SYNTHESIS AND CONFORMATIONAL ANALYSIS OF SELECTED 7-AZA-3-THIABICYCLO[3.3.1]NONANES AND DERIVATIVES

By

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AND DERIVATIVES

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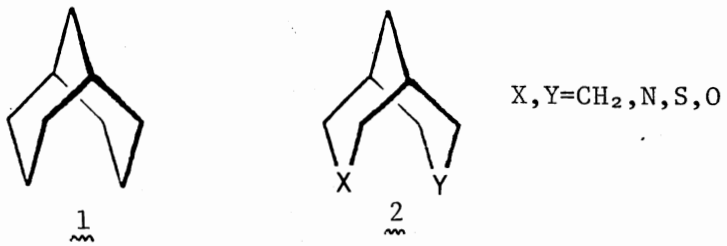
CHAPTER I

HISTORICAL

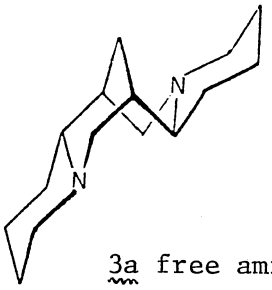
The interest in bicyclo[3.3.1]nonane (1) and its heterocyclic analogs 2 arises from both theoretical and biological points of view. The basic structure is unique in that it can exist in either a chair-chair (1-CC), chair-boat (1-CB), or boat-boat (1-BB) conformation. With various substituents, any of these conformations can be obtained.[42,43] Certain heterocyclic systems 2 where X = Y = N are



1 2

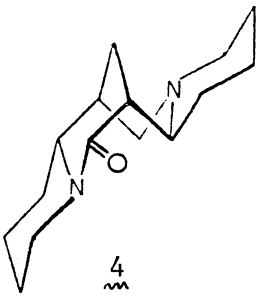
1CC 1CB 1BB

biologically important possibly due to a structural similarity to the natural occurring lupine alkaloids, sparteine (3a) and aphylline (4).



3a free amine

3b $HClO_4$ salt



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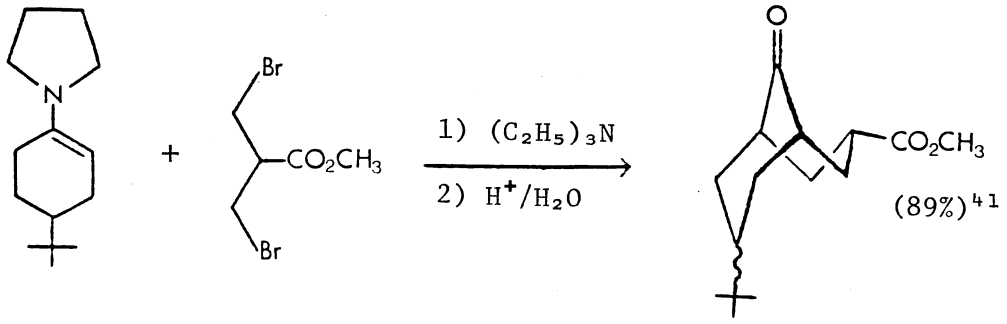
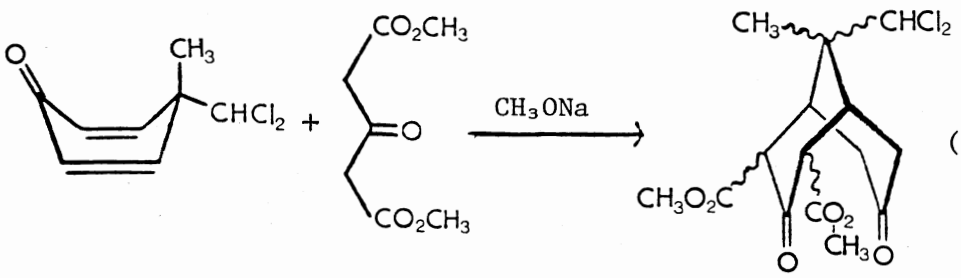
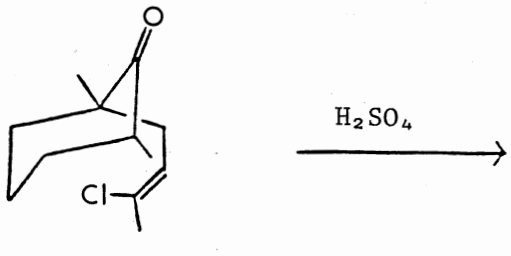
Initially, the discussion will focus on the synthesis of some of the various bicyclo[3.3.1]nonanes and heterocyclic analogs followed by a survey of the conformational studies performed and the biological aspects of selected compounds. The syntheses of the carbocyclic systems have been reviewed several times[15,41,66] with the most recent being by Peters.[41] A variety of starting materials such as cyclohexane and cyclooctane derivatives can be employed in the syntheses of bicyclo[3.3.1]nonanes. Commercially available bicyclo[3.3.1]nonanes and other bicyclic systems have also been used as starting materials.[41] Numerous examples starting from cyclohexane derivatives have been reported. The reactions illustrated are representative methods and generally proceed in fair to good yields.[41]



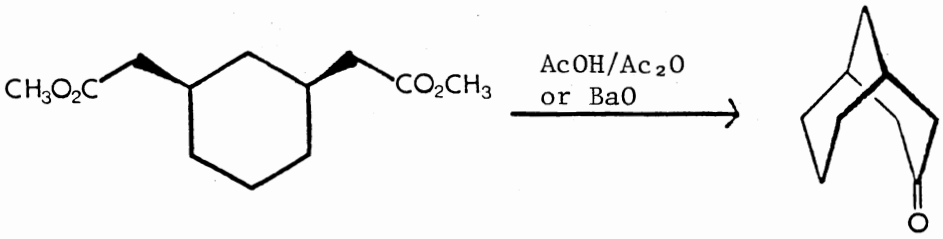
(89%)[41]



(53%)[41]

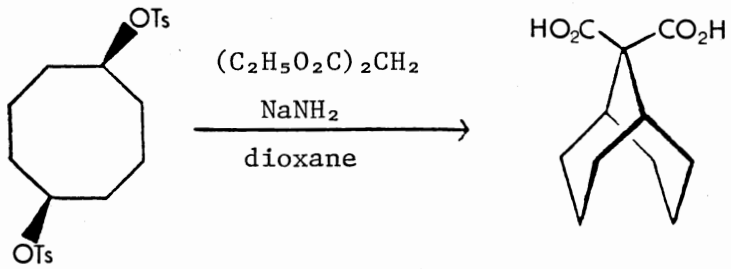


(93%)[41]

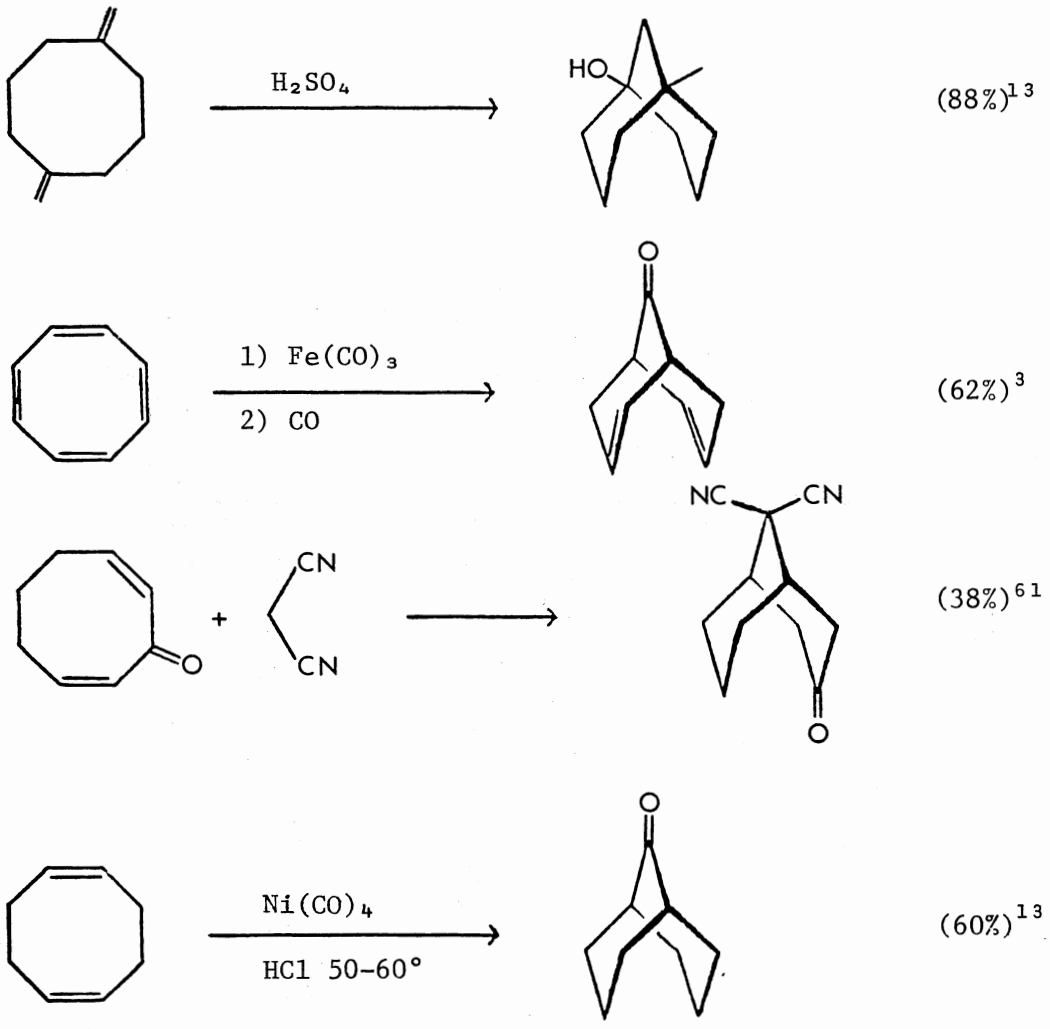


(23%)[41]

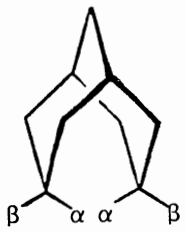
Syntheses beginning from cyclooctane derivatives involve the bridging of the ring in a 1,5-orientation with a single carbon. Compounds commonly used are cyclooctadienes, cyclooctatetraene, or cyclooctanes which have good leaving groups in the 1,5-positions. Examples of syntheses starting from each of the above types of starting materials are shown.[13,41]



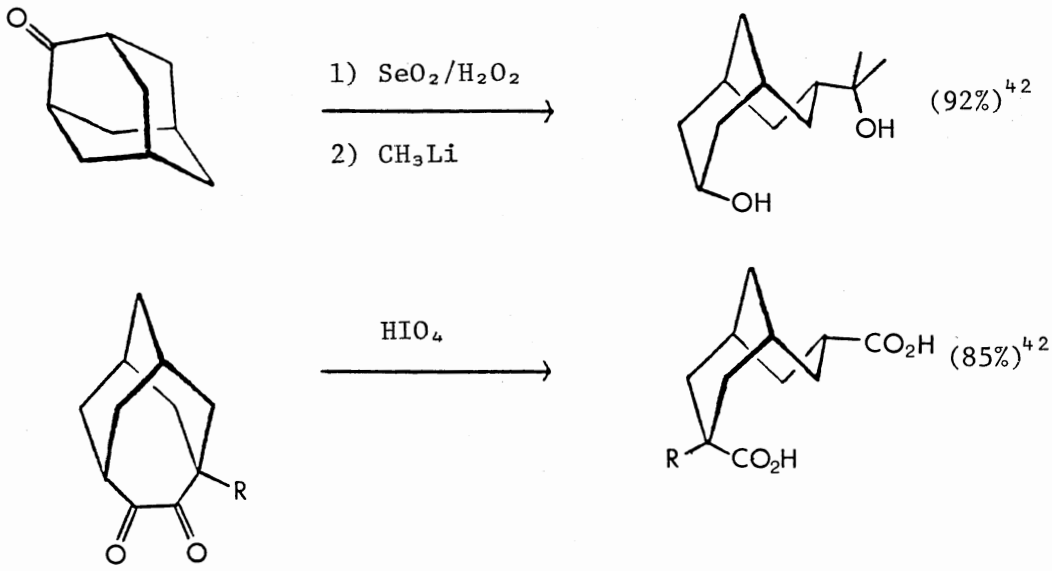
(50%)[61]



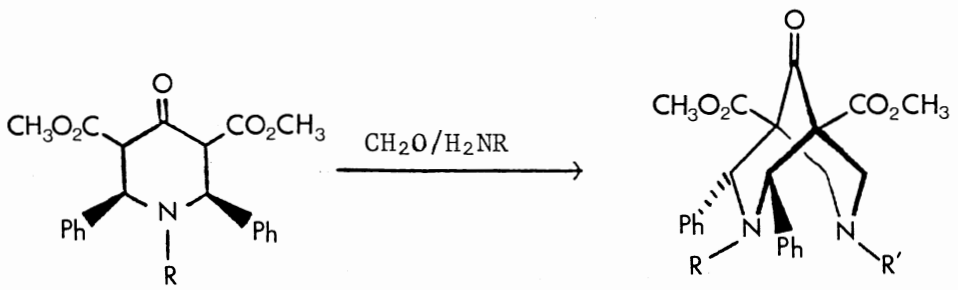
Adamantane derivatives can undergo ring cleavage reactions to give bicyclo[3.3.1]nonanes.[15,66] In some cases, the cleavage can be used to achieve stereoselectivity with one isomer favored over another. This has generally involved the placement of substituents in equatorial or axial arrangements at the 3,7-positions. These positions are generally referred to as α and β in 5. Syntheses of analogs of 5, where substituents are exclusively in the α positions, have been reported,[41,42,43] and the conformational consequences have



been studied. Examples of two ring cleavages are shown.

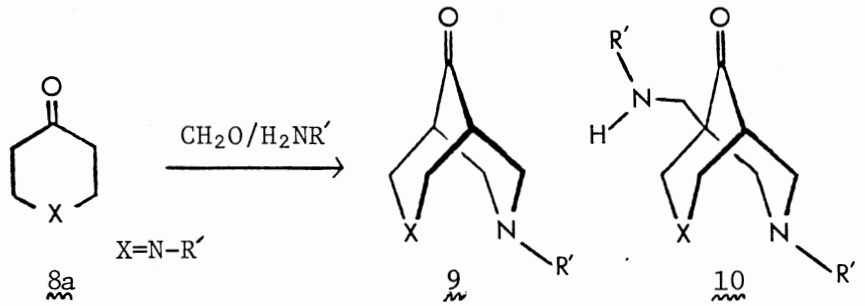


Syntheses and conformational analyses of heterobicyclo[3.3.1]-nonanes have recently been reviewed by Jeyaraman and co-workers.[28] The 3-aza- and 3-aza-7-hetero-bicyclo[3.3.1]nonanes can be prepared easily by way of the Mannich reaction. The first report in the literature was by Mannich and co-workers in 1930.[36] Piperidone 6 reacted with formaldehyde and an amine to give bispidine 7.



6 7

The general method found in the literature to prepare the 3- or 7-aza systems involved the reaction of a cyclic ketone 8a with an excess of formaldehyde and a primary amine in an alcohol solvent.

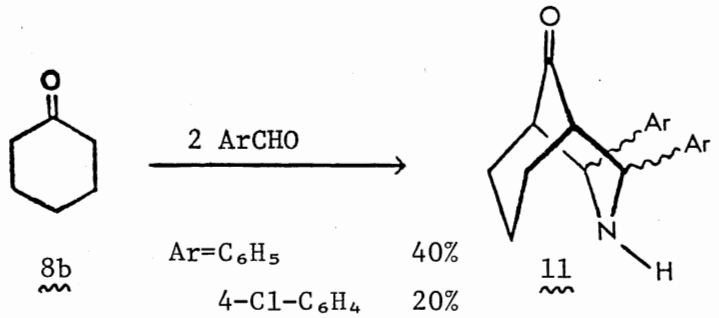


8a 9 10

Douglas and co-workers[16] were the first to synthesize 9 (X = N-CH_3 and R' = CH_3) by this method in moderate yields. This reaction was later studied by Smissman and co-workers[56] who found that the formation of 10 was competitive with the formation of 9. There are a large number of 3-aza- and 3,7-diazabicyclo[3.3.1]nonanes that have been obtained by this method in the literature and which differ only in the identity of the R group.[50,51]

The use of substituted ketones and aldehydes, other than formaldehyde, has led to ring substituted products. Aromatic aldehydes undergo condensation with ammonium acetate and cyclohexanone to give 2,4-

diaryl-3-azabicyclo[3.3.1]nonan-9-one 11.[28] Ketones examined other



8b 11

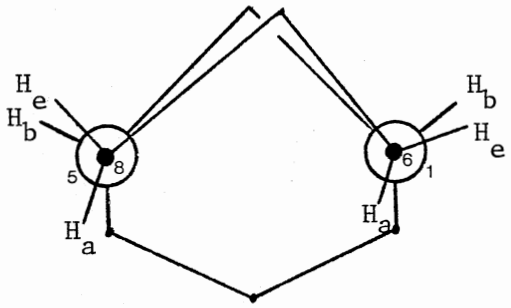
than cyclohexanone, include cis-2,6-diphenyl-4-piperidone,[10] cis-2,6-diphenyltetrahydrothiopyran-4-one,[10] cis-2,6-diphenyltetrahydrothiopyran-4-one,[10], cis-2,6-diphenylcyclohexanone,[11] cis-2,6-diphenyltetrahydropyran-4-one,[5] tetrahydrothiopyran-4-one,[7] and tetrahydropyran-4-one.[30]

The conformations of bicyclo[3.3.1]nonane (1) and its derivatives have been studied by a number of methods such as X-ray diffraction, dipole moment measurements, IR, ^{1}H DNMR and ^{13}C DNMR spectroscopy.[28,41,19,53,68] Bicyclo[3.3.1]nonane (1) can exist in three conformations, namely a 1-CC, 1-CB, or 1-BB as cited previously. In each of the conformations, there are non-bonded interactions that

1-CC 1-CB 1-BB

produce internal strain. The chair-chair (1-CC) conformer exhibits a repulsive interaction between the two endo hydrogens on C(3) and

C(7) as illustrated (1-CC). This repulsion has the effect of increasing the distance between C(3) and C(7) with concommitant ring flattening. Consequently, these terminal carbons are closer to the transition state for conversion of either ring to a boat conformation. The chair-boat conformer 1-CB has a repulsive interaction between H(3) and H(9) which destabilizes the boat ring. There is also an eclipsing of hydrogens in the boat ring of the molecule. Conformer 1-CC minimizes eclipsing while 1-CB has interaction between H_e and H_b and between H_a and C(6,8) as shown in the Newman drawing 12. The net



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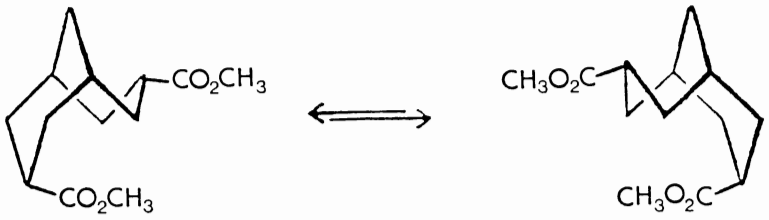
result of these interactions is the significant lowering of the energy barrier for the 1-CC ⇋ 1-CB which is estimated to be 2.7-3.7 kcal/mole in comparison to the 5-6 kcal/moles associated with the chair ⇋ boat interconversion of cyclohexane.[37,66,68] In solution, ^{1}H NMR analysis of 12 indicates that the chair-chair conformation 1-CC predominates[62] as two flattened chairs.

Substitution of the ring at the endo 3,7-positions with large groups can introduce steric factors which require the molecule to be in a conformation other than a chair-chair. This is illustrated by the diester 13 which has been shown to exist as two rapidly interconverting chair-boat conformers by ^{1}H NMR analysis.[43] This observation



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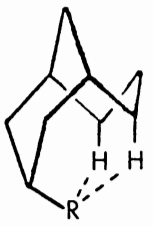
is not unexpected since a chair-chair conformation would require the ester functions to occupy nearly the same space. When the substituents are sufficiently large, there is the added steric factor of a 1,3-diaxial interaction between the 3- or 7-endo substituents and the opposite ring as in 14. The result can be that the only possible conformer is the boat-boat (BB) form as is the case with 15.[43] The



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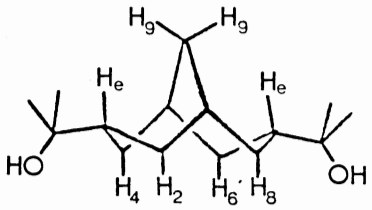
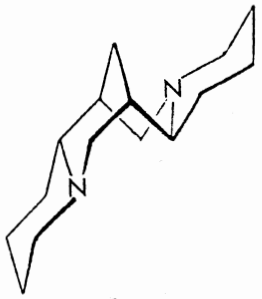


15

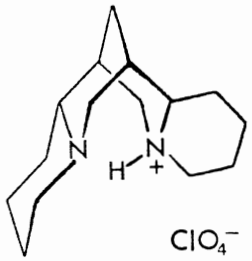
boat-boat conformation has the maximum amount of eclipsing of ring hydrogens. This can be relieved by a twisting of the molecule which in turn results in interaction between H(2) and H(6) or H(4) and H(8).[43]

The presence of heteroatoms in the 3,7-positions can introduce several additional factors which can influence the conformation of the two rings. These include (1) hydrogen bonding, (2) lone pair interactions, or (3) ring distortion due to long C-X bonds. The natural-occurring alkaloid, sparteine (3a), has been shown by careful

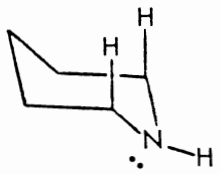
IR analysis and labeling studies to have a chair-boat conformation



3a



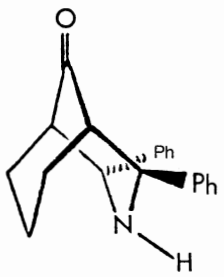
3b



16

for the central two rings.[63] This was evident from the presence of Bohlmann bands in the C-H stretching region. Bohlmann bands are due to the interaction of the p-electrons of nitrogen with the antiperiplanar C-H bonds in the piperidine ring[23] as illustrated in 16. In contrast, the monoperchlorate salt 3b has a chair-chair conformation about the central rings. The change of conformation in the conversion of 3a to 3b has been attributed to hydrogen bonding between the hydrogen of protonation and the two nitrogens in 3b thereby holding each ring in a chair.[55]

Different stereochemical forms have been isolated in the solid state for 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones. When the diphenyl ketone was recrystallized from a nonpolar solvent, conformer 17 was obtained. If a polar solvent was used, the configuration about nitrogen was inverted to give 18.[8,9]



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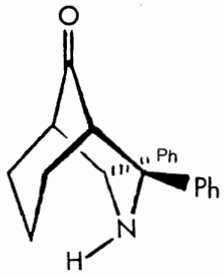

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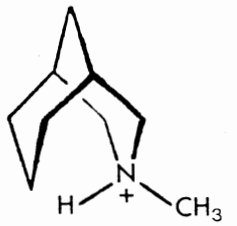
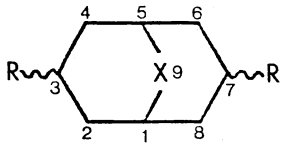


19a HCl salt
b HI salt

The conformations of salts of 3-methyl-3-azabicyclo[3.3.1]nonane 19a,b have been found to depend upon the counter ion present as evidenced via ^{1}H NMR analysis.[34] The salt 19a was found to exist in an equilibrium mixture involving a chair-chair ⇋ chair-boat (5:1). The hydroiodide 19b on the other hand was shown to exist exclusively in a chair-boat conformation.

^{13}C NMR spectroscopy has been a useful tool for conformational analysis.[18,32,44,49,65] Peters and co-workers[44] tabulated the ^{13}C chemical shifts for a number of 3- and 7-substituted bicyclo[3.3.1]-nonanes 20a and the corresponding 9-keto compounds 20b. After correcting for substituent effects, it was found that the chemical



20a X=CH_2
20b X=CO

shifts for corresponding carbons within a series of specific conformations were in close agreement (Table I, II).[44]

Dynamic ^{13}C NMR experiments carried out on 21[59] revealed that near -60°C the carbon singlet for the $\underline{CH}_2$ divided into two peaks of equal intensity. This was explained in terms of a single A ⇋ B

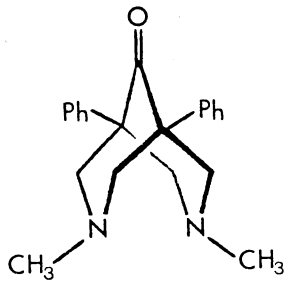


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TABLE I

AVERAGE ^{13}C CHEMICAL SHIFTS OF BICYCLO[3.3.1]NONANES 20a[44]

Conformation	^{13}C Chemical Shift (ppm)					
	C(1,5)	C(2,4)	C(3)	C(6,8)	C(7)	C(9)
chair-chair	28.1	31.5	27.3	31.5	22.3	34.4
chair-boat[A]	25.9	26.7	19.0	33.3	16.4	28.6
boat-boat	26.3	31.4	20.7	31.4	20.7	23.7

[A]C(2,4) and C(3) are assigned to the boat portion.

TABLE II

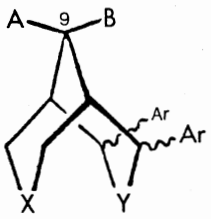
AVERAGE ^{13}C CHEMICAL SHIFTS OF BICYCLO[3.3.1]NONAN-9-ONES 20b[44]

Conformation	^{13}C Chemical Shift (ppm)					
	C(1,5)	C(2,4)	C(3)	C(6,8)	C(7)	C(9)
chair-chair	46.0	34.2	21.0	34.2	21.0	221.4
chair-boat[A]	44.0	29.9	20.6	34.7	15.7	220.6
boat-boat	43.3	33.5	21.6	33.5	21.6	224.7

[A]C(2,4) and C(3) are assigned to the boat portion.

exchange system with a $\Delta G^{\ddagger}$ of 9.7 kcal/mole at -63°C. The observation that the C(1,5) signal remained a sharp singlet throughout the experiment implied the "freezing out" of components of a rapid CB ⇋ BC equilibrium.

A large amount of ^{13}C NMR spectral data has been tabulated for a series of 2,4-diaryl-3,7-diheterobicyclo[3.3.1]nonanes 22, and 2,4-diaryl-3-azabicyclo[3.3.1]nonanes 23, and derivatives.[29] It was found

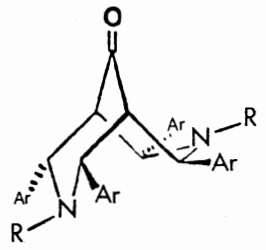


22 X=S Y=NH,NCH_3
A,B= =O
A=H,OH;B=OH,H

23 X=CH_2 Y=NH,NCH_3
A,B= =O
A=H,OH;B=OH,H

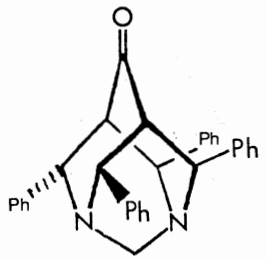
that the configuration at C(9) could be determined easily from the ^{13}C NMR spectra. It was observed that the β $\underline{CH_2}$'s in the ring in which the OH was axial experienced a shielding effect of about 7.5 ppm.

Single crystal X-ray diffraction studies of several bicyclo-[3.3.1]nonane derivatives have been performed.[2,17,27,46,47] The results of the studies revealed a variety of conformations. The 2,4,6,8-tetraaryl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-ones 24 were found to be in chair-boat conformations with all of the aryl groups in equatorial or pseudo equatorial positions. Interestingly it was proven possible to lock groups in a 1,3-diaxial arrangement. For example, 1,3-diazaadamantane 25, which contains two phenyl groups in an unfavorable 1,3-diaxial arrangement, has been prepared by treatment of the amine 26 with formaldehyde.[47]



24a Ar=4-$CH_3C_6H_4$-, R=CH_3

24b Ar=3,5-$(CH_3)_2C_6H_3$-, R=H



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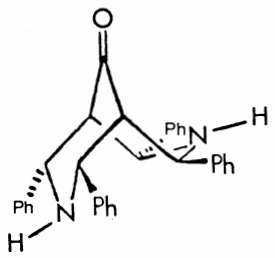

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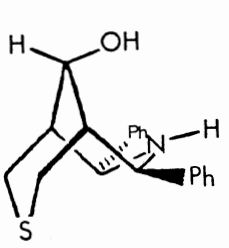
The X-ray analysis of 3-thia-7-aza-6,8-diphenylbicyclo[3.3.1]-nonan-9-ol (27) revealed the piperidine ring to be in a boat conformation while the thiane ring was in a chair form.[17] In contrast, the 6,8-bis(2-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (28)[2] and 6,8-diphenyl-2,4-bis(4-chlorophenyl)-3-azabicyclo[3.3.1]-nonan-9-one (29)[47] were found to have the piperidone rings in chair conformations. The oxygen containing ring of 28 was also found to be in a chair form while in 29 the cyclohexanone ring was in a boat conformation. It should be pointed out that all of these materials 22-29 were prepared by synthetic routes which involved a Mannich type of reaction with NH_4OAc and an aryl aldehyde with the appropriate



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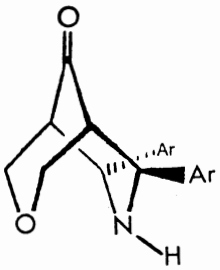
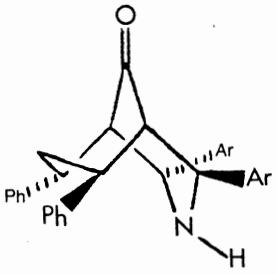


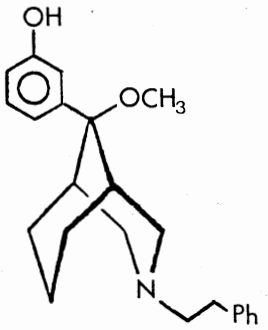
28 Ar=4-Cl-C_6H_4



29

ketone. This has, in all reported cases using 4-thia or 4-aza ketones, led to a nitrogen-containing ring which was in a boat conformation.[39,40,41,42]

The potential antiarrhythmic and analgesic properties of various bicyclo[3.3.1]nonane derivatives have been known for some time.[28] The activity is dependent upon the substituents which are present in the molecule. For example, 30 was found to be more than 400 times as active as 31 in terms of analgesic potency.[39] In comparison to morphine hydrochloride, 30 was found to be about 1600 as potent.[39]



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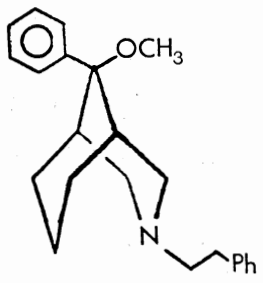

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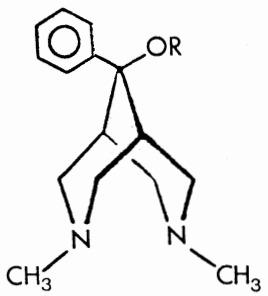


32

However, the acute toxicity (LD_{50}) is about 6.5 times that of morphine hydrochloride. Nevertheless, the high degree of activity gives 30 a therapeutic index (LD_{50}/ED_{50}) of about 67,000 which is much better

than that of morphine hydrochloride (LD_{50}/ED_{50} = 112.0).[39] The 3,7-diazabicyclo[3.3.1]nonanes 32 (R = H, CH_3, and COC_2H_5) have been found to be void of analgesic activity.[51] At high concentrations, 32 displayed only convulsant action.[57]

The antiarrhythmic activity of a number of 3,7-diazabicyclo-[3.3.1]nonanes 33 have been determined.[18,50,51] In general, when R and R' were alkyl groups, the toxicity of 33 was too high (Table III).[50] The therapeutic indices (LD_{50}/ED_{50}) ranged from 0.87-1.46 depending upon R and R'.[50] When an acyl group was attached to nitrogen as in 34, the toxicity was reduced. Several of the amides have therapeutic indices (LD_{50}/ED_{50}) in the 4.0-10.0 range which are comparable to the value found for the antiarrhythmic drug, disopyramide (LD_{50}/ED_{50} = 5.77).[51] The ED_{50} and LD_{50} values for several materials are shown in Table IV.

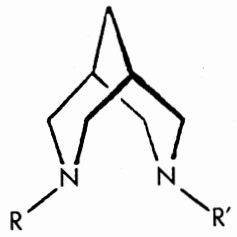
Heart Disease

Heart disease will result in the death of over three quarters of a million Americans this year. This makes heart diseases the leading cause of death in the U.S.[52]

Heart disease is actually a wide assortment of disorders. The most common cause of many coronary disorders is atherosclerosis.[52] Atherosclerosis is the narrowing of arteries caused by the buildup of plaque (fatty deposits) on the inner arterial walls. If this occurs in an artery that supplies blood to the heart, it can restrict the amount of oxygen being supplied to the heart. In some individuals who have lost appreciable blood flow, this manifests itself as angina pectoris (anginal pain).[12,52]

TABLE III

ANTIARRHYTHMIC PROPERTIES OF 33[50]



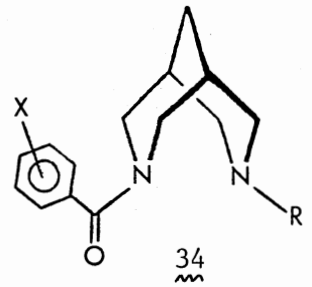
33

R	R'	ED_{50}[A]	LD_{50}[A]	LD_{50}/ED_{50}
CH_3	n-C_4H_9	192	207	1.08
CH_2	CH_2-C_6H_5	154	189	1.23
n-C_4H_4	-CH_2-C_6H_5	159	198	1.25

[A] µmol/kg in mice.

TABLE IV

ANTIARRHYTHMIC PROPERTIES OF 34[51]



34

X	R	ED_{50} [A]	LD_{50} [A]	LD_{50}/ED_{50}
H	CH_3	85	621	7.29
4-O-CH_3	CH_3	78	463	5.93
4-Cl	CH_3	49	535	10.89
3,4-di-Cl	CH_3	470	492	1.05
disopyramide		90	517	5.77

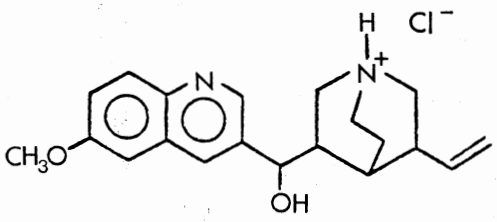
[A] μmol/kg in mice.

When there is an abrupt reduction in the coronary blood supply due to obstruction caused by a narrowed artery or by a blood clot or if the demand for O_2 far exceeds the supply, a myocardial infarction can occur.[12] Myocardial infarction can result in severe damage to part of the heart muscle. This predominantly effects the left ventricle but may extend into the right ventricle or the atria.[12] Of all deaths occurring from acute myocardial infarction, 50% die within 2.5 hours of the onset of clinical symptoms. At this point, ventricular arrhythmia is the most immediate threat to life.[12]

Ventricular fibrillation is the irregular and chaotic contraction of the ventricular myocardium. This uncoordinated activity results in the loss of cardiac output and blood pressure. Ventricular fibrillation is a fatal condition unless it is corrected immediately. Treatment is directed towards control of ventricular premature beats since this arrhythmia is the initiator of ventricular fibrillation. If fibrillation does occur, immediate DC defibrillation is the only effective therapy.[12]

Depending upon the type of arrhythmia that is observed, different treatments are employed. Arrthythmias of the atria are generally treated with digitalis which is a mixture of compounds that are isolated from the dried leaves of Digitalis pururea L., Scrophulariaceae.[64] Digitalis decreases conduction through the myocardial tissues thereby reducing the ventricular response. When the ventricular rate has been acceptably slowed, longer acting drugs such as quinidine (35) or procainamide (36) are given to control ventricular arrhythmias that are a result of atrial flutter or fibrillation.[12] There are drawbacks to each of these drugs. For example, an overdose of digitalis can cause

arrhythmias worse than those already present. Quinidine (35) and procainamide (36) reduce ventricular function but also lower blood pressure.[12] Nausea and vomiting as well as sudden death due to



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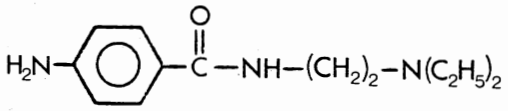
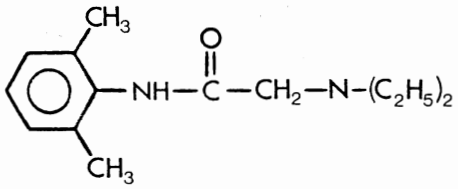


36

overdoses are also associated with these two drugs.[1]

Ventricular arrhythmia are commonly controlled with lidocaine (37). However, when the arrhythmia has progressed to a tachycardia or a fibrillation, the first choice of treatment is DC defibrillation.[12] The side-effects of 37 are largely associated with the central nervous system and include nausea and tremors. The most adverse reaction to 37 comes from the injection of large amounts of compounds which can result in heart block, hypotension, and respiratory arrest.[1]

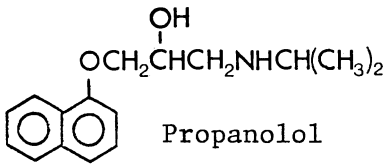
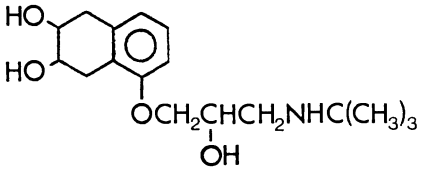
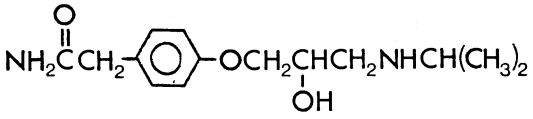
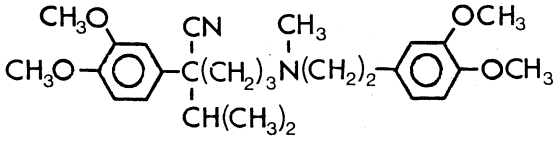
A number of new drugs are available for controlling various heart diseases. The structures and uses of some of the newer drugs are shown in Table V. A more detailed discussion of these drugs and mode of action is available.[52]



37

TABLE V

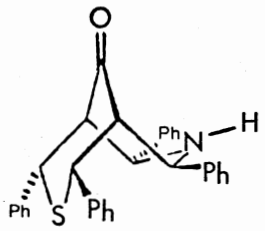
STRUCTURES AND USES OF HEART DRUGS[52]

	Use
 Propanolol	Arrhythmias Hypertension Angina
 Nadolol	Angina Hypertension
 Atenolol	Hypertension
 Verapamil	Arrhythmia Angina

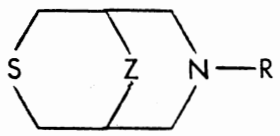
CHAPTER II

RESULTS AND DISCUSSION

Heterocyclic bicyclo[3.3.1]nonanes are novel structures and have theoretical interest as well as potential biological activity.[28,66,67] Nitrogen analogs of bicyclo[3.3.1]nonane have been studied extensively and have recently been reviewed.[28] Systems with heteroatoms such as O, S, and P have been limited primarily to highly substituted materials.[17,28,29,66,67] To date, all 7-aza-3-thiabicyclo[3.3.1]nonanes reported have had aryl groups substituted on the ring alpha to the N and/or S atom.[17,22,29] The objectives of the present work were the synthesis and conformational analysis of 2,4,6,8-tetraphenyl-7-aza-3-thiabicyclo[3.3.1]nonan-9-one (38)[11] and N-alkyl-7-aza-3-thiabicyclo-[3.3.1]nonanes with the general structure 39.



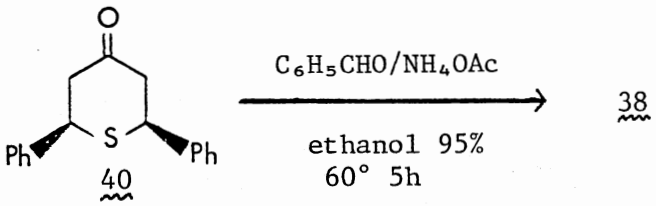
38

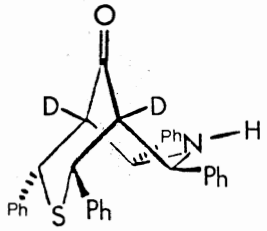


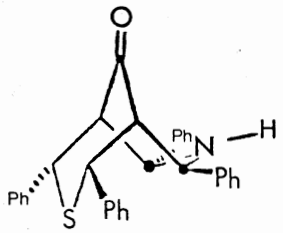
39a Z= CO
39b Z= CH_2
39c Z= CH(OH)
39d Z= $CC_6H_5(OH)$

Synthesis of 38 was accomplished by treating cis-2,6-diphenyl-tetrahydrothiopyran-4-one (40) with benzaldehyde and ammonium acetate in ethanol at 60°C. For purposes of ^{13}C NMR analysis, two labeled materials, namely 41 and 42, were prepared in a similar manner.

Deuterated ketone 41 was prepared from cis-2,6-diphenyl-3,3,5,5-

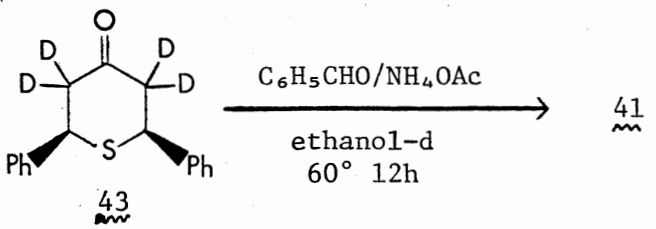






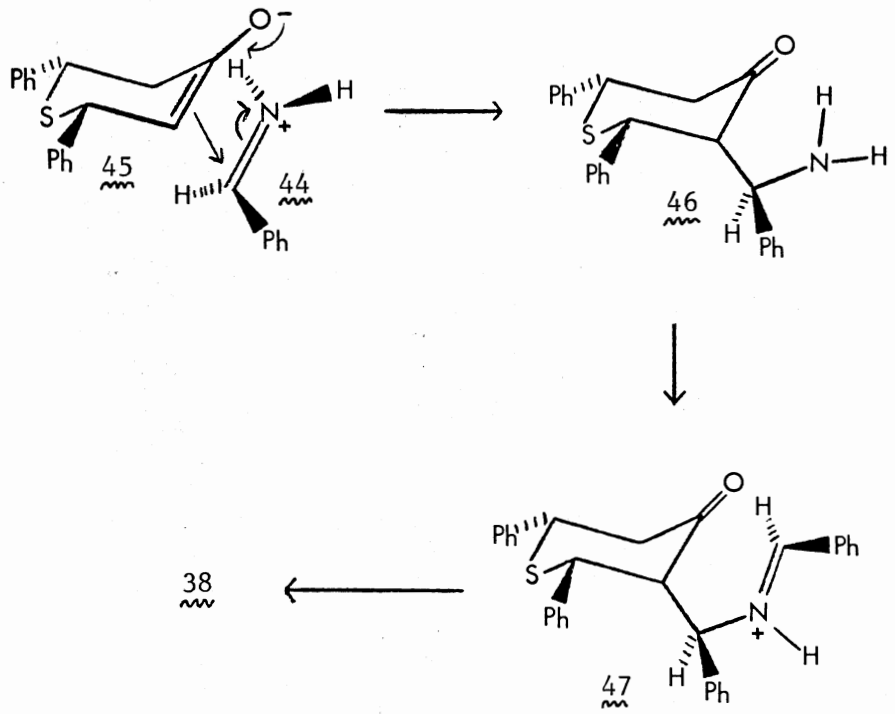
● = ^{13}C

tetradeuterio-4-thianone (43) using the method described above but with absolute C_2H_5OD as a solvent. Synthesis of 42 involved an identical procedure as for 38 except the benzaldehyde used was diluted with benzaldehyde-α-^{13}C (9.6%).



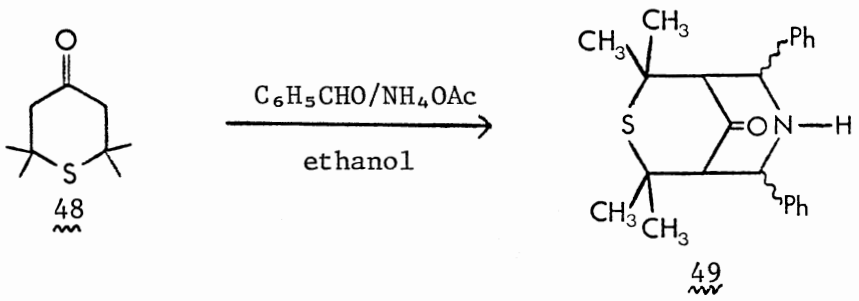
X-Ray analysis as discussed later has shown that 38 exists in a chair-boat conformation with the thianone ring in a chair and the piperidone ring in a boat form. This finding is consistent with results reported in the literature for related compounds.[17,27,46,47] This observation can be explained by considering the accepted mechanism

of the Mannich reaction. The condensation of the iminium ion 44 with the enol 45 gives 46 as shown. The Mannich base 46 may then react



with another equivalent of aldehyde to give 47. This is followed by an intramolecular Mannich reaction to give 38. A possible reason why attack of the iminium ion 44 does not occur from the opposite face is steric interaction between the phenyl group in 44 and the enol 45. The orientation shown has the phenyl group away from the ring 45 thereby minimizing steric interactions.[47]

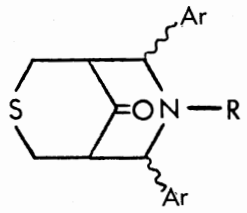
Treatment of 2,2,6,6-tetramethylthiapyan-4-one (48) with ammonium acetate and benzaldehyde gave 49. In light of the conformation found for 38 in the X-ray analysis and the results of Eliel[17] and Muller,[27,46,47] it is reasonable to conclude that 49 might exist as a chair-boat. However, the possibility of a boat-boat conformation,



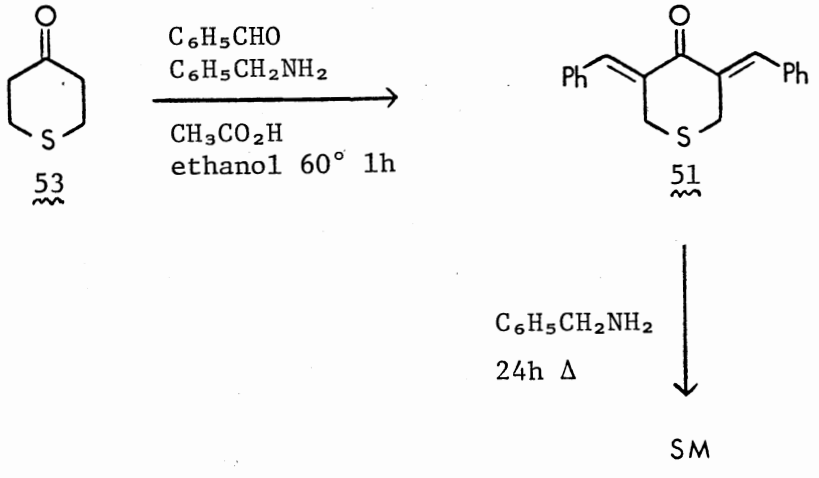
48 49

which could minimize internal strain, cannot be excluded.

Synthesis of N-benzyl-6,8-diphenyl-7-aza-3-thiabicyclo[3.3.1]-nonan-9-one (50a) using the conditions shown was not successful. The only product isolated was 3,5-dibenzylidenetetrahydro-4H-thiapyran-4-one (51) (56%). The preparation was attempted at various temperatures



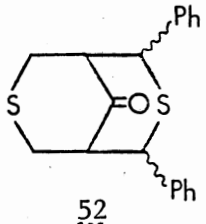
50a R=$CH_2C_6H_5$
50b R=H



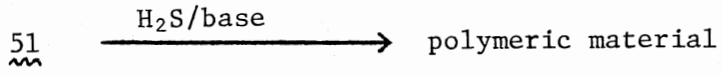
53 51

using both methanol and ethanol as solvents. It is interesting to note that a large number of compounds with the general structure 50b have been prepared with R=H.[17,29] The side product 51 was heated

at reflux for 24 h with benzylamine in an attempt to force a double Michael addition to yield 50a. However, only the starting ketone 51 was recovered along with decomposition materials. An attempt to prepare 2,4-diphenyl-3,7-dithiabicyclo[3.3.1]nonan-9-one (52) from 51 by the addition of H_2S resulted only in the formation of polymeric materials. These results are not unexpected since, after one addition



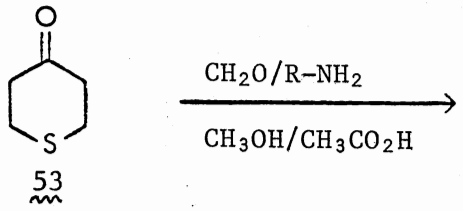
52



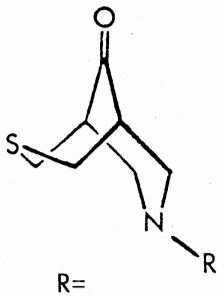
of H_2S or RNH_2 in a Michael fashion, an intramolecular Michael addition would have to occur. This intramolecular addition is unlikely since the pendent double bond appears far removed from the attacking nucleophile in the possible intermediate. Thus, it can be assumed that dienones like 51 are probably not intermediates in the formation of the bicyclic products discussed.

The synthesis of N-alkyl-7-aza-3-thiabicyclo[3.3.1]nonan-9-one (39a, Z = CO) was accomplished by the double Mannich condensation involving 53 with an excess of paraformaldehyde and the appropriate amine in methanol. This reaction was found to depend upon several experimental parameters. The best yields were obtained when methanol was used as the solvent. If ethanol or 2-propanol was employed, the desired product was not obtained. Instead, only polymeric materials were formed. The literature method for performing the Mannich

reaction involves the slow addition of the cyclic ketone to a solution of the aldehyde and the amine.[16,51] This was found to give decreased yields in comparison to adding 53 to the reaction in one portion. Ketones 54 to 60 were prepared as shown.



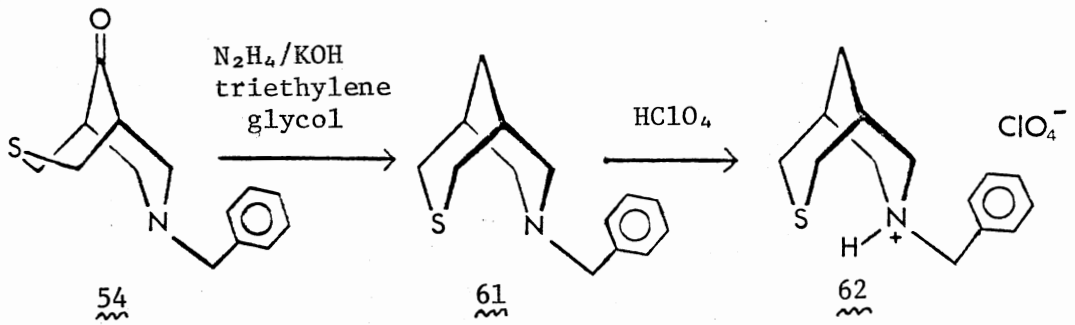
53



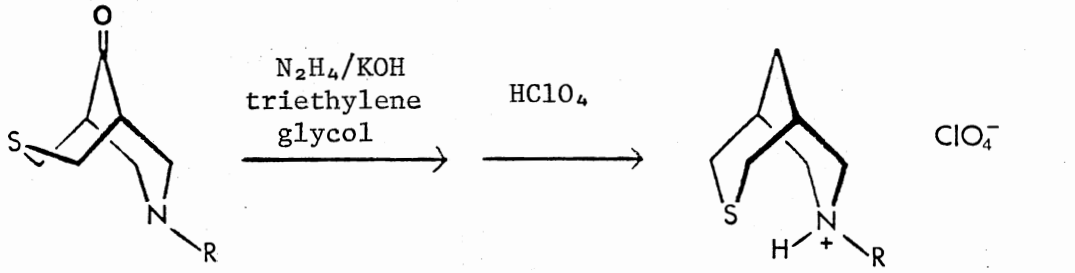
	R=
54	$CH_2C_6H_5$
55	$CH_2CH_2C_6H_5$
56	$CH_2C_6H_4OCH_3$-4
57	$CH_2CH_2C_6H_4OCH_3$-4
58	$CH_2C_6H_3(OCH_3)_2$-3,4
59	$CH_2CH_2C_6H_3(OCH_3)_2$-3,4
60	$CH_2C_6H_4Cl$-4

Reduction (Wolff-Kishner) of 54 to 61 proceeded in good yield; however, the product was an oil. The oil 61 was converted to the perchlorate 62 (82% overall) for ease of purification and handling. Isolation of the free amines from the reduction mixtures of other simple ketones 55, 56, and 59 was not attempted. Instead, the amines were converted directly to the perchlorates 63, 64, and 65, respectively. The tetraphenyl ketone 38 was also found to undergo Wolff-Kishner reduction to give 66 in good yield (74%).

Preparation of 61 was attempted initially by converting ketone 54 to the tosylhydrazone derivative which was treated with $NaBH_3CN$.[26] The only material isolated was the starting ketone 54. This finding



54 61 62

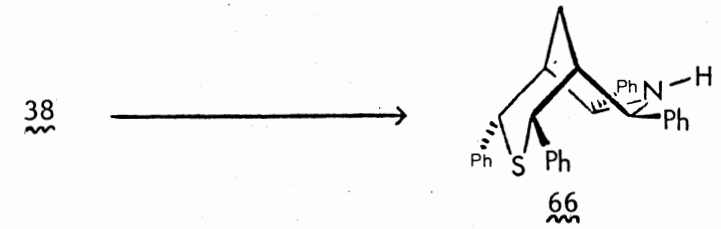


R=

54 63 $CH_2CH_2C_6H_5$

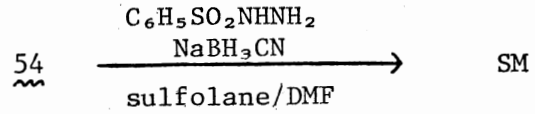
56 64 $CH_2C_6H_4OCH_3$-4

59 65 $CH_2CH_2C_6H_3(OCH_3)_2$-3,4



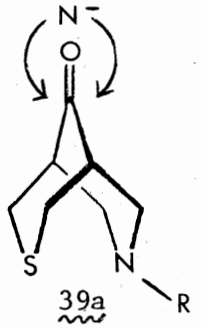
66

would suggest that the tosylhydrazone derivative was not formed under the reaction conditions used.

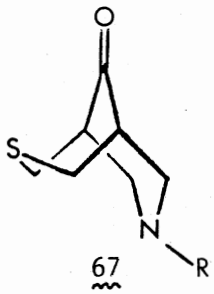


The addition of a nucleophile to the C(9) carbonyl group can result in two isomeric products depending upon which face of the

carbonyl is attacked by the entering nucleophile. If the bicyclic ketone was in a chair-chair conformation 39a (Z = CO), it would be expected that the nucleophile would have equal opportunity to add



39a



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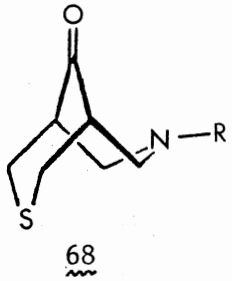
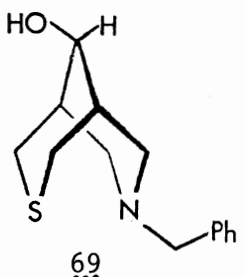


68

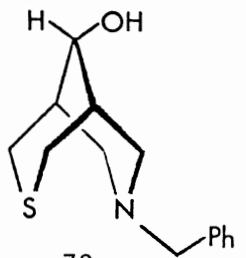
to either face of the carbonyl. If one of the chair-boat conformers 67 or 68 was the predominate species, then the two faces of the carbonyl obviously would not be equivalent. An entering nucleophile might simply be blocked from the carbonyl face in the boat ring, with the S atom or N atom in 67 and 68, respectively. This could lead to predominately one addition product. If the nucleophile is an organometallic (Grignard) reagent, coordination between the metal ion and the lone pairs of electrons on sulfur or nitrogen could result. This coordination could enhance the preferential addition of the nucleophile to one face of the ketone, again resulting in the formation of predominately one addition product.

Reduction of 54 with $NaBH_4$ in 2-propanol gave a mixture of alcohols. ^{13}C NMR analysis of the crude mixture indicated that the major isomer was 69 while the minor isomer was 70 (65:35). The ^{13}C NMR analysis will be discussed later. The major isomer was isolated in pure form by fractional crystallization from Skelly B.

The addition of excess methylmagnesium chloride to 54 gave a mixture of alcohols 71 and 72. Examination of the crude reaction

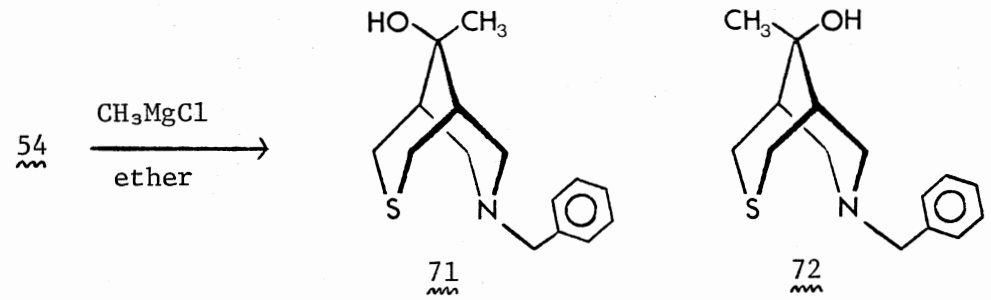


69



70

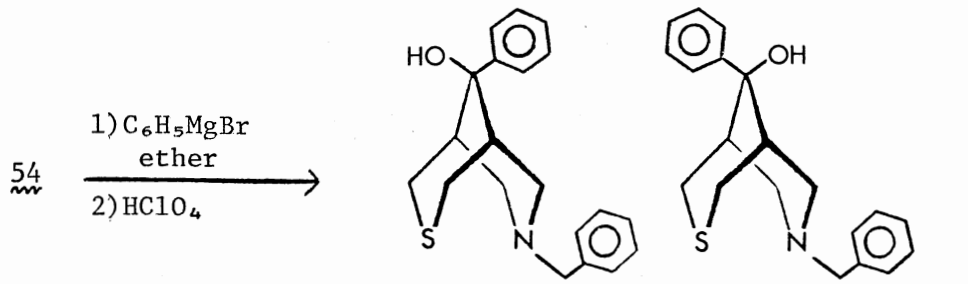
mixture by ^{13}C NMR revealed a 3:2 ratio of 71:72. The major isomer



71 72

71 was isolated in pure form by fractional crystallization from Skelly B (38%).

Alcohol 73 was prepared by addition of two equivalents of phenylmagnesium bromide to ketone 54 in ether. Examination of the crude reaction mixture by ^{13}C NMR revealed a mixture of alcohols 73b and 74b (84:16). The crude product in ether was treated with perchloric acid,

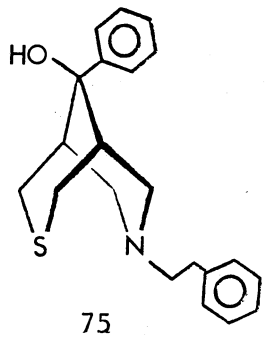


73a $HClO_4$ salt 74a $HClO_4$ salt
73b free amine 74b free amine

and the resulting solid was recrystallized from 95% ethanol to give only one pure isomer 73a (81%). The structure of 73a was confirmed by single crystal X-ray analysis.

The observed product ratios for the addition of various nucleophiles to 54 show a preference for attack from the N face, thus suggesting hinderance to the S face or N-coordination to Mg^{+2} and/or Na^{+}. This is not unreasonable in view of the chair-boat conformation found for 54 by X-ray analysis. If it is assumed that 54 is a chair-boat in solution, then the S atom may be blocking attack at the carbonyl. Eliel and co-workers have noted that attack of a nucleophilic type occurred from the least hindered side of cis-2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones,[17] which have chair-boat conformations in the solid state.

The addition of phenylmagnesium bromide to 55, 56, and 57 gave 75, 76, and 77, respectively. The structures were confirmed by spectral analysis and the configuration at C(9) was determined by ^{13}C NMR analysis which will be discussed later. Only the isomers 75, 76, and 77 were isolated; however, the crude reaction mixtures were not



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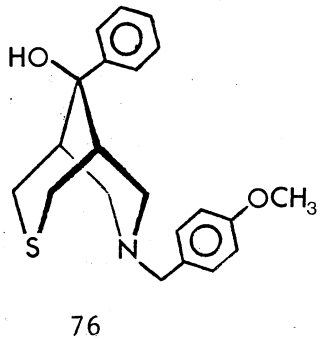
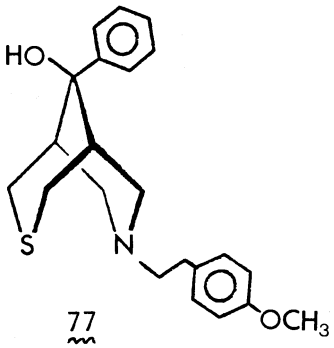


76

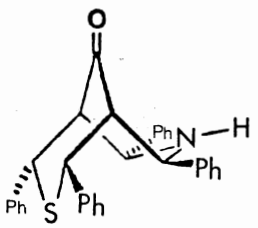


77

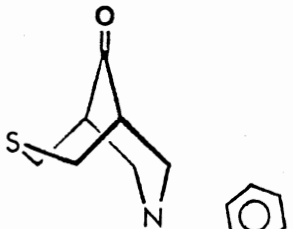
examined for the presence of the other possible isomers. It is expected that isomers resulting from addition to the S face are produced in small amounts as is the case with ketone 54.

Single Crystal X-ray Analysis

The X-ray analysis of 38, 54, and the perchlorate 73a were performed by D. van der Helm and co-workers at the University of Oklahoma. The crystal structure of 62 was determined by E. M. Holt at Oklahoma State University. The analysis of 38 revealed the presence of 1.5 molecules of benzene per molecule of 38. Ketone 38 was found to exist in a chair-boat with the thianone ring in a chair and the piperidone ring in a boat conformation (Figure 1).



38



54

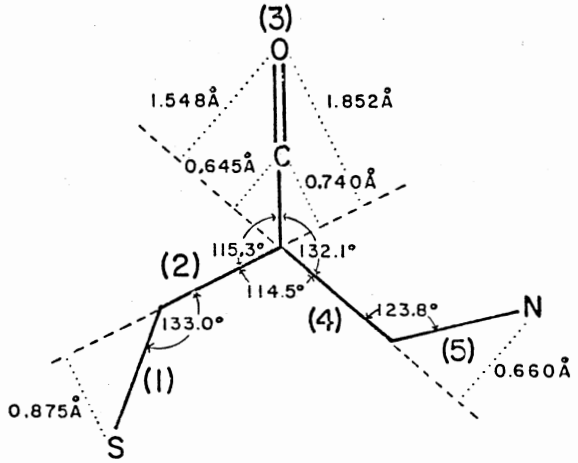
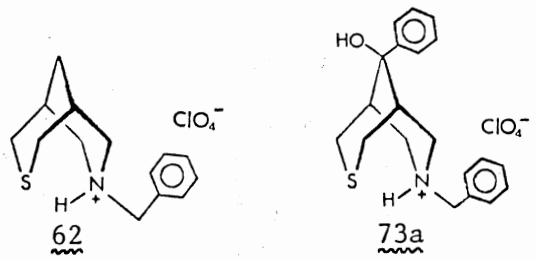


Figure 1. Angles Between Planes of 38

In the solid state, ketone 54 exists in a chair-boat conformation with the sulfur-containing ring in a boat form and the nitrogen containing ring in a chair form. There are two distinct molecules in the crystalline lattice; however, the fused ring portions of the two molecules are virtually identical (Figure 2).



62 73a

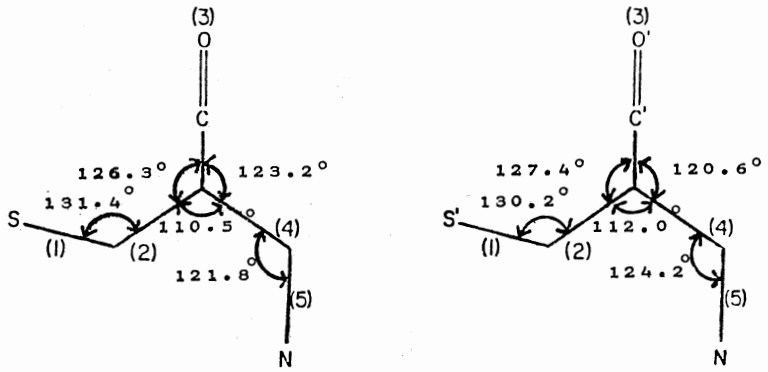


Figure 2. Angles Between Planes of 54

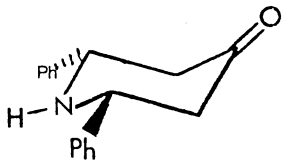
In both 38 and 54, the C(1)-C(9)-C(5) angle is smaller (113.3°) than ideal geometry (116°) for bicyclo[3.3.1]nonan-9-one,[35] suggesting some strain in the carbonyl groups. In both molecules of 54 in the crystalline structure, C(9) is displaced slightly (0.027 and 0.037 Å) from the plane formed by C(1), C(5), and O(10) in the direction of the

sulfur atom. In 38, C(9) is displaced slightly towards the nitrogen by 0.026 Å. Thus, these data suggest that in both 38 and 54 there is some small interaction between C(9) and the heteroatom at the opposite end of the boat conformation.

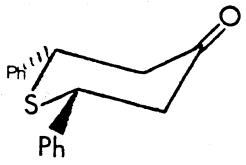
Both hydroperchlorates 62 and 73a exist in chair-chair conformations (Figures 3 and 4, respectively). In both molecules, the hydrogen from the perchloric acid is transferred to the nitrogen. The bond distances for S...H and N-H are 2.42(4) and 0.94(4) Å, respectively, for 62 with a S...H-N angle of 128.8(29)°. These are somewhat different from the values found for 73a (S...H, N-H, and S...H-N are 2.38(4) Å, 0.87(4) Å and 134(3)°, respectively). Table VI contains all pertinent crystal data for 38, 54, 62, and 73a. Bond distances and angles are given in Tables VII and VIII.

^{13}C NMR Analysis

^{1}H NMR analyses were relatively uninformative except for the obvious signals for the benzylic and methoxy protons. These data are shown in the Experimental Section. The ^{13}C NMR chemical shifts (Table IX) for 38 were compared with those of model compounds 40 and 78.[48] Initially, on the basis of these comparisons and electronegativity



78



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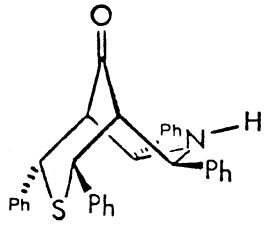


38

considerations, the signal at 61.05 ppm in 38 was assigned to C(6,8)

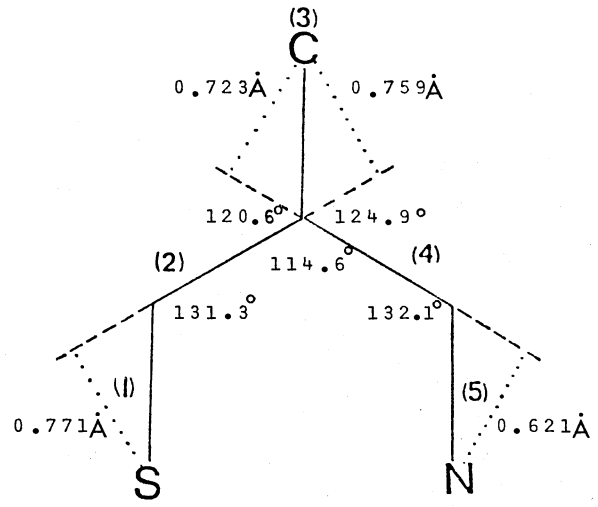


Figure 3. Angles Between Planes of 62.

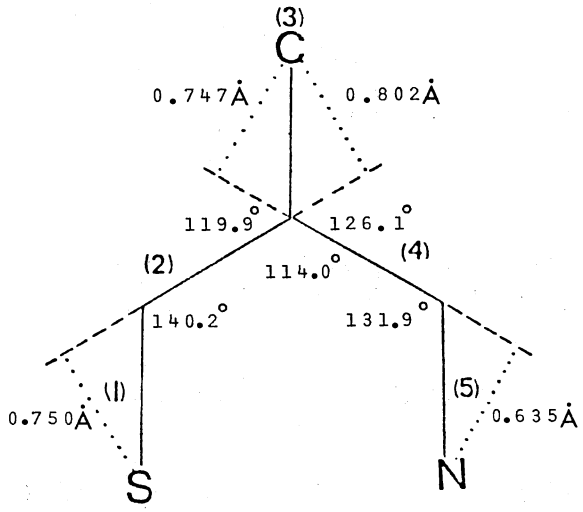


Figure 4. Angles Between Planes of 73a.

TABLE VI

CRYSTAL DATA FOR 38, 54, 62 AND 73a

	38	54	62	73a
Space Group	$P\bar{1}$	$P\bar{1}$	$P2_12_12_1$	$P_{nA}2_1$
Cell Dimensions				
A	8.910(2)	11.105(7)	6.604(3)	10.046(3) Å
b	9.754(2)	12.033(6)	14.742(9)	14.858(6)
c	19.342(3)	9.899(4)	16.177(5)	13.084(5)
α	92.09 (2)	104.64 (4)	90.0	90.0°
β	98.84 (2)	85.40 (5)	90.0	90.0
γ	110.75(2)	92.39 (4)	90.0	90.0
Density (Calcd)	1.243	1.289	1.416	1.407 g/cm^3
Temp. of Data Collection	138 ± 2	138 ± 2	298 ± 2	138 ± 2 K
Number of Reflection Obser.	4797	3317	1764	1621
Final R	0.055	0.0762	0.037	0.033
R_w	0.047	0.0813		0.034
Recrystallization Solvent	Benzene	Skelly B	Ethanol	Ethanol

TABLE VII

SELECTED BOND DISTANCES (Å) FOR 38, 54, 62 AND 73a

	38	54[a]	62	73a
C(1)-C(2)	1.556(2)	1.559(5)	1.503(7)	1.533(5)
C(2)-S(3)	1.817(2)	1.814(3)	1.831(5)	1.817(4)
S(3)-C(4)	1.821(1)	1.813(4)	1.820(4)	1.825(4)
C(4)-C(5)	1.556(2)	1.550(5)	1.505(6)	1.524(5)
C(5)-C(6)	1.562(3)	1.543(4)	1.533(6)	1.535(5)
C(6)-N(7)	1.468(2)	1.459(4)	1.506(5)	1.502(4)
N(7)-C(8)	1.477(2)	1.459(4)	1.512(5)	1.510(4)
C(8)-C(1)	1.557(3)	1.543(4)	1.538(5)	1.518(5)
C(5)-C(9)	1.509(2)	1.505(4)	1.547(6)	1.547(4)
C(9)-C(1)	1.511(2)	1.512(5)	1.510(6)	1.552(4)
C(9)-O(10)	1.212(2)	1.218(4)	—	1.433(4)

[a]Only data for one crystalline modification is given.

TABLE VIII

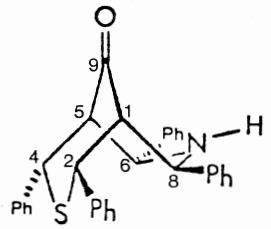
SELECTED BOND ANGLES (°) FOR 38, 54, 62, AND 73a

	38	54[a]	62	73a
C(1)-C(2)-S(3)	111.5(1)	111.9(2)	114.7(3)	115.5(2)
C(2)-S(3)-C(4)	98.7(1)	98.0(2)	99.3(2)	99.8(2)
S(3)-C(4)-C(5)	113.2(1)	112.9(2)	114.5(3)	113.8(2)
C(4)-C(5)-C(6)	114.9(1)	110.5(3)	114.2(3)	113.2(3)
C(5)-C(6)-N(7)	108.4(1)	109.3(3)	111.8(3)	113.1(3)
C(6)-N(7)-C(8)	114.9(1)	110.8(3)	112.6(3)	110.9(2)
N(7)-C(8)-C(1)	107.6(1)	109.3(2)	111.4(3)	111.6(3)
C(8)-C(1)-C(2)	114.4(1)	110.7(3)	114.6(4)	114.6(3)
C(2)-C(1)-C(9)	107.1(1)	111.7(2)	111.9(4)	111.7(3)
C(4)-C(5)-C(9)	108.6(1)	111.0(3)	111.4(3)	112.4(3)
C(8)-C(1)-C(9)	109.7(1)	106.4(3)	109.4(3)	110.1(3)
C(6)-C(5)-C(9)	108.9(1)	107.0(2)	109.6(3)	110.9(3)
C(1)-C(9)-C(5)	113.5(1)	113.3(3)	109.6(3)	106.7(2)
C(1)-C(9)-O(10)	123.3(1)	123.2(3)	—	110.4(3)
C(5)-C(9)-O(10)	123.1(1)	123.3(3)	—	105.3(3)

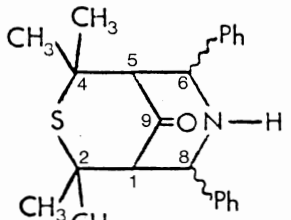
[a]Only data for one crystalline modification is given.

TABLE IX

^{13}C CHEMICAL SHIFTS (PPM) FOR 38, 49 AND MODEL COMPOUNDS

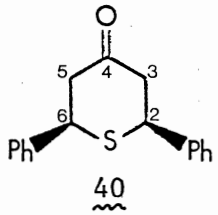


38



49

	C(2,6)	C(1,5)	C(2,4)	C(9)	Ar-C and Others
38[a]	59.24	61.05	52.13	211.54	144.40, 137.33, 128.46, 127.94, 127.72, 127.36, 127.01, 126.53
49[a]	62.94	64.40	50.45	211.47	CH_3a 28.66, CH_3e 32.45, 127.53, 127.69, 128.45, 144.47



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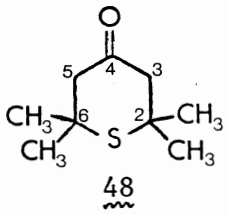

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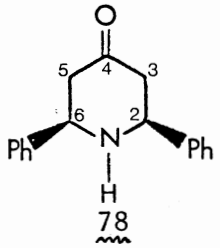


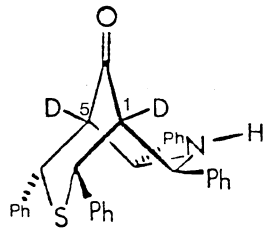
78

	C(2,6)	C(3,5)	C(3,5)	
40[48]	48.15	50.24	206.78	139.06, 128.43, 137.61, 126.78
78[48]	60.89	50.10	206.68	126.31, 127.48, 128.36, 142.60
48[48]	46.40	55.80	208.86	32.29 (CH_3)

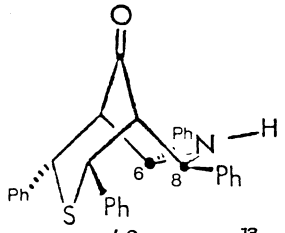
[a] Assignments given are correct according to labeling studies or HETCOR 2-D experiment.

which were attached to the nitrogen atom. This chemical shift was remarkably similar to that (60.84 ppm) found for C(2,6) in the piperidone 78.[48] Likewise, the resonance at 52.13 ppm for C(2,4) was not sharply different from that (48.15 ppm) for C(2,6) in thianone 40. Thus, it appeared that a dramatic deshielding of C(1,5) had occurred in 38 to give a signal at 59.24 ppm quite downfield from the values (50.10 and 50.24 ppm) found for C(3,5) in 78 and 40, respectively.

In order to confirm these assignments, the labeled compounds 41 and 42 were prepared. Interestingly, ^{13}C NMR analysis of 41 revealed



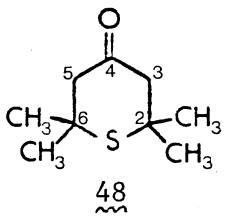
41



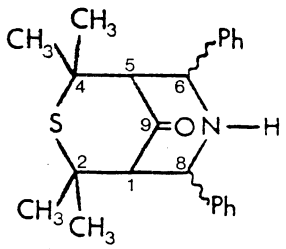
42 • = ^{13}C

signals at 52.11 ppm [C(2,4)] and 59.26 ppm [C(6,8)] while the signal at 61.05 ppm was complex and greatly diminished because of C(1,5)-D coupling. The ^{13}C NMR analysis of 42 clearly showed the ^{13}C label at 59.24 ppm for C(6,8) which were attached to nitrogen. Consequently, bridgehead carbons C(1,5) must give the resonance at 61.05 ppm. Quite possibly, this downfield shift of the C(1,5) resonance arose from deshielding imposed by the phenyl groups.

Initially, the ^{13}C NMR assignments for 49 were made by comparison to model compounds 48 and 78 (Table IX). In the mobile system 48, the methyl groups are all equivalent (32.29 ppm), but in the biased system 49 signals are observed at 28.66 ppm for an axial methyl and 32.45 ppm for an equatorial methyl. The C(2,4) signal at 50.45 ppm



48



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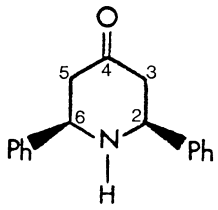
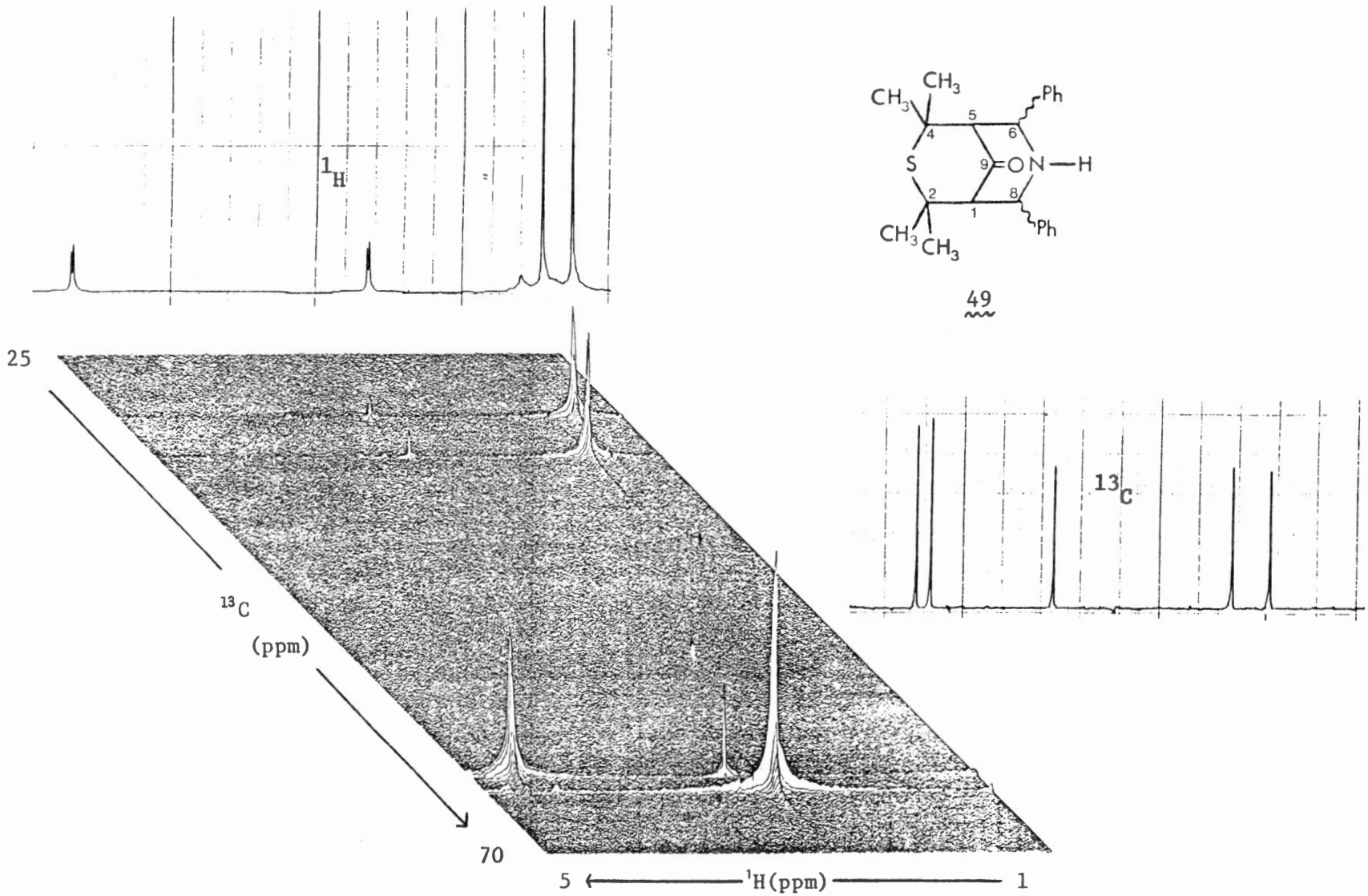


78

was downfield from the original (46.40 ppm) for corresponding carbons in 48. However, assignments of the signals at 62.94 and 64.40 ppm in 49 were complicated in the same way as were the assignments for 38. Absolute assignments for these signals were made using the results of a heteronuclear correlated 2-dimensional (HETCOR 2-D) NMR experiment[61] (Figure 5). This experiment was performed in the ^{13}C region of approximately 25-70 ppm and in the ^{1}H region of approximately δ 1-5. At the lower right hand corner of Figure 5, the proton decoupled ^{13}C spectrum for 49 in this region is shown, while in the upper portion of Figure 5 the proton spectrum in this region is shown. If all of the peaks in the HETCOR 2-D spectrum are compressed into one horizontal plane, the spectrum obtained is identical to the ^{1}H spectrum shown. If the 2-D spectrum is observed from the right-hand side, and all of the peaks are compressed into one vertical plane, the spectrum obtained is identical to the ^{13}C spectrum shown.

A HETCOR 2-D experiment can be used to correlate the ^{1}H signal for a particular set of protons with the ^{13}C signal for the carbon to which those protons are attached.[21] In order to utilize the information contained in the 2-D spectrum, either the ^{1}H or ^{13}C NMR spectrum must be assigned unequivocally. In this case, the ^{1}H NMR spectrum of

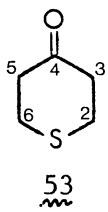


49

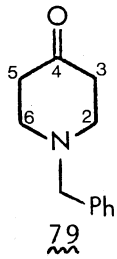
Figure 5. HETCOR 2-D Spectrum of 49.

49 can be assigned easily. The signal at δ 4.62 in the ^{1}H spectrum was assigned to H(6) and H(8), and the signal at δ 2.60 was assigned to H(1) and H(5). Using the HETCOR 2-D spectrum, it was found that the protons at δ 2.60 were attached to the carbon giving a signal at 64.40 ppm in the ^{13}C spectrum. The signal at 64.40 ppm was, therefore, assigned unequivocally to C(1,5). Similarly, H(6) and H(8), which gave a doublet at δ 4.62 in the ^{1}H spectrum, were attached to the carbon that gave a signal at 62.94 ppm in the ^{13}C spectrum. Thus, the carbons alpha to nitrogen gave rise to the signal at 62.94 ppm in the ^{13}C spectrum. Interestingly, the bridge-head carbons [C(1,5)] in 38 and 49 were 11 and 14 ppm downfield, respectively, in comparison to model compounds 40, 48 and 78 (Table IX).[48] This deshielding effect of C(1,5) possibly arose from the influence of the nearby phenyl groups and/or distortion effects of the phenyl and methyl groups.

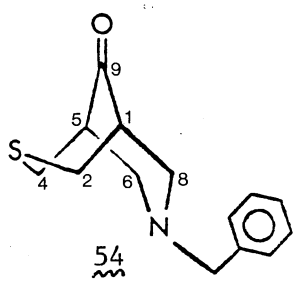
The ^{13}C NMR assignments for carbons in ketone 54 were made by comparison with model compounds 53 and 79 (Table X).[24] In general,



53



79



54

the signals for carbons in the bicyclic ring or 54 were found to be 4-6 ppm downfield from the chemical shifts found for corresponding carbons in 53 and 79.

The ^{13}C signals for C(2,4), C(6,8), C(1,5) and C(9) of ketones

55-60 were all very similar to those found for 54. See the Experimental Section for details.

TABLE X

^{13}C NMR ASSIGNMENTS (PPM) FOR 54 AND MODELS 53 AND 79

	C(2,4)	C(1,5)	C(6,8)	C(9)	C(1')	Ar-C
54	34.67	47.06	58.40	212.84	61.42	127.3, 128.2, 128.6, 137.9
	C(2,6)	C(3,5)	C(4)	C(1')		Ar-C
53[24]	30.0	44.0	208.0	—		
79[24]	52.8	41.0	207.7	61.8		127.2, 128.3, 128.6, 138.1

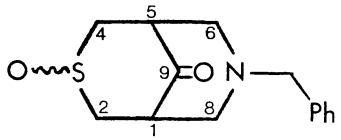
The sulfoxide 80 was prepared by the treatment of ketone 54 with $NaIO_4$ in aqueous methanol. The carbons alpha to sulfur showed a drastic downfield shift compared to 54. Suprisingly, the signal for C(1,5) was also shifted slightly downfield. This is not expected since the beta carbons in a sulfoxide are usually shifted upfield (Table XI).

It is interesting that the signal for the carbonyl carbon of 80 is shifted upfield 4 ppm compared to that in 54. This suggests a possible interaction between the sulfoxide and C(9). This upfield shift indicates that the sulfur-containing ring may reside in a boat

conformation.

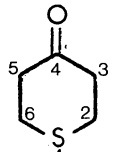
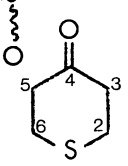
TABLE XI

SELECTED ^{13}C CHEMICAL SHIFTS (PPM) FOR 54, 80 AND MODELS



80

	C(2,4)	C(1,5)	C(6,8)	C(9)	C(1')
80	59.34	47.70	58.06	208.7	61.27
54	34.67	47.06	58.40	212.84	61.42

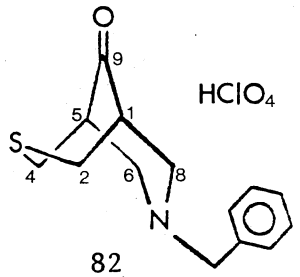
		C(2,6)	C(3,5)	C(4)
81[43]		46.8	31.9	204.4
53		30.0	44.0	208.0

Interestingly, the perchlorate 82 of ketone 54 did not have a signal for C(9) around 212 ppm. Instead, C(9) gave rise to a signal

at 88.5 ppm (Table XII). The observed chemical shift is indicative of a carbon with geminal dioxy groups.[31] IR analysis of 82 also did not reveal an absorption band for C=O ($\nu_{C=O}$ 1720 cm^{-1} was observed for 54), but a broad, intense absorption occurred at 3280-3460 cm^{-1}. These data suggest that the perchlorate of 54 exists as the hydrate 83.[25] The perchlorate 84 of N-benzyl-7-aza-3-oxabicyclo[3.3.1]-nonan-9-one is also reported to exist as the hydrate. In 84, a signal at 92.9 ppm was observed for C(9) in the ^{13}C NMR spectrum.[2] Hydration of the carbonyl of certain piperidin-4-ones[31] and phosphorinan-4-ones[14] have also been reported. In these, the hydrated carbon has a ^{13}C chemical shift of 101.7 and 94.4 ppm, respectively.

TABLE XII

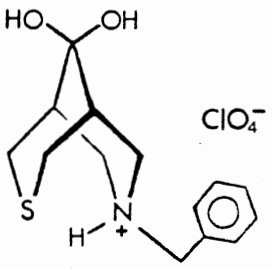
^{13}C NMR CHEMICAL SHIFTS (PPM) FOR 82[a]



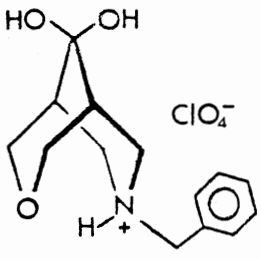
82

C(2,4)	C(1,5)	C(6,8)	C(9)	C(1)[1]	Ar-C
29.0	37.3	54.7	88.5	57.9	129.0, 129.4, 129.9, 130.3

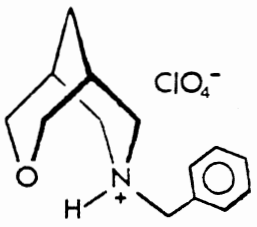
[a]X-Ray analysis has shown that 82 actually exists as the hydrate 83.



83



84



85

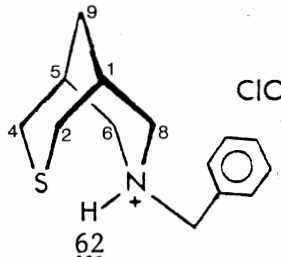
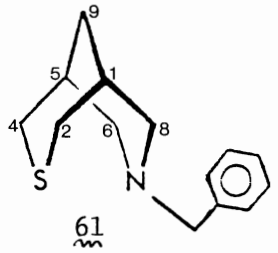
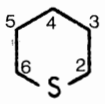
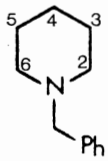
^{13}C NMR spectral analysis of perchlorate 62 was performed using DMSO-d_6 as a solvent. The ^{13}C assignments were made by comparison to those in appropriate model compounds 85 and 86[24] and via off-resonance ^{13}C NMR experiments (Table XIII). As was the case with the ketones 54-60, the ^{13}C signals for analogous carbons of all of the perchlorates 62-65 were very similar. See the Experimental Section for details. It should be noted that in going from the free amines 54 (Table X) and 61 (Table XIII) to the perchlorates 83 and 62, respectively, a 2-6 ppm shielding effect is observed for all carbons in the bicyclic ring system. This was not entirely expected since C(2,4), C(6,8) and C(9) of N-benzyl-7-aza-3-oxabicyclo[3.3.1]nonane hydroperchlorate (87) are slightly deshielded in comparison to the free amine.[2]

The ^{13}C NMR assignments of alcohols 69, 71, and 73b were made by comparison to the parent compound 54 (Table XIV). Assignments for the bridgehead carbons [C(1,5)] were made using an off-resonance ^{13}C NMR experiment. In general, conversion of bicyclo[3.3.1]nonan-9-ones to the corresponding alcohols reportedly results in an upfield shift of about 7.5 ppm for the pair of methylene carbons syn to the hydroxyl

group.[29] In contrast, the pair of methylene carbons anti to the hydroxyl group exhibits no significant change.[29]

TABLE XIII[a]

^{13}C NMR CHEMICAL SHIFTS (PPM) FOR 61, 62 AND MODEL COMPOUNDS[24]

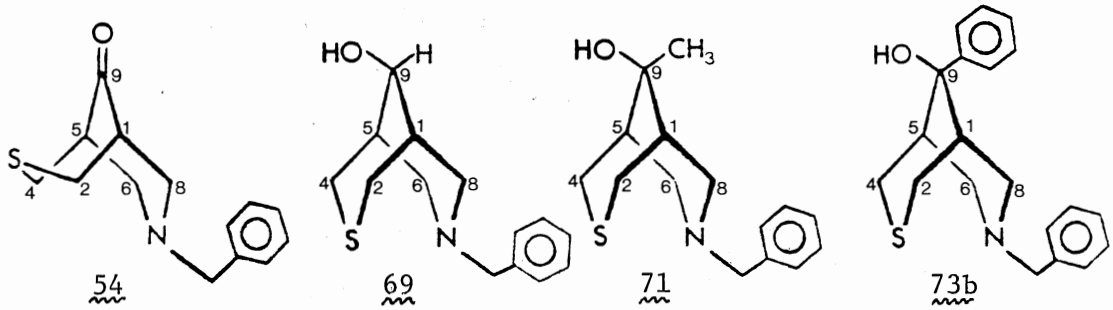
	C(2,4)	C(1,5)	C(6,8)	C(9)	C(1')	Ar-C
 62	29.89	24.90	55.65	27.67	59.99	128.24, 128.66, 129.09, 129.45
 61	31.49	27.14	58.54	29.76	67.18	126.35, 127.84, 128.37, 138.96
	C(2,6)	C(3,5)	C(4)	C(1')		
85 	29.1	27.9	26.6			
86 	54.6	26.0	24.5	64.0		126.8, 128.0, 129.1, 138.6

[a]Shifts for 62 determined in DMSO-d_6. Shifts for model compounds determined in $CDCl_3$.

In alcohols 69, 71, and 73b, signals for C(2,4) are shifted upfield in comparison to the analogous carbons in 54. This would indicate that the hydroxyl group resides on the S side of the ring system in 69, 71, and 73b. This has been confirmed for the perchlorate salt 73a by X-ray analysis. In 69, the chemical shift of C(6,8) (58.22 ppm) is essentially the same as that (58.40 ppm) of the analogous carbons in 54. In 71 and 73b, however, C(6,8) exhibited a 2-4 ppm upfield shift in comparison to ketone 54. This upfield shift may result from a compression effect at C(6,8) caused by the methyl or phenyl group at C(9).

TABLE XIV

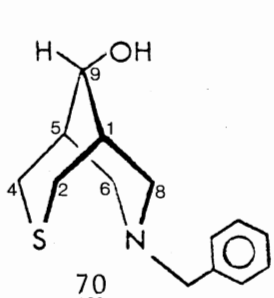
^{13}C NMR ASSIGNMENTS (PPM) FOR 54, 69, 71 AND 73b



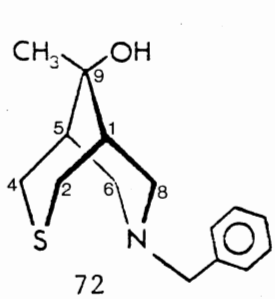
54 69 71 73b

	C(2,4)	C(1,5)	C(6,8)	C(9)	C(1')
69	26.54	34.19	58.22	70.97	62.21
71	28.95	38.67	56.58	69.09	62.36
73b	28.84	35.24	55.21	70.68	61.91
54	34.67	47.06	58.40	212.84	61.42

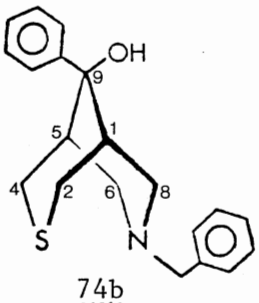
Considering the above observations, signals for C(6,8) (syn to the OH group) in the minor isomers, 70, 72, and 74b, would be expected to be shifted upfield in comparison to 54. Compounds 70, 72, and 74b were not isolated as pure materials, but the ^{13}C chemical shifts for each



70



72



74b

could be determined from the crude reaction mixture (Table XV). As was expected, the signals for C(6,8) in 70, 72, and 74b are shifted upfield in comparison to those in 54. The upfield shifts of C(2,4) in 72 and 74b again may indicate a compression effect on these carbons by the methyl or phenyl group at C(9). Of course, it is not possible to eliminate the possibility that a deformed ring system could be present in 70, 72, and 74b.

TABLE XV

SELECTED ^{13}C NMR CHEMICAL SHIFTS (PPM) FOR 54, CRUDE 70, CRUDE 72 AND CRUDE 74b

	C(2,4)	C(1,5)	C(6,8)	C(1')	C(9)	
70	33.41	34.25	52.17	61.83	70.87	
72	32.07	37.43	53.08	61.22	68.48	23.48 (CH_3)
74b	31.49	34.04	52.94	61.10	72.87	
54	34.67	47.06	58.40	61.42	212.84	

Variable temperature ^{13}C NMR experiments were performed on 54 and 61. At temperatures up to 100°C in nitrobenzene-d_5, no changes were observed in the spectra of the two compounds. Compound 61 in Freon 21:$CDCl_3$ (1:1) was studied at temperatures as low as -120°C with no observed changes in the ^{13}C spectrum. A similar low temperature study of 54 in toluene-d_8:Freon 21 (1:1) showed no changes down to -85°C. However, at -85°C the signals between 30-65 ppm started to broaden, and, at -90°C, small additional signals were observed. At -100°C a second complete set of signals were observed (Figure 6). The appearance of a second set of signals is suggestive of the presence of two conformers or two invertomers. A gated (no NOE) ^{13}C NMR experiment at -100°C revealed a 78.5:21.5 ratio of the two conformations. At this time it is not possible to ascertain which of the possible conformers are present at these temperatures. However, one might expect the major conformer present to be the chair-boat form found in the solid state.

^{15}N NMR

Analysis of ^{15}N NMR spectra for structure diagnosis of nitrogen-containing compounds has been recognized as a useful tool.[33] ^{15}N chemical shifts extend over a range of several hundred parts per million ($NH_3(\ell)$, 0.0 ppm; CH_3NO_2 (neat), 380.23 ppm). Generally ^{15}N resonances are measured in relation to a convenient external standard and referenced to liquid NH_3 at 25°C.[33]

Piperidine and its hydrochloride have ^{15}N resonances (in CH_3OH) at 37.0 and 39.2 ppm.[33] N-Methyl-4-piperidone (neat) has a signal at 36.5 ppm.[33] Recently, Muller and co-workers reported a deshielding

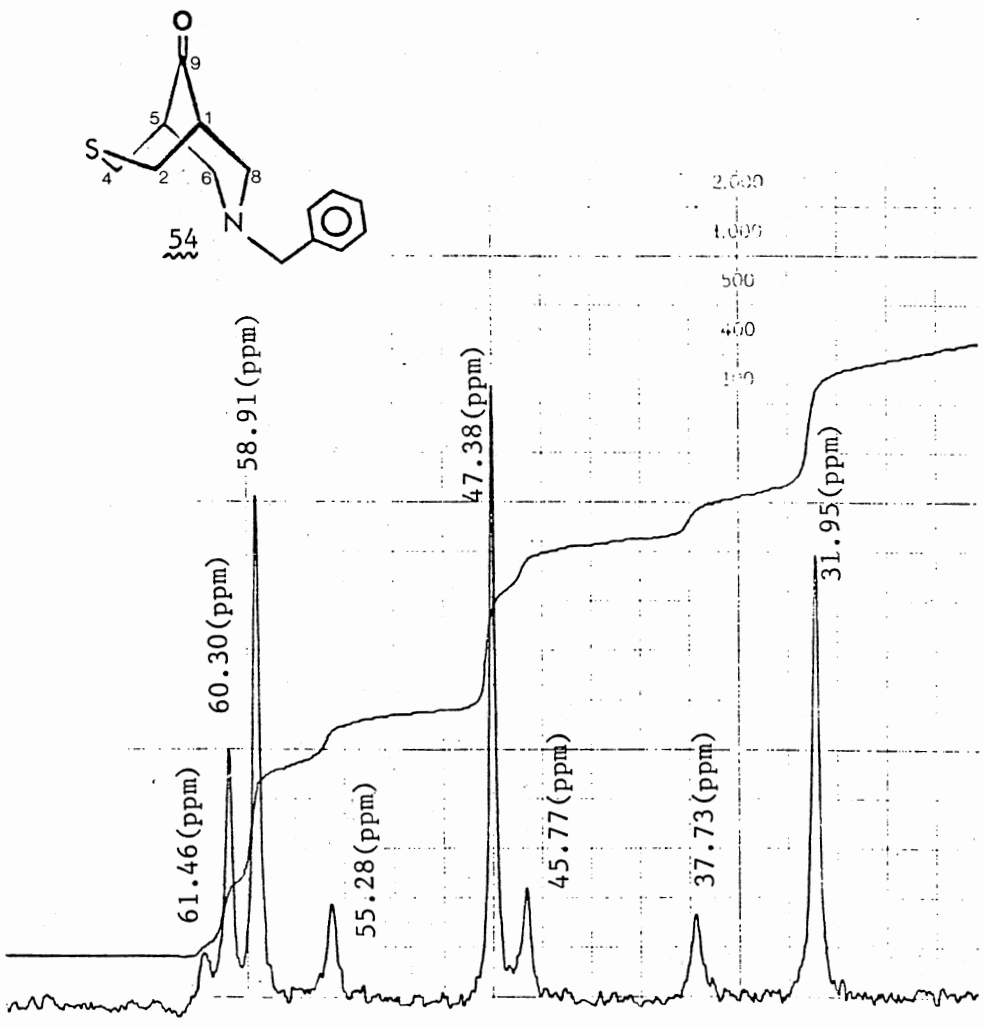
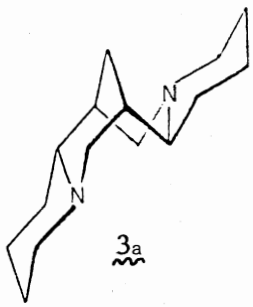
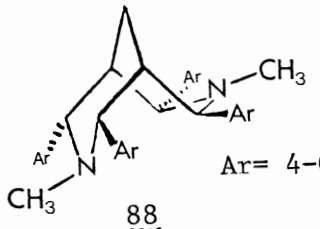


Figure 6. ^{13}C NMR Spectrum of 54 at -100°C.

of the boat nitrogen in compound 88. In the ^{13}C NMR spectrum carbons alpha to the nitrogen in the boat were observed upfield compared to those alpha to nitrogen in a chair. The ^{15}N NMR spectrum of sparteine 3a showed two ^{15}N signals at 48.6 and 49.1 ppm.[19] The signal at higher field was assigned to the boat nitrogen.[19]



3a



Ar= 4-CH_3-C_6H_4

88

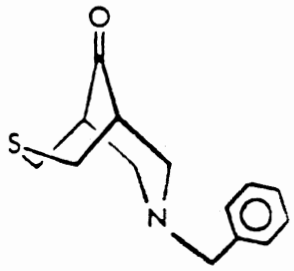
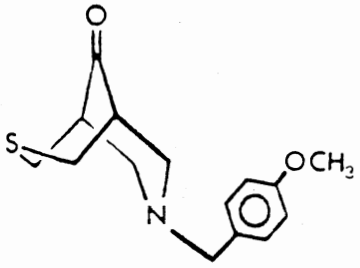
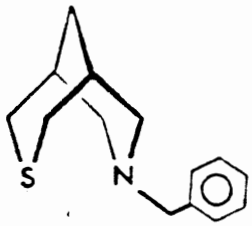
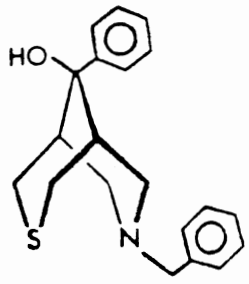
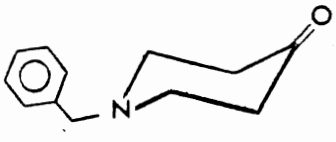
The ^{15}N NMR spectra for selected ketones, a reduced product and one alcohol were recorded. Samples were run in appropriate deuterated solvents (25°C). Signals were referenced to liquid NH_3 (25°C) using neat formamide (112.4 ppm) in a capillary as an external standard.

For closely related compounds very little variation in the ^{15}N resonances was observed (Table XVI). The free amines all showed an upfield shift of 11-13 ppm in comparison to the model 79. This was not unexpected since C(2,4) in each of the bicyclic compounds are γ to the nitrogen, and one would expect a shielding of the nitrogen. The ^{15}N resonances of the perchlorates (Table XVI) were also quite similar to each other. The large deshielding of the ^{15}N signal in 62, 73a, and 83 by 17-19 ppm is well known for protonated amines.[33] The similarities within each series of compounds is not unreasonable since it would be expected that the nitrogens in a given series are most likely in similar environments.

As was observed for the free amines in Table XVI, an upfield

TABLE XVI

^{15}N NMR CHEMICAL SHIFTS

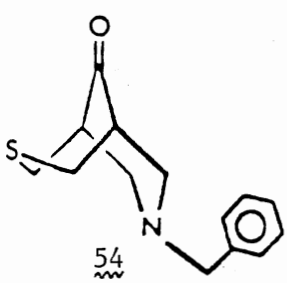
		^{15}N Chemical Shift (ppm)	
		Free Amine ($CDCl_3$)	$HClO_4$ salt (DMSO-d_6)
54		37.36	54.02 83
56		38.02	—
61		36.99	54.16 62
73b		35.45	54.38 73a
79		49.10	—

shift in relation to the model 78 was also found for the ^{15}N signal of 38 (Table XVII). However, the small downfield shift observed for the ^{15}N signal in 49 was unexpected. This observation has not been explained.

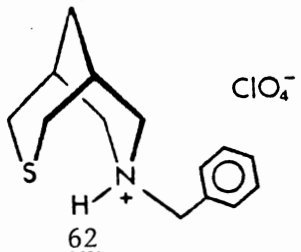
The ^{15}N resonances for 88 and 89 (Table XVII) have been reported by Muller and co-workers.[46] There is a correlation between the ^{15}N signals of the dinitrogen compounds 88 and 89. However, the observed signals in 88 and 89 differ greatly from those for the sulfur-nitrogen compounds 38 and 49. Comparison of the ^{15}N chemical shifts in Tables XVI and XVII show that the observed ^{15}N resonance is highly dependent upon substituents attached to the ring and nitrogen. At this time it is not possible to establish an exact conformation for 3-azabicyclo-[3.3.1]nonanes based upon ^{15}N NMR alone. Further studies on related bicyclic systems in which the conformations are known unequivocally are needed before ^{15}N NMR analysis can be used to assign a conformation to these systems.

Biological Activity

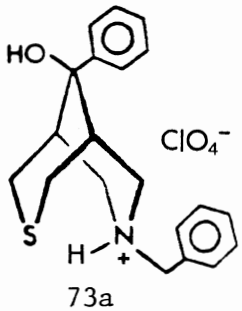
The antiarrhythmic properties of 54, 62, 73a, and 83 were assessed by Benjamin J. Scherlag at the Veterans Administration Medical Center in Oklahoma City. The compounds were studied in mongrel dogs which



54



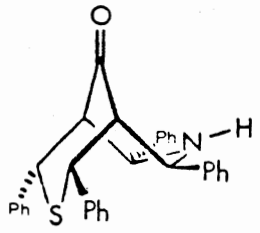
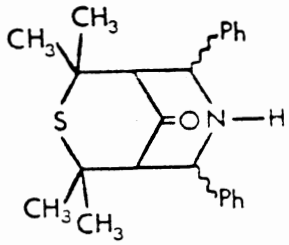
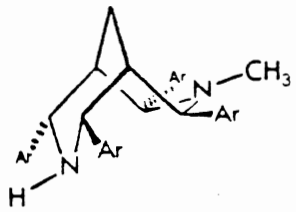
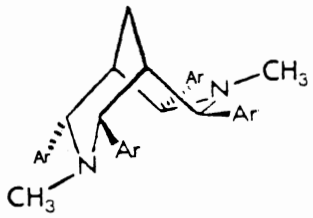
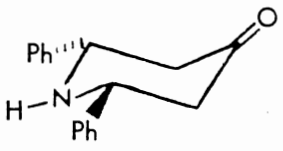
62

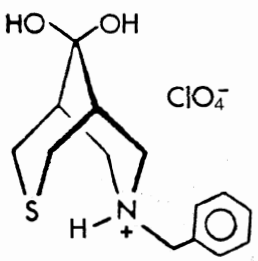


73a

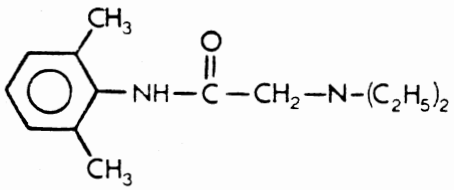
TABLE XVII

^{15}N CHEMICAL SHIFTS FOR 38, 49, 88, 89 AND MODEL 78

		^{15}N Chemical Shift (ppm)	
38		59.73	
49		67.87	
89[46]		49.8(C)	44.5(B)
88[46]		42.7(C)	44.5(B)
78		66.40	



83



37

were examined 24 hours after ligation of the left anterior descending coronary artery. Ligation resulted in an infarct of the heart tissue and the occurrence of irregular contractions interspersed with the normal heart rhythm. The electrical activity of various locations on the heart and the mean arterial blood pressure were monitored continuously. Figure 7 shows a control experiment and a list of the various electrical parameters which were monitored.

Atrial pacing experiments were performed before and after administration of each compound in order to determine the effects of each on conduction in the heart. Ventricular pacing was then instituted by three ventricular paced beats (VPB) at rates between 240/min and 390/min. This pacing has been found to induce a rapid and sustained ventricular tachycardia (Figure 7).[54] If this tachycardia was not terminated within two minutes, it would commonly degenerate into ventricular fibrillation.

Compound 62 was studied in six dogs at doses of 3 and 6 mg/kg of body weight, administered intravenously as a solution in 50% ethanol. Compound 62 caused a 10-15% increase in blood pressure within two minutes in all dogs. In 3 dogs, ventricular tachycardia were completely inhibited even at pacing rates 30-60 beats/min higher than the

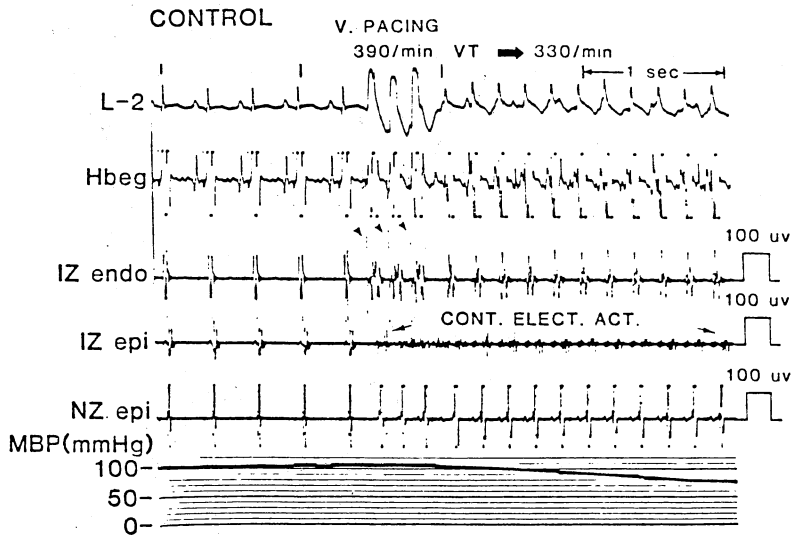
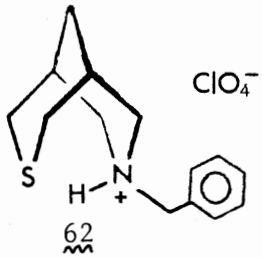
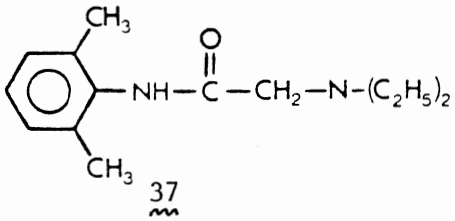


Figure 7. Antiarrhythmic Control Experiment. L-2 = standard lead II of the electrocardiogram. Hbeg = His bundle electrogram. IZ endo = electrode catheter in contact with the endocardium bordering the infarct. IZ epi = composite electrode overlying the infarct epicardium. NZ epi = composite electrode on non-infarcted epicardium. MBP = mean blood pressure.



62



37

rate required to cause tachycardia (Figure 8) before administration of 69 and for 40 min (duration of action) after 62 had been given. In 2 dogs, 62 simply slowed the ventricular tachycardia which were induced by an average of 100 beats/min. However, one dog, which did not show an inductible tachycardia prior to the administration of 62, did exhibit an inductible tachycardia after 62 was administered.

Lidocaine (37), a commonly used antiarrhythmic agent, was used as a model drug in terms of activity on arrhythmias. Lidocaine caused a 5-10% decrease in blood pressure and slowed the rate of induced tachycardia in 3 dogs by an average of 40 beats/min. In one dog, no change in the inducible tachycardia were observed, and in two dogs tachycardia were only inducible after administration of lidocaine. In no dog was the induction of ventricular tachycardia completely abolished as was the case in three instances with 62.

Compound 83 had properties similar to 62, while 54 showed only a slight increase in blood pressure and little antiarrhythmic activity. Alcohol 73a also caused a slight increase in blood pressure but was found to exhibit a markedly depressing effect on conduction not only in abnormal myocardium but also in normal myocardium.

Fifty percent ethanol solutions were injected into the dogs in

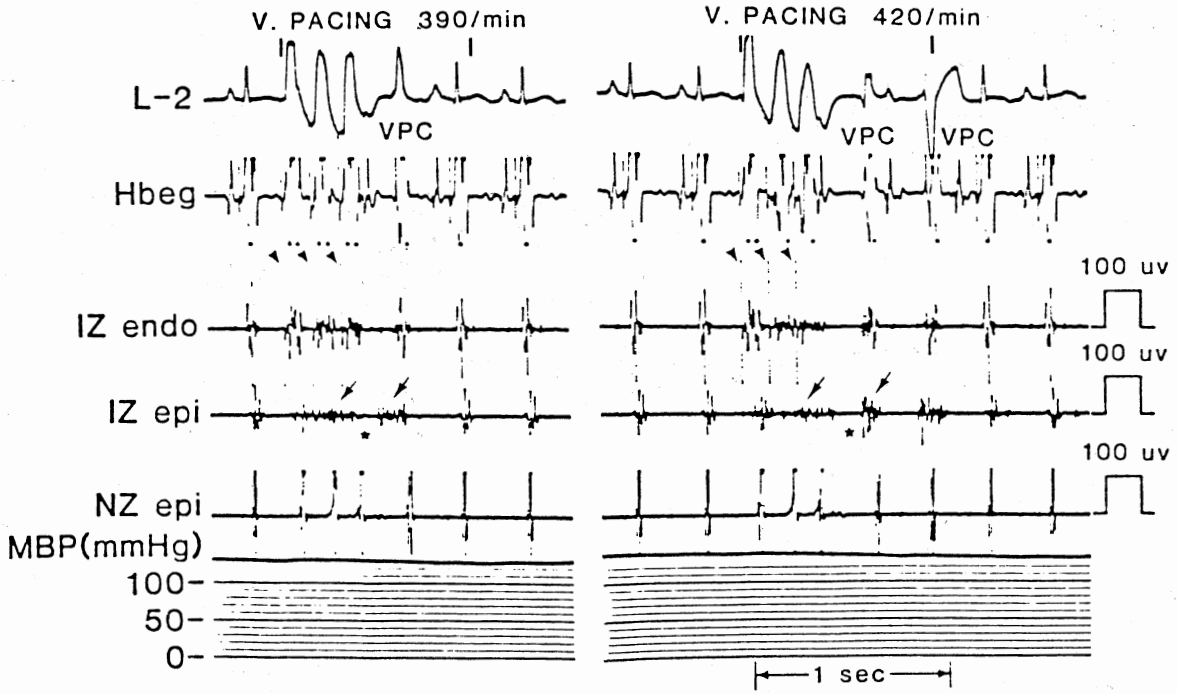
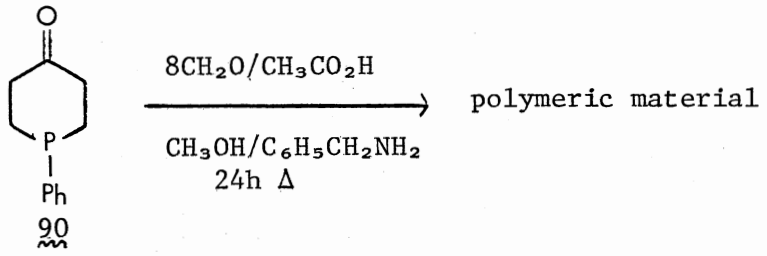


Figure 8. Antiarrhythmic Properties of 62

order to determine if some or any of the effects of 62 were due to the solvent. Ethanol injected intravenously in appropriate volumes produced a small but consistent decrease in arterial blood pressure and no appreciable changes in ventricular activity. Lidocaine 37 and 62 were also given in alternate fashion to some of the dogs that were used in the screening experiments.

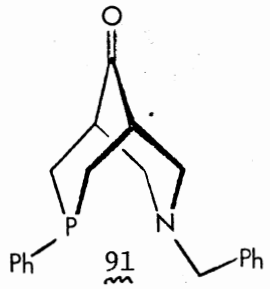
Attempted Preparation

Starting with an appropriate phosphorinan-4-one, several attempts were made to prepare selected 7-aza-3-phosphabicyclo[3.3.1]nonan-9-ones. Compound 90 under the conditions shown gave only an insoluble,



90

red polymeric material. No evidence was found by ^{13}C NMR analysis that the desired product 91 was formed. The reaction was repeated



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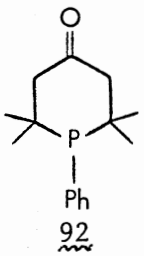

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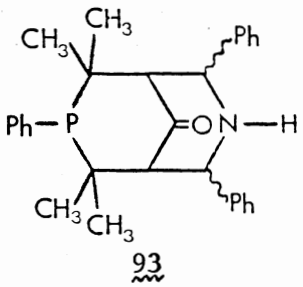
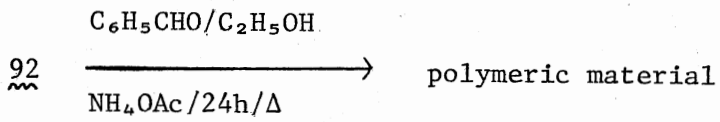


93

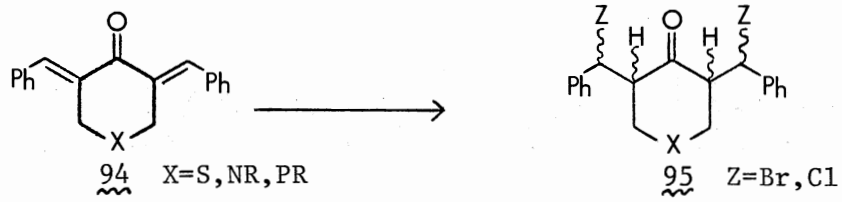
with twice the amount of acetic acid in the belief that the basicity of the phosphorous may effect the reaction, but the same results were obtained.

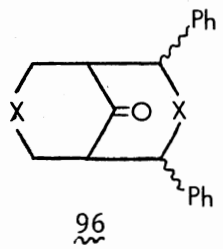
The above reactions were repeated using phosphorinanone 92. However, only polymeric material was obtained as was the case when using 90. Conceivably, the 6,8-diphenyl derivative 93 might be easier to prepare and isolate, and therefore ketone 92 was treated as shown, but again only in polymeric material was obtained.



Suggestions for Future Work

Dienones like 94 should be easily obtainable. These dienones could then be converted to the dihalide 95. Compound 95 would undoubtedly be a mixture of cis-trans isomers. However, when treated with Na_2S, R-NH_2, or R-PH_2 the cis isomer of 95 should condense to give 2,4-diphenyl-3,7-diheterobicyclo[3.3.1]nonan-9-one (96). This

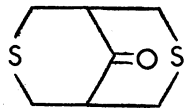




procedure would lead to a cis-trans mixture of 96 which should be

separable by column chromatography.

7,3-Dithiabicyclo[3.3.1]nonan-9-one (97) could be prepared by treating the salt 98 with Na_2S.[30,20] Ketone 97 has been reported but has not been fully characterized.[68]



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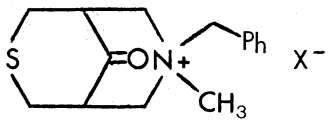
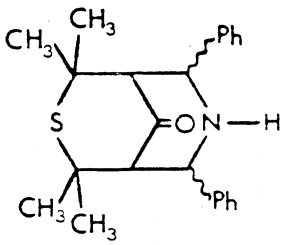
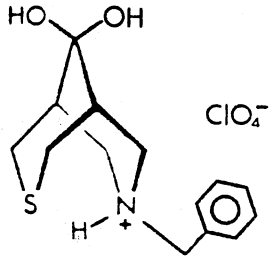


98

X-Ray analysis of 49 should be performed to establish the conformation and structure. The nitrogen ring of 49 is biased by the 6,8-diphenyl groups, but the sulfur ring is potentially mobile. In light of the conformations found for 38 and reported for 88 and 89 (Table XVII), there is the strong possibility that 49 has the nitrogen ring in a boat form. The X-ray analysis of 83 was recently completed and revealed a chair-chair conformation as well as hydration of the carbonyl (gem diol) which had been indicated by IR and ^{13}C NMR analysis.[25]



49



83

CHAPTER III

EXPERIMENTAL

Reactions were carried out under a N_2 atmosphere and magnetically stirred unless otherwise noted. Solvents were removed during workups by means of a rotatory-evaporator. Tetrahydrothiopyran-4-one,[30] cis-2,6-diphenyltetrahydrothiopyran-4-one,[11] and 2,2,6,6-tetramethylthiopyran-4-one[38] were prepared by literature procedures. Hydrazine (Eastman, 95%), benzylamine (Eastman, bp 182-185°C), 2-phenethylamine (Matheson Coleman and Bell, bp 198-200°C), 4-methoxybenzylamine (Aldrich, bp 236-237°C), 2-(4-methoxyphenyl)ethylamine (Aldrich, bp 138-140°C/20 mm), 3,4-dimethoxybenzylamine (Aldrich, bp 180°C/15 mm), 2-(3,4-dimethoxyphenyl)ethylamine (Aldrich, bp 154-158°C/12 mm), $HClO_4$ (Baker), $Na_2S \cdot 9H_2O$ (Aldrich), H_2S (Matheson), phenylmagnesium chloride (Aldrich, 2 M in THF), methylmagnesium chloride (Aldrich, 2 M in THF), N-methyl-4-piperidone (Aldrich), and $NaBH_4$ (Matheson Coleman and Bell) were used as purchased without further purification. Melting points were determined with a Thomas Hoover capillary apparatus and were uncorrected. IR spectral data were obtained on a Perkin-Elmer 681 IR spectrometer. NMR spectra were obtained on a Varian XL-100(15) NMR spectrometer equipped with a Nicolet TT-100 PFT accessory or a Varian XL-300 NMR spectrometer. The ^1H and ^{13}C spectra were recorded as δ values or in parts per million (ppm), respectively, downfield from Me_4Si (TMS) as an internal standard. Single-frequency, off-resonance

spectra were obtained by irradiating with a continuous wave frequency at about δ-5 compared to Me_4Si in the proton spectrum. The ^{15}N spectra were recorded at 30.41 MHz in ppm downfield from liquid NH_3 (25°C) using formamide (neat) (112.4 ppm) in a capillary as an external standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. RT means room temperature.

cis-2,4,6,8-Tetraphenyl-7-aza-3-thiabicyclo[3.3.1]nonan-9-one (38)

A mixture of 1.34 g (0.005 mol) of cis-2,6-diphenyltetrahydrothiopyran-4-one (40),[48] 1.06 g (0.01 mol) of benzaldehyde, 0.40 g (0.005 mol) of ammonium acetate, and 95% ethanol (10 mL) was heated at 60°C for 5 h under N_2 in a 25 mL flask equipped with a condenser. The resulting mixture was cooled and 10 mL of ether was added to keep the resinous material in solution. The solution was cooled to 0°C, and a white solid that separated was filtered off and washed with ether (5 mL). Recrystallization (C_6H_6) gave 0.40 g (17%) of 38; mp 207-209°C (lit.[1] mp 207-209°C); IR (KBr) 3320 (N-H), 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.50 (s, 1 H, NH), 3.21 [t, 2 H, H(1), H(5)], 4.66 [d, 2 H, J = 2 Hz, H(6), H(8)], 4.90 [d, 2 H, J = 4 Hz, H(2), H(4)], 6.76-7.49 (m, 29 H, ArH). ^{15}N NMR ($CDCl_3$) 59.73 ppm. Mass spectral m/e, calcd. for $C_{31}H_{27}NOS$: (M^+) 461.1813; Found: 461.1827.

cis-2,4,6,8-Tetraphenyl-1,5-dideuterio-7-aza-3-thiabicyclo[3.3.1]nonan-9-one (41)

A mixture of 0.10 g (0.37 mmol) of cis-2,6-diphenyl-3,3,5,5-tetradeuterio-4-thianone (43),[48] 0.08 g (0.75 mmol) of benzaldehyde, 0.029 g

(0.38 mmol) of ammonium acetate, and absolute C_2H_5OD (Aldrich, 99.5% D, 1 mL) was heated to 60°C for 5 h under N_2 in a 5 mL flask. The resulting mixture was cooled, and 2 mL of ether was added to keep the resinous material in solution. The solution was cooled to 0°C, and a white solid that separated was filtered off and washed with ether (2 mL). Recrystallization (C_6H_6) gave 23 mg (12%) of 41: mp 207-209°C; IR (KBr) 3320 (N-H), 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.50 (s, 1 H, NH), 4.66 [s, 2 H, H(6), H(8)], 4.90 [s, 2 H, H(2), H(4)], 6.76-6.49 (m, 29 H, ArH); ^{13}C NMR ($CDCl_3$) ppm 52.11 [s, C(6,8)], 59.26 [s, C(2,4)], 61.05 [m, C(1,5)]; Mass spectral m/e, calcd. for $C_{31}H_{25}D_2NOS$: (M^+) 463.1939; Found: 463.1976.

cis-2,4,6,8-Tetraphenyl-7-aza-3-thiabicyclo-[3.3.1]nonan-9-one-2,4-^{13}C (42)

A mixture of 0.20 g (0.7 mmol) of cis-2,6-diphenyltetrahydrothiapyran-4-one (40)[48] and 0.058 g (0.7 mmol) of ammonium acetate in 2 mL of absolute ethanol was prepared in a 5 mL flask equipped with a condenser. To the above, 0.158 g (1.5 mmol) of benzaldehyde (which contained 30.8 mg of 43.86% $C_6H_5{}^{13}CHO$, Merck and Co.) was added, and the resulting mixture was heated to 60°C for 12 h under N_2 with stirring. Upon cooling, 2 mL of dry ether was added to keep the resinous material in solution. The solution was cooled to 0°C, and a white solid that separated was filtered off and washed with ether (2 mL). Recrystallization (C_6H_6) gave 68 mg (19%) of 42: mp 207-209°C; IR (KBr) 3320 (NH), 1710 cm^{-1} (C=O). The NMR analysis (^1H and ^{13}C) of 42 gave identical results as found with 38 except in the ^{13}C NMR spectrum of 42. The signal at 59.24 ppm [C(2,4)] was greatly

enhanced due to the increased percentage of ^{13}C at C(2,4). Mass spectral m/e, calcd. for $C_{31}H_{27}NOS$ (unlabeled); (M^+) 461.1813; Found: 461.1815; calcd. for $^{13}C^{12}C_{30}H_{27}NOS$ (labeled); (M^+) 462.1847; Found: 462.1876.

N-Benzyl-7-aza-3-thiabicyclo[3.3.1]-nonan-9-one (54)

A solution containing 0.46 g (4.3 mmol) of benzylamine, 1.00 g (33.0 mmol) of paraformaldehyde and 15 mL of methyl alcohol in a 50 mL flask equipped with a condenser was made acidic with 0.38 g (6.3 mmol) of gl acetic acid. Tetrahydrothiopyran-4-one (53) 0.50 g (4.3 mmol) was added to the above mixture in one portion. After the resulting mixture was heated at reflux for 6 h, the solvent was removed, and the red oily residue was partitioned between H_2O:ether (30 mL:30 mL). The layers were separated, and the ether layer was discarded. The aqueous layer was made strongly basic with 0.5 g (12.5 mmol) of NaOH pellets. The aqueous mixture was extracted with 4 X 30 mL of ether, and the extracts were combined and dried (Na_2SO_4). The solvent was removed from the yellow solution to give a yellow brown oil that solidified. The solid was digested with 100 mL of Skelly B on a steam bath for 30 min, and the hot solution was decanted from the dark brown residue. Evaporation of the solvent gave 0.5 g of a yellow solid which contained several white crystalline masses. The total solid was placed in a sublimation apparatus and molecularly distilled at 0.025 mm/110°C (oil bath) to give 0.40 g (38%) of 54: mp 91-92°C; IR (KBr) 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.25-3.25 (m, 10 H, ring $C\underline{H}_2$ and $C\underline{H}$), 3.5 (s, 2 H, $C_6H_5-C\underline{H}_2$), 7.25 (m, 5 H, Ar$\underline{H}$);

^{13}C NMR ($CDCl_3$) ppm 34.6 [C(2,4)], 47.1 [C(1,5)], 58.4 [C(6,8)], 61.4 [C(1')], 212.8 [C(9)], 127.3, 128.2, 128.6, 137.9 (Ar-C); ^{15}N NMR ($CDCl_3$) 37.36 ppm. Mass spectral m/e, calcd. for $C_{14}H_{17}NOS$: (M^+) 247.1031; Found: 247.1031. Anal. calcd. for $C_{14}H_{17}NOS$: C, 68.02; H, 6.88; N, 5.67; S, 12.95. Found: C, 68.01; H, 6.96; N, 5.67; S, 13.07.

N-Benzyl-7-aza-3-thiabicyclo[3.3.1]nonan-9,9-diol Hydroperchlorate (83)

A solution of 0.30 g (0.001 mol) of 54 in 30 mL of (1:1) water: ethanol was treated dropwise with 1 mL of $HClO_4$ (60%) over a 5-min period. A white solid precipitated and was redissolved upon heating the mixture on a steam bath. The hot solution was treated with decolorizing carbon and filtered hot. The solution was cooled to -20°C and the solid that formed was filtered to give 0.32 g (76%) of 83: mp 214-215°C; IR (KBr) 3460, 3280 (O-H, N-H), 1100 cm^{-1} (ClO_4^-); ^{1}H NMR (DMSO-d_6) δ 2.4-2.8 (m, 6 H, ring CH_2 and CH), 3.1-3.65 (m, 6 H, ring CH_2, CH and OH), 7.5-7.62 (m, 5 H, Ar-H); ^{13}C NMR (DMSO-d_6) ppm 29.0 [C(2,4)], 37.3 [C(1,5)], 54.7 [C(6,8)], 59.9 (Ar-CH_2), 88.5 [C(9)], 129.0, 129.4, 129.9, 130.3 (Ar-C); ^{15}N NMR (DMSO-d_6) 54.02 ppm; Mass spectral m/e, calcd. for $C_{14}H_{17}NOS \cdot HClO_4 \cdot H_2O$: ($M^+$-$HClO_4 \cdot H_2O$) 247.1031; Found: 247.1028.

N-Benzyl-7-aza-3-thiabicyclo[3.3.1]nonan-9-ol (69)

A mixture of 48 mg (1.3 mmol) of $NaBH_4$ and 0.25 g (1 mmol) of 54 in 10 mL of isopropyl alcohol was stirred at RT for 12 h in a 25 mL flask. The solvent was removed and 20 mL of H_2O was added to the

residue. The aqueous mixture was extracted with ether (4 X 30 mL), and the organic layers were combined and dried (Na_2SO_4). The ether solution was filtered and the solvent was removed to give a pale yellow oil. The oil was dissolved in 30 mL of boiling Skelly B (bp 60-68°C) and, the solution was allowed to cool to RT. White crystals formed and were filtered to give 0.14 g (56%) of 69: mp 99-101°C; IR (KBr) 3240 cm^{-1} (O-H); ^1H NMR ($CDCl_3$) δ 2.2-3.25 (m, 11 H, ring C<u>H</u>$_2$ and C<u>H</u>), 3.55 (s, 2 H, Ar-C<u>H</u>$_2$), 3.75 (s, 1 H, O-<u>H</u>), 7.25-7.5 (m, 5 H, Ar-<u>H</u>); ^{13}C NMR ($CDCl_3$) ppm 26.54 [C(2,4)], 33.41 [C(1,5)], 58.22 [C(6,8)], 62.21 (Ar-<u>C</u>H$_2$), 70.97 [C(9)], 126.65, 128.01, 128.42, 138.70 (Ar<u>C</u>). Mass spectral m/e, calcd. for $C_{14}H_{19}NOS$: (M^+) 249.1187; Found: 249.1209.

<u>N-Benzyl-7-aza-3-sulfoxidebicyclo[3.3.1]-nonan-9-one (80)</u>

A solution of 0.90 g (4.2 mmol) of $NaIO_4$ in 5 mL of water was added to a stirred solution of 0.50 g (2.0 mmol) of 54 in 25 mL of methanol in a 50 mL flask under N_2. The resulting mixture was stirred at RT for 72 h at which time the solvent was removed to give a white solid. The solid was suspended in $CHCl_3$ (20 mL) and the insoluble material was filtered. Evaporation of the solvent gave a yellow solid. Recrystallization (ethyl acetate) gave 0.12 g (23%) of 80: mp 125-127°C; ^1H NMR ($CDCl_3$) δ 2.35-3.20 (m, 8 H, ring C<u>H</u>$_2$ and C<u>H</u>), 3.60-3.82 (m, 2 H, ring C<u>H</u>$_2$ and CH), 3.68 (s, 2 H, Ar-C<u>H</u>$_2$), 7.2-7.45 (m, 5 H, Ar-<u>H</u>); ^{13}C NMR ($CDCl_3$) ppm 47.70 [C(1,5)], 58.06 [C(6.8)], 59.34 [C(2,4)], 61.27 (Ar-<u>C</u>H$_2$), 208.7 [C(9)], 127.6, 128.5, 129.0, 136.5 (Ar-<u>C</u>). Mass spectral m/e, calcd. for $C_{14}H_{17}NO_2S$: (M^+)

263.0980; Found: 263.0982.

General Procedure for N-alkyl-7-aza-3-thia-bicyclo[3.3.1]nonan-9-one (39a)

A mixture containing 25.9 mmol of an amine, 6.20 g (210 mmol) of paraformaldehyde and 90 mL of methyl alcohol in a 250 mL flask equipped with a condenser was made acidic with 2.30 g (38 mmol) of gl acetic acid. In one portion, 3.00 g (25.9 mmol) of tetrahydrothiopyran-4-one (53) was added to the above mixture. The resulting mixture was heated under N_2 at reflux for 6-12 h. The solvent was removed from the red solution to give a red oil. This oil was diluted with 180 mL of H_2O and extracted with 2 X 40 mL of ether which was discarded. The aqueous layer was made basic by the addition of 4.3 g (77 mmol) of KOH pellets and extracted with 4 X 75 mL of ether.

The ether extracts were combined and dried (Na_2SO_4). The above solution was filtered, and the solvent was removed to give a yellow brown oil or a solid. This oil (or solid) was distilled (or digested) in Skelly B (bp 60-68°C). This was followed by decantation of the hot solution, evaporation of the solvent, and molecular distillation of the crude product in a sublimation apparatus. The details are given for each amine.

N-Phenethyl-7-aza-3-thiabicyclo[3.3.1]nonan-9-one (55)

Following the general procedure using 3.1 g (25.9 mmol) of phenethylamine and heating for 12 h gave a reddish yellow solid. This solid was digested with 200 mL of Skelly B for 10 min. The hot

Skelly B solution was decanted and allowed to evaporate to give a white solid. Distillation in a sublimation apparatus at 100-140°C (oil bath) 10^{-4}-10^{-5} mm gave 2.4 g (53%) of 55: mp 87-88°C; IR (KBr) 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 2.65-2.85 (m, 8 H, ring $C\underline{H}_2$ and $C\underline{H}$ and Ar-$C\underline{H}_2$-$C\underline{H}_2$), 3.1-3.26 (m, 6 H, ring $C\underline{H}_2$ and $C\underline{H}$ and Ar-$C\underline{H}_2$-$C\underline{H}_2$), 7.28 (m, 5 H, Ar-$\underline{H}$); ^{13}C NMR ($CDCl_3$) ppm 34.74 (Ar-$\underline{C}H_2$), 34.61 [C(2,4)], 47.04 [C(1,5)], 58.25 [C(6,8)], 58.36 [Ar-CH_2-$\underline{C}H_2$], 212.8 [C(9)], 125.9, 128.2, 128.4, 139.7 (Ar-$\underline{C}$); Mass spectral m/e, calcd. for $C_{15}H_{19}NOS$: (M^+) 261.1187; Found: 261.1183. Anal. calcd. for $C_{15}H_{19}NOS$: C, 68.97; H, 7.28; N, 5.36; S, 12.26. Found C, 69.15; H, 7.39; N, 5.35; S, 12.33.

N-4-Methoxybenzyl-7-aza-3-thiabicyclo-[3.3.1]nonan-9-one (56)

Following the general procedure using 2.4 g (25.9 mmol) of 4-methoxybenzylamine and heating for 12 h gave a red solid. Digestion with 200 mL of Skelly B, followed by decantation of the hot solution and evaporation, gave a yellow solid. Molecular distillation in a sublimation apparatus at 140-145°C (oil bath)/10^{-4} mm gave 2.8 g (39%) of 56: mp 96-7°C; IR (KBr) 1720 (C=O), 3410 cm^{-1} (C=O overtone); ^{1}H NMR ($CDCl_3$) δ 2.6-3.25 (m, 10 H, ring $C\underline{H}_2$ and $C\underline{H}$), 3.5 (s, 2 H, Ar$C\underline{H}_2$), 3.78 (s, 3 H, Ar-O$C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) ppm 34.64 [C(2,4)], 47.01 [C(1,5)], 55.12 ($\underline{C}H_3$-O), 58.16 [C(6,8)], 60.61 (Ar-$\underline{C}H_2$), 212.96 [C(9)], 113.57, 129.71, 129.97, 158.63 (Ar-$\underline{C}$); ^{15}N NMR ($CDCl_3$) 38.02 ppm; Mass spectral m/e, calcd. for $C_{15}H_{19}NO_2S$: (M^+) 277.1136; Found: 277.1133.

N-3,4-Dimethoxyphenethyl-7-aza-3-thiabicyclo[3.3.1]nonan-9-one (59)

Following the general procedure using 4.7 g (25.9 mmol) of 3,4-dimethoxyphenethylamine and heating for 12 h gave a red oil. Distillation through a 3 inch column at 180-190°C (head temp.)/10^{-4}mm gave a yellow oil. This oil was distilled and then dissolved in 20 mL of 95% ethanol, and the solution was placed in a freezer at -5°C for 48 h. The solid that crystallized was filtered off and recrystallization (ethanol) gave 0.7 g (8.4%) of 59: mp 80.5-81°C; IR (KBr) 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.7-2.95 (m, 8 H, ring CH_2, CH and $ArCH_2$-CH_2), 3.1-3.3 (m, 6 H, ring CH_2, CH) and $ArCH_2$), 3.85 (s, 6 H, ortho and para CH_3-O), 6.85 (s, 3 H, ArH); ^{13}C NMR ($CDCl_3$) ppm 33.28 (Ar-CH_2), 34.62 [C(2,4)], 46.96 [C(1,5)], 55.68 (CH_3-O), 55.75 (CH_3-O), 58.34 [C(6,8)], 58.43 (Ar-CH_2-CH_2), 212.74 [C(9)], 111.13, 111.88, 120.32, 132.46, 147.11, 148.54 (Ar-C); Mass spectral m/e, calcd. for $C_{17}H_{23}NO_3S$: (M^+) 321.1399; Found: 321.1408.

N-4-Methoxyphenethyl-7-aza-3-thiabicyclo[3.3.1]nonan-9-one (57)

Following the general procedure using 3.9 g (25.9 mmol) of 4-methoxyphenethylamine and heating for 12 h gave a yellow oil. The oil was distilled through a 3 inch column at 180-200°C (head temp.)/-10^{-2}-10^{-5} mm. The clear oil obtained was dissolved in 20 mL of ethanol (95%), and the solution was placed in a freezer (-5°C) overnight. The white solid that crystallized was filtered off and gave 1.6 g (21%) of 57: mp 79-80°C; IR (KBr) 1725 cm^{-1} (C=O);

^{1}H NMR ($CDCl_3$) δ 2.6-2.9 (m, 8 H, ring C$\underline{H}_2$, C$\underline{H}$ and Ar-C$\underline{H}_2$-C$\underline{H}_2$), 3.1-3.2 (m, 6 H, ring C$\underline{H}_2$, C$\underline{H}$ and Ar-C$\underline{H}_2$-C$\underline{H}_2$), 3.75 (s, 3 H, C$\underline{H}_3$-O), 6.75-7.2 (q, 4 H, Ar-$\underline{H}$); ^{13}C NMR ($CDCl_3$) ppm 32.88 (Ar-$\underline{C}H_2$), 34.69 [C(2,4)], 47.07 [C(1,5)], 55.5 ($\underline{C}H_3$-O), 58.42 [C(6,8)], 58.56 (Ar-CH_2-$\underline{C}H_2$), 212.75 [C(9)], 113.68, 129.32, 131.78, 157.78 (Ar-$\underline{C}$); Mass spectral m/e, calcd. for $C_{16}H_{21}NO_2S$: (M^+) 291.1293; Found: 291.1302.

N-3,4-Dimethoxybenzyl-7-aza-3-thiabicyclo-[3.3.1]nonan-9-one (58)

Following the general procedure using 4.40 g (26.5 mmol) of 3,4-dimethoxybenzylamine and heating for 12 h gave an orange oil. Distillation of the oil through a 3 inch column at 185-200°C (head temp.)/10^{-4}-10^{-5} mm gave a clear oil which was dissolved in 15 mL of 95% ethanol. The resulting solution was placed in a freezer (-5°C) overnight. The white solid that crystallized was filtered off and dried at RT and 1 mm for 1 h. This procedure gave 0.53 g (6.5%) of 58: mp 81-83°C; IR (KBr) 1725 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 2.70-2.84 (m, 4 H, ring C$\underline{H}_2$ and C$\underline{H}$), 3.09-3.25 (m, 6 H, ring C$\underline{H}_2$ and C$\underline{H}$), 3.54 (s, 2 H, ArC$\underline{H}_2$), 3.90 (S, 3 H, C$\underline{H}_3$-O), 3.92 (s, 3 H, C$\underline{H}_3$O), 6.8-7.0 (m, 3 H, Ar-$\underline{H}$); ^{13}C NMR ($CDCl_3$) ppm 34.84 [C(2,4)], 47.01 [C(1,5)], 57.77 (ortho and para $\underline{C}H_3$-O), 58.11 [C(6,8)], 60.90 [C(1')], 212.76 [C(9)], 110.77, 111.62, 120.61, 130.64, 148.01, 148.77 (Ar-$\underline{C}$); Mass spectral m/e, calcd. for $C_{16}H_{21}NO_3S$: (M^+) 307.1242; Found: 307.1243.

2,2,4,4-Tetramethyl-6,8-diphenyl-7-aza-3-thiabicyclo[3.3.1]nonan-9-one (49)

A mixture of 0.45 g (5.8 mmol) of ammonium acetate, 1.23 g (11.6 mmol) of benzaldehyde, and 1.00 g (5.8 mmol) of 2,2,6,6-tetramethylthiapyran-4-one (48)[22] in 10 mL of 95% ethanol was heated at reflux for 48 h under N_2 in a 25 mL flask. A white precipitate formed upon cooking to RT, and 0.5 mL of ether was added to the mixture which was then placed in the freezer (-10°C) for 1 h. The precipitated white solid was filtered and washed with 2 mL of ether. Recrystallization (95% ethanol) gave 0.53 g (25%) of 49: mp 253-254°C; IR (KBr) 3325 (N-H), 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.25 (s, 6 H, CH_{3a}), 1.45 (s, 6 H, CH_{3e}), 1.6 (s, 1 H, NH), 2.6 [d, 2 H, J = 5 Hz, H(6), H(8)] 7.2-7.5 (m, 10 H, Ar-H); ^{13}C NMR ($CDCl_3$) ppm 28.66 (CH_{3a}), 32.45 (CH_{3e}), 50.45 [C(2,4)], 62.94 [C(6,8)], 64.40 [C(1,5)], 211.47 [C(9)], 127.53, 127.69, 128.45, 144.47 (Ar-C); ^{15}N NMR ($CDCl_3$) 67.87 ppm; Mass spectral m/e, calcd. for $C_{23}H_{27}NOS$: (M^+) 365.1813; Found: 365.1800.

N-Benzyl-7-aza-3-thiabicyclo[3.3.1]nonane Hydroperchlorate (62)

To a solution of 10 mL of triethylene glycol and 2.00 g (59.4 mmol) of hydrazine (95%) in a 25 mL flask equipped with a condenser, which had a fractional take off below the water jacket, was added 0.50 g (2.0 mmol) of 54. Then, 3.50 g (62.5 mmol) of KOH pellets were added, and the resulting mixture was heated to 145-155°C (oil bath) under N_2 with stirring for 4 h. During this time, 1.5 mL of distillate was

removed by way of the fractional take off. The solution was cooled to RT, diluted with 30 mL of H_2O, and extracted with 3 X 30 mL of ether. The organic layers were combined and dried (Na_2SO_4). The solution was then filtered and cooled. To the cooled solution, 2 mL of $HClO_4$ (60%) was added slowly. A white solid separated and was filtered and washed with 50 mL of fresh dry ether. Recrystallization (95% ethanol) gave 0.55 (82%) of 62: mp 155-156°C; IR (KBr) 3400 (NH), 1100 cm^{-1} (ClO_4^-); ^1H NMR (DMSO-d_6) δ 1.6-3.1 (m, 12 H, ring CH_2 and CH), 4.27 (d, 2 H, $C_6H_5-CH_2$), 7.5 (m, 5 H, Ar-H); ^{13}C NMR (DMSO-d_6) ppm 24.90 [C(1,5)], 27.67 [C(9)], 29.89 [C(2,4)], 58.54 [C(6,8)], 63.18 [C(1')], 126.4, 127.8, 128.4, 139.0 (Ar-C); ^{15}N NMR (DMSO-d_6) 54.16 ppm; Mass spectral m/e, calcd. for $C_{14}H_{19}NS \cdot HClO_4$: ($M^+-HClO_4$) 233.1238; Found: 233.1228. Anal. calcd. for $C_{14}H_{19}NS \cdot HClO_4$: C, 50.37; H, 6.00; N, 4.19; S, 9.60. Found: C, 49.99; H, 6.07; N, 4.13; S, 9.68.

N-Phenethyl-7-aza-3-thiabicyclo[3.3.1]-nonane Hydroperchlorate (63)

To a solution of 10 mL of triethylene glycol and 2 g (59.4 mmol) of hydrazine (95%) in a 25 mL flask equipped with a condenser, which had a fractional take off below the water jacket, was added 0.5 g (1.9 mmol) of 55. Then, 3.5 g (62.5 mmol) of KOH pellets were added, and the resulting mixture was heated to 150-155°C (oil bath) under N_2 with magnetic stirring for 4 h. During this time, 1.5 mL of distillate was removed by way of the fractional take off. The solution was cooled to RT, diluted with 30 mL of H_2O and extracted with ether (3 X 30 mL). The organic layers were combined and dried (Na_2SO_4).

The solution was then filtered and cooled (ice bath). To the cooled solution, 2 mL of $HClO_4$ (60%) was added slowly. A white solid separated and was filtered and washed with 50 mL of fresh dry ether. Recrystallization (95% ethanol) gave 0.3 g (45%) of 63: mp 255-258°C; IR (KBr) 3420 (N-H), 1600, (Ar, C=C), 1100 cm^{-1} (ClO_4^-); ^1H NMR (DMSO-d_6) δ 1.85 [s, 2 H, H(9)], 2.25-3.5 (m, 12 H, ring CH_2), CH and Ar-CH_2), 3.85 (d, 2 H, Ar-CH_2-CH_2), 7.33 (s, 5 H, Ar-H), 9.0 (s, 1 H, N-H); ^{13}C NMR (DMSO-d_6) ppm 25.71 [C(1,5)], 28.28 [C(9)], 29.88 (Ar-CH_2-CH_2), 30.64 [C(2,4)], 56.38 [C(6,8)], 59.03 (Ar-CH_2-CH_2), 126.67, 128.46, 136.33 (Ar-C); Mass spectral m/e, calcd. for $C_{15}H_{19}NS \cdot HClO_4$: ($M^+$-$HClO_4$) 245.1238; Found: 245.1125.

N-4-Methoxybenzyl-7-aza-3-thiabicyclo-[3.3.1]nonane Hydroperchlorate (64)

To a solution of 10 mL of triethylene glycol and 2 g (59.4 mmol) of hydrazine (95%) in a 25 mL flask equipped with a condenser which had a fractional take off below the water jacket was added 0.5 g (1.8 mmol) of 56. Then, 3.5 g (62.5 mmol) of KOH pellets were added and the resulting mixture was heated to 155-160°C (oil bath) under N_2 with magnetic stirring for 4 h. During this time, 1.5 mL of distillate was removed by way of the fractional take off. The solution was cooled to RT, diluted with 30 mL of H_2O, and extracted with ether (3 X 30 mL). The organic layers were combined and dried (Na_2SO_4). The solution was then filtered and cooled (ice bath). To the cooled solution, 2 mL of $HClO_4$ (60%) was added slowly. A white solid separated and was filtered and washed with 50 mL of fresh dry ether. Recrystallization (95% ethanol) gave 0.4 g (85%)

of 64: mp 201-202°C; IR (KBr) 3450 (N-H), 1100 cm^{-1} (ClO_4^-); ^1H NMR (DMSO-d_6) δ 1.80-3.60 (m, 12 H, ring CH_2 and CH), 3.80 (s, 3 H, CH_3-O), 4.21 (s, 2 H, Ar-CH_2), 7.08 (d, 2 H, J = 9 Hz, Ar-H), 7.52 (d, 2 H, J = 9 Hz, Ar-H), 9.1 (s, 1 H, N-H); ^{13}C NMR (DMSO-d_6) ppm 25.83 [C(1,5)], 28.60 [C(9)], 30.78 [C(2,4)], 55.12 (CH_3-O), 56.21 [C(6,8)], 60.40 (Ar-CH_2), 114.30, 121.54, 131.84, 159.83 (Ar-C). Anal. calcd. for $C_{15}H_{21}NOS \cdot HClO_4$: C, 49.52; H, 6.05. Found: C, 50.11; H, 6.23.

N-3,4-Dimethoxyphenethyl-7-aza-3-thiabicyclo-[3.3.1]nonane Hydroperchlorate (65)

To a solution of 10 mL of triethylene glycol and 2.0 g (59.4 mmol) of hydrazine (95%) in a 25 mL flask equipped with a condenser, which had a fractional take off below the water jacket, was added 0.50 g (1.6 mmol) of 59. Then, 3.50 g (62.5 mmol) of KOH pellets were added, and the resulting mixture was heated to 145-155°C (oil bath) under N_2 with magnetic stirring for 4 h. During this time, 1.5 mL of distillate was removed by way of the fractional take off. The solution was cooled to RT, diluted with 30 mL of H_2O, and extracted with ether (3 X 30 mL). The organic layers were combined and dried (Na_2SO_4). The solution was then filtered and cooled (ice bath). The the cooled solution, 2 mL of $HClO_4$ (60%) was added slowly. An oil separated and the mixture was placed in the freezer (-5°C) overnight during which time crystals formed. The solid was filtered and washed with dry ether (50 mL) to give 0.15 g (24%) of 65: mp 161-162°C; IR (KBr) 3400 (N-H), 1100 cm^{-1} (ClO_4^-); ^1H NMR (DMSO-d_6) δ 1.7-3.5 (m, 16 H, ring CH_2, CH and Ar-CH_2-CH_2), 3.74 (s, 3 H, ortho or para CH_3-O), 3.78

(s, 3 H, ortho or para CH_3-O), 6.9 (m, 3 H, Ar-H); ^{13}C NMR (DMSO-d_6) ppm 25.79 [C(1,5)], 28.39 [C(9)], 29.54 (Ar-CH_2-), 30.74 [C(2,4)], 55.39 (CH_3-O), 56.50 [C(6,8)], 59.30 ($ArCH_2$-CH_2), 112.11, 112.44, 120.55, 128.51, 147.66, 148.73 (Ar-C). Anal. calcd. for $C_{17}H_{26}NO_2S \cdot HClO_4$: C, 50.06; H, 6.38. Found: C, 49.91; H, 6.49.

2,4,6,8-Tetraphenyl-7-aza-3-thiabicyclo[3.3.1]nonane (66)

To a solution of 4 mL of triethylene glycol and 1.0 g (29.7 mmol) of hydrazine (95%) in a 15 mL flask equipped with a condenser, which had a fractional take off below the water jacket, was added 0.15 g (0.3 mmol) of 38. Then, 1.5 g (26.8 mmol) of KOH pellets were added, and the resulting mixture was heated to 150-155°C (oil bath) under N_2 with magnetic stirring for 4 h. During this time, 0.5 mL of distillate was removed by way of the fractional take off. The solution was cooled to RT and diluted with 30 mL of H_2O. A white solid separated and was filtered and washed with 50 mL of H_2O. Recrystallization (95% ethanol) gave 0.11 g (74%) of 66: mp 255-256°C; IR (KBr) ^1H NMR ($CDCl_3$) δ 1.29 (s, 1 H, NH), 1.70 [D of t, d, J = 12 Hz, t, J = 3 Hz, 1 H, H(9)], 2.50 [s, 2 H, H(1), H(5)], 2.94 [d of t, d, J = 12 Hz, T, J = 5 Hz, 1 H, H(9)], 4.35 [d, 2 H, J = 4 Hz, H(2), H(4)], 4.50 [d, 2 H, J = 3 Hz, H(6), H(8)], 6.6-7.5 (m, 20 H, ArH); ^{13}C NMR ($CDCl_3$) ppm 30.40 [C(9)], 41.87 [C(2,4)], 51.91 [C(6,8)], 56.23 [C(1,5)], 126.38, 127.16, 127.87, 127.93, 128.04, 128.30, 140.33, 147.71 (Ar-C); Mass spectral m/e, calcd. for $C_{31}H_{29}NS$: (M^+) 447.2021; Found: 447.1998.

N-Benzyl-9-phenyl-7-aza-3-thiabicyclo[3.3.1]-nonan-9-ol Hydroperchlorate (73a)

An ether solution of phenylmagnesium bromide was prepared from 0.94 g (0.006 mmol) of bromobenzene, 0.20 g (0.0084 g at) of Mg and 40 mL of dry ether in a 100 mL flask. To the above Grignard reagent was added 0.50 g (0.002 mol) of 54 in 25 mL of dry ether over a 15 min period. The resulting mixture was stirred at RT for 1 h. The reaction mixture was cooled (ice bath), and 20 mL of 9 M H_2SO_4 was added with stirring. After 1 h, the aqueous layer was separated and cooled (ice bath). The cold solution was made basic by the addition of 1 g (18 mol) of KOH pellets followed by dilution with 100 mL of H_2O. The aqueous mixture was extracted with ether (3 X 20 mL). The organic extracts were combined and dried (KOH). The solution was filtered, and $HClO_4$ (60%) was added dropwise with stirring. The white precipitate which resulted was filtered and washed with ether (50 mL). Recrystallization (twice from ethanol) gave 1.37 g (81%) of 17; mp 249-250°C; IR (KBr) 3490 (O-H and N-H), 1100 cm^{-1} (ClO_4); ^1H NMR (DMSO-d_6) δ 1.5-3.15 (m, 10 H, ring CH_2 and CH), 3.3 (s, 2 H, Ar-CH_2), 3.6 (s, 1 H, O-H), 7.2-7.45 (m, 10 H, ArH); ^{13}C NMR (DMSO-d_6) ppm 27.3 [C(2,4)], 33.4 [C(1,5)], 55.1 [C(6,8)], 59.6 (Ar-CH_2), 67.42 [C(9)], 125.2, 127.8, 128.7, 128.9, 129.4, 129.9, 130.1, 141.8 (Ar-C); ^{15}N NMR (DMSO-d_6) 54.38 ppm; Anal. calcd. for $C_{20}H_{23}NOS \cdot HClO_4$: C, 56.40; H, 5.64; N, 3.29; S, 7.52; Cl, 8.34. Found: C, 56.53; H, 5.70; N, 3.27; S, 7.65; Cl, 8.70.

N-Phenethyl-9-phenyl-7-aza-3-thiabicyclo-[3.3.1]nonan-9-ol (75)

A solution of phenylmagnesium chloride (1.9 mL, 2 M in THF) was added dropwise to a stirred solution of 0.5 g (1.9 mmol) of 55 in 35 mL of dry ether in a 100 mL flask. The resulting mixture was stirred at RT for 12 h under N_2. A saturated NH_4Cl (2 mL) solution was slowly added to the mixture followed by stirring for 1 h. The ether solution was decanted from the white precipitate, and the precipitate was washed with ether (3 X 15 mL). The ether solutions were combined and dried (KOH). The solution was filtered, and the ether was evaporated to give a white solid. Recrystallization (Skelly B, bp 60-68°C) gave 0.5 g (62%) of 75: mp 110-111°C; IR (KBr) 3420 cm^{-1} (O-H); ^1H NMR ($CDCl_3$) δ 2.2-2.9 (m, 11 H, OH ring, $C\underline{H}_2$, $C\underline{H}$ and Ar-$C\underline{H}_2$), 2.95-3.1 (m, 2 H, ring $C\underline{H}_2$ and $C\underline{H}$), 3.65-3.85 (m, 2 H, Ar-CH_2-$C\underline{H}_2$), 7.05-7.5 (m, 10 H, ArH); ^{13}C NMR ($CDCl_3$) ppm 29.33 [C(2,4)], 33.38 (Ar-$\underline{C}H_2$), 35.33 [C(1,5)], 56.23 (Ar-CH_2-$\underline{C}H_2$), 59.87 [C(6,8)], 71.46 [C(9)], 125.36, 125.53, 127.55, 127.95, 128.45, 140.47, 143.92 (Ar$\underline{C}$); Mass spectral m/e, calcd. for $C_{21}H_{25}NOS$: (M^+) 339.1657; Found: 339.1651.

N-4-Methoxybenzyl-9-phenyl-7-aza-3-thia-bicyclo[3.3.1]nonan-9-ol (76)

A solution of phenylmagnesium chloride (1.8 mL, 2 M in THF) was added dropwise to a stirred solution of 0.50 g (1.8 mmol) of 56 in 35 mL of dry ether in a 100 mL flask. The resulting mixture was stirred at RT for 12 h under N_2. Saturated aqueous NH_4Cl (2 mL) was slowly added to the mixture followed by stirring for 1 h. The ether solution

was decanted from the white precipitate, and the precipitate was washed with ether (3 X 15 mL). The ether solutions were combined and dried (KOH). The solution was filtered, and the ether was evaporated to give a white solid. Recrystallization (95% ethanol) gave 0.42 g (66%) of 76: mp 131-132°C; IR (KBr) 3400 cm^{-1} (O-H); ^1H NMR ($CDCl_3$) δ 1.5-3.0 (m, 11 H, O-H, ring CH_2 and CH), 3.25 (s, 2 H, Ar-CH_2), 3.8 (s, 3 H, CH_3-O), 6.75-7.6 (m, 10 H, ArC); ^{13}C NMR ($CDCl_3$) ppm 29.27 [C(2,4)], 35.66 [C(1,5)], 55.07 (CH_3O), 55.47 [C(6,8)], 61.45 (Ar-CH_2), 71.43 [C(9)], 113.28, 125.24, 127.43, 128.46, 129.27, 131.08, 144.50, 158.10 (ArC); Mass spectral m/e, calcd. for $C_{21}H_{25}NO_2S$: (M^+) 355.1606; Found: M^+ not observed; calcd. for $C_{13}H_{16}NO_2S$: ($M^+-C_8H_9O$) 234.0953; Found: 234.0933; calcd. for C_8H_9O: ($M^+-C_{13}H_{16}NOS$) 121.0653; Found: 121.0665.

N-4-Methoxyphenethyl-9-phenyl-7-aza-3-thia-bicyclo[3.3.1]nonan-9-ol (77)

A solution of phenylmagnesium chloride (1.4 mL, 2 M in THF) was added dropwise to a stirred solution of 0.40 g (1.4 mmol) of 57 in 35 mL of dry ether in a 100 mL flask. The resulting mixture was stirred at RT for 12 h under N_2. A saturated NH_4Cl solution (2 mL) was slowly added to the mixture followed by stirring for 1 h. The ether solution was decanted from the white precipitate and the precipitate was washed with ether (3 X 15 mL). The ether solutions were combined and dried (KOH). The solution was filtered, and the ether was evaporated to give a white solid. Recrystallization (95% ethanol) gave 0.37 g (72%) of 77: mp 133-134°C; IR (KBr) 3400 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 1.5-3.2 (m, 15 H, OH, ring CH_2, CH, Ar-CH_2CH_2),

3.8 (s, 3 H, $C\underline{H}_3$-O), 6.75-7.6 (m, 10 H, Ar$\underline{H}$); ^{13}C NMR ($CDCl_3$) ppm 29.30 [C(2,4)], 32.42 (ArCH$_2$-$\underline{C}H_2$), 35.75 [C(1,5)], 55.04 ($\underline{C}H_3$-O), 56.24 (Ar-$\underline{C}H_2$), 60.12 [C(6,8)], 71.41 [C(9)], 113.40, 125.34, 127.50, 128.46, 129.31, 132.57, 143.92, 157.41 (Ar$\underline{C}$); Mass spectral m/e, calcd. for $C_{22}H_{27}NO_2S$: (M^+) 369.1762; Found: M^+ not observed; calcd. for $C_{14}H_{18}NOS$: (M^+-C_8H_9O) 248.1109; Found: 248.1109; calcd. for C_8H_9O: (M^+-$C_{14}H_{18}NOS$) 121.0653; Found: 121.0653.

N-Benzyl-9-methyl-7-aza-3-thiabicyclo-[3.3.1]nonan-9-ol (71)

A solution of methylmagnesium chloride (2 mL, 3 M in THF) was added dropwise to a stirred solution of 0.5 g (2.0 mmol) of 54 in 35 mL of dry ether in a 100 mL flask. The resulting mixture was stirred at RT for 12 h under N_2. Saturated aqueous NH_4Cl (2 mL) was slowly added to the mixture followed by stirring for 1 h. The ether solution was decanted from the white precipitate, and the precipitate was washed with ether (3 X 15 mL). The ether solutions were combined and dried (Na_2SO_4). The solution was filtered, and the ether was evaporated to give a white solid. Recrystallization (Skelly B, bp 60-68°C) gave 0.2 g (38%) of 71: mp 126-127°C; IR (KBr) 3410 cm^{-1} (O-H); ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 3 H, $C\underline{H}_3$), 1.8-3.5 (m, 10 H, ring $C\underline{H}_2$ and $C\underline{H}$), 3.6 (s, 2 H, Ar-$C\underline{H}_2$), 7.2-7.5 (m, 5 H, Ar$\underline{H}$); ^{13}C NMR ($CDCl_3$) ppm 27.72 ($\underline{C}H_3$), 28.95 [C(2,4)], 38.67 [C(1,5)], 56.58 [C(6,8)], 62.36 (Ar-$\underline{C}H_2$), 69.09 [C(9)], 126.68, 128.11, 128.45, 138.64 (Ar-$\underline{C}$); Mass spectral m/e, calcd. for $C_{15}H_{21}NOS$: (M^+) 263.1344; Found: 263.1345.

Attempted Preparation of 6,8-Diphenyl-7-benzyl-7-aza-3-thiabicyclo[3.3.1]-nonan-9-one (50a)

Method I. A mixture of 1.00 g (8.6 mmol) of ketone 53, 1.82 g (17.2 mmol) of benzaldehyde 0.52 g (8.6 mmol) of acetic acid and 0.92 g (8.6 mmol) of benzylamine in 50 mL of 95% ethanol was heated at 60°C for 24 h. Upon cooling (ice bath), a yellow solid precipitated 1.4 g, mp. 149-152°C, which was identified by mixture melting point as the dienone 51.

Method II. A mixture of 51 (1.0 g/3.4 mmol) and 0.36 g (3.4 mmol) of benzylamine in 20 mL of 95% ethanol was heated at reflux for 24 h. Upon cooling (ice bath), a brown solid precipitated 0.8 g, mp. 144-149°C. The major component was identified as 51 by mixture melting point.

Attempted Preparation of 6,8-Diphenyl-3,7-dithiabicyclo[3.3.1]nonan-9-one (52)

Into a solution of 1.0 g (3.4 mmol) of dienone 51 and 0.3 g (3.4 mmol) of sodium acetate in 95% ethanol (25 mL) was passed H_2S (gas), and the solution was heated at reflux for 2 h. After 1 h, a white solid was filtered (0.7 g). The solid did not melt but softened at 110°-180°C. The ^1H NMR showed only to very broad signals centered at about δ 3.0 and 6.9.

Attempted Preparation of N-Benzyl-3-phenyl-7-aza-3-phosphabicyclo[3.3.1]nonan-9-one (91)

Method I. A mixture of 90 [0.5 g (2.6 mmol)], paraformaldehyde

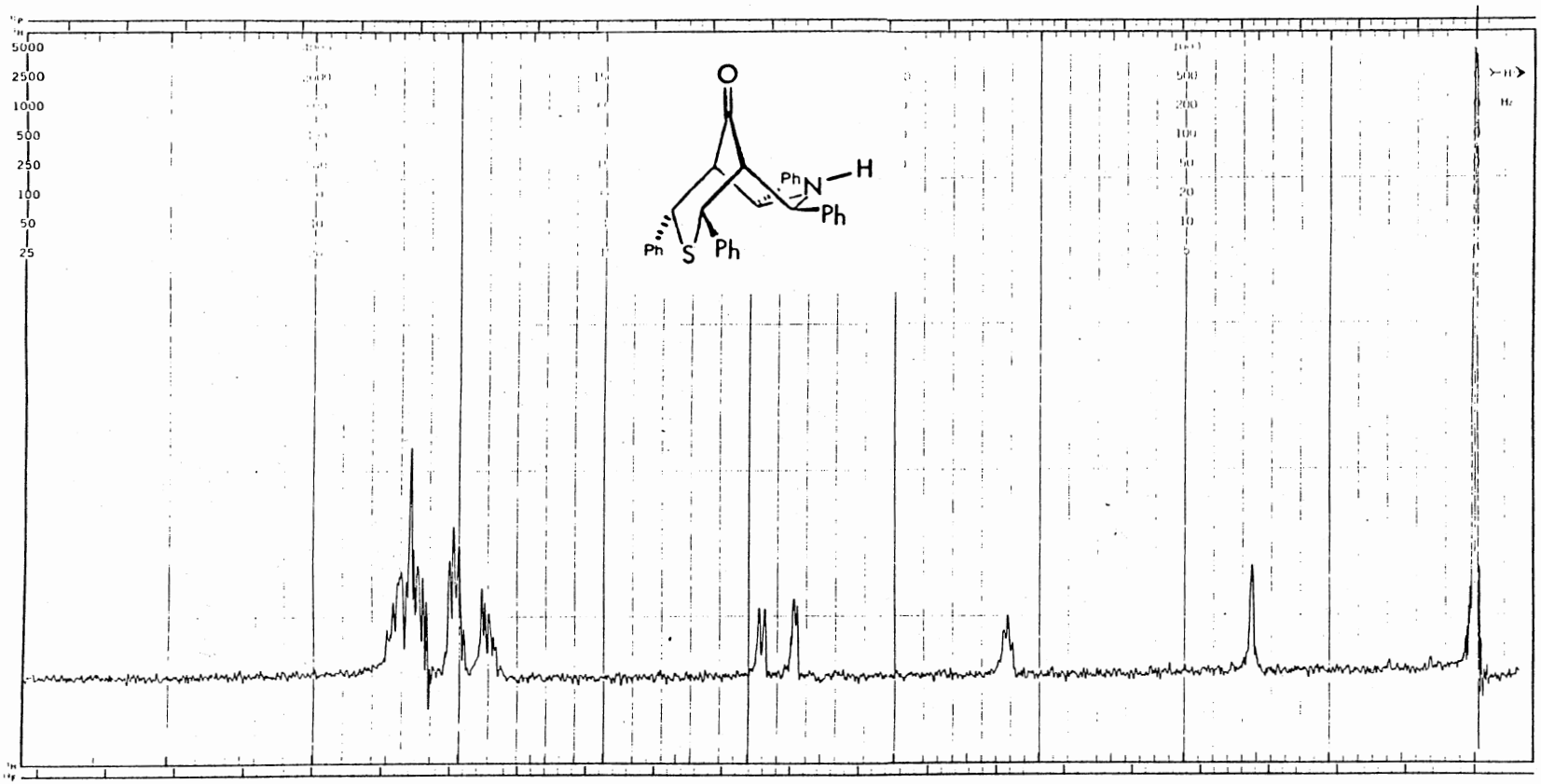
(0.63 g, 21 mmol), acetic acid (0.16 g, 2.6 mmol) and benzylamine (0.28 g, 2.6 mmol) in methanol (20 mL) was heated at reflux for 4 h. During this time, a red solid formed in the flask. The solvent was removed and the solid was found to have very limited solubility in chloroform. ^{13}C NMR analysis did not show any of the desired product to be present but had signals in the region for alipatic and aromatic carbons.

Method II. The procedure was the same as above but 0.32 (5.2 mmol) of acetic acid was used. A red solid was obtained and ^{13}C NMR analysis did not show any of the desired product to be present.

Attempted Preparation of 2,2,4,4-Tetramethyl-3,6,8-triphenyl-7-aza-3-phosphabicyclo-[3.3.1]nonan-9-one (93)

A mixture of phosphorinanone 92 (0.65 g, 2.6 mmol), benzaldehyde (0.55 g, 5.2 mmol), and ammonium acetate (0.2 g, 2.6 mmol) in 20 mL of 95% ethanol was heated at 60°C for 4 h. The solution was cooled to RT, and the solvent removed to give a red solid. ^{13}C NMR analysis did not show any of the desired product to be present but head signals in the region for aliphatic and aromatic carbons.

PLATE I



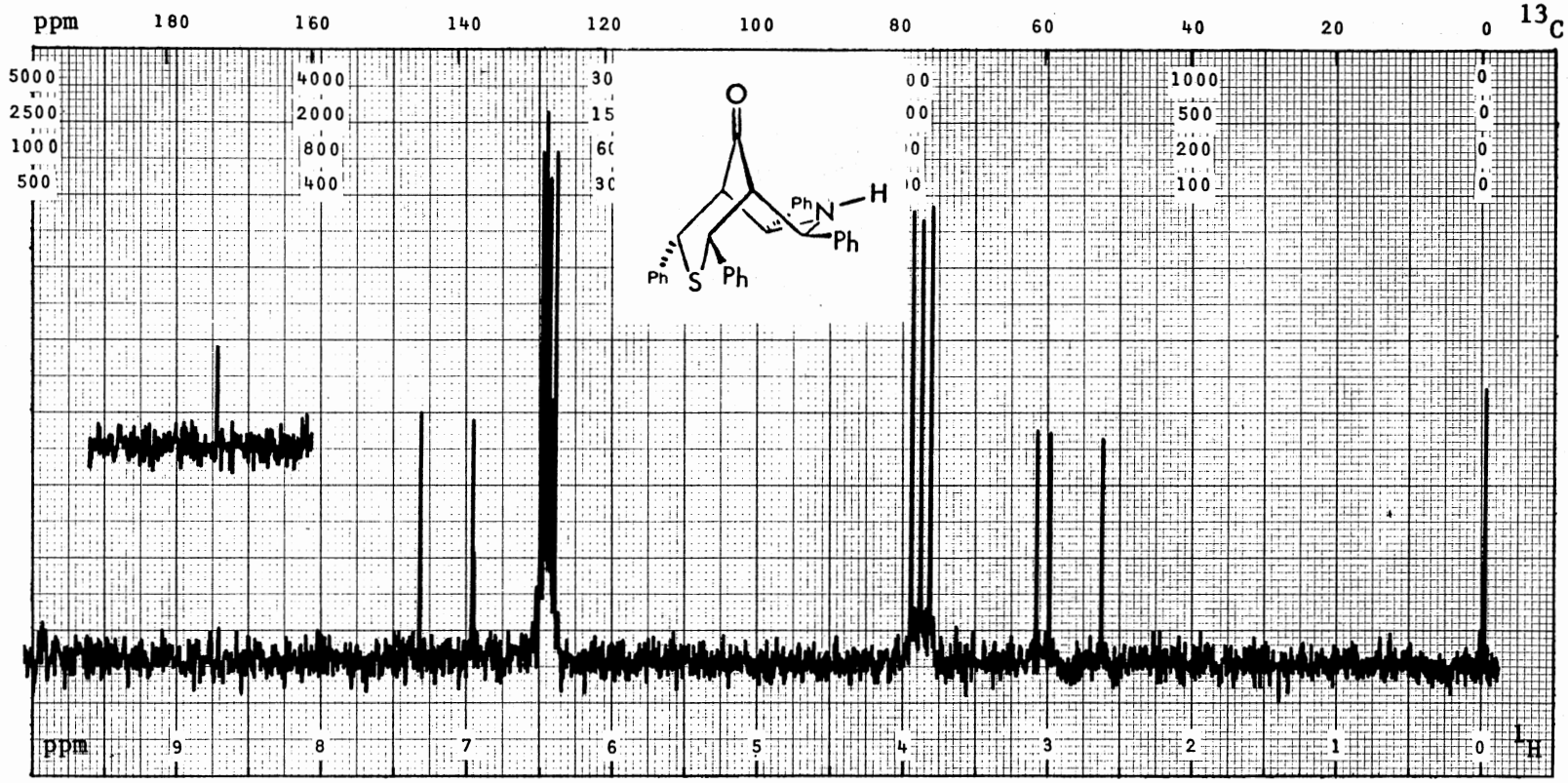
^{1}H NMR Spectrum of 38

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 85771 Hz; PW. . 1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 62 μs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE II



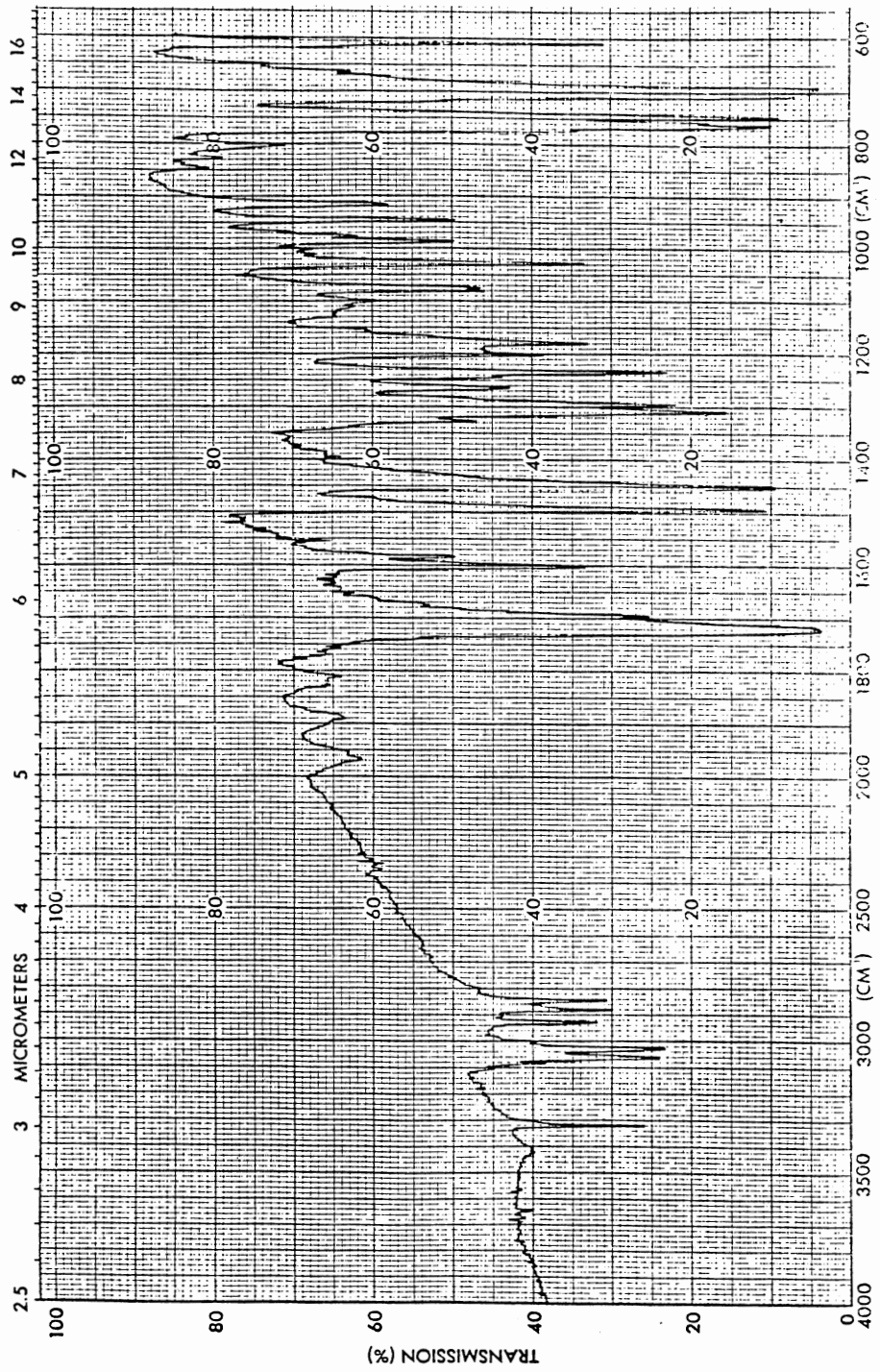
^{13}C NMR Spectrum of 38

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 35101 Hz; PW. . 5000 Hz; T. . 30 °C; Acq/SA. .440

Size. . 8 K; P2/RF. . 10 μs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^{2}H ; D5/ST. . 5 s

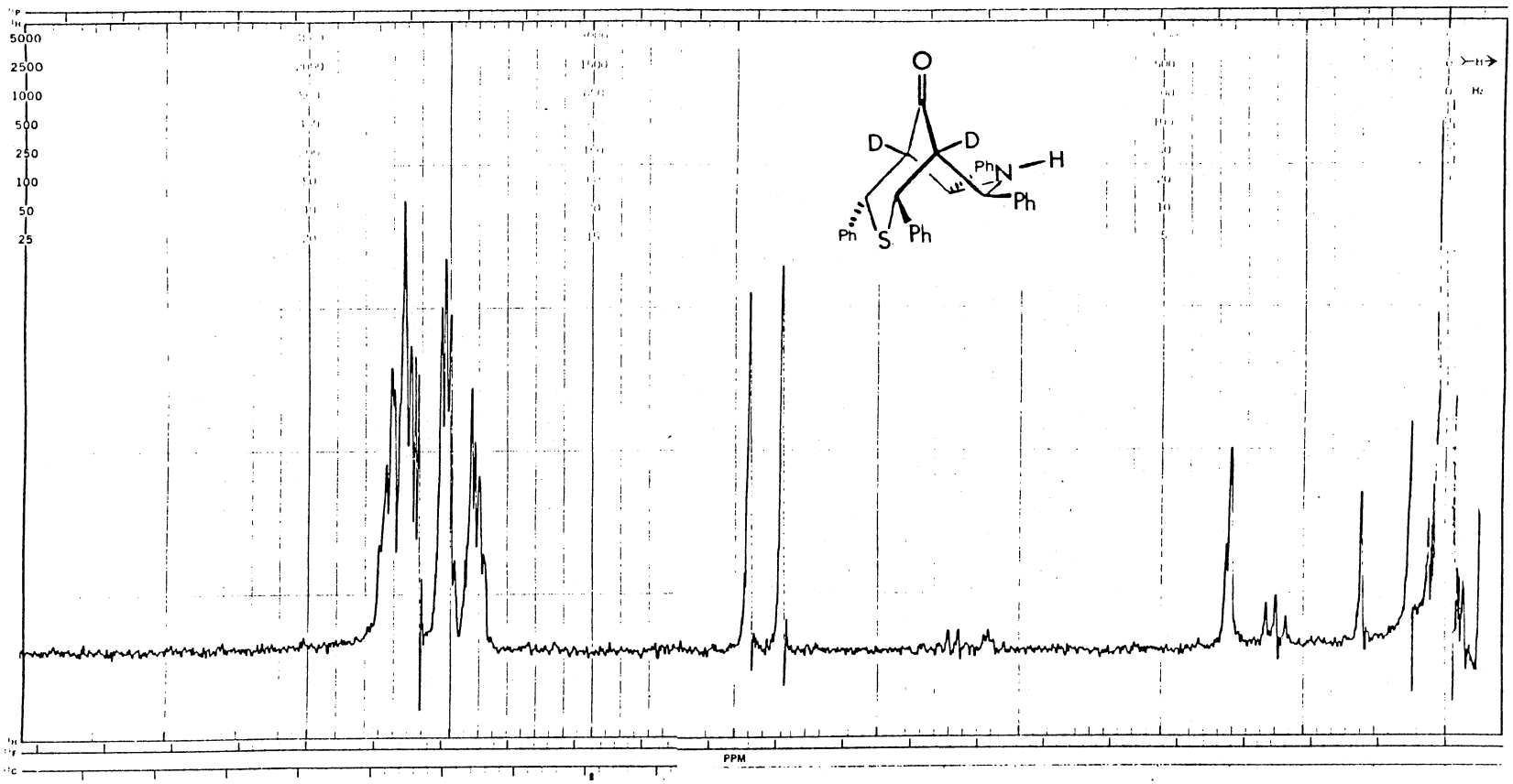
DC. . ^{1}H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE III



IR Spectrum of 38

PLATE IV



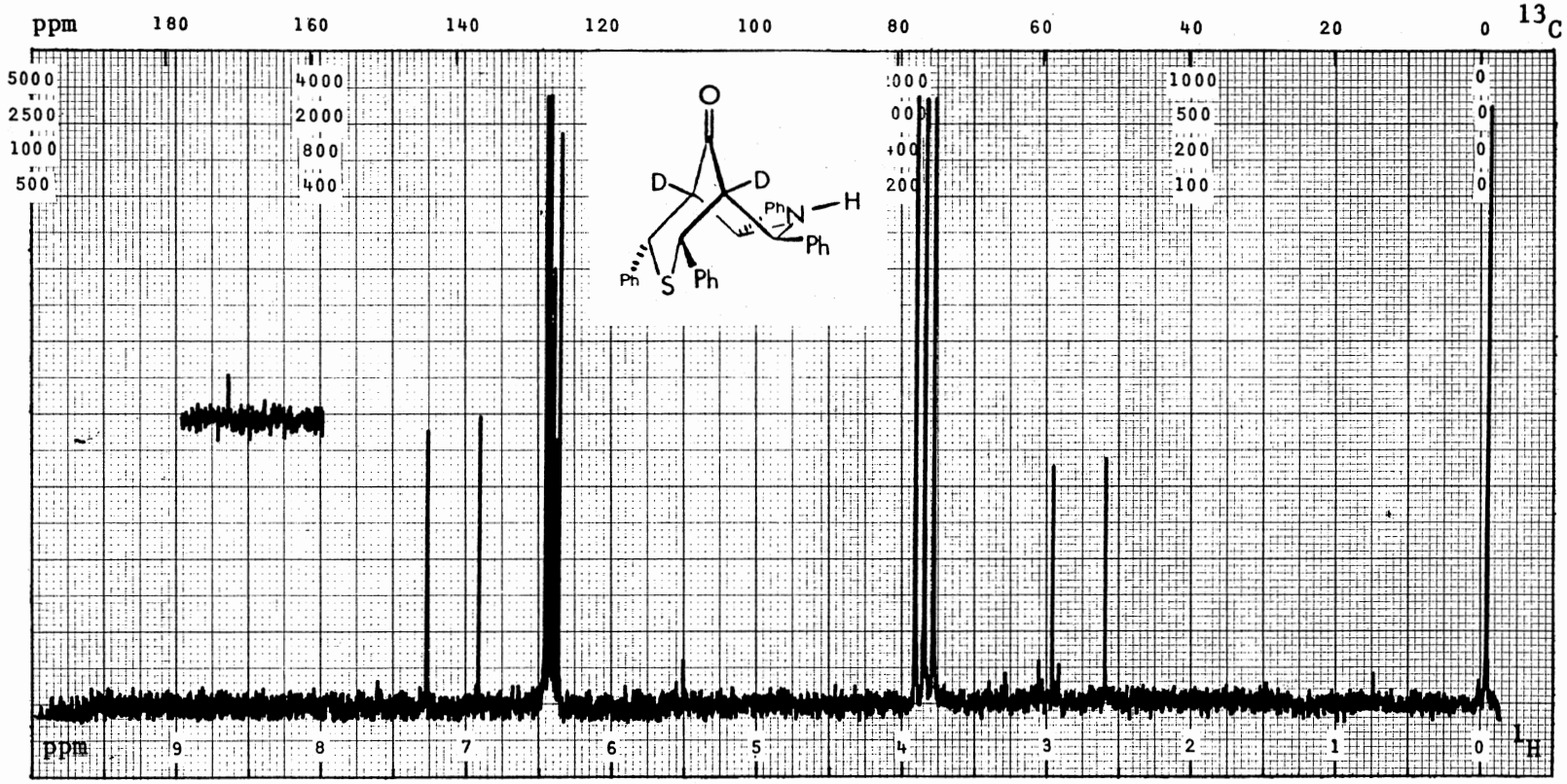
^{1}H NMR Spectrum of 41

PFT _ CW X ; Solvent. . $CDCl_3$; SO. . 85771 Hz; PW. . 1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 60 µs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE V



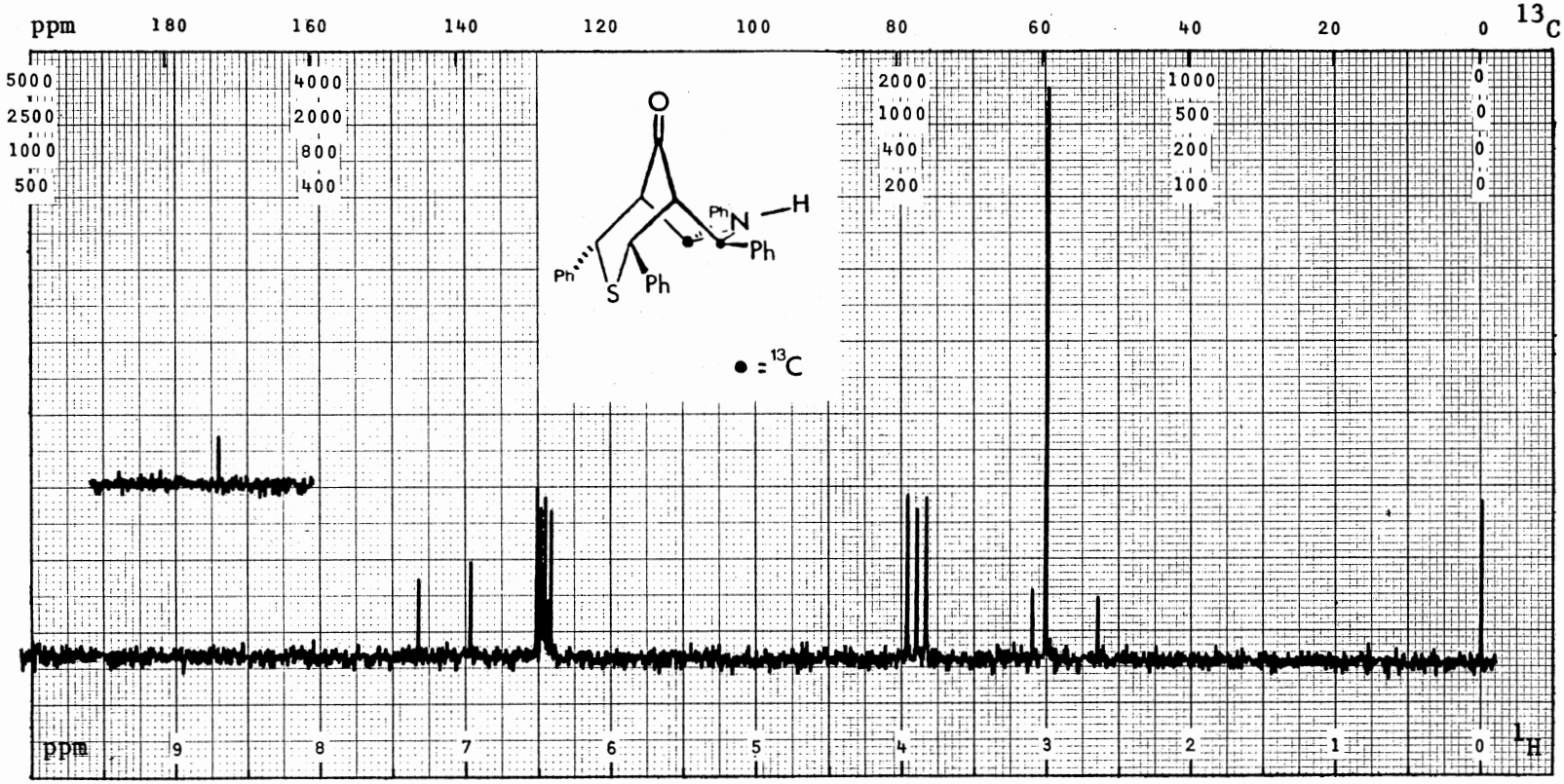
^{13}C NMR Spectrum of 41

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 35101 Hz; PW. .5000 Hz; T. . 30 °C; Acq/SA. .440

Size. . 8 K; P2/RF. . 10 μs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^2H ; D5/ST. . 5 s

DC. . ^1H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE VI



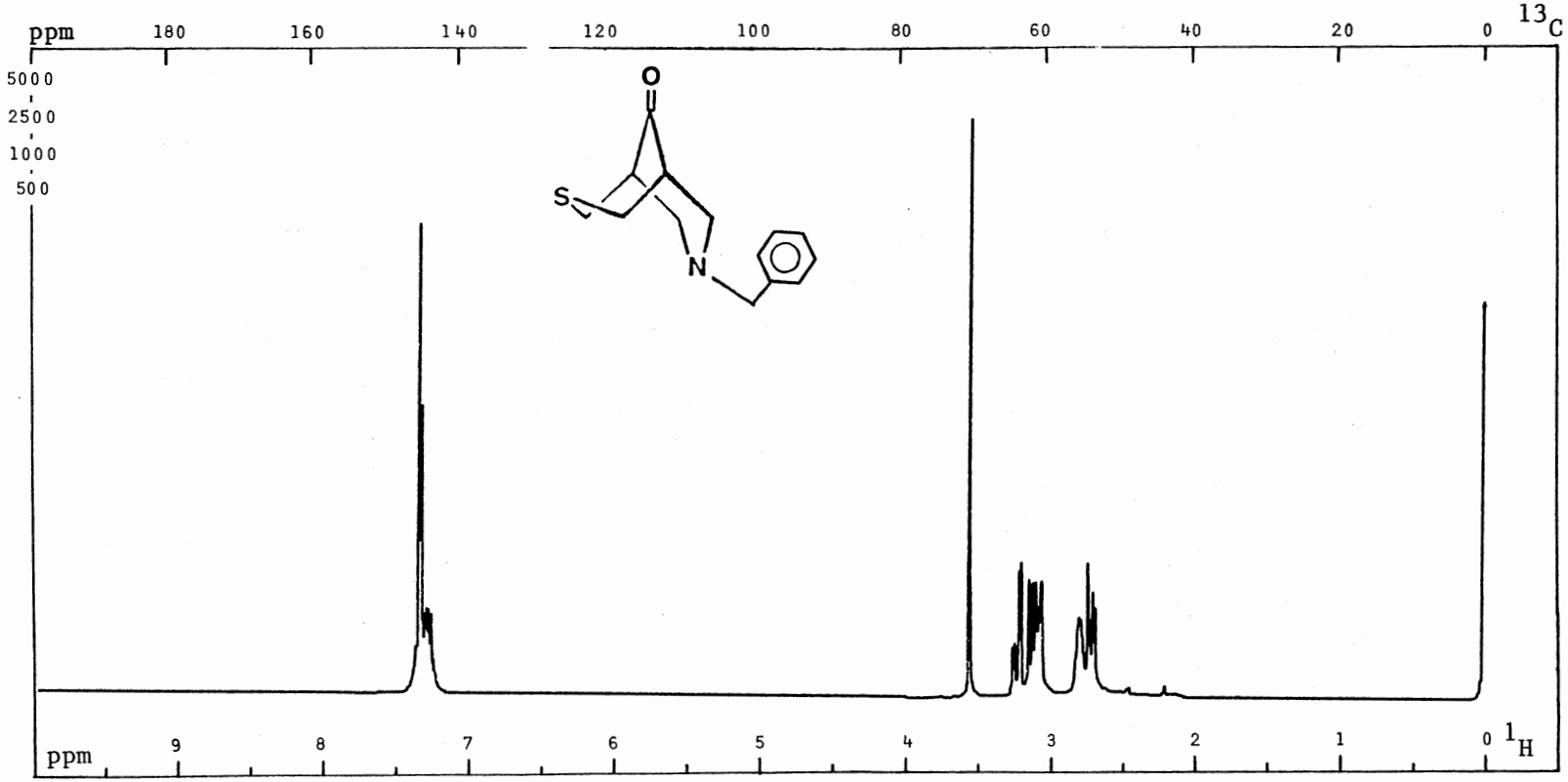
^{13}C NMR Spectrum of 42

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 35101 Hz; PW. .5000 Hz; T. . 30 °C; Acq/SA. . 440

Size. . 8K; P2/RF. . 10 µs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^{2}H ; D5/ST. . 5 s

DC. . ^{1}H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE VII



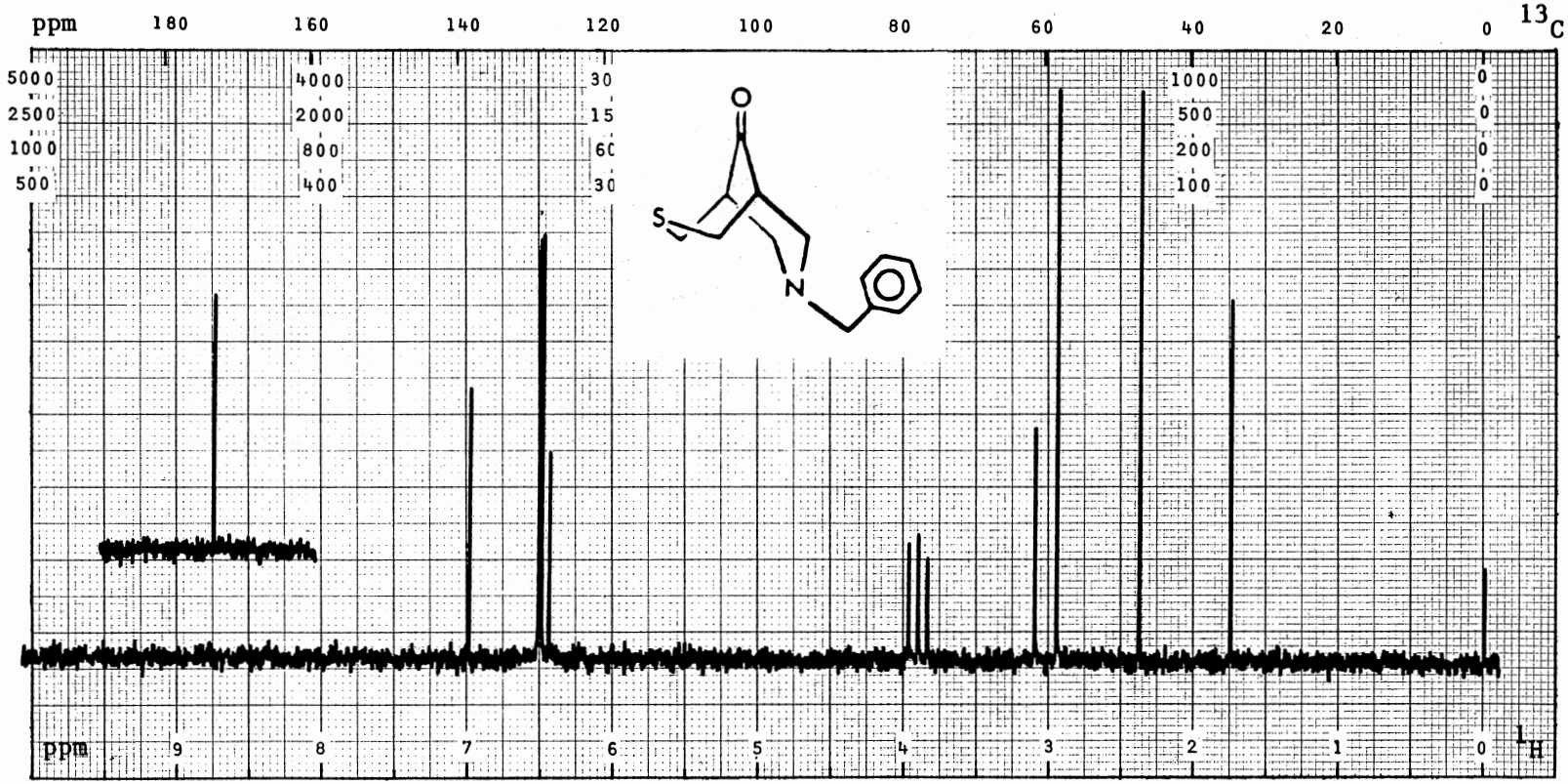
^{1}H NMR Spectrum of 54

PFT _ CW X ; Solvent. . $CDCl_3$; SO. . 85771 Hz; PW. .1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 58 µs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE VIII



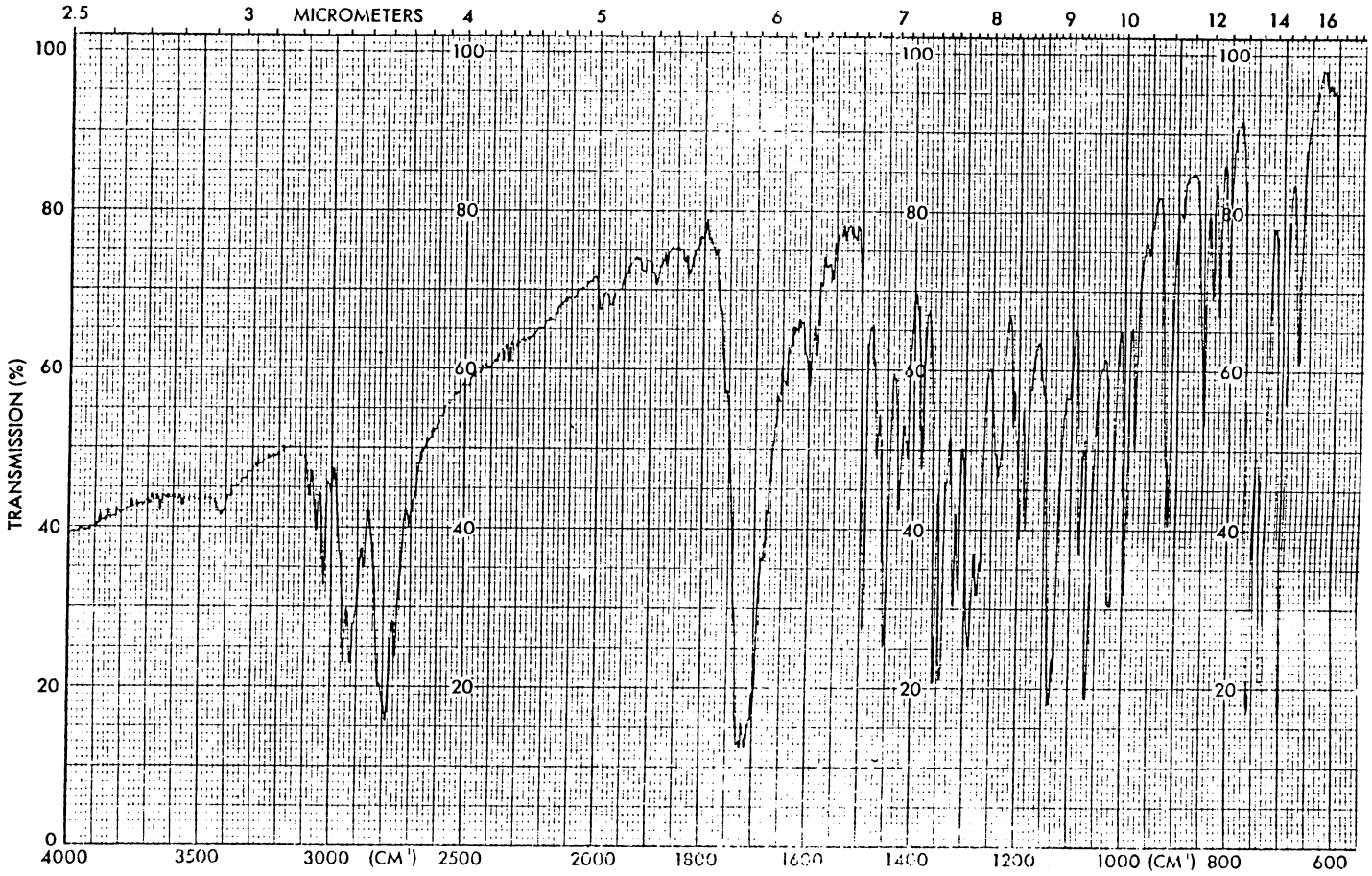
^{13}C NMR Spectrum of 54

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 35101 Hz; PW. . 1000 Hz; T. . 30 °C; Acq/SA. . 440

Size. . 8 K; P2/RF. . 10 μs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^{2}H ; D5/ST. . 5 s

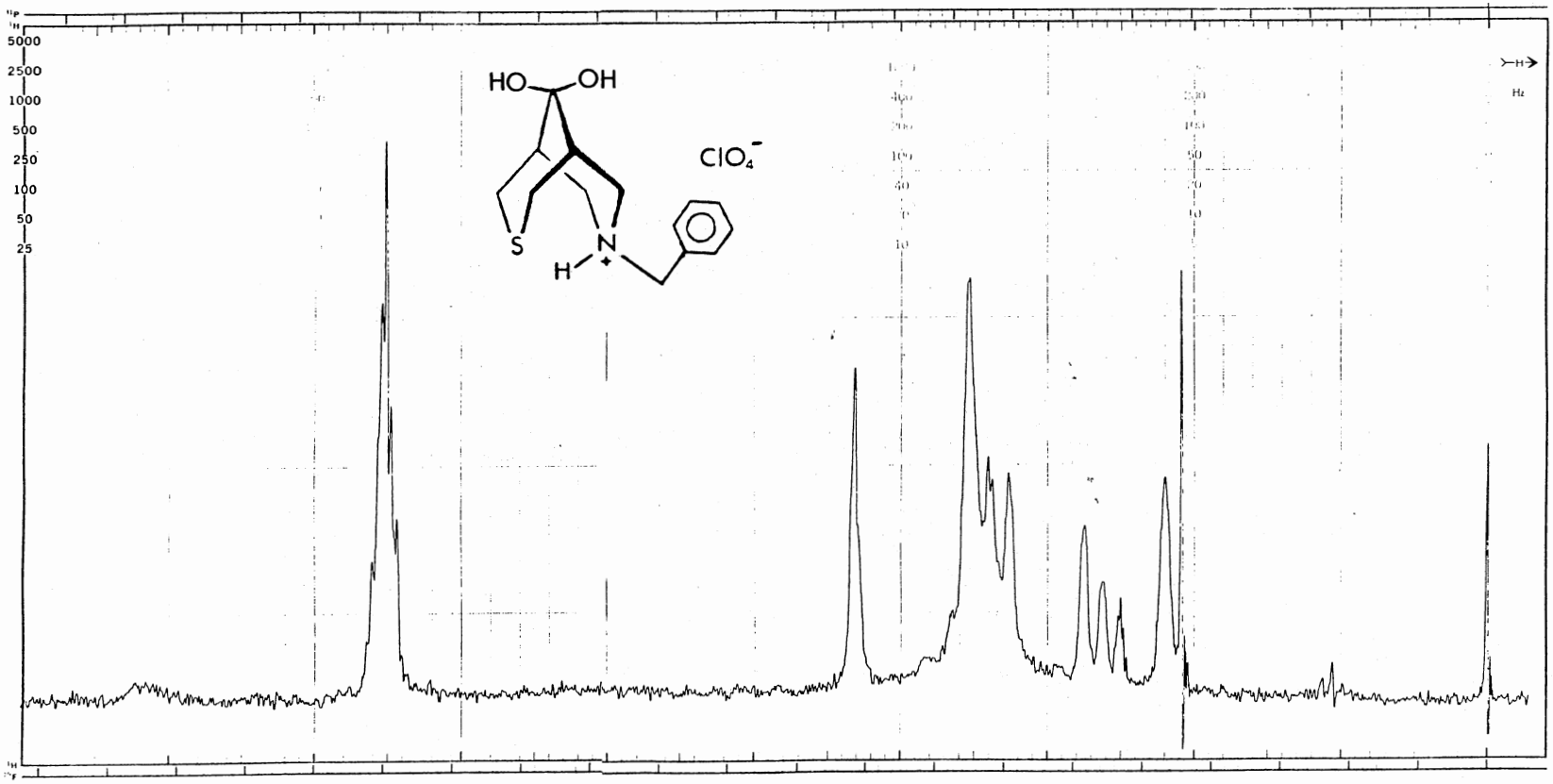
DC. . ^{1}H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE IX



IR Spectrum of 54

PLATE X



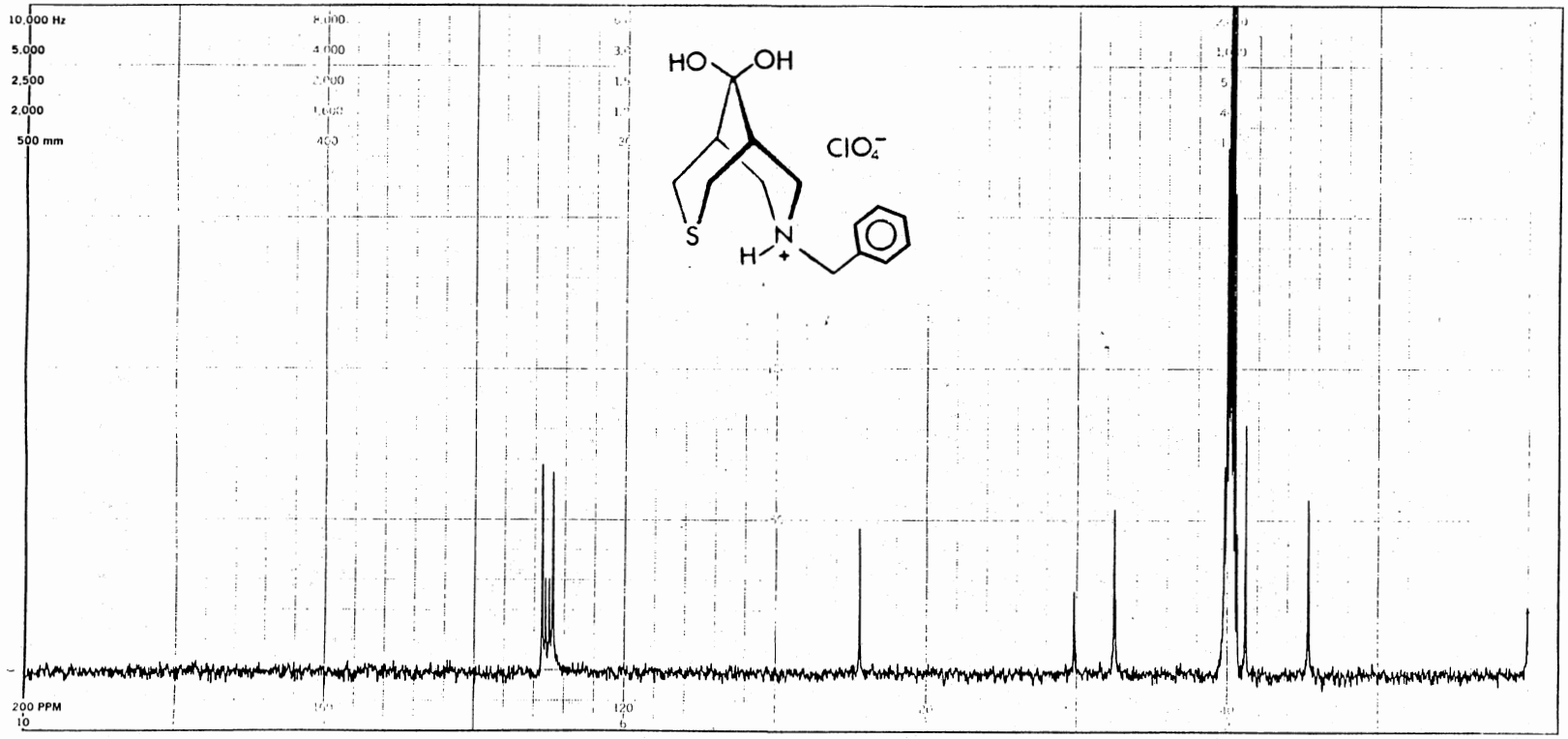
^1H NMR Spectrum of 83

PFT _ CW X ; Solvent. . DMSO-d_6 ; SO. . 86242 Hz; PW. .1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 61 µs/dB; SF. .100.1 Hz; FB. . 2 Hz; Lock. . ^2H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XI



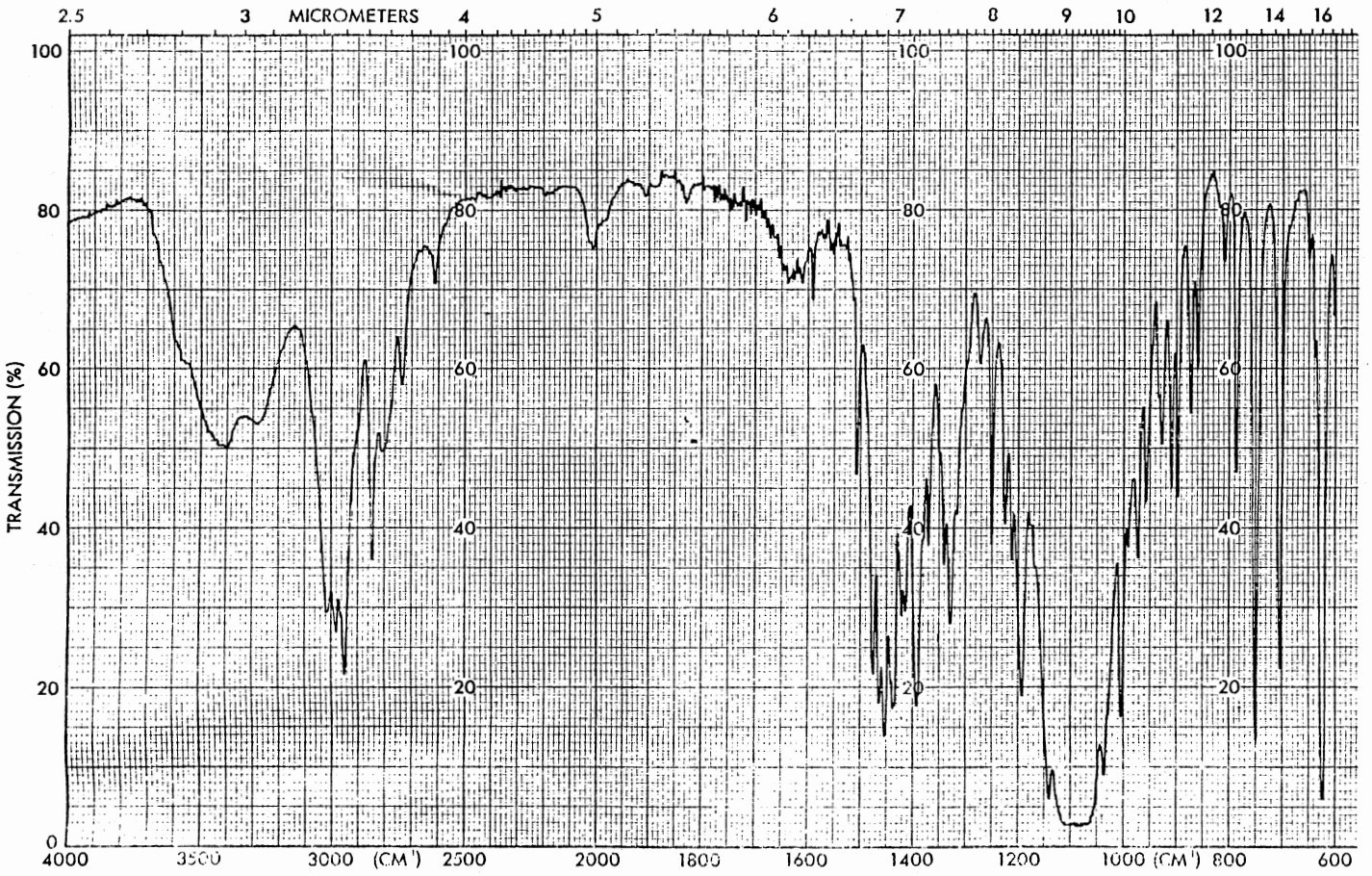
^{13}C NMR Spectrum of 83

PFT X CW _ ; Solvent. . DMSO-d_6 ; SO. . 35201 Hz; PW. .5000 Hz; T. . 30 °C; Acq/SA. .440

Size. . 8 K; P2/RF. . 10 µs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^2H ; D5/ST. . 5 s

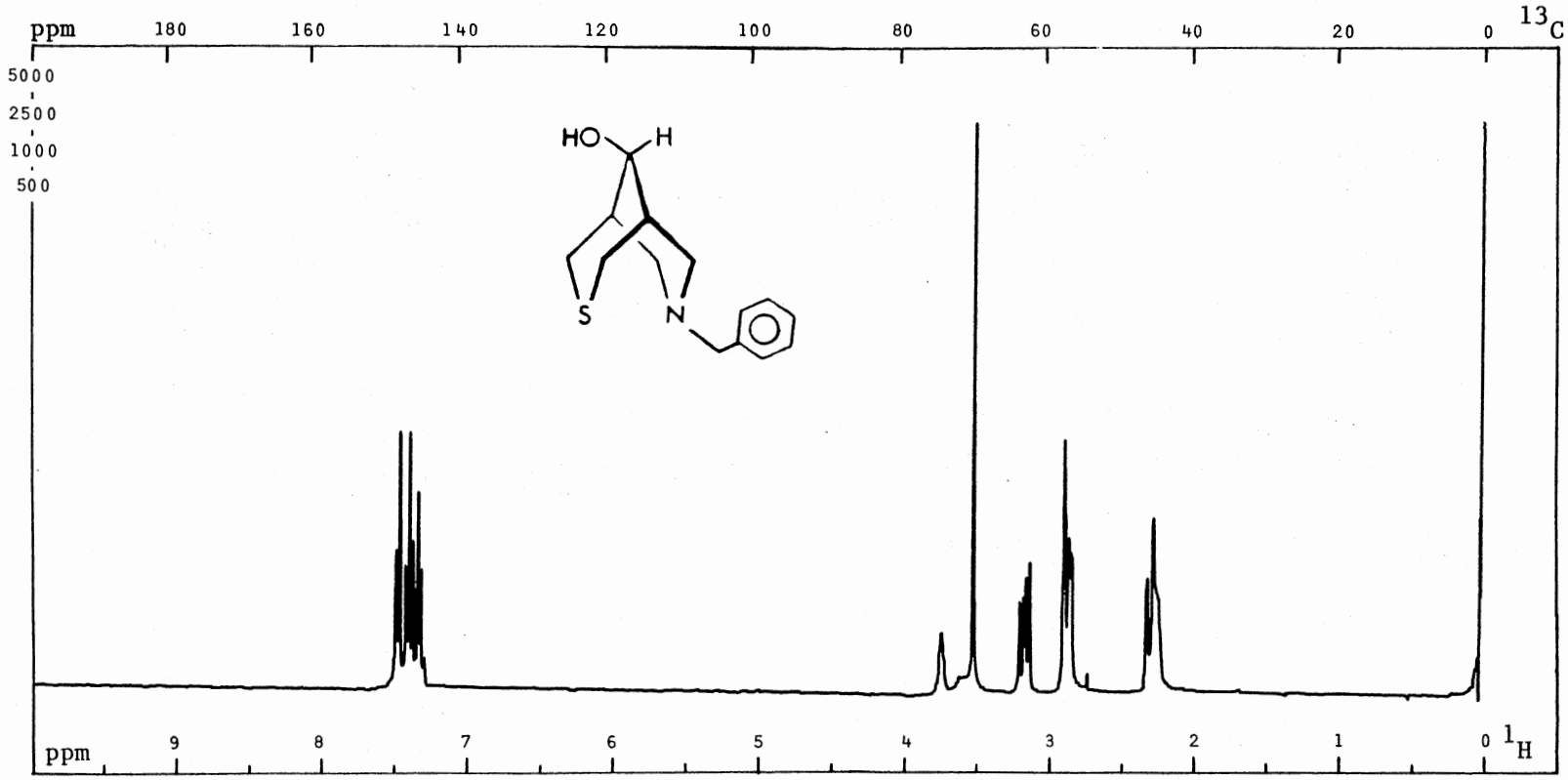
DC. . ^1H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE XII



IR Spectrum of 83

PLATE XIII



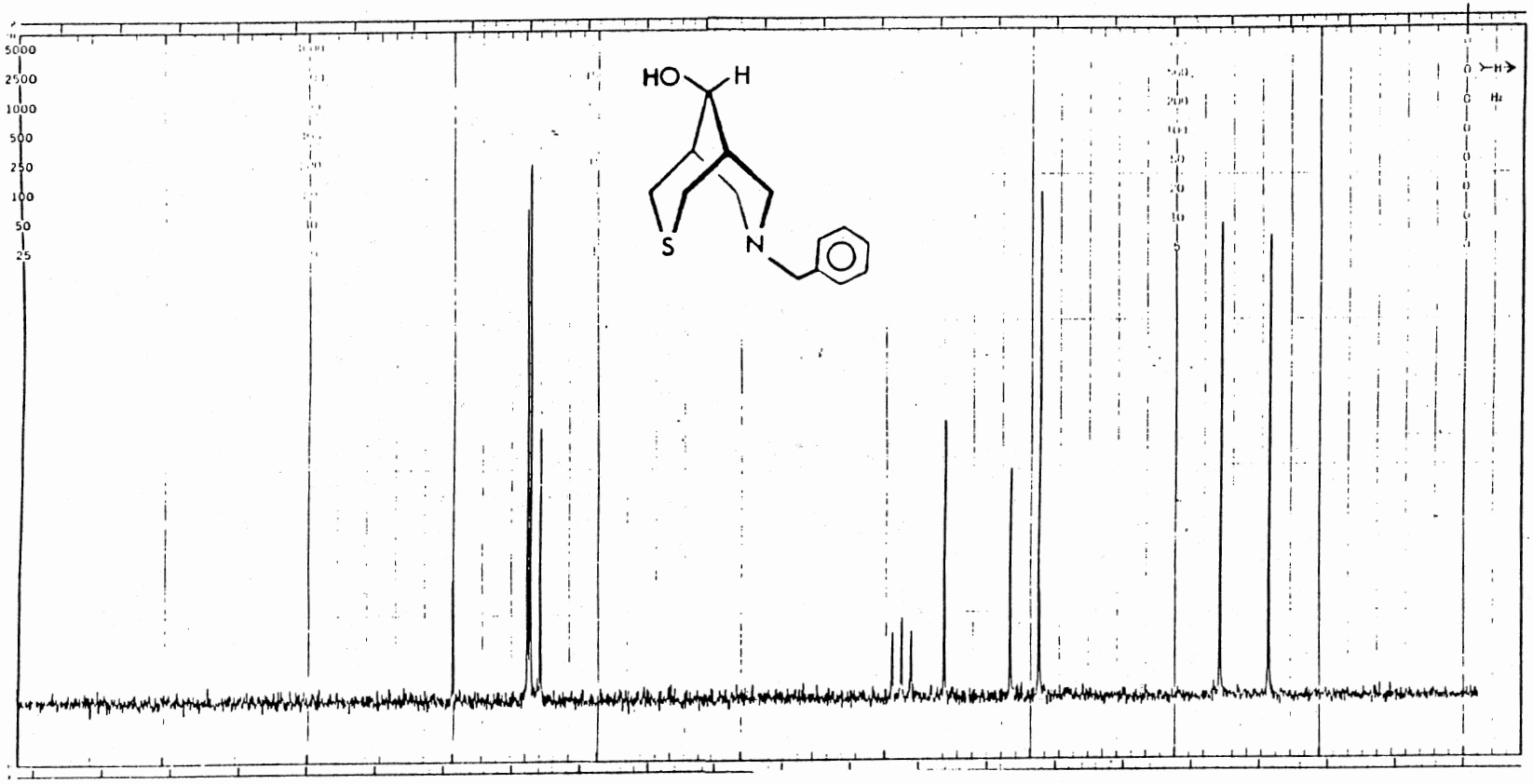
^{1}H NMR Spectrum of 69

PFT _ CW X ; Solvent. . $CDCl_3$; SO. . 35101 Hz; PW. . 1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 59 µs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XIV



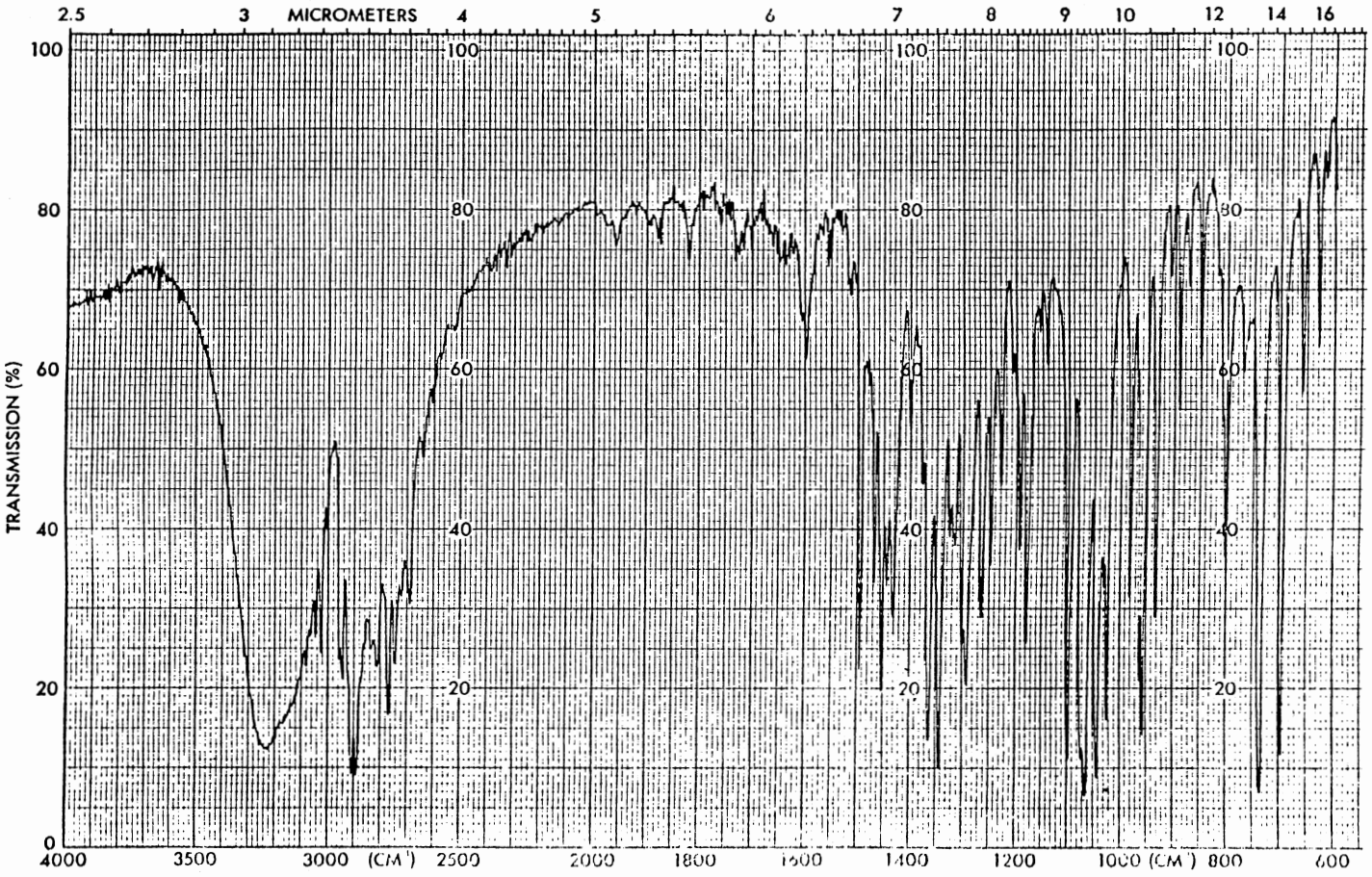
^{13}C NMR Spectrum of 69

PFT X CW _ ; Solvent. . $CDCl_3$; SO. .35101 Hz; PW. .5000 Hz; T. . 30 °C; Acq/SA. .440

Size. . 8 K; P2/RF. . 10 μs/dB; SF. .25.2 Hz; FB. . Hz; Lock. . ^2H ; D5/ST. . 5 s

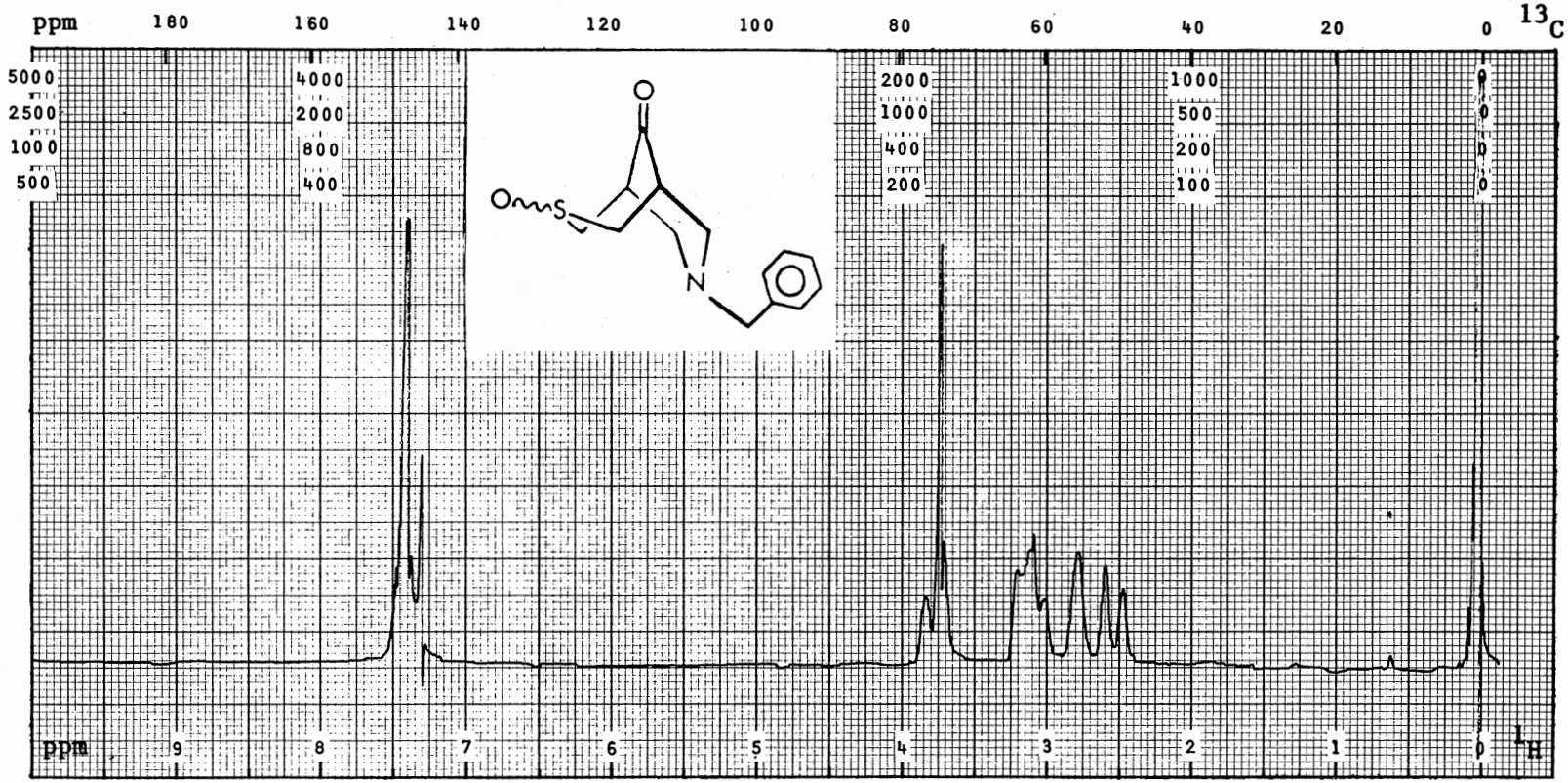
DC. . ^1H ; Gated Off. . . ; Offset. .45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE XV



IR Spectrum of 69

PLATE XVI



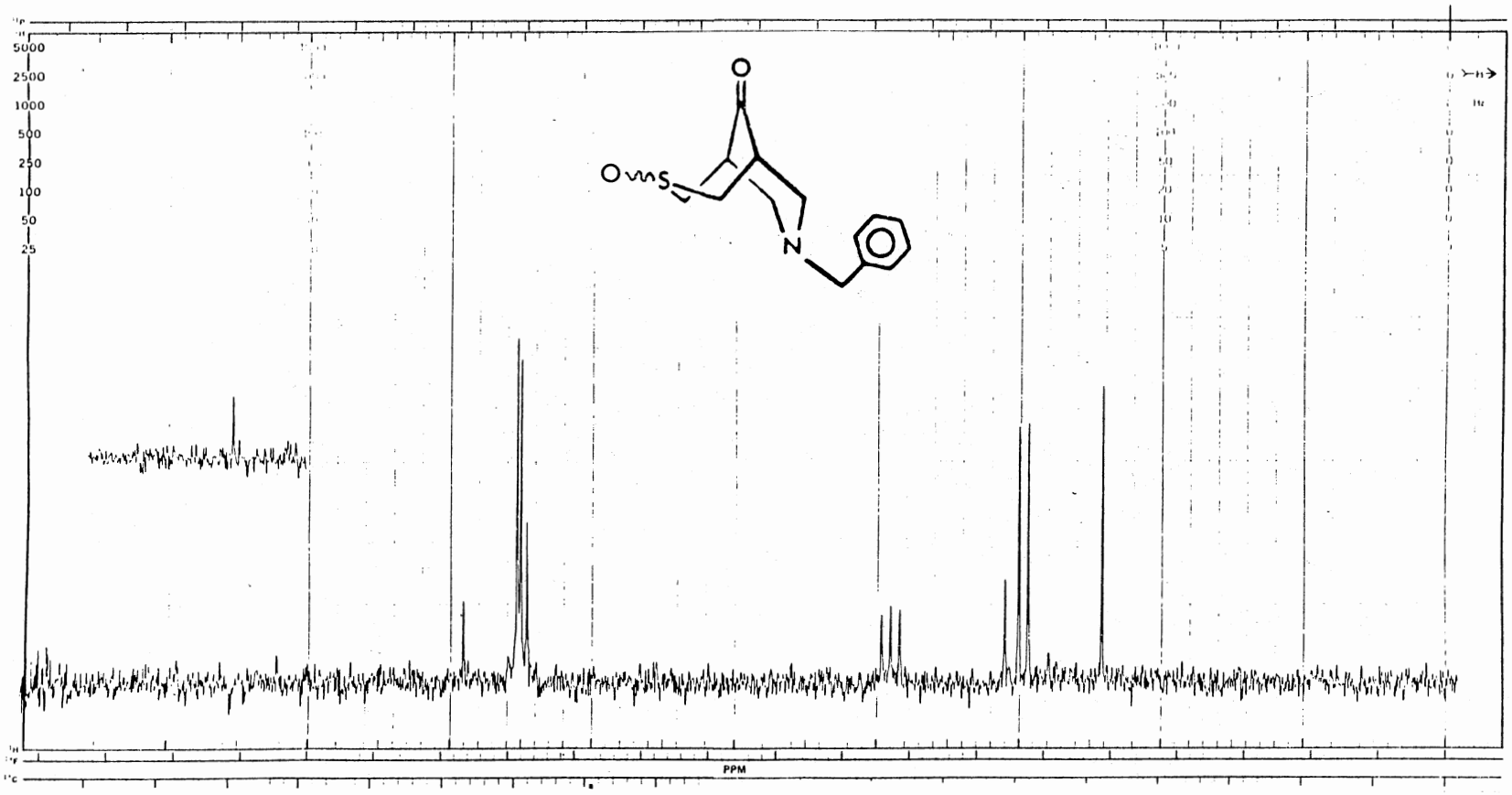
^{1}H NMR Spectrum of 80

PFT _ CW X ; Solvent. . $CDCl_3$; SO. . 85771 Hz; PW. . 1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 63 µs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XVII



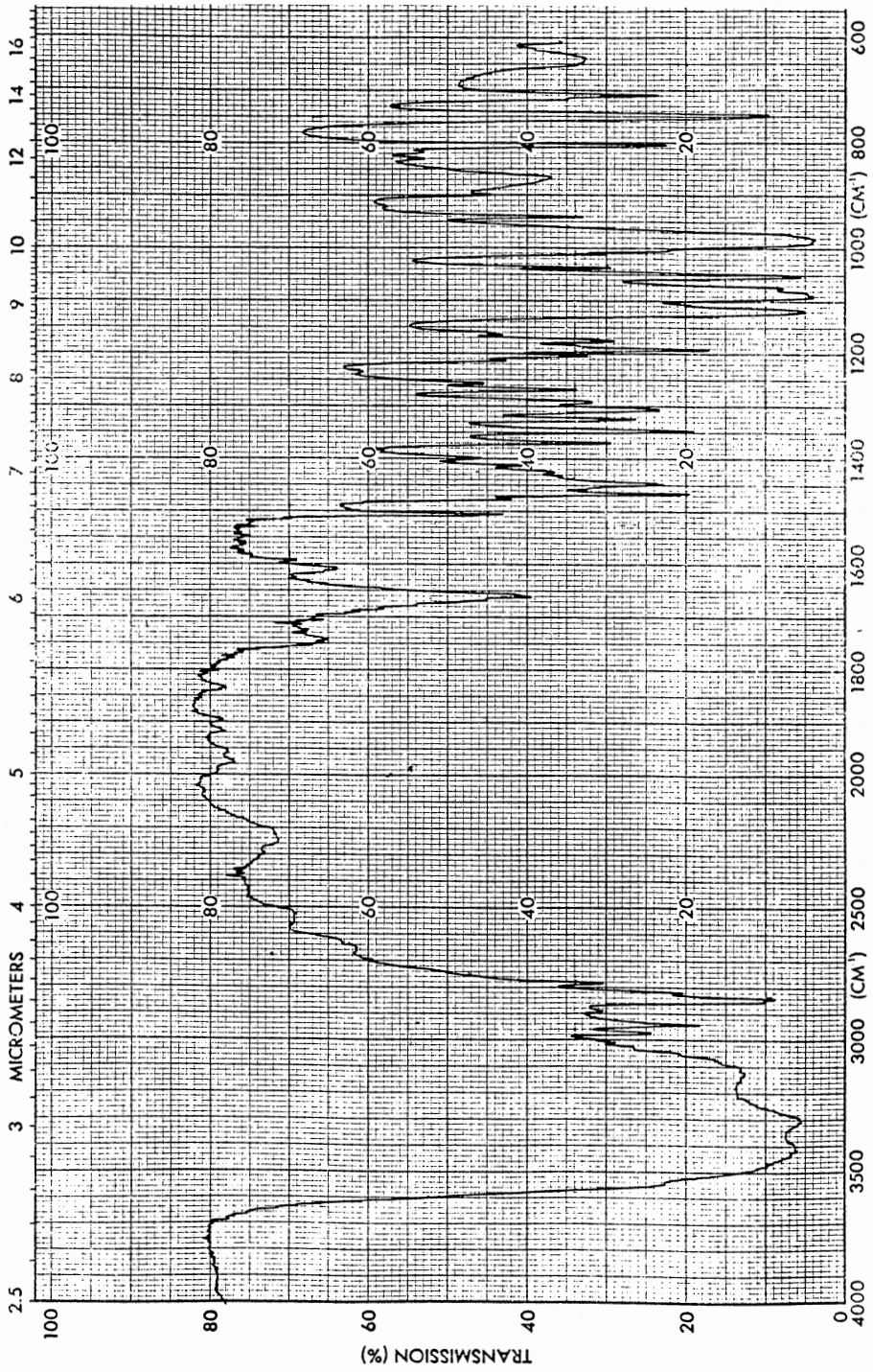
^{13}C NMR Spectrum of 80

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 35101 Hz; PW. . 5000 Hz; T. . 30 °C; Acq/SA. . 440

Size. . 8 K; P2/RF. . 10 µs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^2H ; D5/ST. . 5 s

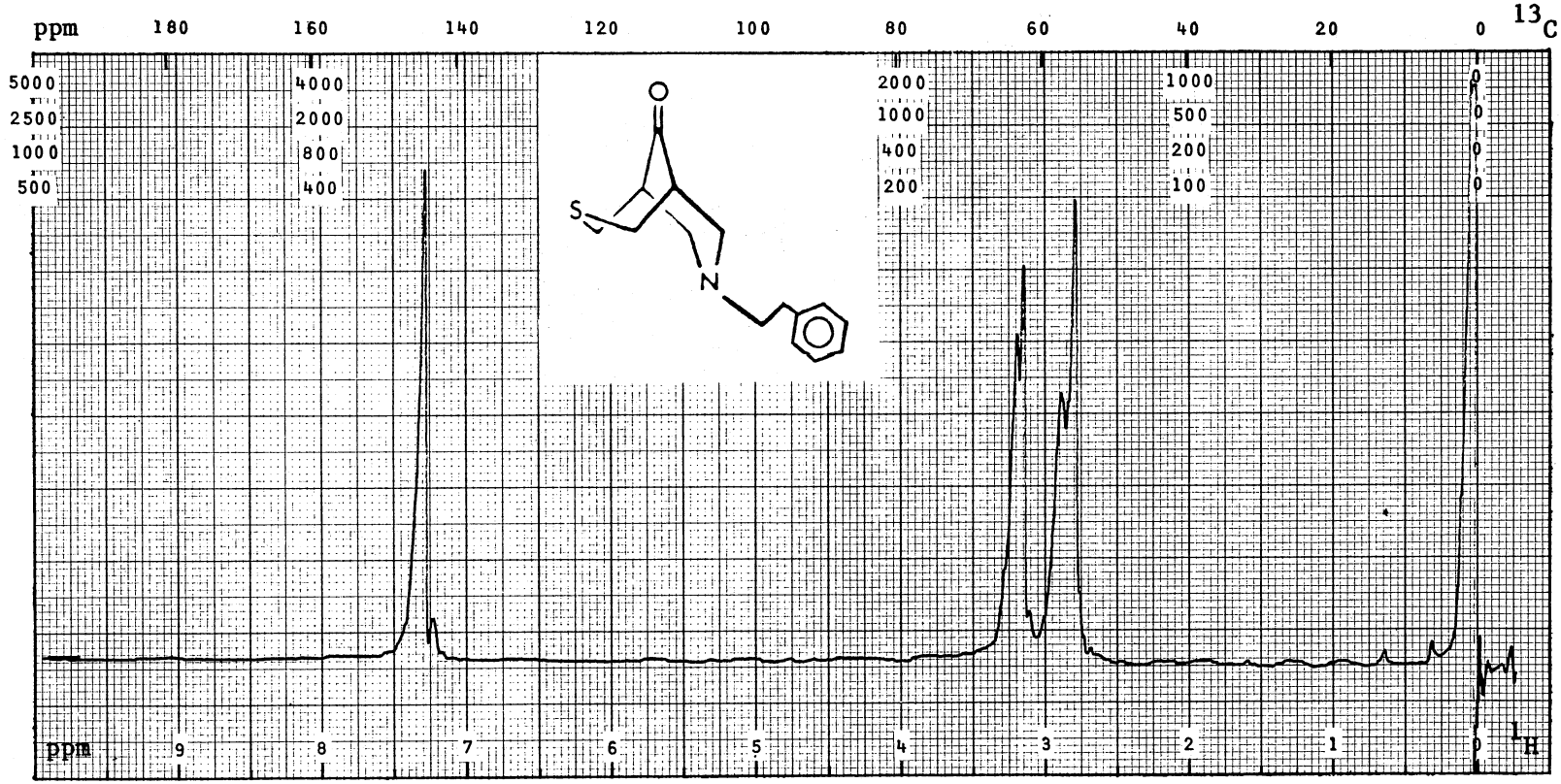
DC. . ^1H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE XVIII



IR Spectrum of 80

PLATE XIX



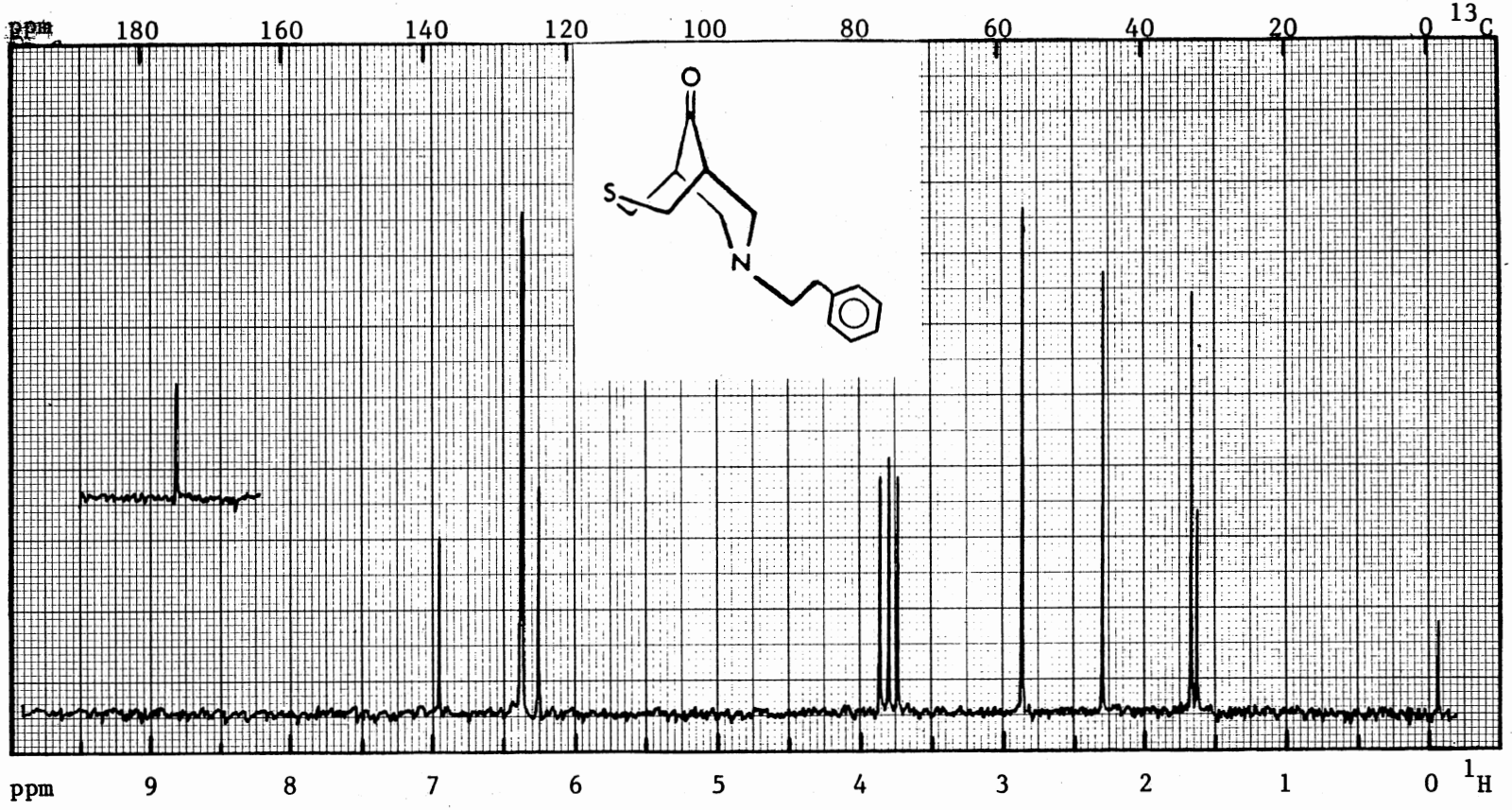
^{1}H NMR Spectrum of 55

PFT _ CW X ; Solvent. . $CDCl_3$; SO. . 85771 Hz; PW. . 1000 Hz; T. . 30°C; Acq/SA. .

Size. . K; P2/RF. . 61 μs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XX

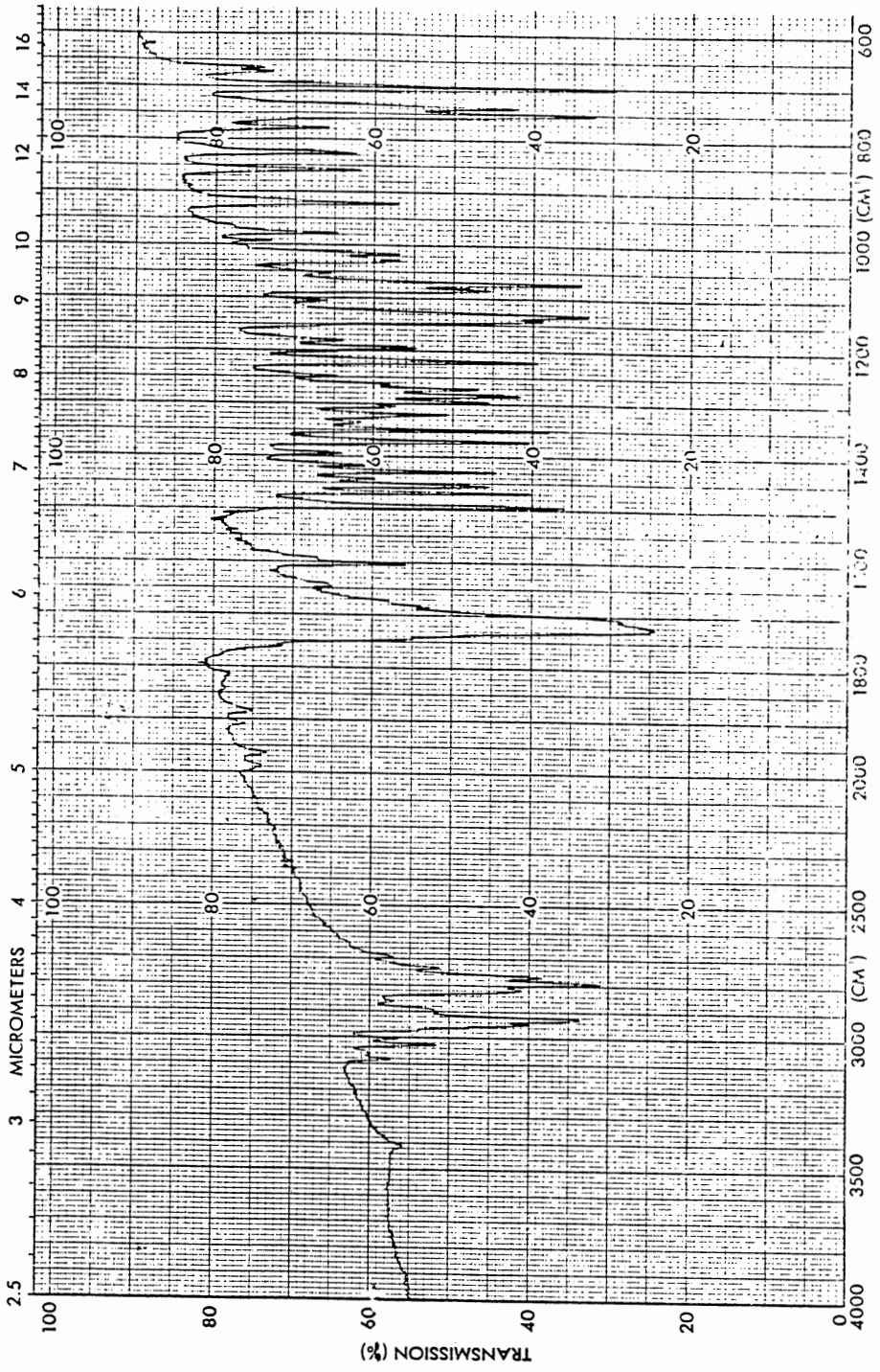


^{13}C NMR Spectrum of 55

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 35101 Hz; PW. . 5000 Hz; T. . 30°C; Acq/SA. . 440

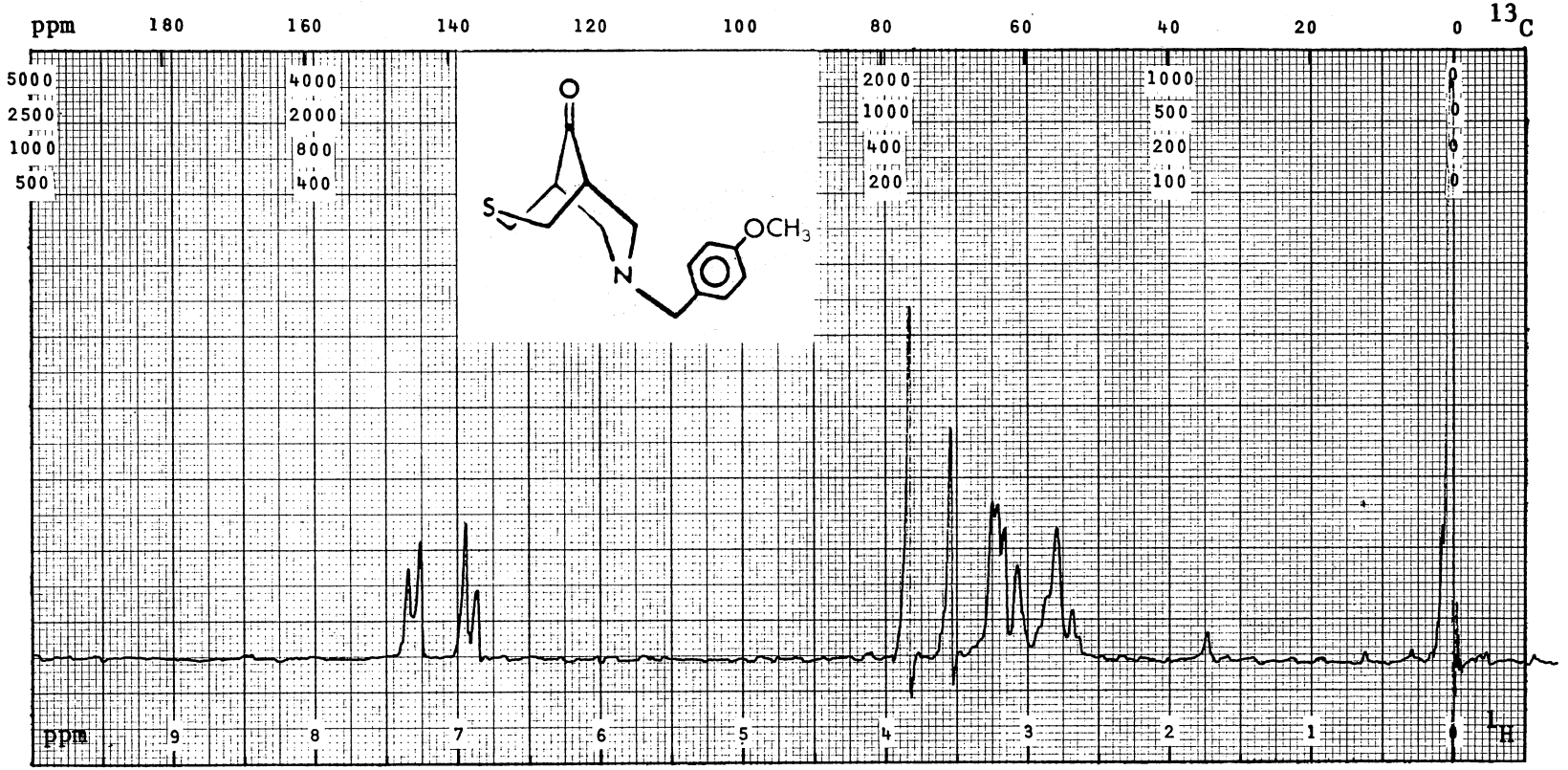
Size. . 8 K; P2 RF. . 10 μs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^2H; D5/ST. . 5 s

PLATE XXI



IR Spectrum of 55

PLATE XXII



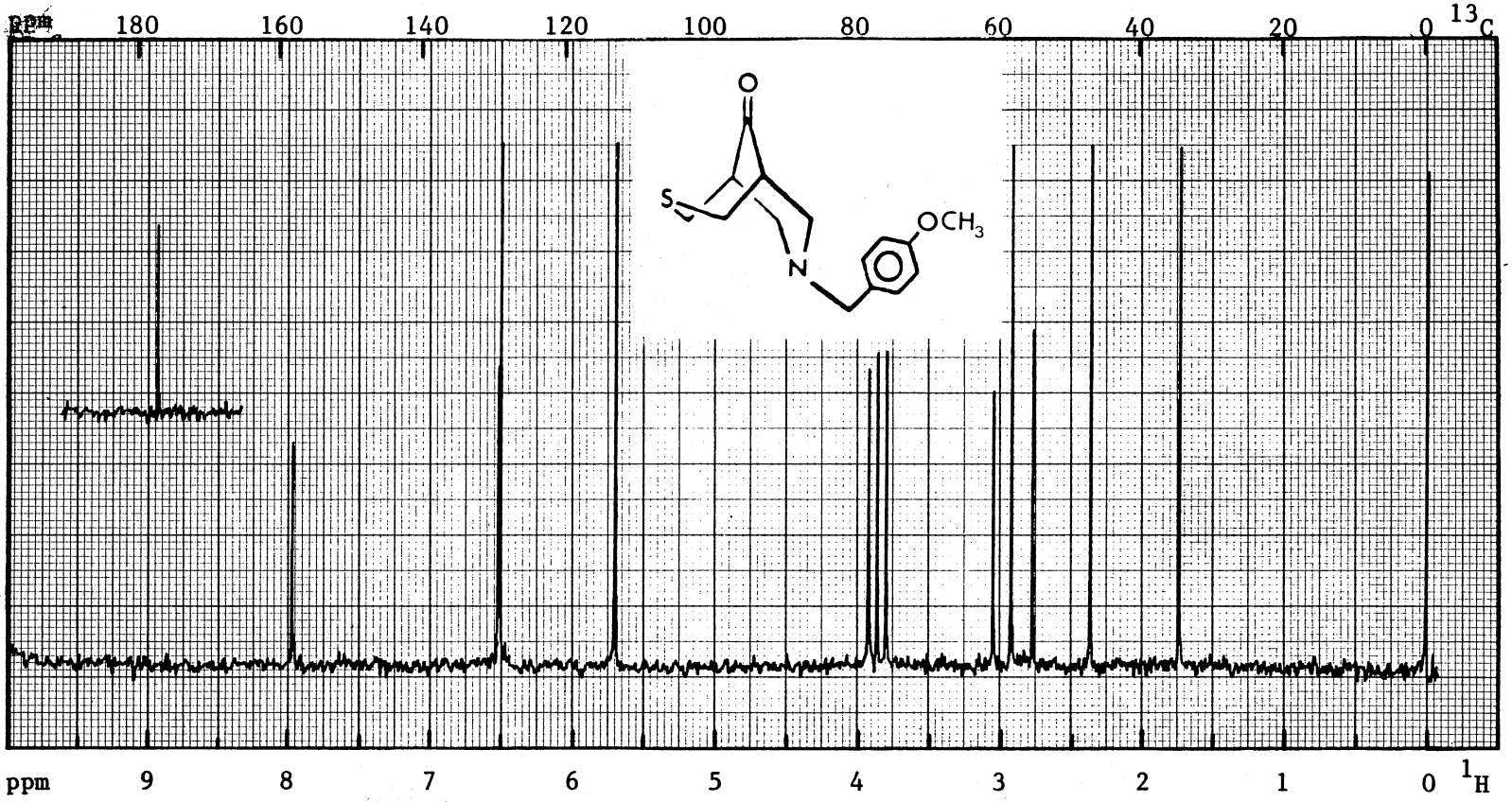
^{1}H NMR Spectrum of 56

PFT _ CW X ; Solvent. . $CDCl_3$; SO. .85771 Hz; PW. .1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 59 µs/dB; SF. .100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XXIII

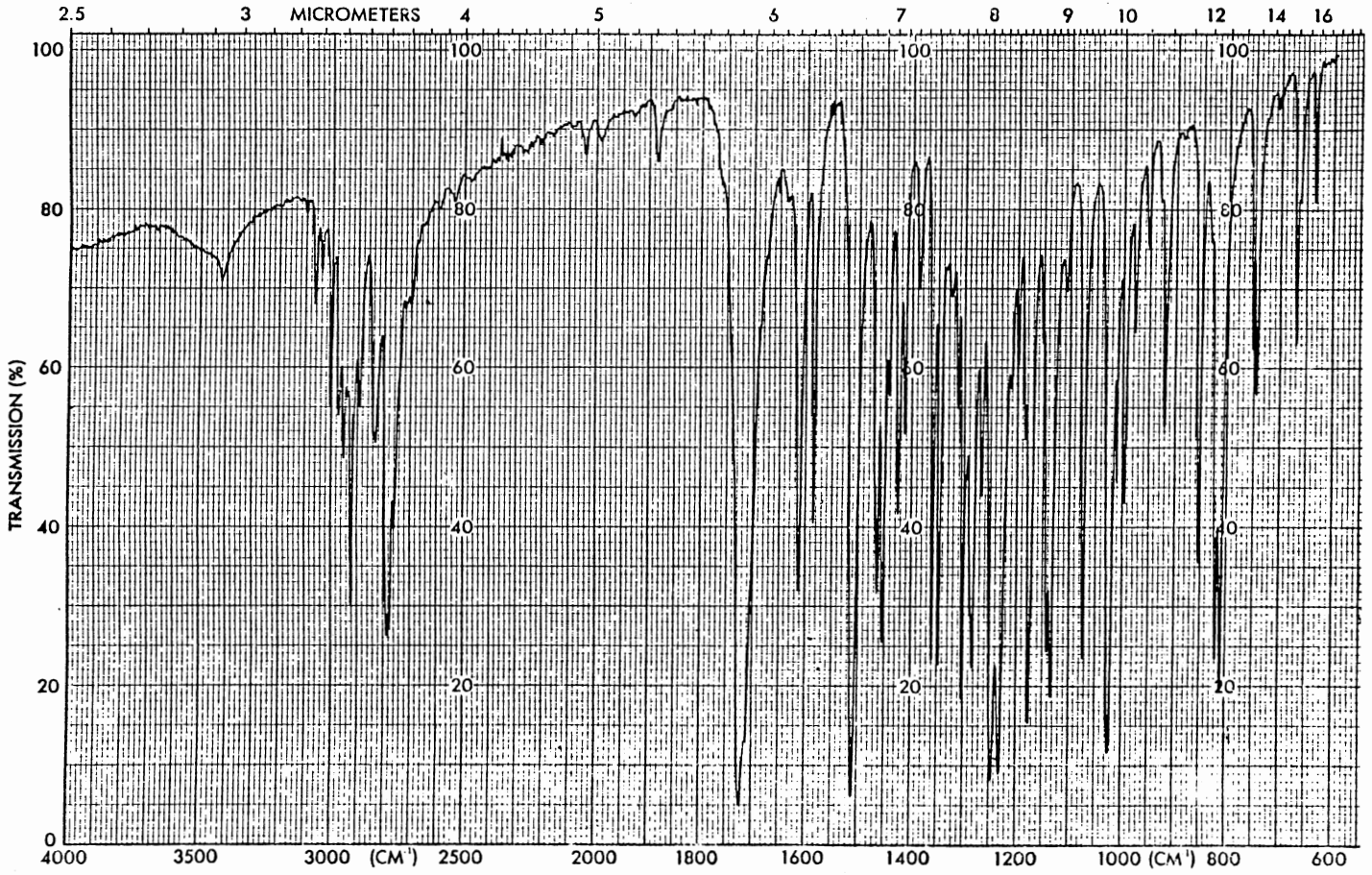


^{13}C NMR Spectrum of 56

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 35101 Hz; PW. . 5000 Hz; T. . 30°C; Acq/SA. . 440

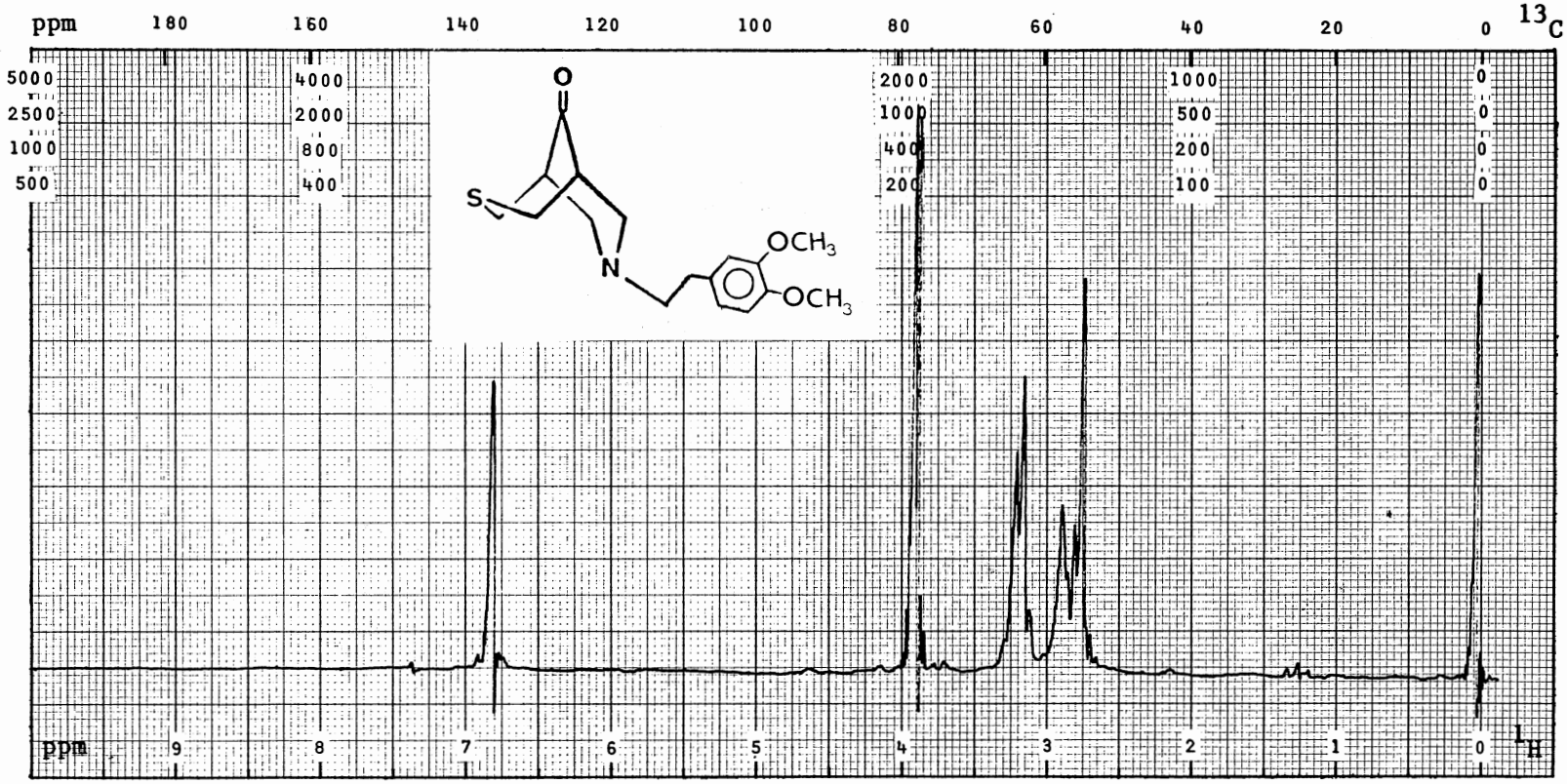
Size. . 8 K; P2 RF. . 10 µs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^2H; D5/ST. . 5 s

PLATE XXIV



IR Spectrum of 56

PLATE XXV



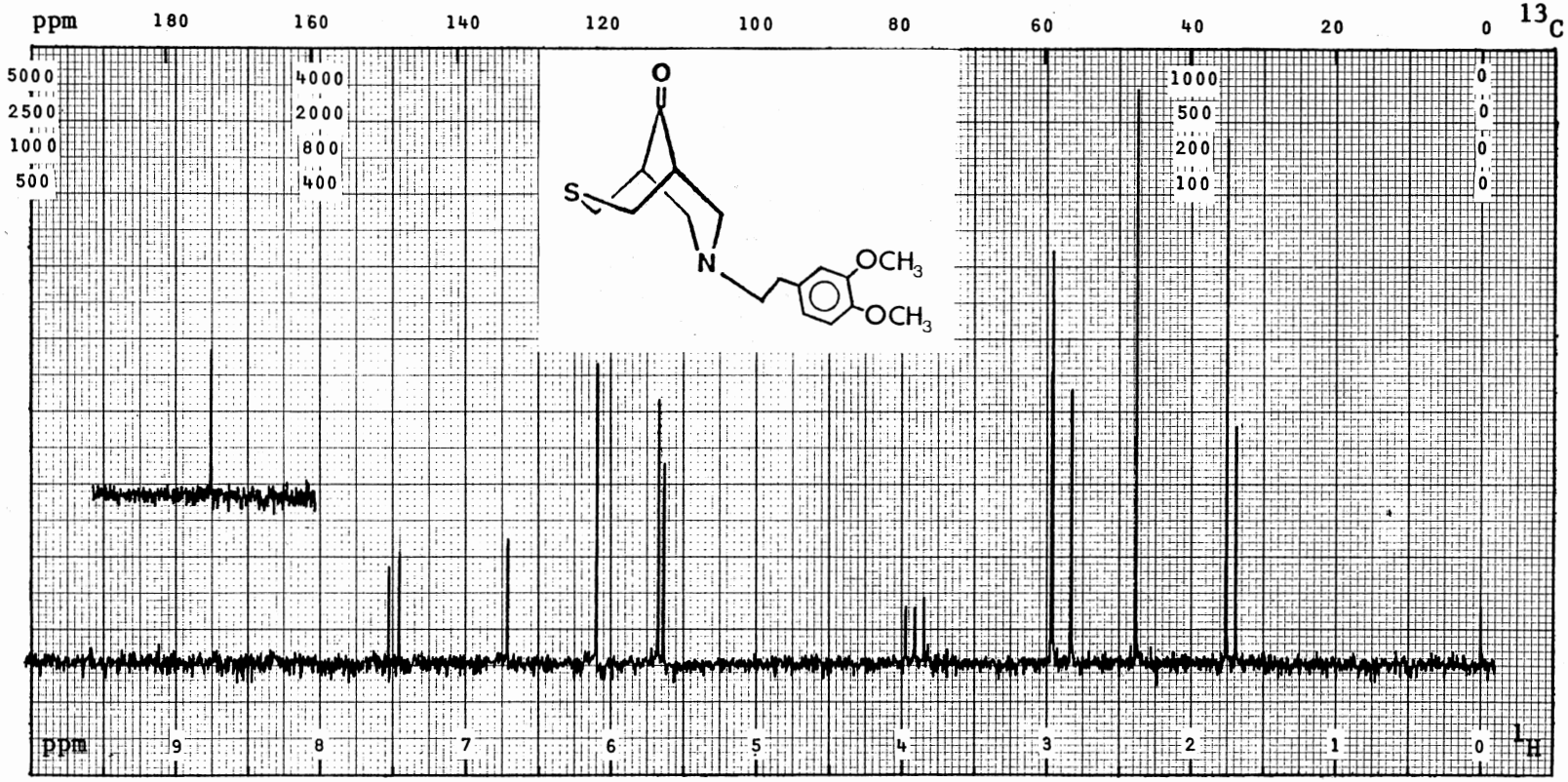
^{1}H NMR Spectrum of 59

PFT _ CW X ; Solvent. . $CDCl_3$; SO. . 85771 Hz; PW. . 1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 60 µs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XXVI



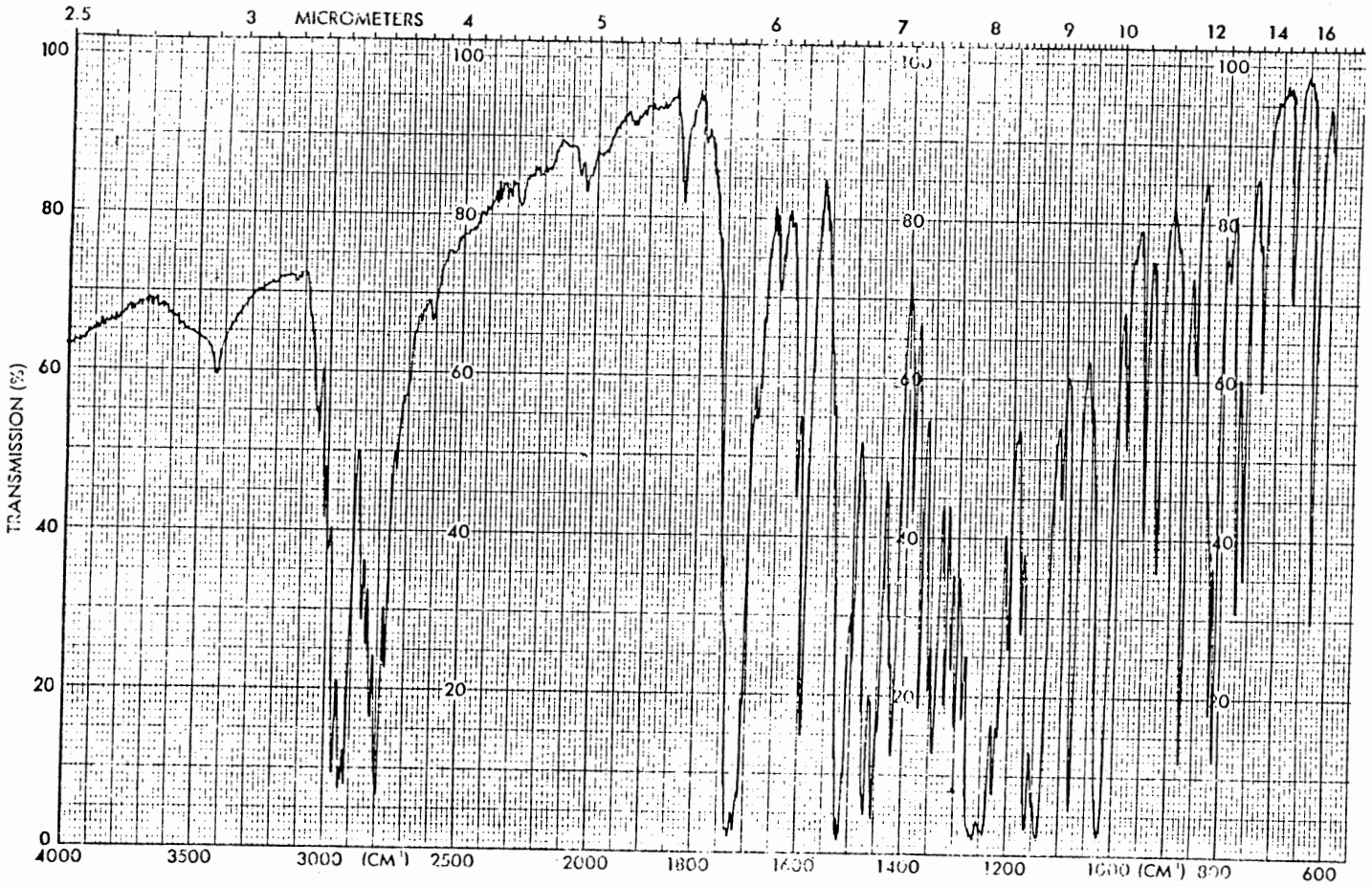
^{13}C NMR Spectrum of 59

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 35101 Hz; PW. . 5000 Hz; T. . 30 °C; Acq/SA. .440

Size. . 8 K; P2/RF. . 10 µs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^{2}H ; D5/ST. . 5 s

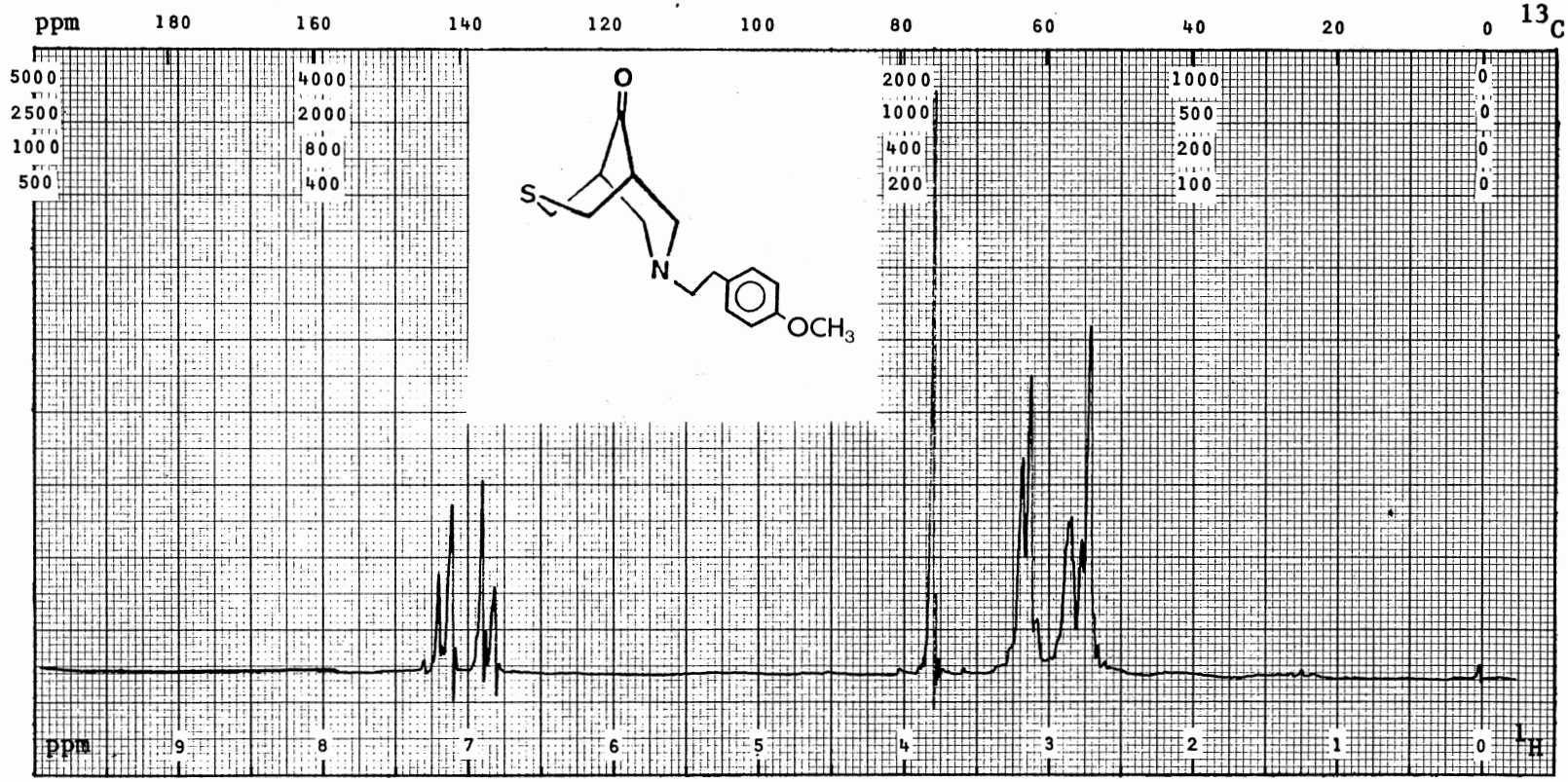
DC. . ^{1}H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE XXVII



IR Spectrum of 59

PLATE XXVIII



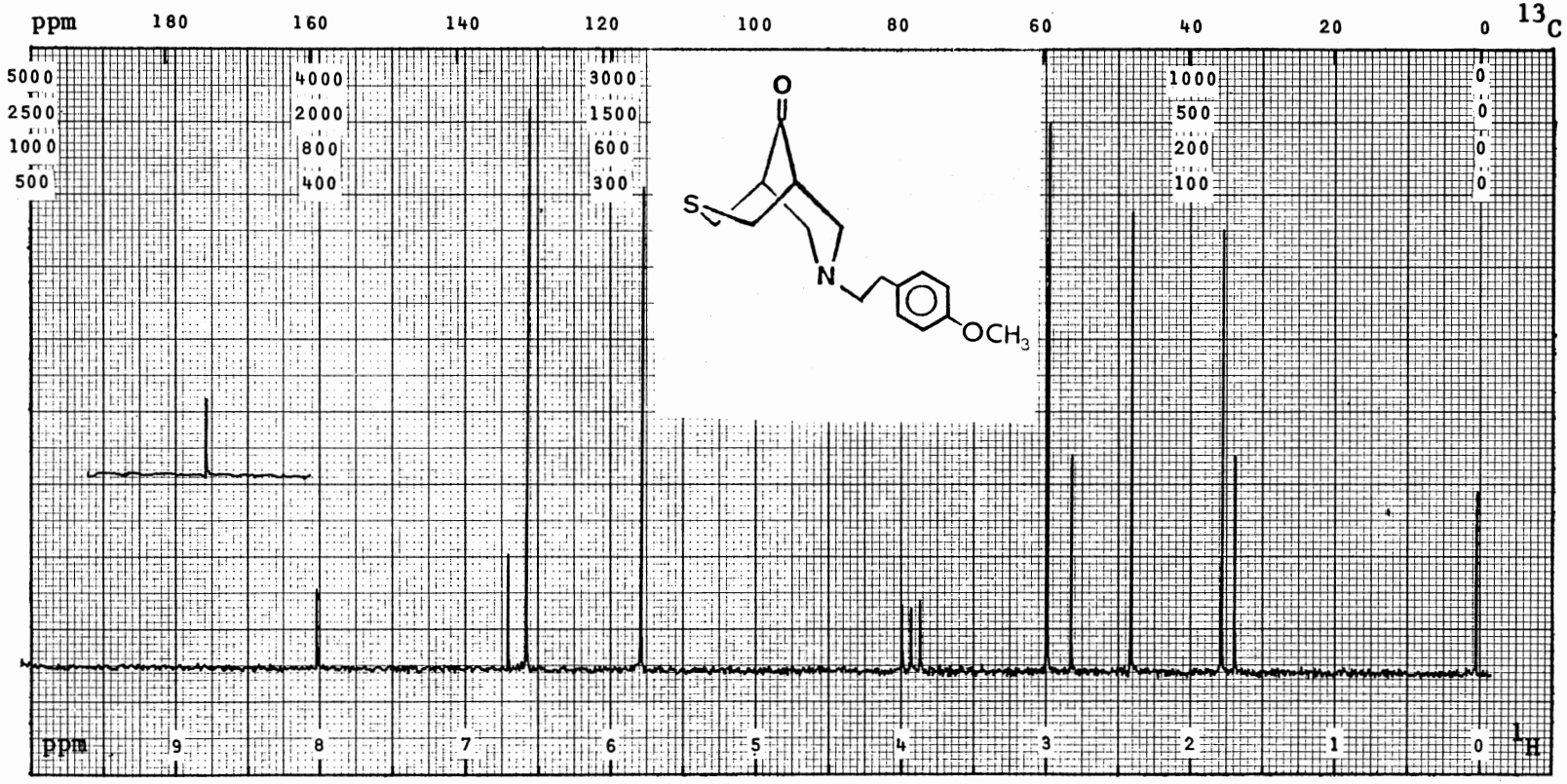
^{1}H NMR Spectrum of 57

PFT _ CW X ; Solvent. . $CDCl_3$; SO. . 85771 Hz; PW. . 1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 58 µs/dB; SF. . 25.2 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XXIX



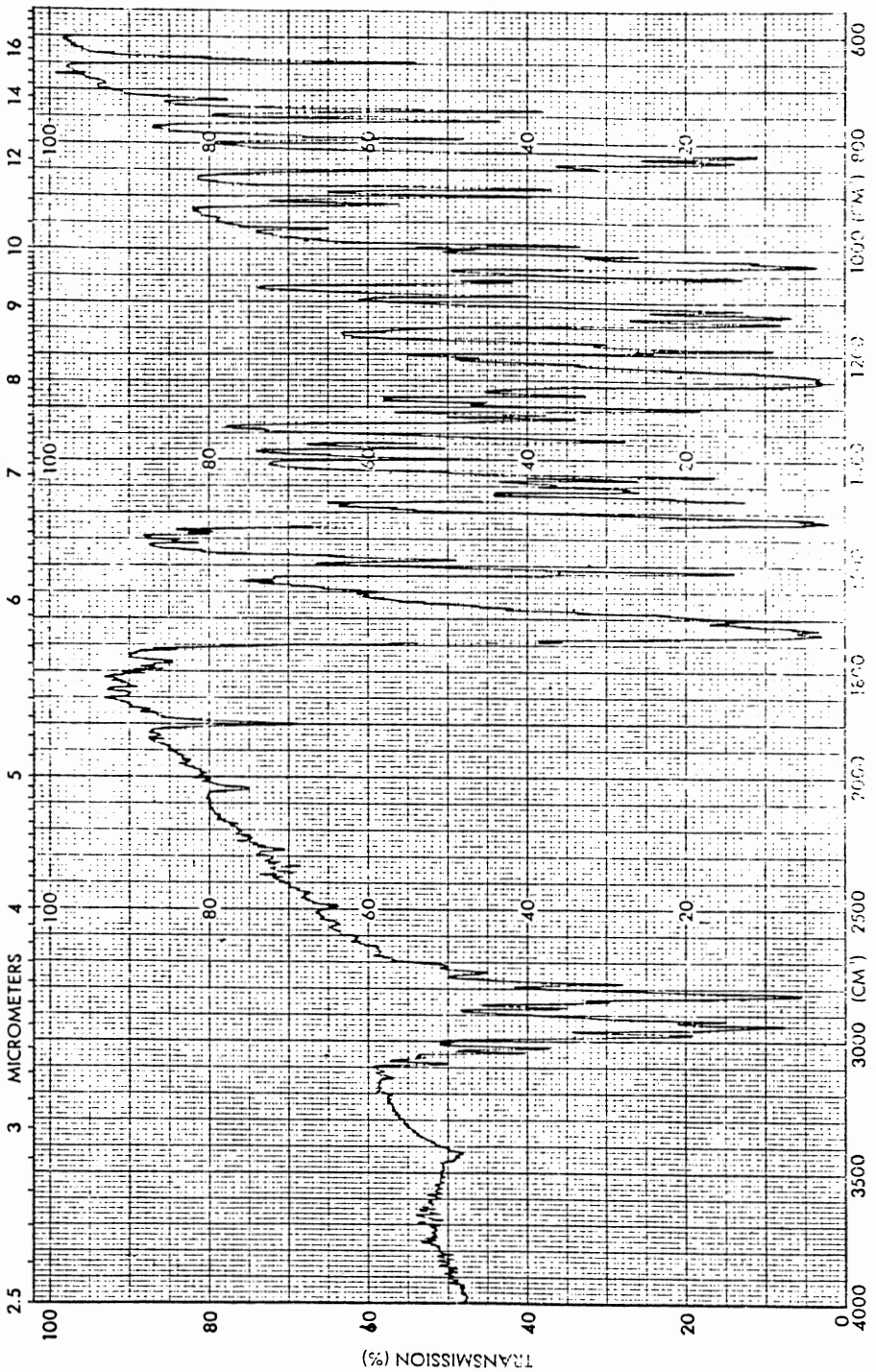
^{13}C NMR Spectrum of 57

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 35101 Hz; PW. . 5000 Hz; T. . 30 °C; Acq/SA. . 440

Size. . 8 K; P2/RF. . 10 µs/dB; SF. . 25.2 Hz; FB. . 2 Hz; Lock. . ^2H ; D5/ST. . 5 s

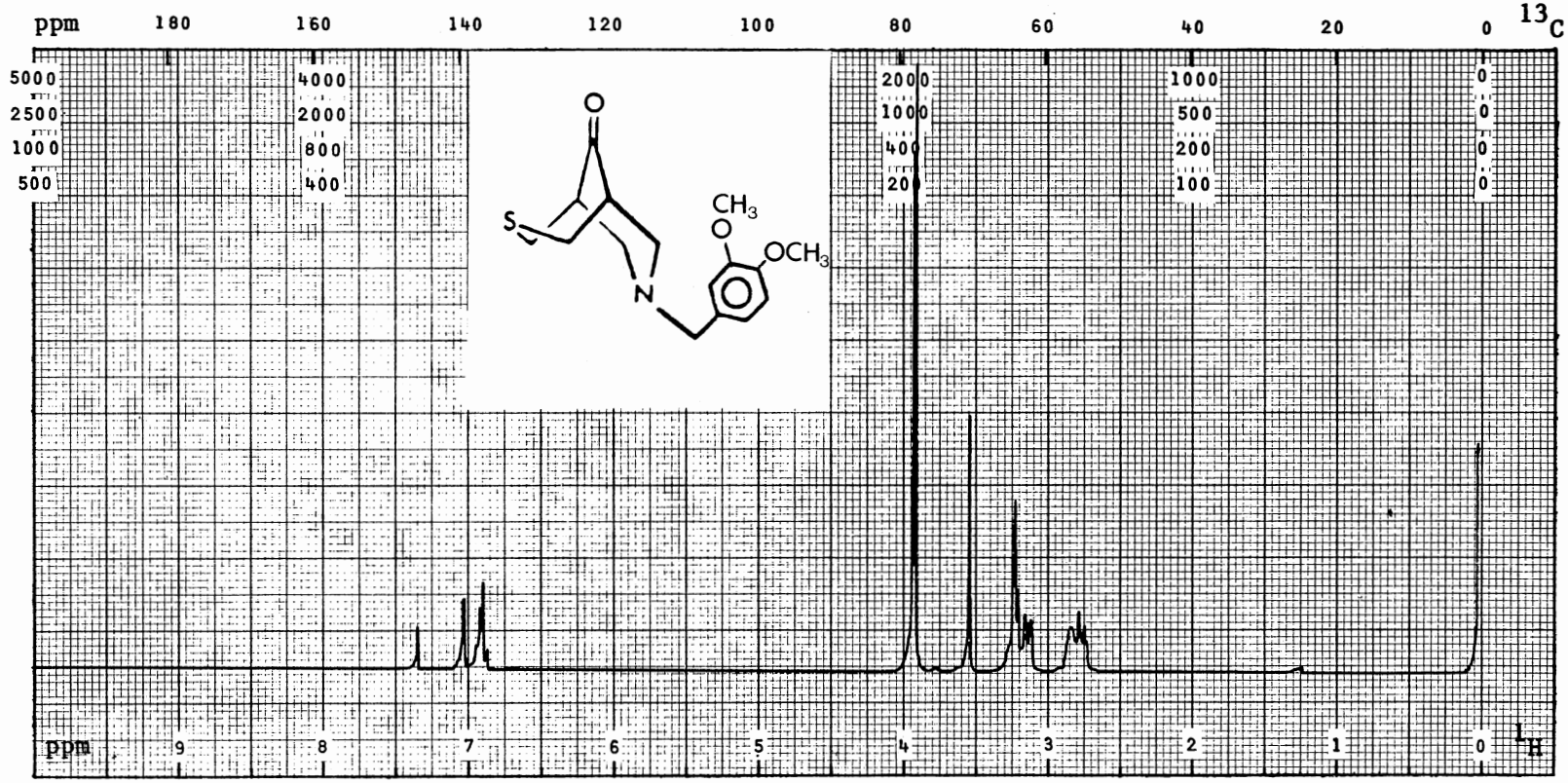
DC. . ^1H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE XXX



IR Spectrum of 57

PLATE XXXI



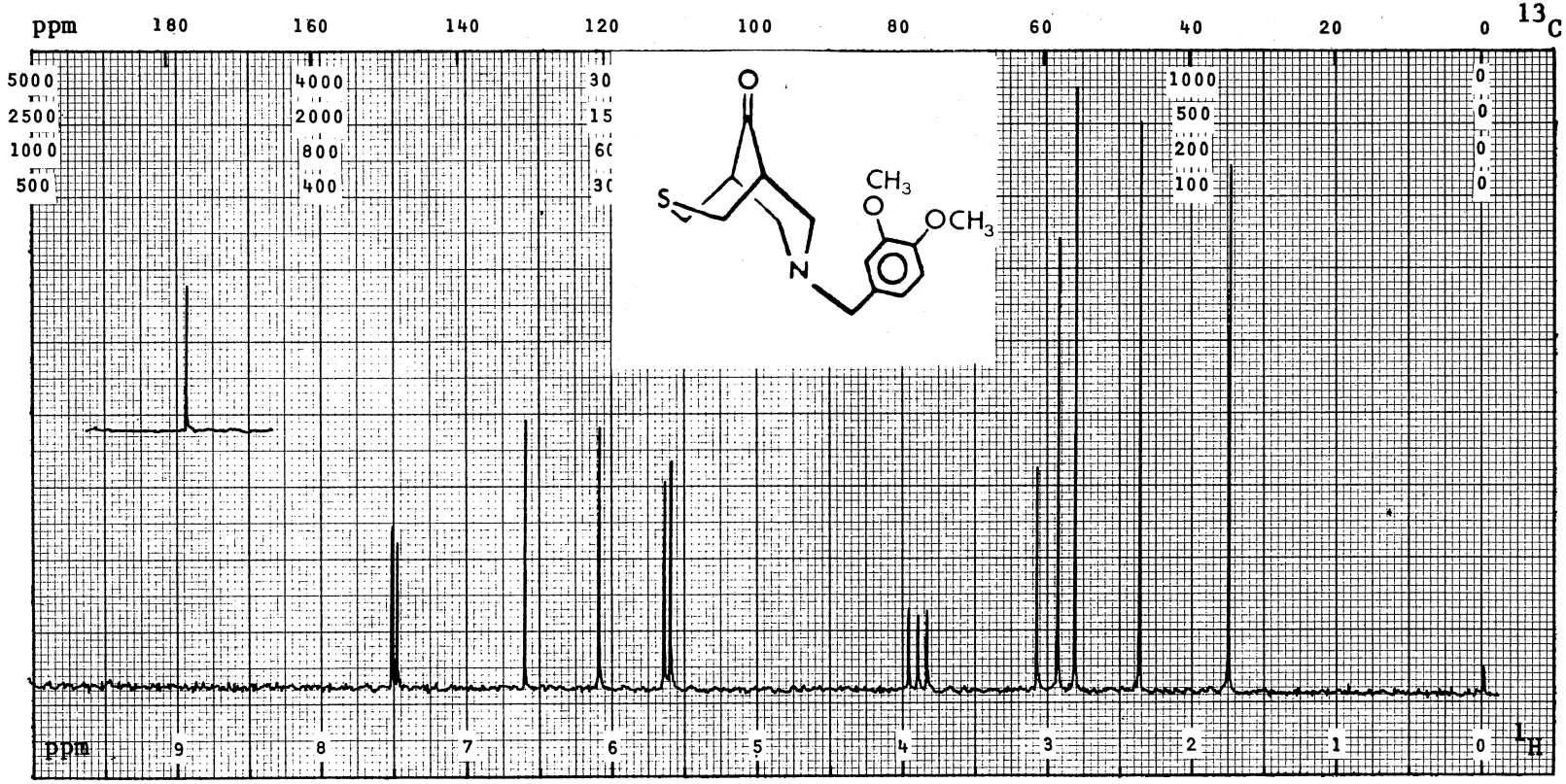
^{1}H NMR Spectrum of 58

PFT _ CW X ; Solvent. . $CDCl_3$; SO. . 85771 Hz; PW. . 1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 62 µs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XXXII



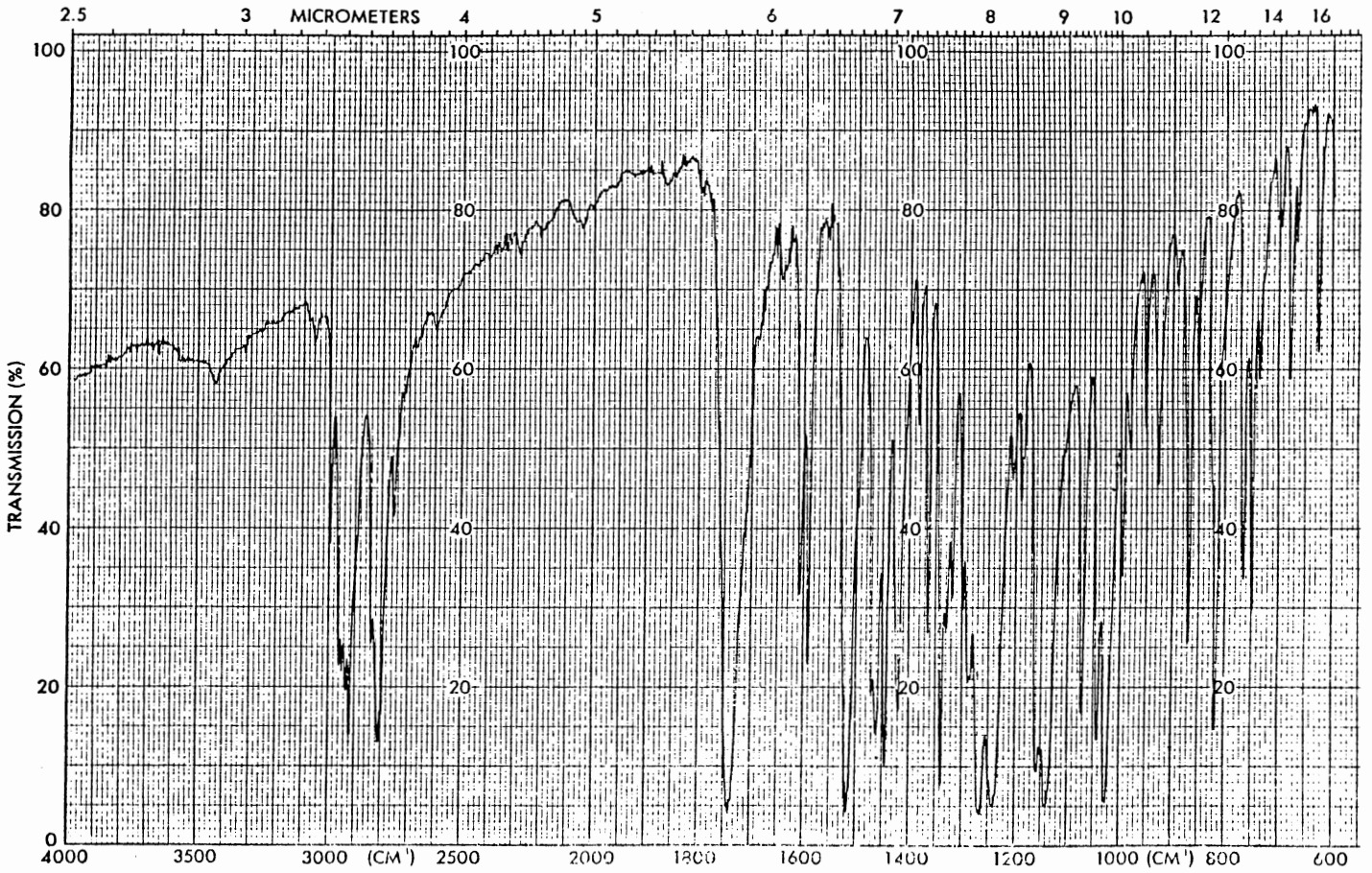
^{13}C NMR Spectrum of 58

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 35101 Hz; PW. . 5000 Hz; T. . 30 °C; Acq/SA. . 440

Size. . 8 K; P2/RF. . 10 µs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^{2}H ; D5/ST. . 5 s

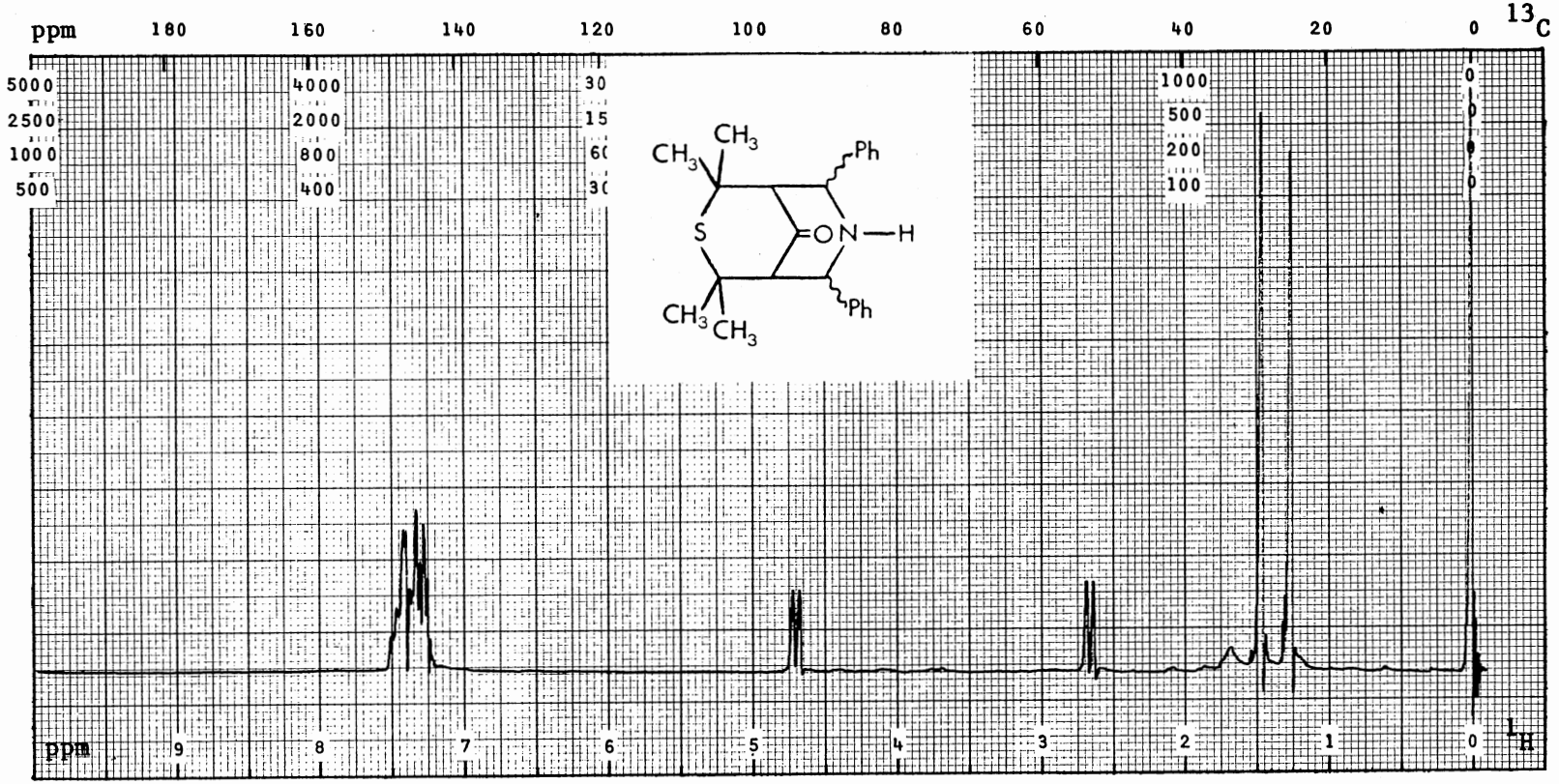
DC. . ^{1}H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE XXXIII



IR Spectrum of 58

PLATE XXXIV



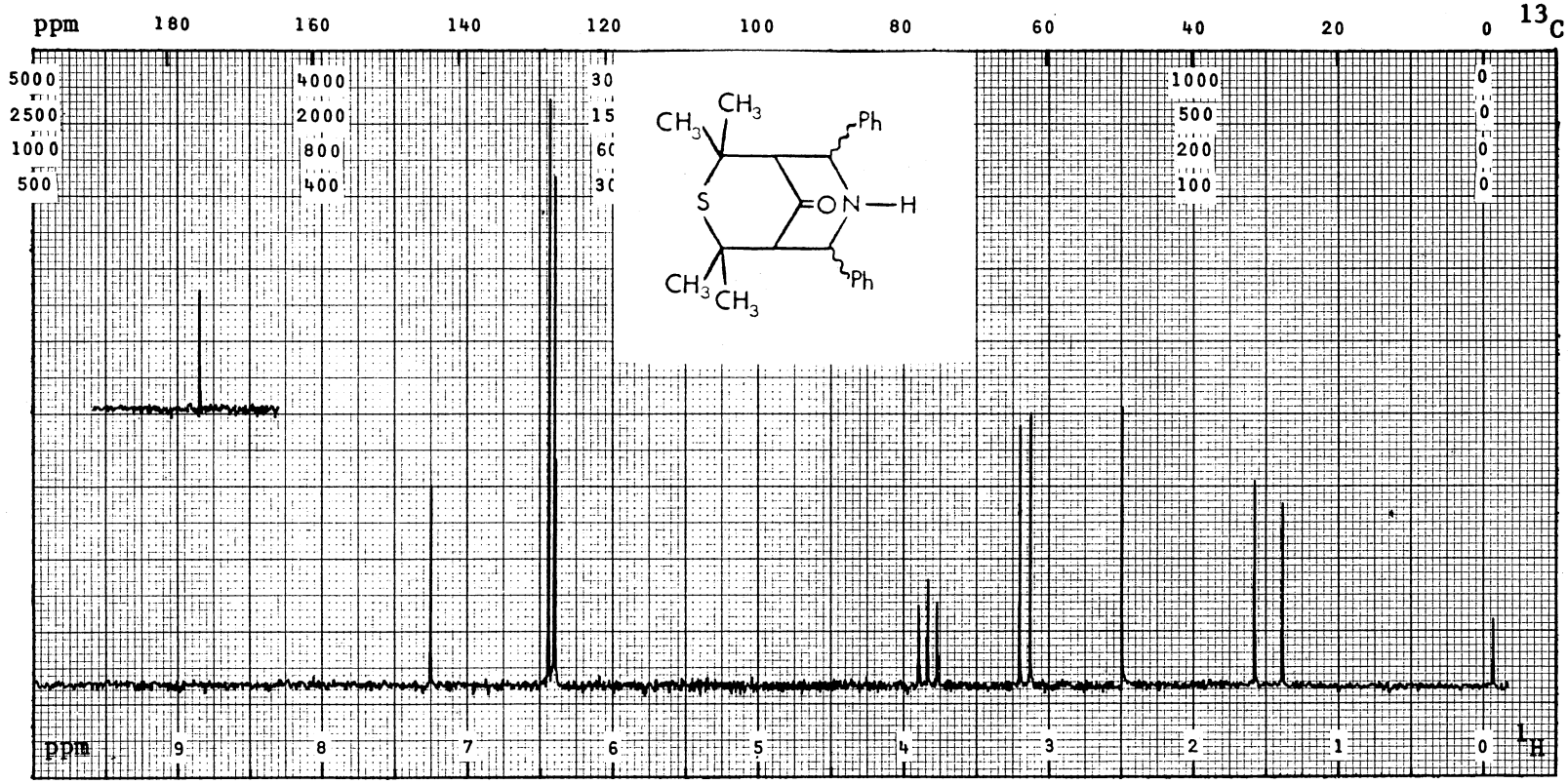
^{1}H NMR Spectrum of 49

PFT _ CW X ; Solvent. . $CDCl_3$; SO. . 85771 Hz; PW. . 1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 59 μs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . . Hz; RF. . W/dB; NBW. . Hz

PLATE XXXV



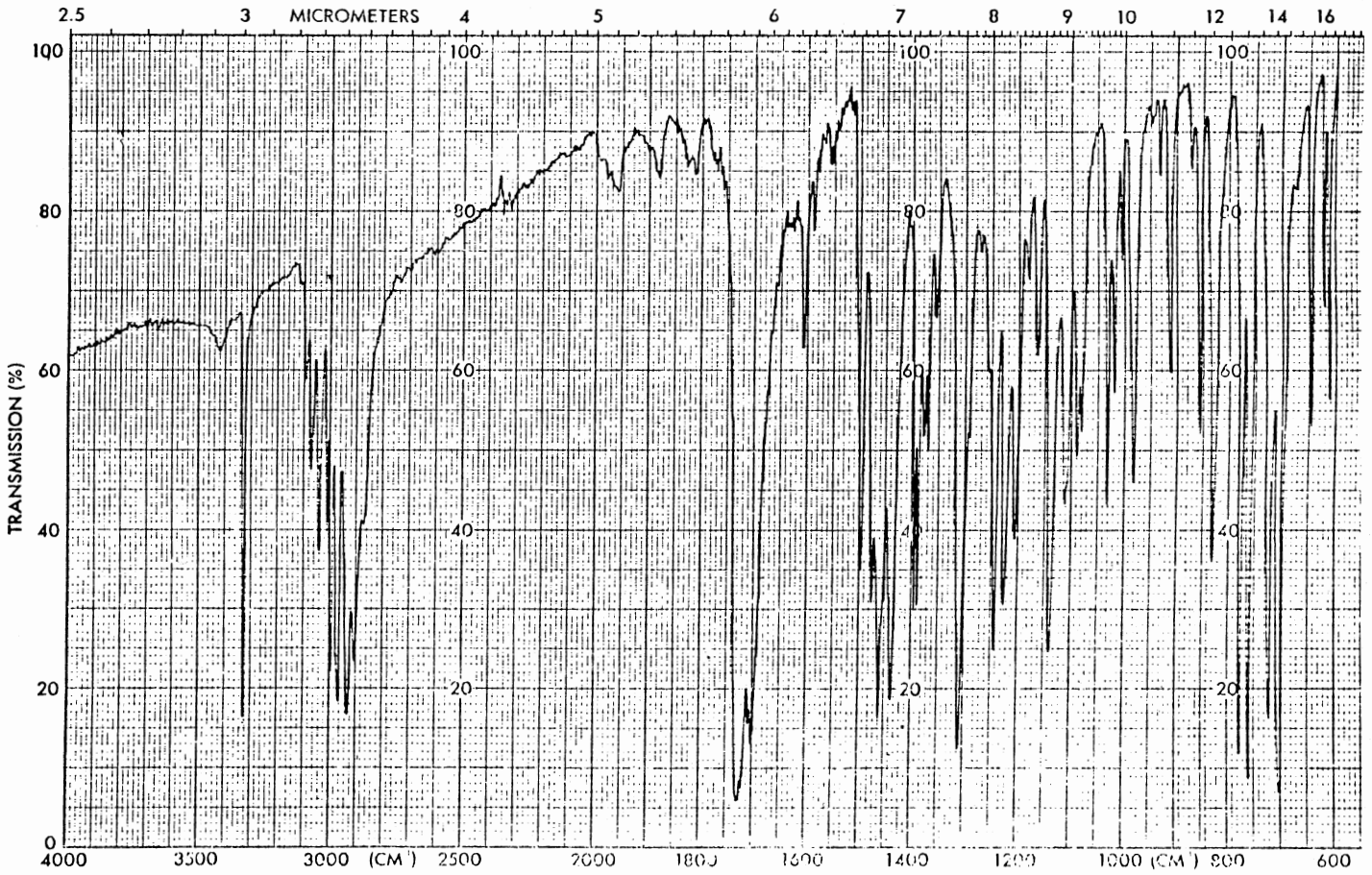
^{13}C NMR Spectrum of 49

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 35101 Hz; PW. . 5000 Hz; T. . 30 °C; Acq/SA. .440

Size. . 8 K; P2/RF. . 10 µs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^2H ; D5/ST. . 5 s

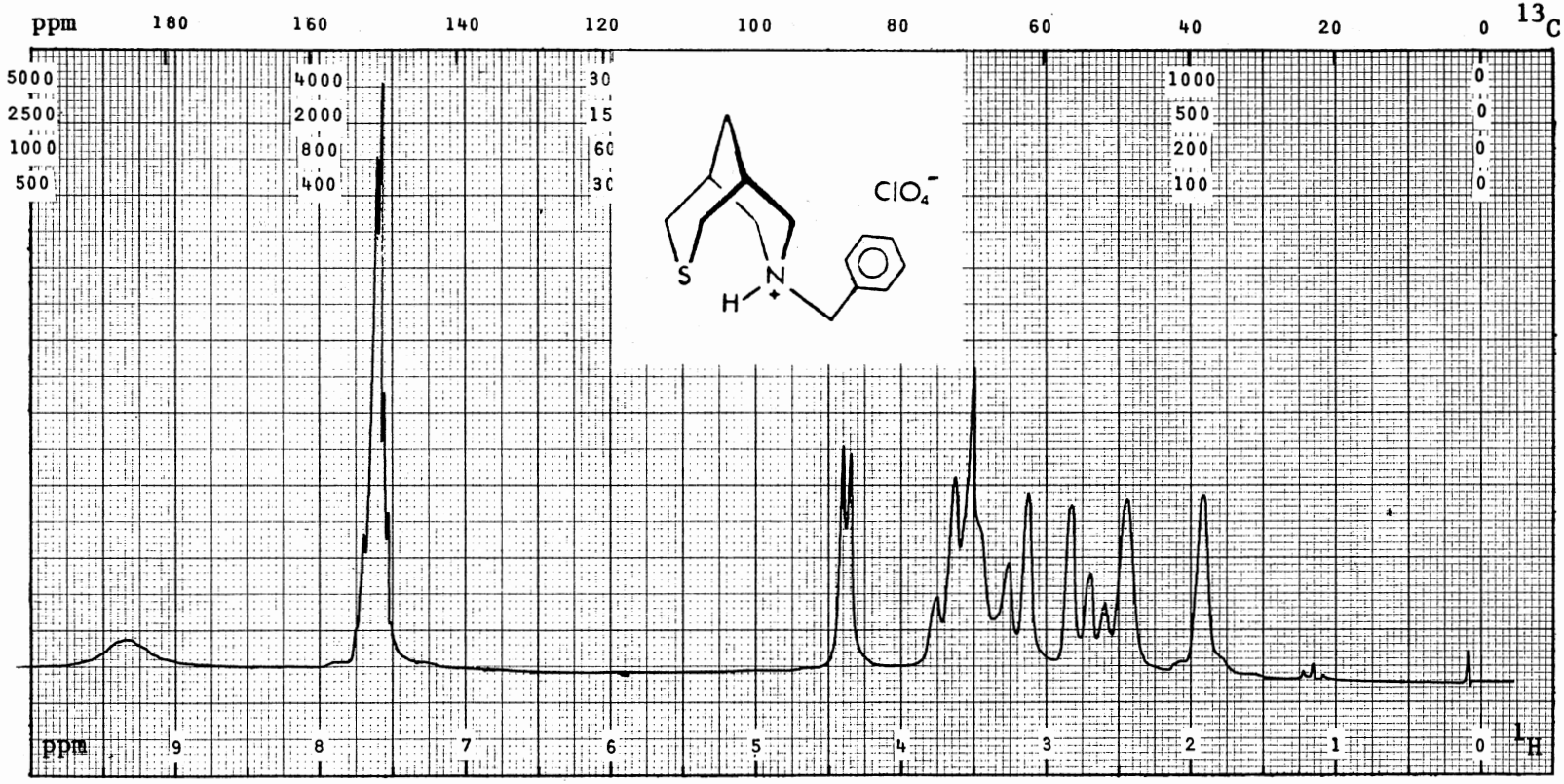
DC. . ^1H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE XXXVI



IR Spectrum of 49

PLATE XXXVII



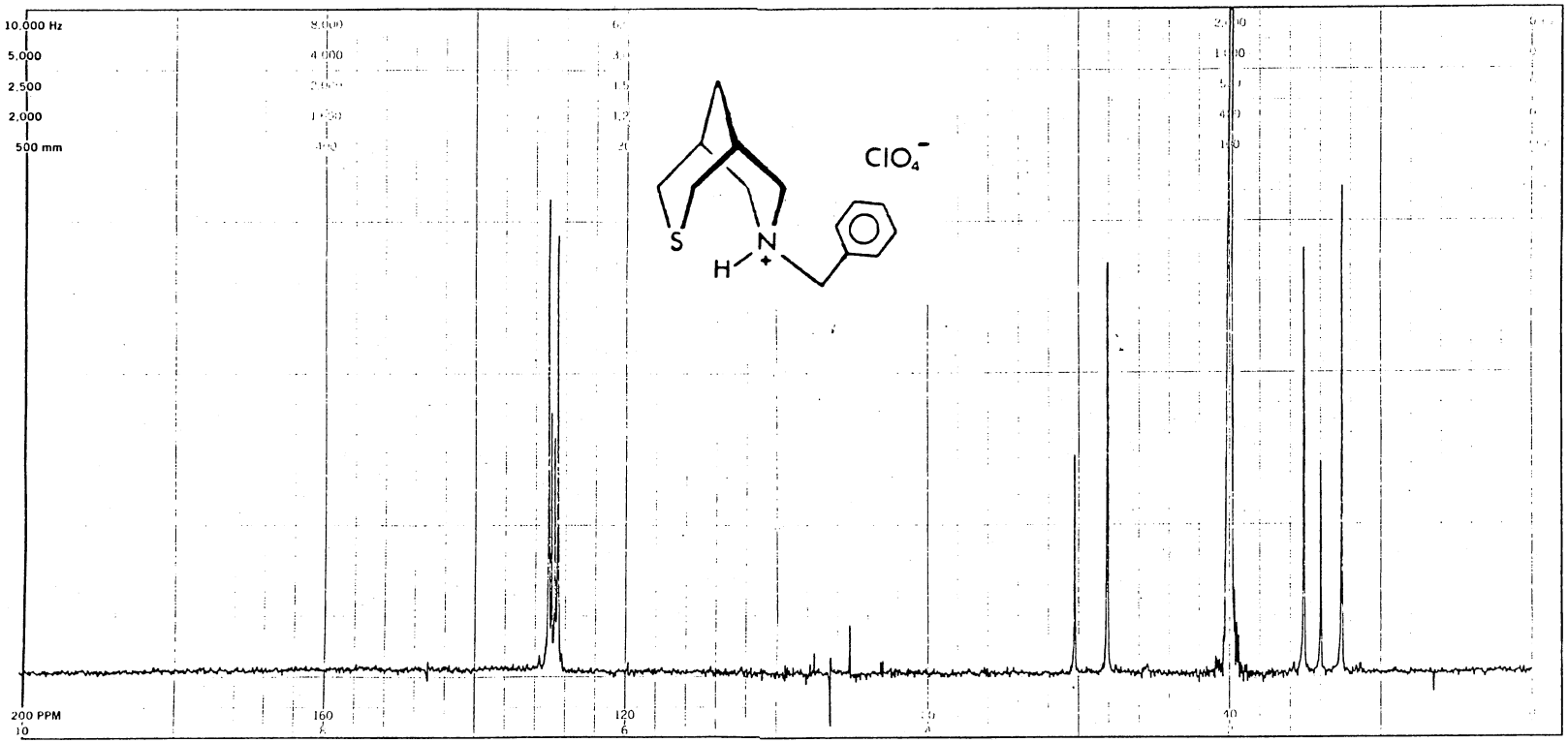
^{1}H NMR Spectrum of 62

PFT _ CW X ; Solvent. . DMSO-d_6 ; SO. . 86242 Hz; PW. . 1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 65 µs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XXXVIII



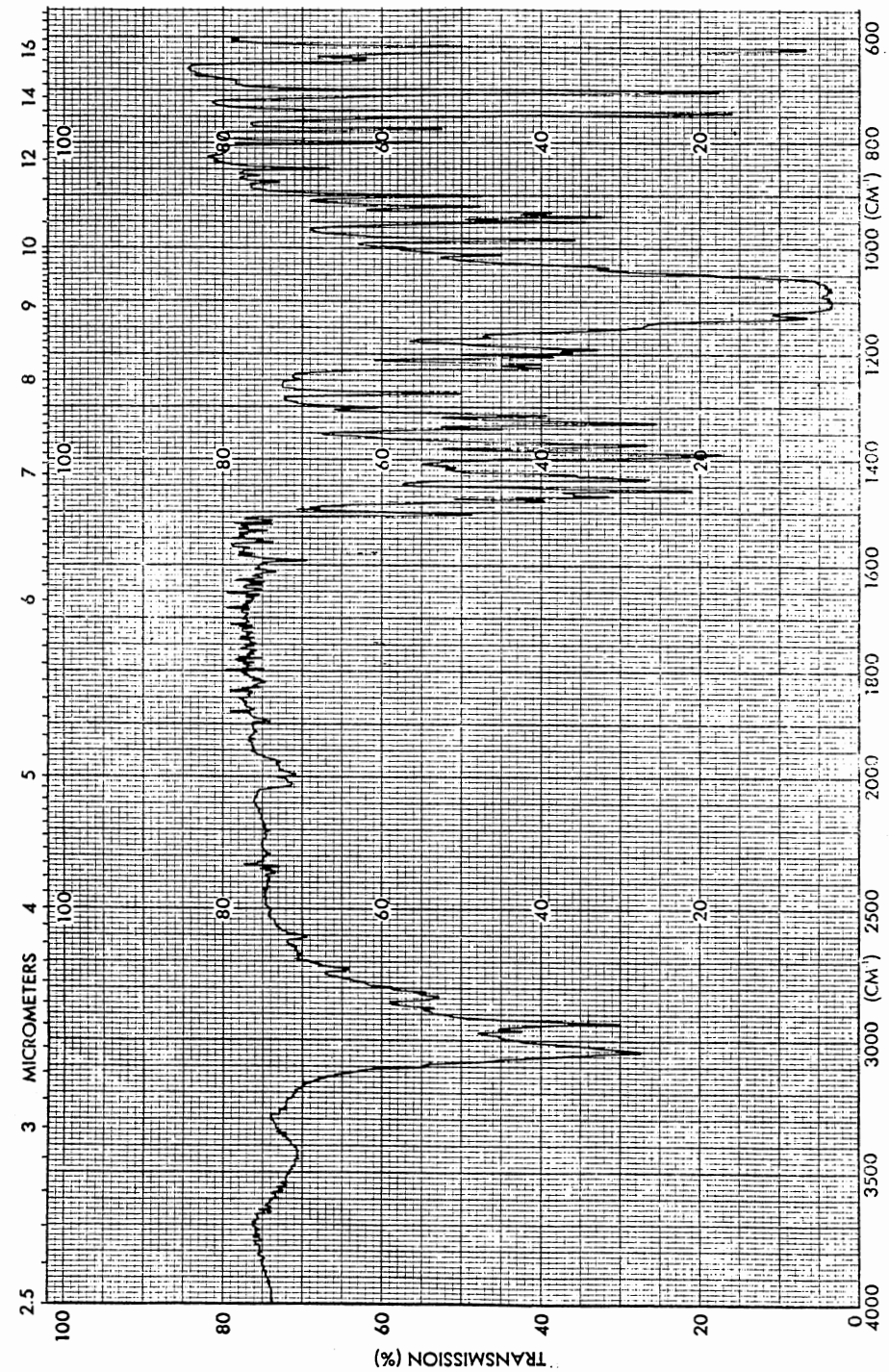
^{13}C NMR Spectrum of 62

PFT X CW _ ; Solvent. . DMSO-d_6 ; SO. . 35201 Hz; PW. . 5000 Hz; T. . 30 °C; Acq/SA. .440

Size. . 8 K; P2/RF. . 10 μs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^{2}H ; D5/ST. . 5 s

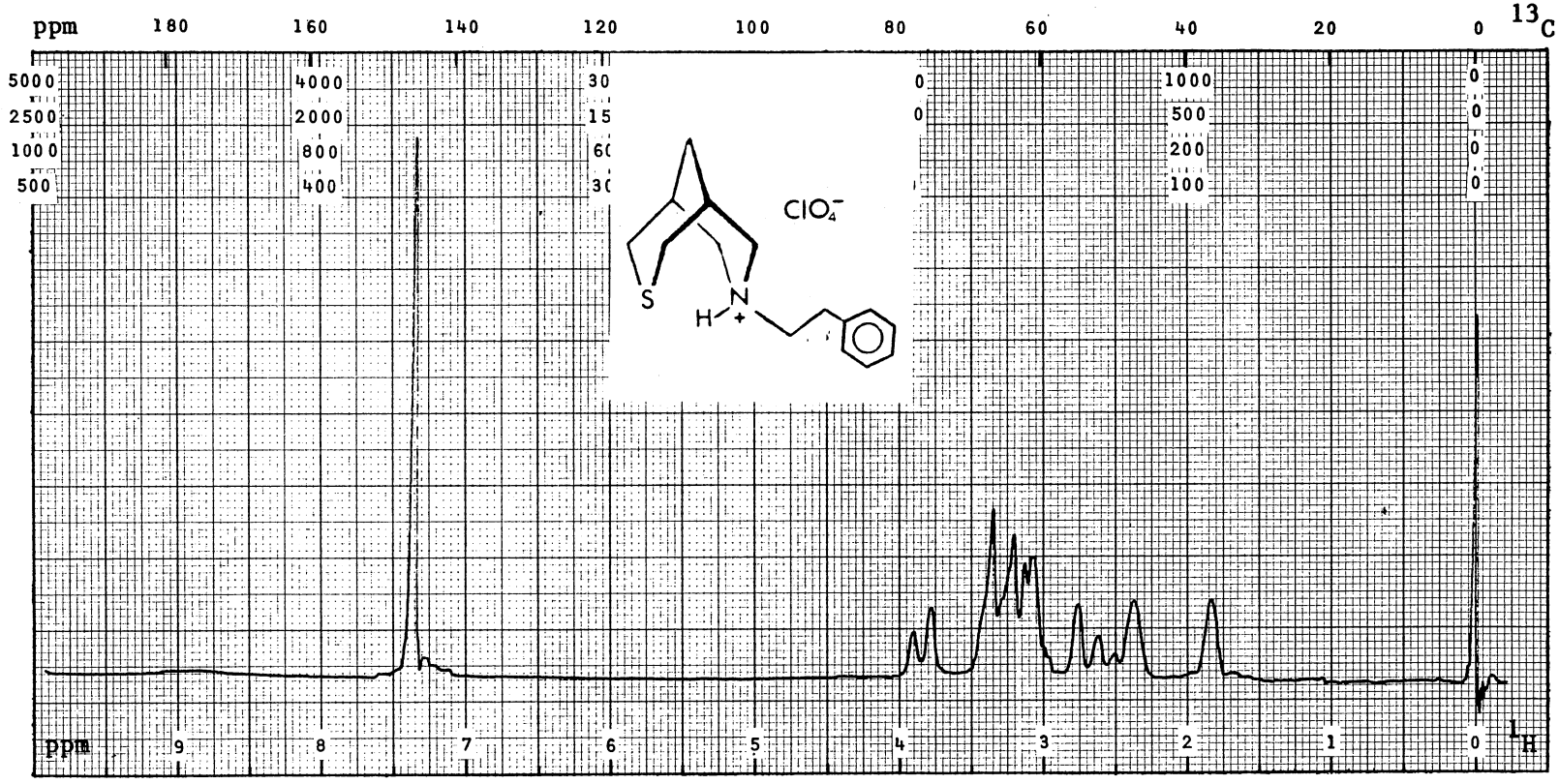
DC. . ^{1}H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE XXXIX



IR Spectrum of 62

PLATE XL



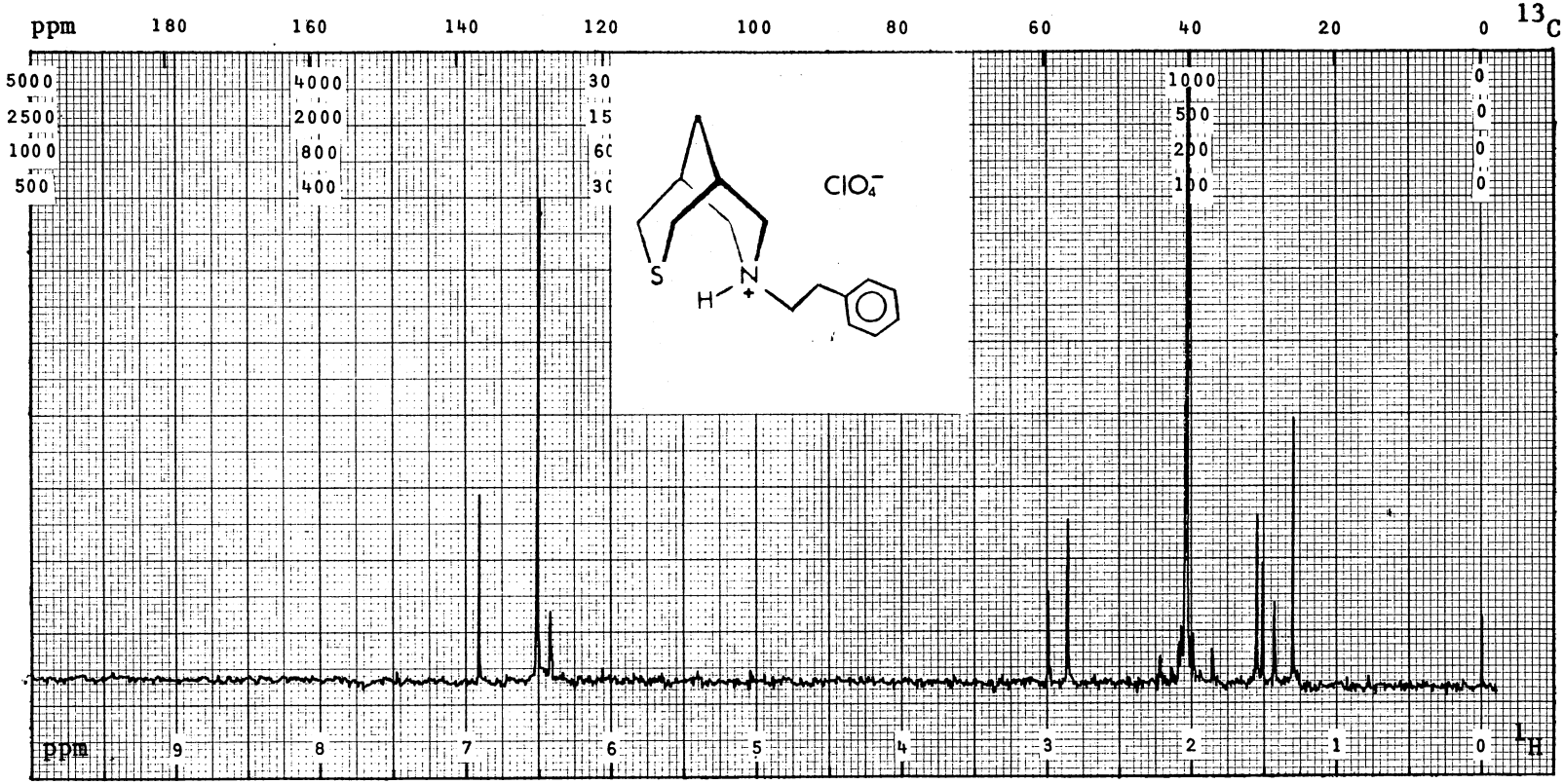
^{1}H NMR Spectrum of 63

PFT _ CW X ; Solvent. . DMSO-d_6 ; SO. . 86242 Hz; PW. . 1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 65 µs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XLI



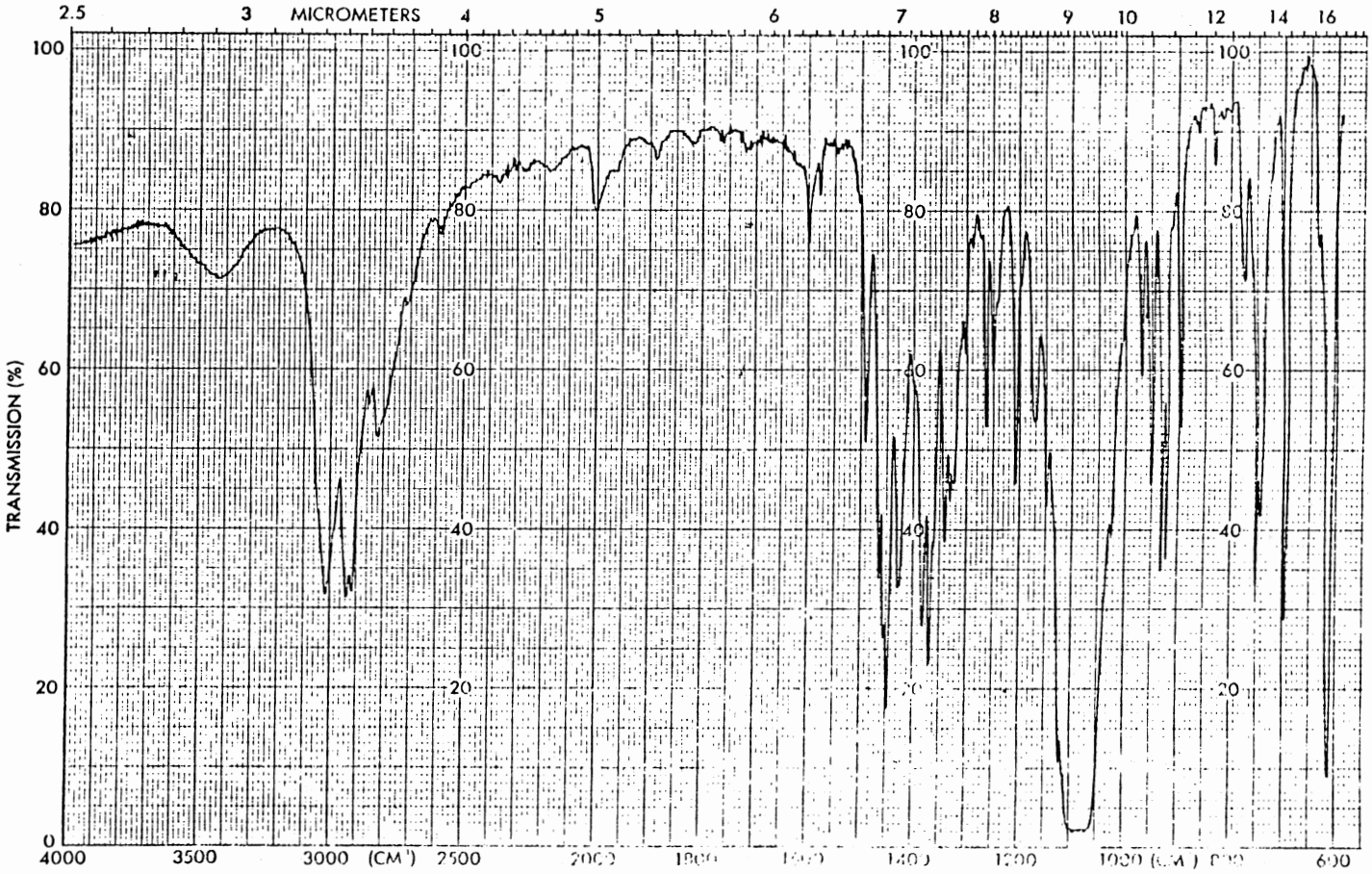
^{13}C NMR Spectrum of 63

PFT X CW _ ; Solvent. . DMSO-d_6 ; SO. .35201 Hz; PW. . 5000 Hz; T. . 30 °C; Acq/SA. .440

Size. . 8 K; P2/RF. . 10 μs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^{2}H ; D5/ST. . 5 s

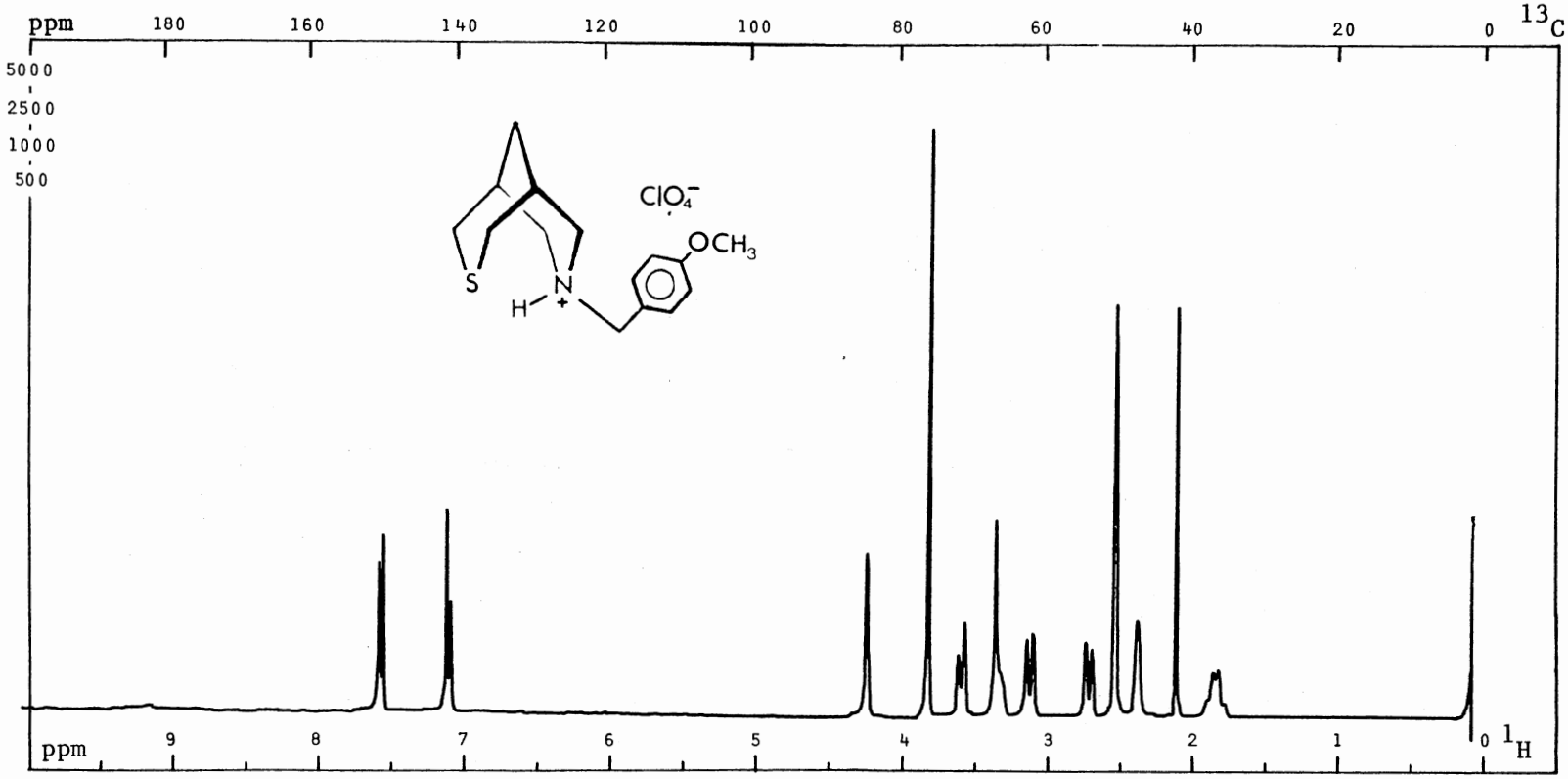
DC. . ^{1}H ; Gated Off. . ; Offset. .45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE XLII



IR Spectrum of 63

PLATE XLIII



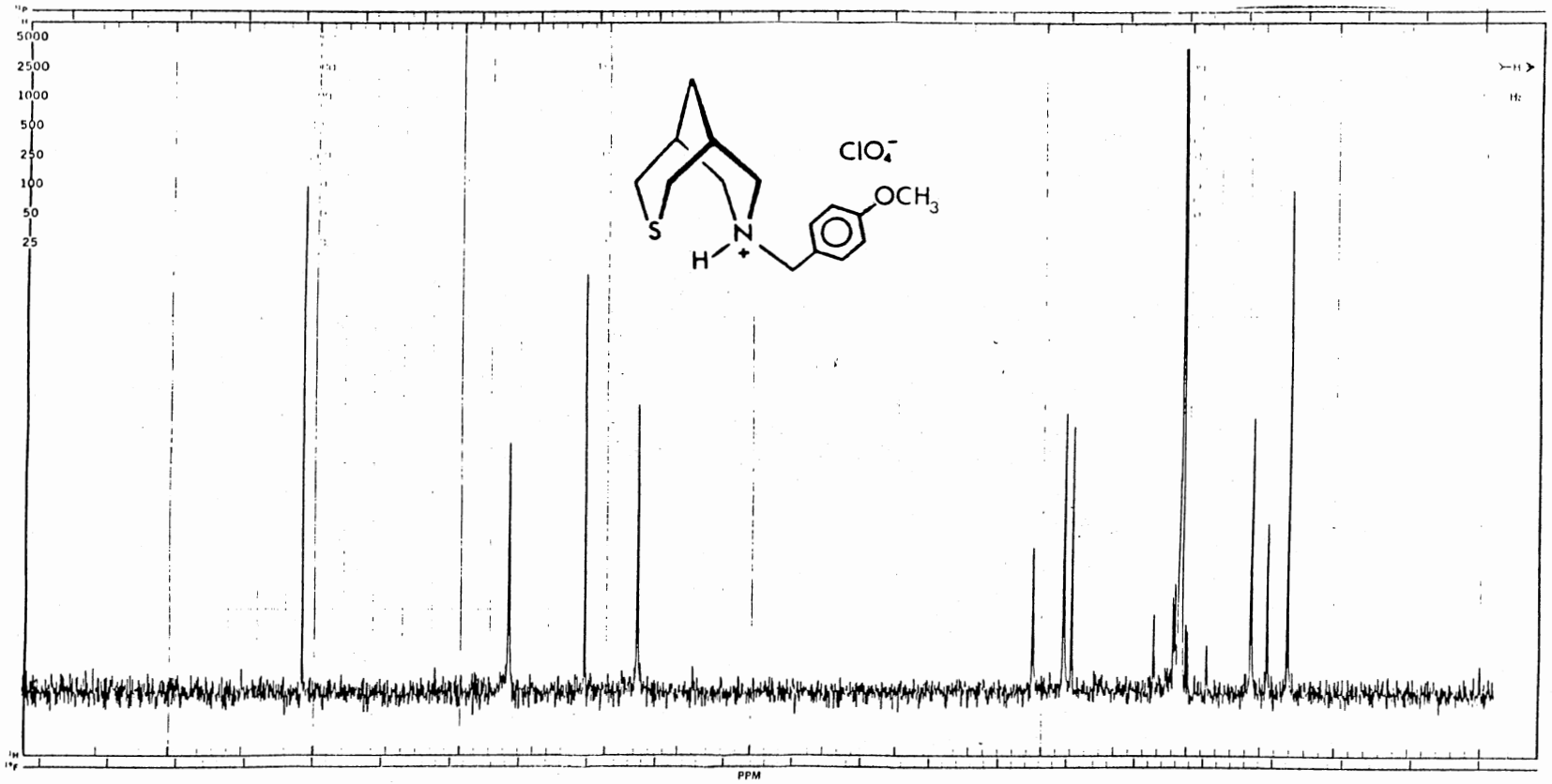
^{1}H NMR Spectrum of 64

PFT _ CW X ; Solvent. . DMSO-d_6 ; SO. . 86242 Hz; PW. .1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 59 µs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XLIV



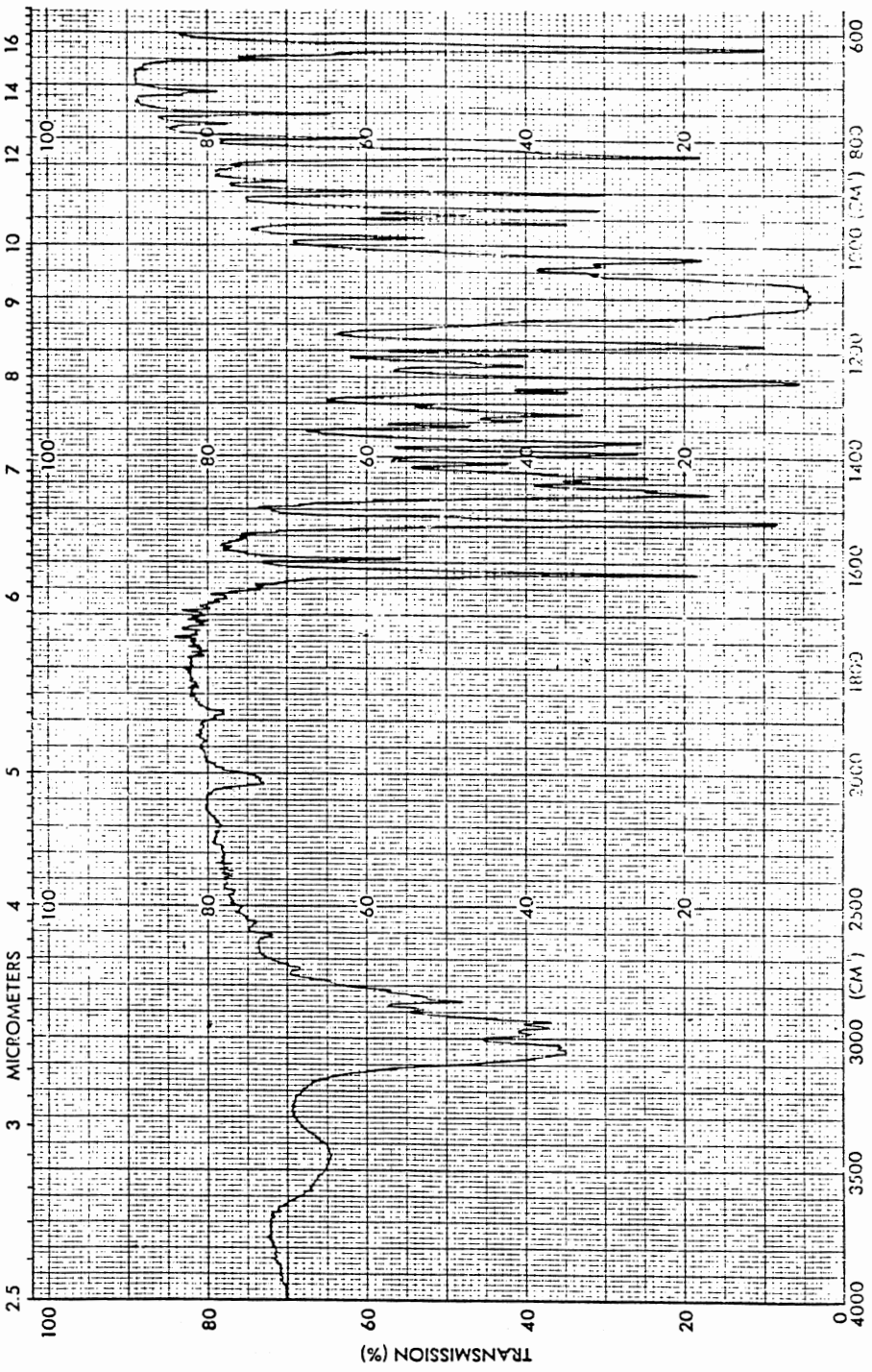
^{13}C NMR Spectrum of 64

PFT X CW _ ; Solvent. . DMSO-d_6 ; SO. . 35201 Hz; PW. . 5000 Hz; T. . 30 °C; Acq/SA. .440

Size. . 8 K; P2/RF. . 10 µs/dB; SF. . 25.2 Hz; FB. . 2 Hz; Lock. . ^2H ; D5/ST. . 5 s

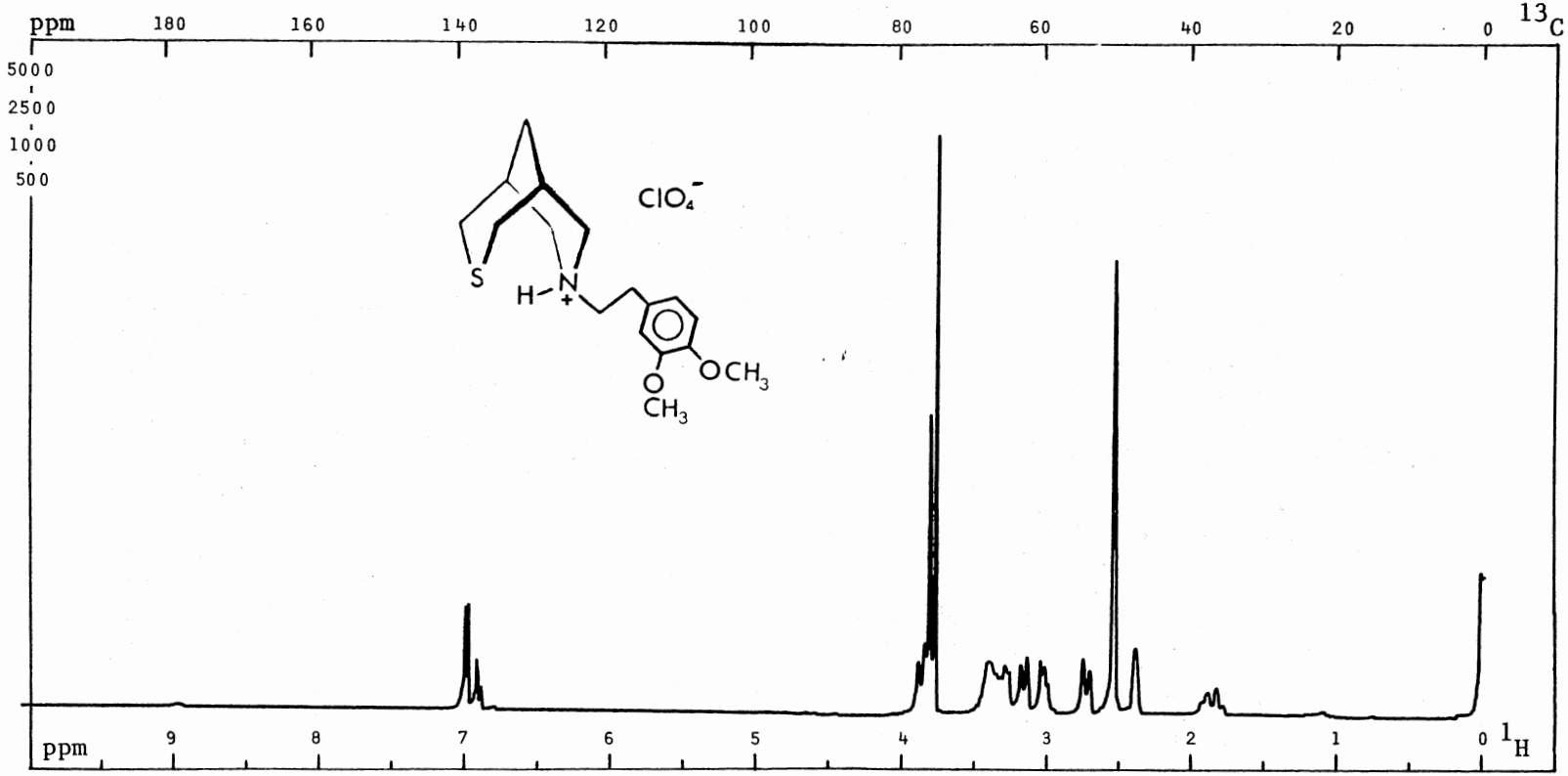
DC. . ^1H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE XLV



IR Spectrum of 64

PLATE XLVI



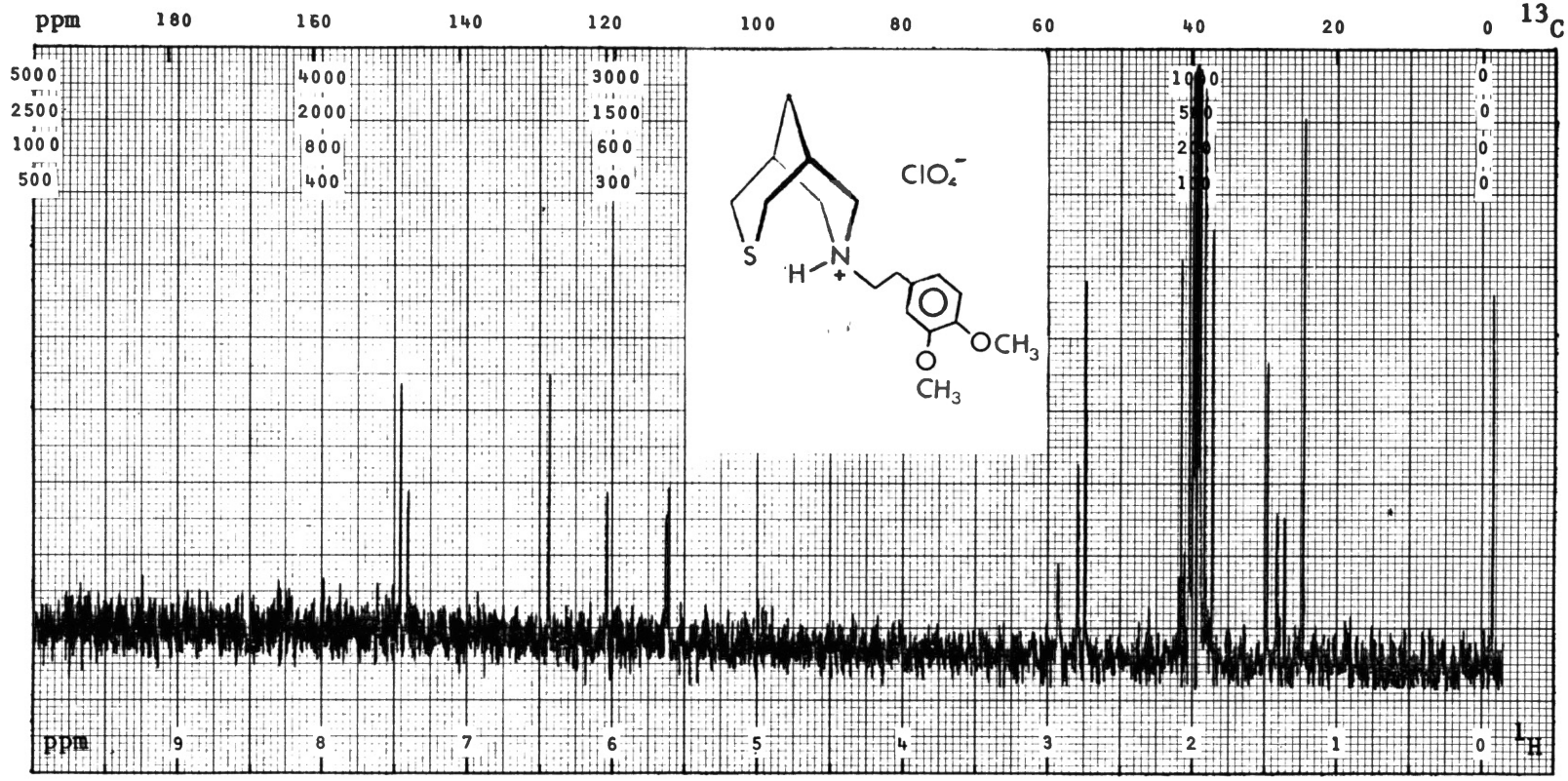
^{1}H NMR Spectrum of 65

PFT _ CW X ; Solvent. . DMSO-d_6 ; SO. . 86242 Hz; PW. . 1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 63 µs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XLVII



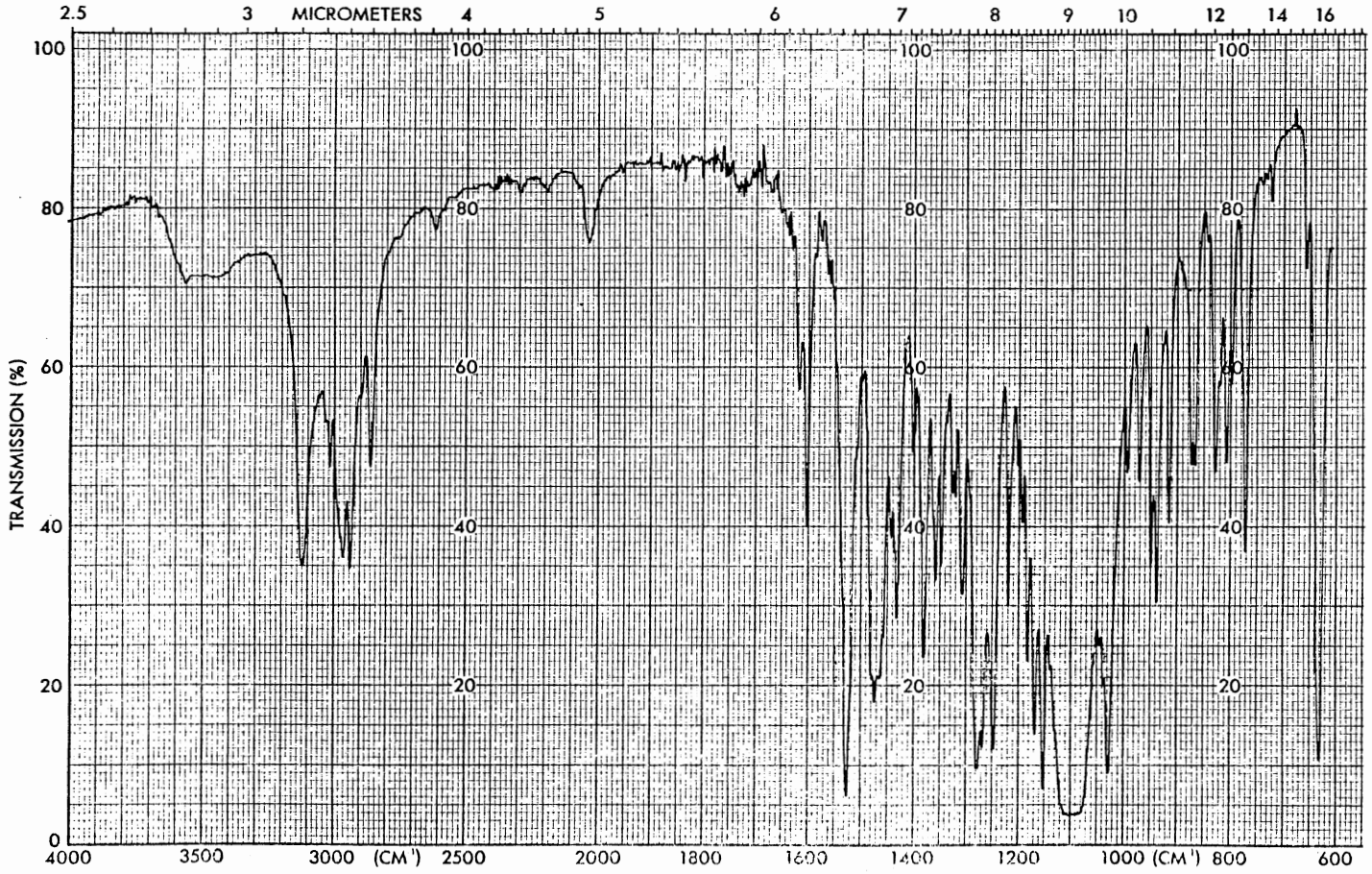
^{13}C NMR Spectrum of 65

PFT X CW _ ; Solvent. . DMSO-d_6 ; SO. . 35201 Hz; PW. . 5000 Hz; T. . 30 °C; Acq/SA. . 440

Size. . 8 K; P2/RF. . 10 µs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^{2}H ; D5/ST. . 5 s

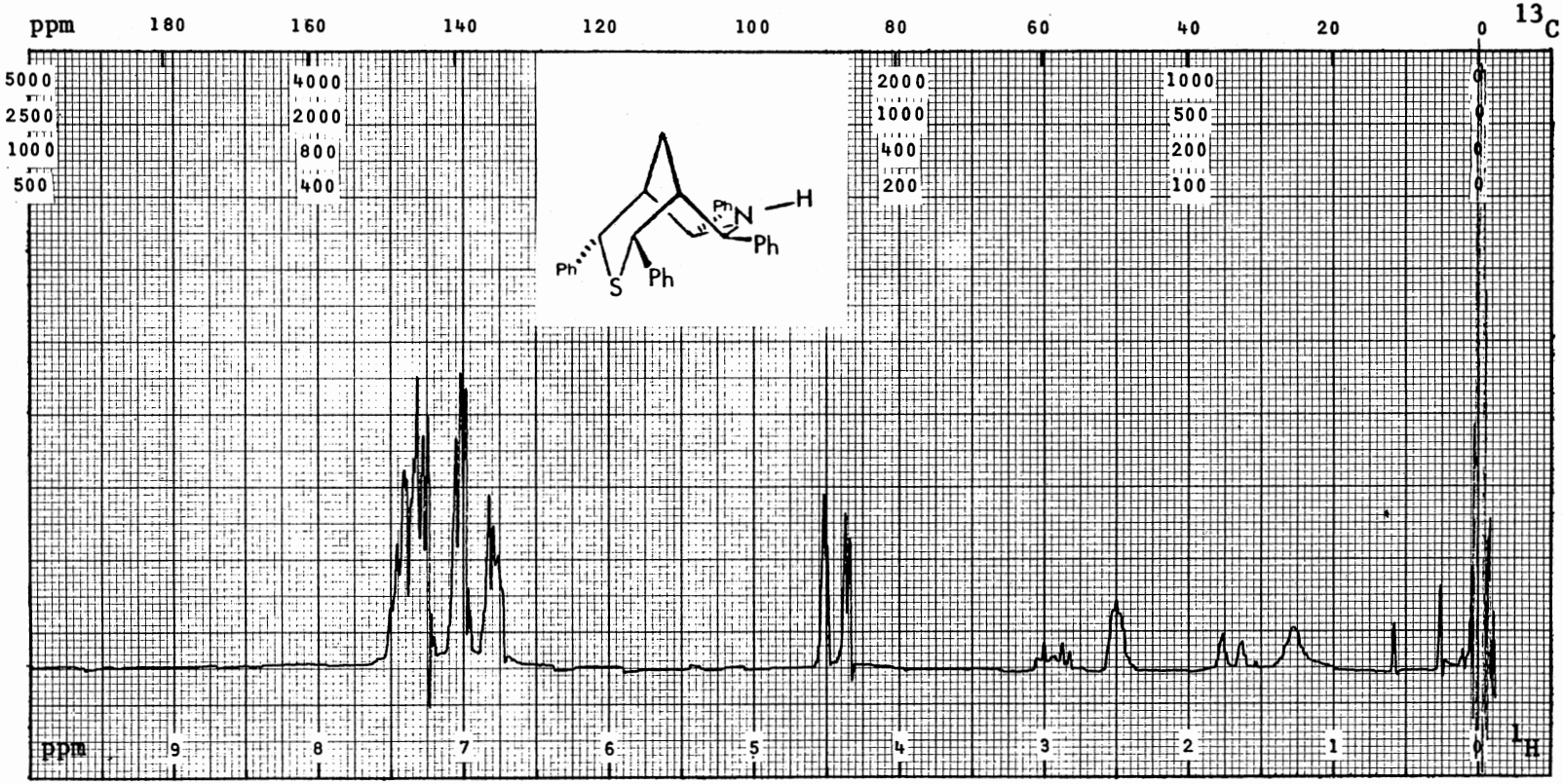
DC. . ^{1}H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE XLVIII



IR Spectrum of 65

PLATE XLIX



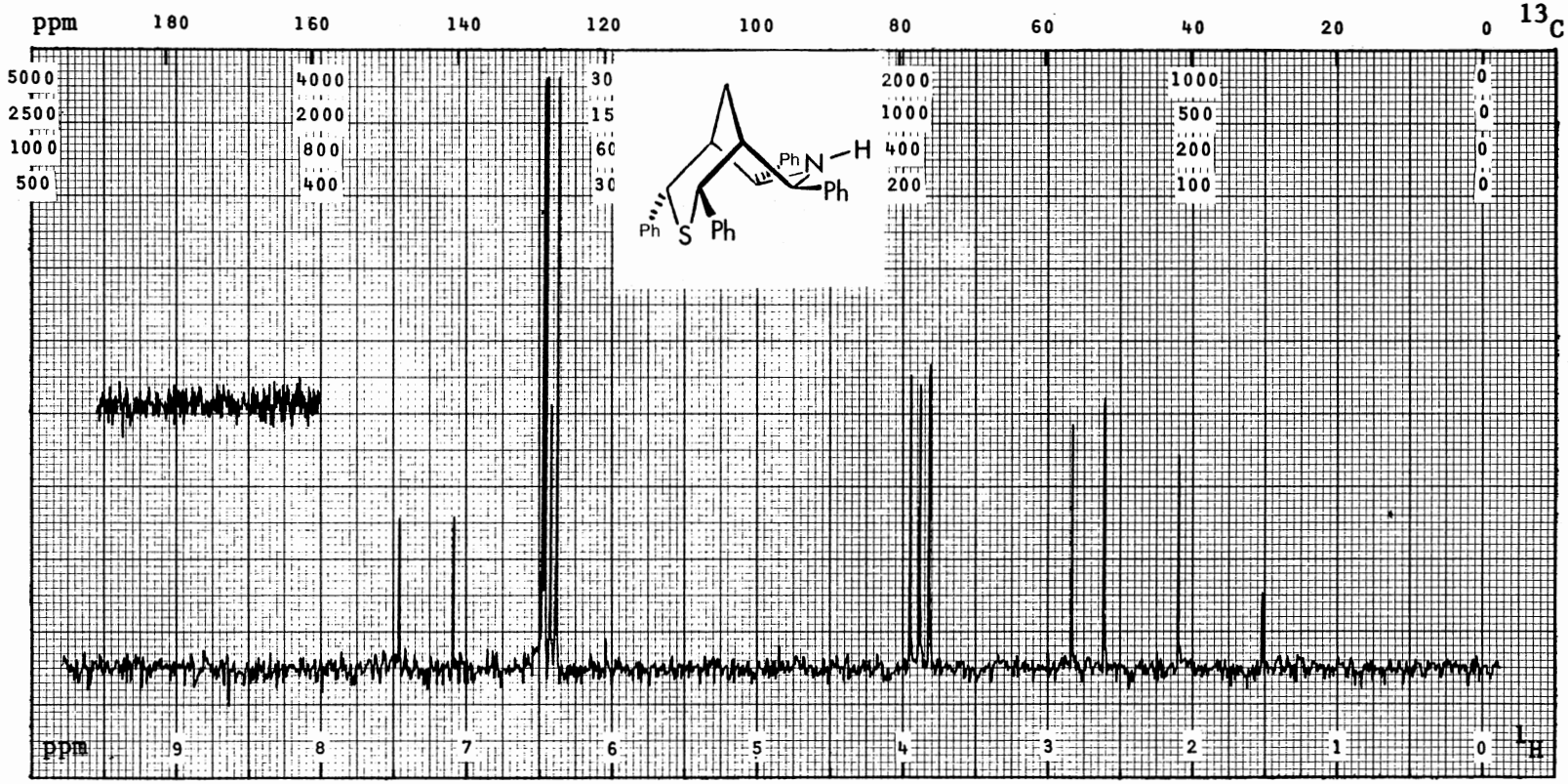
^{1}H NMR Spectrum of 66

PFT _ CW X ; Solvent. . $CDCl_3$; SO. .85771 Hz; PW. . 1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 61 µs/dB; SF. .100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE L



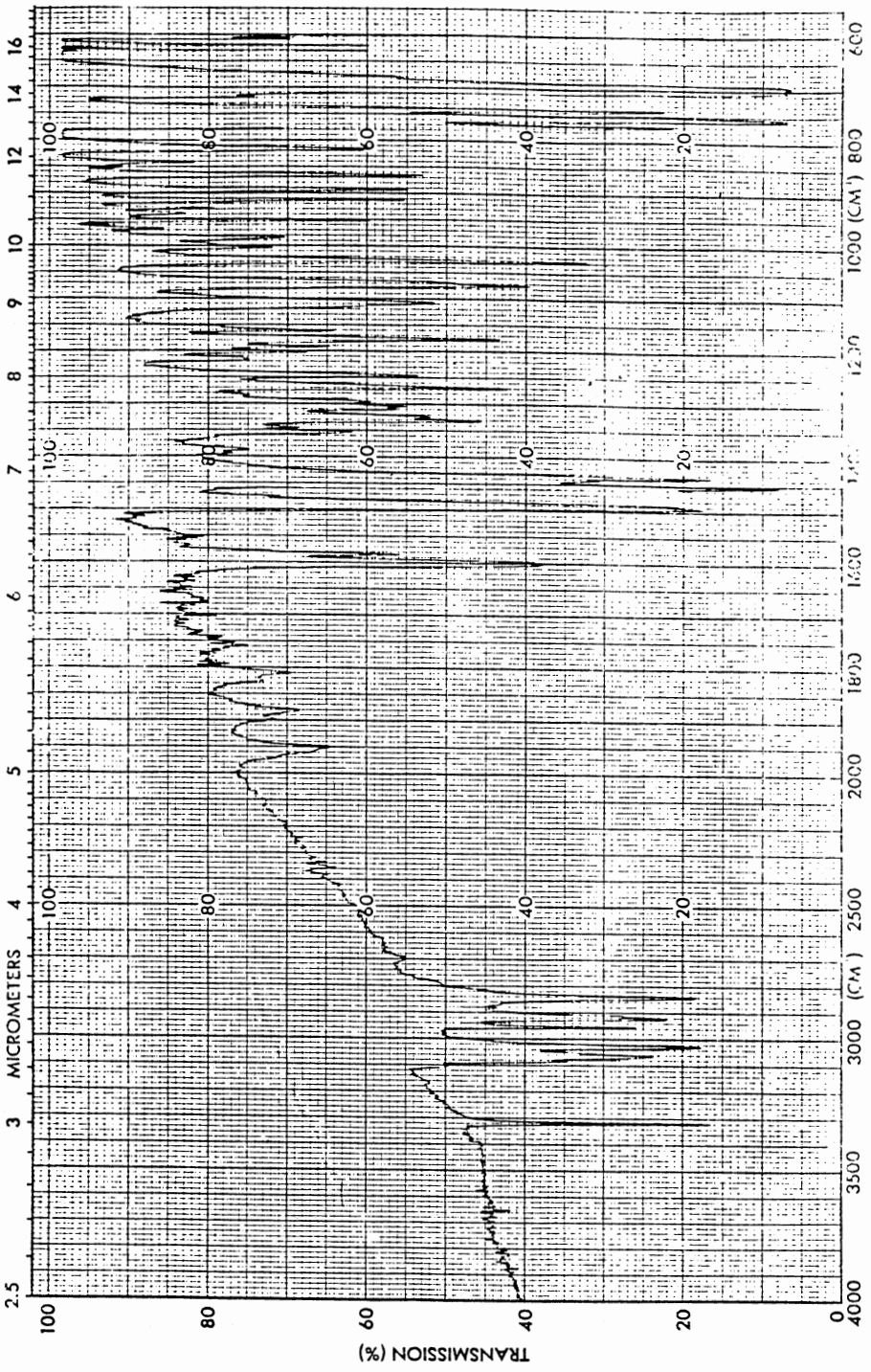
^{13}C NMR Spectrum of 66

PFT X CW _ ; Solvent. . $CDCl_3$; SO. .35101 Hz; PW. .5000 Hz; T. . 30 °C; Acq/SA. . 440

Size. . 8 K; P2/RF. . 10 μs/dB; SF. . 25.2 Hz; FB. . 2 Hz; Lock. . ^2H ; D5/ST. . 5 s

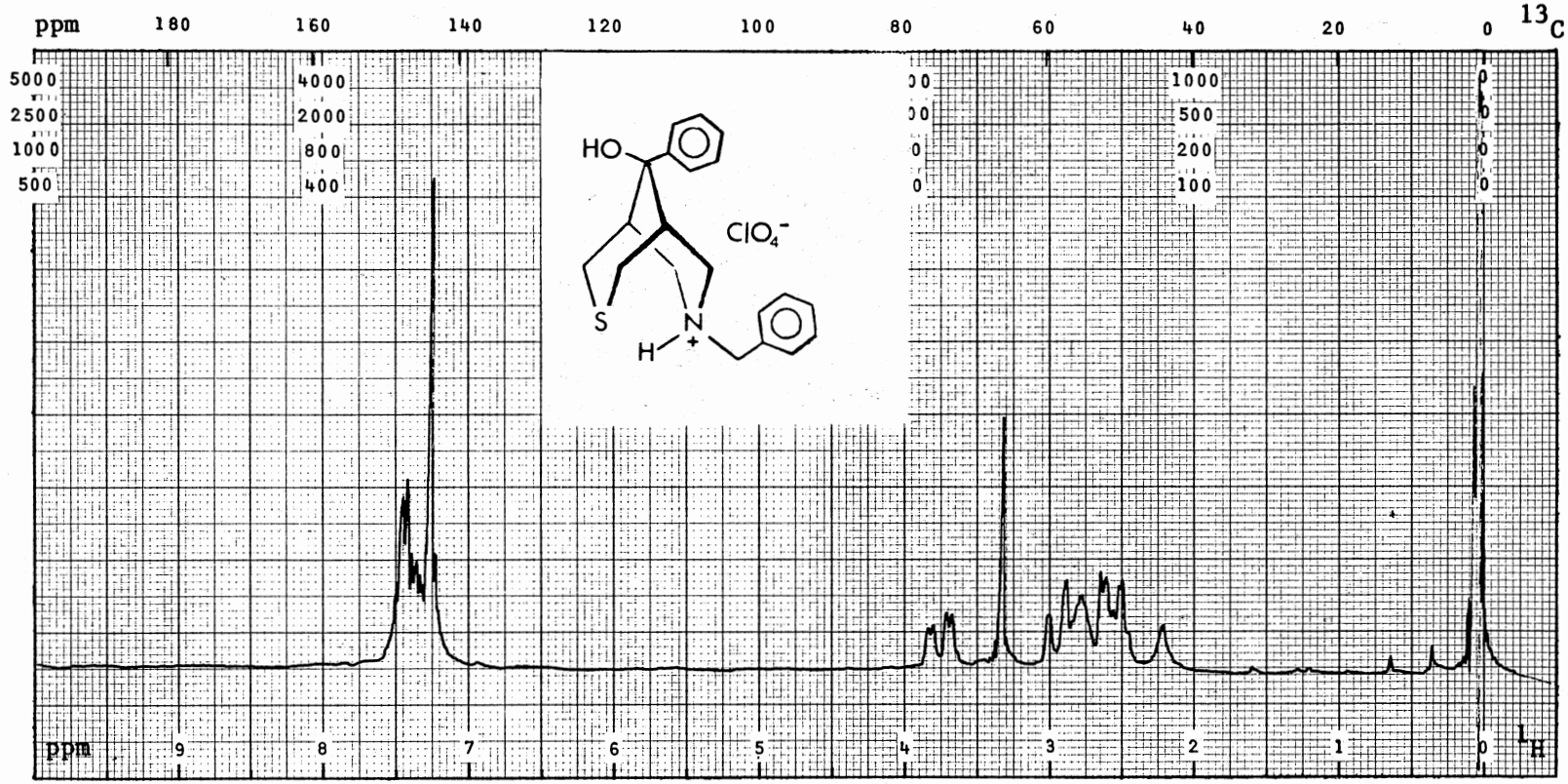
DC. . ^1H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE LI



IR Spectrum of 66

PLATE LII



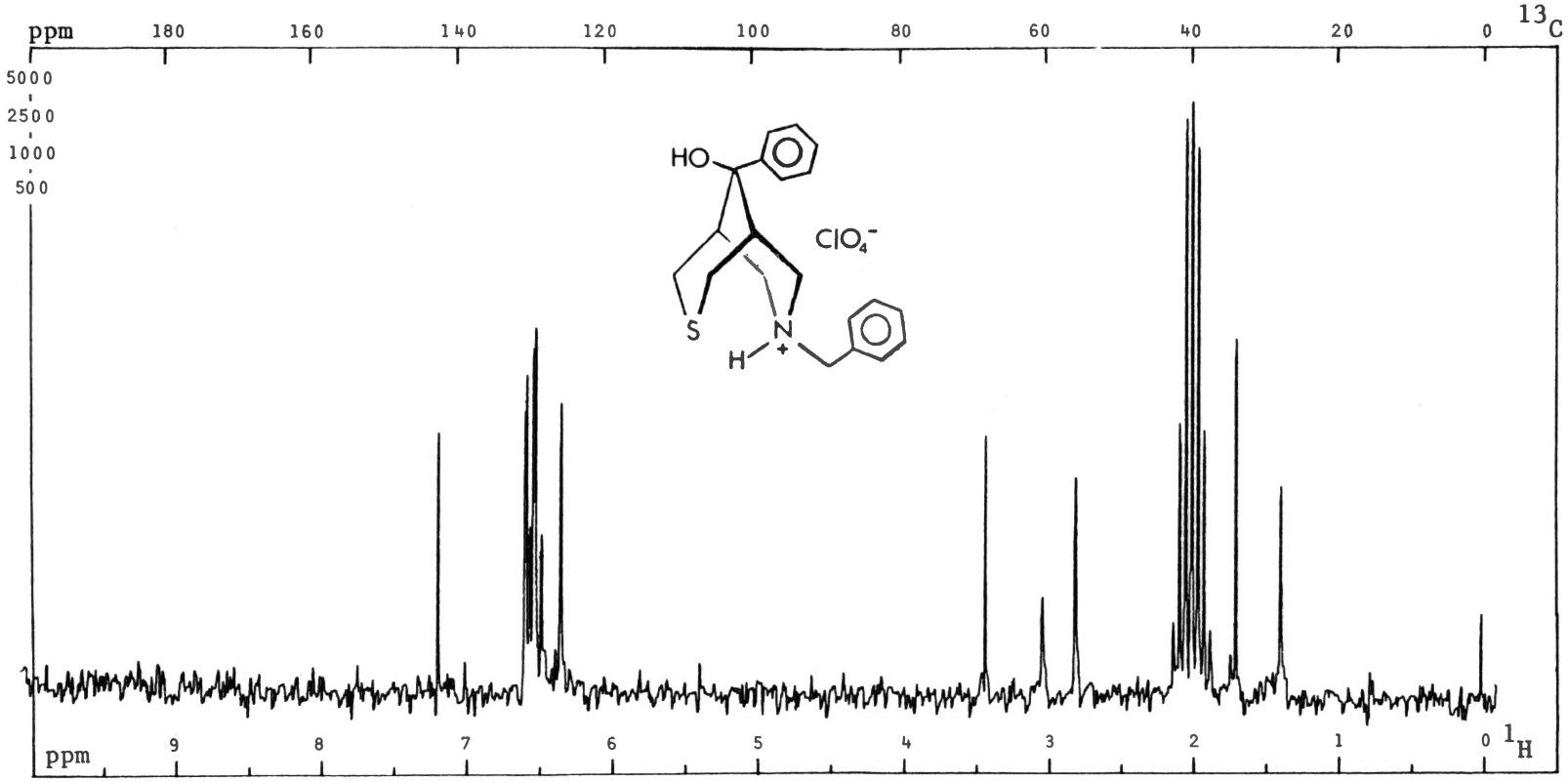
^{1}H NMR Spectrum of 73a

PFT _ CW X ; Solvent. . DMSO-d_6 ; SO. . 86242 Hz; PW. .1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 59 µs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LIII



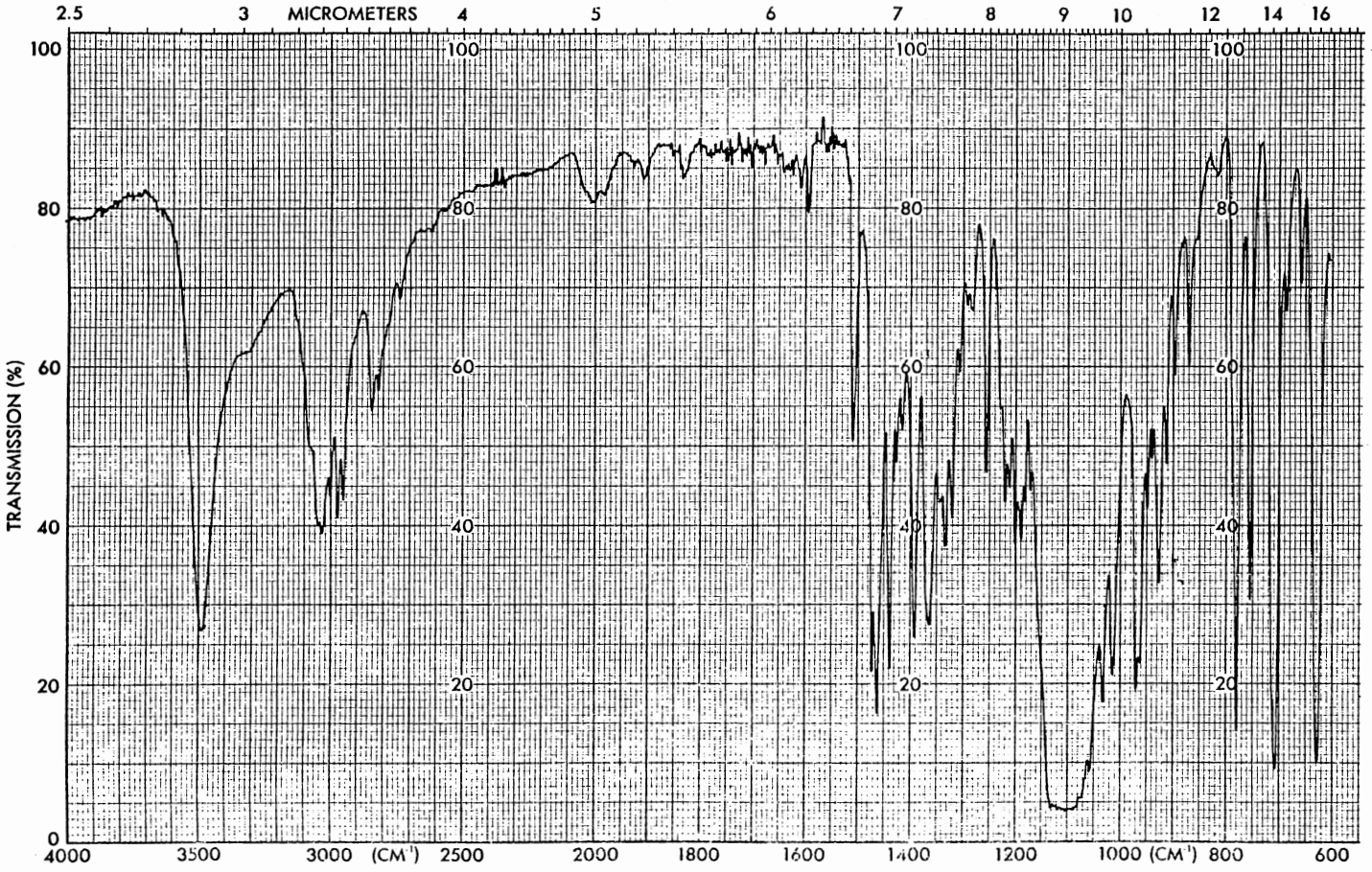
^{13}C NMR Spectrum of 73a

PFT X CW _ ; Solvent. . DMSO-d_6 ; SO. . 35201 Hz; PW. . 5000 Hz; T. . 30 °C; Acq/SA. . 440

Size. . 8K; P2/RF. . 10 µs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^{2}H ; D5/ST. . 5 s

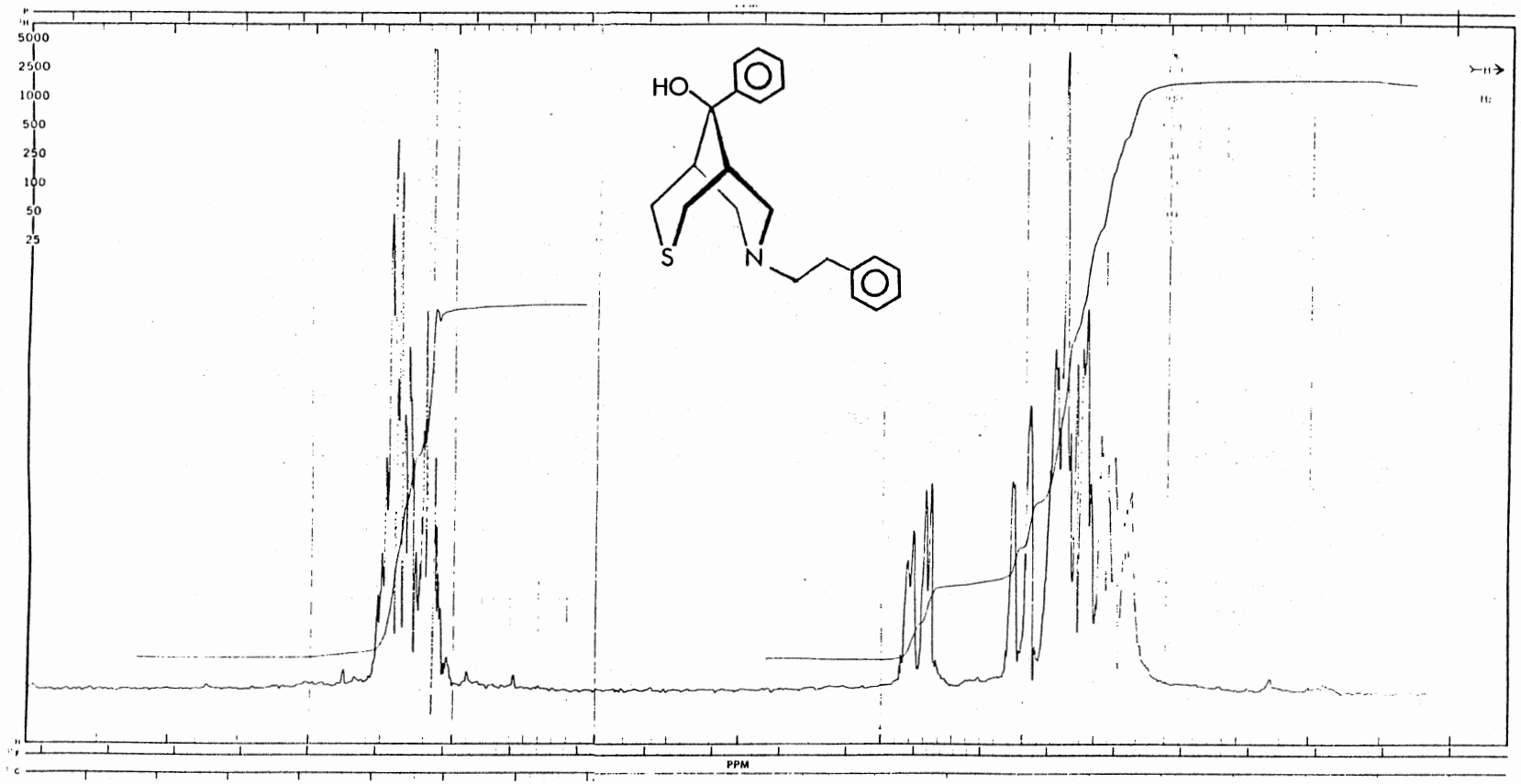
DC. . ^{1}H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE LIV



IR Spectrum of 73a

PLATE LV



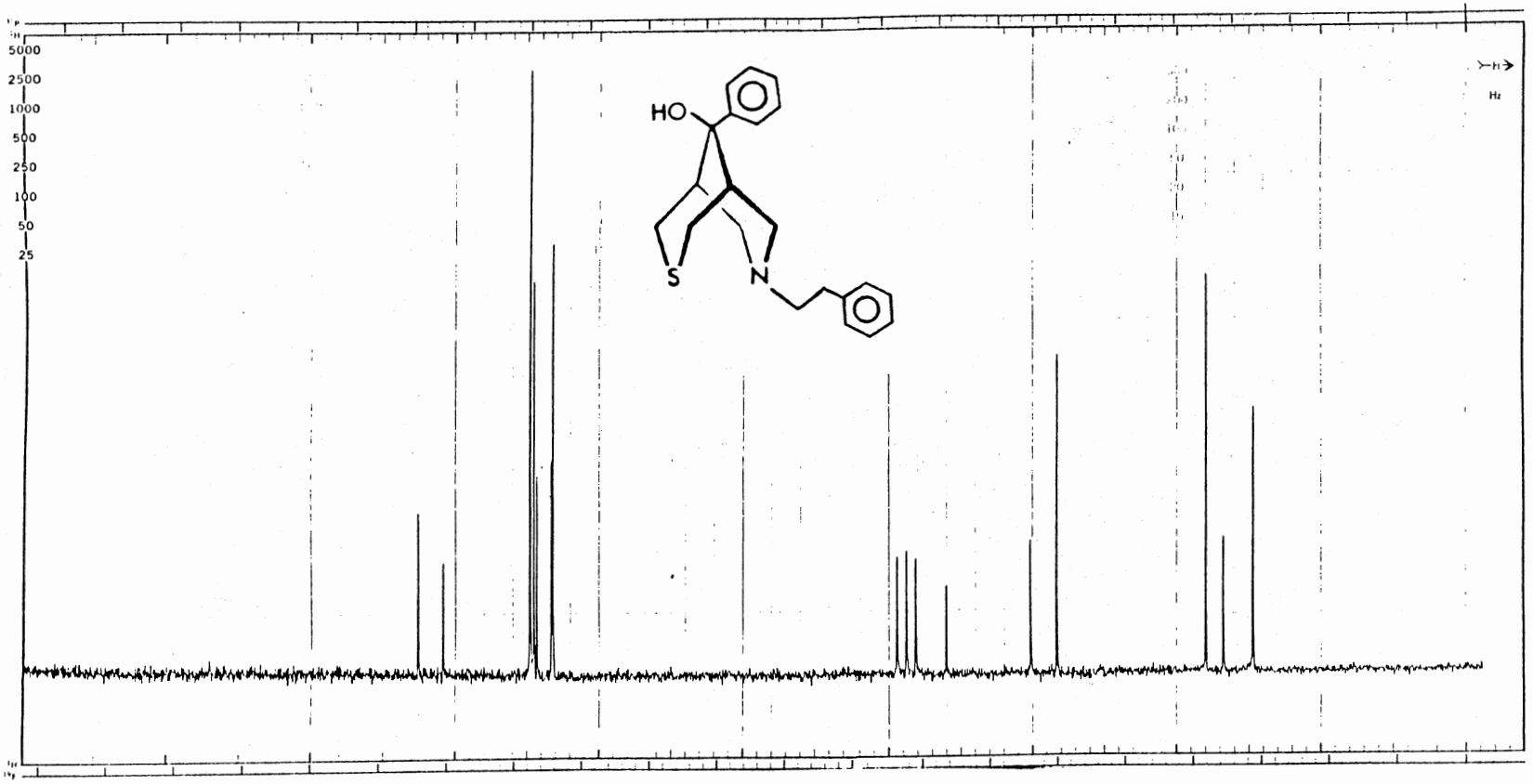
^{1}H NMR Spectrum of 75

PFT _ CW X ; Solvent. . $CDCl_3$; SO. . 85771 Hz; PW. . 1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 64 µs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LVI



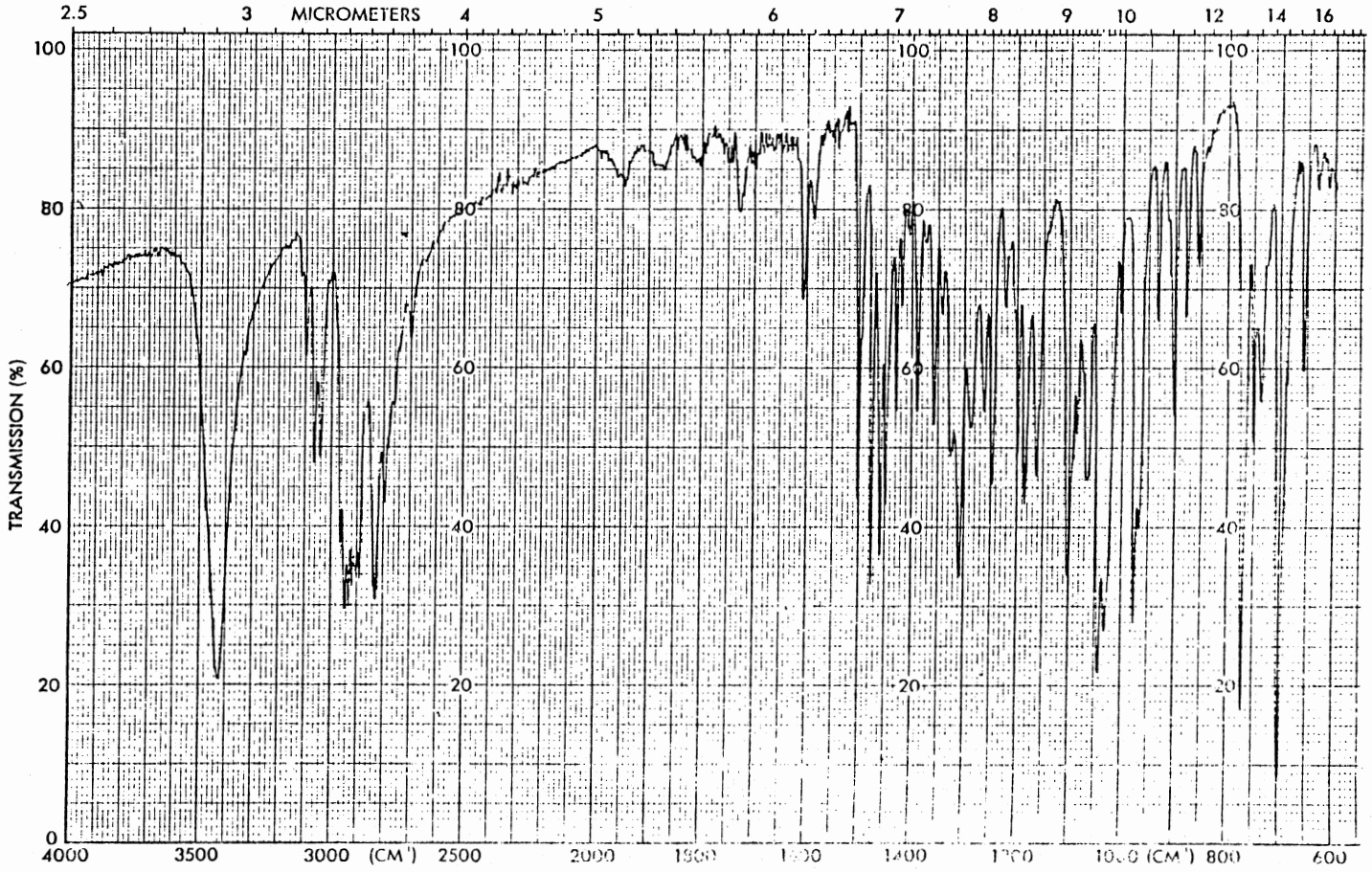
^{13}C NMR Spectrum of 75

PFT X CW _ ; Solvent. . $CDCl_3$; SO. .35101 Hz; PW. .1000 Hz; T. . 30 °C; Acq/SA. . 440

Size. . 8 K; P2/RF. . 10 μs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^2H ; D5/ST. . 5 s

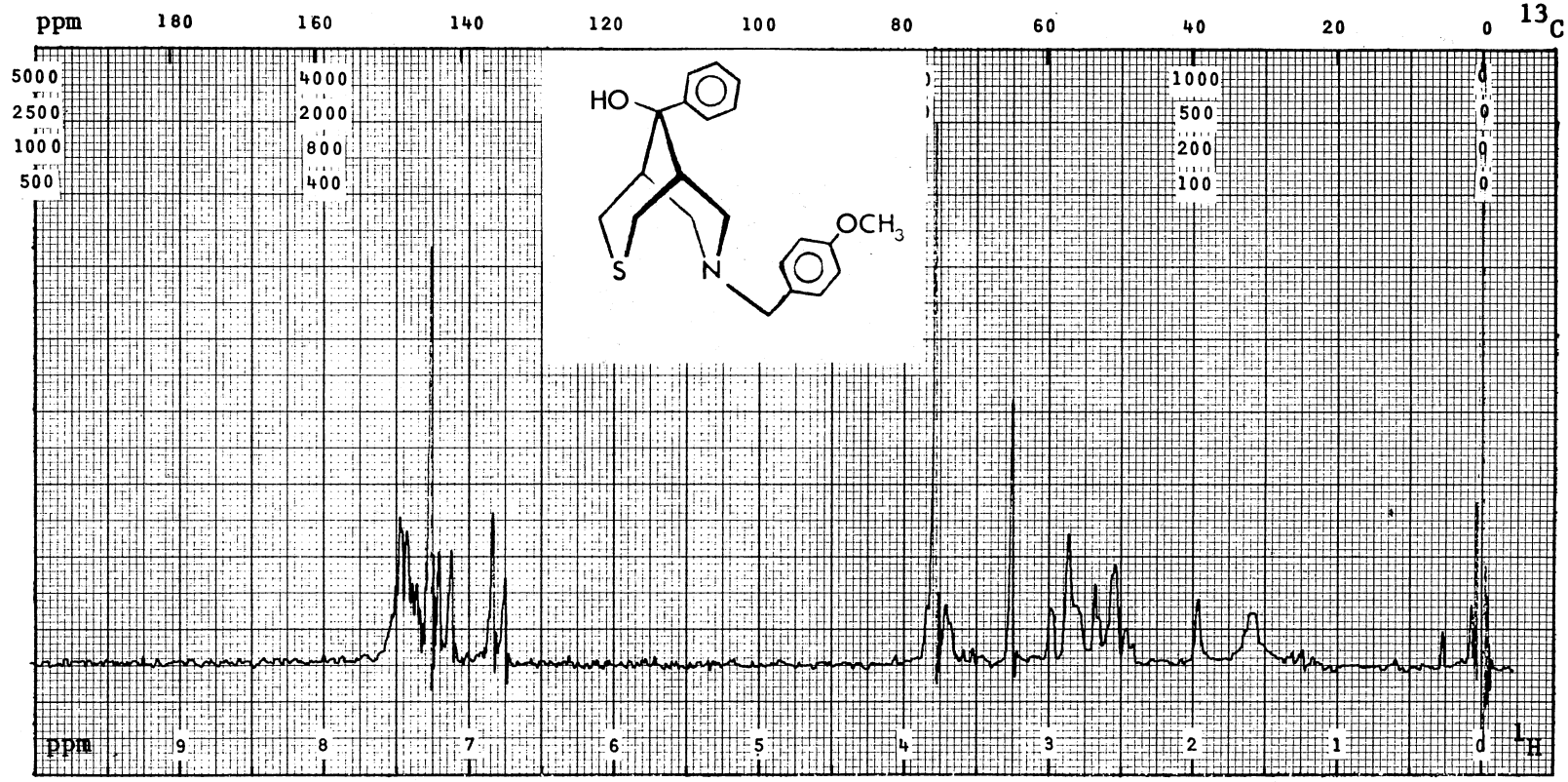
DC. . ^1H ; Gated Off. . ; Offset. .45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE LVII



IR Spectrum of 75

PLATE LVIII



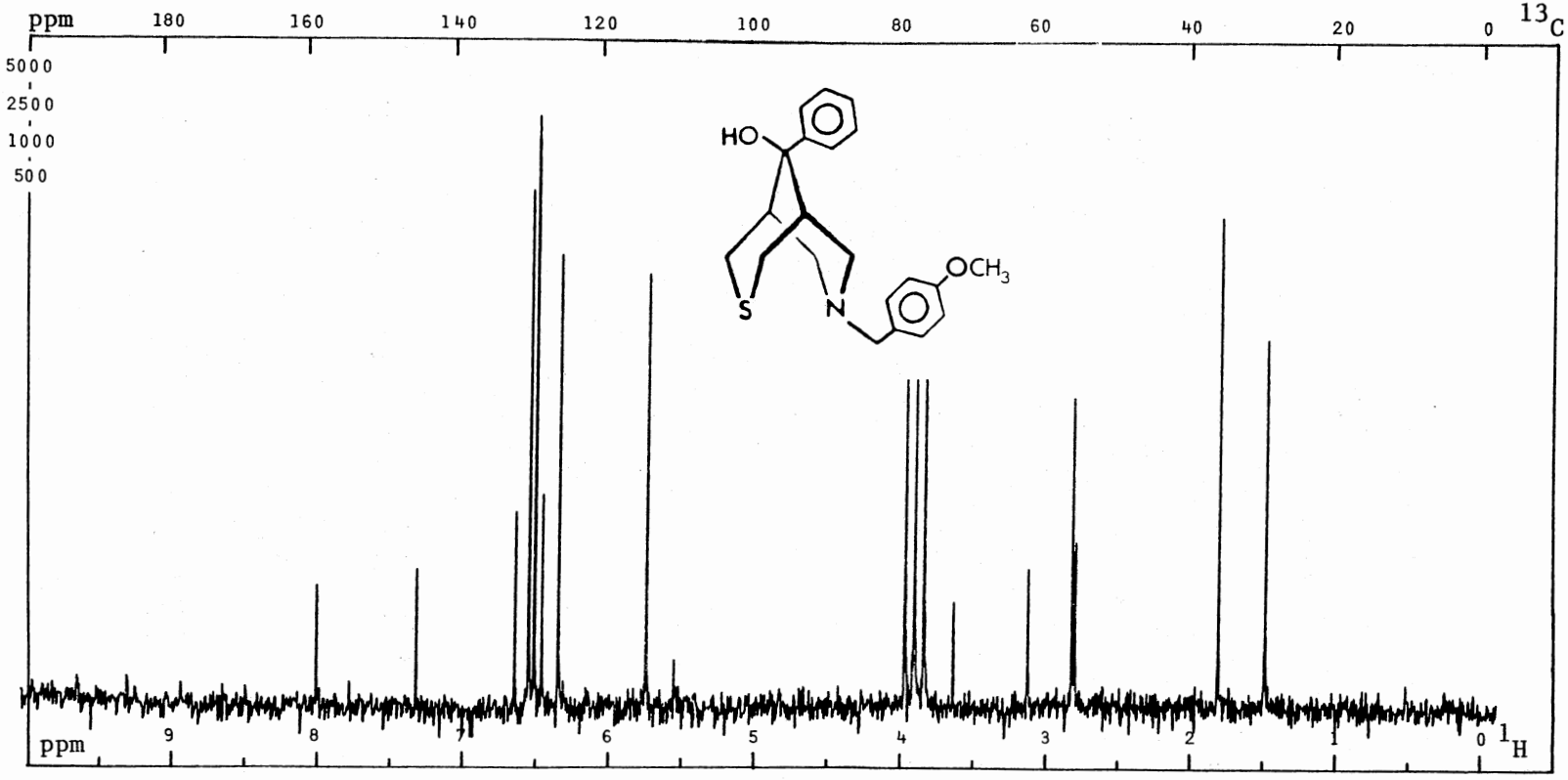
^{1}H NMR Spectrum of 76

PFT _ CW X ; Solvent. . $CDCl_3$; SO. .85771 Hz; PW. .1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 61 µs/dB; SF. .100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LIX



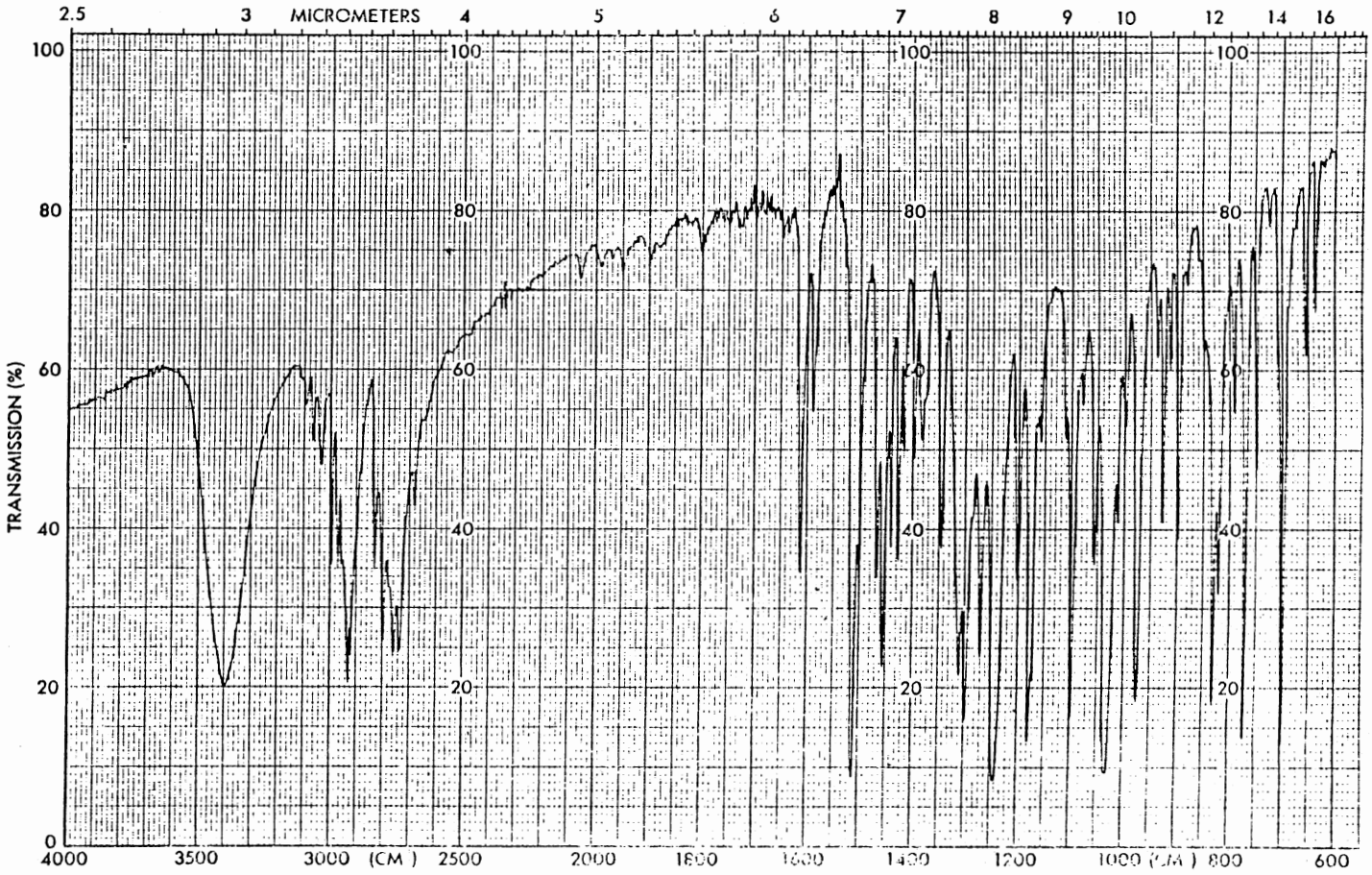
^{13}C NMR Spectrum of 76

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 35101 Hz; PW. . 5000 Hz; T. . 30 °C; Acq/SA. . 440

Size. . 8 K; P2/RF. . 10 μs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^{2}H ; D5/ST. . 5 s

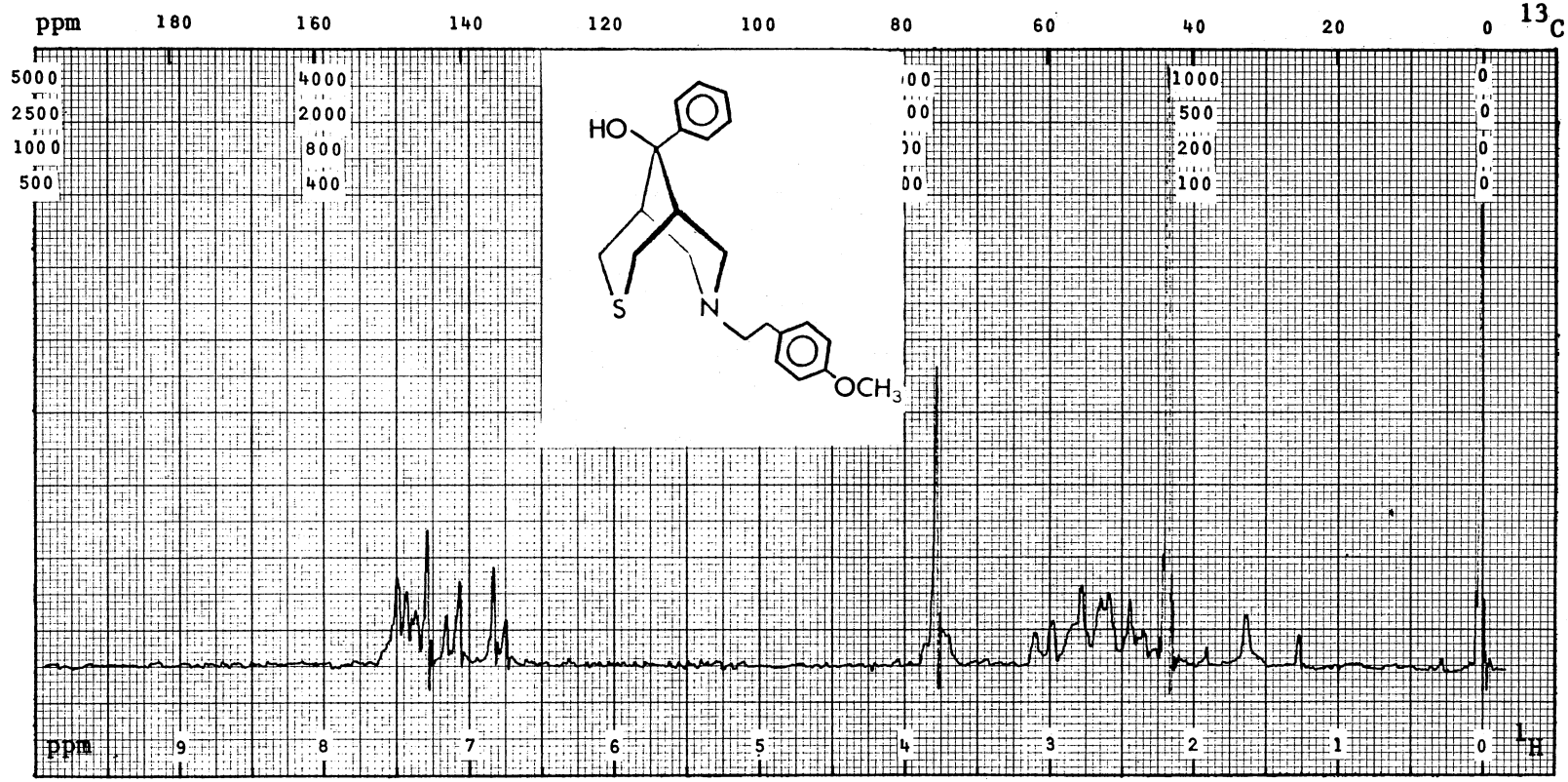
DC. . ^{1}H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE LX



IR Spectrum of 76

PLATE LXI



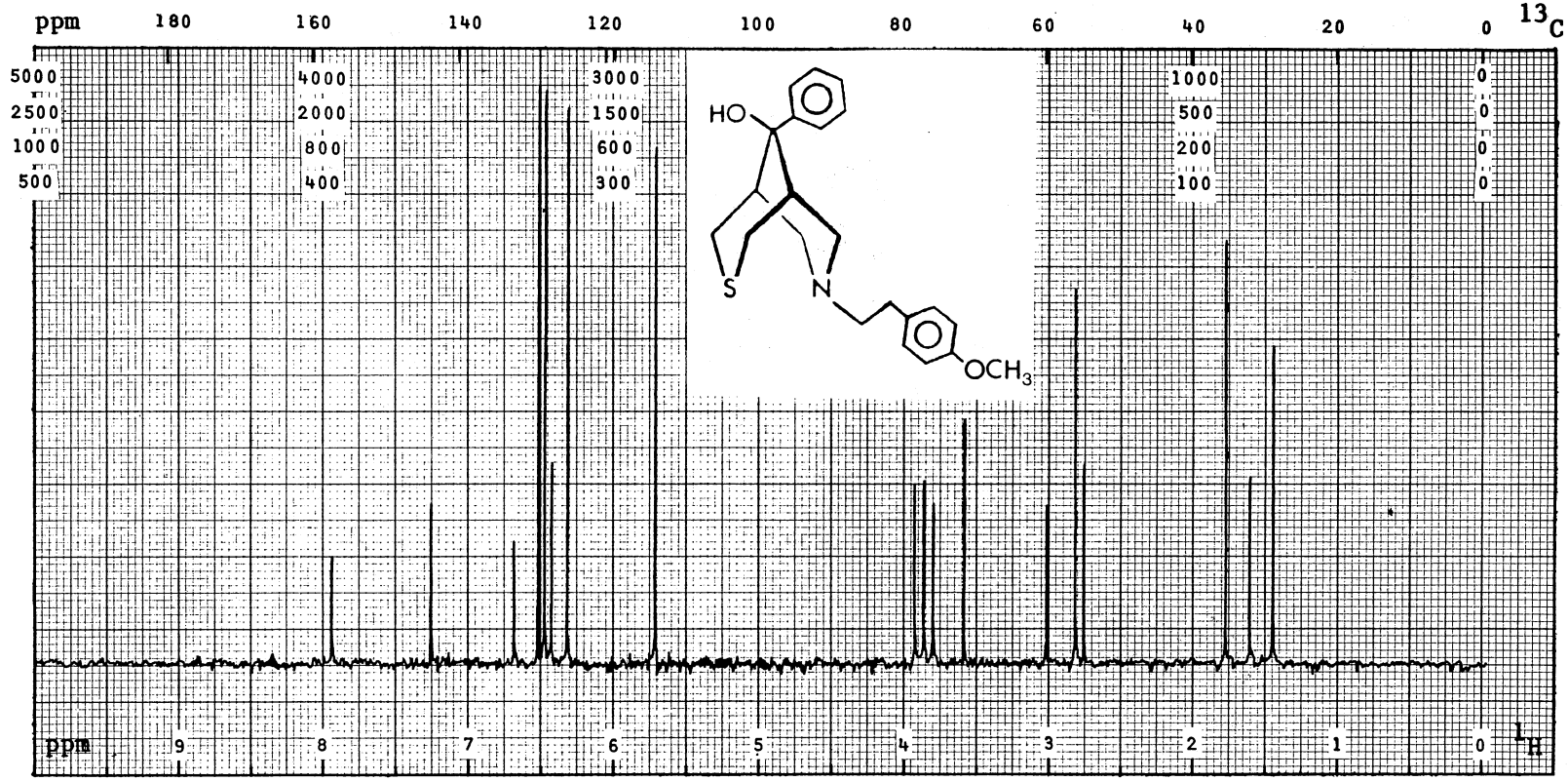
^{1}H NMR Spectrum of 77

PFT _ CW X ; Solvent. . $CDCl_3$; SO. . 85771 Hz; PW. . 1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 59 µs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . . Hz

PLATE LXII



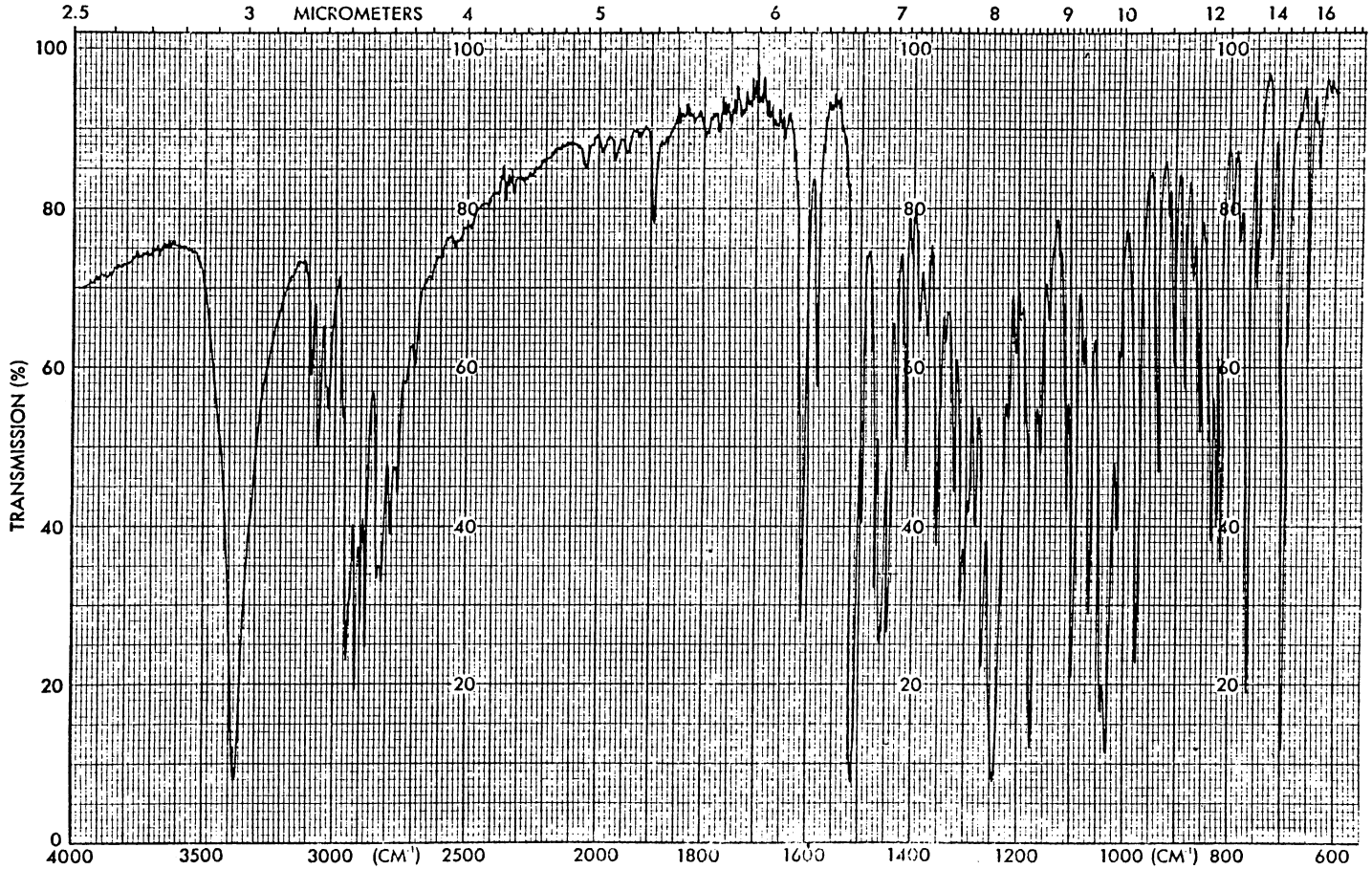
^{13}C NMR Spectrum of 77

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 35101 Hz; PW. . 5000 Hz; T. . 30 °C; Acq/SA. . 440

Size. . 8 K; P2/RF. . 10 μs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^{2}H ; D5/ST. . 5 s

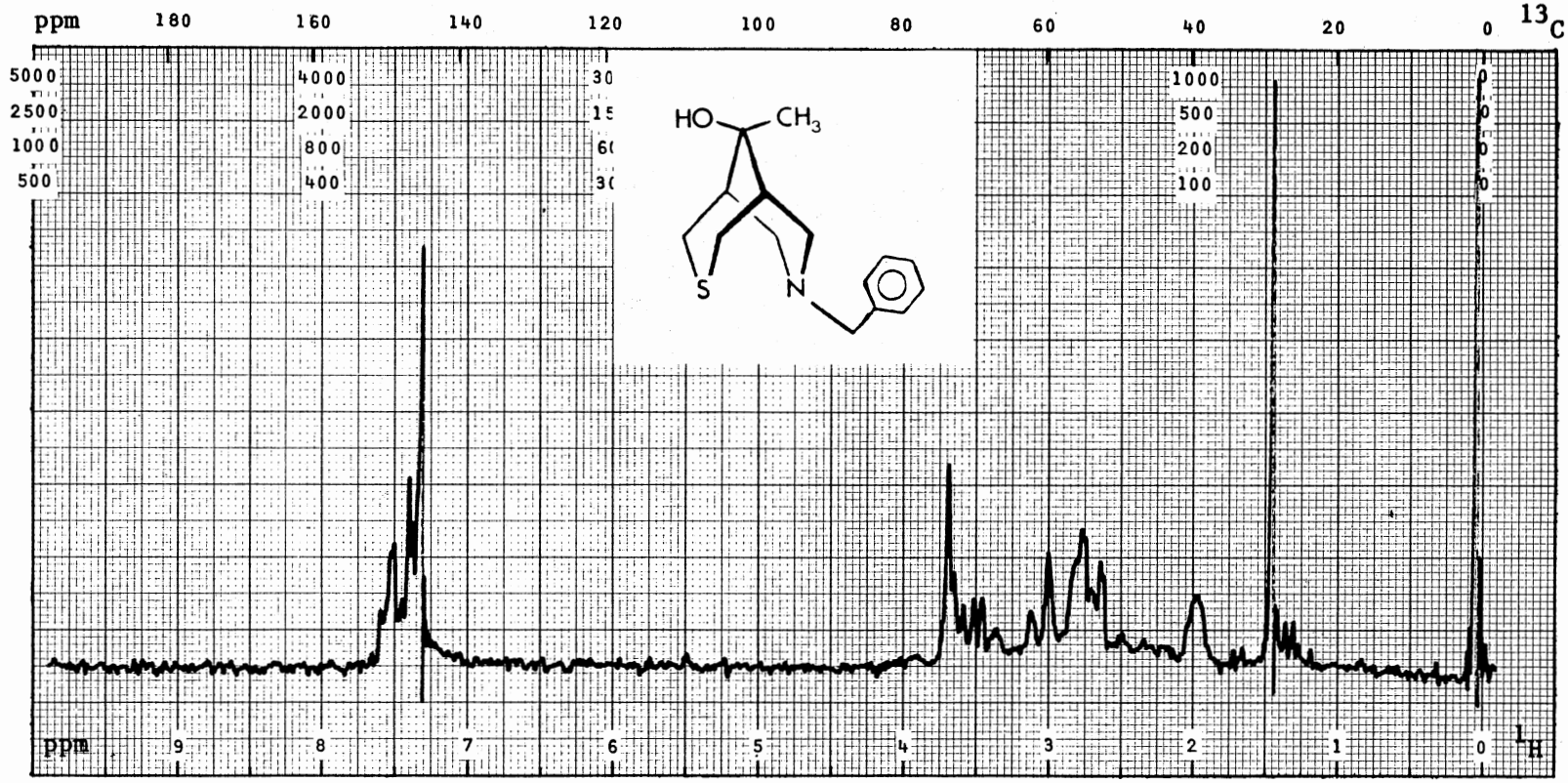
DC. . ^{1}H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE LXIII



IR Spectrum of 77

PLATE LXIV



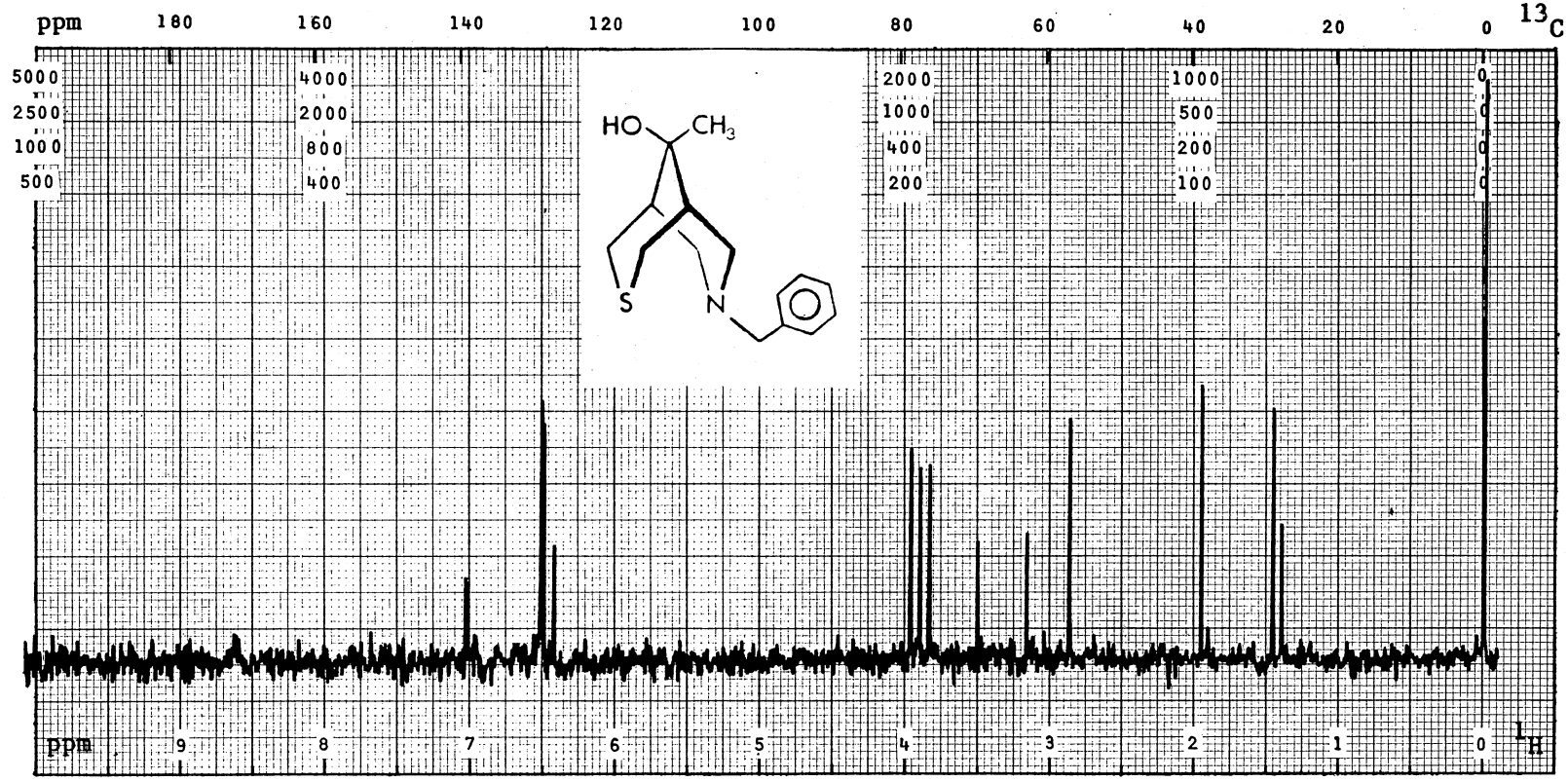
^{1}H NMR Spectrum of 71

PFT _ CW X ; Solvent. . $CDCl_3$; SO. .85771 Hz; PW. .1000 Hz; T. . 30 °C; Acq/SA. .

Size. . K; P2/RF. . 60 µs/dB; SF. .100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H ; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LXV



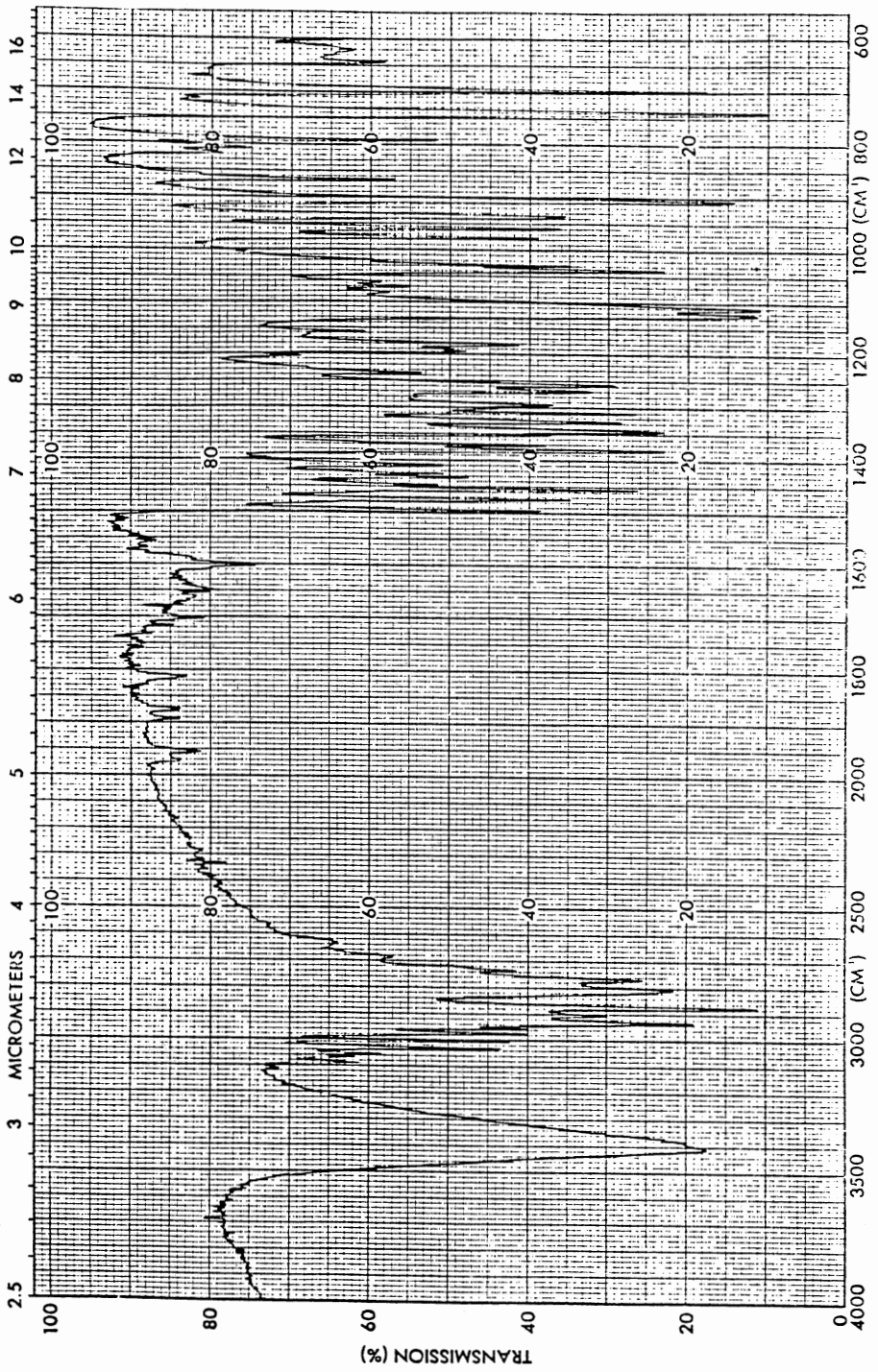
^{13}C NMR Spectrum of 71

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 35101 Hz; PW. . 5000 Hz; T. . 30 °C; Acq/SA. . 440

Size. . 8 K; P2/RF. . 10 µs/dB; SF. . 25.2 Hz; FB. . Hz; Lock. . ^{2}H ; D5/ST. . 5 s

DC. . ^{1}H ; Gated Off. . ; Offset. . 45051 Hz; RF. . 9 W/dB; NBW. . Hz

PLATE LXVI



IR Spectrum of 71

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