 Hz; T: amb. °C; NT: 10K .

Size: 16 K; PW/RF: 10.0 µs/dB; TO: 35101 Hz; FB: Hz; Lock: DMSO-d_6; D1,D5: 5 s.

DC: Y, N ; Gated Off: A or D ; DO: 45316 Hz; RF(Power): 119 W/dB; NBW: Hz; LB: 0.5 Hz.

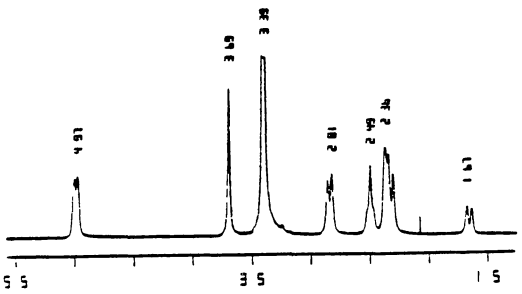
Plate L. HETCOR NMR Spectrum of 33b





Correlations:

^{13}C (ppm)	^{1}H (δ)
24.7	1.67
24.7	2.49
33.9	2.36
55.9	2.36
55.9	2.81
57.1	4.97
61.5	3.69



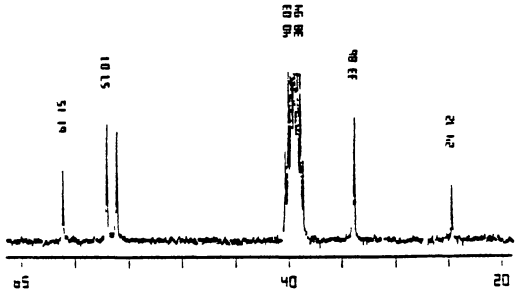
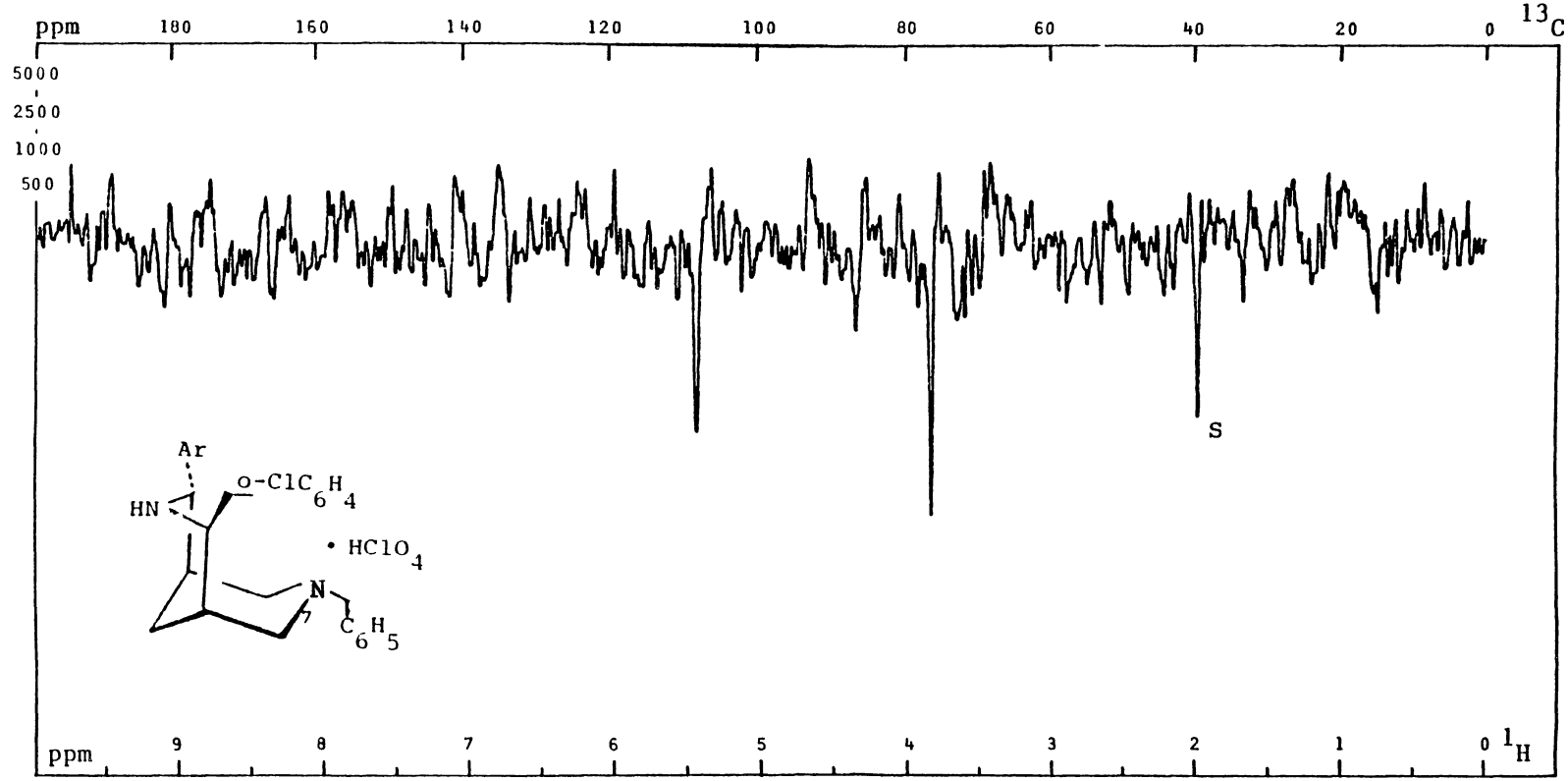


Plate LI. ^{15}N NMR Spectrum of 33b



PFT X CW _ ; Solvent: DMSO-d_6 ; SF: 30.406 MHz; WC: 3040 Hz; T: amb. °C; NT: 6000 .

Size: 12 K; PW/RF: 40 µs/dB; SO: -11600 Hz; FB: Hz; Lock: DMSO-d_6; Delay: 8 s.

DC: Y ; Gated Off: ; Offset: Hz; RF: 0 W/dB; NBW: Hz; LB: 3.00 .

Plate LII. IR Spectrum of 70d

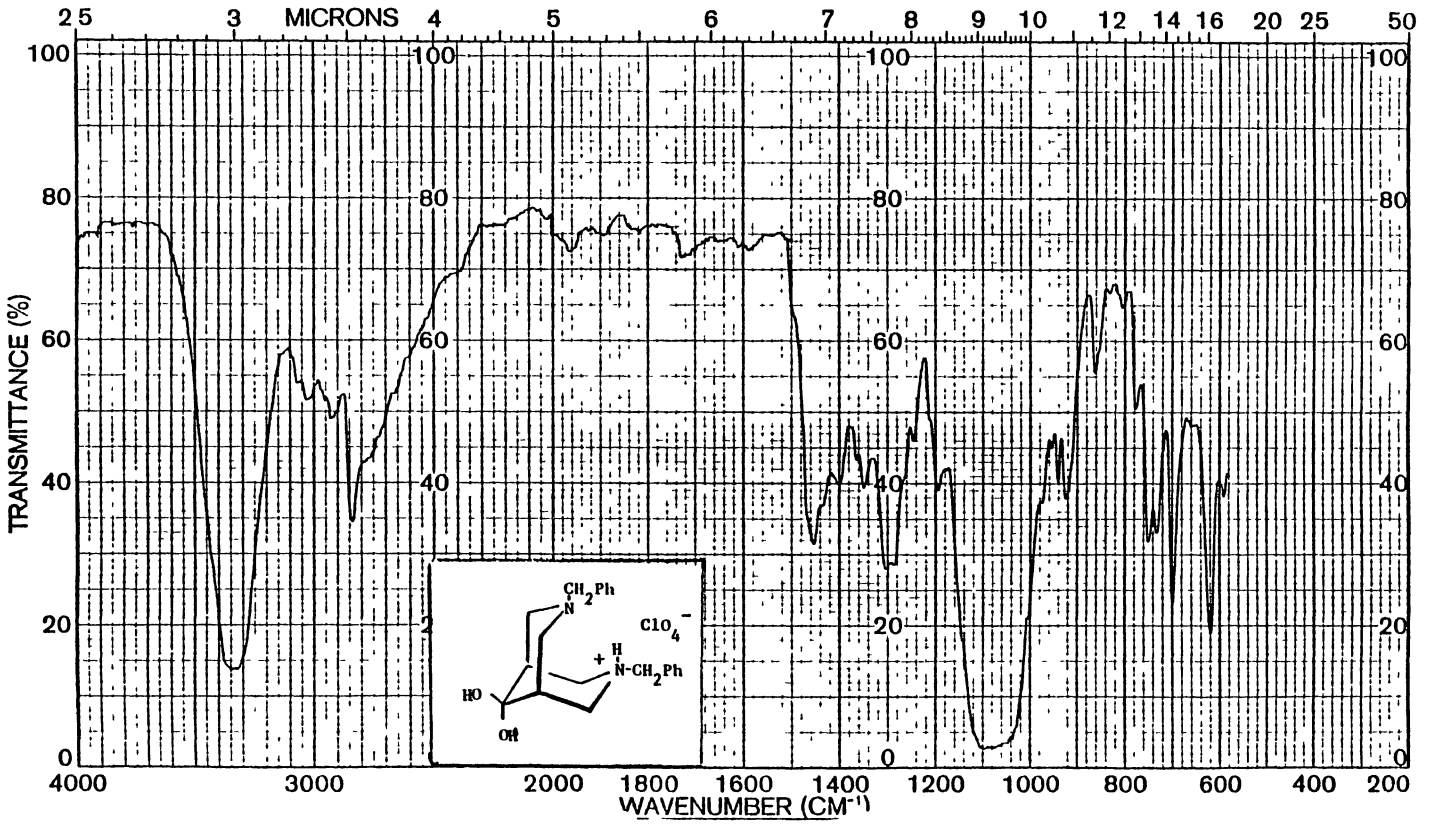
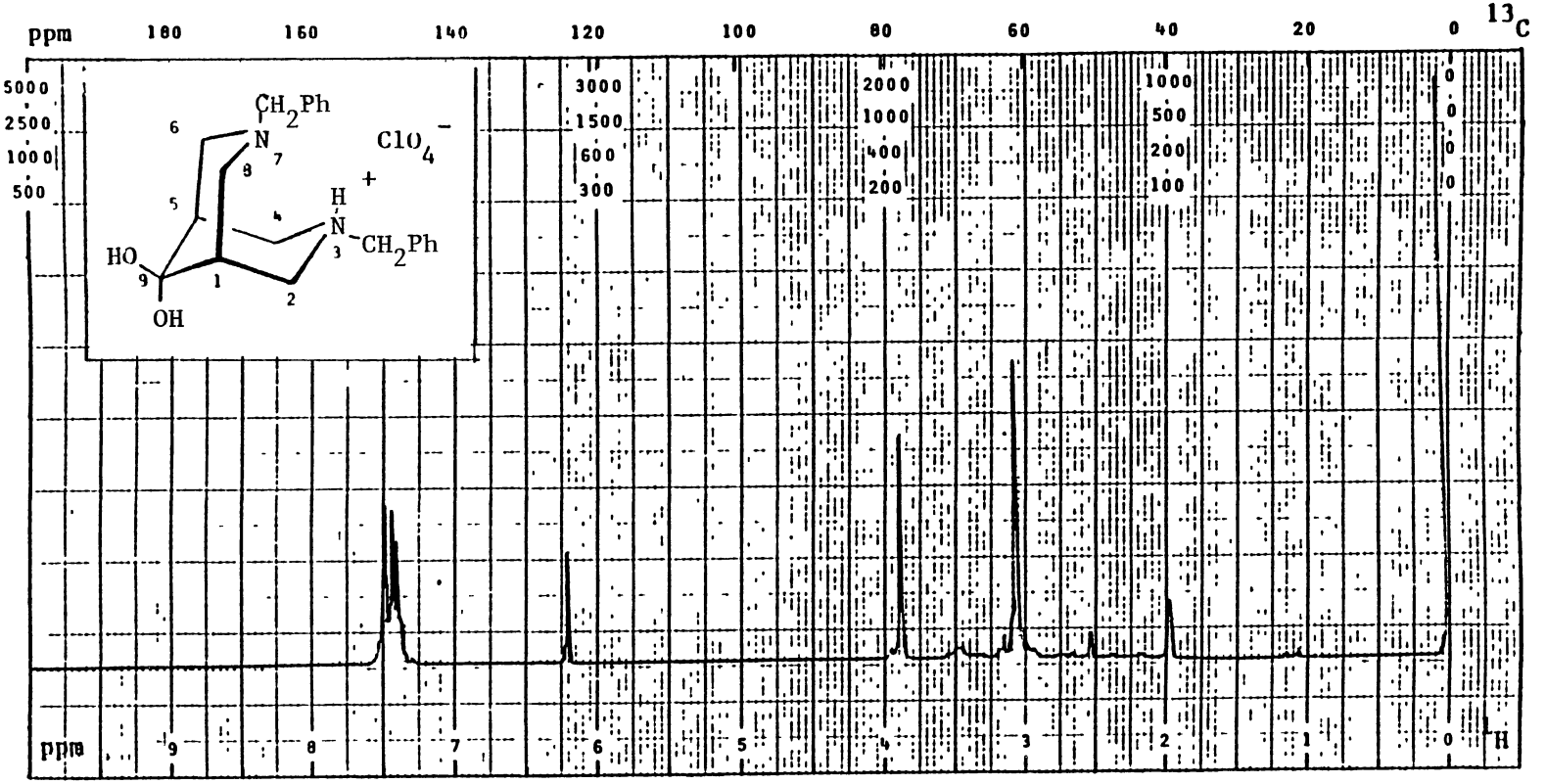


Plate LIII. ^{1}H NMR Spectrum of 70d

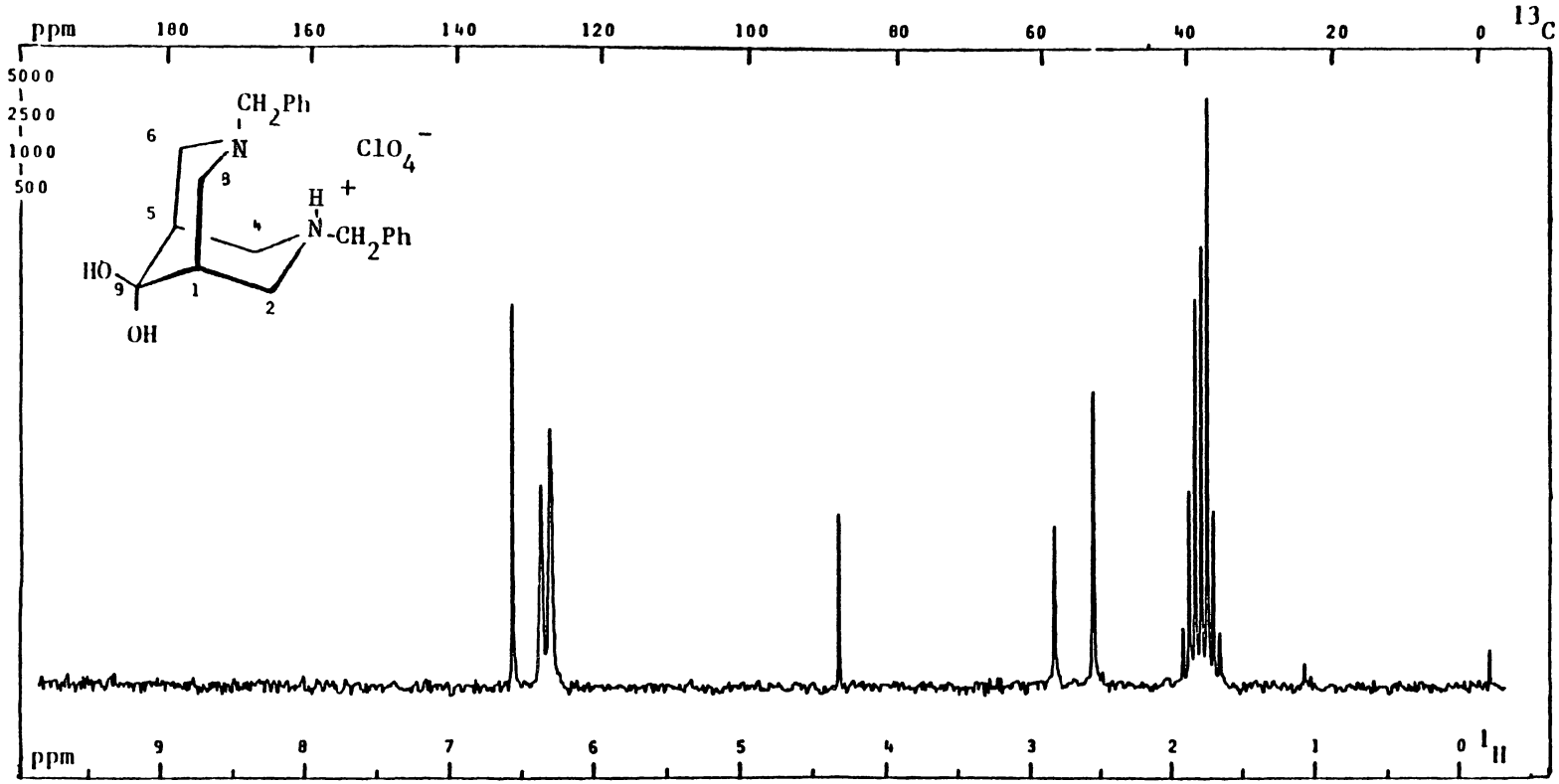


PFT X CW _ ; Solvent: DMSO-d_6 ; SF: 299.944 MHz; WC: 3000 Hz; T: amb. °C; NT: 32 .

Size: 8 K; PW/RF: 5.0 µs/dB; TO: 1500 Hz; FB: Hz; Lock: DMSO-d_6; D1,D5 : 0.5 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power):20 W/dB; NBW: Hz; LB: - Hz.

Plate LIV. ^{13}C NMR Spectrum of 70d

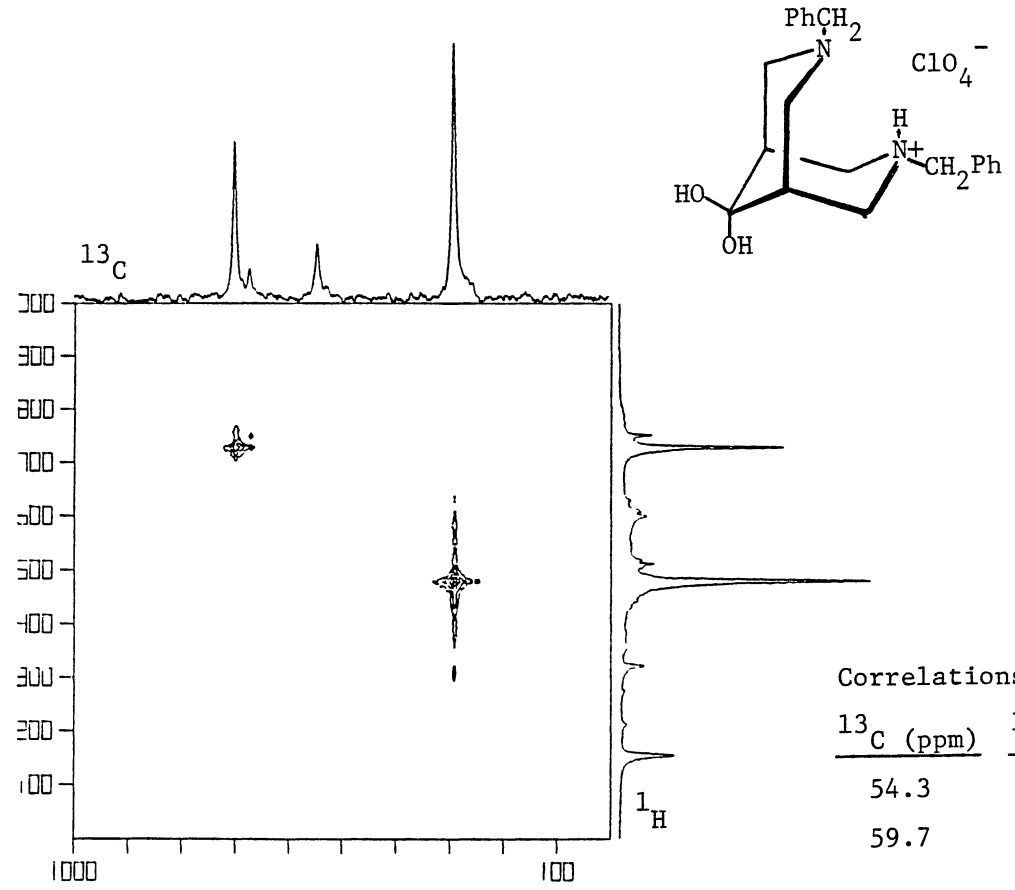


PFT x CW _ ; Solvent:DMSo-d_6 ; SF: 25.20 MHz; WC: Hz; T: amb. °C; NT: 5000 .

Size: 16 K; PW/RF: 14.0 μs/dB; TO:35201 Hz; FB: Hz; Lock:DMSO-d_6 ; D1,D5: 5 s.

DC: Y, N ; Gated Off:A or D ; DO: 45316 Hz; RF(Power): 119 W/dB; NBW: Hz; LB: 0.5 Hz.

Plate LV. HETCOR NMR Spectrum of **70d**



Correlations:

^{13}C (ppm)	^{1}H (δ)
54.3	3.05
59.7	3.89

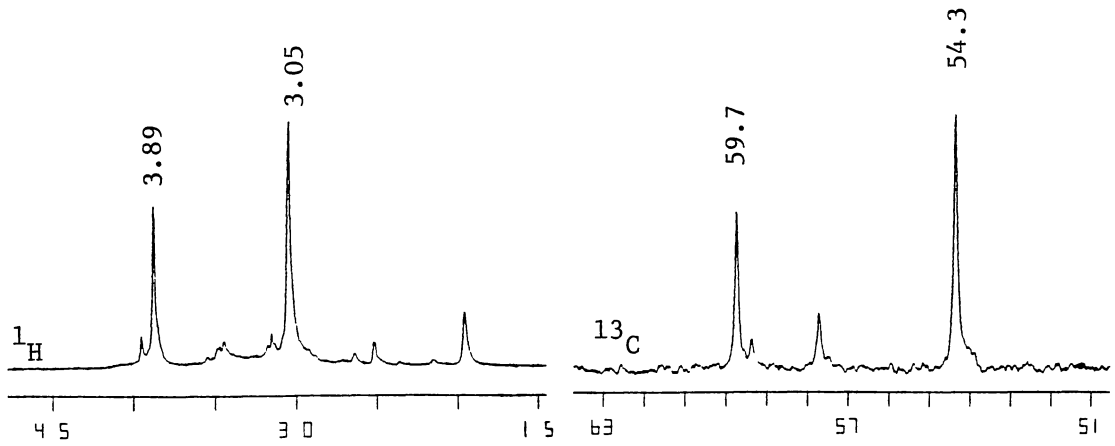
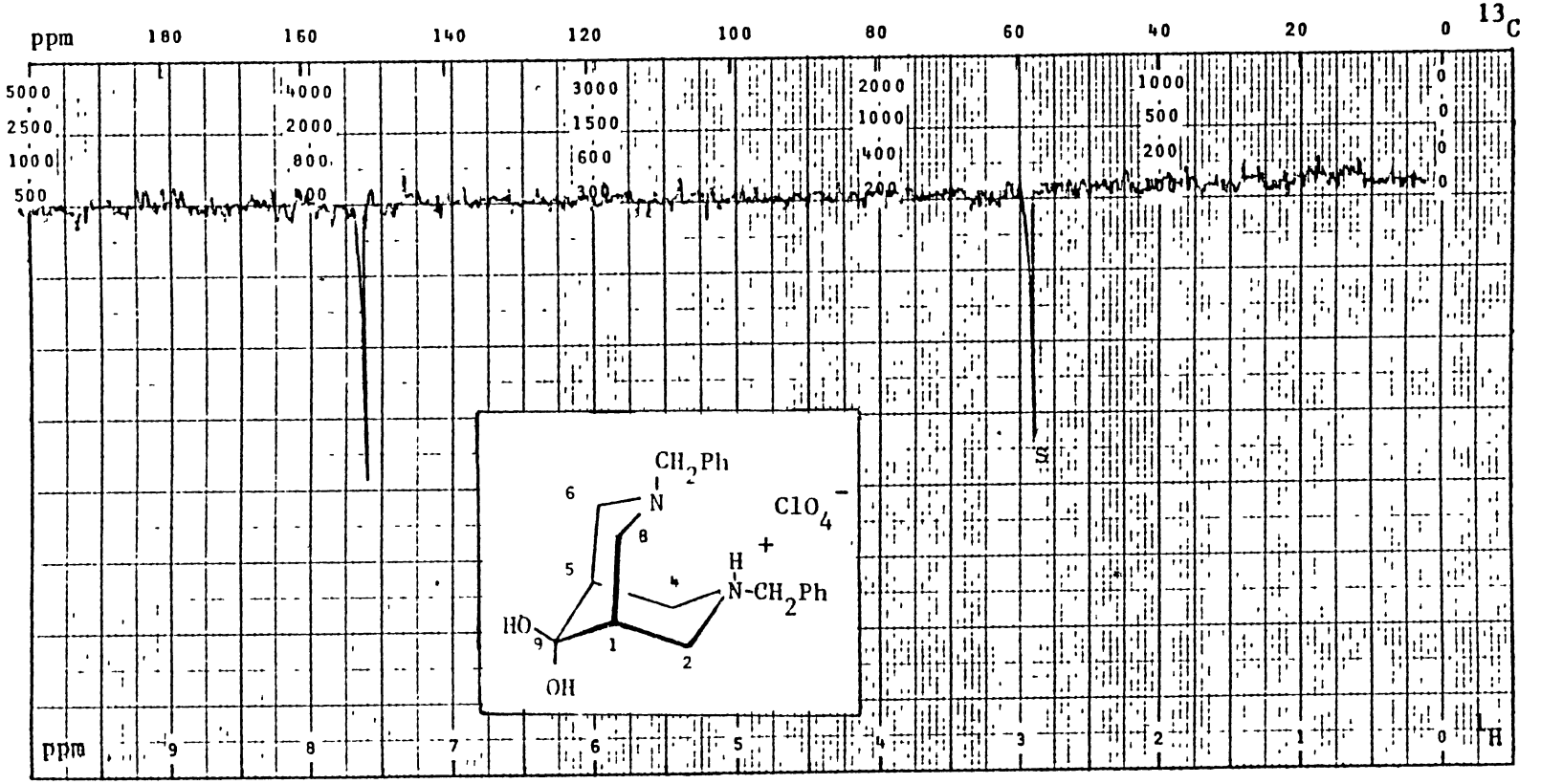


Plate LVI. ^{15}N NMR Spectrum of 70d



PFT^{x}_ CW _ ; Solvent: DMSO-d_6 ; SF: 30.406 MHz; WC: 2128 Hz; T: amb. °C; NT: 5144 .

Size: 24 K; PW/RF: 40 µs/dB; TO: -11600 Hz; FB: Hz; Lock: DMSO-d_6; D1,D5 : 5.5 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: Hz; LB: 1.5 Hz.

Plate LVII. IR Spectrum of **102a**

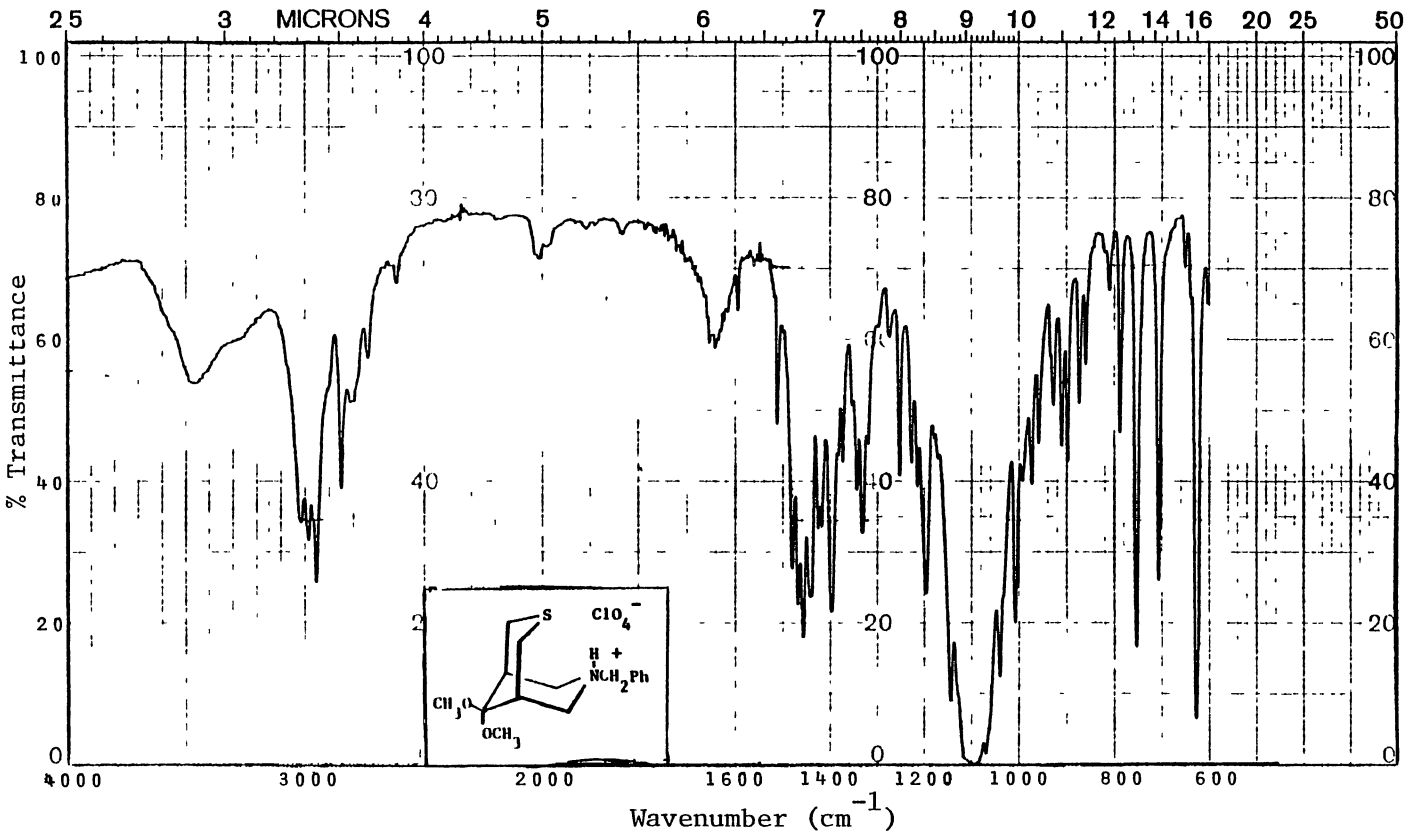
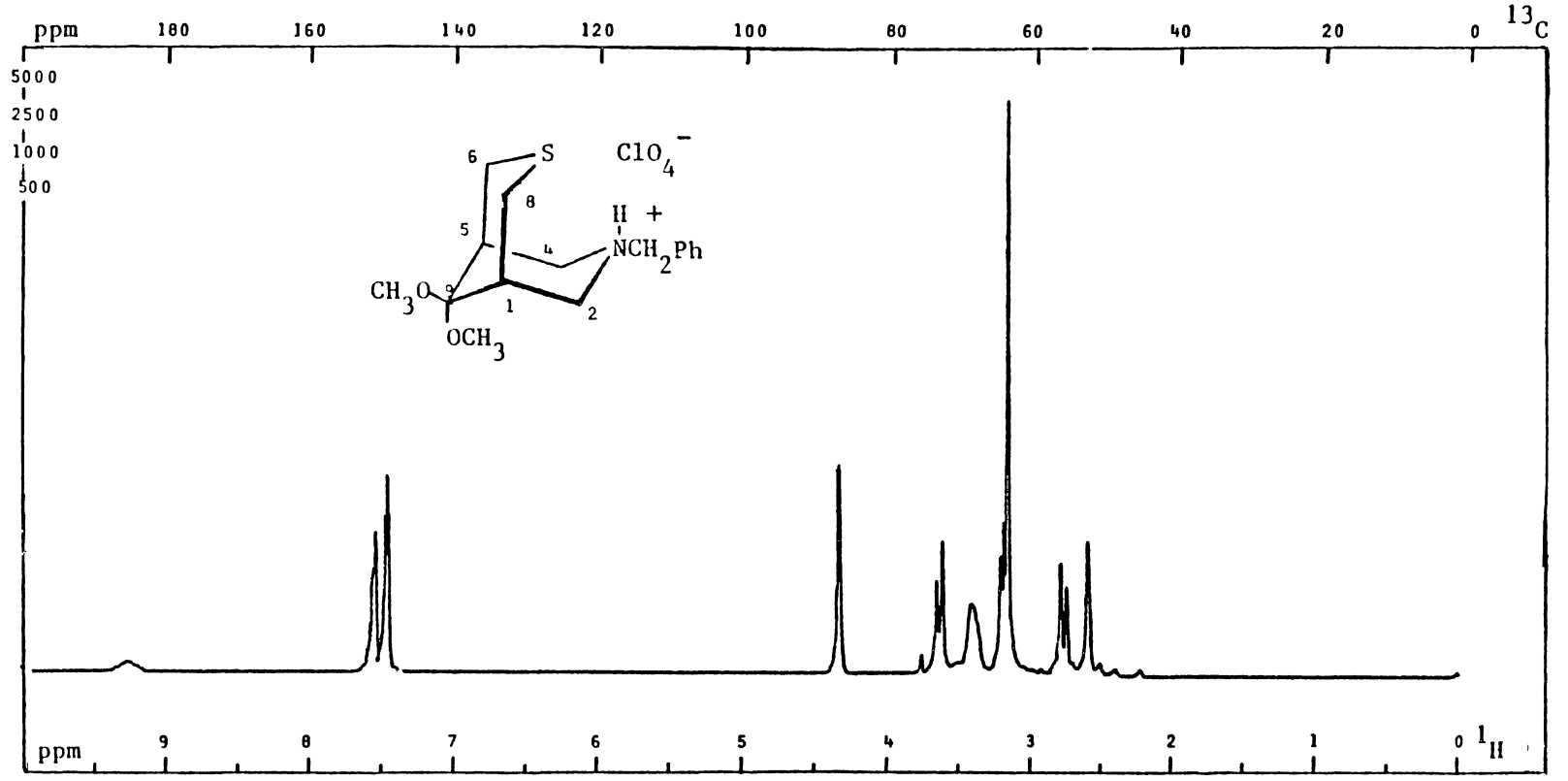


Plate LVIII. ^{1}H NMR Spectrum of 102a

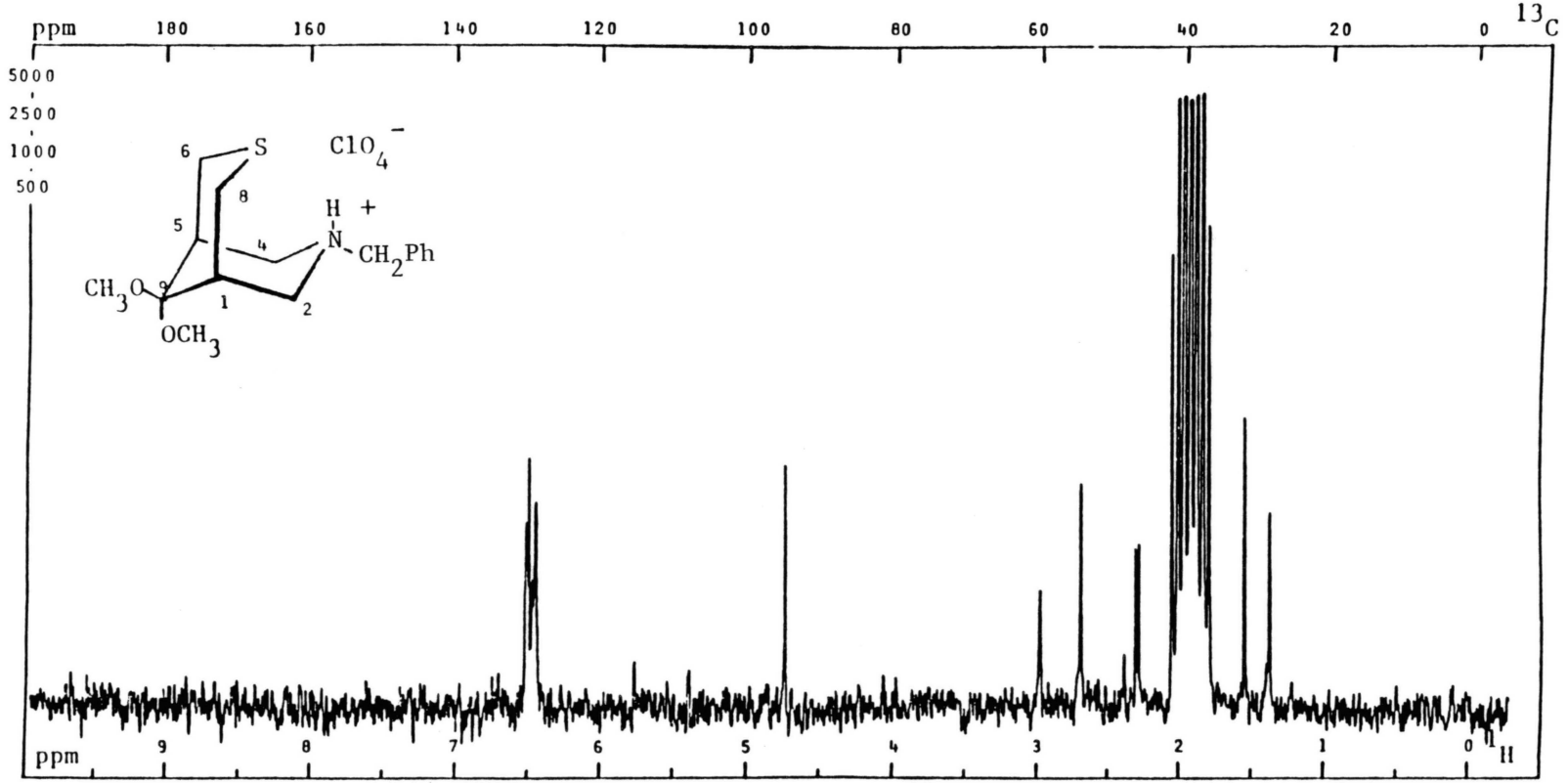


PFT x CW _ ; Solvent: DMSO-d6 ; SF: 299.944 MHz; WC: 2759.2 Hz; T: amb. °C; NT: 16

Size: 12 K; PW/RF: 5 µs/dB; TO: 1500 Hz; FB: Hz; Lock: DMSO-d6 ; D1,D5: 0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB:_ Hz.

Plate LIX. ^{13}C NMR Spectrum 102a

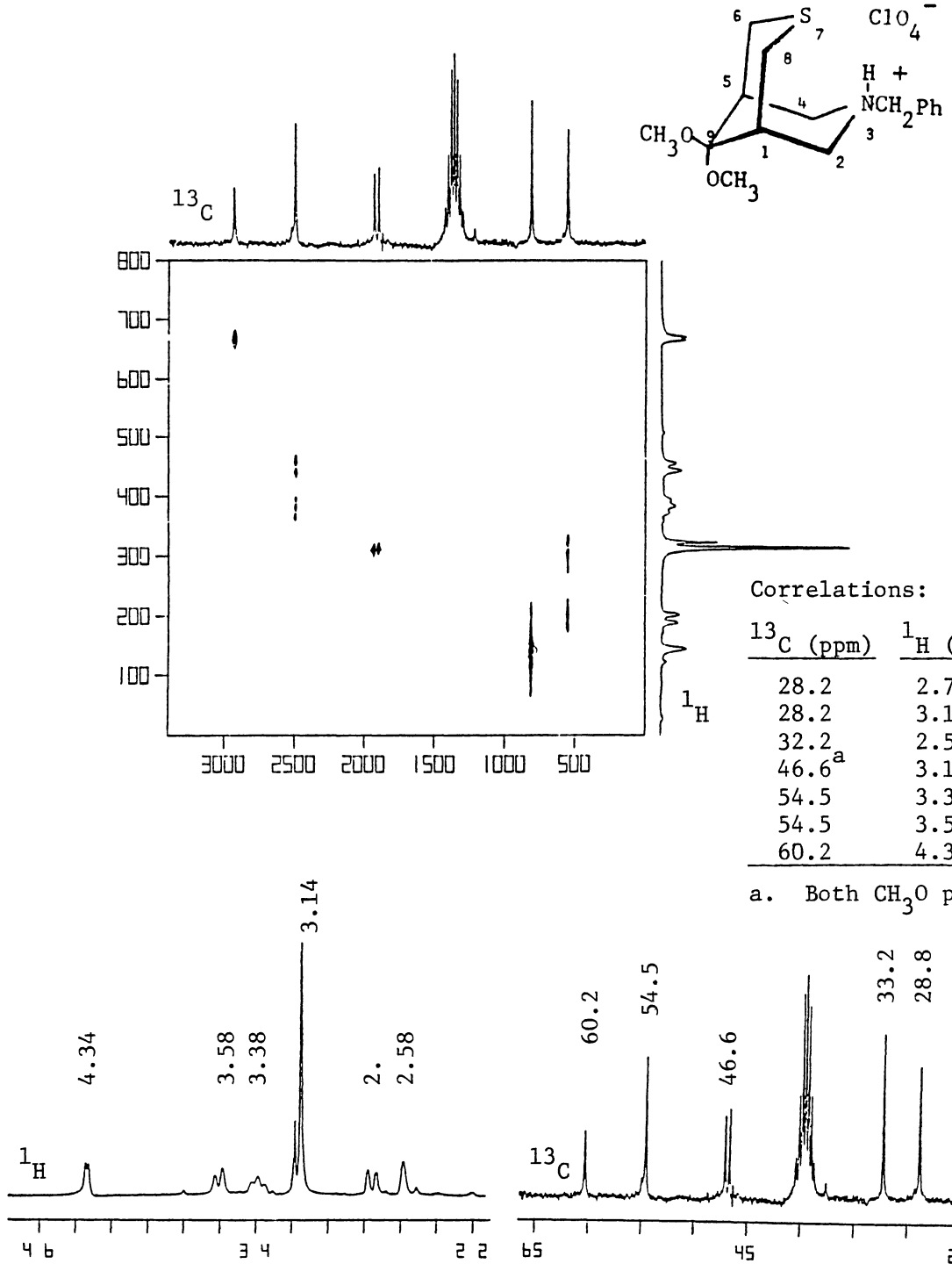


PFT x CW _ ; Solvent: DMSO-d_6 ; SF: 25.20 MHz; WC: 1000 Hz; T: amb. °C; NT: 4000 .

Size: 16 K; PW/RF: 10 μs/dB; TO: 35201 Hz; FB: Hz; Lock: DMSO-d_6 ; D1,D5: 20 s.

DC: Y, N ; Gated Off: A or D ; DO: 45316 Hz; RF(Power): 119 W/dB; NBW: Hz; LB: 1.5 Hz.

Plate LX. HETCOR NMR Spectrum of **102a**

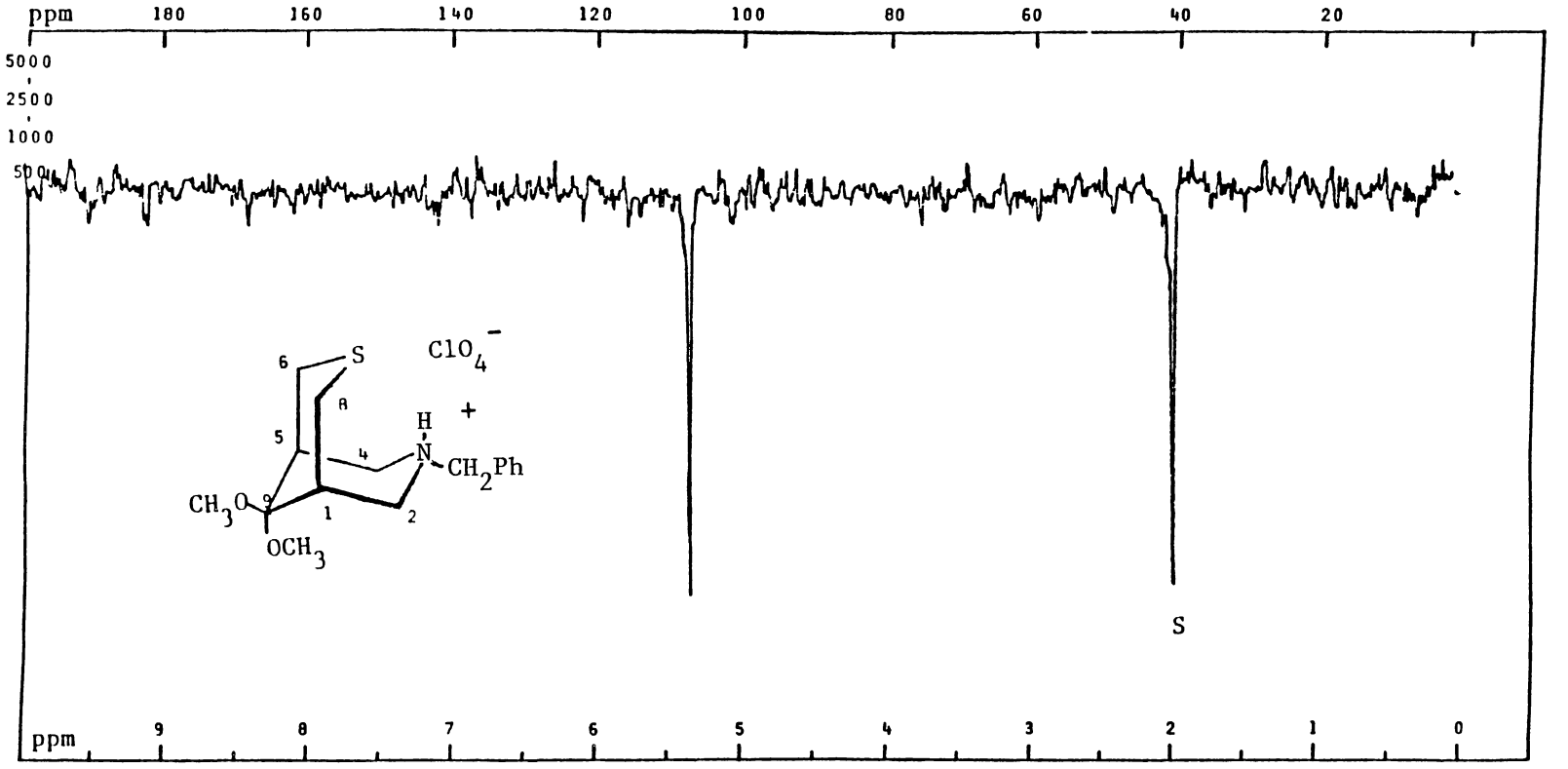


Correlations:

^{13}C (ppm)	^{1}H (δ)
28.2	2.77
28.2	3.14
32.2[a]	2.58[a]
46.6[a]	3.14[a]
54.5	3.38
54.5	3.58
60.2	4.34

a. Both CH_3O peaks

Plate LXI. ^{15}N NMR Spectrum of **102a**



PFT$_x$_ CW _ ; Solvent: DMSO-d_6 ; SF: 30.406 MHz; WC: 3040 Hz; T: amb. °C; NT: 6000 .

Size: 12 K; PW/RF: 40 µs/dB; TO: -11600 Hz; FB: Hz; Lock: DMSO-d_6 ; D1,D5: 8 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): W/dB; NBW: Hz; LB: 8 Hz.

Plate LXII. IR Spectrum of 102b

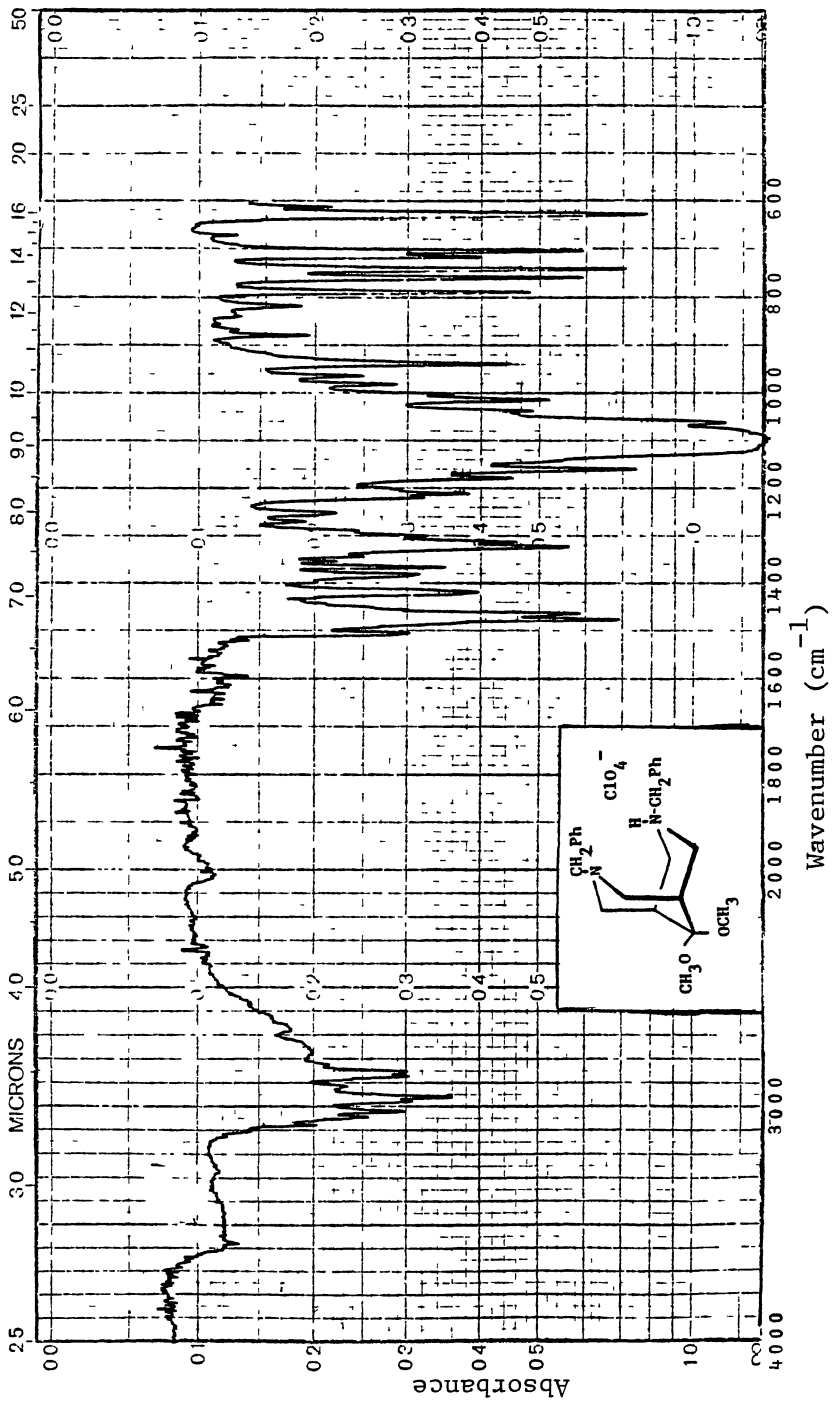
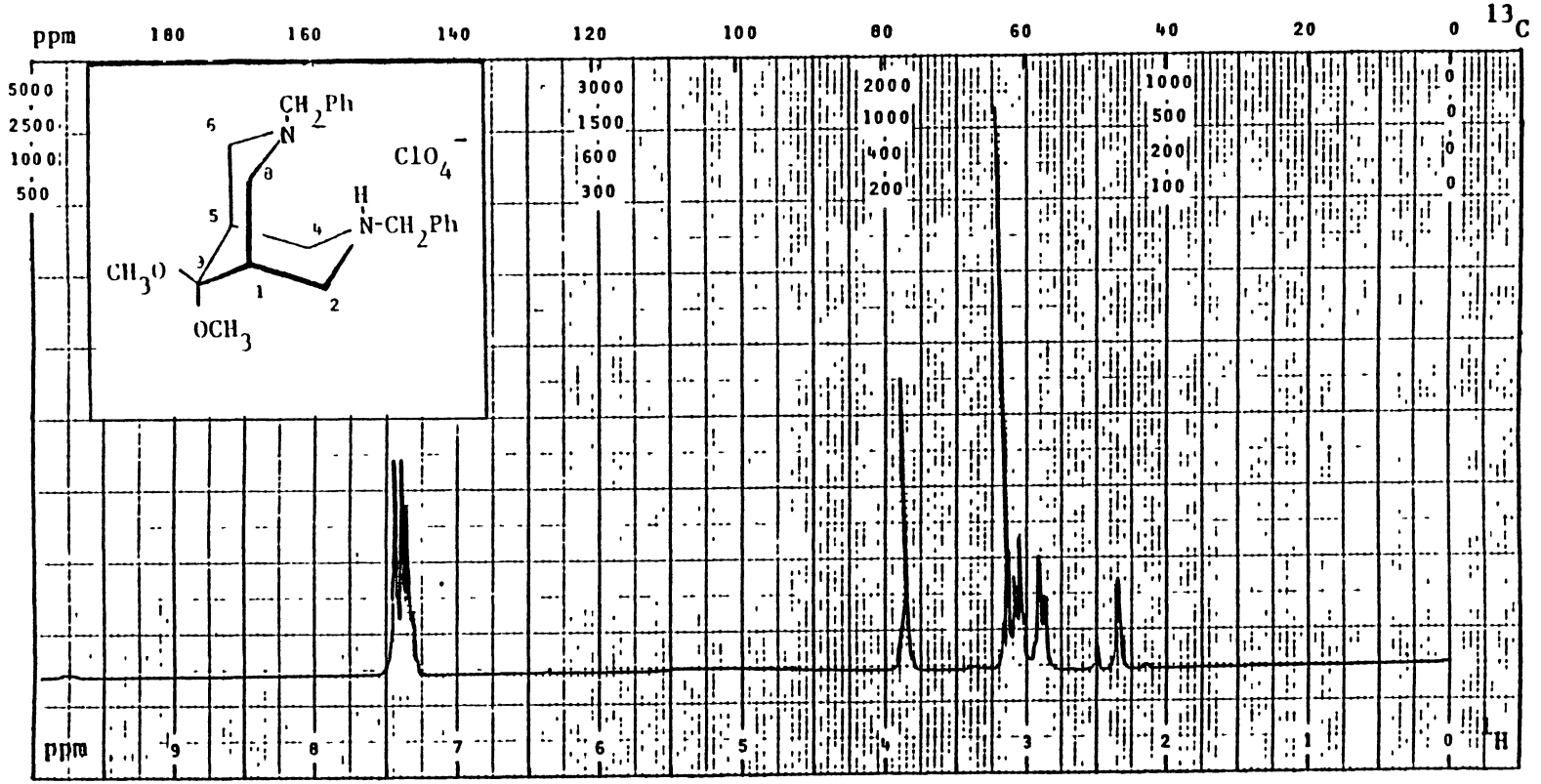


Plate LXIII. ^{1}H NMR of 102b

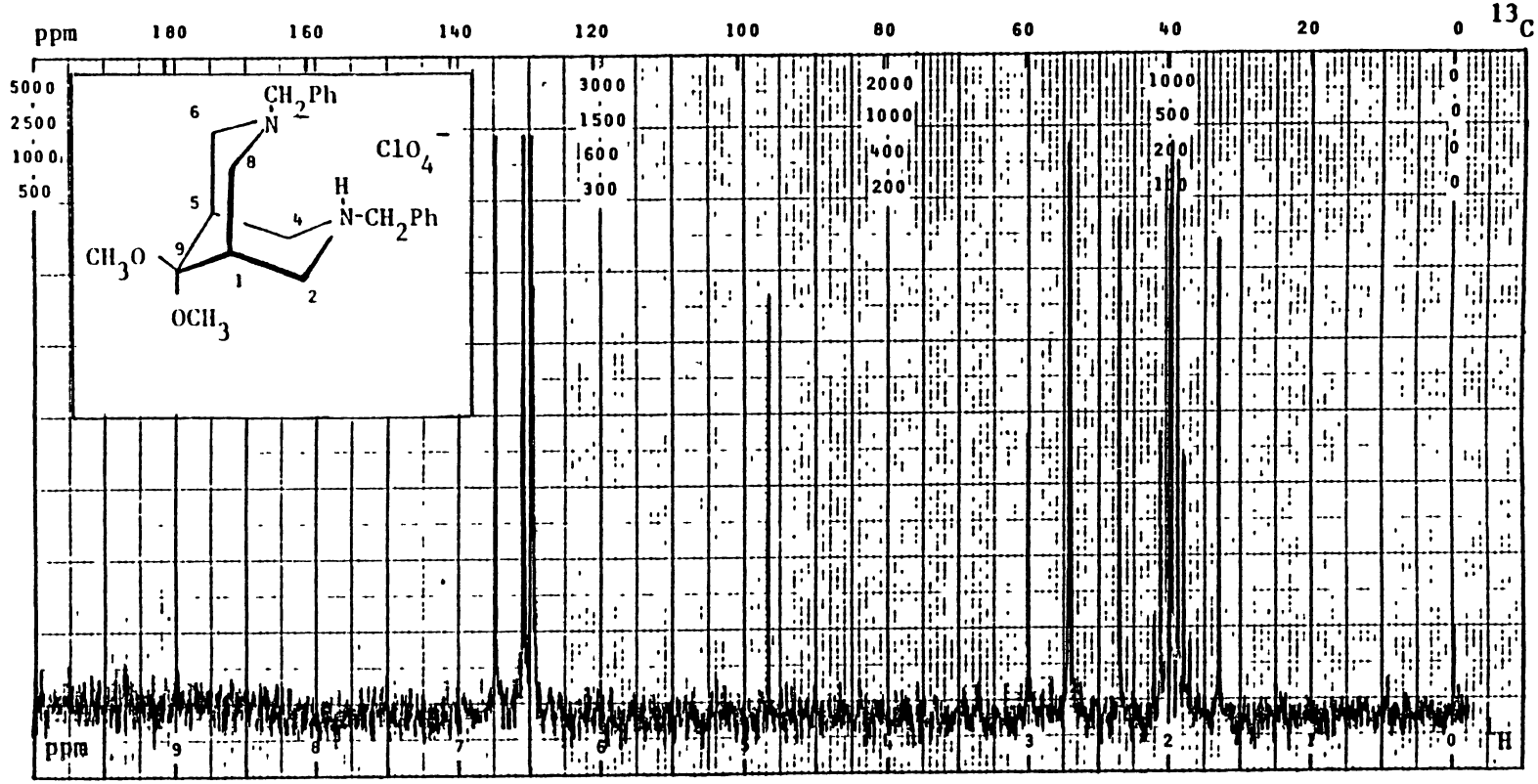


PFTx_ CW _ ; Solvent: DMSO-d_6 ; SF: 299.944 MHz; WC: 3000 Hz; T: amb. °C; NT: 16 .

Size: 8 K; PW/RF: 2 µs/dB; TO: 1500 Hz; FB: Hz; Lock: DMSO-d_6; D1,D5 :0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: Hz; LB: - Hz.

Plate LXIV. ^{13}C NMR Spectrum of **102b**

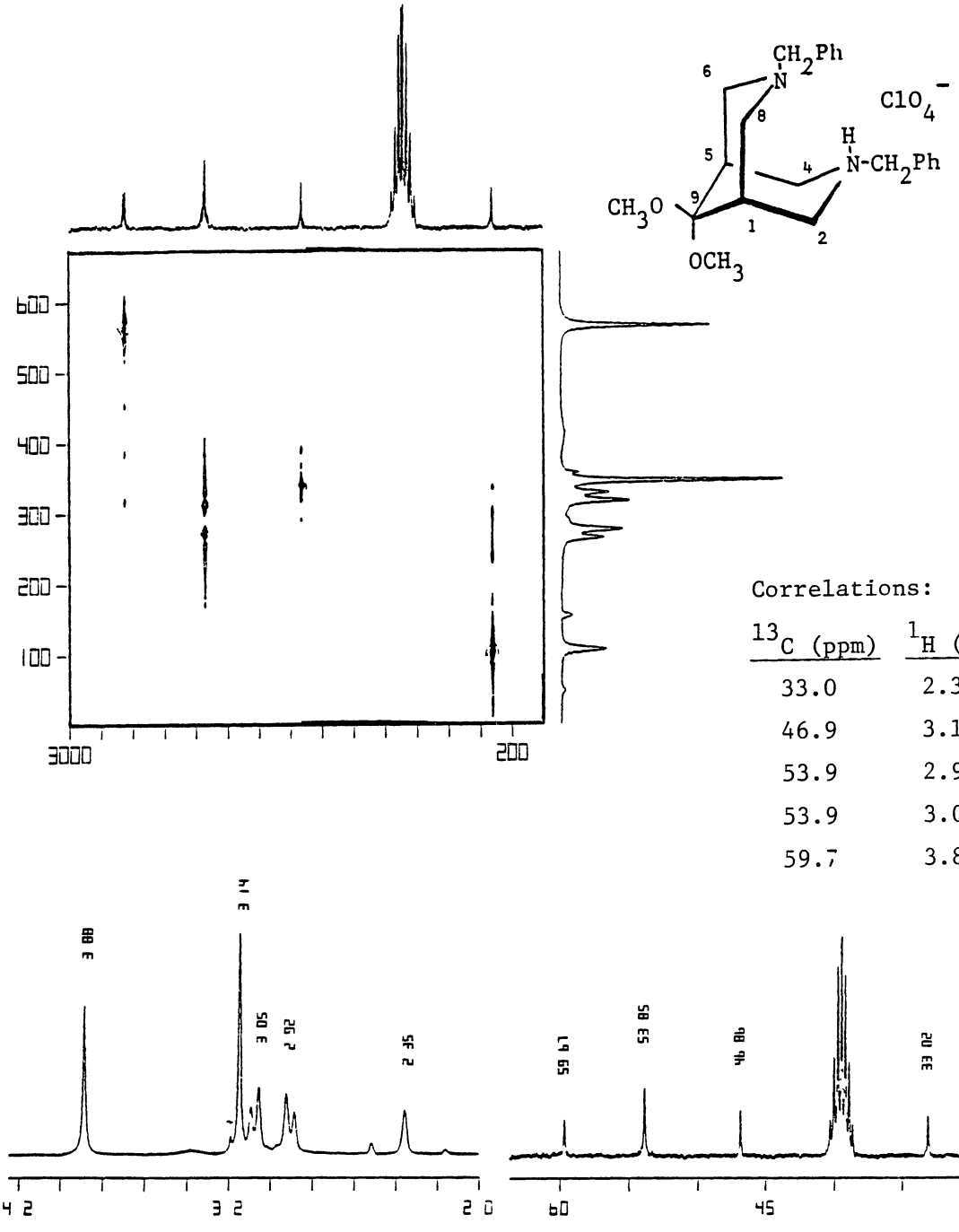


PFT x CW _ ; Solvent: DMSO-d_6 ; SF: 25.2 MHz; WC: 5000 Hz; T: amb. °C; NT: 1400 .

Size: 16 K; PW/RF: 14 µs/dB; TO: 35101 Hz; FB: Hz; Lock: DMSO-d_6 D1,D5 : 5 s.

DC: Y, N ; Gated Off: A or D ; DO: 35101 Hz; RF(Power): 4531 W/dB; NBW: Hz; LB: 1.5 Hz.

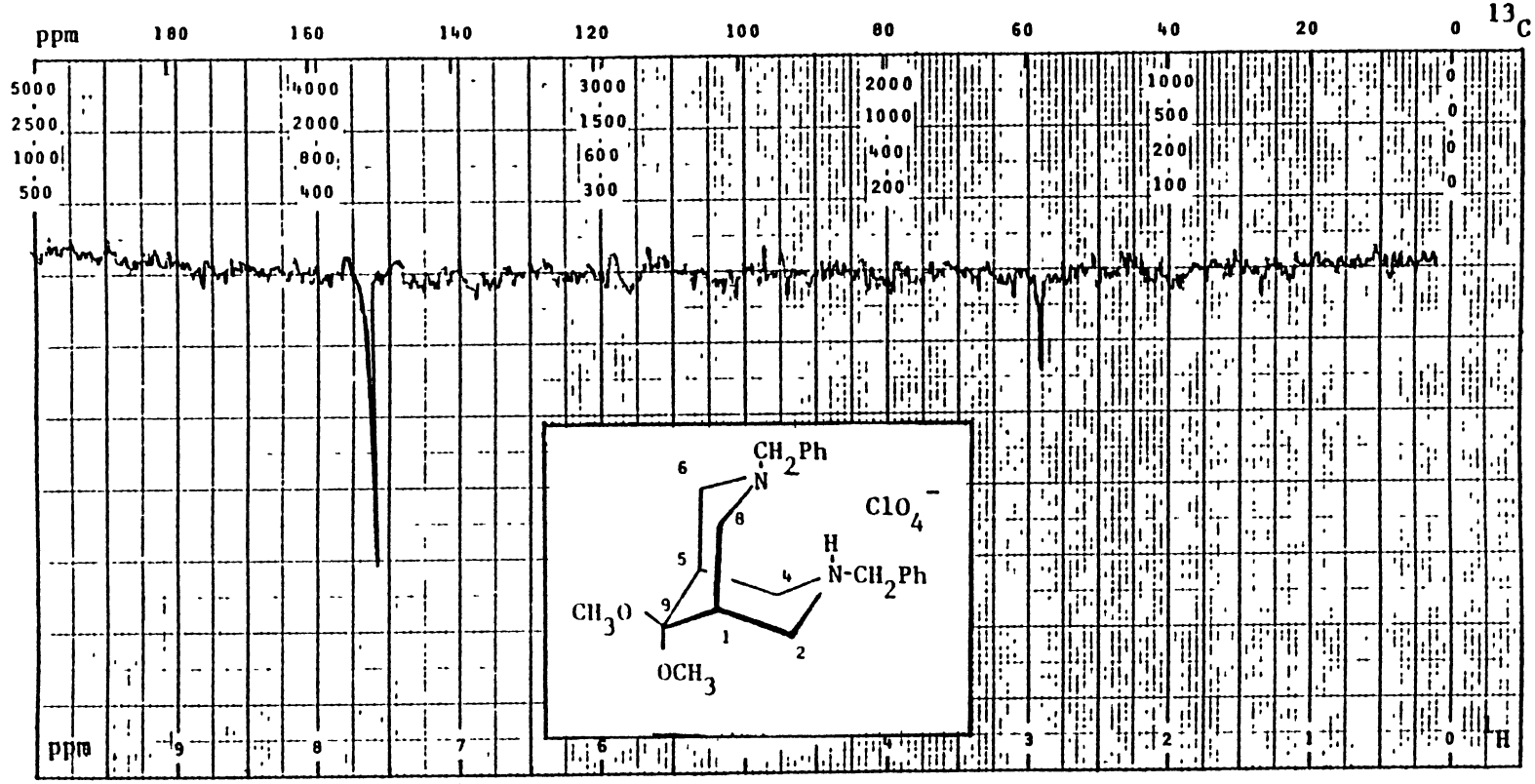
Plate LXV. HETCOR NMR Spectrum of **102b**



Correlations:

^{13}C (ppm)	^{1}H (δ)
33.0	2.35
46.9	3.14
53.9	2.92
53.9	3.05
59.7	3.88

Plate LXVI. ^{15}N NMR Spectrum of 102b



PFT x CW _ ; Solvent: DMSO-d_6 ; SF: 30.406 MHz; WC: 3040 Hz; T: amb. °C; NT: 6000 .

Size: 12 K; PW/RF: 40 μs/dB; TO: -11600 Hz; FB: Hz; Lock: DMSO-d_6; D1,D5 : 8 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: Hz; LB: 8 Hz.

Plate LXVII. IR Spectrum of 103a

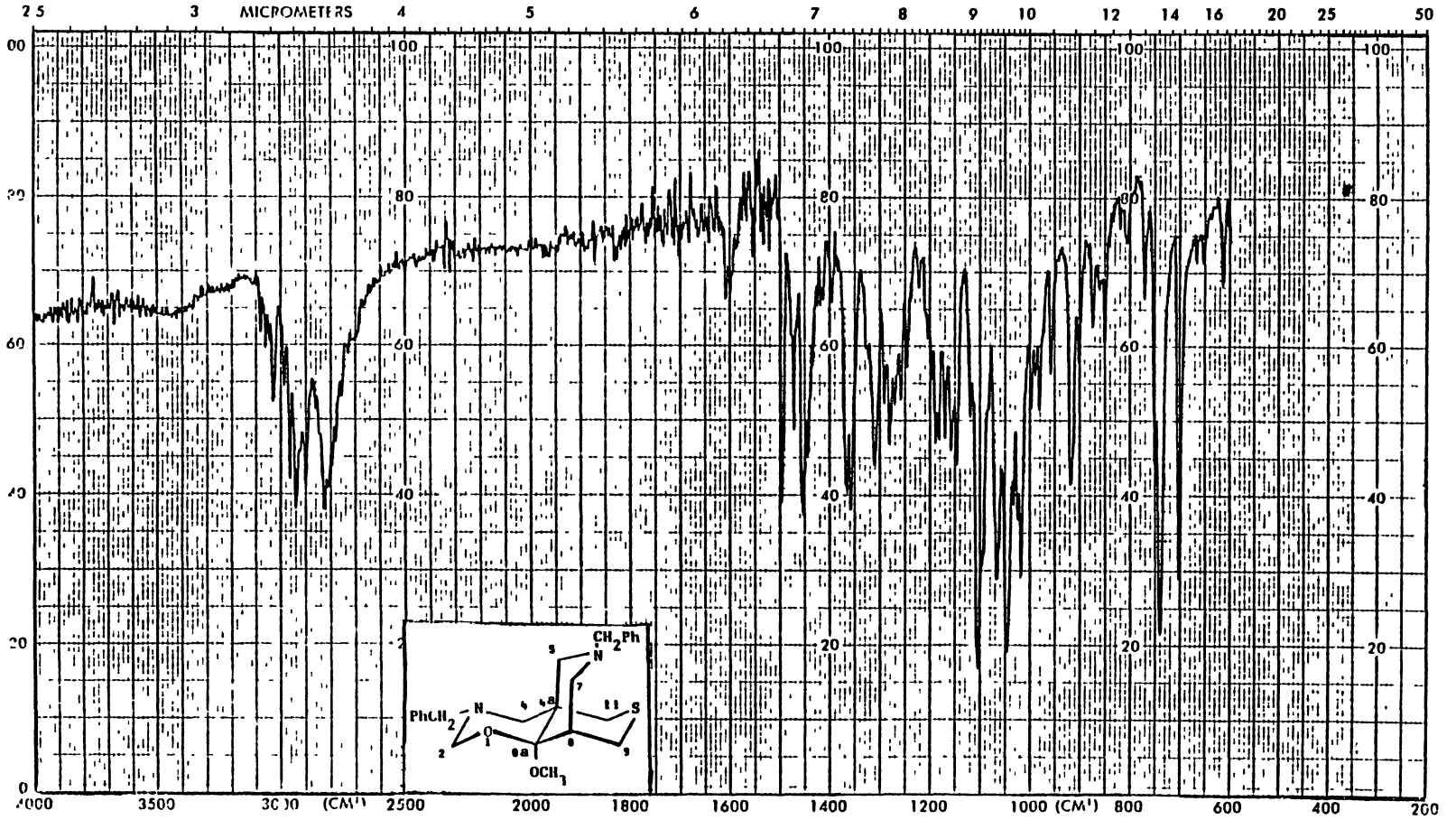
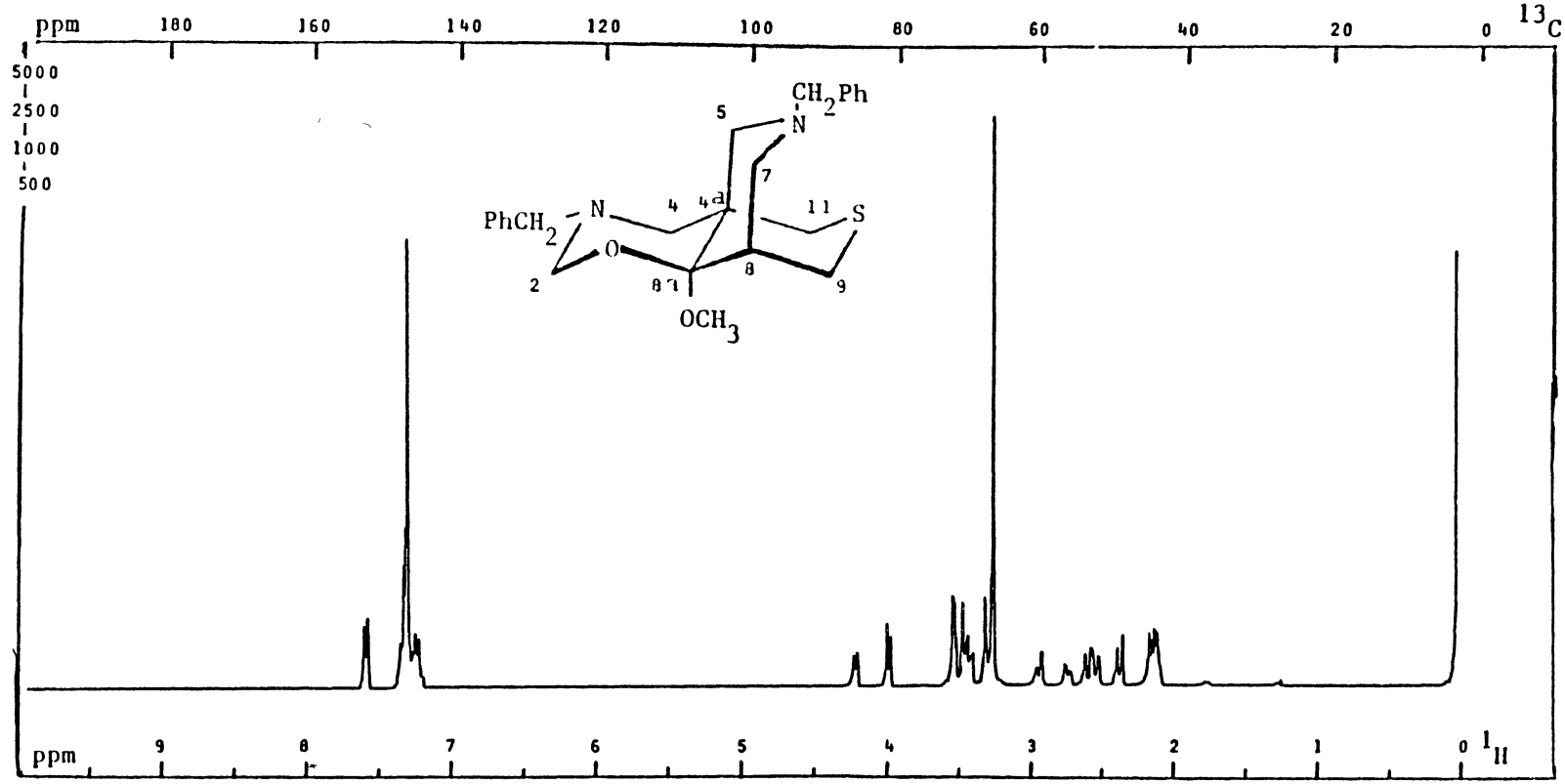


Plate LXVIII. ^{1}H NMR Spectrum of 103a

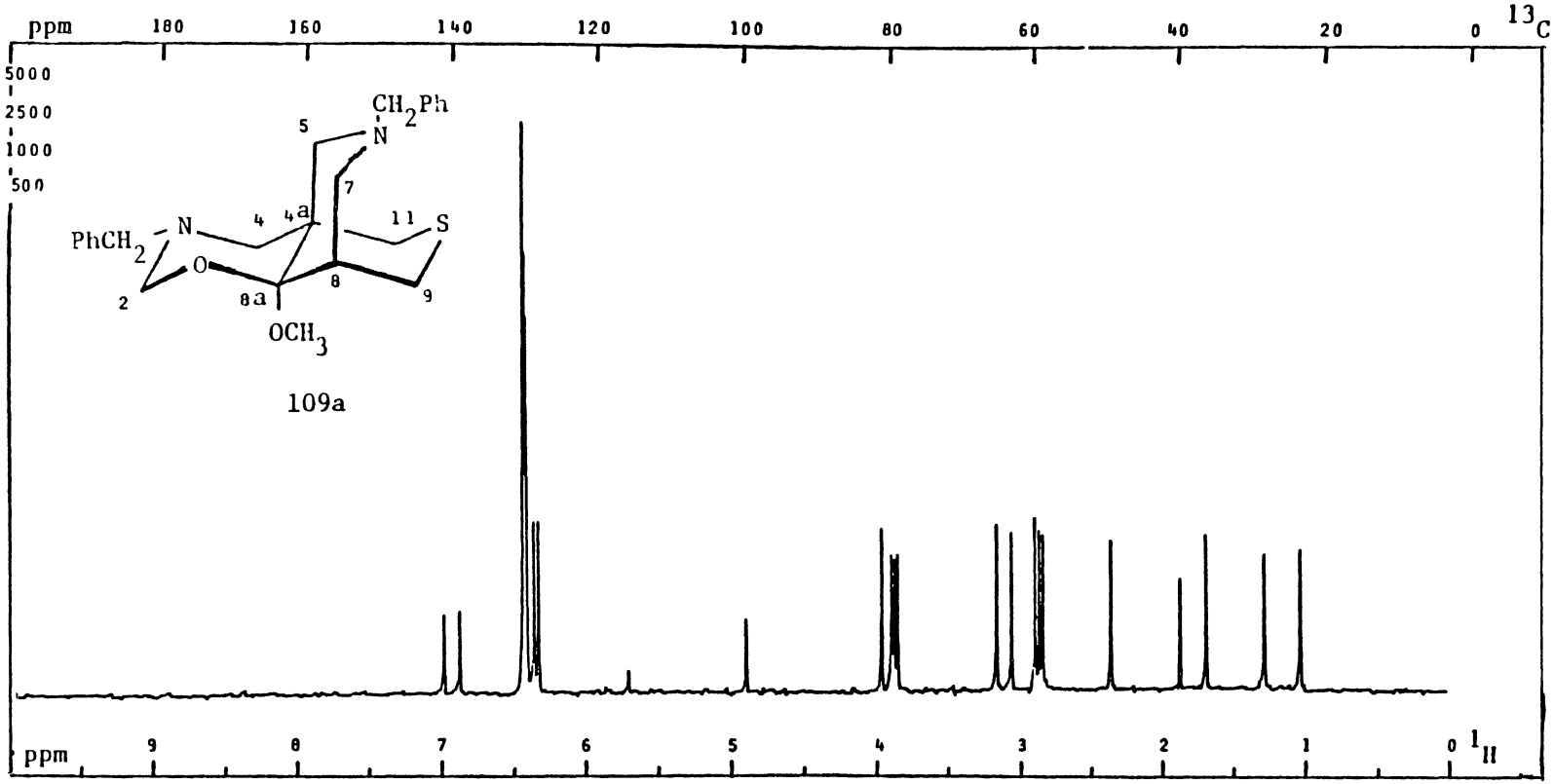


PFT x CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 3000 Hz; T: amb. °C; NT: 16 .

Size: 12 K; PW/RF: 5 μs/dB; TO: 0 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: Hz; LB: - Hz.

Plate LXIX. ^{13}C NMR Spectrum of 103a



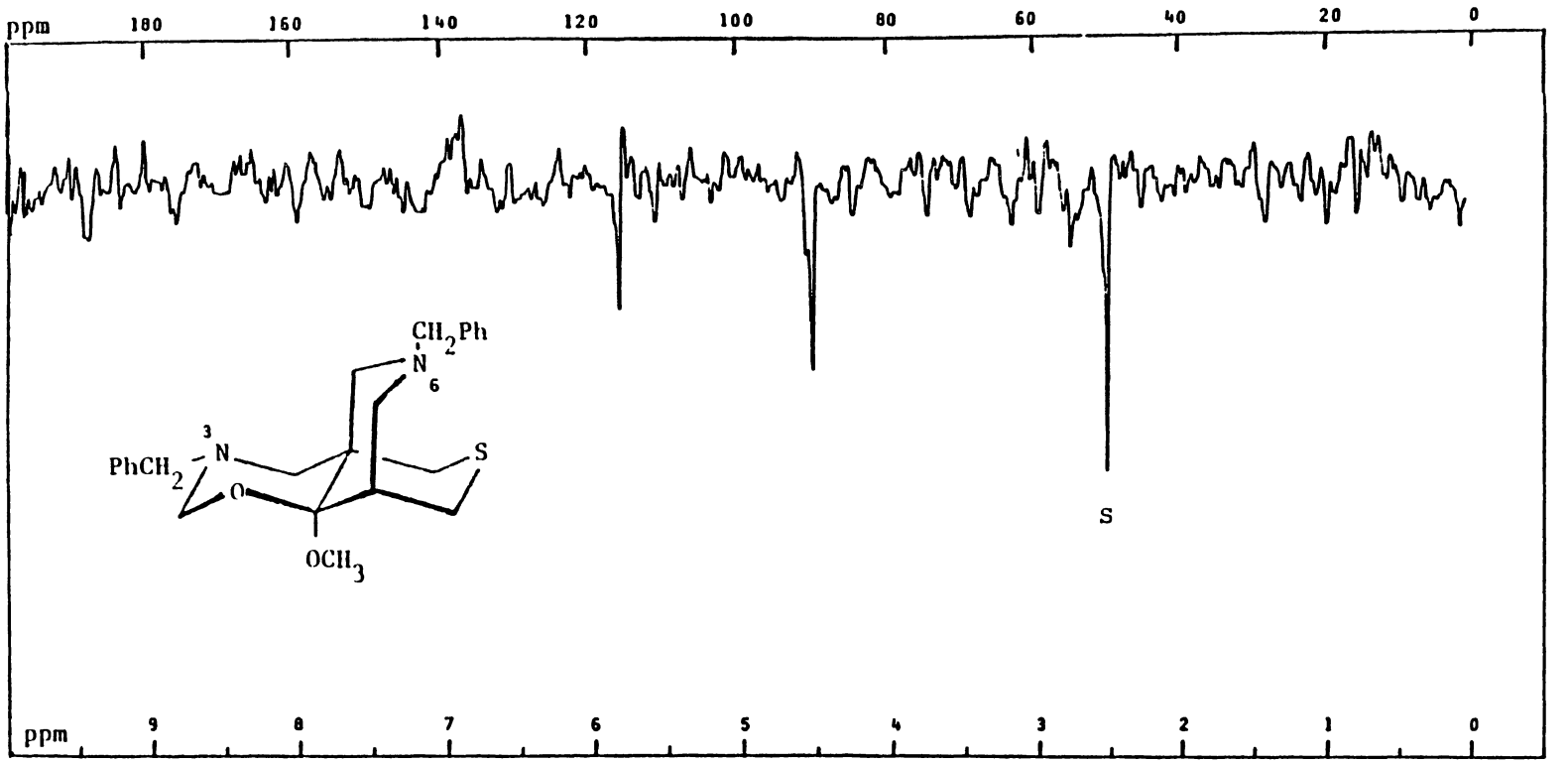
109a

PFT _x CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085 Hz; T: amb. °C; NT: 1000 .

Size: 20 K; PW/RF: 12 μs/dB; TO: 1000 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 4 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 1.5 Hz.

Plate LXX. ^{15}N NMR Spectrum of 103a



PFT x CW _ ; Solvent: $DCCl_3$; SF: 30.406 MHz; WC: 2432.5 Hz; T: amb. °C; NT: 8000 .

Size: 12 K; PW/RF: 40 µs/dB; TO: -11600 Hz; FB: Hz; Lock:$DCCl_3$; D1,D5: 8 s.

DC: Y, N ; Gated Off:A or D ; DO:0 Hz; RF(Power):0 W/dB; NBW: Hz; LB: 4 Hz.

Plate LXXI. IR Spectrum of **103b**

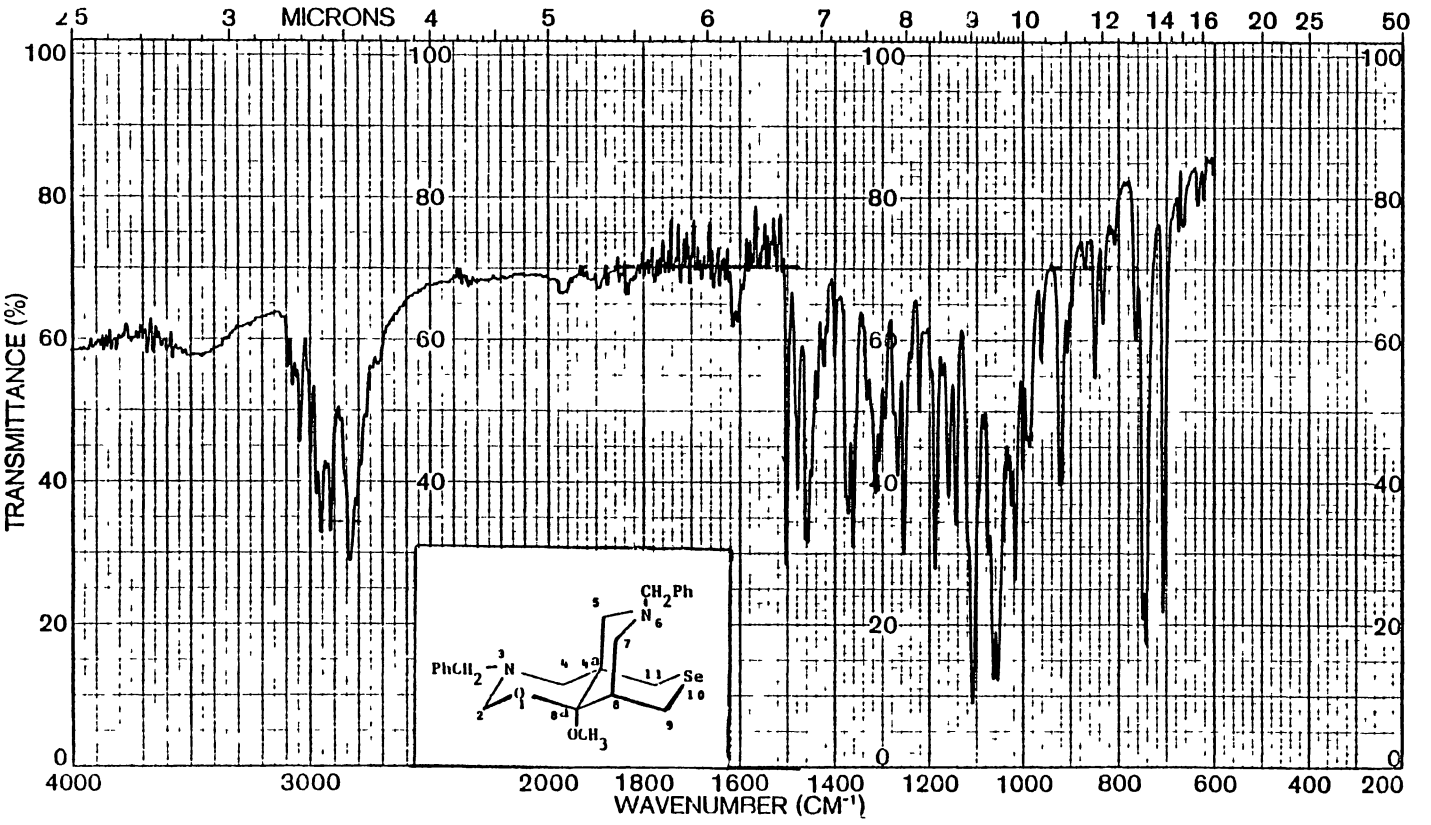
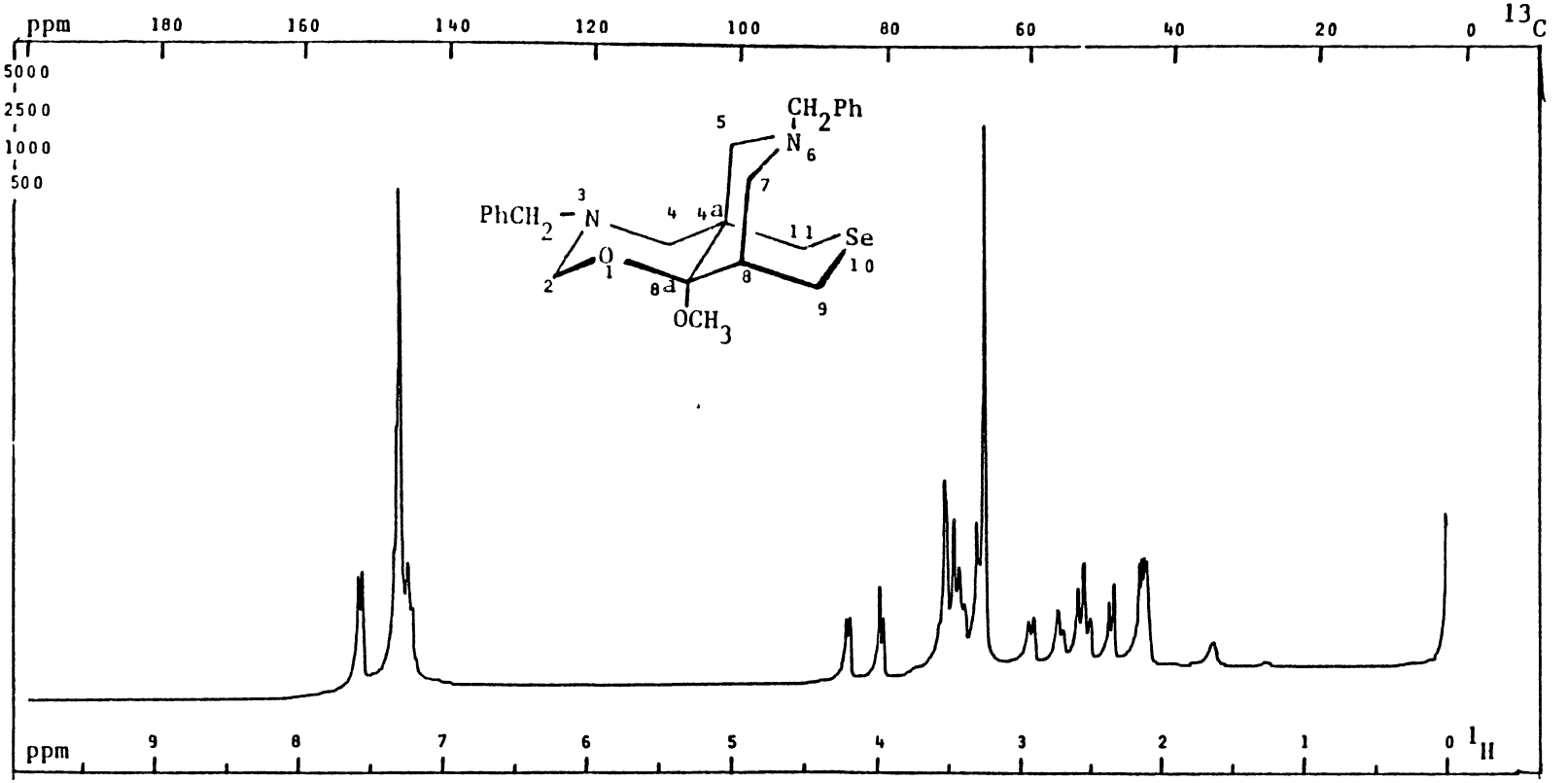


Plate LXXII. ^{1}H NMR Spectrum of 103b

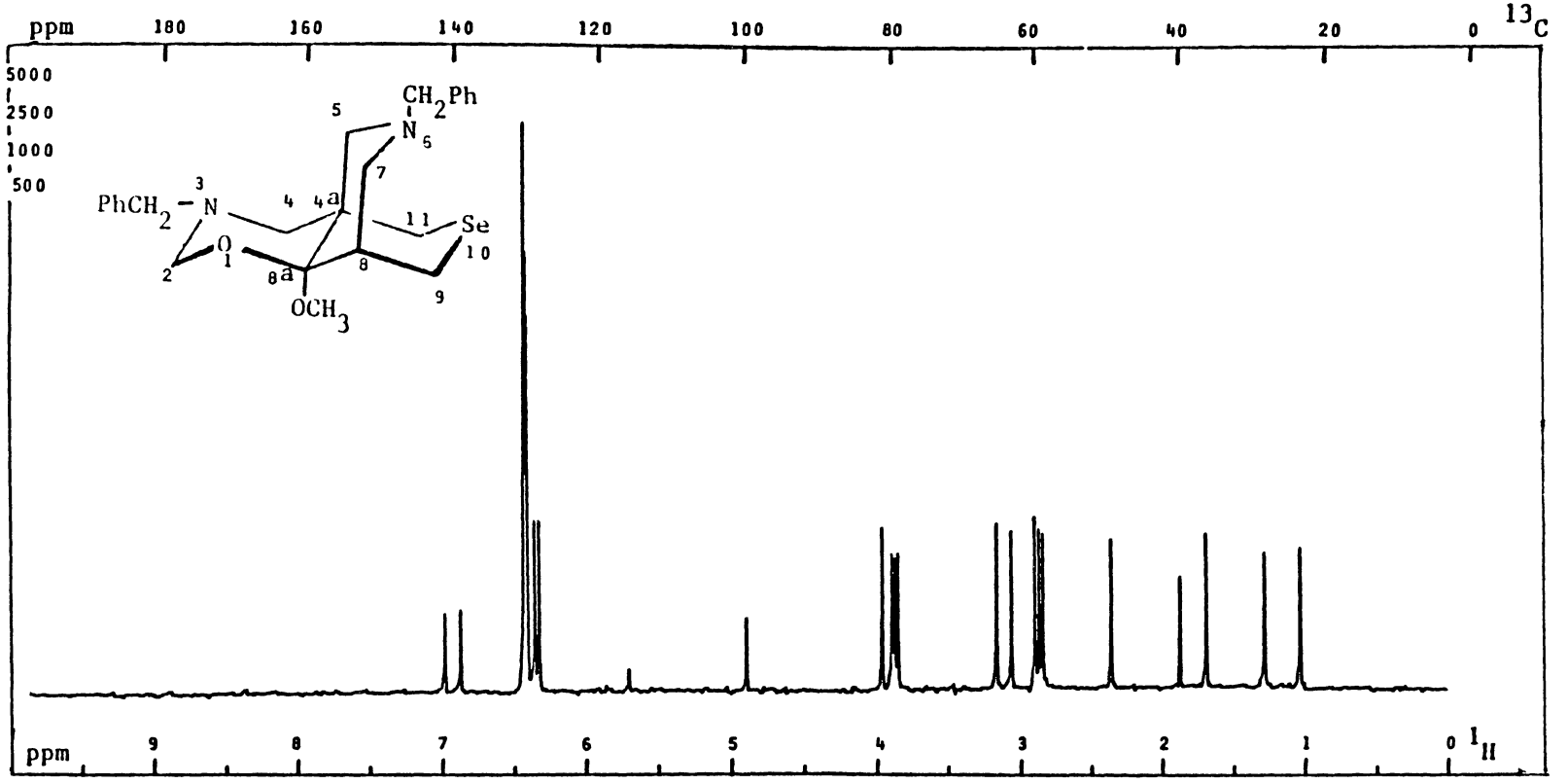


PFT x CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 3000 Hz; T:amb. °C; NT: 8 .

Size: 8 K; PW/RF: 5 μs/dB; TO: 0 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: Hz; LB: - Hz.

Plate LXXIII. ^{13}C NMR Spectrum of 103b

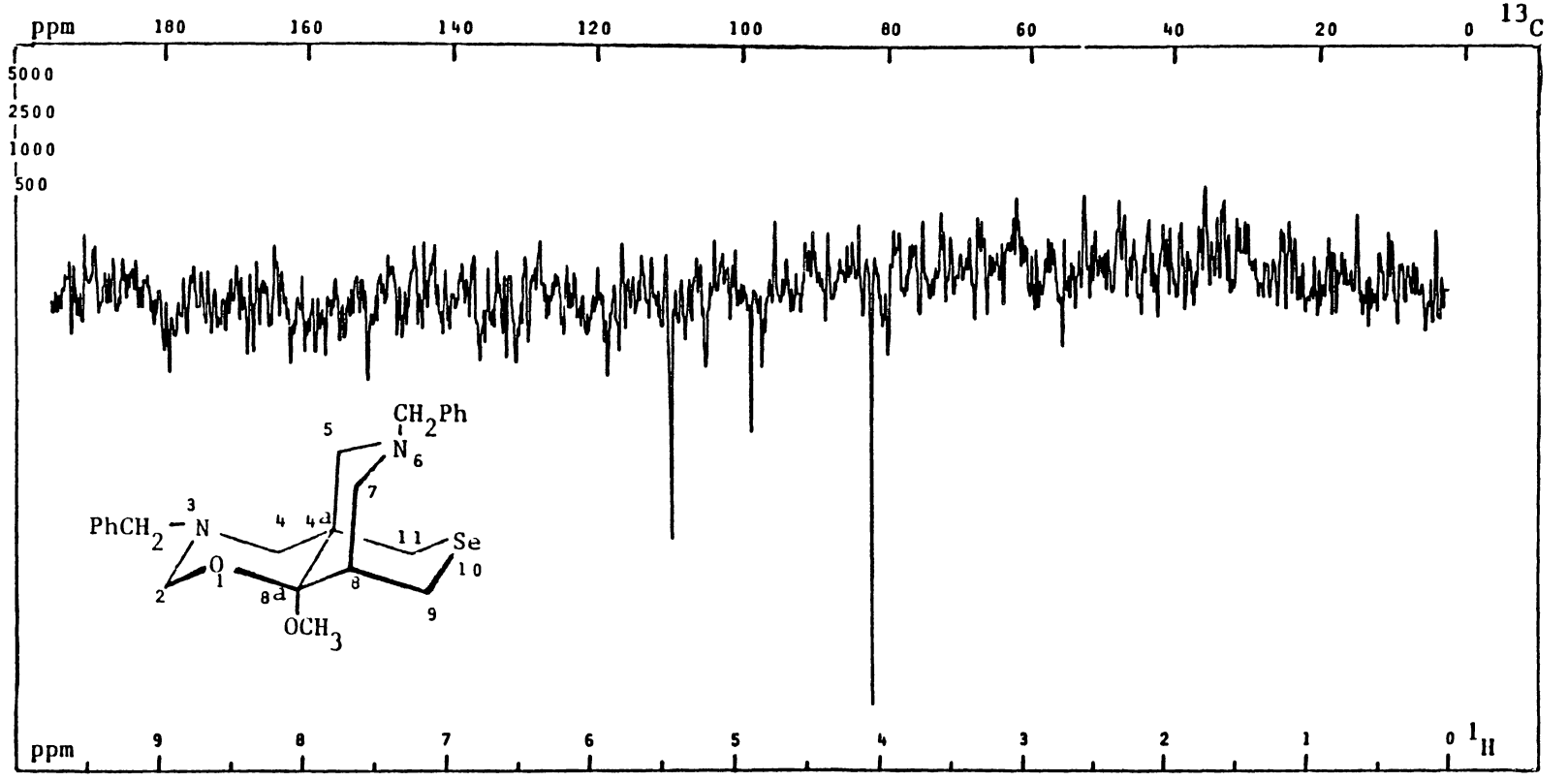


PFT $\underline{x}$ CW $\_$; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085 Hz; T: amb. °C; NT: 720 .

Size: 20 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 1 s.

DC: $\underline{Y}$, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 4.0 Hz.

Plate LXXIV. ^{15}N NMR Spectrum of 103b

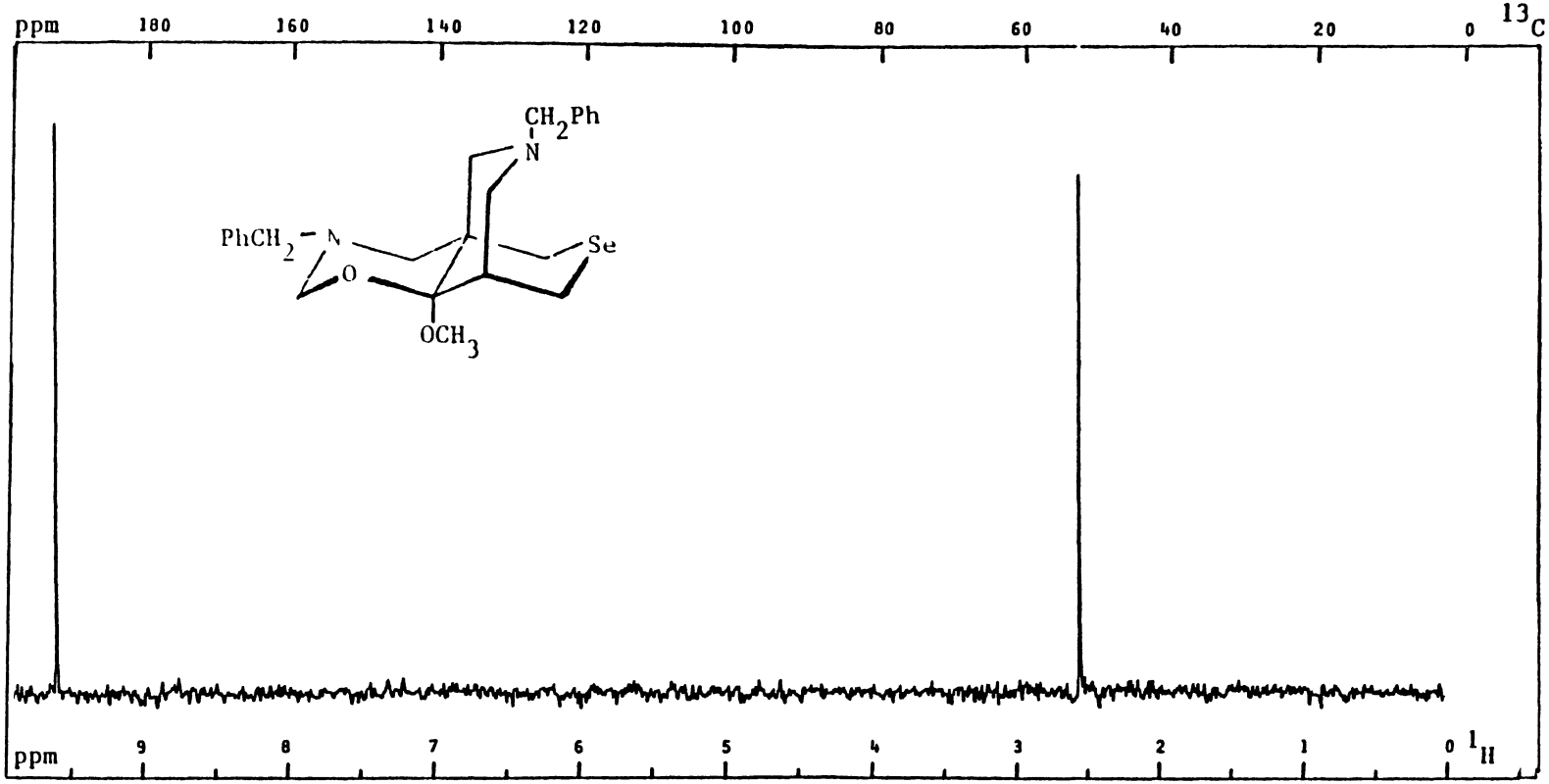


PFT x CW _ ; Solvent: $DCCl_3$; SF: 30.406 MHz; WC: 2432 Hz; T: amb. °C; NT: 8000 .

Size: 12 K; PW/RF: 40 µs/dB; TO: -11600 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 25 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: Hz; LB: 4 Hz.

Plate LXXV. ^{77}Se NMR Spectrum of **103b**



PFT x CW _ ; Solvent: $DCCl_3$; SF: 17.22 MHz; WC: 30127 Hz; T: amb. °C; NT: 192 .

Size: 20 K; PW/RF: 35 μs/dB; TO: 500 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 9 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 5.0 Hz.

Plate LXXVI. IR Spectrum of **103c**

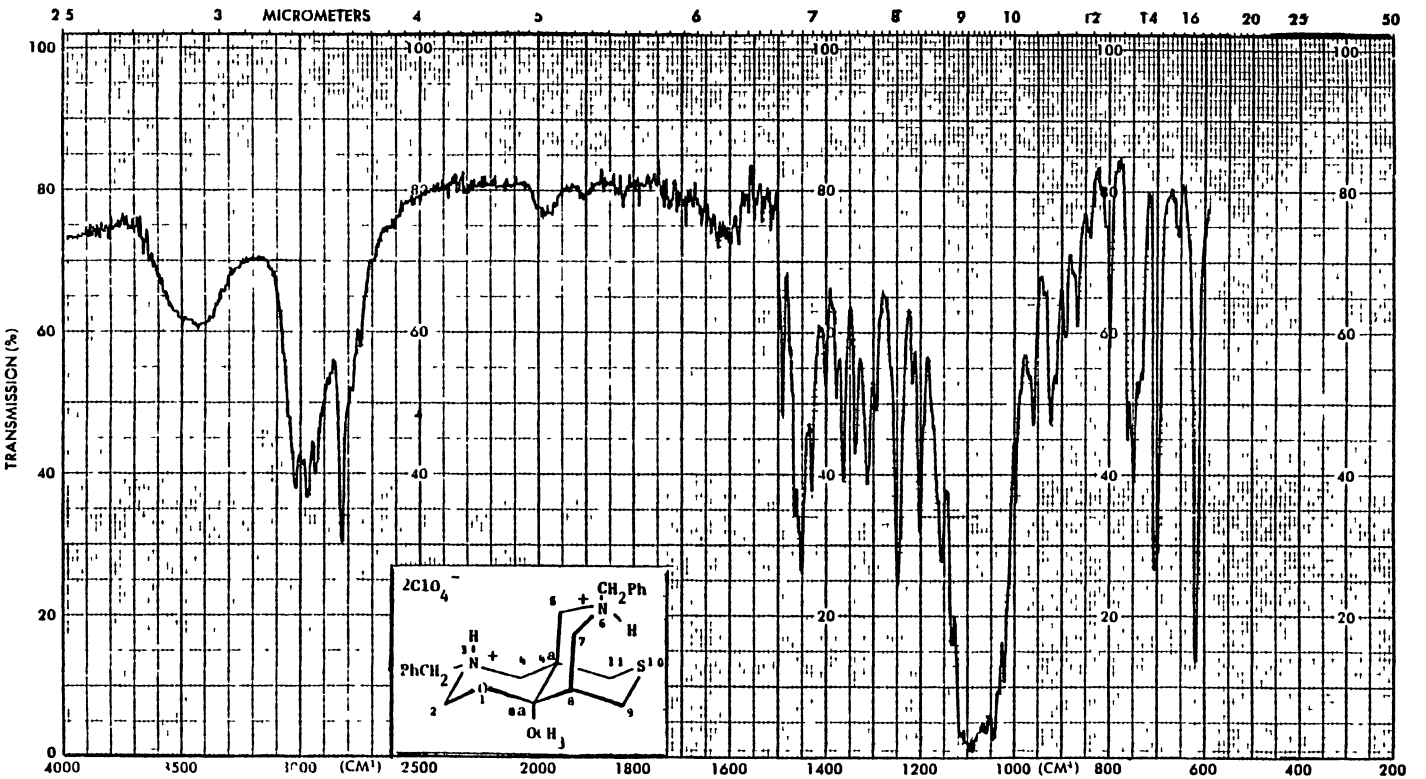
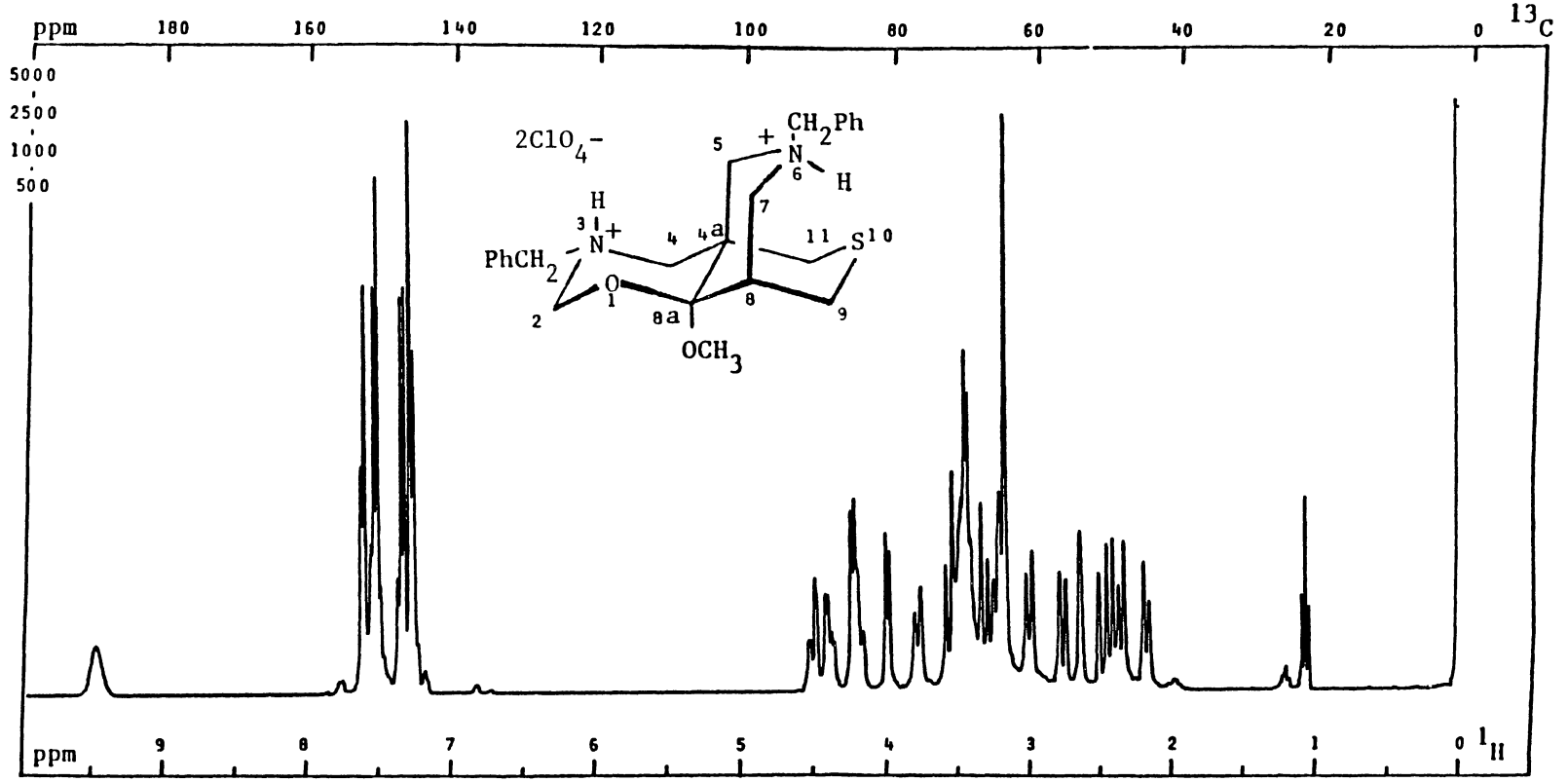


Plate LXXVII. ^{1}H NMR Spectrum of 103c

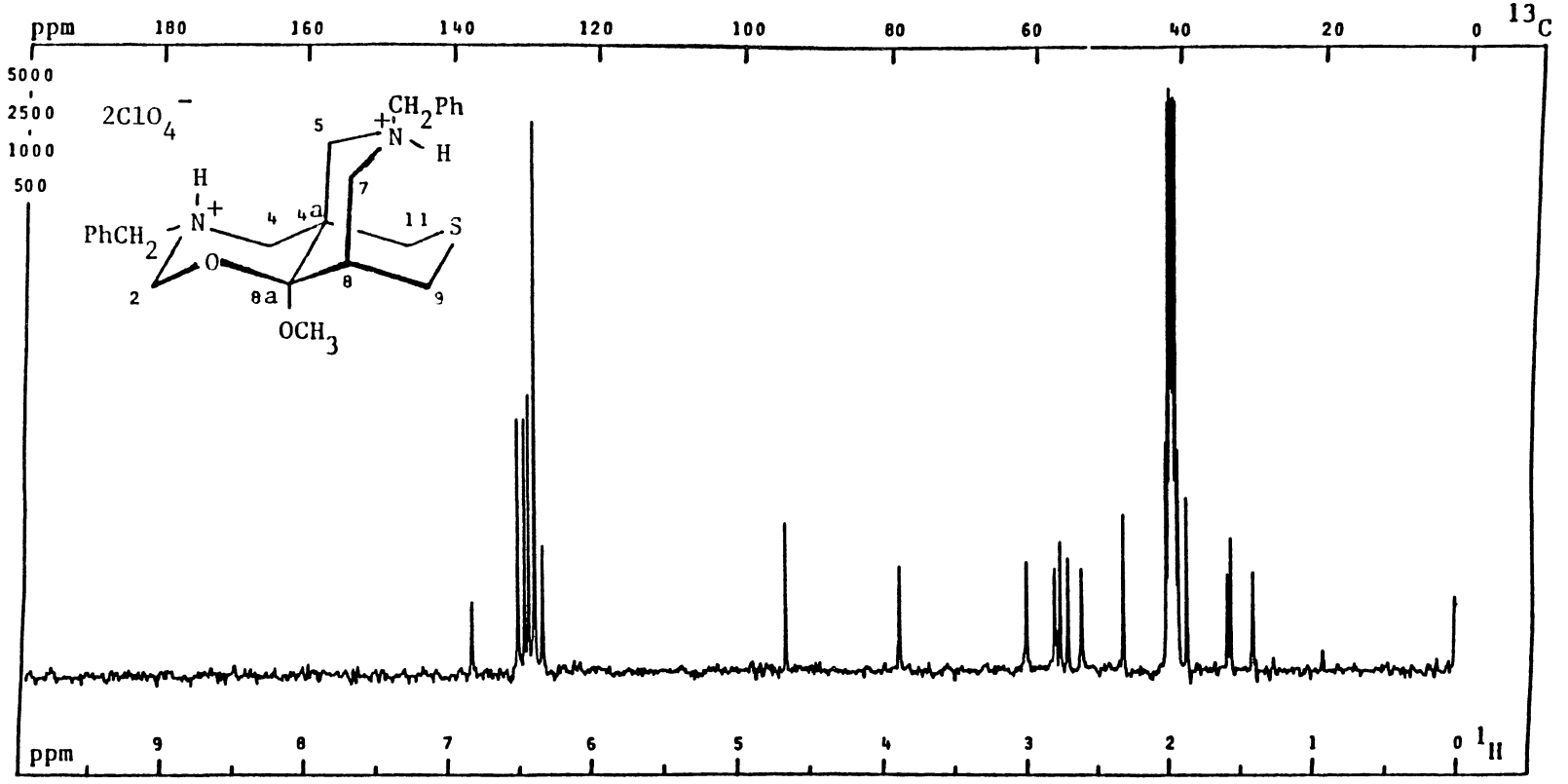


PFT x CW _ ; Solvent: DMSO-d_6 ; SF: 299.944 MHz; WC: 3000 Hz; T: amb. °C; NT: 466 .

Size: 24 K; PW/RF: 5 µs/dB; TO: 1500 Hz; FB: Hz; Lock: DMSO-d_6 ; D1,D5: 0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: Hz; LB: - Hz.

Plate LXXVIII. ^{13}C NMR Spectrum of 103c

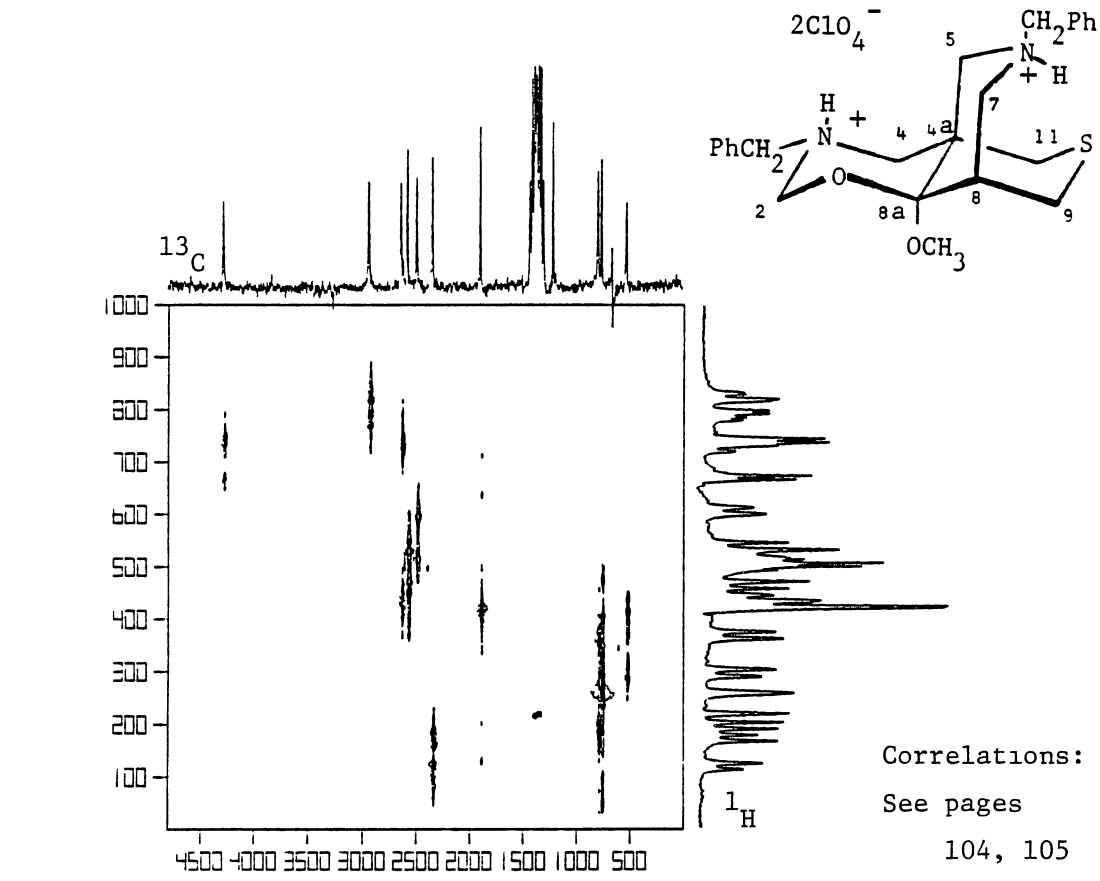


PFT x CW _ ; Solvent: DMSO-d_6 ; SF: 75.429 MHz; WC: 15085 Hz; T: amb. °C; NT: 264 .

Size: 20 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: Hz; Lock: DMSO-d_6 ; D1,D5: 4.0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 3 Hz.

Plate LXXIX. HETCOR NMR Spectrum of **103c**



Correlations:

See pages 104, 105

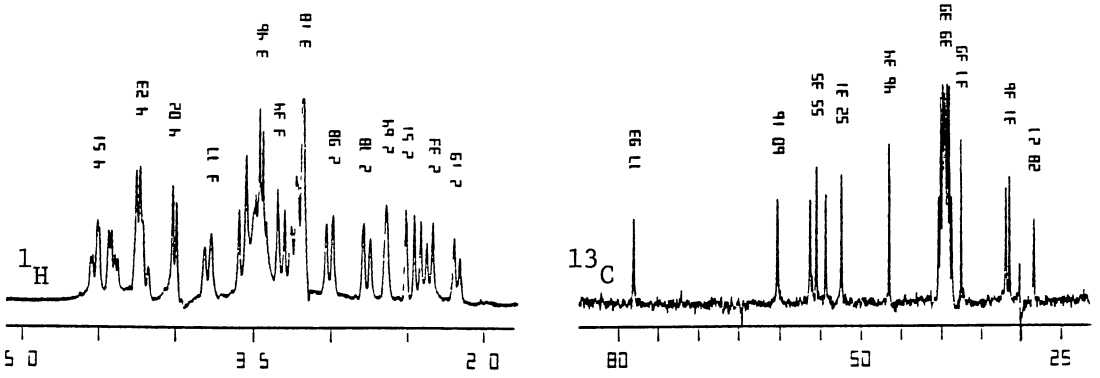


Plate LXXX. IR Spectrum of 104a

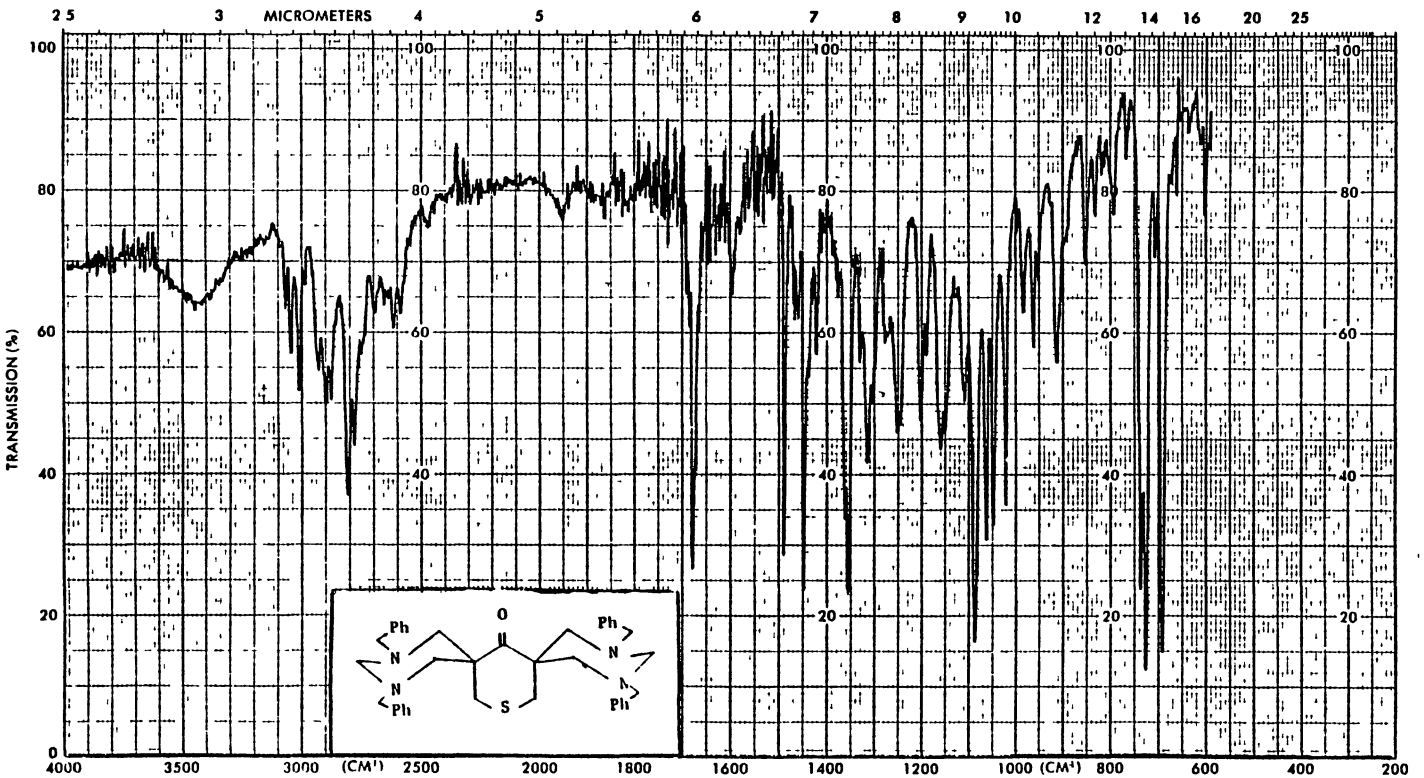
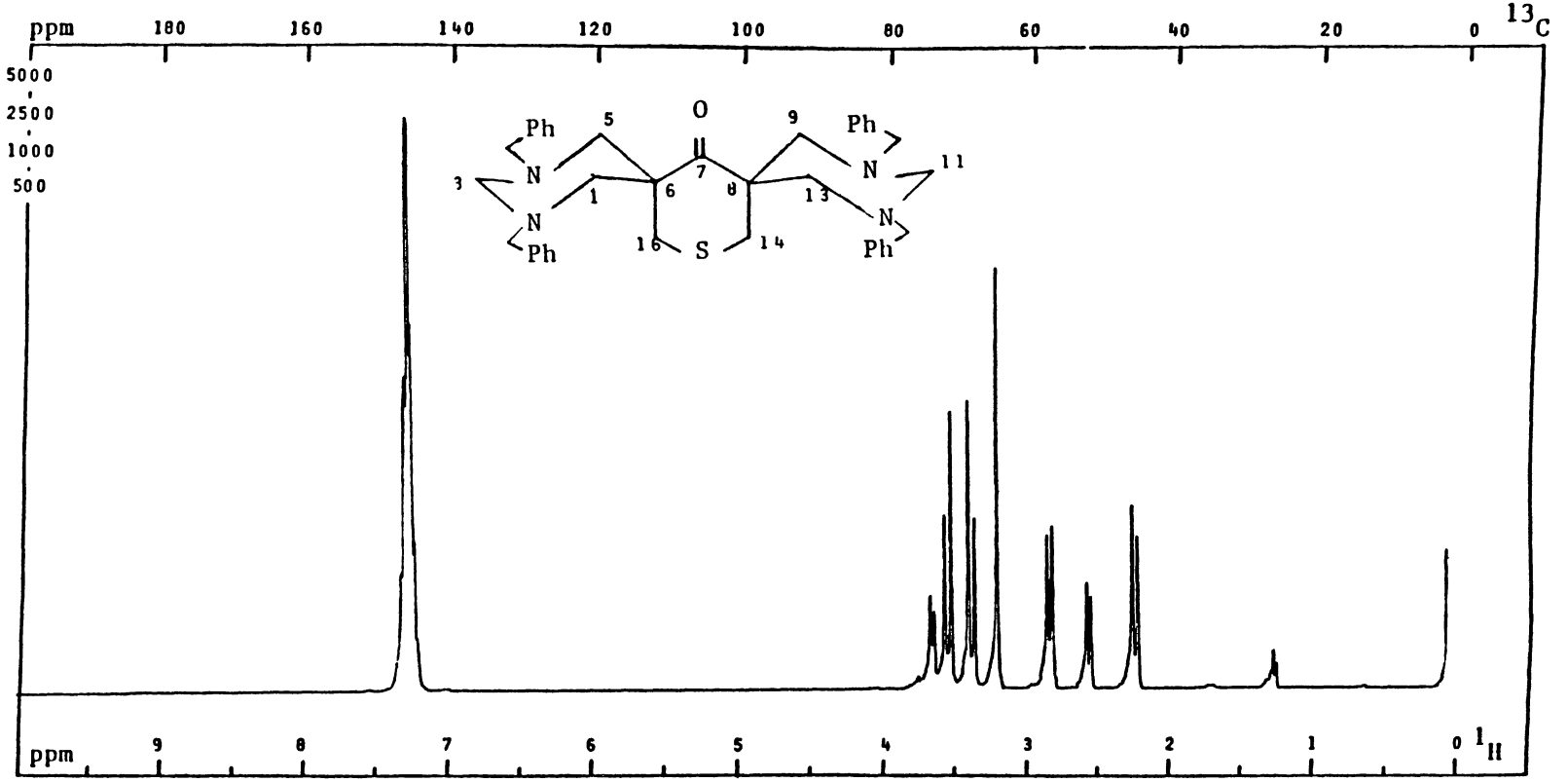


Plate LXXXI. ^{1}H NMR Spectrum of 104a

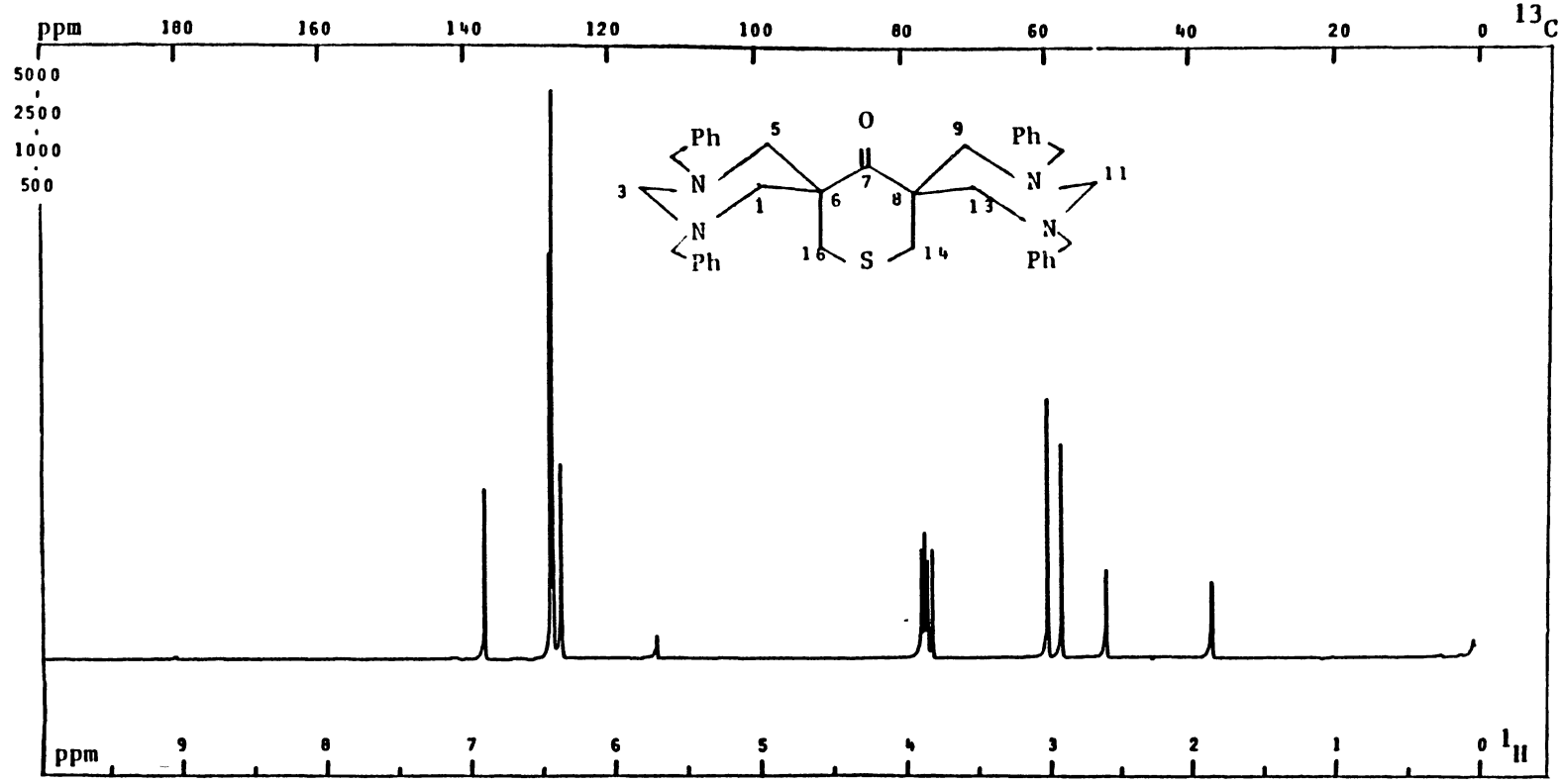


PFT x CW _ ; Solvent: $CDCl_3$; SF: 299.944 MHz; WC: 3000 Hz; T: amb. °C; NT: 4 .

Size: 12 K; PW/RF: 5 µs/dB; TO: 0 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: Hz; LB: 0.5 Hz.

Plate LXXXII. ^{13}C NMR Spectrum of 104a



PFT _xCW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085 Hz; T: amb. °C; NT: 120 .

Size: 8 K; PW/RF: 12 μs/dB; TO: 1000 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 4 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 2.5 Hz.

Plate LXXXIII. HETCOR NMR Spectrum of **104b**

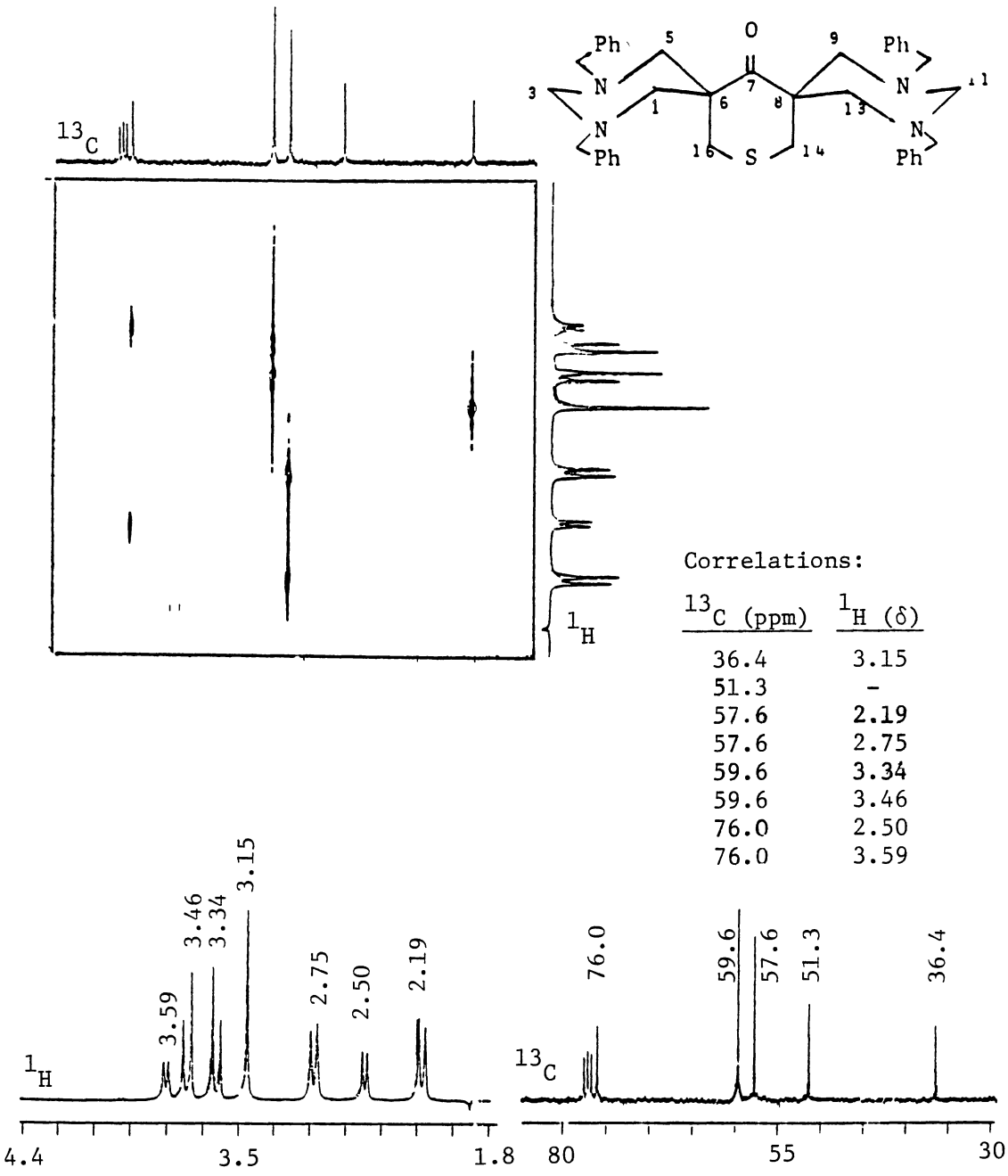
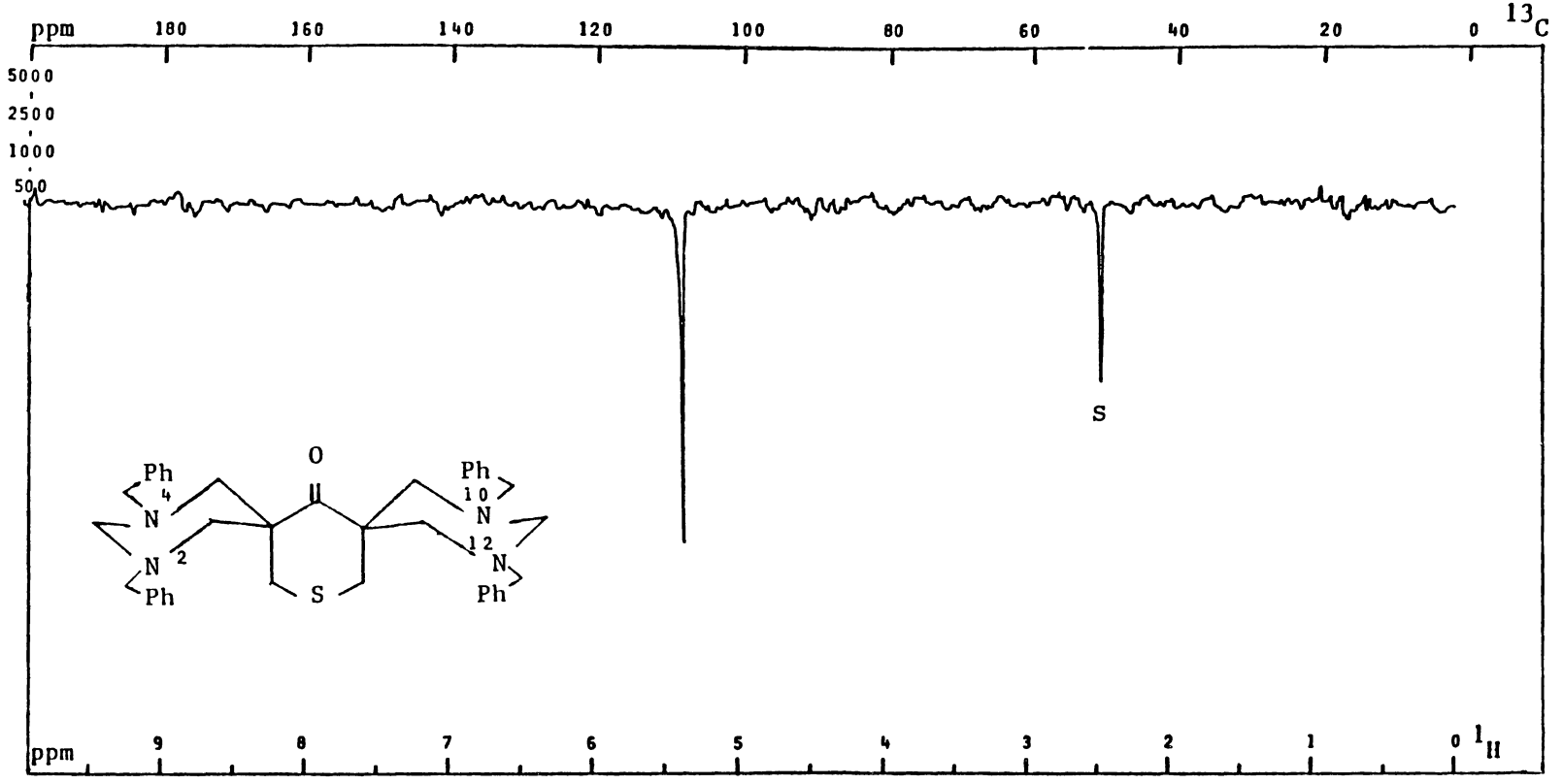


Plate LXXXIV. ^{15}N NMR Spectrum of 104a



PFT X CW _ ; Solvent: $DCCl_3$; SF: 30.406 MHz; WC: 3040.6 Hz; T: amb. °C; NT: 2788 .

Size: 12 K; PW/RF: 40 µs/dB; TO: -11600 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 30 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: Hz; LB: 2.0 Hz.

Plate LXXXV. IR Spectrum of 104b

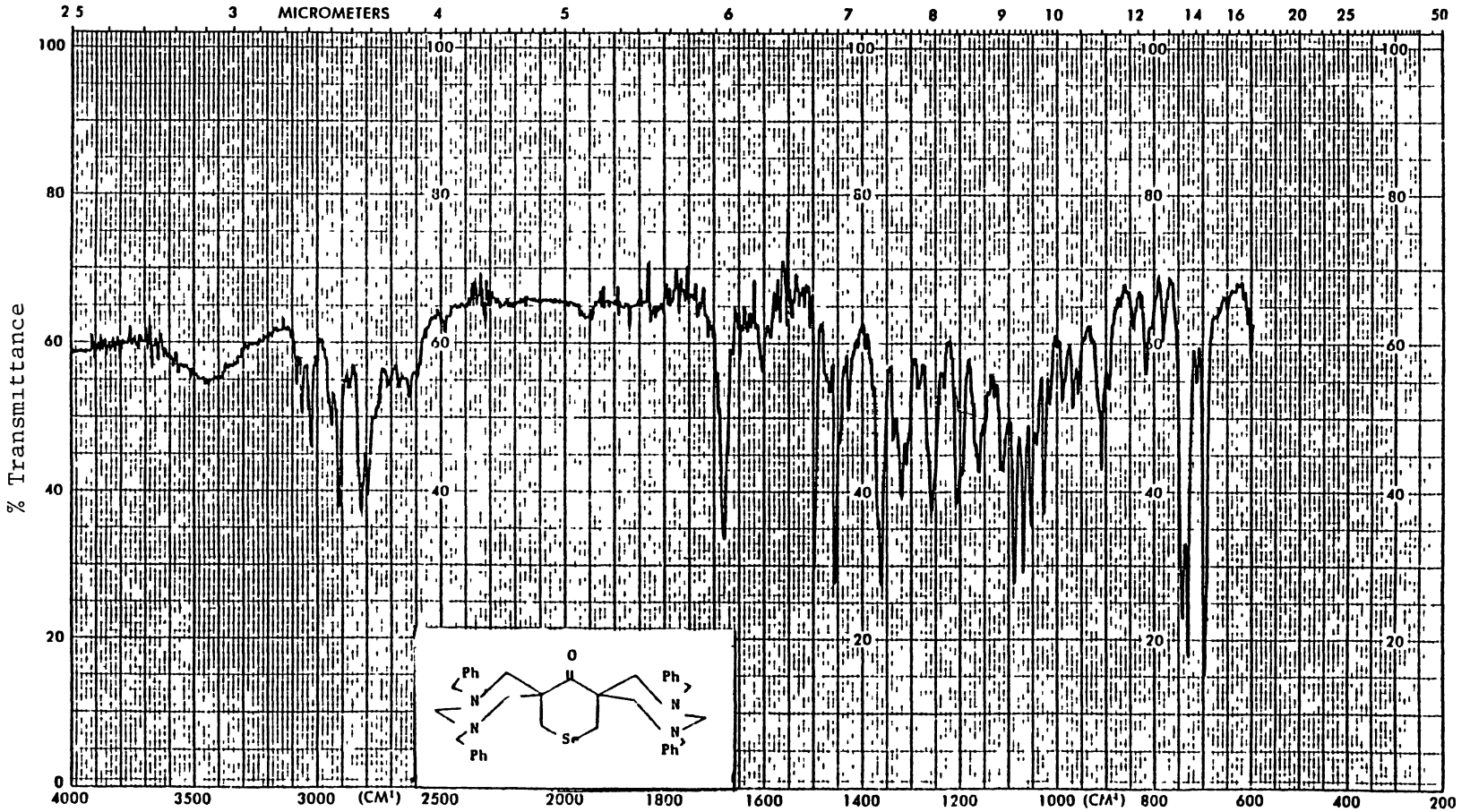
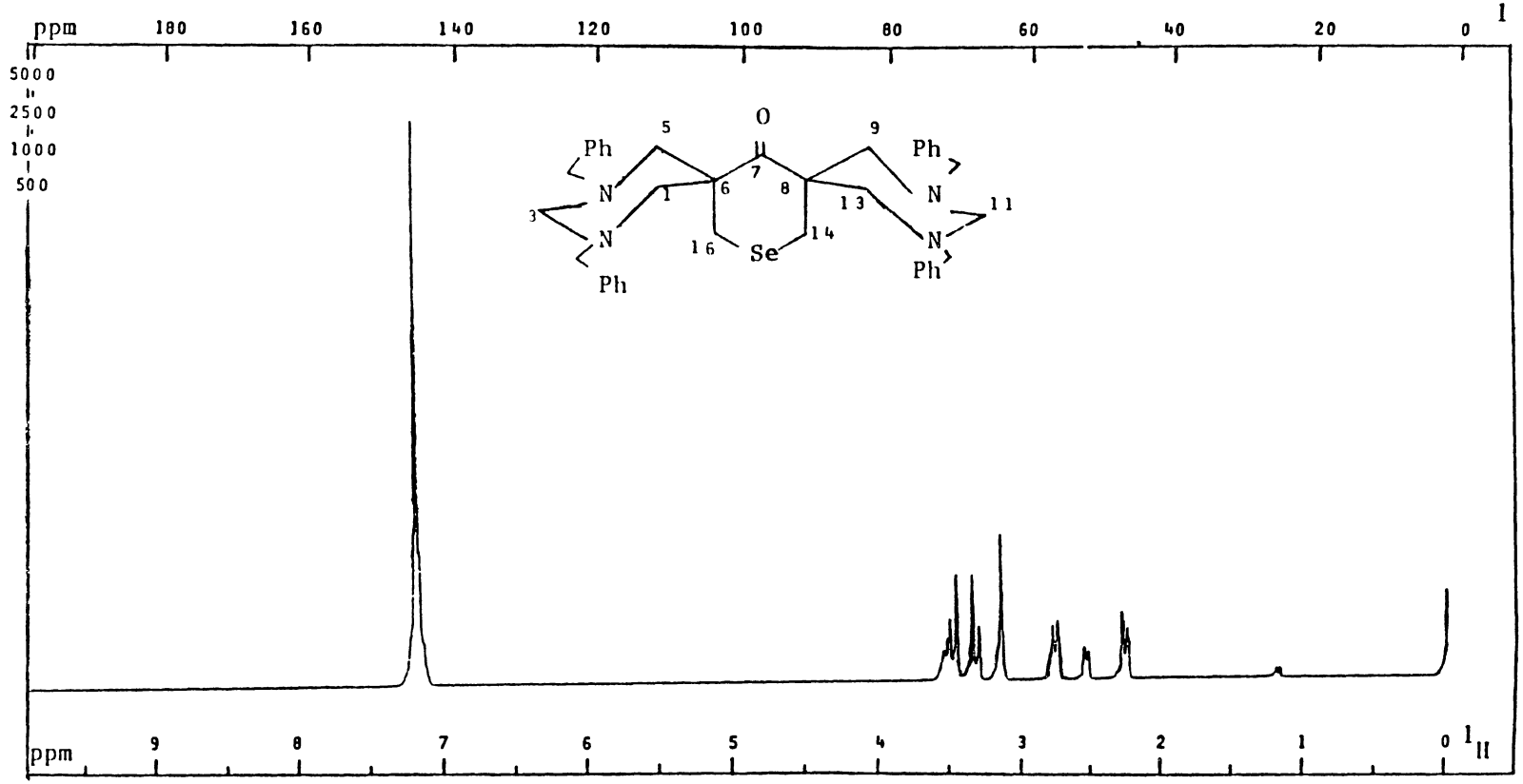


Plate LXXXVI. ^{1}H NMR Spectrum of 104b

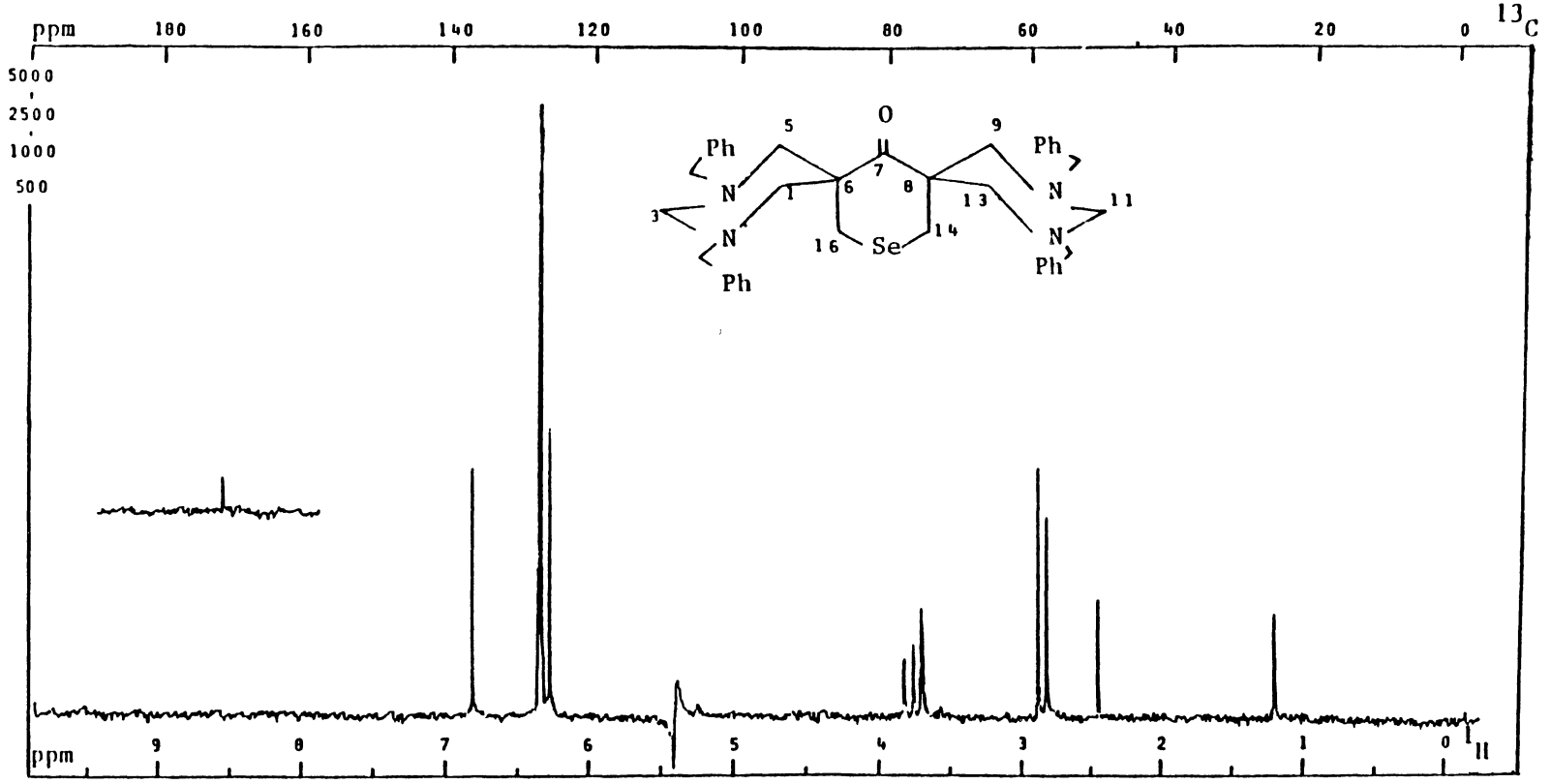


PFT x CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 3000 Hz; T: amb. °C; NT: 8 .

Size: 8 K; PW/RF: 5 μs/dB; TO: 0 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 0.5 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: Hz; LB: 0.5 Hz.

Plate LXXXVII. ^{13}C NMR Spectrum of 104b

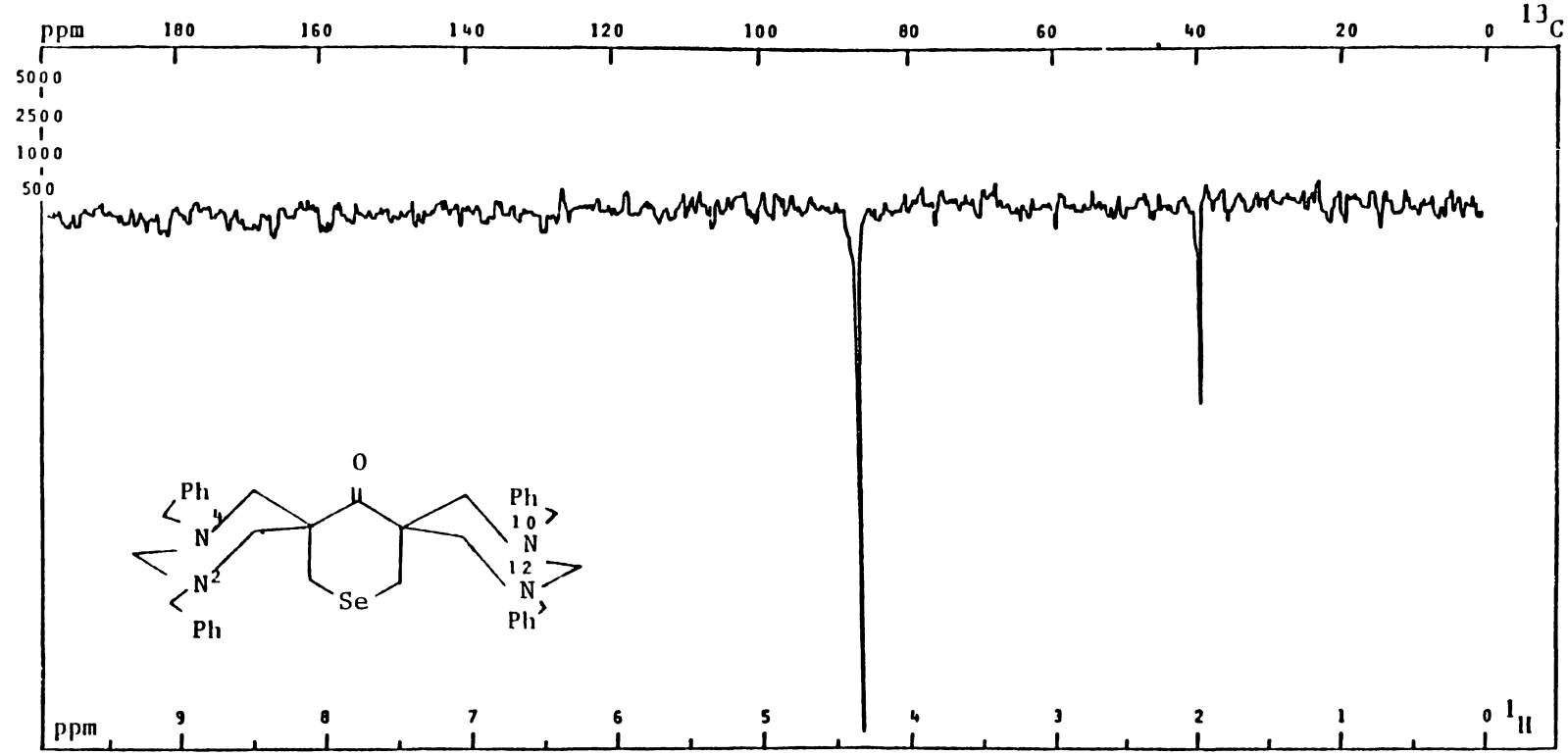


PFT x CW _ ; Solvent: $DCCl_3$; SF: 25.20 MHz; WC: 5000 Hz; T: amb. °C; NT: 2000 .

Size: 8 K; PW/RF: 20 µs/dB; TO: 35101 Hz; FB: Hz; Lock:$DCCl_3$; D1,D5: 4.0 s.

DC: Y, N ; Gated Off:A or D ; DO: 45616 Hz; RF(Power): 119 W/dB; NBW: Hz; LB: 1.0 Hz.

Plate LXXXVIII. ^{15}N NMR Spectrum of 104b

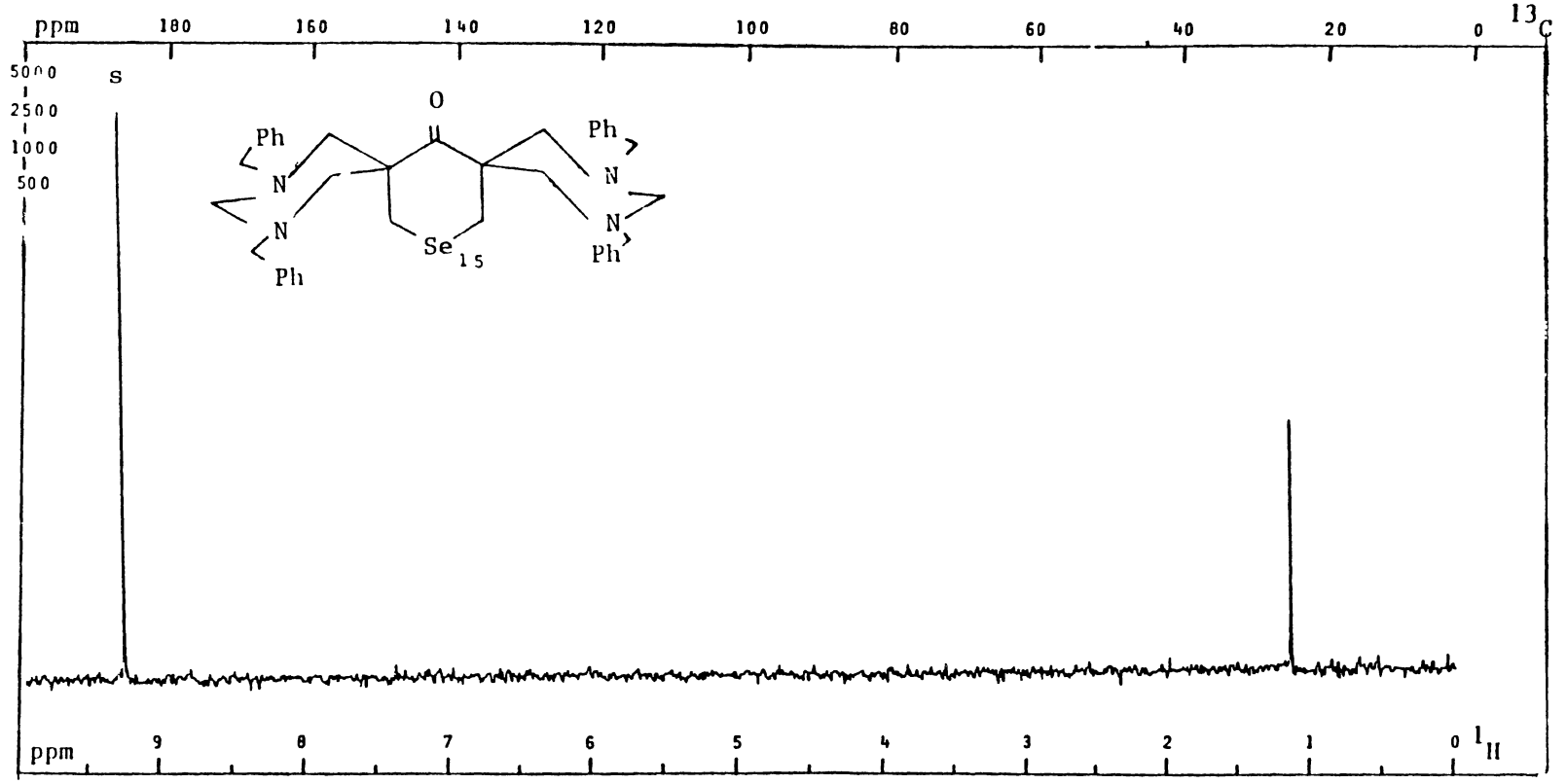


PFT x CW _ ; Solvent: $DCCl_3$; SF: 30.406 MHz; WC: 1040 Hz; T: amb. °C; NT: 2788 .

Size: 12 K; PW/RF: 40 µs/dB; TO: 11600 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 30 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: Hz; LB: 2.0 Hz.

Plate LXXXIX. ^{77}Se NMR Spectrum of **104b**



PFT _x_ CW _ ; Solvent: $DCCl_3$; SF: 17.22 MHz; WC: 30127 Hz; T: amb. °C; NT: 192 .

Size: 20K ; PW/RF: 35 µs/dB; TO: 500 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 9 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 5.00 Hz.

Plate XC. IR Spectrum of 108

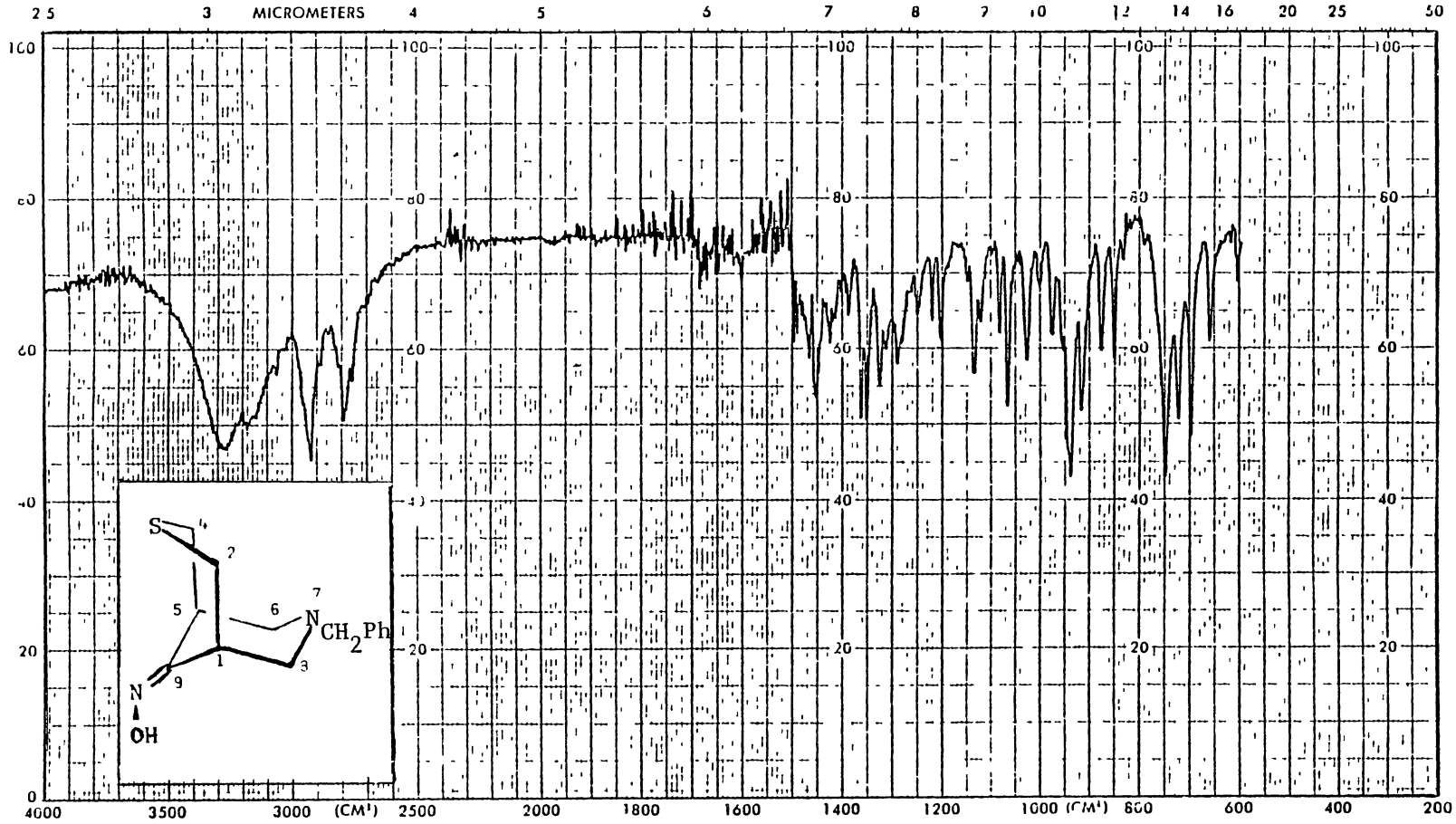
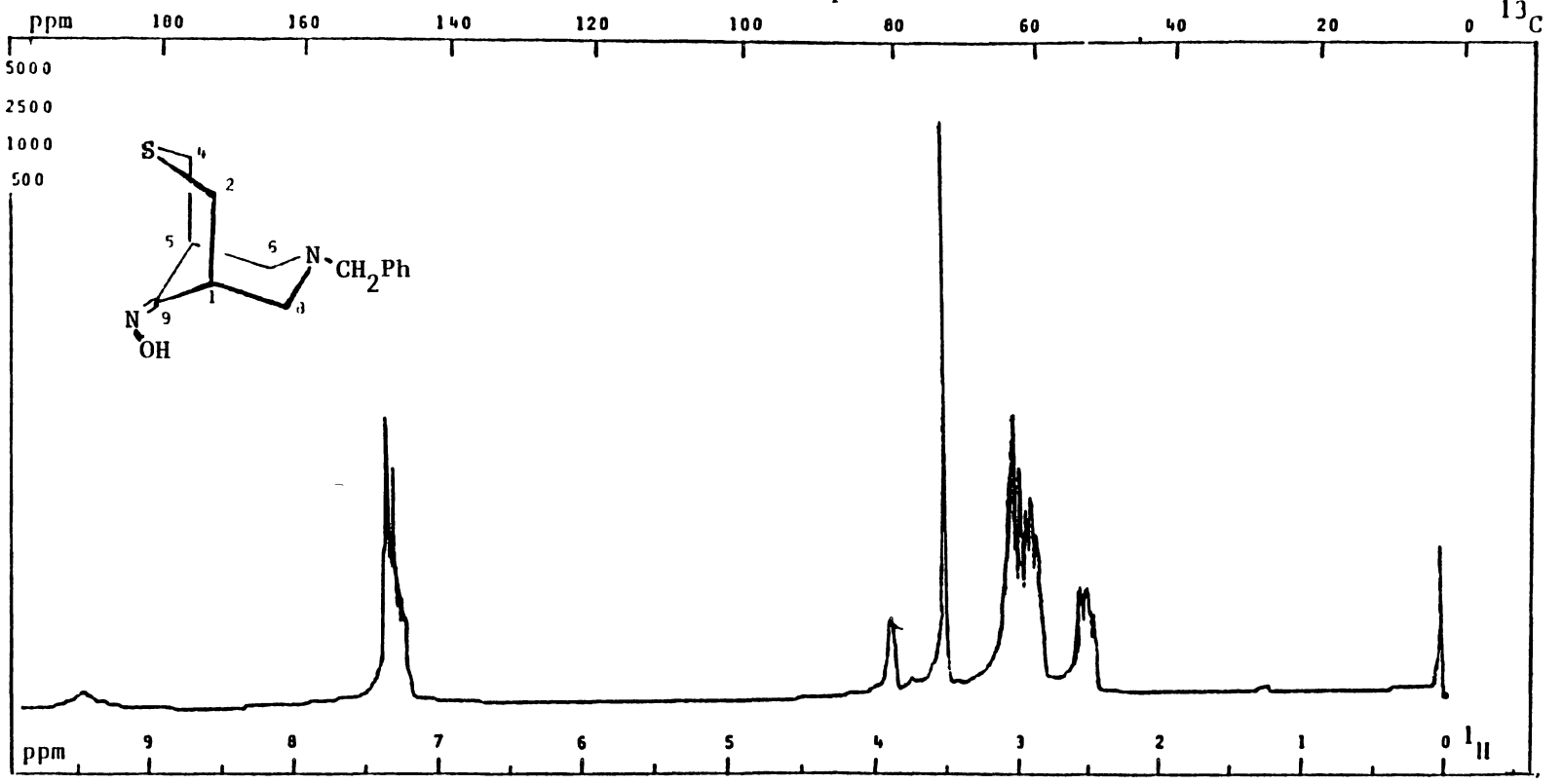


Plate XCI. ^{1}H NMR Spectrum of 108

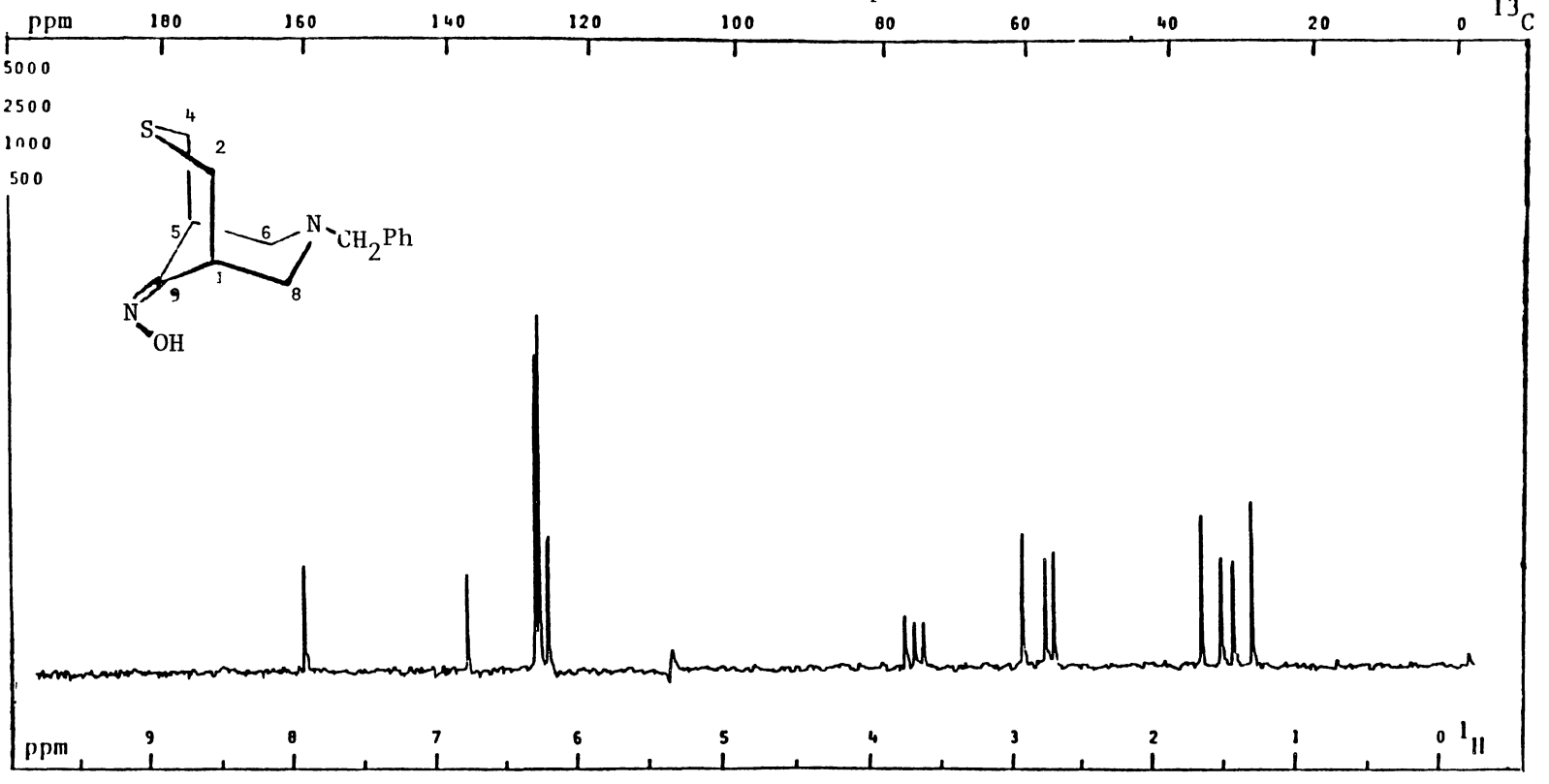


PFT x CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 3000 Hz; T: amb. °C; NT: 100

Size: 8 K; PW/RF: 10 μs/dB; TO: 0 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 0.500 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): W/dB; NBW: Hz; LB: 0.5 Hz.

Plate XCII. ^{13}C NMR Spectrum of 108

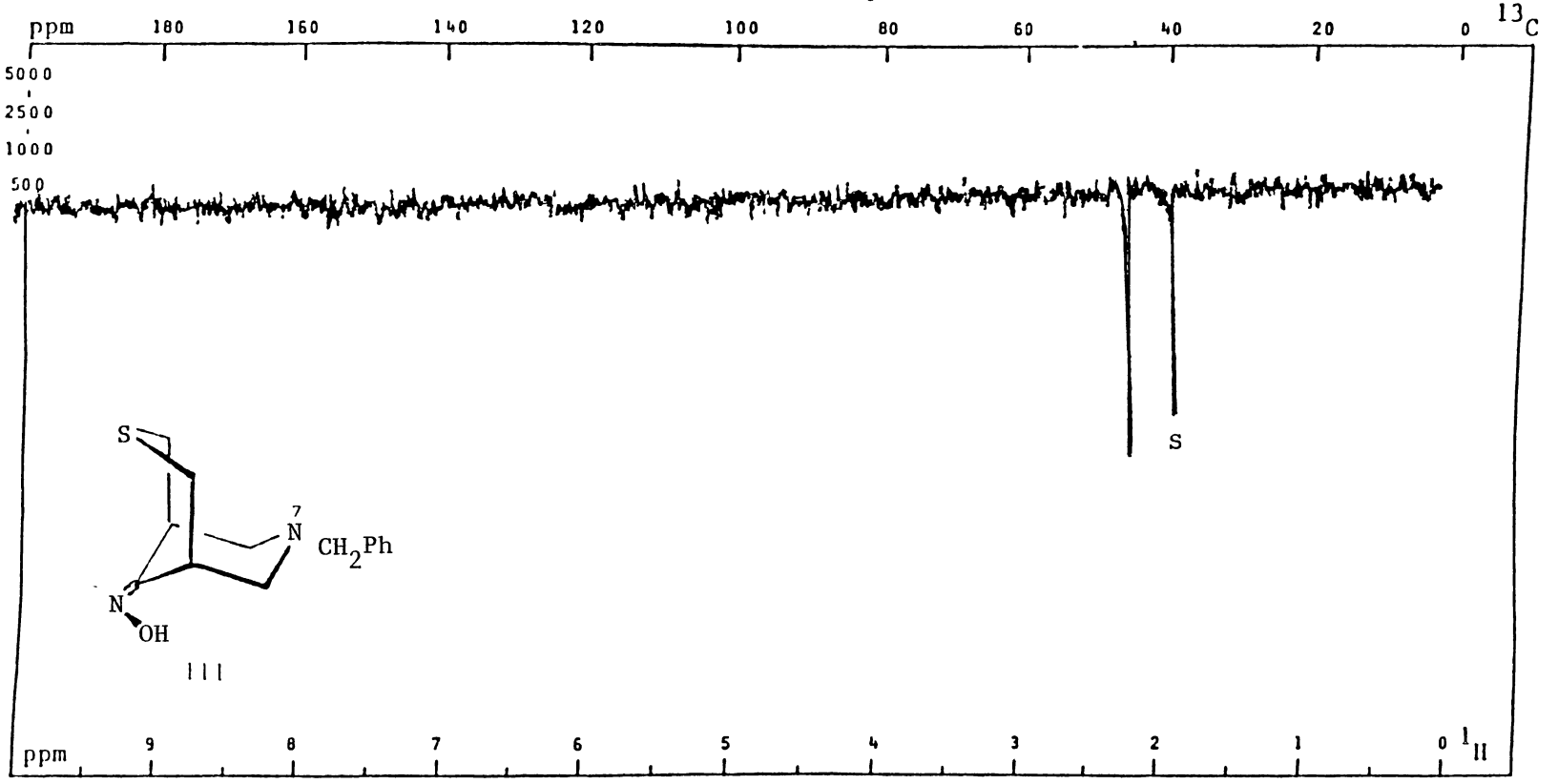


PFT x CW _ ; Solvent: $DCCl_3$; SF: 25.2 MHz; WC: 5000 Hz; T: RT °C; NT: 1000 .

Size: 8 K; PW/RF: 20.00 µs/dB; TO: 35101 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 4.00 s.

DC: Y, N ; Gated Off:A or D ; DO: 45316 Hz; RF(Power): 119 W/dB; NBW: Hz; LB: 1.00 Hz.

Plate XCIII. ^{15}N NMR Spectrum of 108



PFT x CW _ ; Solvent: $DCCl_3$; SF: 30.406 MHz; WC: 16000 Hz; T: amb °C; NT: 7316 .

Size: 32 K; PW/RF: 40.0 μs/dB; TO: -7000 Hz; FB: Hz; Lock: $DCCL_3$; D1,D5: 30.0 s.

DC: Y, N ; Gated Off: A or D ; DO: o Hz; RF(Power): W/dB; NBW: Hz; LB: 2.0 Hz.

Plate XCIV. IR Spectrum of 109a

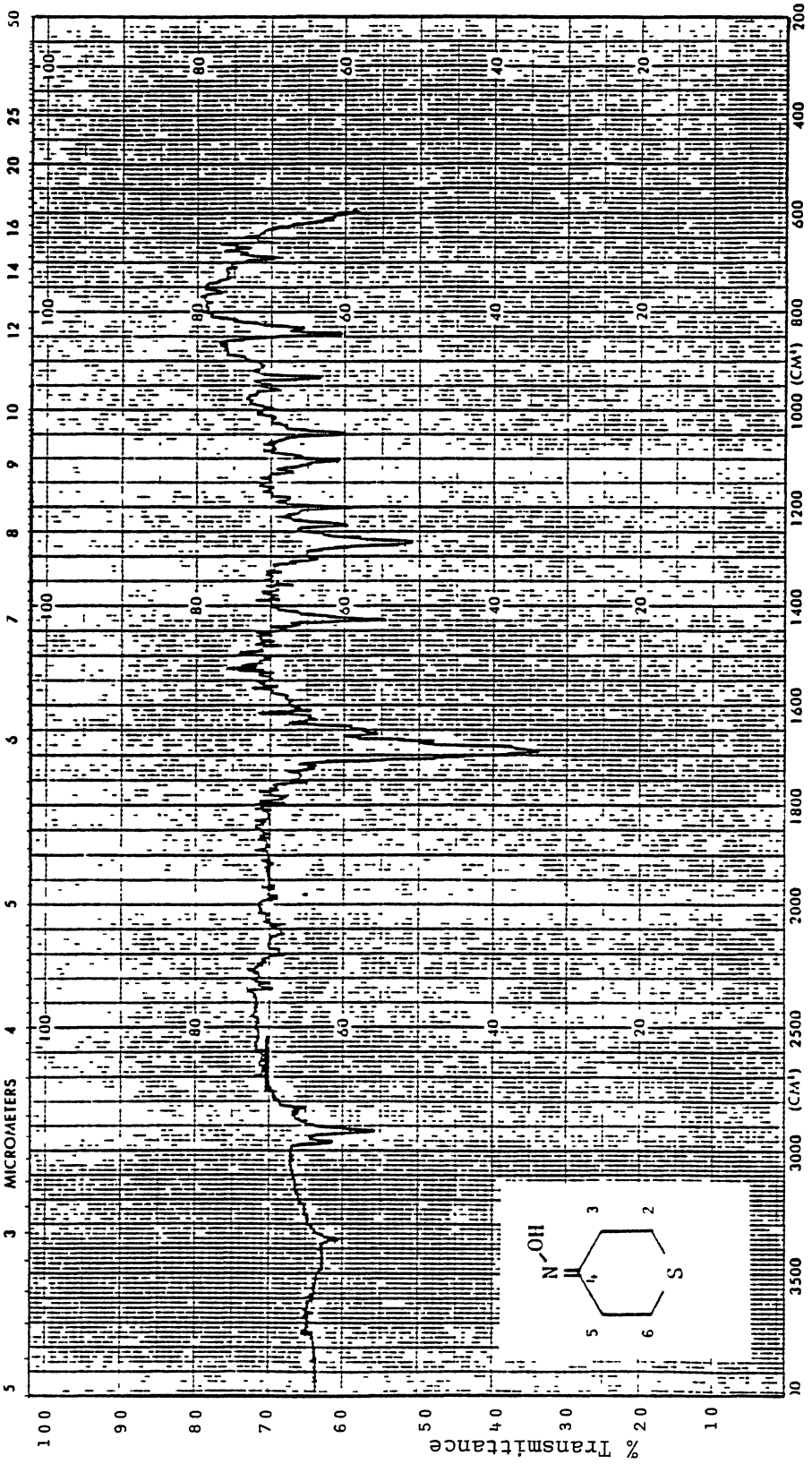
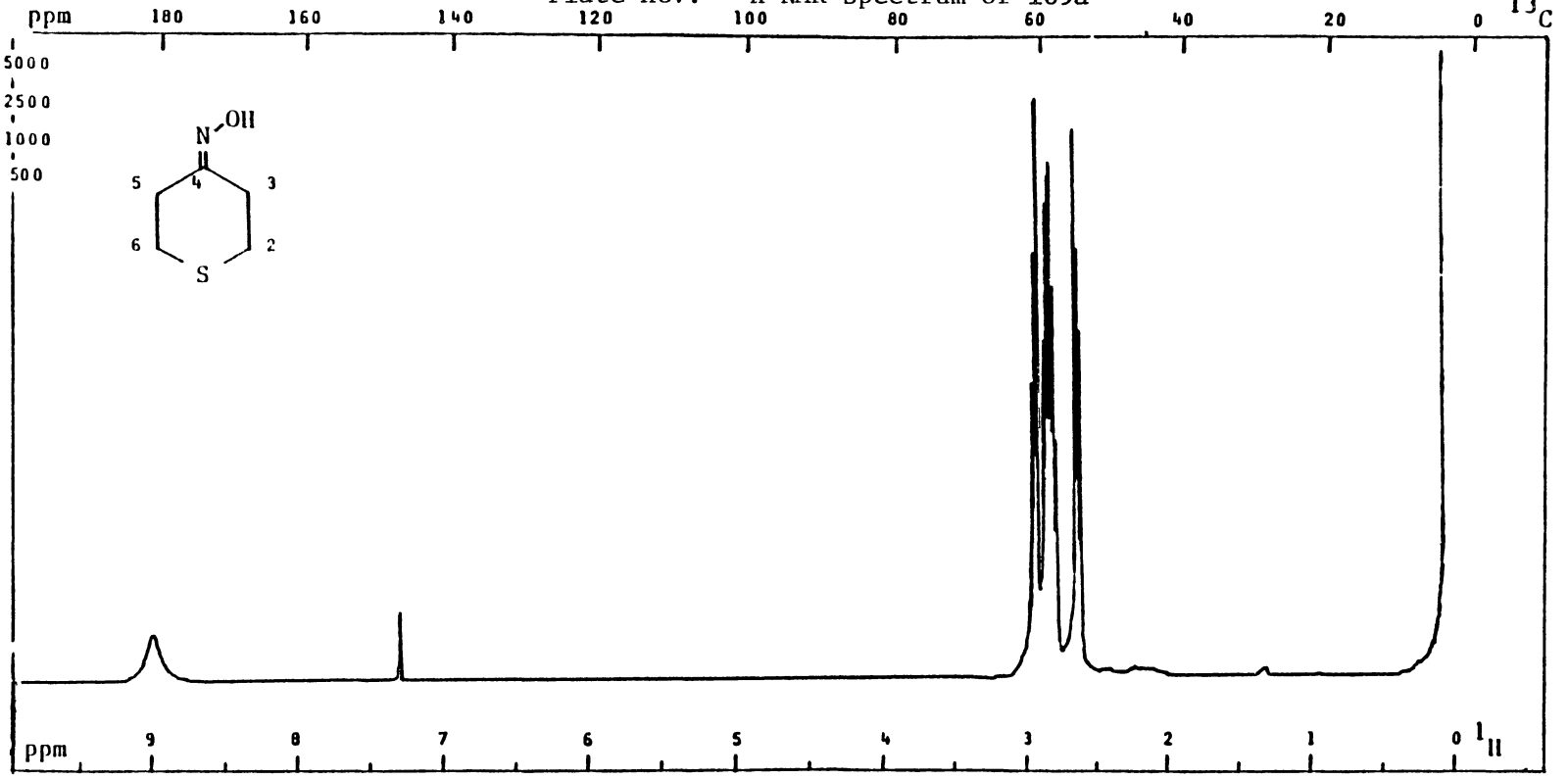


Plate XCV. ^{1}H NMR Spectrum of 109a

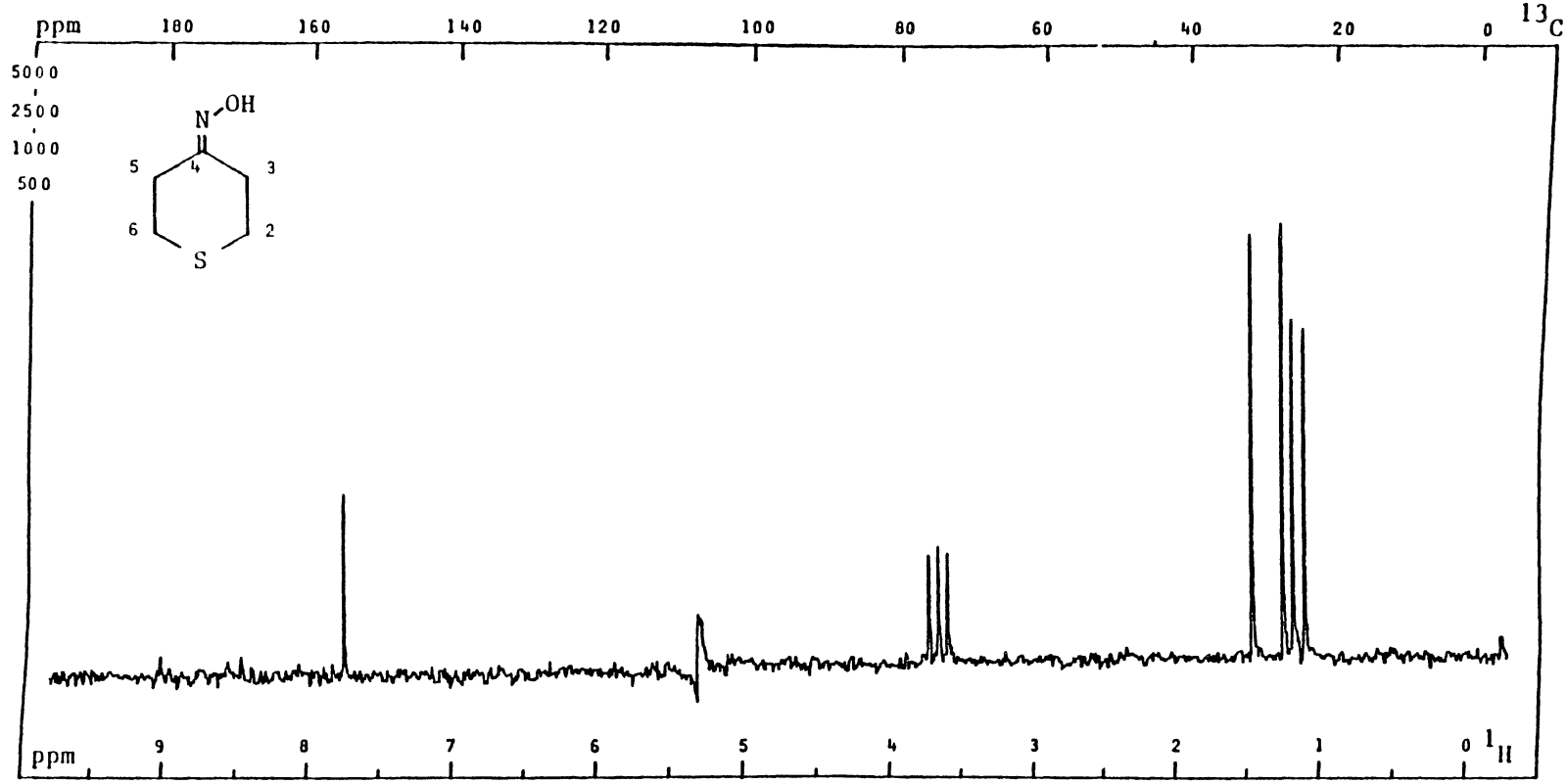


PFT x CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 3000 Hz; $T_{amb.}$ °C; NT: 4 .

Size: 16 K; PW/RF: 10.0 µs/dB; TO: 0 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 1 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: - Hz.

Plate XCVI. ^{13}C NMR Spectrum of 109a



PFTx_ CW _ ; Solvent: $DCCl_3$; SF: 25.20 MHz; WC: 5000 Hz; T:amb. °C; NT: 480 .

Size: 8 K; PW/RF: 20 μs/dB; TO: 35101 Hz; FB: Hz; Lock:$DCCl_3$;D1,D5: 5 s.

DC: Y, N ; Gated Off:A or D ; DO: 45316 Hz; RF(Power): 119 W/dB; NBW: Hz; LB:1.5 Hz.

Plate XCVII. IR Spectrum of **110a**

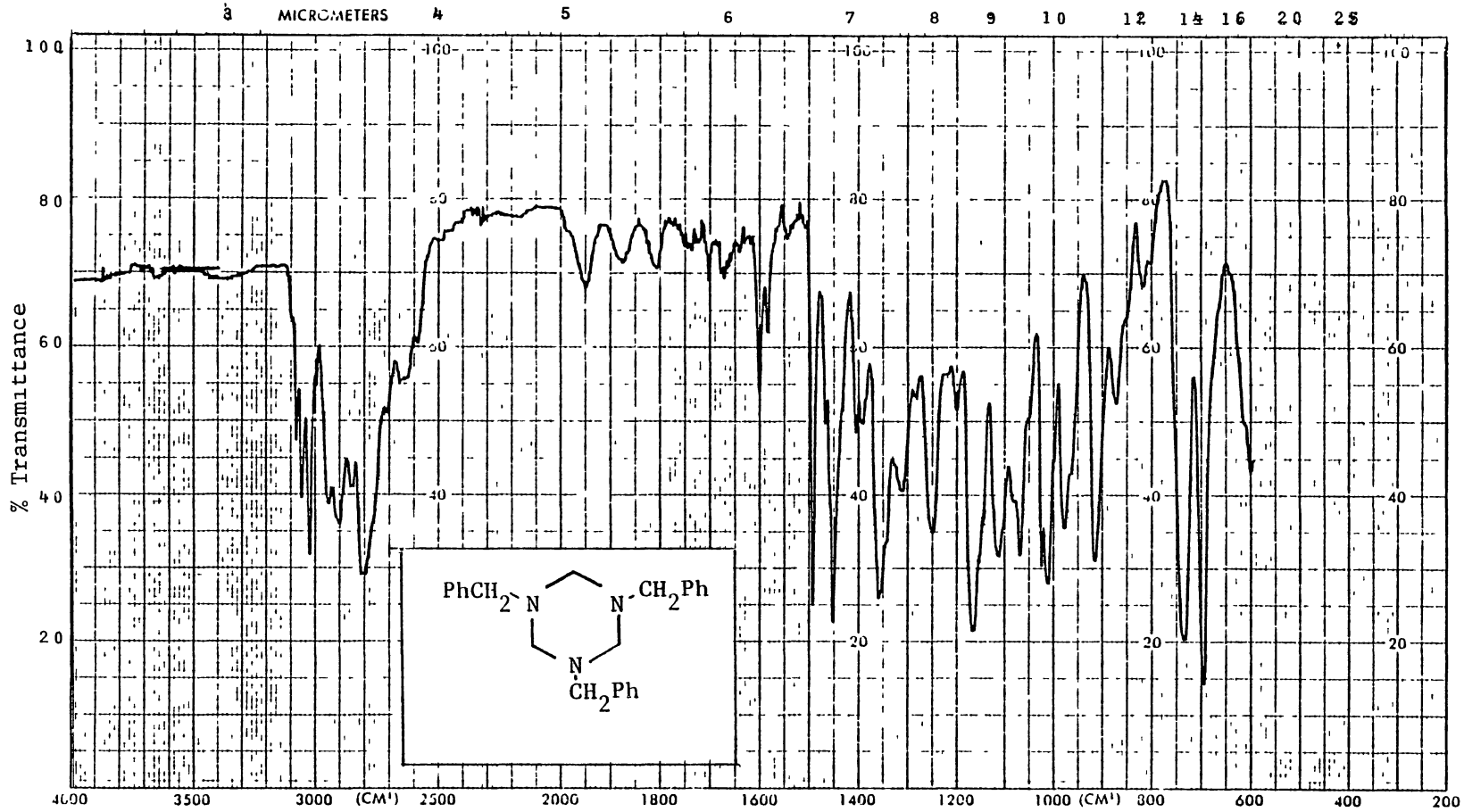
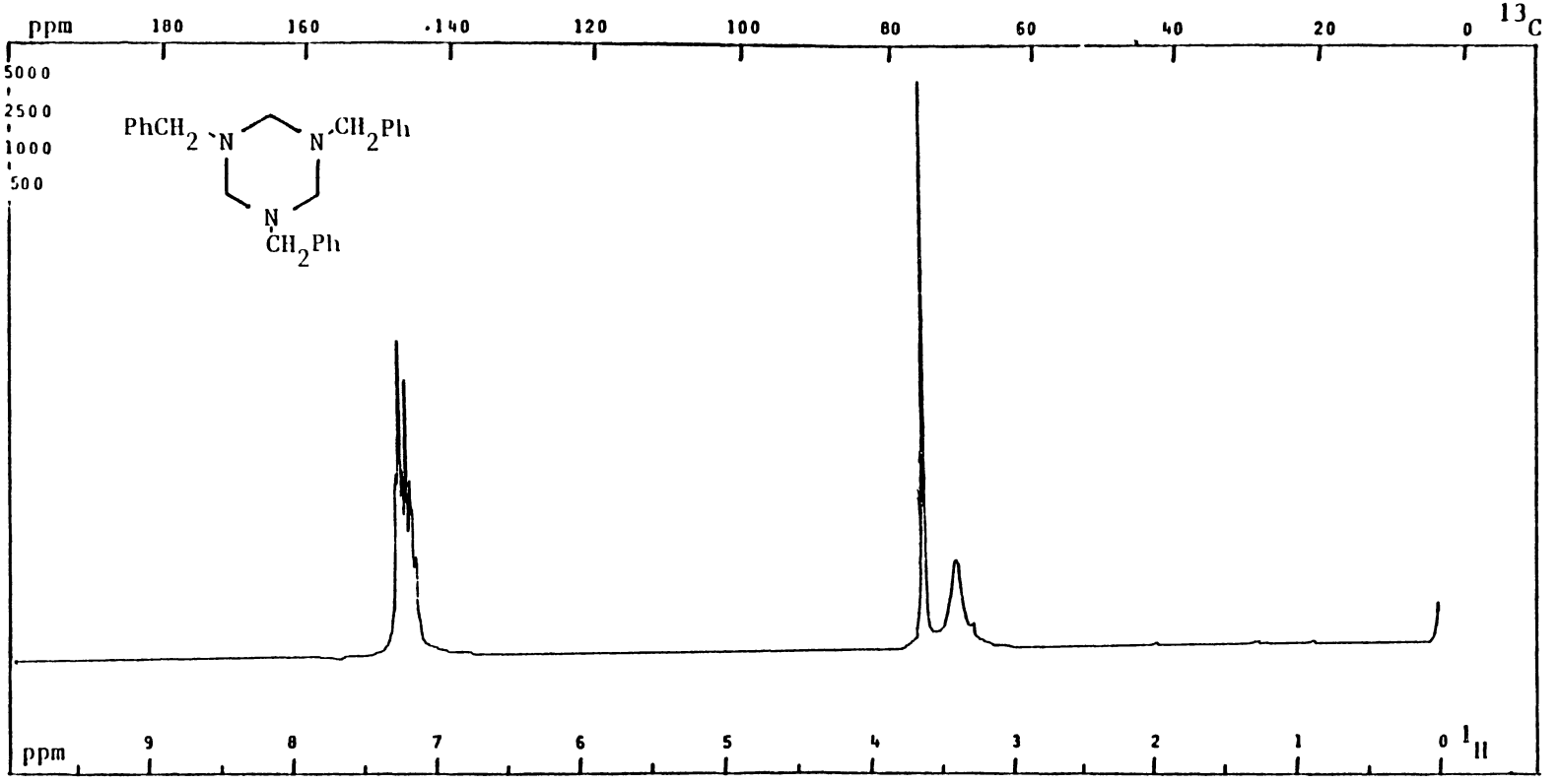


Plate XCVIII. ^{1}H NMR Spectrum of 110a

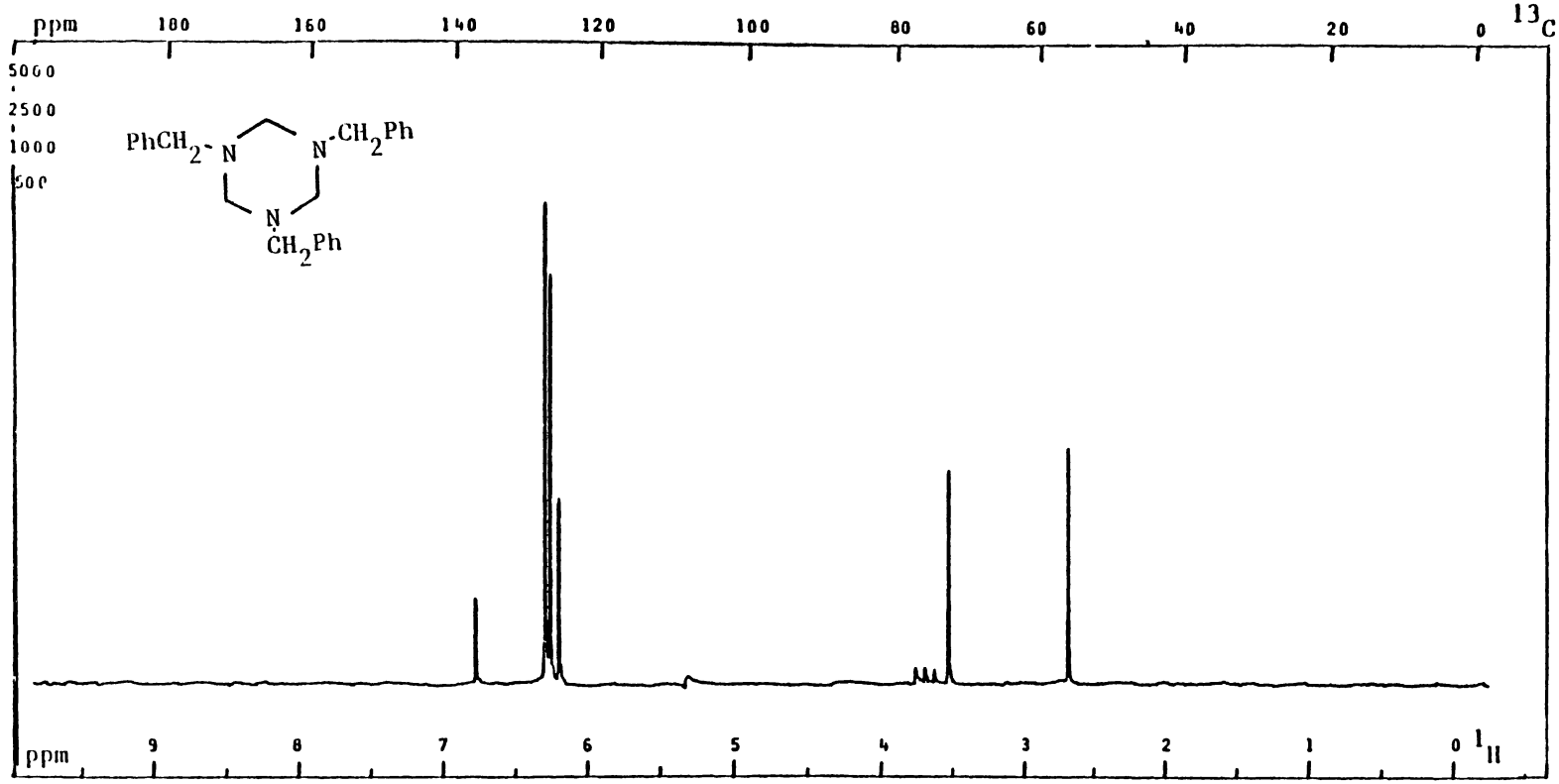


PFT x CW _ ; Solvent:$DCCl_3$; SF: 299.949 MHz; WC: 3000 Hz; T: amb. °C; NT: 4 .

Size: 16 K; PW/RF: 9 µs/dB; TO: 0 Hz; FB: Hz; Lock:$DCCl_3$; D1,D5: 1 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: - Hz.

Plate XCIX. ^{13}C NMR Spectrum of 110a

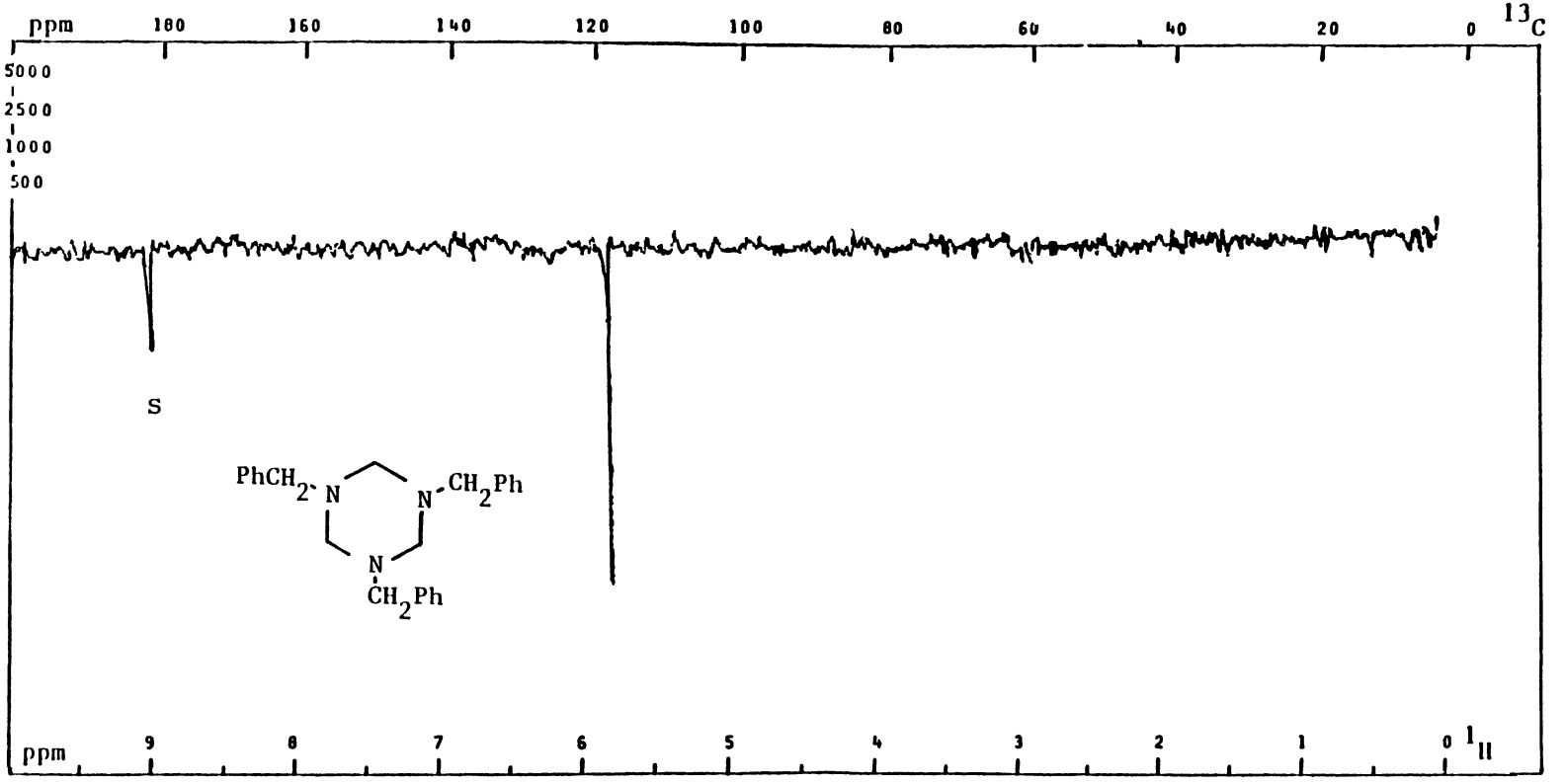


PFT $_x$ CW _ ; Solvent: $DCCl_3$; SF: 25.2 MHz; WC: 5000 Hz; T: amb. °C; NT: 800 .

Size: 8 K; PW/RF: 20 µs/dB; TO: 35101 Hz; FB: Hz; Lock: $DCCl_3$; D1,D5: 4 s.

DC: Y, N ; Gated Off: A or D ; DO: 44616 Hz; RF(Power): 119 W/dB; NBW: Hz; LB: 1.5 Hz.

Plate C. ^{15}N NMR Spectrum of 110a



PFT x CW _ ; Solvent: $DCCl_3$; SF: 30.406 MHz; WC: 6000 Hz; T: amb. °C; NT: 12000 .

Size: 12 K; PW/RF: 40 μs/dB; TO: -11600 Hz; FB: Hz; Lock:$DCCl_3$; D1,D5: 25 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: Hz; LB: 2.0 Hz.

BIBLIOGRAPHY

1. Agababyan, A. G.; Gevorgyan, G. A.; Mndzhoyan, O. L. Russ. Chem. Rev. **1982**, 51, 387-396.

2. AMA Department of Drugs "AMA Drug Evaluations", 4th Edition, Wiley, New York, 1980.

3. Andrisano, R.; Angeloni, A.S.; Gottarelli, G. Gazz. Chim. Ital. **1967**, 97, 1762-1769.

4. Aranda, G.; Bernassau, J. M.; Fetizon, M.; Hanna, I. J. Org. Chem. **1985**, 50, 1156-1161.

5. Arjunan, P.; Berlin, K. D.; Barnes, C. C.: Van der Helm, D. J. Org. Chem. **1981**, 46, 3196-3204.

6. Avenhaus, H.; Grohmann, H.; Z. Kreislaufforsch 1969, 58, 54-60; Biol. Abstr. **1971**, 52, 62487.

7. Azerbaev, I. N.; Omarov, T. T.; Al'mukhanova, K.; Baisalbaeva, S. A. J. Org. Chem. USSR (Engl. Transl.) **1976**, 12, 1213-1215; Zh. Org. Khim. **1976**, 12, 1207-1209.

8. a. Baky, S. H.; Kirsten, E. B. "Verapamil" in "Pharmacological and Biochemical Properties Of Drug Substances", Vol. 3, M. E. Goldberg (Ed.), American Pharmaceutical Association, Washington, D. C., 1981, pp. 226-261. b. Dean, R. R.; McDermott, D. J.; Smith, W. S. "Disopyramide" ibid. Vol. 2, 165-185. c. Lee, R. J.; Krasula, R. W.; Real, M.; Hoyt, H. J. "Bretylium Tosylate" ibid., Vol. 2, 148-164.

9. Baliah, V.; Jeyaraman, R. Ind. J. Chem. **1971**, 9, 1020-1021.

10. Baliah, V.; Usha, R. Ind. J. Chem. **1977**, 15B, 684-689.

11. Baliah, V.; Jeyaraman, R. Ind. J. Chem., **1977**, 15B, 796-797.

12. Baliah, V.; Mangalam, G. Ind. J. Chem. **1978**, 16B, 237-238.

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

14. Bailey, B. R.; Berlin, K. D.; Holt, E. M.; Scherlag, B. J.; Lazzara, R.; Brachmann, J.; Van der Helm, D.; Powell, P. R.; Panteleo, N. S., Reunitz, P. C. J. Med. Chem. **1984**, 27, 758-767.

15. Bailey, B. R.; Berlin, K. D.; Van der Helm, D.; Powell, P. R. Phosphorus and Sulfur **1984**, 21, 121-133.

16. Binnig, F.; Raschack, M.; Treiber, H.-J. U.S. Patent 3 962 449, 1976; Chem. Abstr. **1976**, 84, 150675x.

17. Binnig, F; Friedrich; L. Hofmann, H. P.; Kreiskott, H; Mueller, C.; Raschack, M. U.S. Patent 4 183 935, 1979; Chem. Abstr. 1979, 90, 121568h.

18. Blicke, F. F Org. React. **1942**, 1, 303-341.

19. Bohlmann, F.; Schumann, D.; Arndt, C. Tetrahedron Lett. **1965**, 31, 2705-2711.

20. Bohlmann, F.; Zeisberg, R. Chem. Ber. **1975**, 108, 1043-1051.

21. Breitman, E.; Haas, G.; Voelter, W. "Atlas of Carbon-13 NMR Data" Heyden and Sons, Philadelphia, Pennsylvania, 1979, Vol. 1, compound no. 311, Vol. 2., compound no. 1349.

22. Buchanon, G. L. in Topics in Carbocyclic Chemistry, Vol. 1, D. Lloyd, Ed.; Logos, London, **1969**, pp. 199.

23. Curran, A. C. W. U.S. Patent 3 829 427, 1974; Chem. Abstr. 1974, 81, 135998z.

24. Chung, E. K. "Principles of Cardiac Arrhythmias", 2nd Edition, Williams and Wilkins, Baltimore, Maryland, 1977, Chapters 9, 20.

25. Darnbrough, G.; Knowles, P.; O'Connor, S. P.; Tierney, F. J. Tetrahedron **1986**, 42, 2339-2344.

26. Diedreich, K. W.; Beeck, J.; Z. Kreislaufforsch, **1970**, 59, 736-743; Biol. Abstr. **1971**, 52, 56383.

27. Douglass, J. E.; Ratliff, T. B. J. Org. Chem. **1968**, 33, 355-359.

28. Eisenberg, M. S.; Bergner, L.; Hallstrom, A. P., Cummins, R.O. Scientific American **1986**, 254(5), 37-43.

29. Eliel, E. L.; Manoharan, M.; Hodgson, D. J.; Eggleston, D. S.; Jeyeraman, R. J. Org. Chem. **1982**, 47, 4353-4356.

30. Fanso-Free, S. N. Y.; Furst, G. T.; Srinivasan, P. R.; Lichter, R. L.; Nelson, R. B.; Panetta, J. A.; Gribble, G. W. J. Am. Chem. Soc. **1979**, 101, 1549-1553.

31. Fowler, N. O. (Ed.) "Cardiac Arrhythmias: Diagnosis and Treatment", Harper and Row, Hagarstown, Maryland, 1977. See several articles by contributors.

32. Galvez, E.; Arıas, M. S.; Bellanato, J.; Garcıa-Ramos, J. V.; Florencio, F.; Smith-Verdier, P.; Garcia-Blanco, S. J. Mol. Struct. **1985**, 127, 185-201.

33. Goncharov, A. V.; Kurkutova, E. N.; Zefirov, N. S.; Iluykhin, V. V.; Belov, N. V. Zh. Struct. Khim. **1975**, 16, 154-156; Chem. Abstr. **1975**, 82, 163636u.

34. Goncharov, A. V.; Kurkutova, E. N.; Zefirov, N. S.; Iluykhin, V. V.; Belov, N. V. Koor. Khim. **1976**, 2, 571-574; Chem. Abstr. **1976**, 82, 27566f.

35. Gray, G. A. Org. Magn. Reson. **1983**, 21, 111-118.

36. Graymore, J. J. Chem. Soc. **1932**, 1353-1357.

37. Haller, R. Arzneimittel-Forsch. **1965**, 15, 1327; Chem. Abstr. 1966, 64, 6629d.

38. Haller, R.; Unholzer, H. Arch. Pharm. **1971**, 304, 867-871.

39. Haller, R.; Unholzer, H. Arch. Pharm. **1972**, 305, 855-863.

40. Hankovsky, O. H.; Hideg, K.; Bodi, I.; Frank, L. J. Med. Chem. **1986**, 29, 1138-1152.

41. Hellman, H. Newer Methods Prep. Org. Chem. **1963**, 2, 277-302.

42. Heumann, A.; Kolshorn, H. Tetrahedron **1975**, 31, 1571-1575.

43. House, H. O.; Wickham, P. P.; Mueller, H. C. J. Am. Chem. Soc. **1962**, 84, 3139.

44. Huang-Mınlon, J. Am. Chem. Soc., **1946**, 68, 2487-2488.

45. Jennings, R. B.; Reimer, K. A. "The Fate of the Ischemıc Myocardial Cell" ın "Myocardial Infarctıon: New Perspectives in Dıagnosis and Management", E. Corday and H. J. C. Swan (Eds.), Williams and Wilkıns, Baltimore, Maryland, 1973, Chapter 2.

46. Jeyaraman, R.; Avila, S. Chem. Rev. **1981**, 81, 149-174.

47. Jeyaraman, R.; Jawaharsıngh, C. B.; Avila, S.; Ganapathy, K.; Eliel, E. L.; Manoharan, M.; Morris-Natschke, S. J. Heterocyclic Chem., **1982**, 19, 449-458.

48. Johnson, P. Y.; Berchtold, G. A. J. Org. Chem. **1970**, 35, 584-591.

49. Levina, O. I.; Kurkutova, E. N.; Potekhın, K. A. Cryst. Struct. Comm. **1982**, 11, 1915-1919.

50. Levina, O. I.; Potekhin, K. A.; Kurkutova, E. N. Cryst. Struct. Comm. **1982**, 11, 1909-1913.

51. Levina, O. I.; Potekhin, K. A.; Rau, V. G.; Struchkov, T. T. Cryst. Struct. Comm. **1982**, 11, 1073-1076.

52. Lucchesi, B. "Antiarrhythmic Drugs" in "Cardiovascular Pharmacology", M. J. Antonaccio (Ed.), Raven, New York, 1977, 269-335.

53. Margulies, E. (Ed.) "Myocardial Infarction and Cardiac Death", Academic, New York, 1983. See articles by several contributors.

54. Mastryukov, V. S.; Osina, E. L.; Dorofeeva, O. V.; Popik, M. V.; Vilkov, L. V.; Belikova, N. A. J. Mol. Struct. **1979**, 52, 211-224.

55. Mastryuov, 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, 1333-1337.

56. McEuen, J. M.; Nelson, R. P.; Lawton, R. G. J. Org. Chem. **1970**, 35, 690-696.

57. Mironov, G. S.; Farberov, M. I.; Orlova, I. M. Zh. Obshch. Khim. **1963**, 33, 1512-1517; Chem. Abstr. **1964**, 60, 5324h.

58. Mironov, G. S.; Farberov, M. I.; Timoshenko, G. N.; Bulgina, M. N.; Chinnikova, V.A. Khim. Prom. (Moscow) **1969**, 45, 727-729; Chem. Abstr. **1970**, 72, 31162v.

59. Miyano, S.; Sumoto, K.; Satoh, F.; Shima, K.; Hayashimatsu, M, Morita, M.; Aisaka, K.; Noguchi, T. J. Med. Chem. **1985**, 28, 714-717.

60. Nador, K.; Gabor, K.; Katalin, S.; Paroczai, M.; Karpati, E.; Szporny, L. U.S Patent 4 451 473, 1984; Chem. Abstr. **1983**, 99, 5654v.

61. Okhi, E.; Oida, S.; Ohashi, Y.; Yoshida, A.; Kamoshita, K.; Takagi, H. Chem. Pharm. Bull. **1974**, 2, 1014-1021; Chem. Abstr. **1974**, 81, 99241m. Belleau, B.; Gulini, U.; Gour-Salin, B. Can. J. Chem. **1985**, 63, 1268-1274.

62. Ossina, E. L.; Mastryukov, V. S.; Vilkov, L.V.; Belikova, N. A. Chem. Comm. **1976**, 12.

63. Panteleo, N. S.; van der Helm, D.; Ramarajan, K.; Bailey, B. R.; Berlin, K. D. J. Org. Chem. **1981**, 46, 4199-4204.

64. Pauling, Linus "The Nature of the Chemical Bond", 3rd Edition, Cornell University, Ithaca, New York, 1960, p. 257.

65. Peters, J. A. Synthesis, **1979**, 321.

66. Peters, J. A.; Remijnse, J. D.; van der Weile, A.; van Bekkum, H. Tetrahedron Lett. **1971**, 3065.

67. Peters, J. A.; van der Toorn, J. M.; van Bekkum, H. Tetrahedron **1974**, 30, 633-640.

68. Peters, J. A.; van der Toorn, J. M.; van Bekkum, H. Tetrahedron **1975**, 31, 2273-2281.

69. Peters, J. A.; van der Toorn, J. M.; van Bekkum, H. Tetrahedron **1977**, 33, 349-351.

70. Przybylska, M.; Barnes, W. H. Acta Cryst. **1953**, 6, 377-384.

71. Quast, H.; Muller, B. Chem. Ber. **1980**, 113, 2959-2975.

72. Quast, H.; Muller, B.; Peters, E.-M.; Peters, K.; von Schnering, H. G. Chem. Ber. **1983**, 115, 2872-2891.

73. Quast, H.; Muller, B.; Peters, E.-M.; Peters, K.; von Schnering, H. G. Chem. Ber. **1983**, 116, 424-437.

74. Raber, D. J.; Janks, C. M.; Johnston, M. D.; Raber, N. K. Tetrahedron Lett., **1980**, 21, 677-680.

75. Reynolds, D. D.; Cossar, B. C. J. Heterocyclic Chem. **1971**, 8, 605-610.

76. Rice, L. M.; Grogan, C. H. J. Org. Chem. **1958**, 23, 844-846.

77. Robertson, D. W.; Beedle, E. E.; Krushinski, J. H.; Polock, G. D.; Wilson, H.; Wyss, V. L. J. Med. Chem. **1985**, 28, 717-727.

78. Ruenitz, P. C.; Mokler, C. M. J. Med. Chem. **1977**, 20, 1668-1671.

79. Ruenitz, P. C.; Mokler, C. M. J. Med. Chem. **1979**, 22, 1142-1145.

80. Ruenitz, P. C.; Smissman, E. E. J. Org. Chem. **1977**, 42, 937-940.

81. Sadykov, A. S., Kamayev, F. G.; Korenevsky, V. A.; Leont'ev, V. B.; Ustynyuk, Y. A. Org. Magn. Reson. **1972**, 4, 837-846.

82. Sanders, H. J. Chem. Eng. News **1982**, 60(28), 26-38.

83. Schilt, A. A. "Perchloric Acid and Perchlorates", Smith Chemical, Columbus, Ohio, 1979, Chapter 3.

84. Scherlag, B. J. Veterans Administration Medical Center, Oklahoma City, Oklahoma, personal communication.

85. Scherlag, B. J.; El-Sherif, N. Hope, R.; Lazzara, R. Circ. Res. **1974**, 35, 372-383.

86. Scherlag, B. J.; Kabell, G.; Brachmann, J.; Harrison, L.; Lazzara, R. Am. J. of Cardiology **1979**, 51, 207-213.

87. Schneider, W.; Gotz, H. Arch. Pharm. **1961**, 294, 506-518.

88. Siebner, H. Deut. Med. Wochenschr. **1970**, 95, 2203; Biol. Abstr. 1971, 52, 5151.

89. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. "Spectrometric Identification of Organic Compounds", 4th Edition, Wiley and Sons, New York, 1981, p. 270.

90. Skolik, J.; Wiewiorowski, M.; Krueger, P. J. J. Mol. Struct. **1970**, 5, 461-476.

91. Smissman, E. E.; Ruenitz, P. C.; Weis, J. A. J. Org. Chem. **1975**, 40, 251-252.

92. Smissman, E. E.; Ruenitz, P. C. J. Heterocyclic Chem. **1976**, 13, 1111-1113.

93. Smissman, E. E.; Ruenitz, P. C. J. Org. Chem. **1976**, 41, 1593-1597.

94. Smith-Verdier, P.; Florencio, F.; Garcia-Blanco, S. Acta Cryst. **1983**, 39C, 101-103.

95. Speckamp, W. N.; Dijkink, J.; Dekkers, A. W. J. P.; Huisman, H. O. Tetrahedron **1971**, 27, 3143-3156.

96. Stetter, H.; Merten, R. Chem. Ber. **1957**, 90, 869-875.

97. Stetter, H.; Schafer, J.; Dieminger, K. Chem. Ber. **1959**, 91, 598-604.

98. Stout, M.; Matier, W. L.; Barcelon-Yang, C.; Reynolds, R. D.; Brown, B. S. J. Med. Chem. **1983**, 26, 808-813.

99. Stout, M.; Matier, W. L.; Barcelon-Yang, C.; Reynolds, R. D.; Brown, B. S. J. Med. Chem. **1984**, 27, 1347-1350.

100. Stout, M.; Matier, W. L.; Barcelon-Yang, C.; Reynolds, R. D.; Brown, B. S. J. Med. Chem. **1985**, 28, 295-298.

101. Subramanian, P. K.; Ramalingam, K.; Satyamurthy, N.; Berlin, K. D. J. Org. Chem. **1981**, 46, 4376-4383.

102. Takeuchi, Y,; Schrieber, P.; Takada, K. J. Chem. Soc., Chem. Comm. **1980**, 403.

103. Tanz, R. A. Ann. Rep. Med. Chem., 1965, C. A. Cain (Ed.), Academic, New York, 1966, pp. 85-91.

104. Thomis, J.; Tenthouy, P. Ann. Rep. Med. Chem., Vol. 18, H. J. Hess (Ed.), Academic, New York, 1983, pp. 99-108.

105. Thompson, B. B. J. Pharm. Sci. **1968**, 57, 715-733.

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

107. 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., in press (1986).

108. Thompson, M. D.; Smith, G. S.; Berlin, K. D. Org. Prep. Proc. Int., in press (1986).

109. Thompson, M. D.; Holt, E. M.; Berlin, K. D. J. Org. Chem. **1985**, 50 2580-2581.

110. Tramontini, M. Synthesis, **1973**, 703-775.

111. Wiewiorski, M. Edwards, O. E.; Bratek-Wiewiorowska, M. D. Can. J. Chem., **1967**, 45, 1447-1457.

112. Wink, M.; Hartmann, T.; Witte, L. Planta Med., **1979**, 18, 31-39.

113. Zefirov, N. S.; Rogozina, S. V. J. Chem. Soc., Chem. Commun. **1974**, 261.

114. Zefirov, N. S.; Rogozina, S. V. Russ. Chem. Rev. **1973**, 42, 190-198.

115. Zefirov, N. S. Russ. Chem. Rev. **1975**, 44, 196-211.

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