NOVEL DIOLS/SALTS/METAL COMPLEXES OF 3,7-DIHETERABICYCLO[3.3.1]NONANES AND DERIVATIVES

By

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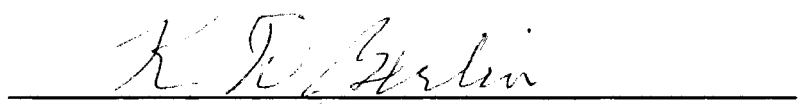
Thesis Approved:



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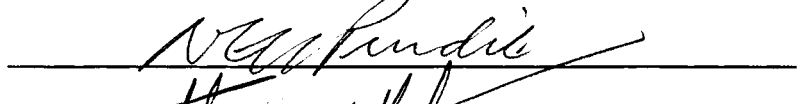

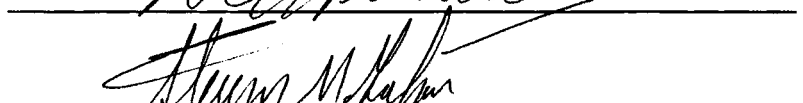

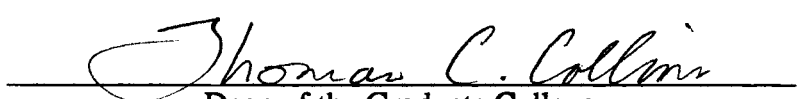

Dean of the Graduate College

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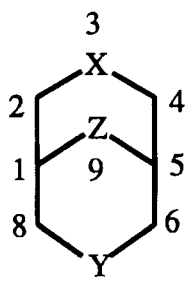
CHAPTER I

HISTORICAL

Introduction

Several members of the 3,7-diheterabicyclo[3.3.1]nonanes (DHBCN) family [28,58] **1** have been of great interest due to their excellent antiarrhythmic action.[4,6,11,22,45] Antiarrhythmic agents are generally classified into five types on the basis of their modes of action,[54] namely class Ia, Ib, Ic, II, III, IV, or V. To date, DHBCNs have been found

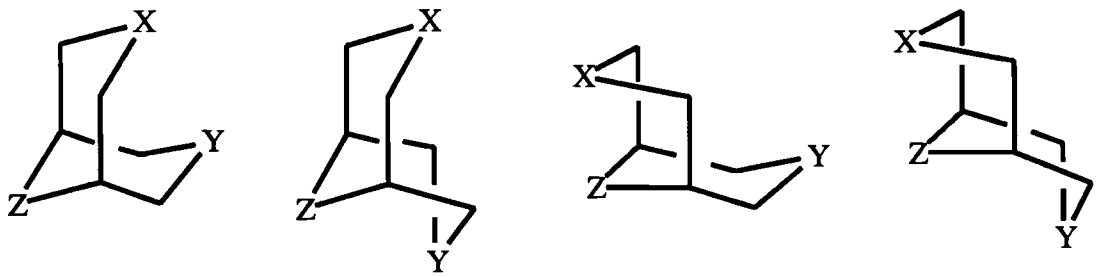


1

to exhibit Class Ib and III activity, but testing for other class actions in this family is in progress.[4,7,45] By obtaining structure-activity relationships, it has been found that certain structural modifications in the 3- and 7-positions of DHBCNs can significantly change the observed Class Ib and III antiarrhythmic activity.[4,8,22,37,38] Introduction of some specific functional groups can lead to agents with enhanced activity and more than one class of action. Apart from being good antiarrhythmic agents, it has also been found that certain DHBCNs, like 1,5-diaryl-3,7-diazabicyclo[3.3.1]nonanes, possess hypotensive activity[14] and also act as good local anaesthetics.[20,57]

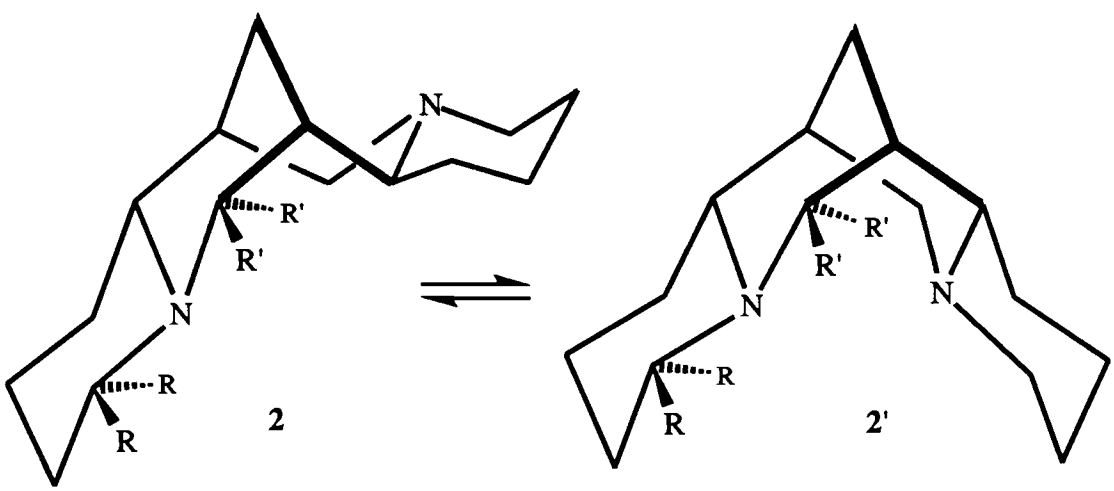
DHBCNs possess conformational mobility and as a result can adopt four different

conformations,[28,35,58] namely a chair-chair (**1-CC**), boat-chair (**1-BC**), chair-boat (**1-CB**) and/or boat-boat (**1-BB**). The dynamic properties of these bicyclic system may result in equilibration between the above four conformers.[58] The conformational preferences of these systems appears critical for their biological activity and mechanism of action.[45]



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

The DHBCN ring moiety is found in naturally occurring C-15 lupine alkaloids like sparteine (**2a**), aphylline (**2b**), lupanine (**2c**), and α-isosparteine (**2'd'**).[26,27,34,40,56] Sparteine (**2a**), the most common among the four alkaloids, has been used in the manage-



a R, R' = H
b R', R' = O, R = H
c R, R = O, R' = H

d' R, R' = H

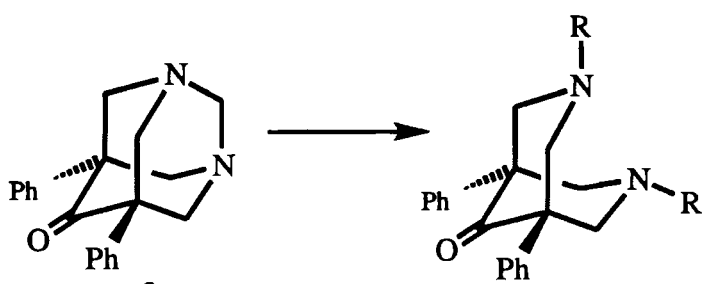
ment of cardiac arrhythmias.[37] It was concluded from these early studies that sparteine prolonged the action potential duration (APD) and induced an increase in the refractory period of heart action in rats.[10,39] The structure of sparteine (**2a**) is shown as the chair-

boat conformation, but IR and NMR analyses has concluded that in the liquid state conformer **2d'** is also present.[41]

The discussion here will focus on the 3,7-diazabicyclo[3.3.1]nonan-9-ones (3,7-DABCNONs) and 3,7-diazabicyclo[3.3.1]nonan-9,9-diols (3,7-DABCN-9,9-diols). The conformational properties and synthetic methodology for constructing these ring systems will be reviewed. The metal complexation properties of 3,7-DABCNONs and the effects of various substituents at the 2-, 3-, 4- and 7-positions on complexation will be discussed.

Synthetic Methodology

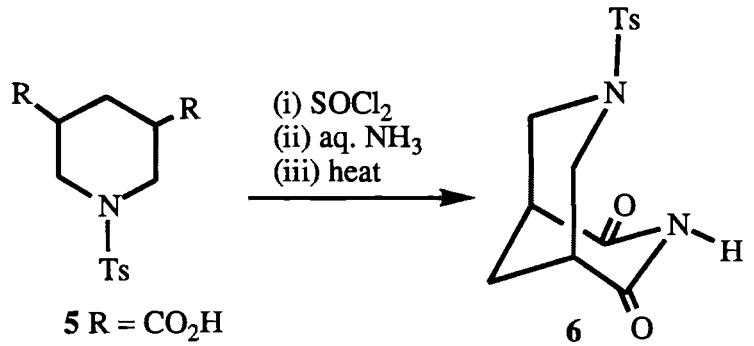
The synthesis of the few known 3,7-DABCNONs has been examined and reviewed.[28,58] It was reported that certain 3,7-diazabicyclo[3.3.1]nonanes (3,7-DABCNs-also known as bispidines) were obtained as by-products during the preparation of piperidinones from ketones, aldehydes, and amines.[9] A ring cleavage of certain 1,5-



3 **4**

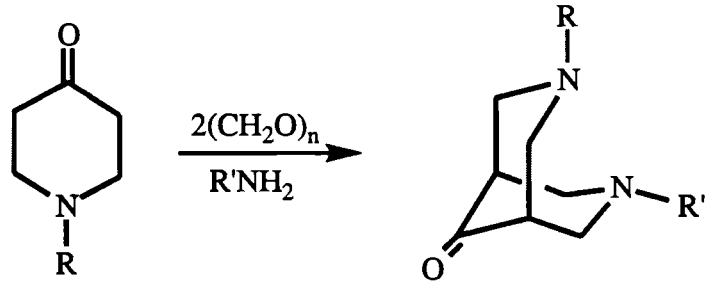
a R = MeC(O)
b R = Tosyl
c R = CHO
d R = PhC(O)
e R = NO

diaryl substituted diazaadamantanes[15,31,51] like **3**, under acidic conditions, produces 1,5-diaryl bispidinones, such as **4**. Alternatively, intramolecular cyclization using *N*-tosyl-piperidine-3,5-dicarboxylic acid[48,49,50] (**5**) with ammonia can form **6**.



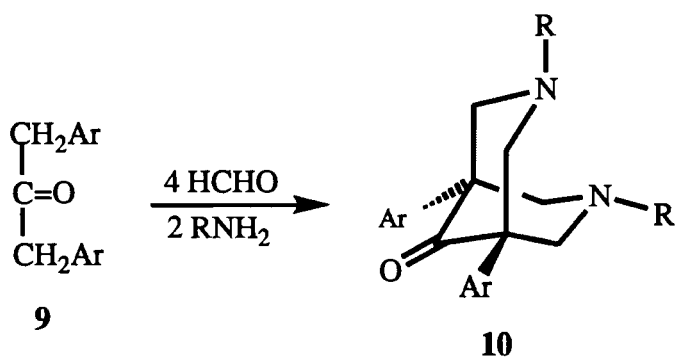
5 R = CO_2H **6**

A double Mannich condensation reaction of the 1-alkyl-4-piperidin-4-ones **7** with paraformaldyde and various primary amines under acidic conditions has proven to be one of the better and commonly used methods for constructing the 3,7-DABCNONs **8**.[28,58]



7 **8**

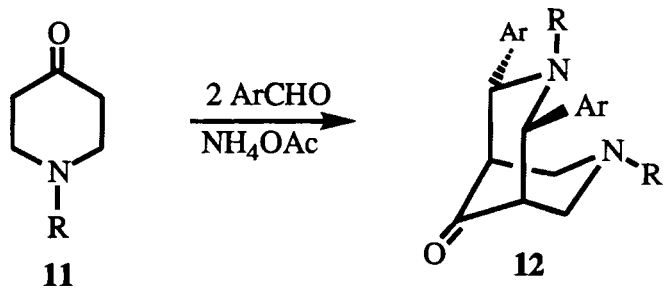
A series of 3,7-dialkylbispidinones **8** (bispidinones is a commonly used name synomous with 3,7-diazabicyclo[3.3.1]nonan-9-ones) were synthesized in modest yields (40-55%) by Douglass and Ratliff.[21] Similarly, other research groups have employed various *N*-alkylpiperidin-4-ones as well as other primary amines.[8,21,42,43,44] The ketones are



9 **10**

usually isolated as crude materials via an aqueous workup. Oils are purified by distillation under reduced pressure and crude solids by recrystallization.[8,21] Numerous 1,5-diaryl-3,7-DABCNONs **10** have been synthesized[1,15-19,57] by condensing 1,3-diarylacetone (**9**) with paraformaldehyde and an amine. The aryl group may be phenyl, *p*-chlorophenyl, *p*-anisyl, or *o*-methoxyphenyl groups.

A number of 2,4-diaryl-3,7-diazabicyclo[3.3.1]nonan-9-ones **12** have also been prepared by Haller[24,25] The commonly used aryl groups are phenyl, *o*-chlorophenyl, *p*-chlorophenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl. These reactions were generally carried

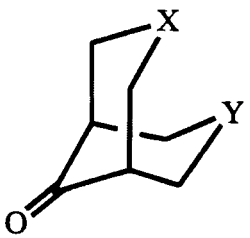


11 **12**

out by boiling an ethanolic solution of the reactants for a few minutes up to several hours. The products frequently precipitated from the reaction mixtures upon the addition of a nonpolar solvent such as ether. A common problem associated with the Mannich reaction for synthesizing 3,7-DABCNONs is the low yields. This undesireable feature was overcome in studies of a double Mannich condensation[3,33,37,38,45,59] in which an amine, paraformaldehyde, a piperidin-4-one, and acetic acid (and/or conc HCl in methanol) were employed. It was discovered that the addition of conc HCl increased the yield of some 3,7-DABCNONs from 20-40% to 56-60%.[7,59] It was speculated that the pH plays a critical role in the reaction kinetics, perhaps in accelerating formation of the intermediate iminium ion. As a part of our continuing efforts to improve the yields in Mannich reactions, we found that the addition of a second equal amount of paraformaldehyde after 10 hours of reflux increased the isolated yields of certain ketones from 16.3-27.8% (Table I).

TABLE I

YIELDS OF KETONES **13**, **14**, AND **15** BY PREVIOUS AND NEW METHODS

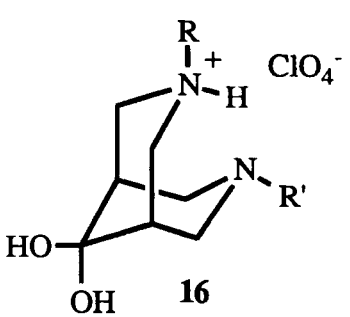


Compd	X	Y	Yield from previous method	Yield from new method
13	$NCH(CH_3)_2$	NCH_2Ph	57.2%[59]	73.5%[22]
14	NCH_3	NCH_2Ph	45.0%[4,32]	72.8%[22]
15	NCH_2Ph	NCH_2Ph	58.2%[8a]	69.1%[22]

[22]Unpublished data

A rationale for this phenomenon is not well defined, but a partial explanation might be that some paraformaldehyde is lost during the reaction via the formation of the side products. Replenishment of this lost reagent may increase the yield of ketone.

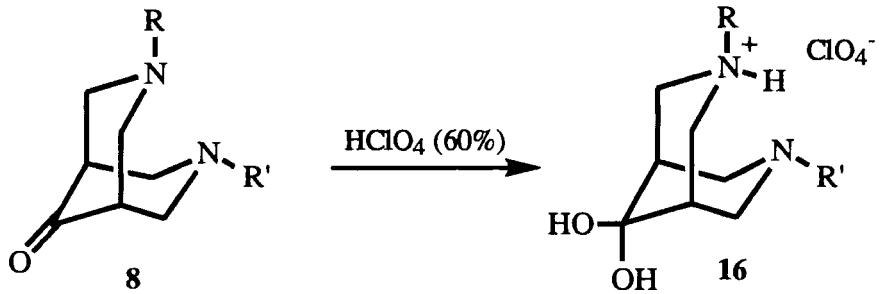
It has been known for some time that certain carbonyl compounds can form gem diols in aqueous acid. In the family of DHBCNs only one paper has been reported on this type of compound, namely**16**.[5] Indeed, very few 3,7-DABCNONs and very few



16

3,7-DABCN-9,9-diols have been recorded or investigated for conformational preferences. Conceivably, 3,7-DABCN-9,9-diols of the type **16** might be obtained by treatment of 3,7-

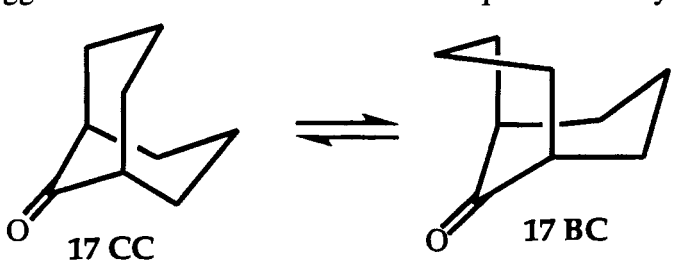
DABCNONs of the general type **8** with mineral acids like perchloric acid, hydrobromic acid, or hydrochloric acid. Such diols with other heteroatoms at the 3- and 7-positions have therefore been relatively unexplored. The diols discovered and described in the current work are remarkably stable in air and appear to be only slightly hygroscopic. The diols are also reasonably soluble in aqueous medium in spite of the large



hydrocarbon content. It should be emphasized that the although the general reaction is illustrated using CC conformers, such as a CC-**8** → CC-**16**, a CB conformer for **8** is also quite possible in some examples.

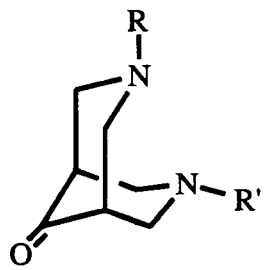
Conformational Analysis

As previously mentioned, 3,7-DABCNs **1** can exist in four different conformations when X and Y are non-equivalent. Some of the factors that probably influence the conformation of these systems are (i) steric repulsion of the heteroatoms, (ii) dipole repulsion, (iii) lone pair orbital repulsion, and/or (iv) intramolecular hydrogen bonding involving a proton on one heteratom at the 3-position, for example, with the heteroatom at the 7-position.[2,36] A solid state ^{13}C NMR analysis of bicyclo[3.3.1]nonan-9-one **17** at 42 °C suggested the existence of the CC form predominantly.[55] This was



further supported by analysis of the solution ^1H NMR shifts induced by the lanthanide shift reagent $Eu(fod)_3$ on **17** in CCl_4.[36] A distribution of 78:22 favoring the CC conformer was observed by comparing the experimental shifts with those predicted by the pseudocontact equations using geometries obtained from empirical force field (EFF) calculations.

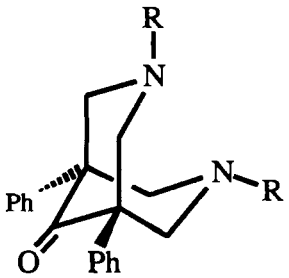
Conformational analyses of several 3,7-DABCNONs **8a-g** using ^1H, ^{13}C NMR, and IR spectral techniques were performed by Galvez and co-workers.[2] Their analyses suggested that ketones **8** adopt a flattened CC conformation in solution, and an increase



8

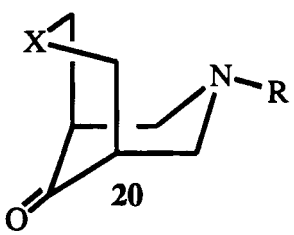
	R	R'		R	R'
a	CH_3	CH_3	**e**	CH_3	CH_2Ph
b	CH_3	CH_2CH_3	**f**	CH_2Ph	CH_2Ph
C	CH_3	$CH(CH_3)_2$	**g**	CH_3	CH_2CH_2Ph
d	CH_3	$CH_2CH_2CH_3$	**h**	$CH(CH_3)_2$	CH_2Ph

in distortion from an ideal CC takes place in the series from the methyl to the isopropyl substituents.[2] This was deduced in view of an increase in the $[\delta_{C(6,8)}-\delta_{C(2,4)}]$ values in the ^{13}C NMR data observed in the series **8a-8c**, which was taken as an indication of a more flattened CC conformation as the size of the *N*-alkyl substituent increased. It was implied that rings with R, R' > Me were more flattened than the ring containing R, R' = Me. However, an X-ray analysis of **8e**, for example showed a BC conformation in the solid state.[46] On the other hand, variable temperature (VT) ^{13}C NMR spectral studies performed by Takeuchi[52] on **18** and **19** suggested a BC⇄CB equlibrium at -63 °C.

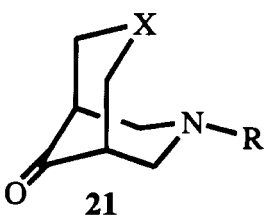


18 R = Me
19 R = *t*-Bu

Our group has done extensive NMR work on several members of the 3-hetera-7-azabicyclo[3.3.1]nonan-9-ones[3,4,53] which include ketones **20-21**. An X-ray diffraction



20



21

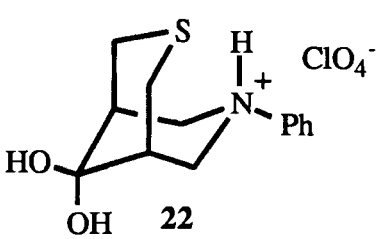
	X	R
20a	S	CH_2Ph
20b	Se	CH_2Ph
20c	S	CH_2CH_2Ph
20d	Se	CH_2CH_2Ph
21	O	CH_2Ph

analysis of solid ketones **20a** and **20b** showed a preference for a BC conformation which was further supported by VT NMR studies of **20a** in the solution.[4] A flattened CC conformation was suggested for **21** in solution.[3] More recently, an enhanced population of the BC conformation in D_3CCN solution at 70 °C was assigned to ketones **8h**, **8j**, and **20a** by ^{17}O NMR spectroscopy.[32] In each case, the ring bearing the benzyl group existed in a chair form and thus appeared to be somewhat biased. This assignment was derived on the basis of the observation that an upfield shift for C=O of 5-7 ppm [due to increased shielding at C(9)] was observed for each system. This observation appeared defensible

only if a significant interaction existed between the lone pair on the heteroatom and the π orbital of the carbon of the carbonyl group. Thus, it was tentatively concluded that a BC conformer could give rise to such an effect.

Based on the studies carried out by our group[3,4,53] and the others,[2,52,58] it is reasonable to believe that many 3,7-DABCNONs may have a high population of a BC conformation in solution with a BC⇄CB equlibrium. The existence of this equilibrium is likely in all systems but where one of the fused rings has large substitutents, there appears to be a conformational bias. This hints that systems like **8a-8g** and **20a-20d** may not exhibit an easily detectable BC⇄CB equilibrium at room temperature since large groups are attached to N. It appears that some simple 3,7-DABCNONs exhibit a BC⇄CC equilibrium in solution with an increased population of a BC form at higher temperatures (greater than or equal to that at RT) and an increased population of a CC form at low temperatures (-50 °C to -100 °C).[3,4,52,53]

Few 3,7-DABCNONs and very few 3,7-DABCN-9,9-diols of the type **16** have been reported and examined for their conformational preferences.[28] As stated previously, the only diol system investigated is *N*-benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9,9-diol hydrogen perchlorate (**22**).[5] On the basis of ^{13}C NMR spectrum and X-ray analysis, this

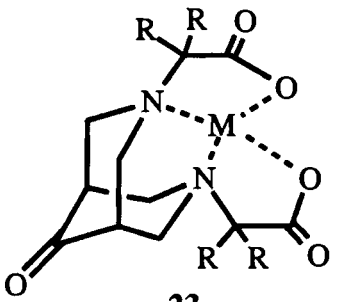


22

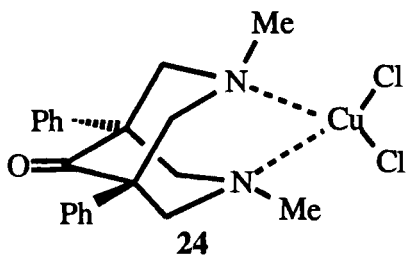
system was assigned a CC conformation in the solid state with little ring distortion near the gem diol group in the molecule. The conformation in solution could not be wholly defined due to the lack of model systems of known conformation by which to make comparisons of spectral data.

Metal Complexation Properties

There have been very few examples of 3,7-DABCNON derivatives bound to metals. The only examples reported are complexes **23**,[47] the 1:1 adducts **24**,[29] and the 2:1 adducts **25**,[51] which are illustrated below with reasonable configurations at nitrogen.



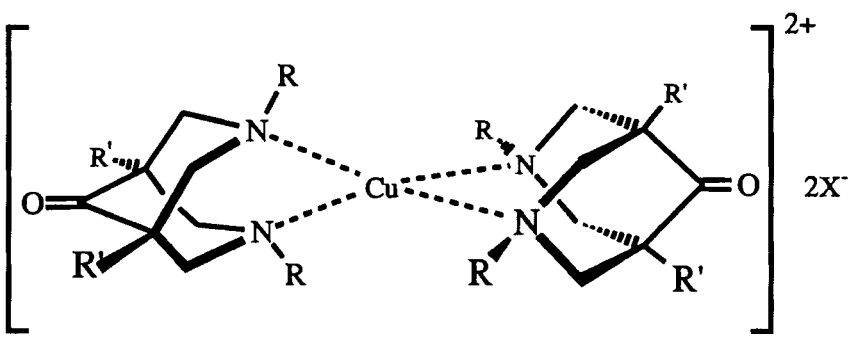
23



24

R = Me M = Co(II), Ni(II), Cu(II)
R = H M = Co(II), Ni(II), Cu(II)

However, only IR spectral data and elemental analysis were provided to support the structures. Thus the interpretation is considered tentative. In all cases, divalent transition metals have been employed, the most common being copper. In addition to forming complexes with transition metals, it was stated by Ruenitz that a few 3,7-DABCNs also



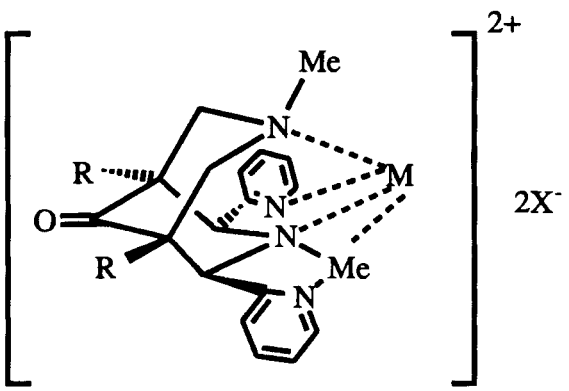
25

R' = Ph, R = H, $X = CH_3CO_2^-$
R' = H, R = Me, $X = ClO_4^-$

react with alkaline earth metals Ca^{2+} and Mg^{2+} and form certain complexes.[37] Formation of such complexes was illustrated by performing titration experiments on 3,7-

DABCNs solutions with known concentrations of Ca^{++} and Mg^{++} ions in ether. These data were in the form of observations of ^1H chemical shifts in the NMR spectrum, but no complexes of Ca^{2+} or Mg^{2+} were isolated. Moreover, the monoprotonated form of certain 3,7-DABCNs did *not* form metal complexes with transition metals or with alkaline earth metals.[37] Very little evidence exists to support most of the structures suggested in the literature except for elemental analyses, and those were only present in a very few cases.

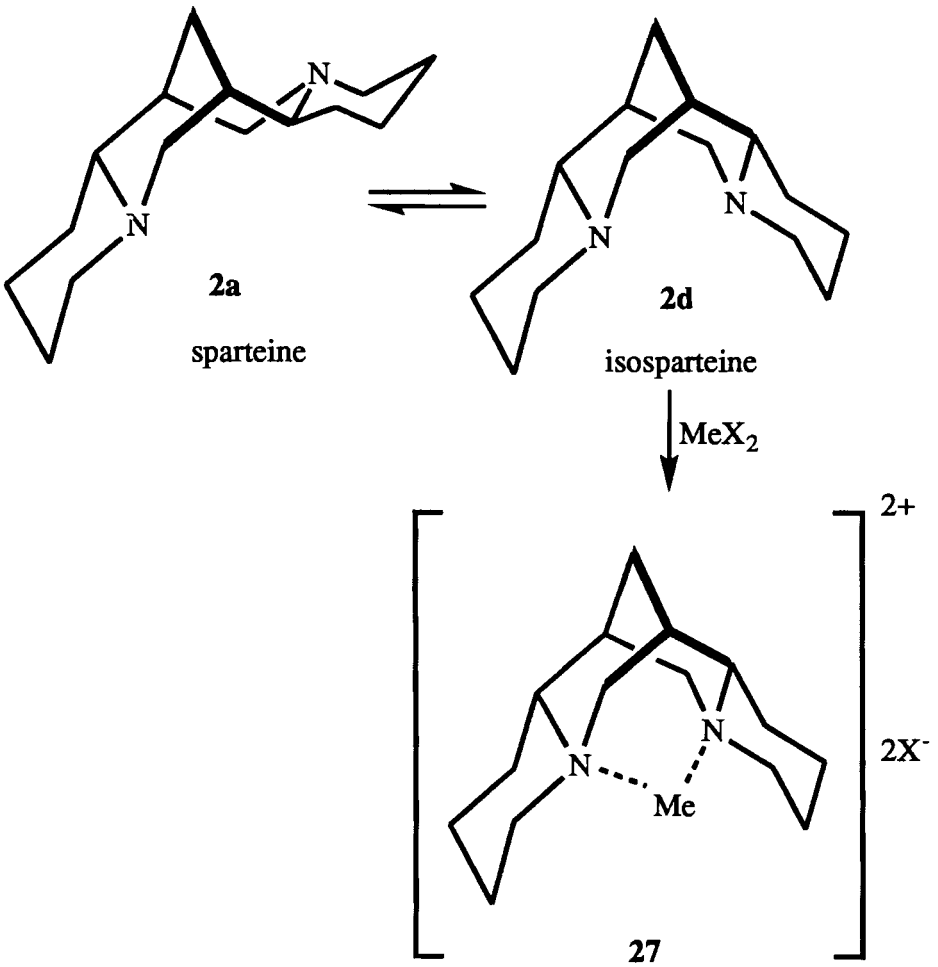
A very small number of metal complexes of the ethoxycarbonyl derivative (R = CO_2Et) of the 6,8-substituted 3,7-DABCNONs **26** have also been reported with the transition metals shown.[24,25] Based only on IR spectral data, it was suggested that the



26

M = Cu(II), Mn(II), Co(II), Ni(II) X = SCN

N atoms in the pyridine ring, along with the N atoms at 3- and 7-positions, were involved in the complexation to the metal ion. It was suggested, on the basis of elemental analyses alone, that all members of **26** were monodentate chelates in the above systems. Apart from 3,7-DABCNONs, it was shown by Mason and Peacock[30] that (-)-sparteine (**2a**) also formed bidentate metal complexes of the general formula [M(sparteine), 2 X^-] **27** with transition metal ions like Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}. These complexes were stable in ethanol and chloroform. Complexes with Fe(III) and Mn(II) were also prepared but were found to be stable only in the solid state. Magnetic moments, electronic spectra, and the



Me = Co(II), Ni(II), Cu(II), Mn(II)

X = Cl, Br

circular dichroism absorption pattern (down to 5000 cm^{-1}) were reported for $[Ni(sp)Cl_2]$. The electronic structures of the cobalt(II) and nickel(II) complexes were discussed in terms of an effective C_{2v} chromophoric symmetry. Based on the formation of stable complexes (such as **27**) by sparteine, one might speculate that its antiarrhythmic activity may be due, in part, to a direct interference with the dynamic behaviour of membrane-associated cations such as magnesium and calcium. At this stage, there is little evidence regarding the exact mechanism of action of most antiarrhythmic agents including the 3,7-DABCNs. This is mainly due to a lack of knowledge about the physiological aspects of arrhythmias. However, very recent work with a few DHBCNs suggest that some

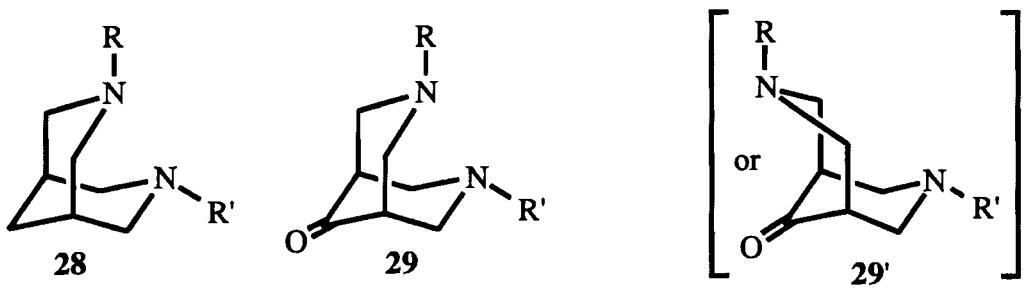
alteration in the function of Na^+/K^+-ATPase enzyme may be the cause of antiarrhythmic activity.[11,12] It is known also that lipophilic character can influence Na^+/K^+-ATPase action.[11,12]

Although research in recent years has enhanced our understanding of the cellular mechanisms of arrhythmias, the general approach to the therapy has been to develop agents with specific class actions. Such agents are under development in many laboratories.

CHAPTER II

RESULTS AND DISCUSSION

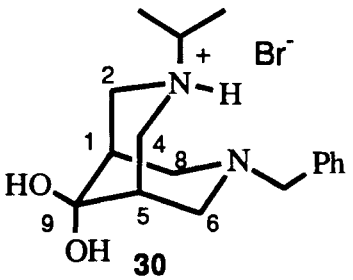
The next three pages summarize our research followed by a more detailed discussion. One aim of the project was to determine if metal chelates could be prepared from DHBCNs-**28** and DHBCNONs **29** since such agents may complex calcium or magnesium in the process of controlling arrhythmias in ischemic tissues.[11,12] This investigation has resulted in the development of new methodology to obtain novel 9,9-



	R	R'
a	$CH(CH_3)_2$	CH_2Ph
b	$CH(CH_3)_2$	H_2C, OCH_3, OCH_3
c	H_2C	CH_2Ph
d	$CH(CH_3)_2$	$CH(CH_3)_2$

diols of DHBCNs **29** and derivatives thereof. The DHBCNs are well known for possessing useful antiarrhythmic properties.[13,37,38,59] Initial work focused upon the generation of metal chelates from selected members of **28** and **29** with $MgBr_2$ and $CaBr_2$ in absolute ethanol from which heavy oils were obtained. Interestingly, in absolute ethanol no chelates formed. However, we discovered that certain 3,7-diheterabicyclo[3.3.1]nonan-9-ones **29** with $CoBr_2$, $CaBr_2$, and $MgBr_2$ in slightly wet

THF led to the formation of stable 9,9-diols **30-33** which are also salts via protonation on nitrogen. No stable chelates could be isolated from any of these reactions mixtures. It was reasoned that the metal bromide probably reacted with water and generated some HBr which initiated a reaction of the ketones to form the diols and protonated the nitrogen to create the bromide.



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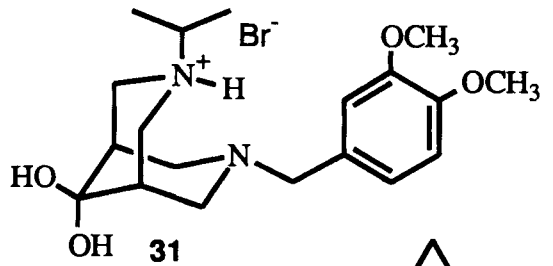

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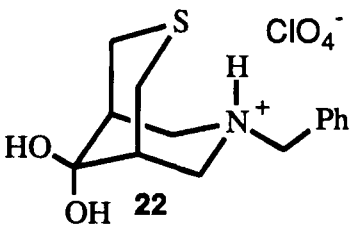

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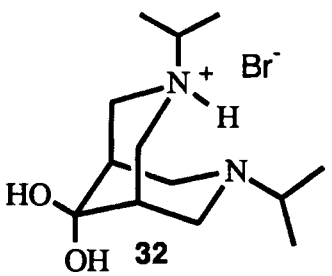

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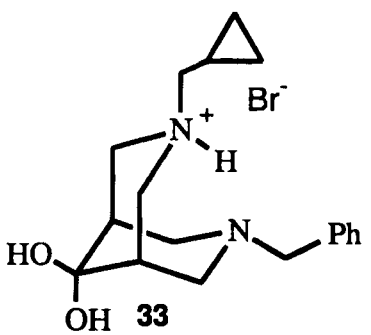
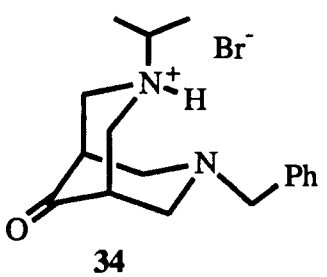


33

Stable diols such as **30-33** are very rare and not well studied in terms of physical properties as well as chemical properties. Although such diols may possess useful



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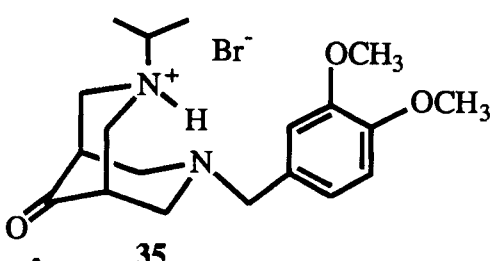

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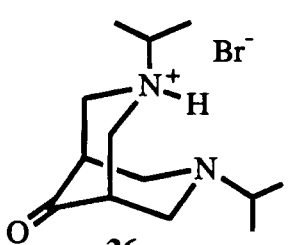

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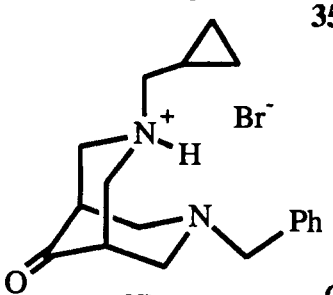

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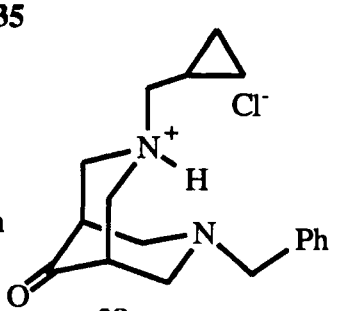
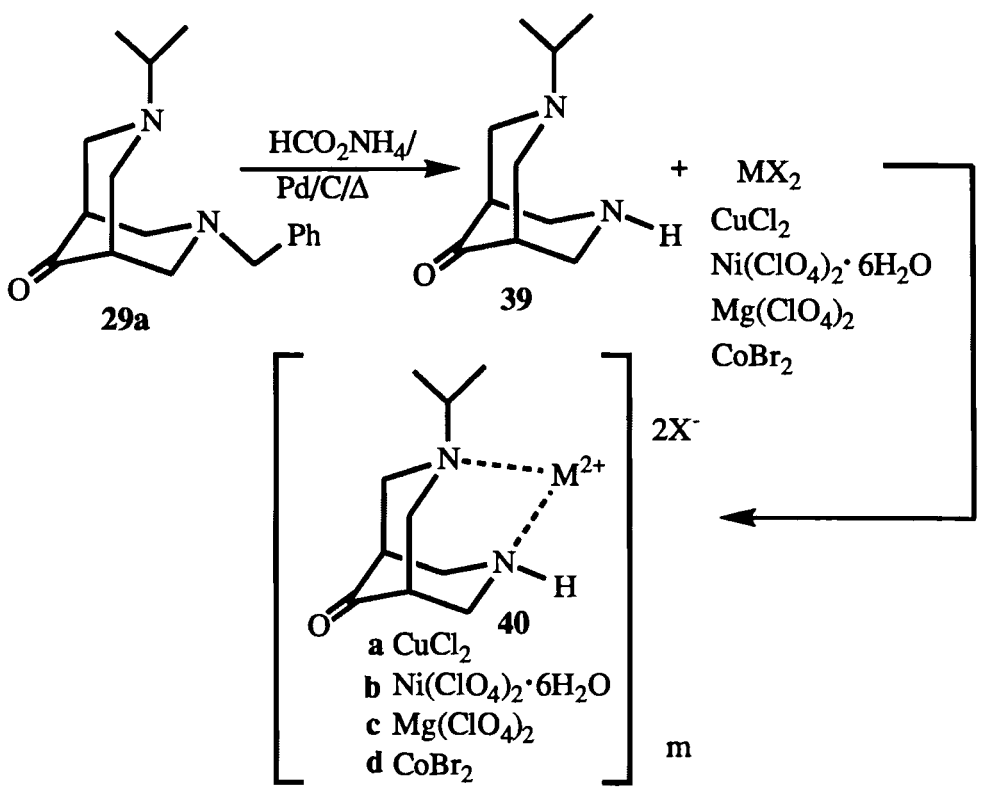


38

antiarrhythmic activity, the one such diol **22** reported and examined for antiarrhythmic activity in dog models did not exhibit cardiovascular properties of the specific type desired. Of course, other examples might be useful in this area of chemotherapy.

In order to gain support for the working hypothesis that water was critical for generating the diols, the ketone precursors of **30-33** were dissolved in anhydrous ether and subjected to a stream of dry HBr gas. Bromides **34-37** were isolated, and, although hygroscopic, had observable $\lambda_{C=O}$ groups in the IR spectra. These salts were characterized spectroscopically and are the first reported in this family.

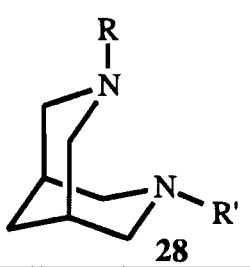
The last objective was to synthesize DHBCNs which would chelate metal ions by minimizing the steric congestion around one of the nitrogen atoms. This was achieved by



the debenzylation of the benzyl group in **29a** to give a less sterically hindered secondary amine **39**. An ethanolic solution of **39** was then treated with metal salts $CuCl_2$,

$Ni(ClO_4)_2 \cdot 6H_2O$, $Mg(ClO_4)_2$, and $CoBr_2$ to form solids **40a-d**, which were characterized by IR spectral studies. Based on the elemental analysis data for **40a**, a monodentate structure may be assigned to it tentatively. The analyses on the other complexes is currently under investigation.

A detailed discussion of the results now follows. It has been shown by our group and others that certain amides and sulfoxides exhibit good antiarrhythmic activity.[6] Specifically, some amides and sulfoxides prepared in our laboratory have shown good class III antiarrhythmic activity.[7] A detailed pharmacological study and the mechanism of action of these agents are currently under investigation. As discussed earlier, attempts were made to prepare metal complexes of different derivatives of **28** and **29**. Based on this information, it seemed plausible to investigate the metal complexation properties of the amides **28a-c** as their activity may be due in part to binding with metal ions like Ca^{2+} and Mg^{2+}. Chelation of **28a-c** with metal salts like $CaBr_2$ and $MgBr_2$ were tried in polar solvents like ethanol and methanol, but resulted in the formation of either heavy oils or suspensions.



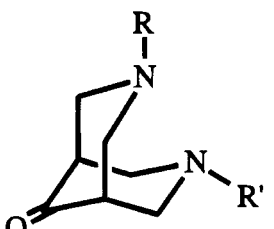
28

	R	R'
a	$CH(CH_3)_2$	$C(O)C_6H_4F(p)$
b	$CH(CH_3)_2$	$C(O)C_6H_4NO_2(p)$
c	$CH(CH_3)_2$	$SO_2C_6H_4NO_2(p)$

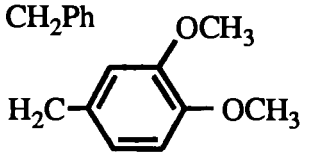
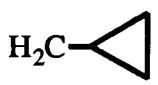
Attention was then directed towards DHBCNs of the type **29**. Due to the presence of a carbonyl group at the 9-position in **29**, such bicyclic ring systems are more flattened than the corresponding DHBCNs **28** thereby increasing the "gap" between the nitrogen

atoms at 3- and 7-positions. This might mean that **29** systems may incorporate a metal ion more easily than **28**. A literature search on the metal complexes of DHBCNs revealed only a few complexes had been made from systems like **29**[7,13,24,25] although there was no mention about a flattened nature of such ring systems.

The derivatives **29a-d** were selected for metal complexation. The approach involved the mixing of a hot ethanolic solutions of the metal salts and the ketones **29a-d**

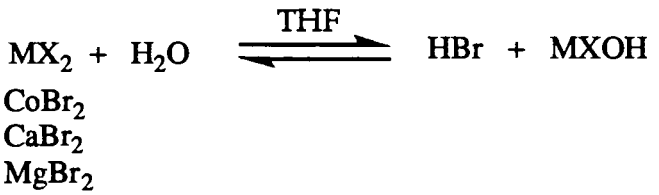


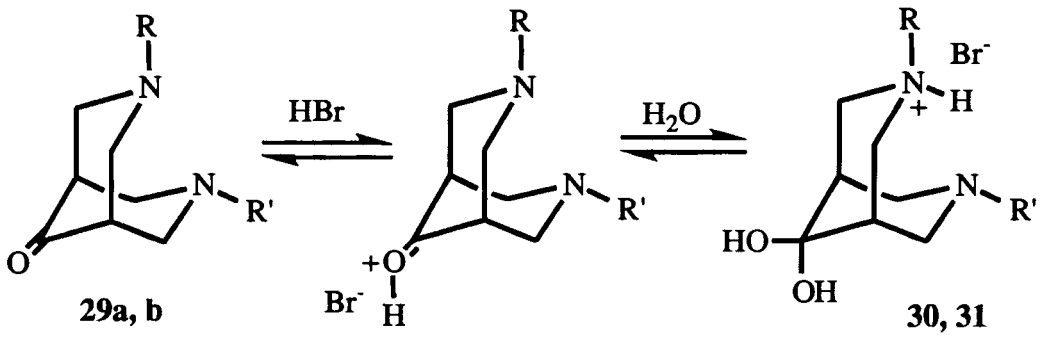
29

	R	R'
a	$CH(CH_3)_2$	CH_2Ph
b	$CH(CH_3)_2$	
c		CH_2Ph
d	$CH(CH_3)_2$	$CH(CH_3)_2$

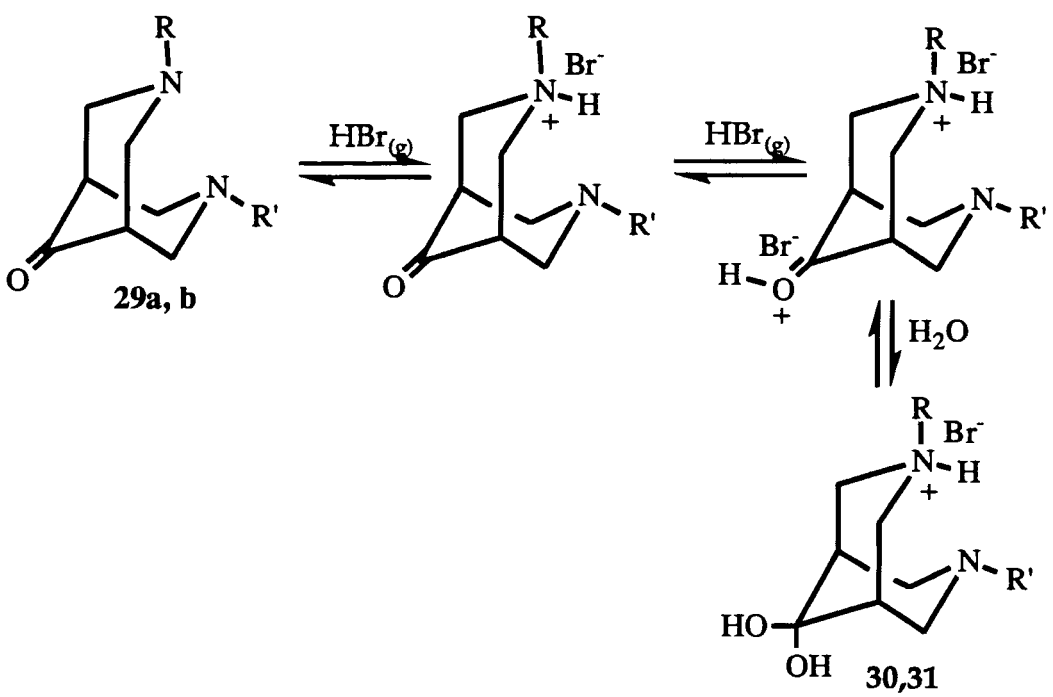
and boiling the resulting solution mixture, followed by cooling the solutions to 0 °C. This method gave suspensions or slurries. Another method involved mixing dry THF solutions of the metal salts and the ketones **29a-c** and then gradually evaporating the solvent under a gentle stream of N_2. This approach also did not form chelates. However, when solution of **29a-b** and metal salts like, $CaBr_2$, $MgBr_2$, and $CoBr_2$ in wet THF were mixed and allowed to sit in dark at room temperature for approximately 72 hours, crystals formed. The X-ray analyses showed the crystals to be diols **30** and **31** and not metal complexes.[7] The formation of such diols may be envisioned by a possible reaction between the metal halide and moisture present in the THF to produce hydrobromic acid. The hydrobromic acid then probably protonates the carbonyl oxygen in **29a-b**, followed

by a nucleophlic addition of a water molecule to the activated carbonyl group to produce the diols **30** and **31**. Such diols are stable and have good solubility in polar solvents.



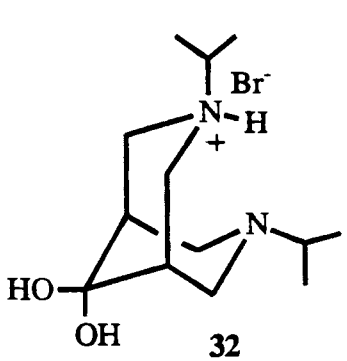


Another mechanism that may be possibly operating involves the protonation of N(3), which probably activates the C=O group for protonation, followed by a nucleophilic attack of H_2O on the carbonyl group to produce **30, 31**.

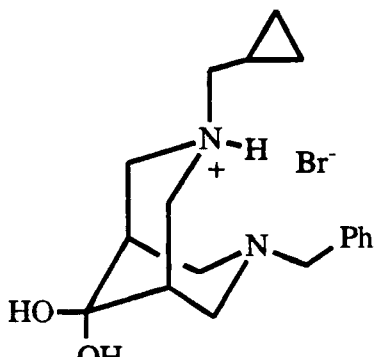


Synthesis and conformational analysis of such diols have not been explored in great detail as stated earlier. The only example reported and studied so far in this family is **22**.[5]

In order to support the proposed mechanism of formation of **30** and **31**, ether solutions of **29c** and **29d** were treated with 48% HBr in 2-propanol to give diols **32** and **33**. It thus appears that small amounts of water and acid can lead to the formation of the



32



33

diols. This fact was further corroborated by reacting a dry ether solution of **29a-d** with **dry** HBr gas to produce the hydrobromides **34-37**, respectively, which exhibit a carbonyl stretch in the infrared spectra. These results lend credence to our theory and proposed mechanism of formation of diols. The hydrobromides **34-37** were found to be extremely hygroscopic and showed a strong tendency to absorb moisture from the atmosphere to produce the corresponding diols. In attempted high resolution mass spectral analysis of **36**, for example, it was found that approximately 45% of the molecules had absorbed water and had been converted to **32**. An exact reason for the highly hygroscopic nature of such salts is not very clear at this point. A hydrochloride of **29d** was also prepared by the same method and was found to be equally sensitive to moisture.

IR, ^{1}H NMR, ^{13}C NMR, and high resolution mass spectral studies were performed on the diols **30-33** and hydrobromides **34-38**. A comparison of the ^{1}H and ^{13}C NMR shifts in **30-33** was made with the corresponding ketones **29a-d**, and the results have been summarized in Tables II-V. Such a comparison reveals an informative pattern.

Table II.

COMPARISON OF ^{1}H and ^{13}C CHEMICAL SHIFTS (δ from TMS) OF **29a**, **30**, **34**

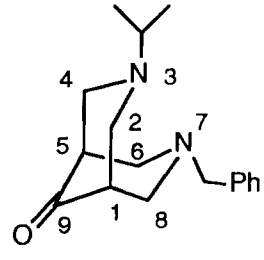
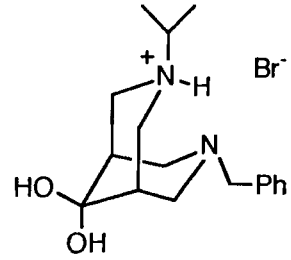
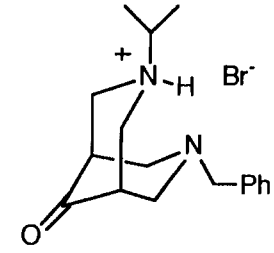
Compound			
	29a	**30**	**34**
$C\underline{H}(CH_3)_2$	2.87 (m)	3.57 (m)	3.58 (m)
$CH(C\underline{H}_3)_2$	1.02 (d)	1.16 (d)	1.17 (d)
$H(2,4)_{ax}$	2.87 (m)	2.81 (d)	2.81 (d)
$H(2,4)_{eq}$	3.03 (dd)	2.97 (d)	3.01 (d)
H(9)	----	6.15, 6.18 (s)	----
$\underline{C}H(CH_3)_2$	53.41	55.26	53.07
$CH(\underline{C}H_3)_2$	18.25	16.29	17.54
C(2,4)	53.71	50.47	50.27
C(9)	215.20	89.37	192.85

Table III.

COMPARISON OF ^{1}H and ^{13}C CHEMICAL SHIFTS (δ from TMS) OF **29b**, **31**, **35**

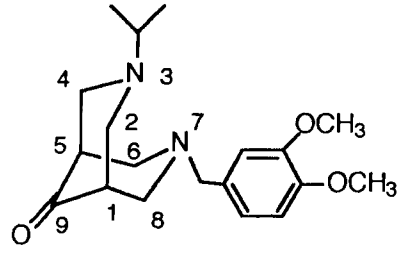
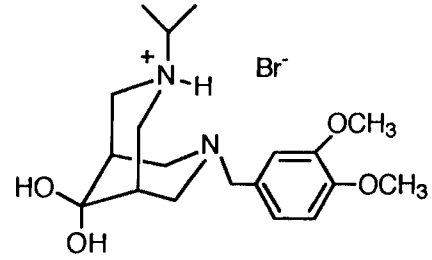
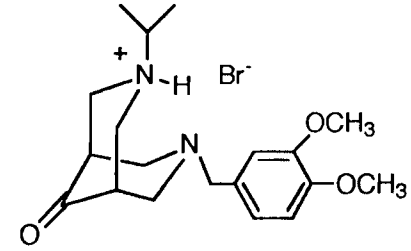
Compound	 **29b**	 **31**	 **35**
$C\underline{H}(CH_3)_2$	2.81-2.90 (m)	3.15-3.51 (m)	3.50 (m)
$CH(C\underline{H}_3)_2$	1.03 (d)	1.16 (d)	1.14 (d)
$H(2,4)_{ax}$	2.81-2.90 (m)	2.51 (d)	2.86 (d)
$H(2,4)_{eq}$	2.98 (dd)	2.85 (d)	3.24 (d)
H(9)	----	6.19, 6.21 (s)	----
$\underline{C}H(CH_3)_2$	53.40	54.92	57.76
$CH(\underline{C}H_3)_2$	18.17	16.46	17.17
C(2,4)	53.86	50.30	50.54
C(9)	215.27	89.45	206.62

Table IV.

COMPARISON OF ^{1}H and ^{13}C CHEMICAL SHIFTS (δ from TMS) OF **29c**, **32**, **36**

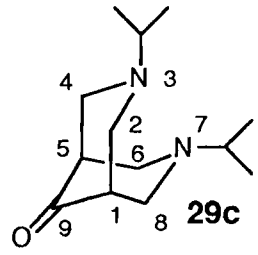
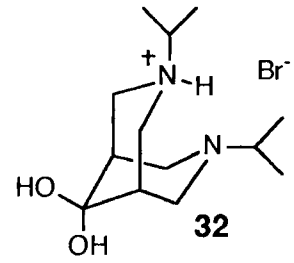
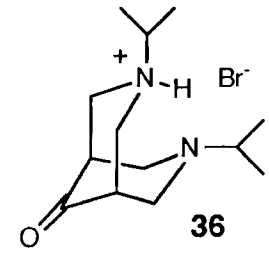
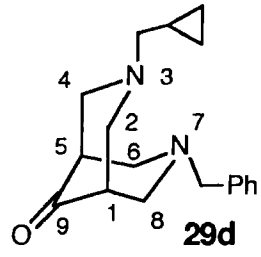
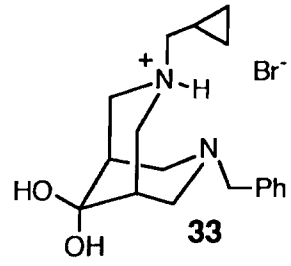
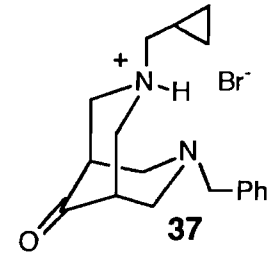
Compound	 **29c**	 **32**	 **36**
$C\underline{H}(CH_3)_2$	2.87 (m)	3.13 (m)	3.25-3.48 (m)
$CH(C\underline{H}_3)_2$	1.02 (d)	1.36 (d)	1,14 (d)
$H(2,4)_{ax}$	2.87 (m)	3.44 (d)	3.16-3.23 (m)
$H(2,4)_{eq}$	3.04 (dd)	3.61 (d)	3.25-3.48 (m)
H(9)	----	3.98 (bs)	----
$\underline{C}H(CH_3)_2$	53.17	67.36	65.40
$CH(\underline{C}H_3)_2$	17.90, 18.02	16.98	16.69, 17.02
C(2,4)	53.27 or 53.36	49.10	53.45
C(9)	215.18	87.02	----

Table V.

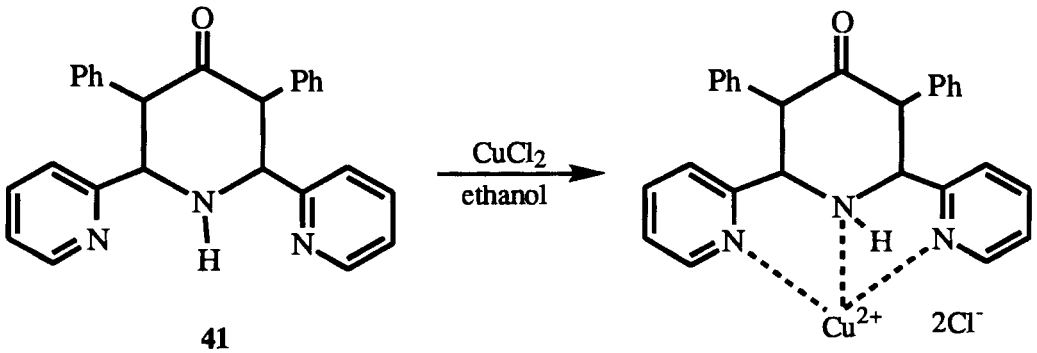
COMPARISON OF ^{1}H and ^{13}C CHEMICAL SHIFTS (δ from TMS) OF **29d, 33 37**

Compound	 **29d**	 **33**	 **37**
C<u>H</u>$_2$-cyclopropyl	2.32	2.54 (d)	3.11 (d)
C<u>H</u>-cyclopropyl	0.89 (m)	1.08 (m)	1.34 (m)
$H(2,4)_{ax}$	2.94 (dd)	3.20 (d)	3.72 (d)
$H(2,4)_{eq}$	3.12 (dd)	3.33-3.62 (m)	3.88 (d)
H(9)	----	6.23, 6.33 (s)	----
<u>C</u>H$_2$-cyclopropyl	61.85	60.80	63.93
<u>C</u>H-cyclopropyl	8.53	6.16	5.25
C(2,4)	58.19	53.90	52.24
C(9)	214.85	89.63	----

It was found that in diols **30-33** versus ketones **34-38** there was a significant downfield shift for the methine proton as well as the carbon of the isopropyl group. The $H(2,4)_{ax}$ and $H(2,4)_{eq}$ protons in **30-33** appear upfield relative to the ketone precursors **29a-d**. Another interesting observation was that the ^{13}C and ^{1}H signals for the bridge carbon [C(9)] in **30-33** appeared in a range of 87-102 ppm from TMS while the ^{1}H signals appeared at 3.40-6.25 ppm from TMS. It is thus clear that not only the heteroatom present but substitution on the ring is also important for determining the chemical shift for the gem-diol carbon C(9). In the salts **34-38**, the C(9) appeared in the range of 205-210 ppm from TMS which is approximately 10-15 ppm *upfield* than in ketones **29a-d**. Possibly, the inductive effect of the positive nitrogen atom induces more double bond character into the carbonyl group with the carbon atom becoming more shielded.

As stated earlier, another objective of this work is to prepare metal complexes of 3,7-DABCNONs. The centers involved in the chelation process are the nitrogens at 3- and 7-positions. An optimum binding is likely to occur if the bispidinones are in a chair-chair conformation. Although such systems exist in a BC⇄CC equilibrium, with predominantly a BC form at and above room temperature,[2,4,52] only a few stable transition metal complexes for such systems have been synthesized and very few characterized.[22,52,53] Since various approaches to produce chelates of this type of *N*-substituted system gave negative results, it was reasoned that perhaps the bulky groups attached to the nitrogen atoms at the 3- and 7-positions could cause a steric crowding and possibly interfere with the complexation of the metal ion. One way to reduce the steric congestion in **29a,b,d** was to remove the benzyl group by debenzylation to form a less crowded secondary amine like **39**. Debenzylation of **29a** with ammonium formate and palladium on activated charcoal gave **39** which displayed a characteristic N-H stretch (3326 cm^{-1}) in the IR spectrum. An ethanolic solution of crude **39** was mixed with metal salts like $CuCl_2$, $Ni(ClO_4)_2 \cdot 6H_2O$, $Mg(ClO_4)_2$, and $CoBr_2$ dissolved in ethanol. Heating the solution resulted in the precipitation of complexes **40a-d**. All the complexes showed

a shift in the N-H absorption band to a lower wave number (3200-3151 cm^{-1}) compared to that in amine **39** (3326 cm^{-1}), suggesting the formation of a complex.

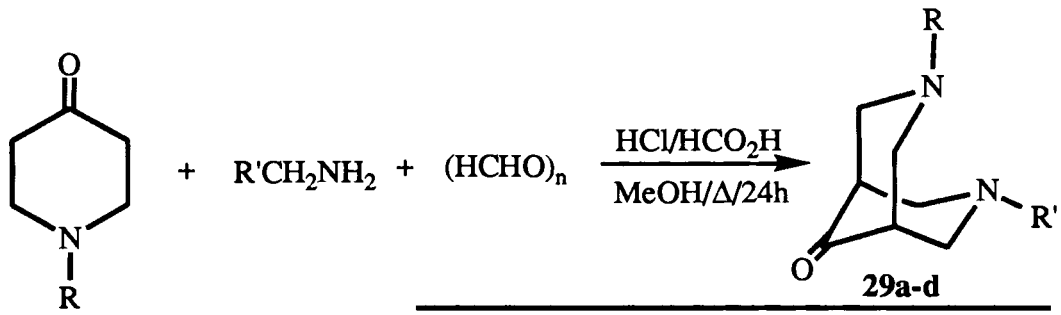


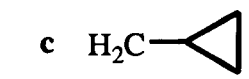
41 **42**

Another approach that could possibly enhance the binding of the metal ion with the bispidinones was to introduce pyridyl ring at 2- and 4-positions. To investigate the role of the pyridine ring in complexation, model system 3,5-diphenyl-2,6-dipyridyl-4-piperidinone (**41**) was prepared. An ethanolic solution of **41** was mixed with anhydrous copper chloride dissolved in absolute ethanol. Upon heating the solution, crystals of a light blue solid **42** precipitated. The N-H and the C=N absorption bands in the IR spectrum of **41** appear at 3317 cm^{-1} and 1593 cm^{-1}, respectively, while in **42** the N-H and the C=N band occur at 3151 cm^{-1} and 1607 cm^{-1}, respectively. These results suggest a complex, formed between the secondary amine **41** and copper ions. No NMR studies have been performed on **42** to date due to its insolubility in commonly used NMR solvents. The exact number of ligand molecules attached to the copper ion remains unclear at this stage.

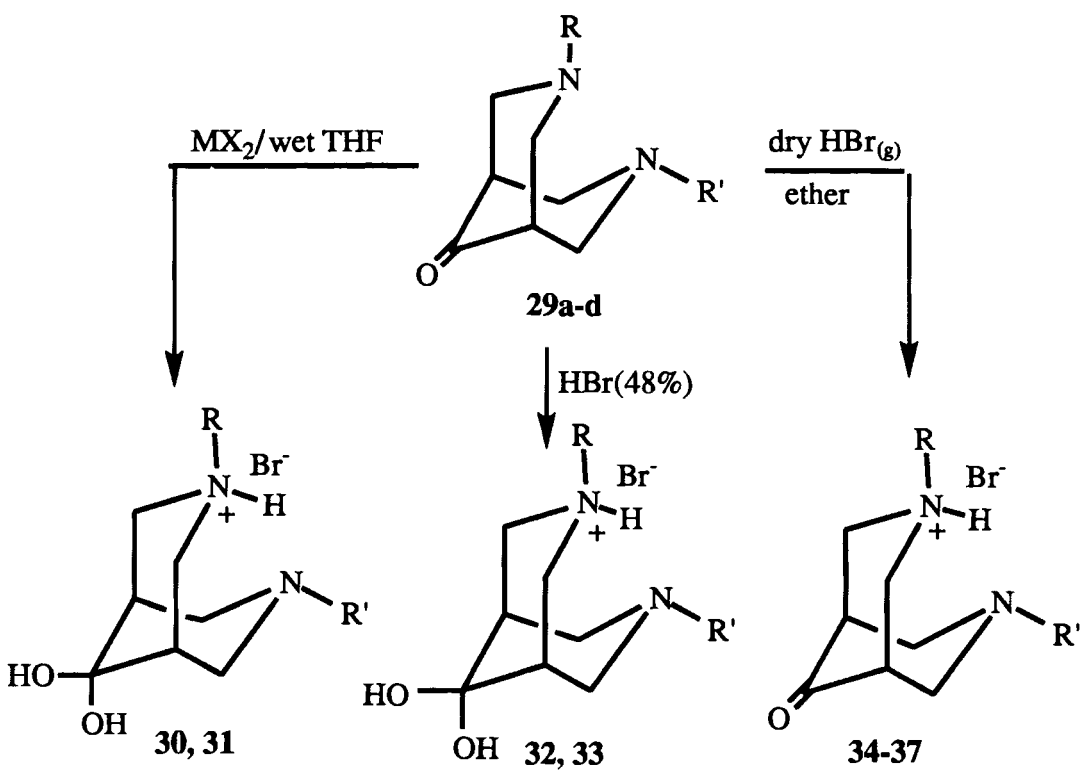
Synthetic Methodology

The synthesis of 3,7-DABCNONs **29a-d** was performed by a modified double Mannich reaction. Condensation of a piperidinone, an amine, paraformaldehyde, acetic acid, and hydrochloric acid in methanol gave **29a-d**. Mixing a solution of **29a** with



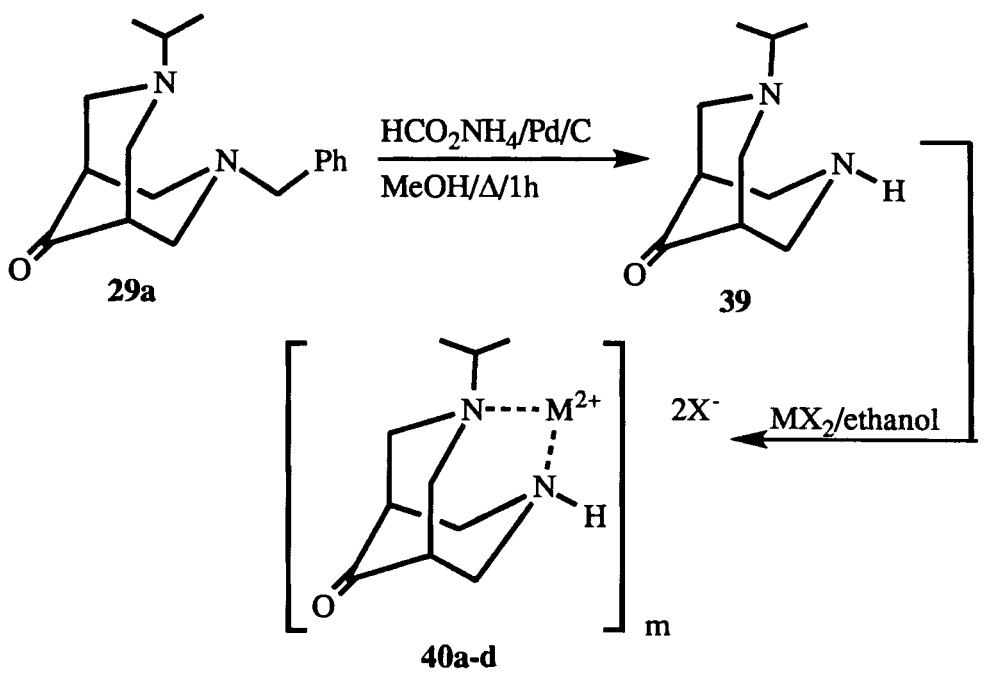
	R	R'
a	$CH(CH_3)_2$	CH_2Ph
b	$CH(CH_3)_2$	C_6H_3-3,4-$(OCH_3)_2$
c	H_2C 	CH_2Ph
d	$CH(CH_3)_2$	$CH(CH_3)_2$

$CaBr_2$ and $MgBr_2$ each in THF and a solution of **29b** with $CoBr_2$ in THF produced the diols **30** and **31**, respectively. Diols of the 3,7-DHBCNONs were also made by reacting such systems with aqueous solutions of mineral acids like hydrogenperchloric acid or



hydrobromic acids in the synthesis of **32** and **33**. Salts **34-37** were prepared by passing a stream of dry HBr gas to the dry ether solutions of **29a-d**, respectively. Salt **38** was prepared by the same method but by using a stream of dry HCl gas. Such salts were purified by washing with the dry ether since purification via recrystallization was difficult to achieve due to their very hygroscopic nature.

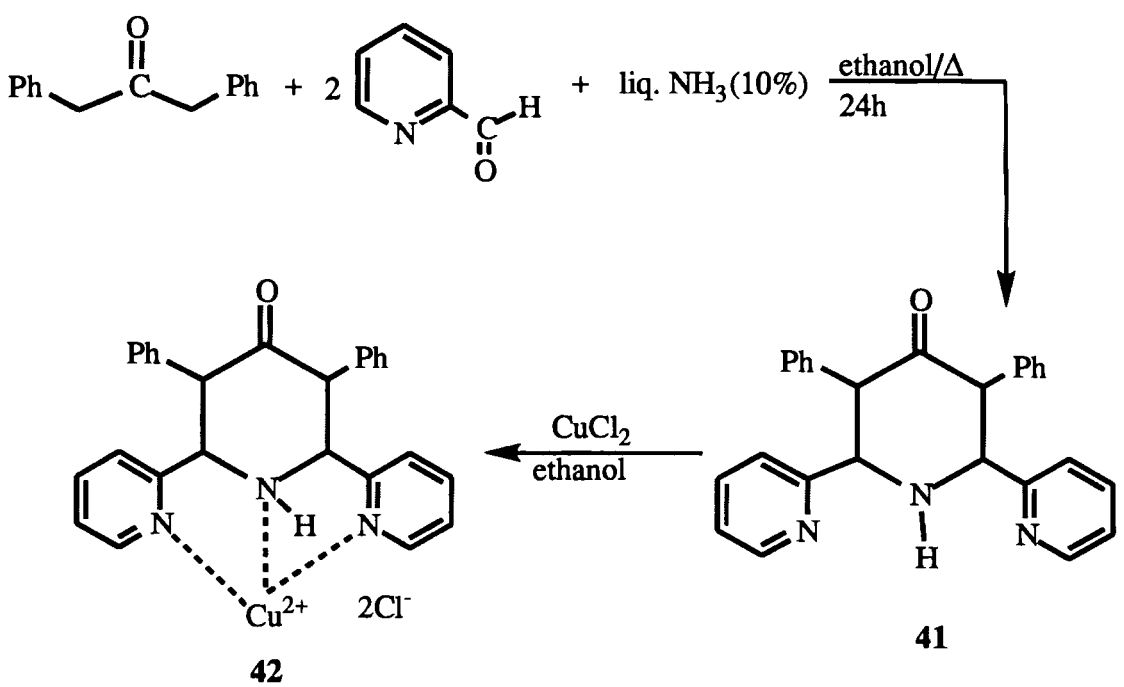
The metal complexes **40a-d** were prepared by the debenzylation of **29a** using using Pd/C and ammonium formate to give the secondary amine **39** as an oil. Ammonium formate acts as a hydrogen source in the reaction, a technique developed recently in these heterocycles.[59] The order of addition appears critical to the reaction. After the Pd/C was placed in the flask and the system was flushed with nitrogen, methanol was slowly added, followed by the addition of the bispidinone and the ammonium formate to give the best yields. Purification of **39** has not been achieved as yet since it changed color upon standing for a short time and appeared vulnerable to air oxidation during purification. An ethanolic solution of the crude **39** and the metal salts



29a **39** **40a-d**

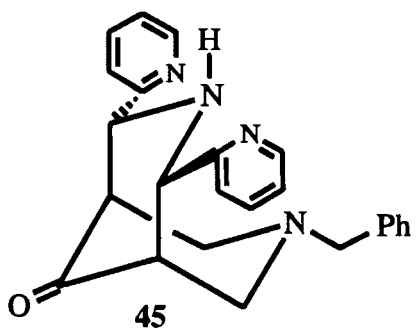
$CuCl_2$, $Ni(ClO_4)_2 \cdot 6H_2O$, $Mg(ClO_4)_2$, and $CoBr_2$ were combined and boiled for 5-10 minutes to produce **40a-d**. The complexes usually precipitated or crystallized from the solution. If this did not occur, the reaction mixture was concentrated and precipitation could be induced by the addition of a solvent with low dissolving power for the complex. The complexes were purified by crushing and washing in dry methanol, dry ethanol and anhydrous ether. Surprisingly, the solubility of all the complexes was low in polar solvents like methanol, ethanol, isopropyl alcohol, acetonitrile or dimethyl sulfoxide. The infrared spectra of the nickel perchlorate **40b** and the magnesium perchlorate complex **40c** exhibited strong broad absorption bands around 1105 cm^{-1} and medium absorption bands at approximately 915 cm^{-1}, indicating the presence of a perchlorate anion in the complexes.[22]

The preparation of **42** was achieved by a Mannich reaction under basic conditions. Condensation of 1,3-diphenylacetone, pyridine-2-carboxaldehyde, and a 10% solution of liquid ammonia in ethanol gave **41**. An ethanolic solution of **41** and copper chloride were mixed, and the resulting solution was boiled to produce light blue crystals of **42**



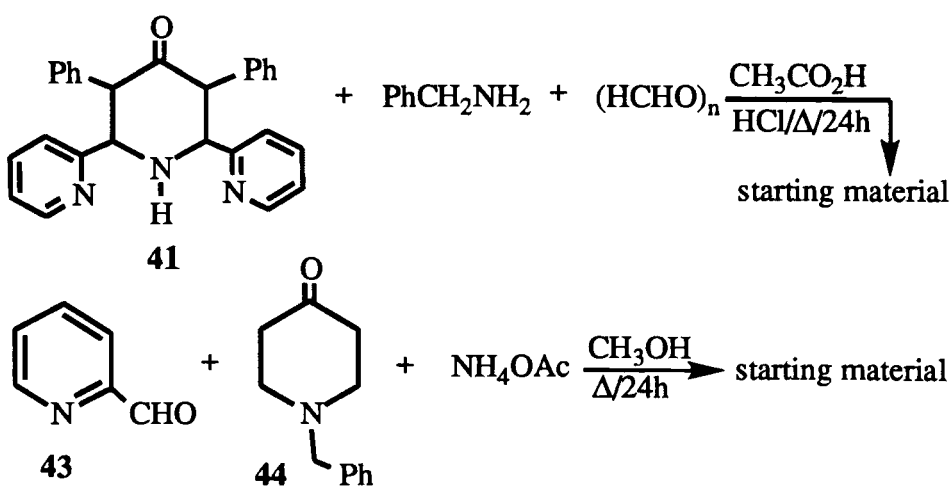
which were characterized by the IR spectral data. It is not known at this time if **42** contains one or more organic ligand systems, although we have represented it as a monodentate.

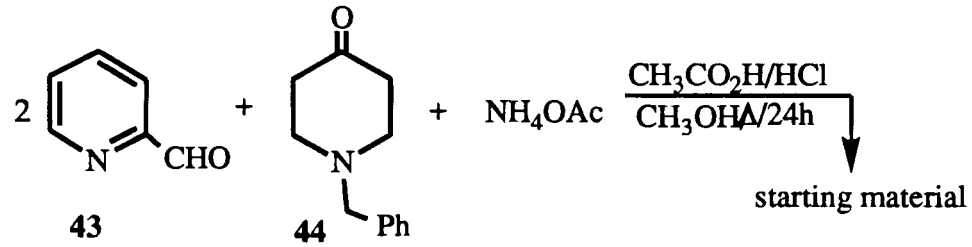
Preparation of 7-benzyl-2,4-bis(2-pyridyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (**45**) was attempted by a Mannich reaction. Condensation of 3,5-diphenyl-2,6-dipyridyl-4-piperidinone (**41**) was initiated with a mixture of benzylamine, HCl, glacial acetic acid and paraformaldehyde. A mixture of starting materials was recovered and identified by spectroscopic analysis. A different approach, which involved a double Mannich condensation of pyridine-2-carboxyaldehyde (**43**), *N*-benzyl-4-piperidinone (**44**) and ammonium formate, was also attempted. ^{1}H, ^{13}C, and IR spectral analysis of the reaction mixture



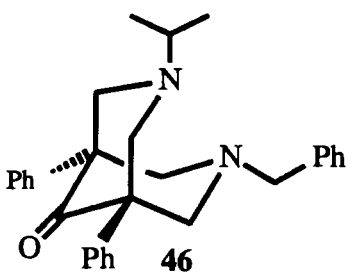
45

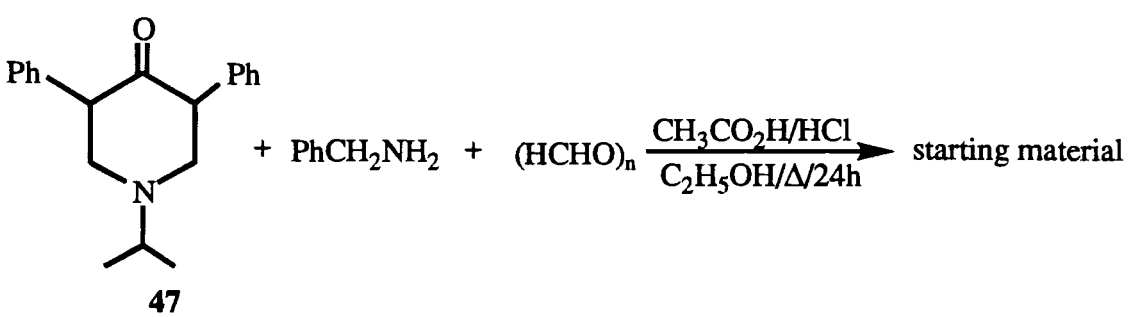
indicated the presence of starting materials. The same reaction was also tried under acidic conditions using HCl and glacial acetic acid, but identical results were obtained.





A synthesis of 7-benzyl-3-isopropyl-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**46**) by a Manich condensation involving *N*-isopropyl-3,5-diphenyl-4-piperidinone (**47**), benzylamine, and paraformaldehyde in the presence of HCl and glacial acetic acid was attempted. Spectral analysis of the product indicated it to be starting material **47**. It is not clear why this reaction failed under conditions that have been productive to generate **29**, for example.



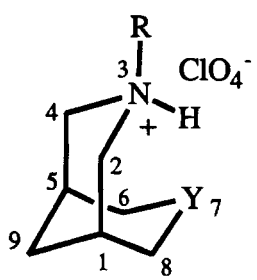


Conformational Analysis

NMR spectroscopy and X-ray crystallography are useful methods in determining the conformational preferences of 3,7-diazabicyclo[3.3.1]nonan-9-ones. Such analyses can be helpful in understanding the biological properties and possibly the mechanism of

action of such compounds. While X-ray crystallographic analysis describes the conformation in the solid state, debate over the preferred conformation in solution usually remains. Variable temperature (VT) ^{13}C NMR spectral studies on certain 3,7-DABCNONs (as described in Chapter I) support the existence of a boat-chair conformation possibly in a BC⇄CB equilibrium in some systems.[2,4,32,36,45] It was proposed that 3,7-DABCNONs exhibit a BC⇄CC equilibrium in solution with an increased population of a BC form at higher temperature and CC form at lower temperature. Several reduced forms of 3,7-DABCNONs namely DHBCNs and their salts have been examined[4,45,53] and found to prefer the CC conformation in solution in many cases.

^{1}H, ^{13}C, and ^{15}N NMR spectral studies have been reported by our group on certain DHBCNs[4,53] salts such as **48**. The studies suggested a CC conformation for such



48a-f

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

systems.[4,53] Some factors that support these results are: (1) hydrogen bonding between the proton on one heteroatom and the other heteroatom and (2) a reluctance to consider a boat ring which could result in severe bow-sprit interaction with the C(9) protons.

The ^{13}C NMR spectral analysis for **48a-e** proved more informative than the ^{1}H NMR spectra. The methine carbons of the isopropyl groups in **48a-e** were deshielded (56.0-58.6 ppm) compared to the same carbons (53.40-53.45 ppm) in the ketone precursors of **48a-e**. This implied that protonation occurred at N(3). Interestingly, this deshielding did *not* occur at C(2,4). In fact, the C(2,4) ^{13}C shifts in the ketone precursors were *shielded* (52.74-52.85 ppm) more than in the corresponding salts (53.71-53.86 ppm). This was explained by assuming a γ shielding effect on C(2,4) by the C(6)-N(7) and C(8)-N(7) bonds thereby offsetting to some extent the deshielding of C(2,4) resulting from protonation of N(3). Similar shifts are seen in our diols **30** and **31** compared to the ketone precursors.

Like the 3,7-DABCNONs, few 3,7-DABCN-9,9-diols have been synthesized and studied in terms of conformational preferences both in the solid state and in solution. An X-ray analysis of the diols **31** revealed a chair-chair conformation with the nitrogen atoms at 3 position protonated (Figure I).[7] The same configuration exists for **30**.[7] The preference for chair-chair arrangement probably arises due to favorable hydrogen bonding between the N(7) and the proton at N(3). Although no crystallographic data are available on **32** and **33** at present, a chair-chair conformation is strongly suspected for each case. The preferred conformation in solution for **30-33** remains undefined. In **30-33**, the methine proton and carbon of the isopropyl group attached to N(3) are downfield relative to the ketone precursors **29a-d** (see Tables II-V). This deshielding is not observed at C(2,4), especially in **30** and **31**, possibly due to the fact that the stabilized CC form of the diols possess a pronounced γ shielding effect by the C(6)-N(7) and N(7)-C(8) bonds on C(2,4). This shielding offsets to some degree any deshielding contribution

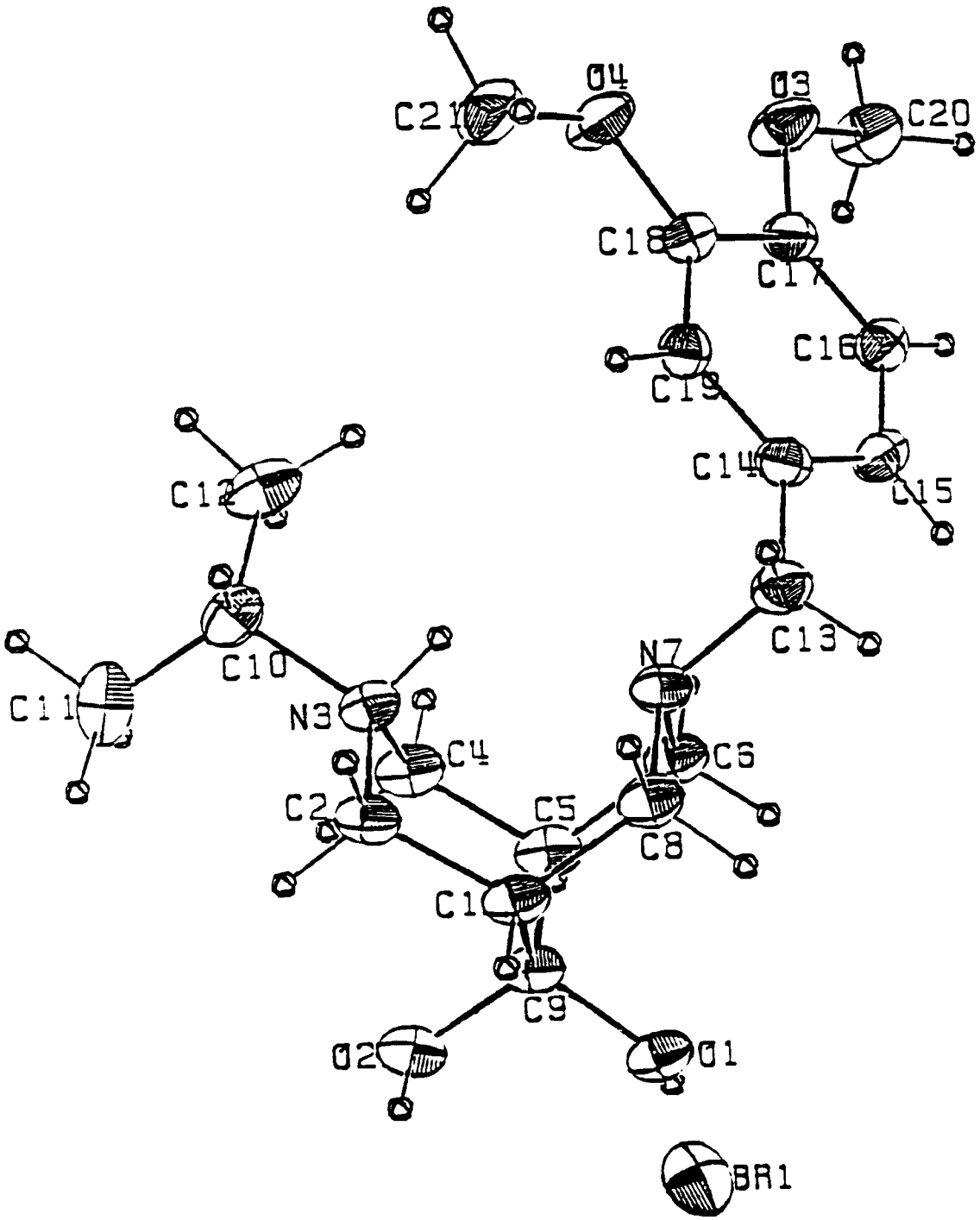
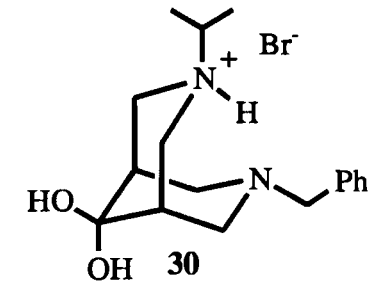
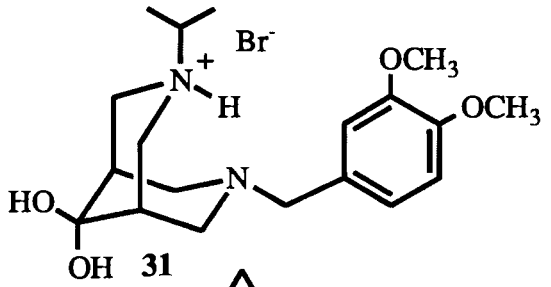


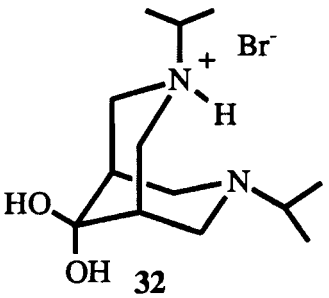
FIGURE I. ORTEP Diagram of **31**



30



31



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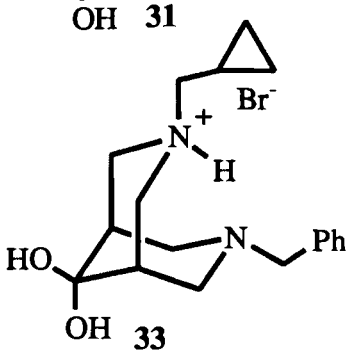


33

which results from protonation of N. For instance, the shifts for C(2,4) in **29a,b** are 53.71-53.86 ppm versus 50.30-50.47 ppm in diols **30** and **31**, respectively. In contrast, C(6,8) have signals at 57.92-58.01 ppm in **29a,b** while in **30** and **31** the signals occur at 53.65-53.82 ppm. These chemical shifts suggest a chair-chair conformation for **30** and **31** in solution. Such a trend in chemical shifts is also observed in salts **48a-c**. Based on such comparisons, chair-chair conformation may be tentatively assigned to **30-33** in solution. Similarly, the hydrobromides **34-37** show a deshielding of the methine proton and carbon of the isopropyl group, indicating protonation of the N(3). The C(9) in such systems appears at 205-210 ppm versus 215-218 ppm in **29a-d**. Due to the lack of model systems, it is difficult to assign absolutely any conformational preferences to **34-37** in solution. The possibility of a hydrogen bonding between the N(7) and the proton at N(3), resulting in a chair-chair conformation both in solution as well as in solid state, can not be ruled out.

Suggestion For Future Work

One difficulty encountered was to perform solution NMR studies on the metal complexes. As mentioned in chapter II, this was mainly due to the poor solubility of the

complexes in the commonly used NMR solvents. This problem may find partial solution in solid state ^{1}H, ^{13}C, and ^{15}N NMR studies on the complexes. Such studies are expected to give some indication of the effects of chelation on the chemical shifts of the ring protons and carbons as well as the substituents attached at N(3) and N(7). The exact number of ligand molecules attached to a metal ion may possibly be determined reliably by atomic absorption analysis or X-ray crystallography. It also seems reasonable to obtain the ^{15}N NMR shifts for **30** and **31** since such data has sometimes been helpful in diagnosing the nature of the major conformer present in solution.[45]

Conclusions

Metal complexes of certain 3,7-diazabicyclo[3.3.1]nonan-9-ones have been synthesized. Such complexes were characterized by IR spectral data. Preliminary results on complexes such as **40a** suggests a monodentate complex formation. Formation of such complexes also support our theory that less steric crowding around the N(3) and N(7) is required in order for the amines to form complexes. In addition, a new methodology has been developed to obtain novel 3,7-diazabicyclo[3.3.1]nonan-9,9-diols and 3,7-diazabicyclo[3.3.1]nonan-9-one hydrobromides. Based on the results of X-ray crystallography, a chair-chair conformation has been assigned to diol **31** in solid state. A chair-chair conformation is being proposed tentatively, in solution of such diols, based on the comparisons of the chemical shifts of the ring protons and carbons with those of the salts **48a-c**, as discussed earlier in this Chapter. Such assignment must be considered tentative. Although no X-ray crystallographic data are available for 3,7-diazabicyclo-[3.3.1]nonan-9-one hydrobromides, a chair-chair arrangement may be predicted in the solid state and in solution due to a favorable hydrogen bonding between N(3) and H(7).

CHAPTER III

EXPERIMENTAL SECTION

General. Information: All ^{1}H and ^{13}C spectral data were obtained on a Varian XL-400 NMR spectrometer operating at 399.5 and 100.6 MHz, respectively. Chemical shifts for ^{1}H and ^{13}C-NMR spectra were recorded in ppm values downfield from the TMS. IR spectra were recorded on a Nicolet impact 400 FTIR spectrometer as KBr pellets or as films. Melting points, which were uncorrected, were recorded on a Thomas-Hoover capillary melting point apparatus. High resoultion mass spectral analyses were performed on a VG analytical instrument, model ZAB-2SE. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Syntheses were executed, unless otherwise indicated, under an atmosphere of N_2 with magnetic stirring. The following reagents were obtained commercially and used without further purification: glacial acetic acid, Pd/C (10%), paraformaldehyde, hydrobromic acid, sodium hydroxide, benzyl amine, liquid ammonia, 1,3-diphenylacetone, hydrochloric acid, and sulfuric acid. The following compounds required distillation prior to use: *N*-benzyl-4-piperidinone (bp 120-122 °C/1 mm Hg) and pyridine-2-carboxaldehyde (185-186 °C). *N*-Isopropyl-3,5-diphenyl-4-piperidinone (**46**),[7] 7-benzyl-3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**29a**),[59] 7-(3,4-dimethoxybenzyl)-3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**29b**),[59] 3,7-diiso-propyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**29c**),[22] and 7-benzyl-3-cyclopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**29d**)[22] were prepared by known methods.[59] Ammonium formate and ammonium acetate were dried (vaccum pump, overnight, 0.2 mm Hg) in a dessicator prior to use. All solvents were reagent grade and used without

further purification, unless otherwise indicated. All the metal salts were dried under vaccum at RT in an Abderhalden for 7-10 hours before use.

7-Benzyl-3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9,9-diol Hydrobromide (**30**).

To a 30-mL beaker containing dried $MgBr_2$ (0.092 g, 0.50 mmol) dissolved in 10 mL of THF was added a solution of 7-benzyl-3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**29a**, 0.204 g, 0.75 mmol) in 10 mL of THF. The resulting solution mixture was protected from the atmosphere by covering the beaker with paraffin film and was allowed to stand at room temperature in the dark for approximately 72 h. Crystals formed and were filtered under vaccum, via an aspirator trap and washed with copious amounts of THF. The solid was recrystallized (10 mL, isopropyl alcohol:CH_2Cl_2 1:1) to give 0.140 g (51%) of **30**, mp 159-160 °C. IR (KBr) 3330 (O-H), 3096 (Ar-H), 2943, 2830 (C-H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.16 [d, 6H, CH_3], 1.95 [bs, 2 H, H(1, 5)], 2.81 [d, 2 H, $H(2, 4)_{ax}$], 2.97 [d, 2 H, $H(2, 4)_{eq}$], 3.39-3.62 [m, 2 H, $H(6, 8)_{ax}$], 3.70 [s, 2 H, Ar-CH_2], 3.93 [d, 2 H, $H(6, 8)_{eq}$], 6.15, 6.18 [s, 2 H, OH], 6.36-7.61 [m, 5 H, Ar-H]; ^{13}C NMR (DMSO-d_6) ppm 16.29 [CH_3], 38.45 [C(1, 5)], 50.47 [C(2, 4)], 53.65 [C(6, 8)], 55.25 [$CH(CH_3)_2$], 60.26 [Ar-CH_2], 89.37[C(9)], 126.74, 128.53, 129.80, 137.00 [Ar-C]. Anal. Calcd for $C_{17}H_{27}N_2O_2Br$: C, 51.61; H, 6.87; N, 7.08. Found: C, 51.60 ; H, 7.17 ; N, 6.97.

7-(3,4-Dimethoxybenzyl)-3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9,9-diol Hydrobromide (**31**).

To a 30-mL beaker containing dried $CoBr_2$ (0.109 g, 0.50 mmol) dissolved in 10 mL of THF was added a solution of 7-(3,4-dimethoxybenzyl)-3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**29b**, 0.249 g, 0.75 mmol) in 10 mL of THF. The resulting solution mixture was protected from the atmosphere by covering with paraffin film and was allowed to stand at room temperature in dark for approximately 72 h.

Crystals formed and were filtered under vaccum, via an aspirator trap, and washed with copious amounts of THF. The solid was recrystallized (10 mL, 1:1 isopropyl alcohol:CH_2Cl_2) to give 0.152 g (49%) of **31**, mp 158-159 °C. IR (KBr) 3347 (O-H), 3213 (N-H), 3043 (Ar-H), 2981, 2842 (C-H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.16 [d, 6H, CH_3], 1.95 [bs, 2 H, H(1, 5)], 2.51 [bs, 2 H, $H(2, 4)_{ax}$], 2.85 [d, 2 H, $H(2, 4)_{eq}$], 3.05 [d, 2 H, $H(6, 8)_{ax}$], 3.15-3.51 [m, 3 H, $H(6, 8)_{eq}$, $CH(CH_3)_2$], 3.55 [s, 2 H, Ar-H], 3.87 [s, 3 H, OCH_3], 3.88 [s, 3 H, OCH_3], 6.19, 6.21 [s, 2 H, OH], 6.89-7.15 [m, 3 H, Ar-H]; ^{13}C NMR (DMSO-d_6) ppm 16.46 [CH_3], 40.12 [C(1, 5)], 50.30 [C(2, 4)], 53.82 [C(6, 8)], 54.92 [$CH(CH_3)_2$], 55.52, 55.42 [OCH_3], 59.98 [Ar-CH_2], 89.45[C(9)], 111.37, 113.26, 122.15, 128.10, 148.50, 148.73 [Ar-C]. High resolution mass spectral (FAB) data calcd for $C_{19}H_{31}N_2O_4Br$ m/z (M^+): 351.2283 (-Br). Found: 351.2273.

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonan-9,9-diol Hydrobromide (**32**).

A 50-mL, Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. A solution of HBr (48%, 1.040 g, 6.16 mmol) in 2-propanol (1 mL) was added dropwise over a period of 15 min to a stirred, cold (0 °C, via ice water bath) solution of 3,7-diisopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**29c**, 0.6 g, 2.60 mmol) in wet THF (20 mL) to produce a light yellow oil, which crystallized after 72 hours at -10 °C The crystals were filtered under vaccum, via an aspirator trap, washed with dry ether, and recrystallized (2-propanol:chloroform, 1:1) to give **32** (0.320g, 45%), mp 97-98 °C. IR (KBr) 3403 (O-H), 3040 (Ar-H), 2900, 2850 (C-H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.36 [d, 12 H, CH_3], 1.77 [bs, 2 H, H(1, 5)], 3.13 [m, 1 H, $CH(CH_3)_2$], 3.44 [d, 4 H, $H(2,4,6,8)_{ax}$], 3.61 [d, 4 H, $H(2,4,6,8)_{eq}$], 3.98 [bs, 2 H, OH]; ^{13}C NMR (DMSO-d_6) ppm 16.98 [CH_3], 25.39 [C(1, 5)], 49.10 [C(2, 4)], 60.82 [C(6, 8)], 67.36 [$CH(CH_3)_2$], 87.02 [C(9)]. High resolution mass spectral (FAB) data calcd for $C_{13}H_{27}N_2O_2Br$ m/z (M^+): 243.2072 (-Br). Found: 243.2082.

7-Benzyl-3-cyclopropylmethyl-3,7-diazabicyclo[3.3.1]nonan-9,9-diol Hydrobromide (**33**).

A 50-mL, Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. A solution of HBr (48%, 1.040 g, 6.16 mmol) in 2-propanol (1 mL) was added dropwise over a period of 15 min to a stirred, cold (0 °C, via ice water bath) solution of 7-benzyl-3-cyclopropylmethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**29d**, 0.6 g, 2.20 mmol) in dry ether (20 mL) which produced a white solid. This solid was vaccum filtered, via an aspirator trap, washed with copious amounts of ether, and recrystallized (2-propanol:chloroform, 1:1) to give **33** (0.540 g, 67%), mp 155-156.5 °C. IR (KBr) 3240 (O-H), 3094 (Ar-H), 2933, 2833 (C-H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.54 [m, 2 H, $(CH_2)_{ax}$, cyclopropyl ring], 0.62 [m, 2 H, $(CH_2)_{eq}$, cyclopropyl ring], 1.08 [m, 1 H, C-H, cyclopropyl ring], 2.00 [bs, 2 H, H(1, 5)], 2.77 [d, 2 H, $H(6, 8)_{ax}$], 2.93-2.99 [m, 2 H, CH_2-cyclopropyl ring], 3.06 [d, 2 H, $H(6, 8)_{eq}$], 3.20 [d, 2 H, $H(2,4)_{ax}$], 3.33-3.62 [m, 2 H, $H(2, 4)_{eq}$], 3.70 [s, 2 H, Ar-CH_2], 6.23, 6.32 [s, 2 H, OH], 7.34-7.61 [m, 5 H, Ar-H]; ^{13}C NMR (DMSO-d_6) ppm 4.08 [CH_2, cyclopropyl ring], 6.61 [CH, cyclopropyl ring], 40.01 [C(1, 5)], 53.90 [C(2, 4)], 54.98 [C(6, 8)], 60.09 [Ar-CH_2], 60.80 [CH_2, cyclopropyl ring], 89.63[C(9)], 127.74, 128.53, 129.70, 137.00 [Ar-C]. High resolution mass spectral (FAB) data calcd for $C_{18}H_{27}N_2O_2Br$ m/z (M^+): 303.2071(-Br). Found: 303.2060.

7-Benzyl-3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one Hydrobromide (**34**).

Gaseous HBr was generated in a standard setup with a 250-mL collection flask containing solid KBr. The H_2SO_4 (~15 mL) was added dropwise (~ 1mL/min), and the gas generated was passed through a $CaCl_2$ drying tube. Into a 250-mL Erlenmeyer flask equipped with a magnetic stirrer and an ice bath was bubbled $HBr_{(g)}$ to a chilled solution of 7-benzyl-3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**29a**, 0.250 g, 0.919 mmol) in anhydrous ether (15 mL) over a 15 min period. The mixture was allowed to stir an

additional 15 min at 0-5 °C. A white solid was formed, which was filtered under vaccum, via an aspirator trap and washed with cold ether. The solid was recrystallized (2-propanol/chloroform, 1:1) to give **35** (0.233 g, 72%), mp 152-154 °C. This solid was sensitive to moisture and was not exposed to the atmosphere for more than 5 min. IR (KBr) 3319 (N-H), 3067 (Ar-H), 2982, 2842 (C-H), 1747 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.17 [d, 6 H, CH_3], 1.97 [bs, 2 H, H(1, 5)], 2.81 [d, 2 H, $H(2, 4)_{ax}$], 3.01 [d, 2 H, $H(2, 4)_{eq}$], 3.40-3.56 [m, 5 H, $CH(CH_3)_2$ and ring protons], 3.74 [s, 2 H, $ArCH_2$], 7.37-7.73 [m, 5 H, Ar-H]; ^{13}C NMR (DMSO-d_6) ppm 17.54 [CH_3], 45.16 [C(1, 5)], 50.27 [C(2, 4)], 53.07 [$CH(CH_3)_2$], 57.76 [C(6, 8)], 59.76[$ArCH_2$], 128.87, 129.45, 130.55, 133.14 [Ar-C], 192.85 [C=O]. Anal. Calcd for $C_{17}H_{25}N_2OBr(1H_2O)$: C, 54.99; H, 7.32; N, 7.54. Found: C, 54.70; H, 7.35; N, 7.45.

7-(3,4-Dimethoxybenzyl)-3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one Hydrobromide (**35**).

Gaseous HBr was generated in a standard setup with a 250-mL collection flask containing solid KBr. The H_2SO_4 (~15 mL) was added dropwise (~ 1mL/min), and the gas generated was passed through a $CaCl_2$ drying tube. Into a 125-mL, Erlenmeyer flask equipped with a magnetic stirrer and an ice bath was bubbled $HBr_{(g)}$ to a chilled solution of 7-(3,4-dimethoxybenzyl)-3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**29b**, 0.250 g, 0.75 mmol) in anhydrous ether (15 mL) over a 15-min period. The mixture was allowed to stir an additional 15 min at 0-5 °C. A white precipitate formed and was filtered under vaccum, via an aspirator trap, and washed with cold ether. The solid was recrystallized (2-propanol/chloroform, 1:1) to give **35** (0.198 g, 64%), mp 179-180.5 °C. The solid was hygroscopic and was not exposed to moisture for more than 5 min. IR (KBr) 3326 (N-H), 3039 (Ar-H), 2973, 2865 (C-H), 1735 (C=O), 1620, 1605 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.14 [d, 6 H, CH_3], 1.96 [s, 2 H, H(1, 5)], 2.86 [d, 2 H, $H(2, 4)_{ax}$], 3.05 [d, 2 H, $H(6, 8)_{ax}$], 3.24 [m, 2 H, $H(2,4)_{eq}$], 3.41-3.54 [m, 3 H, $CH(CH_3)_2$ and

$H(6,8)_{eq}$], 3.56 [s, 2 H, $ArCH_2$], 3.75 [s, 3 H, OCH_3], 3.76 [s, 3 H, OCH_3], 6.92-7.22 [m, 3 H, Ar-H]; ^{13}C NMR (DMSO-d_6) ppm 17.17 [CH_3], 45.16 [C(1, 5)], 50.54 [C(2, 4)], 53.55 [C(6,8)], 55.85, 56.46 [OCH_3], 57.76 [$CH(CH_3)_2$], 59.76[$ArCH_2$], 110.92, 113.90, 122.88, 126.81, 149.12, 149.37 [Ar-C], 206.62 [C=O]. High resolution mass spectral (FAB) data calcd for $C_{19}H_{29}N_2O_3Br$ m/z (M^+): 333.2179 (-Br). Found: 333.2196.

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one Hydrobromide (**36**).

Gaseous HBr was generated in a standard setup with a 250-mL collection flask containing solid KBr. The H_2SO_4 (~10 mL) was added dropwise (~ 1mL/min), and the gas generated was passed through a $CaCl_2$ drying tube. Into a 125-mL Erlenmeyer flask equipped with a magnetic stirrer and an ice bath was bubbled $HBr_{(g)}$ to a chilled solution of 3,7-diisopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one **29c** (0.150 g, 0.660 mmol) in anhydrous ether (10 mL) over a 15 min period. A white solid was formed, and the mixture was allowed to stir an additional 15 min at 0-5 °C. The supernatant ether layer was discarded and a fresh 25 mL of anhydrous ether was added. The reaction mixture was stirred for 15 min. This process was repeated 2 times to remove any unreacted **29c**. Residual ether was then removed by rotary evaporator to give **36** as a white solid (0.095 g, 64%). The mp of **36** could not be taken because of its hygroscopic nature. IR (KBr) 3403 (N-H), 2979 (C-H), 1749 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.14 [d, 12 H, CH_3], 1.42-1.48 [m, 2 H, H(1, 5)], 3.16-3.23 [m, 4 H, $H(2,4,6,8)_{ax}$], 3.25-3.48 [m, 5 H, H(2, $4,6,8)_{eq}$ and $CH(CH_3)_2$]; ^{13}C NMR (DMSO-d_6) ppm 16.69, 17.02 [CH_3], 37.57 [C(1, 5)], 53.45 [C(2, 4)], 54.48 [C(6, 8)], 65.40 [$CH(CH_3)_2$]. High resolution mass spectral (FAB) data calcd for $C_{13}H_{25}N_2OBr$ m/z (M^+): 225.1966 (-Br). Found: 225.1957.

7-Benzyl-3-cyclopropylmethyl-3,7-diazabicyclo[3.3.1]nonan-9-one Hydrobromide (**37**).

Gaseous HBr was generated in a standard setup with a 250-mL collection flask containing solid KBr. The H_2SO_4 (~10 mL) was added dropwise (~ 1mL/min), and the

gas generated was passed through a $CaCl_2$ drying tube. Into a 125-mL Erlenmeyer flask equipped with a magnetic stirrer and an ice bath was bubbled $HBr_{(g)}$ to a chilled solution of 7-benzyl-3-cyclopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**29d**, 0.150 g, 0.528 mmol) in anhydrous ether (10 mL) over a 15 min period. A white solid was formed, and was allowed to stir an additional 15 min at 0-5 °C. The supernatant ether layer was discarded and a fresh 25 mL anhydrous ether was added. The reaction mixture was stirred for 15 min. This process was repeated twice to remove any unreacted **29d**. Residual ether was then removed by rotary evaporator to give **37** as a white solid (0.117 g, 64%). The mp of **37** could not be taken because of its hygroscopic nature. IR (KBr) 3240 (O-H), 3094 (Ar-H), 2933, 2833 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.53 [m, 2 H, $(CH_2)_{ax}$, cyclopropyl ring], 0.78 [m, 2 H, $(CH_2)_{eq}$, cyclopropyl ring], 1.34 [m, 1 H, (CH)-cyclopropyl ring], 3.03 [d, 2 H, CH_2-cyclopropyl ring], 3.11 [d, 2 H, $H(6, 8)_{ax}$], 3.52 [d, 2 H, $H(6, 8)_{eq}$], 3.72 [d, 2 H, $H(2, 4)_{ax}$], 3.88 [d, 2 H, $H(2, 4)_{eq}$], 4.42 [s, 2 H, CH_2-Ar], 6.23, 6.32 [s, 2 H, OH], 7.43-7.81 [m, 5 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 4.68 [CH_2, cyclopropyl ring], 5.25 [CH, cyclopropyl ring], 36.67 [C(1, 5)], 52.01 [C(6, 8)], 52.24 [C(2, 4)], 62.84 [Ar-CH_2], 63.85 [NCH_2-cyclopropyl ring], 87.90 [C(9)], 127.09, 128.89, 130.15, 132.09 [Ar-C].

3-Isopropyl-3,7-diazabicyclo-[3.3.1]nonan-9-one (**39**).

A 200-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with a N_2 inlet, and two glass stoppers. The flask was initially charged with 10% Pd/C (0.551 g, 30 mg/mmol of the ketone) and flushed with N_2 for 10 min. Then the solvent methanol (40 mL) was slowly poured over the catalyst, and the mixture was stirred. Extreme caution should be taken while pouring the methanol over Pd/C since the catalyst is pyroforic. The ammonium formate (4.053 g, 64.33 mmol) was added followed by the ketone (**29a**, 5.00 g, 18.38 mmol) in 40 mL of methanol, and the mixture was boiled for 1 h. The mixture was cooled to RT, filtered

over a celite pad in a fritted funnel, and washed with copious amounts of methanol. Methanol was removed by rotary evaporator. The gummy material obtained was redissolved in water (80 mL), and the pH was adjusted to ~12 using 10% NaOH. Combined extracts (CCl_4, 4 x 40 ml) of the aqueous layer were dried (Na_2SO_4, 1 h), filtered, and concentrated (rotary evaporator then vaccum pump, 10 min, RT/0.2 mm Hg) to give a yellow oil **39** (2.234 g, 73%) which was used without further purification for metal complexation. IR (film) 3326(N-H), 2975, 2919, 2814(C-H), 1733(C=O) cm^{-1}.

[3-Isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one]copper(II) Chloride (**40a**).

A 100-mL beaker was equipped with a magnetic stirrer and a heating mantle. A solution of copper (II) chloride (0.258 g, 1.9 mmol) in 10 mL of absolute ethanol was added dropwise over a period of 10 min to a hot, stirred solution of 3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**39**, 0.350 g, 1.92 mmol) in 10 mL of absolute ethanol. The mixture was heated gently until a dark green solid had precipitated. After cooling, the solid was filtered under vaccum, washed successively with ethanol and dichloromethane. The solid was purified by crushing in hot absolute ethanol, methanol anhydrous ether until the filterate was colorless, and dried under vaccum in an Abderhalden overnight at 80 °C to give **40a** (0.424 g, 70%), mp 207-208 °C. IR (KBr) 3410 (N-H), 2975(C-H), 1720(C=O) cm^{-1} Anal. Calcd for $C_{10}H_{18}N_2OCuCl_2$(monodentate·3.5 H_2O): C, 31.61; H, 6.58. Found: C, 31.77; H, 6.43.

[3-Isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one]nickel(II) Perchlorate (**40b**).

A 100-mL beaker was equipped with a magnetic stirrer and a heating mantle. A solution of nickel (II) perchlorate hexahydrate (0.490 g, 1.90 mmol) in 15 mL of absolute ethanol was added dropwise over a period of 5 min to a hot, stirred solution of 3-methyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**39**, 0.350 g, 1.90 mmol) in 15 mL of absolute ethanol. The mixture was heated for additional 10 min. Upon cooling to 0 °C, a light

yellow solid precipitated, which was filtered under vaccum, via an aspirator trap, and washed with ethanol. This solid was then crushed successively in cold ethanol and anhydrous ether and was then filtered under vaccum, via an aspirator trap, and dried under vaccum in an Abderhalden overnight at 80 °C to give **40b** (0.685 g., 82%), mp 263-265 °C (dec). IR (KBr) 3621 (O-H), 3310 (N-H), 2975, 2842 (C-H), 1635 (C=O) cm^{-1}.

[3-Isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one]magnesium(II) Perchlorate (**40c**).

A 100-mL beaker was equipped with a magnetic stirrer and a heating mantle. A solution of magnesium (II) perchlorate (0.424 g, 1.90 mmol) in 15 mL absolute ethanol was added dropwise over a period of 10 min to a hot, stirred solution of 3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**39**, 0.350 g, 1.90 mmol) in 15 mL of absolute ethanol. The mixture was gently heated for 10 min. Upon cooling to 0 °C, a colorless solid precipitated, which was filtered under vaccum, via an aspirator trap, and washed with ethanol. This solid was then crushed successively in cold absolute ethanol and anhydrous ether and was then filtered under vaccum, via an aspirator trap, and dried under vaccum in an Abderhalden overnight at 80 °C to give **40c** (0.485 g., 63%), mp 292-293 °C (dec). IR (KBr) 3596 (O-H), 3315 (N-H), 2986, 2841 (C-H), 1640 (C=O) cm^{-1}.

[3-Isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one]cobalt(II) Bromide (**40d**).

A 100-mL beaker was equipped with a magnetic stirrer and a heating mantle. A solution of cobalt bromide (0.230 g, 1.90 mmol) in 15 mL absolute ethanol was added dropwise over a period of 10 min to a hot, stirred solution of 3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**39**, 0.350 g, 1.90 mmol) in 15 mL of absolute ethanol. The mixture was gently heated for 10 min. Upon cooling to 0 °C, a purple color solid precipitated, which was filtered under vaccum, via an aspirator trap, and washed with ethanol. This solid was then crushed successively in cold absolute ethanol and anhydrous ether and was then filtered under vaccum, via an aspirator trap, and dried under vaccum

in an Abderhalden overnight at 80 °C to give **40d** (0.426 g., 56%), mp 261-262 °C. IR (KBr) 3596 (O-H), 3315 (N-H), 2986, 2841 (C-H), 1640 (C=O) cm^{-1}.

3,5-Diphenyl-2,6-*bis* (2-pyridyl)-4-piperidinone (**41**).

A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with a N_2 inlet and two glass stoppers. A mixture of 1,3-diphenylacetone (8.0 g, 38 mmol), pyridine-2-carboxaldehyde (8.152 g, 76.1 mmol) and liq NH_3 (10%, 30 mL) in 60 mL of absolute ethanol was introduced in one portion. The mixture was boiled for 24 h. Upon cooling to RT, the solution was concentrated (rotary evaporator) to give a light brown solid. To this was added 75 mL water, which resulted in the formation of a brown suspension. This suspension was extracted with ether (4 x 30 mL), and the combined extracts were dried (Na_2SO_4, overnight), filtered, and concentrated (rotary evaporator) to give a white solid. This solid was recrystallized (methanol, 30 mL) to give **41** (2.930 g, 47%), mp 220-221 °C. IR (KBr) 3316.8 (N-H), 3028.6 (Ar-H), 2904.5, 2875 (C-H), 1708.2 (C=O), 1434.5 (C=C), 750, 701 (C-H out of plane, monosubstituted) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.84 [s, 1 H, N-H], 4.39 [d, 2 H, H(1, 6)], 4.56 [d, 2 H, H(3, 5)], 6.70 [d, 2 H, Ar-H], 7.01-7.34 [m, 13 H, Ar-H, Py-H], 8.61 [d, 2 H, Py-H]; ^{13}C NMR ($DCCl_3$) ppm 64.18 [C(2, 6)], 68.60 [C(3, 5)], 122.22, 122.96, 126.42, 127.63, 129.34, 134.86, 135.75, 149.37, 158.04 [Ar-C, Py-C], 205.90 [C=O]. Anal. Calcd for $C_{27}H_{23}N_3O$: C, 79.97; H, 5.71; N, 10.36. Found: C, 79.58; H, 6.07; N, 10.30

[3,5-Diphenyl-2,6-*bis*(2-pyridyl)-4-piperidinonelcopper(II) Chloride (**42**).

A 50-mL beaker was equipped with a magnetic stirrer and a heating mantle. A solution of copper (II) chloride (0.049 g, 0.37 mmol) in 10 mL of absolute ethanol was added dropwise over a period of 10 min to a hot, stirred solution of 3,5-diphenyl-2,6-*bis*-(2-pyridyl)-4-piperidinone (**41**, 0.150 g, 0.37 mmol) in 10 mL of absolute ethanol. The

mixture was heated gently until light blue crystals precipitated. After cooling, the solid was filtered under vacuum, via an aspirator trap, and washed successively with ethanol and dichloromethane. The solid was then crushed successively in cold absolute ethanol and anhydrous ether, filtered under vacuum, via an aspirator trap, and dried under vaccum in an Abderhalden overnight at 80 °C to give **42** (0.092 g, 46.2%), mp 222-223 °C. IR (KBr) 3151 (N-H), 3031 (Ar-H), 2912, 2856 (C-H), 1726 (C=O), 1607 (C=N) cm^{-1}.

Attempted Preparation of 7-Benzyl-2,4-*bis*(2-pyridyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (**45**).

Method A. A 100-mL, three-necked, round bottomed flask was equipped with a magnetic stirrer, a heating mantle, a 50 mL addition funnel, a condenser with a N_2 inlet, and a glass stopper. A mixture of benzylamine (0.395 g, 3.69 mmol), HCl (37%, 1.86 g, 3.69 mmol), glacial acetic acid (0.221 g, 3.69 mmol), and paraformaldehyde (0.443 g, 14.79 mmol) in deoxygenated methanol (30 mL) was stirred and boiled for 15 min under N_2. A solution of 3,5-diphenyl-2,6-*bis*(2-pyridyl)-4-piperidinone (**41,** 1.5 g, 3.69 mmol) in methanol (30 mL) was then added dropwise to the mixture over a period of 15 min through the addition funnel, followed by stirring at reflux for an additional 24 h. Concentration (rotary evaporator) of the solution gave an oil which was redissolved in water (50 mL). An ether extract (40 mL) of this acidic solution was discarded. Basification (pH~13) of the water layer was achieved by the addition of 10% NaOH, resulting in the formation of milky suspension which was extracted with diethyl ether (4 x 40 mL). Combined extracts were dried (Na_2SO_4, 3 h), filtered, and concentrated (rotary evaporator) to give a viscous red oil. The ^1H NMR and ^{13}C NMR spectrum showed peaks which indicated the presence of only the starting materials.

Method B. A 100-mL, three-necked, round bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with a N_2 inlet, and two glass stoppers. The flask was charged with ammonium acetate (2.31 g, 30.0 mmol) and methanol (15

mL), and the flask was flushed with N_2. The slurry was boiled with stirring until all the ammonium acetate dissolved, and then the solution was cooled to RT. A solution of pyridine-2-carboxaldehyde (**43**, 6.426 g, 60 mmol), *N*-benzyl-4-piperidinone (**44**, 5.677 g, 30 mmol), and methanol (30 mL) was added in one portion. The resulting solution was boiled with stirring for an additional 24 h. Upon cooling to RT, the solution was concentrated (rotary evaporator) to give a dark reddish brown oil which was dissolved in water (25 mL). The ether extract of this water layer was discarded. Basification (pH~13) of the water layer was achieved by 10% NaOH, resulting in the formation of a reddish brown suspension. This was extracted with ether (4 x 30 mL), and the combined extracts were dried (Na_2SO_4, 5 h), filtered, and concentrated (rotary evaporator) to give a dark brown oil. The ^1H and ^{13}C NMR spectrum of this oil exhibited a very complex peak pattern, probably indicating that the oil was still impure. This oil was therefore digested with Skelly B (2x100 mL, 20 min), and the supernatant extracts were concentrated (rotary evaporator) to give a brown oil. The IR, ^1H and ^{13}C NMR spectrum showed peaks which indicated the presence of only the starting materials.

Method C. A 100-mL, three-necked, round bottomed flask was equipped with a magnetic stirrer, a heating mantle, a 50 mL addition funnel, a condenser with a N_2 inlet, and a glass stopper. A mixture of ammonium acetate (2.310 g, 30.0 mmol), HCl (37%, 2.960 g, 30.0 mmol), glacial acetic acid (0.900 g, 15 mmol), and pyridine-2-carboxaldehyde (**43**, 6.426 g, 60 mmol) in deoxygenated methanol (30 mL) was stirred and boiled for 15 min under N_2. A solution of *N*-benzyl-4-piperidinone (**44**, 5.677 g, 30 mmol) in methanol (30 mL) was then added dropwise to the mixture over a period of 20 min, followed by stirring at reflux for an additional 24 h. Concentration (rotary evaporator) of the solution gave a dark brown oil which was redissolved in water (40 mL). An ether extract (30 mL) of this acidic solution was discarded. Basification (pH~13) of the water layer was achieved by the addition of 10% NaOH, resulting in the formation of milky suspension which was extracted with ether (4 x 40 mL). Combined

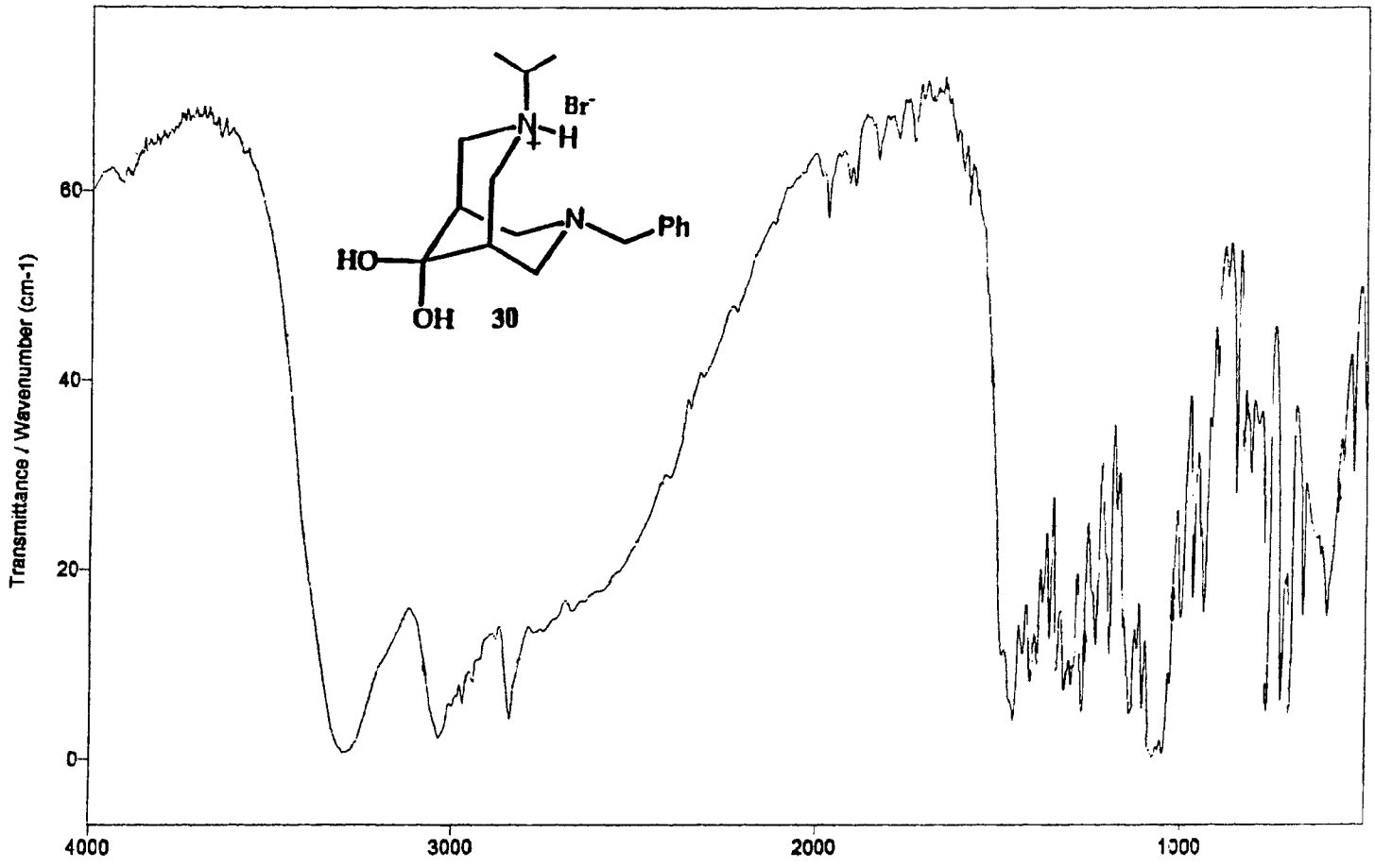
extracts were dried (Na_2SO_4, 5 h), filtered, and concentrated (rotary evaporator) to give a viscous brown oil. The ^1H NMR and ^{13}C NMR analyses of this oil showed a complex peak pattern which indicated that the oil was still impure. The oil was then digested in skelly B (75 mL, 20 min), and the supernatent extracts were concentrated (rotary evaporator) to give a light brown oil. ^1H NMR and ^{13}C NMR analyses indicated the presence of only the starting materials.

Attempted Preparation 7-Benzyl-3-isopropyl-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**46**).

A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with a N_2 inlet, and two glass stoppers. A mixture of benzylamine(2.92 g, 13.651 mmol), glacial acetic acid (0.819 g, 13.651 mmol), HCl (0.498 g, 6.825 mmol), and paraformaldehyde (1.638 g, 54.604 mmol) in absolute ethanol (30 mL) was added to the system and brought to gentle reflux with stirring under N_2 over 15 min. A hot solution of *N*-isopropyl-3,5-diphenyl-4-piperidinone (**47**) in absolute ethanol (30 mL) was added immediately and the resulting solution was boiled for 24 h. Upon cooling to RT, a white solid was obtained which was filtered under vaccum and washed with copious amounts of absolute ethanol. The mother liquor was concentrated on a rotary evaporator and cooled at -10 °C overnight. No additional solid was formed. The original solid was recrystallized from methanol (25 mL) to give a new white solid (3.130 g, 60.3%), which was identified as recovered starting material **47**, mp 179-180 °C. Although this compound had been prepared in our Laboratory by previous students, spectral data had not been recorded previously and is hereby included for the sake of completeness. IR (KBr) cm^{-1} 3060 (Ar-H), 2971, 2842 (C-H), 1720 (C=O), 1440 (C=C), 762, 709 (C-H, out of plane monosubstituted); ^1H NMR (DMSO-d_6) δ 1.12 [d, 6 H, CH_3], 3.02 [m, C-H, isopropyl], 3.18 [d, 4 H, ring proton], 3.52 [d, 4 H, ring proton], 3.54 [s, 2 H, Ar-CH_2], 7.20-7.34 [m, 15 H, Ar-H]; ^{13}C NMR (DMSO-d_6) ppm 18.25

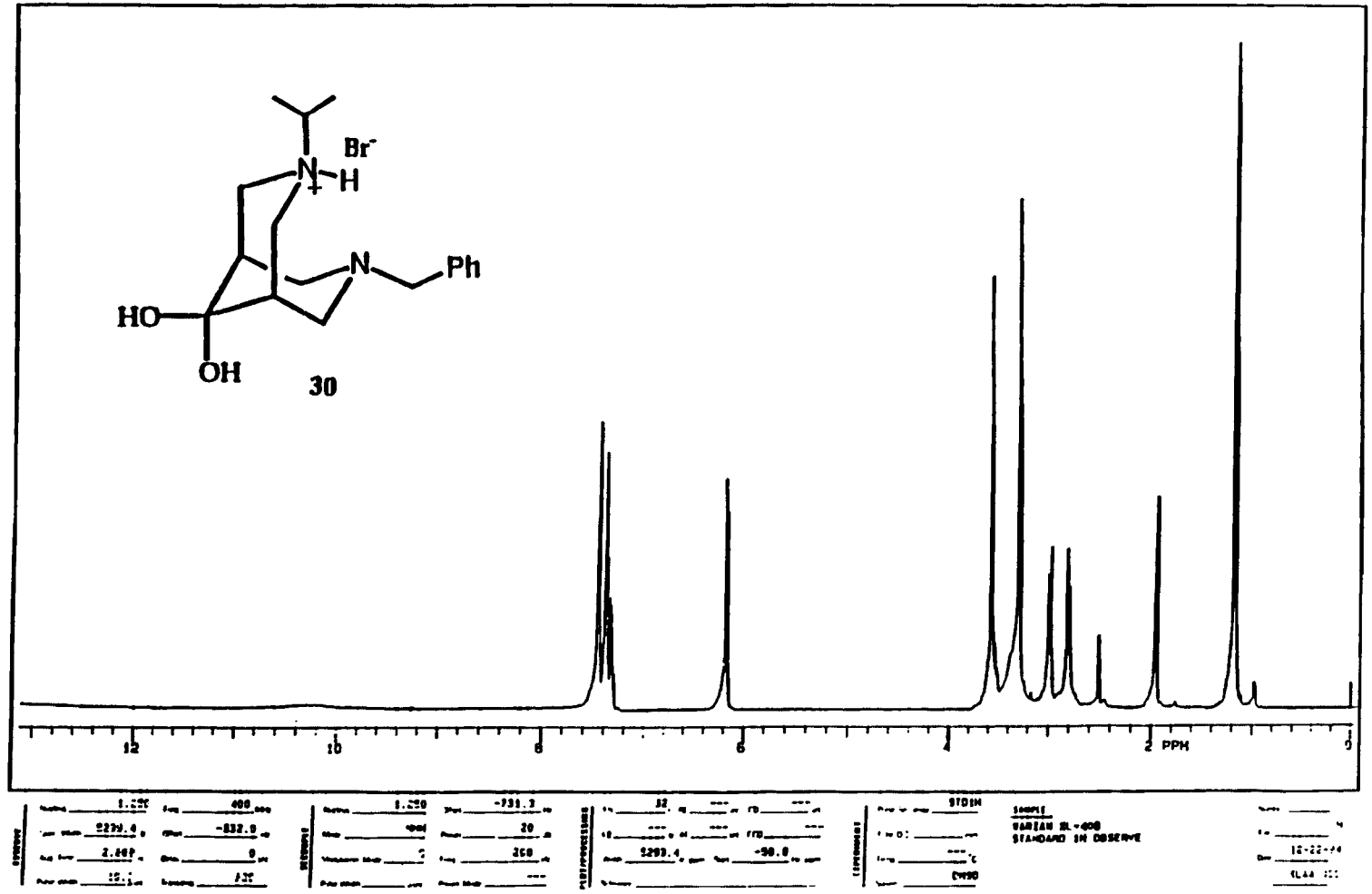
[CH_3], 46.93 [C(1, 5)], 53.41 [$CH(CH_3)_2$], 53.71 [C(2, 4)], 58.07 [C(6, 8)], 61.25 [Ar-CH_2], 125.42, 125.77, 126.03, 127.04, 127.54, 128.61, 128.82, 143.73 [Ar-C], 211.69 [C=O].

Plate I



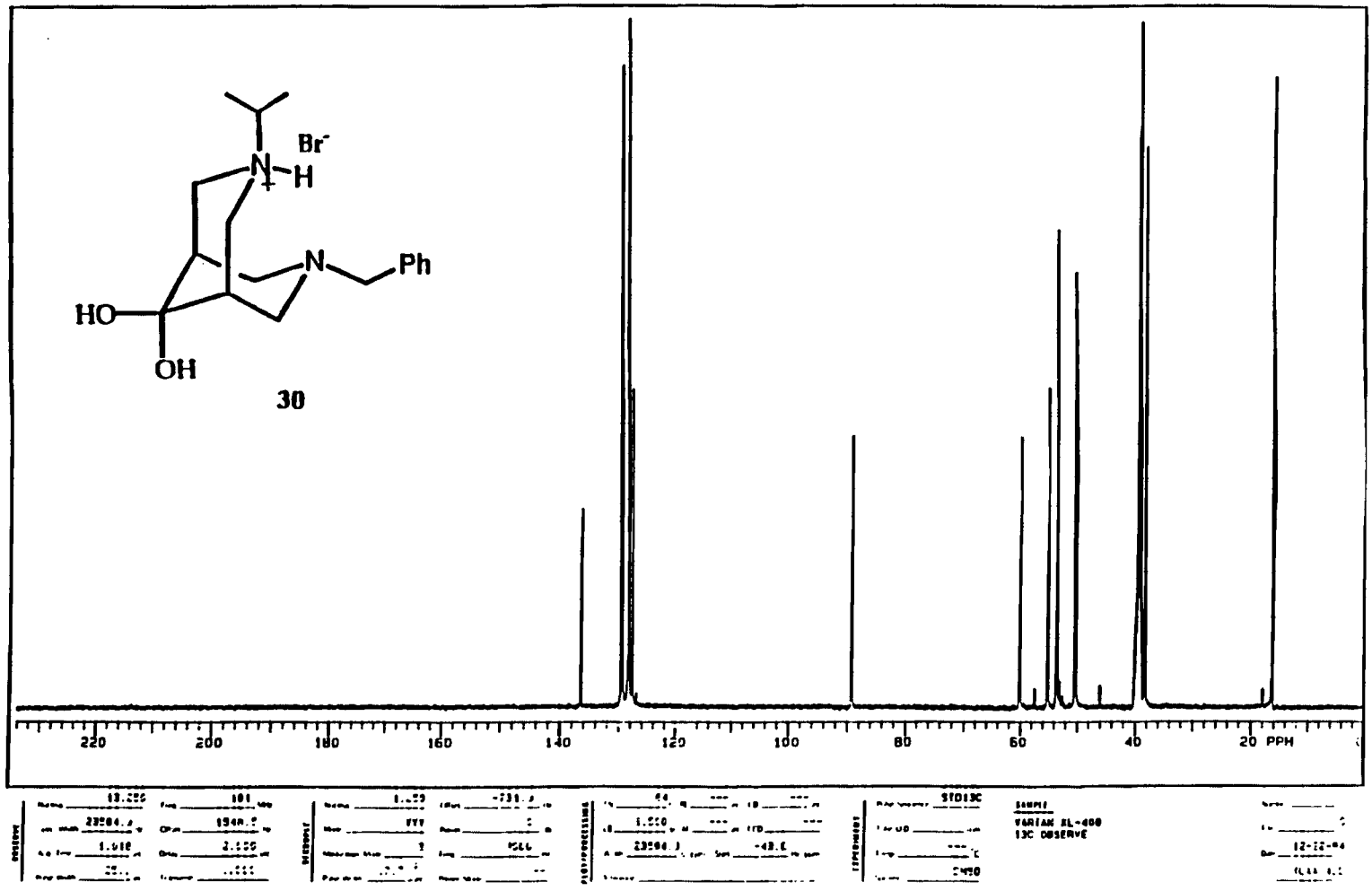
IR Spectrum of **30**

Plate II



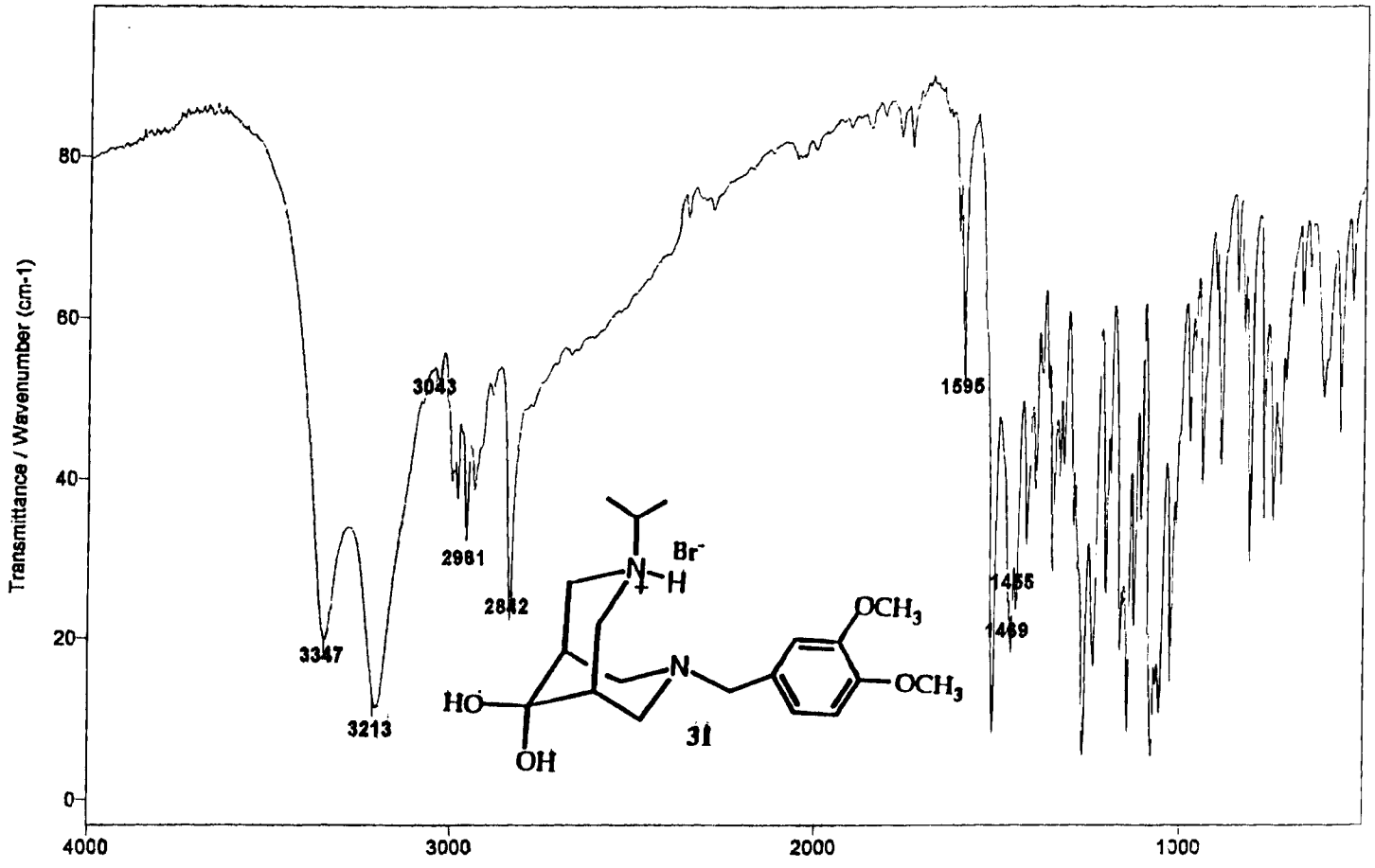
^{1}H NMR Spectrum of **30**

Plate III



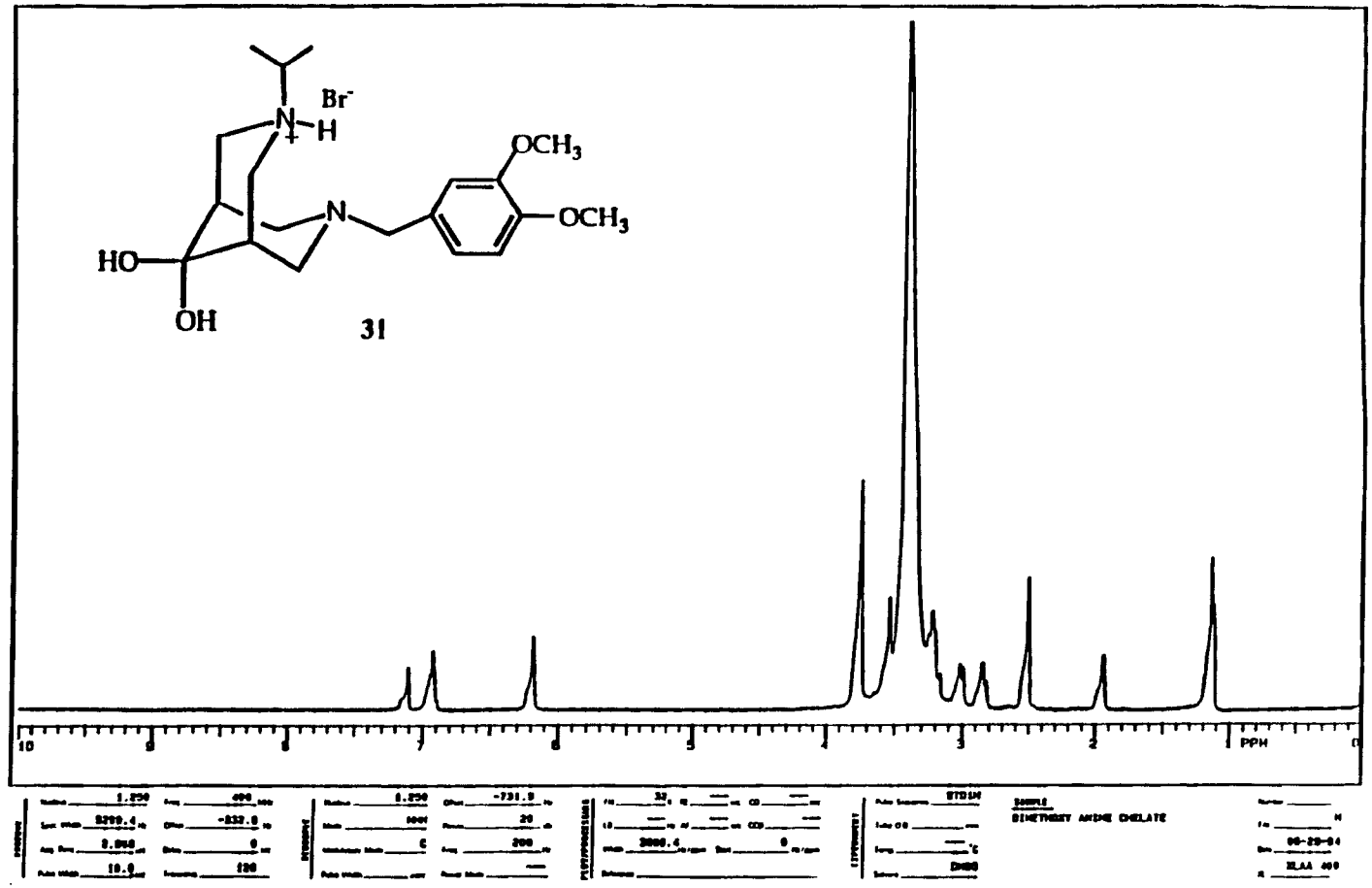
^{13}C NMR Spectrum of **30**

Plate IV

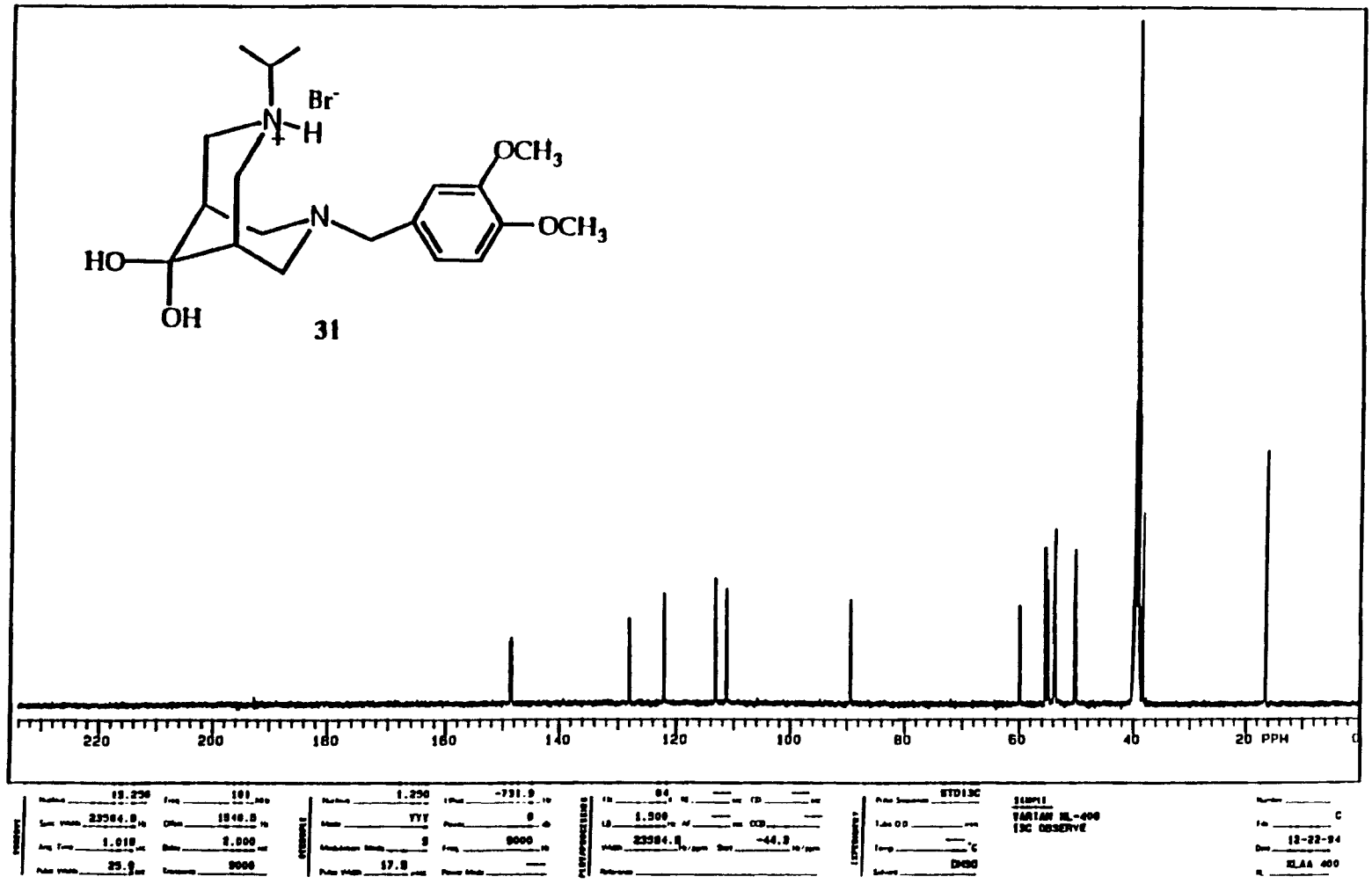


IR Spectrum of **31**

Plate V

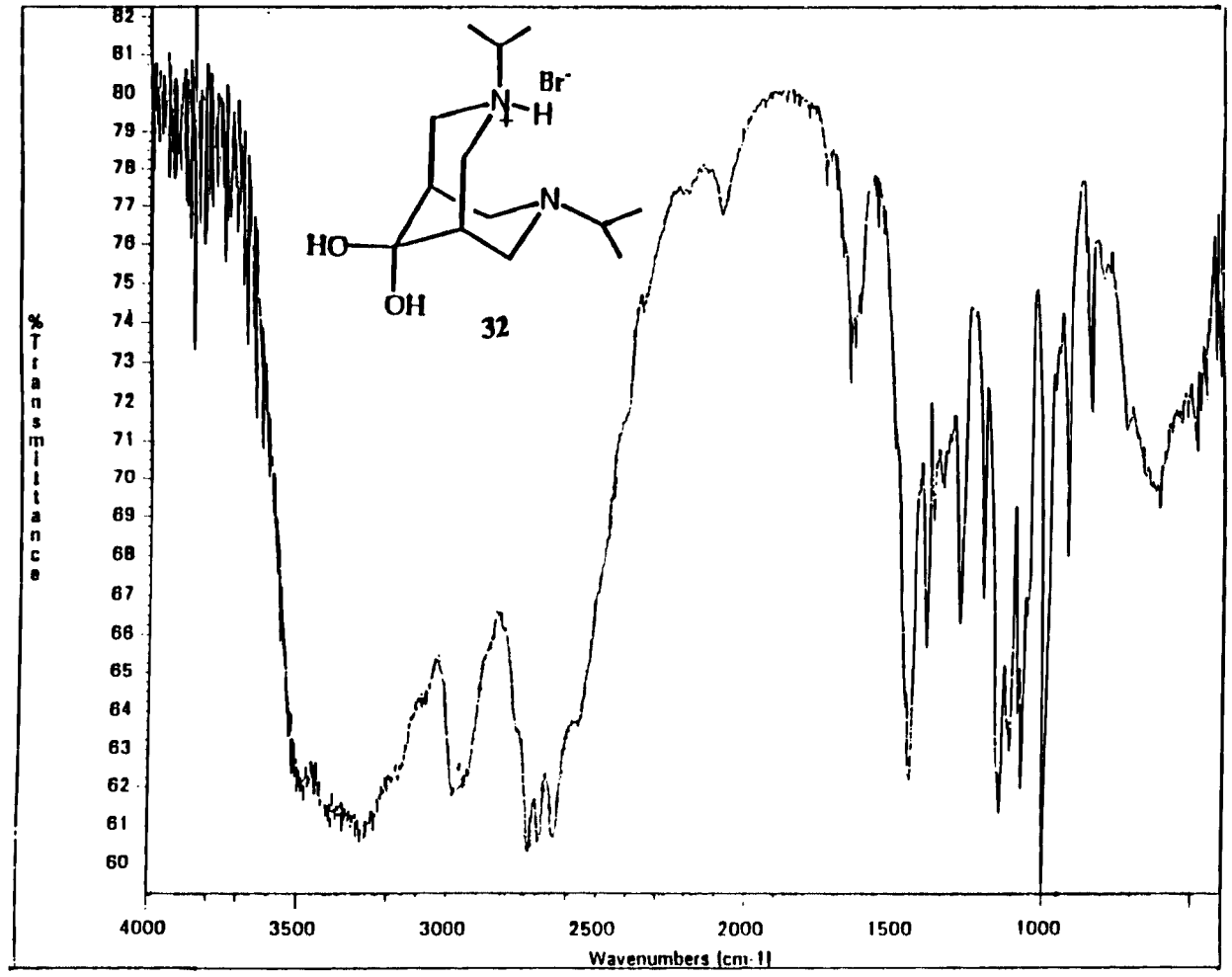


^{1}H NMR Spectrum of **31**



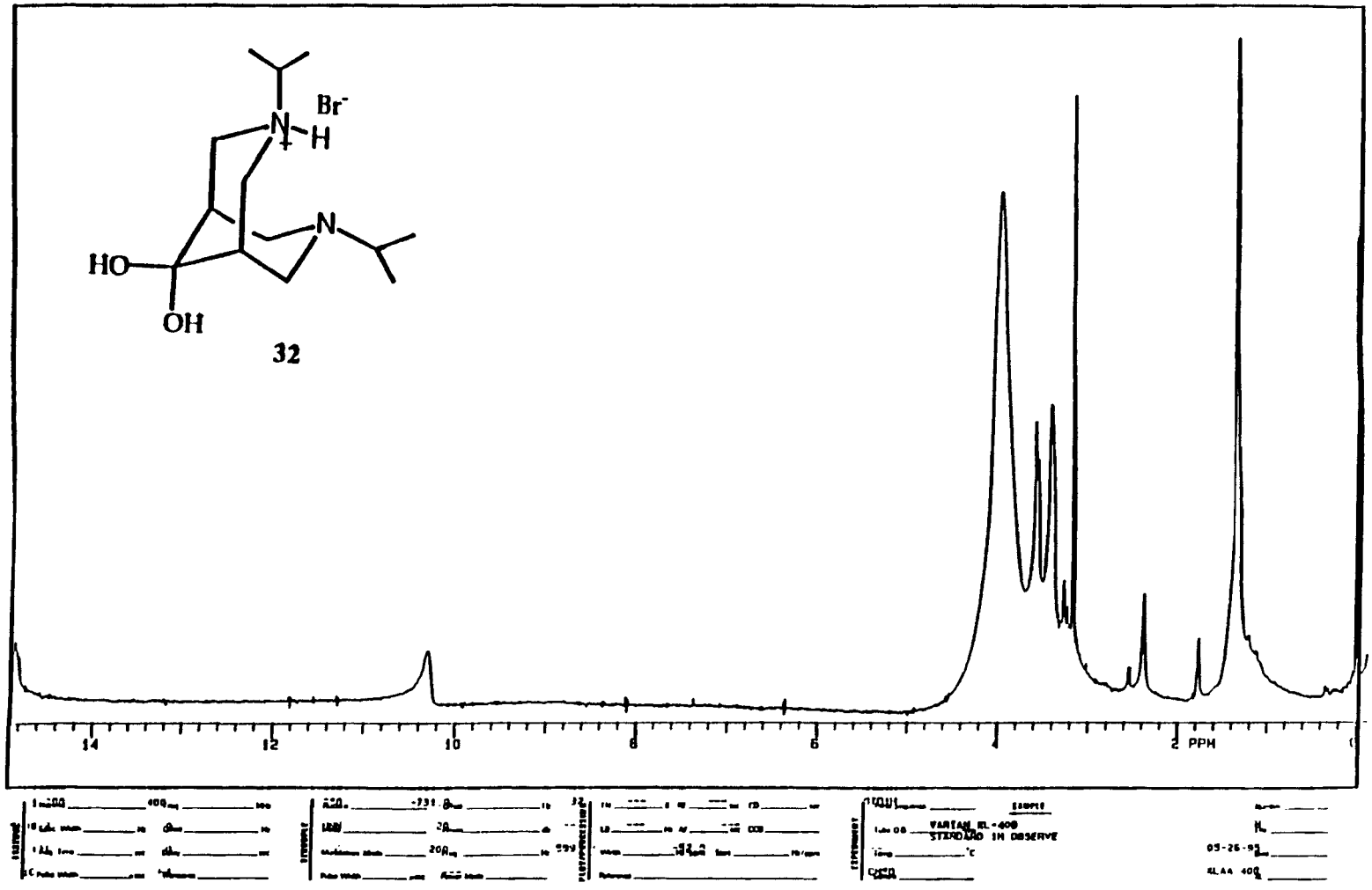
^{13}C NMR Spectrum of **31**

Plate VII



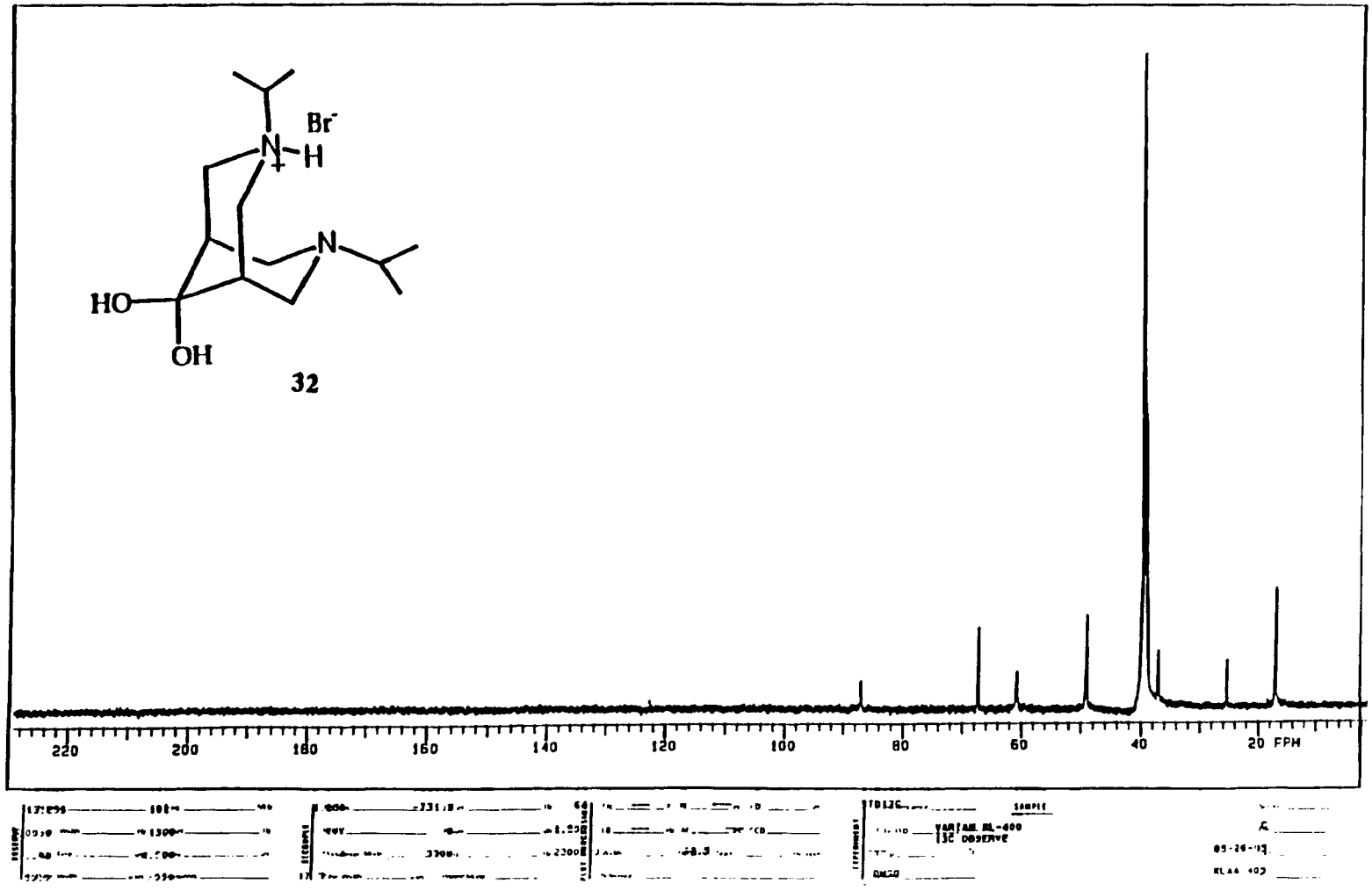
IR Spectrum of **32**

Plate VIII



^{1}H NMR Spectrum of **32**

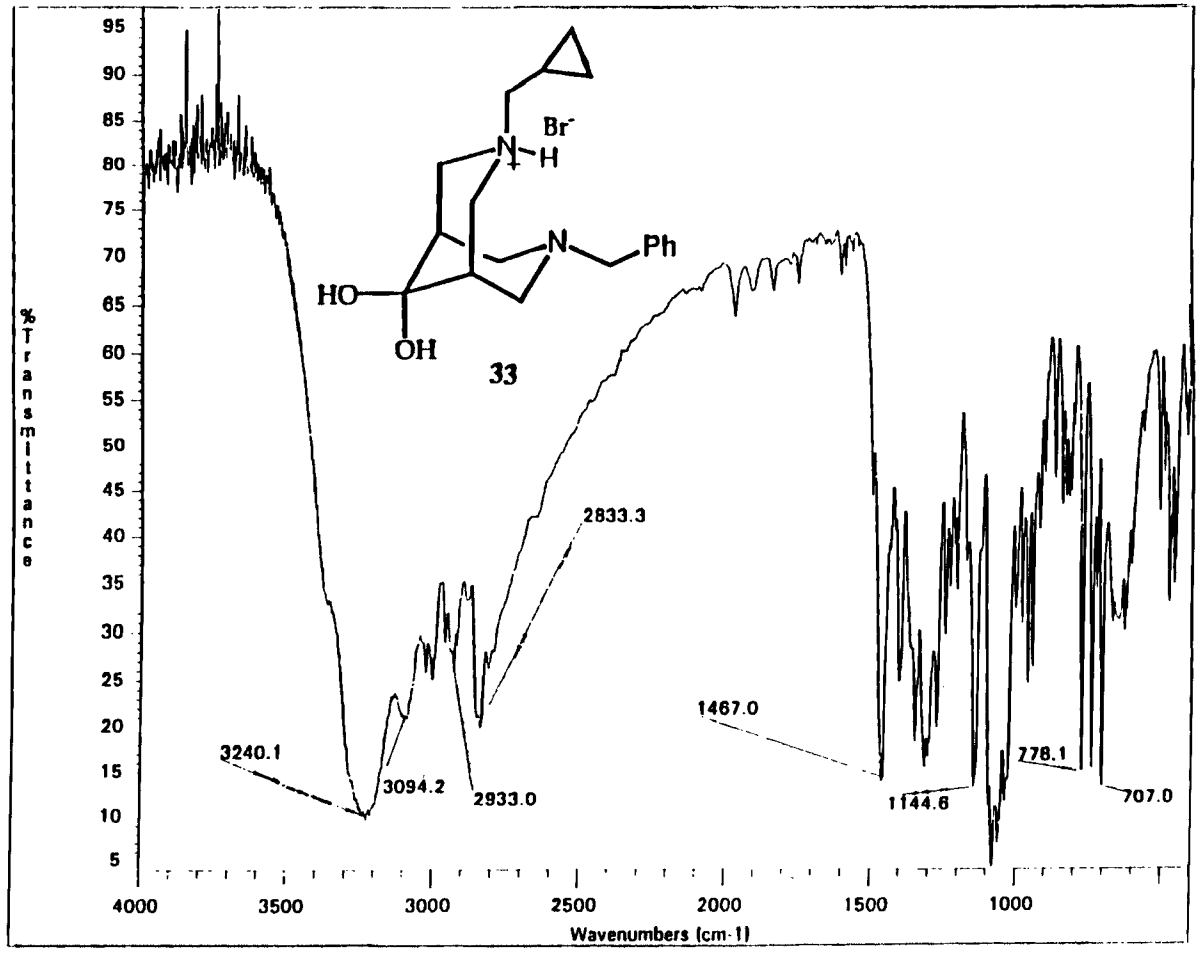
Plate IX



32

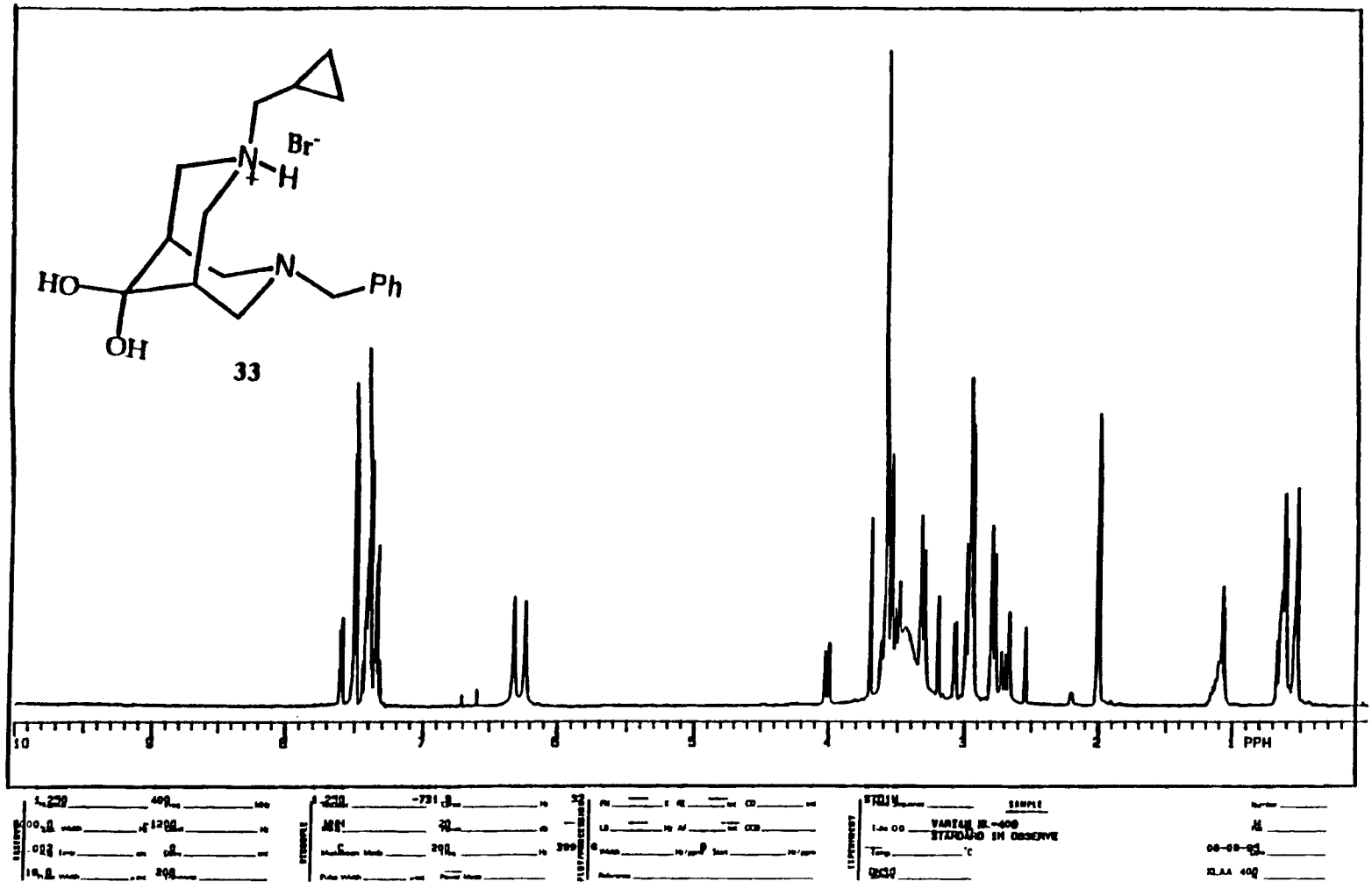
^{13}C NMR Spectrum of **32**

Plate X



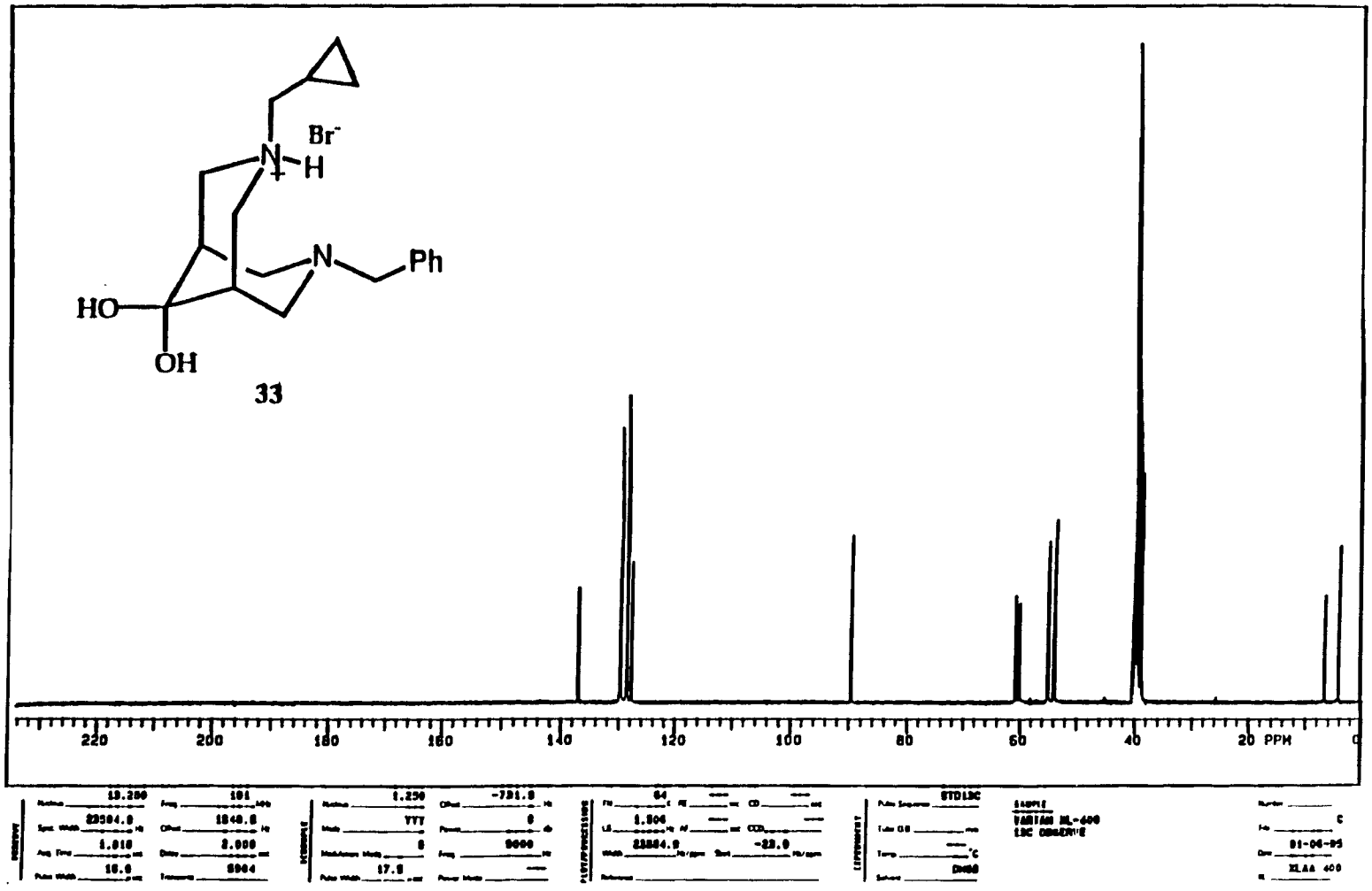
IR Spectrum of 33

Plate XI



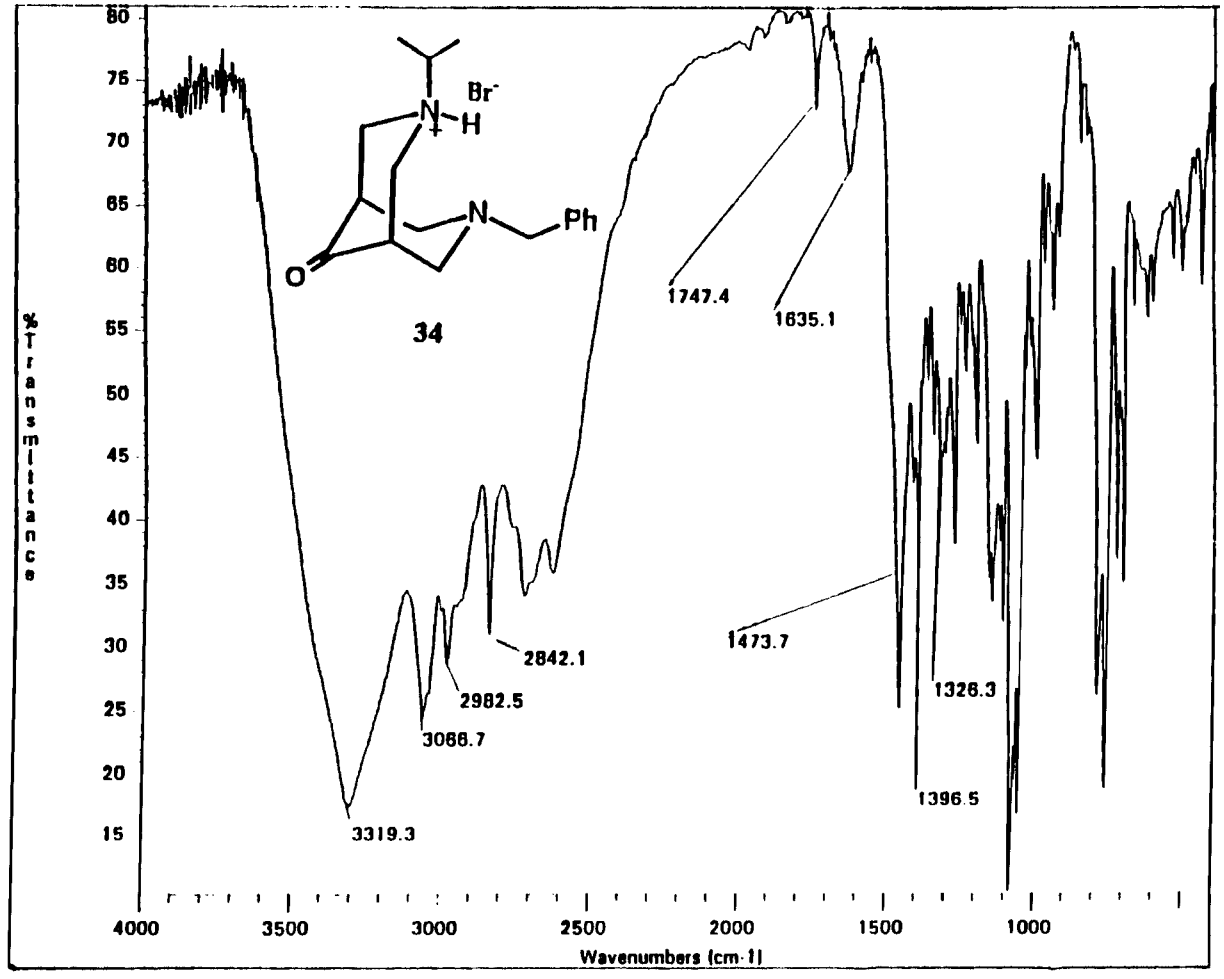
^{1}H NMR Spectrum of 33

Plate XII



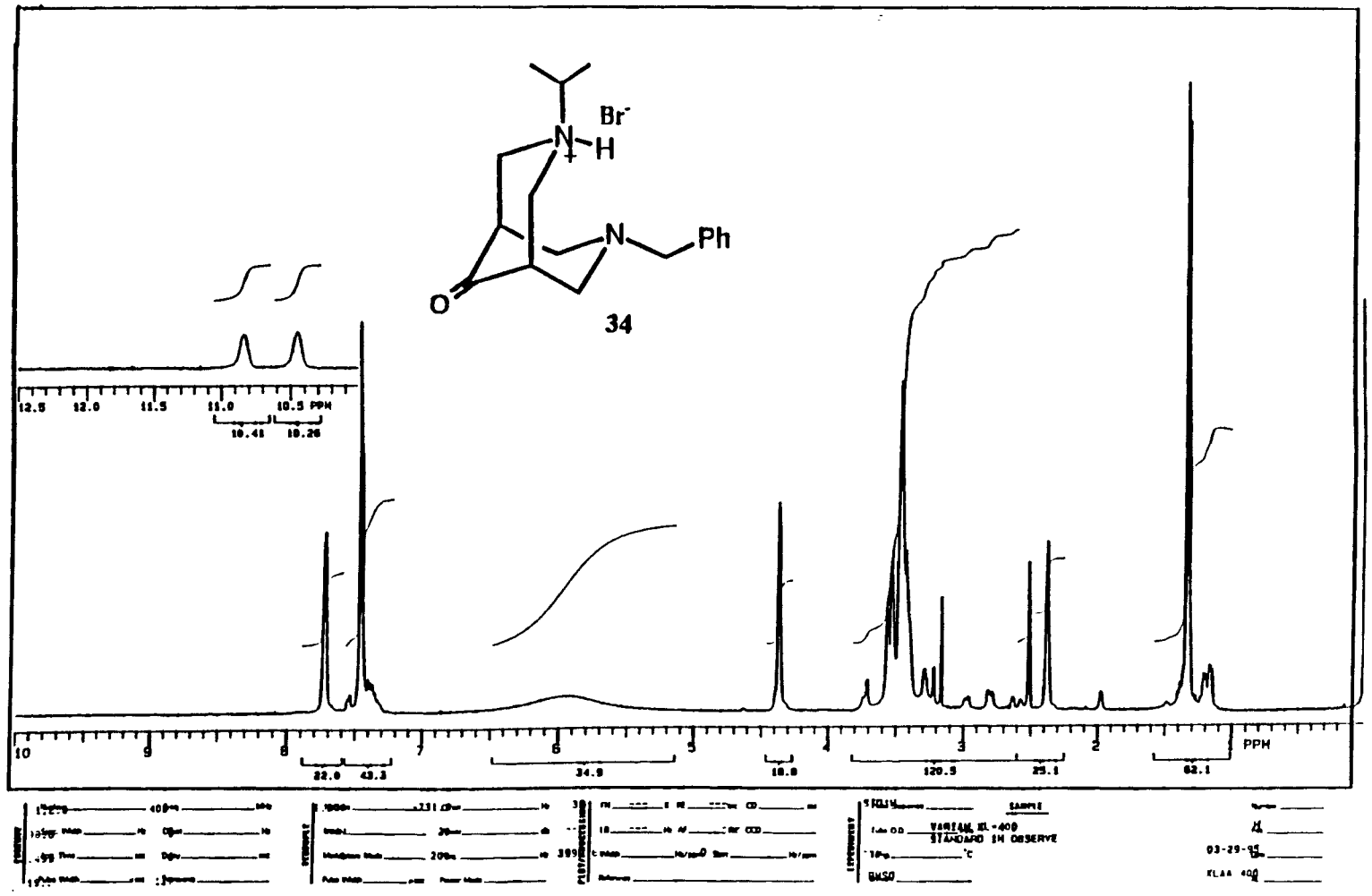
^{13}C NMR Spectrum of **33**

Plate XIII



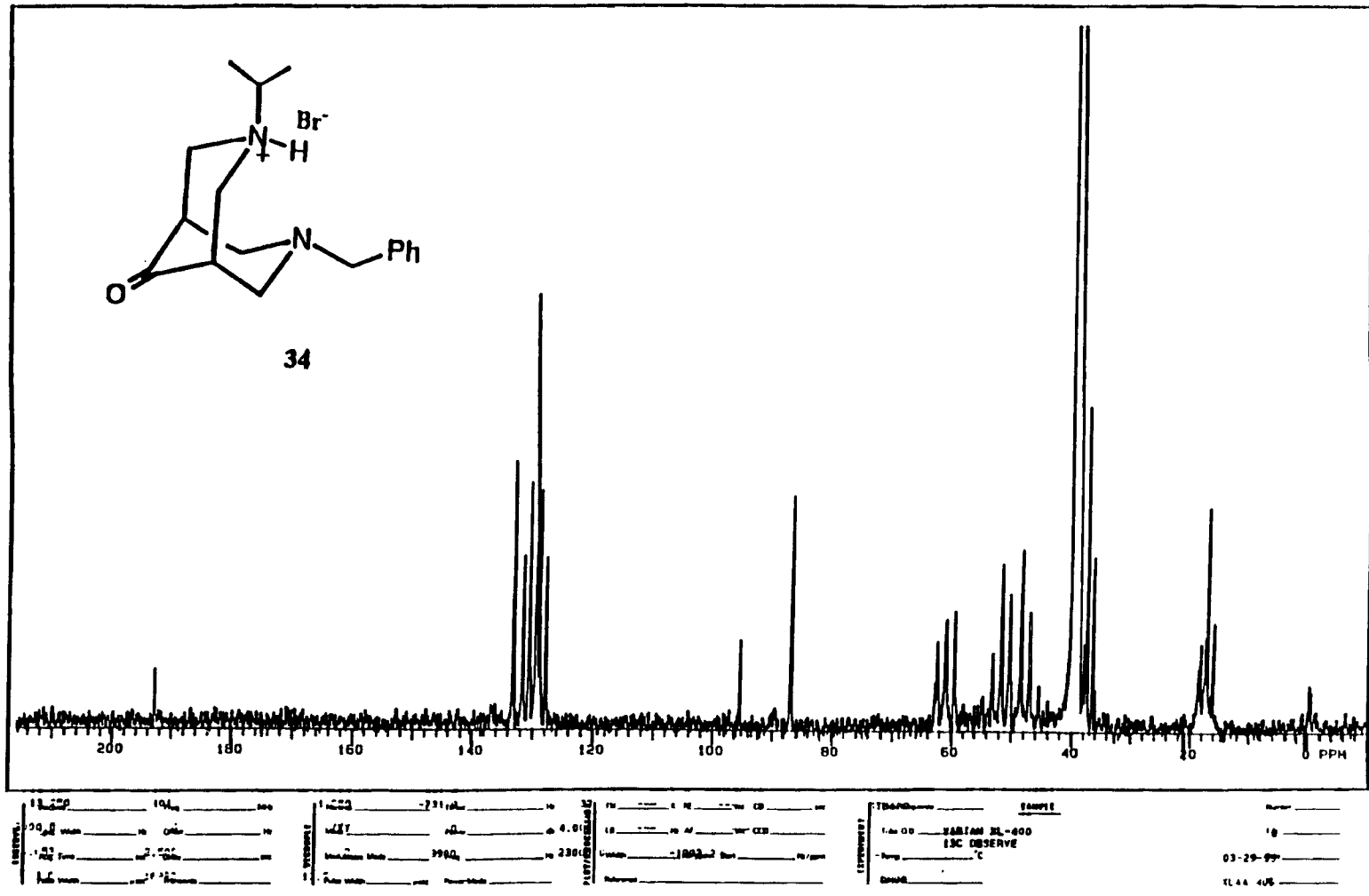
IR Spectrum of 34

Plate XIV



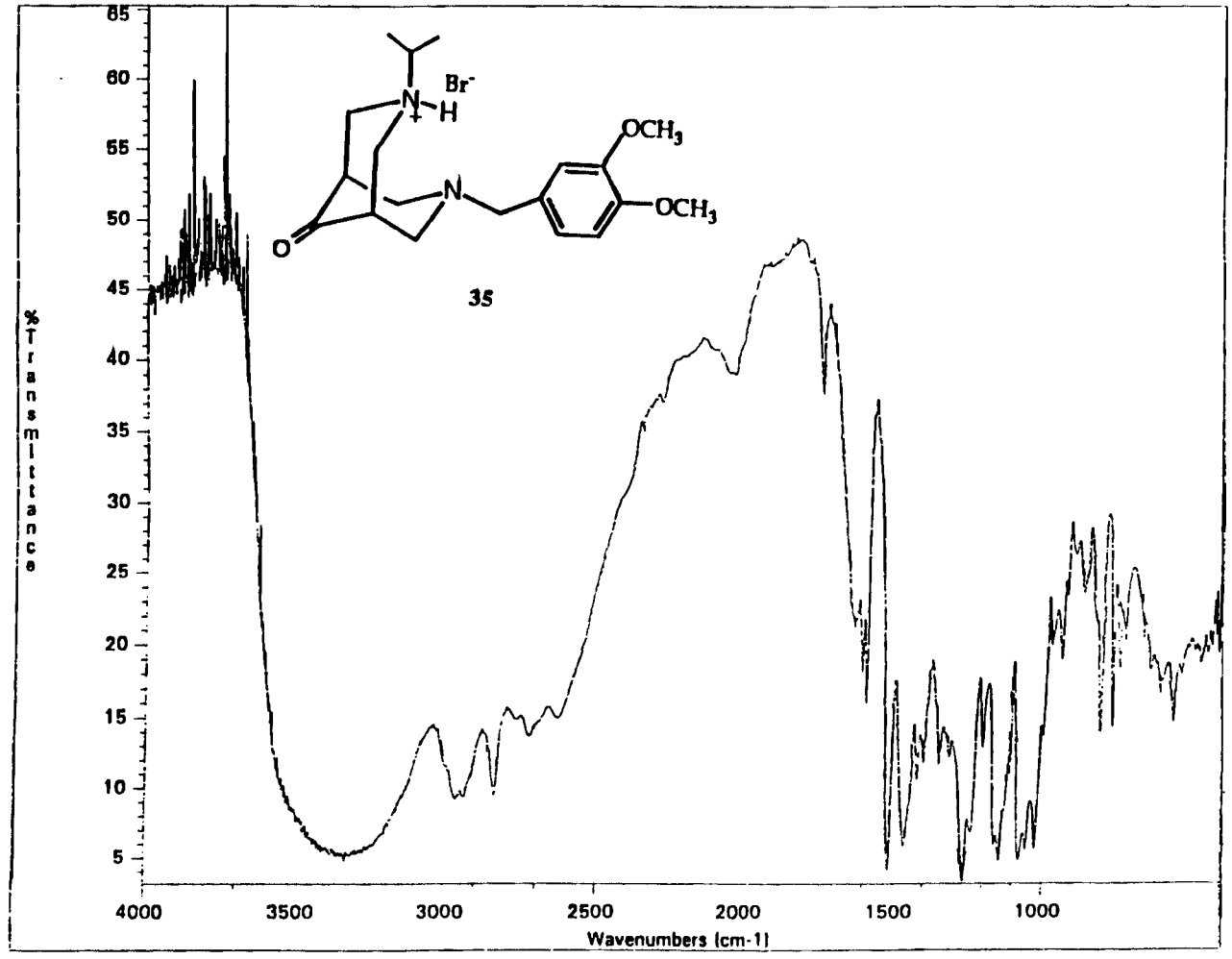
^{1}H NMR Spectrum of **34**

Plate XV



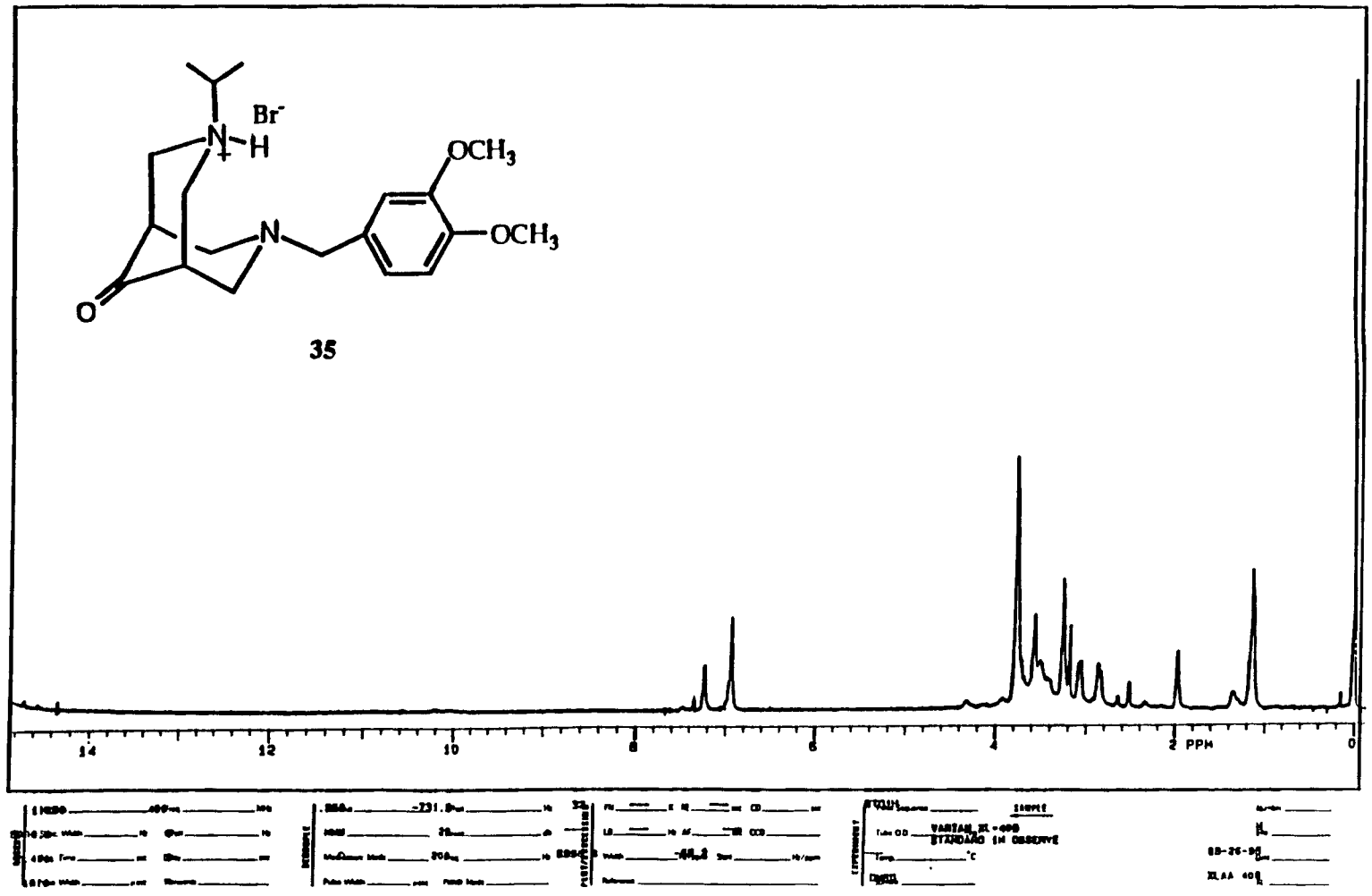
^{13}C NMR Spectrum of **34**

Plate XVI



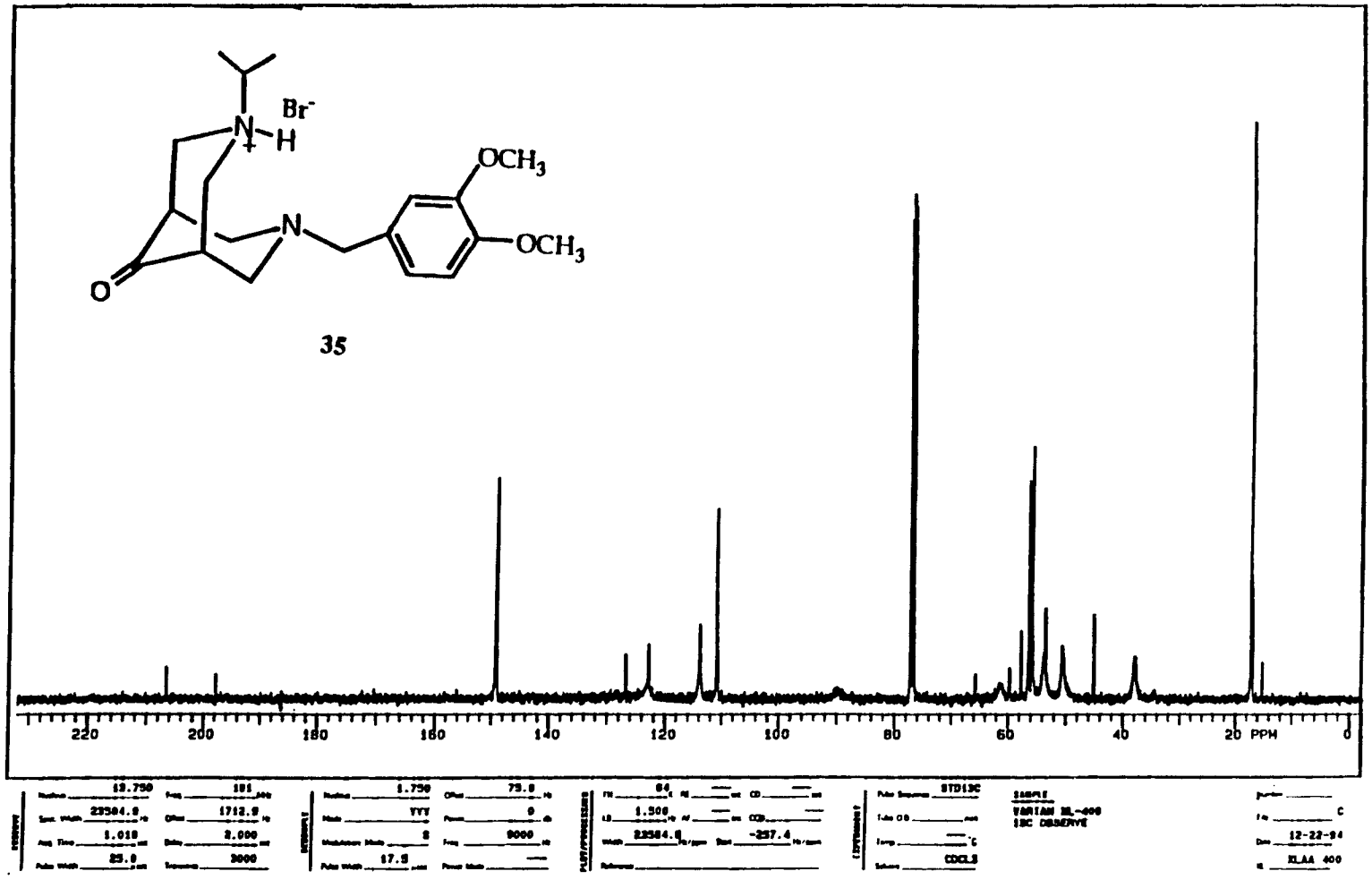
IR Spectrum of **35**

Plate XVII



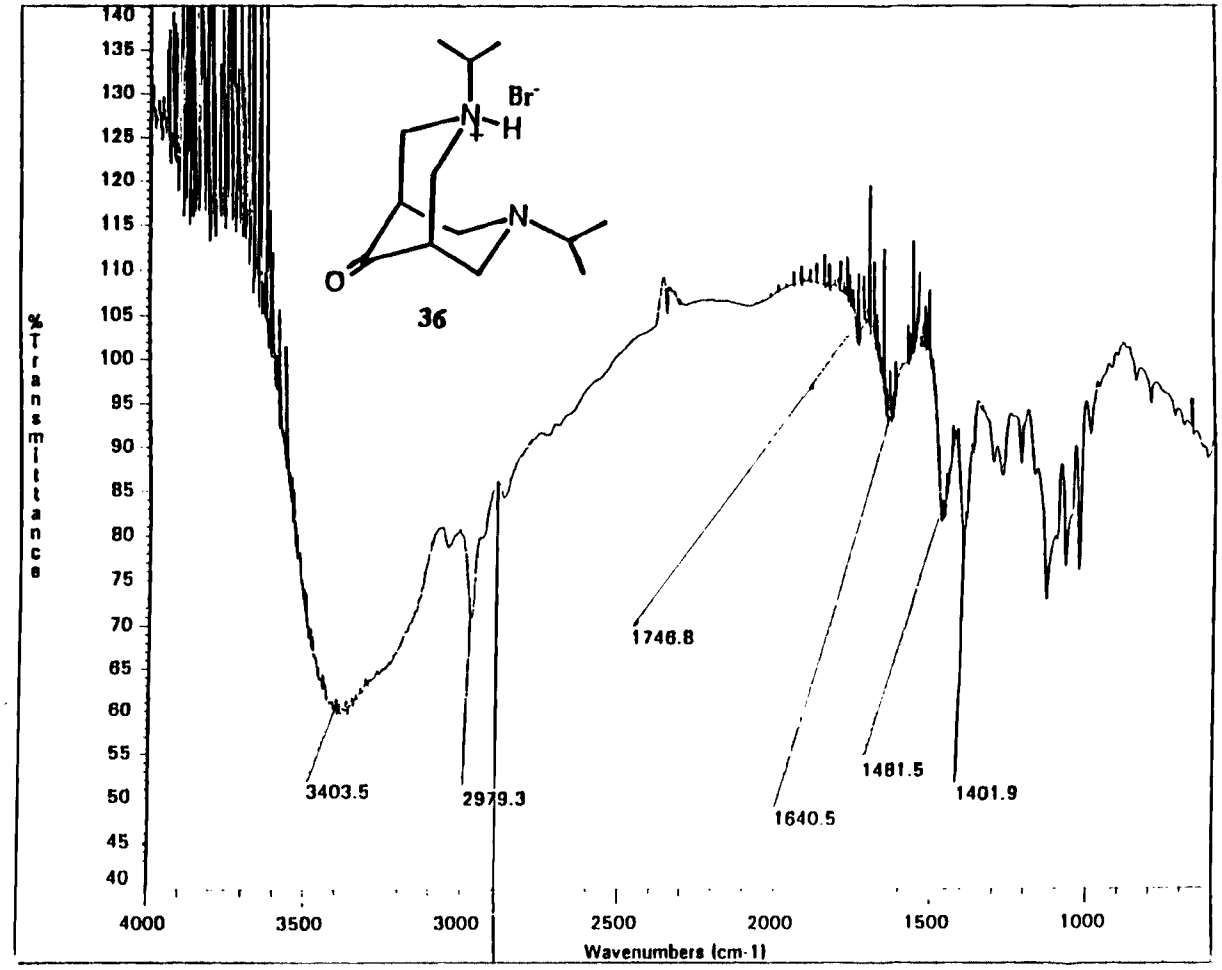
^{1}H NMR Spectrum of **35**

Plate XVIII



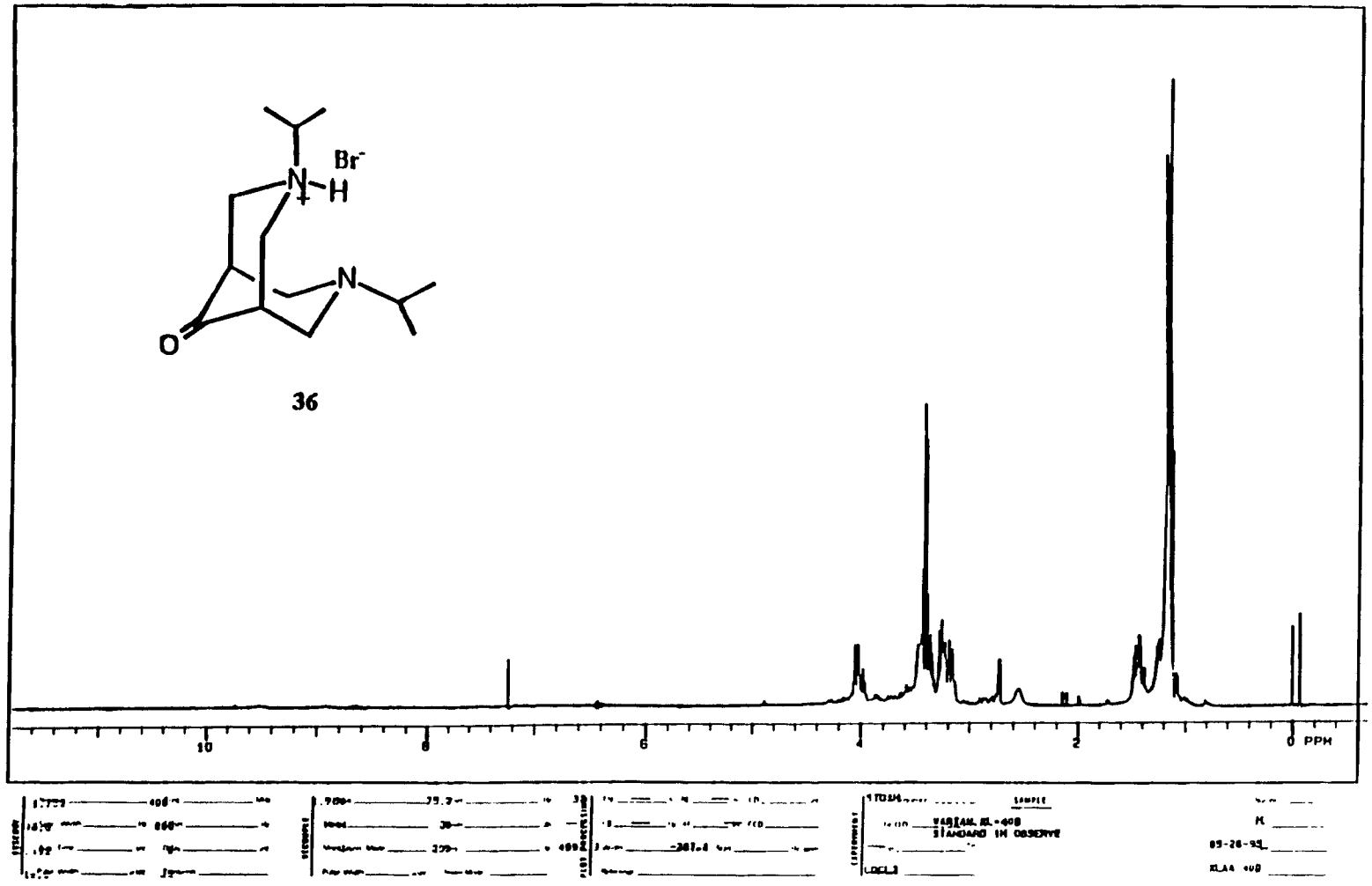
^{13}C NMR Spectrum of **35**

Plate XIX

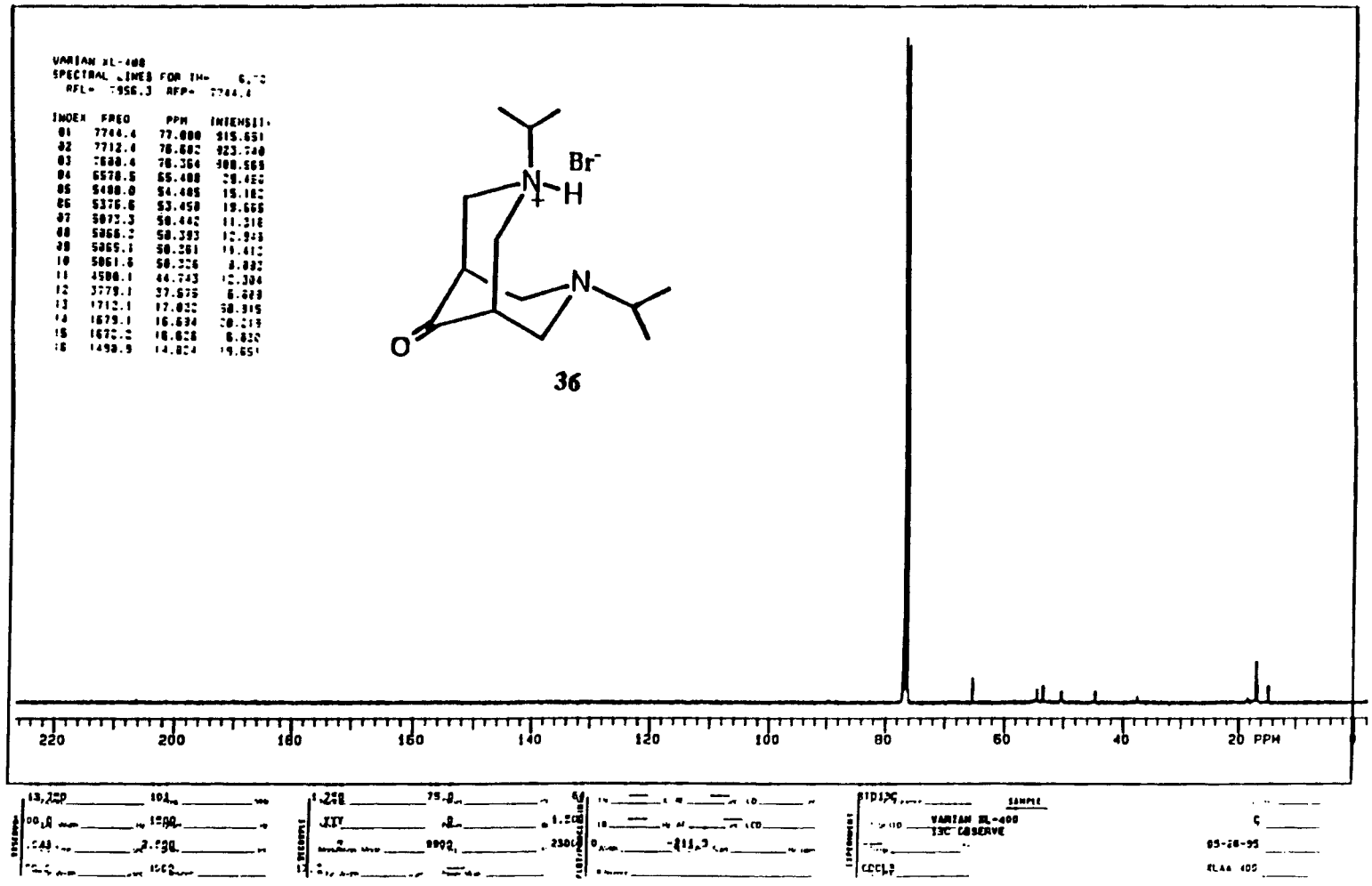


IR Spectrum of **36**

Plate XX



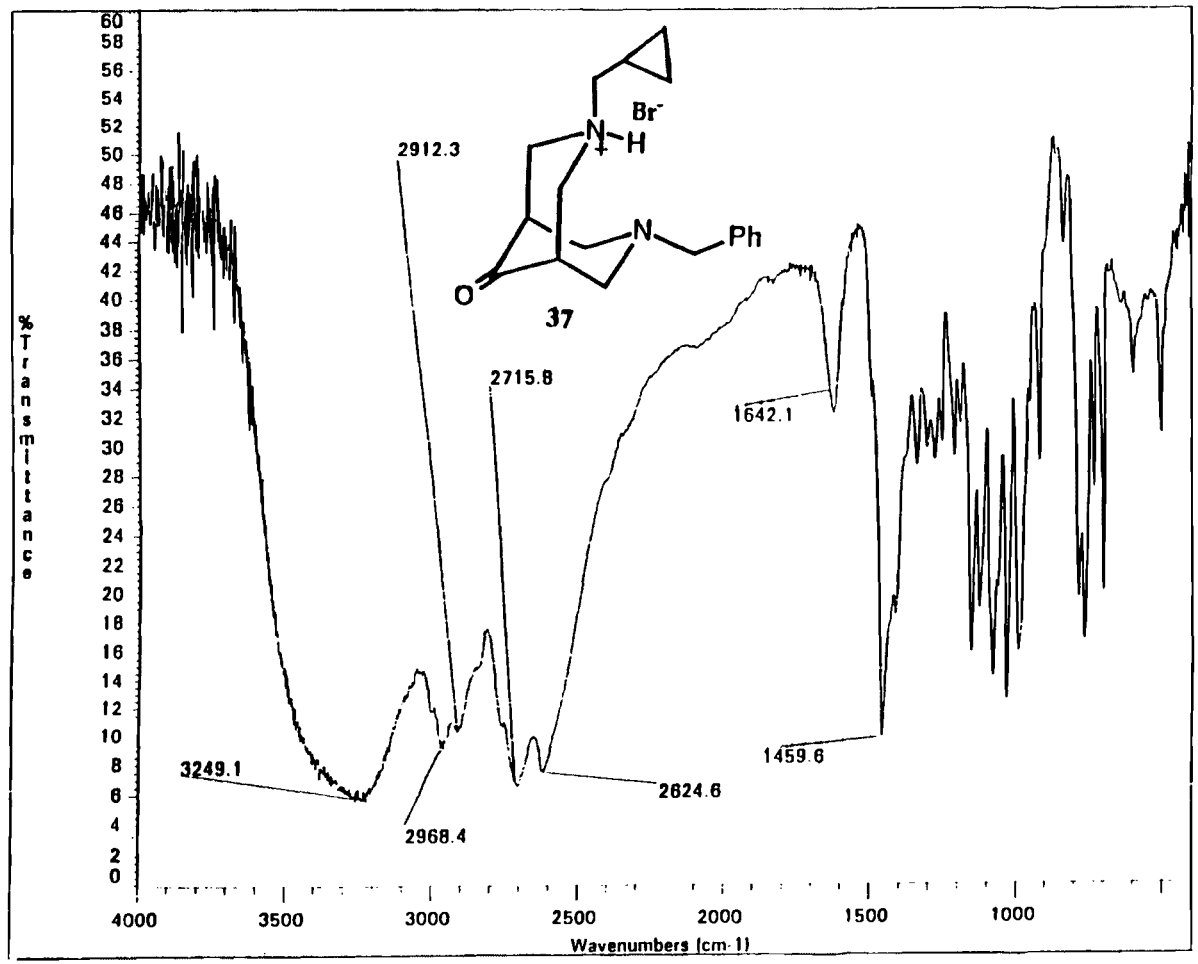
^{1}H NMR Spectrum of **36**



36

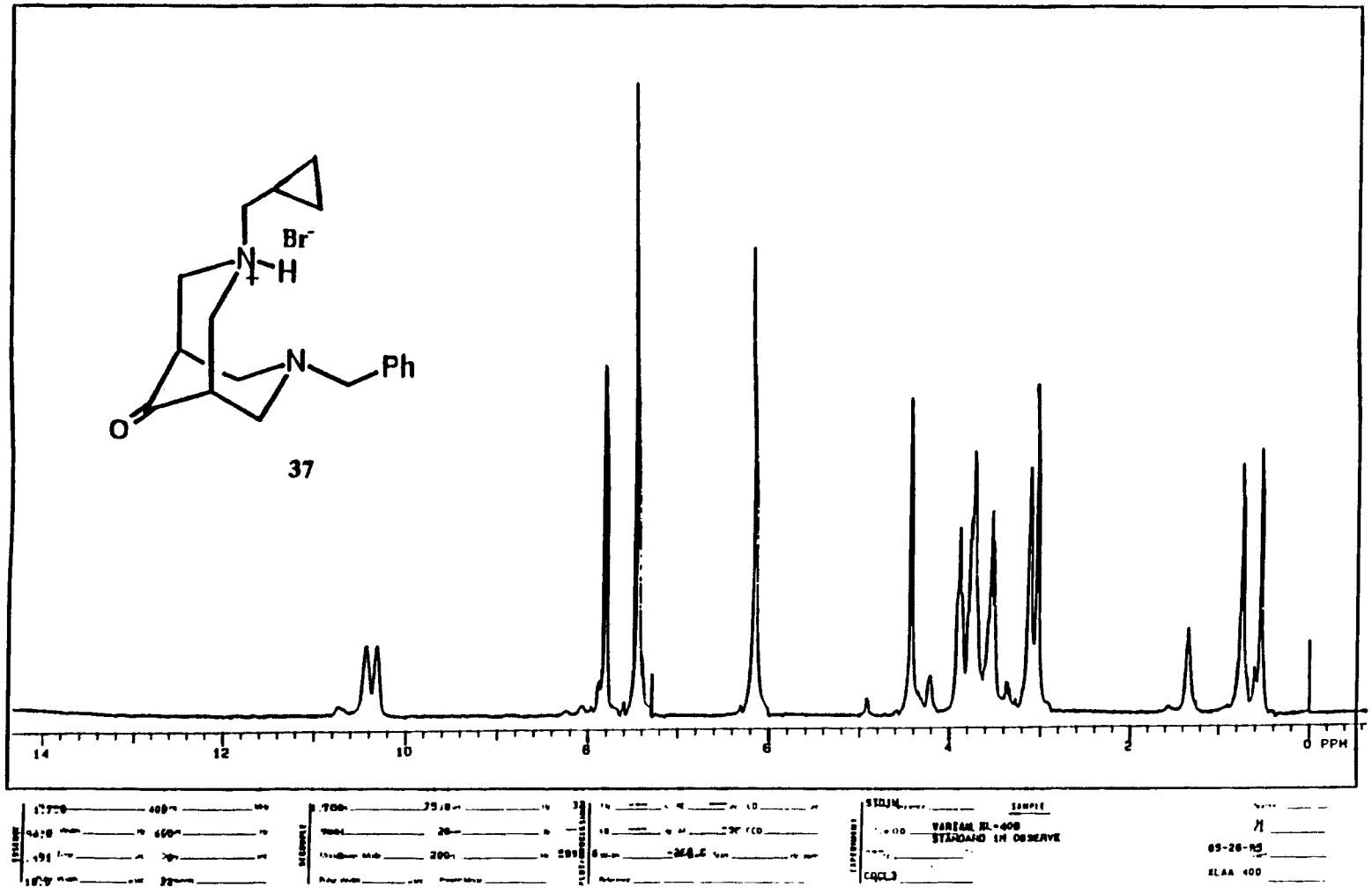
^{13}C NMR Spectrum of **36**

Plate XXII

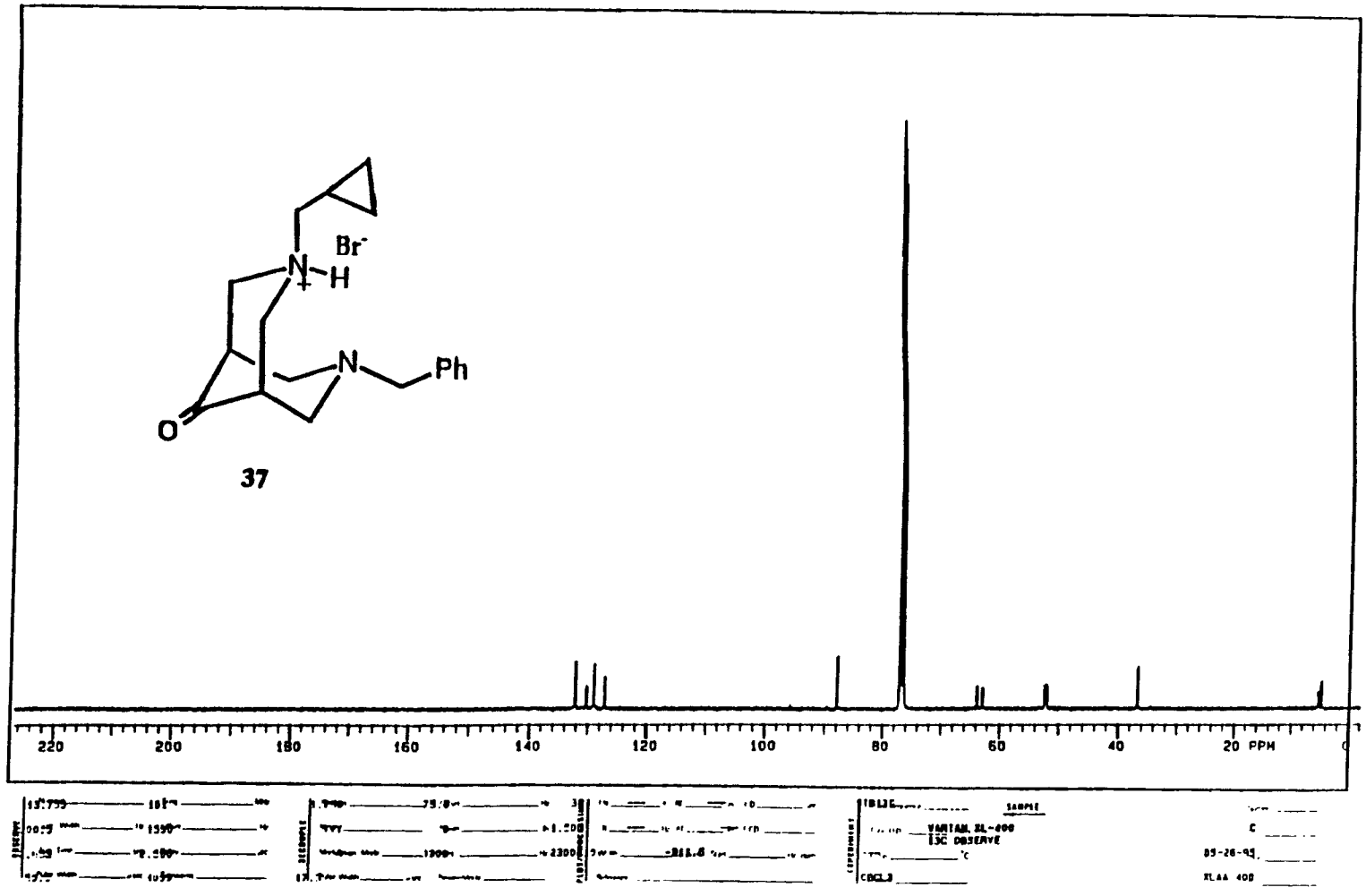


IR Spectrum of **37**

Plate XXIII

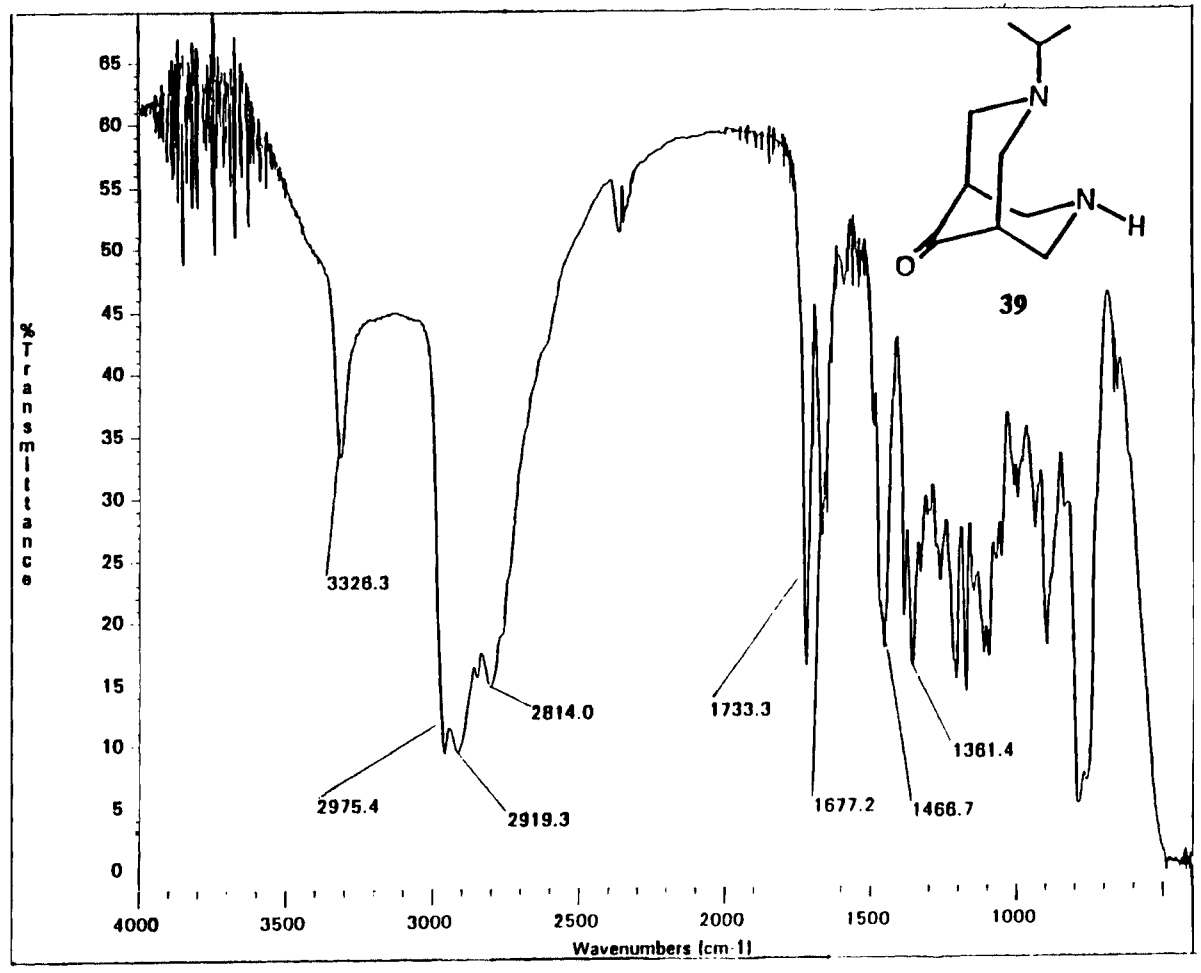


^{1}H NMR Spectrum of **37**



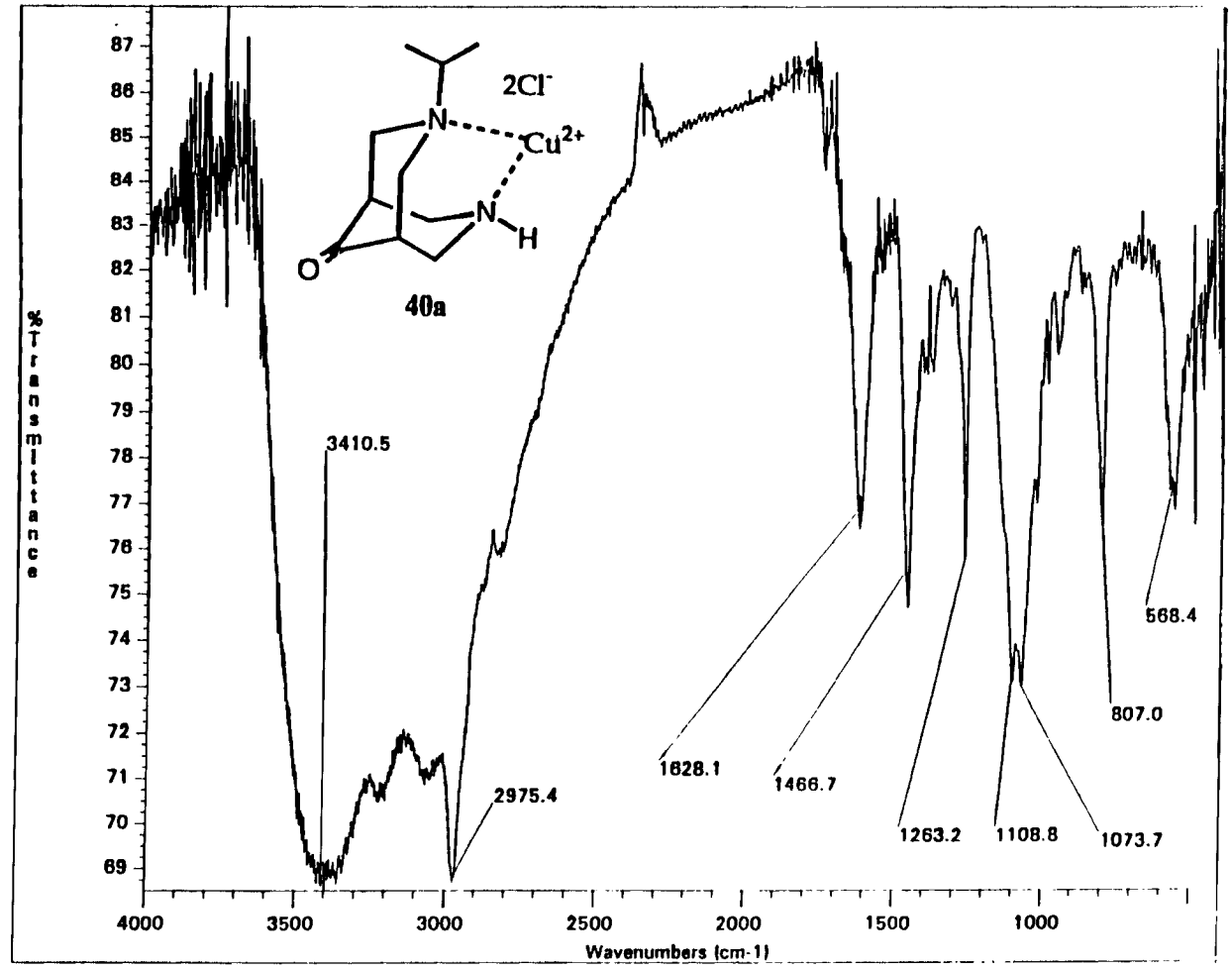
^{13}C NMR Spectrum of **37**

Plate XXV



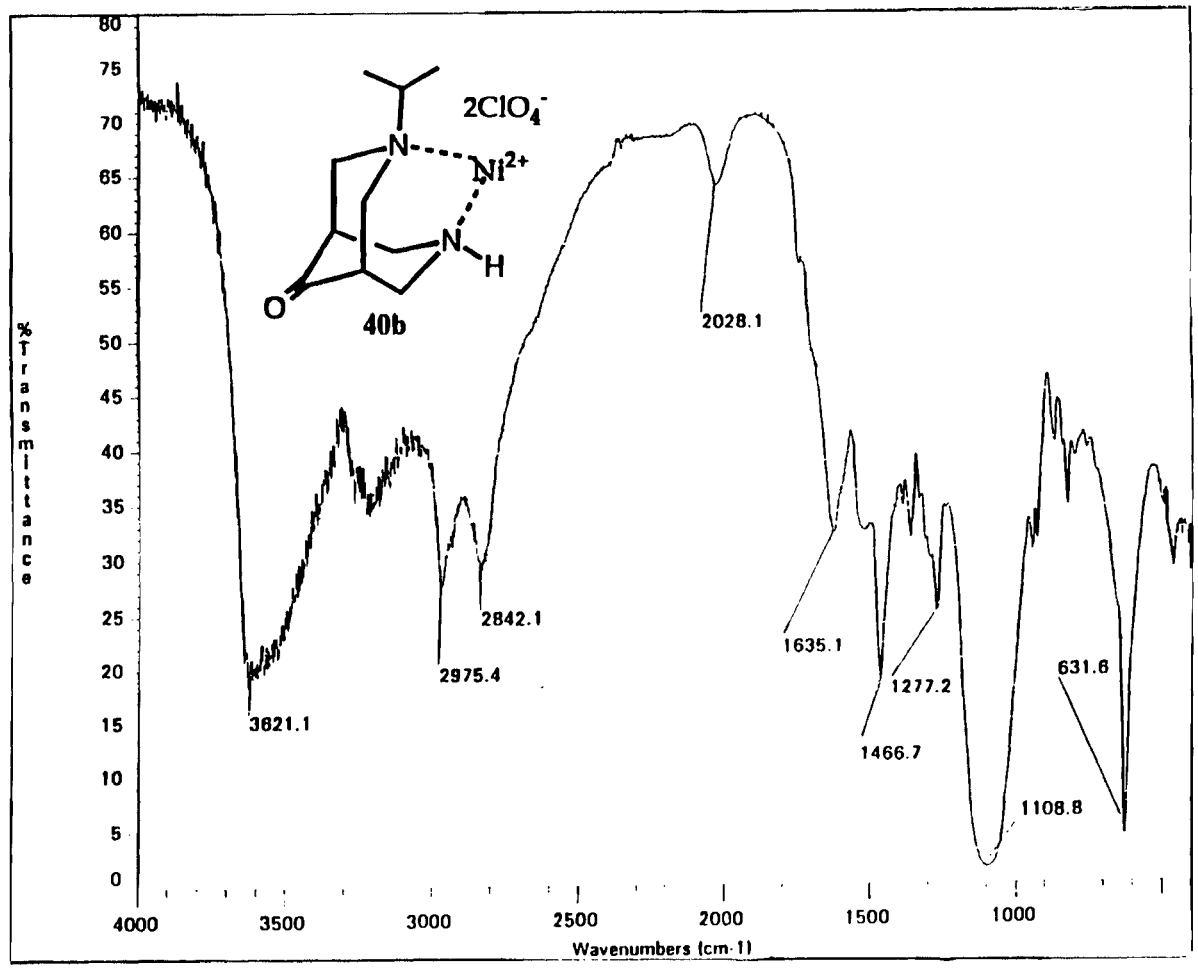
IR Spectrum of **39**

Plate XXVI



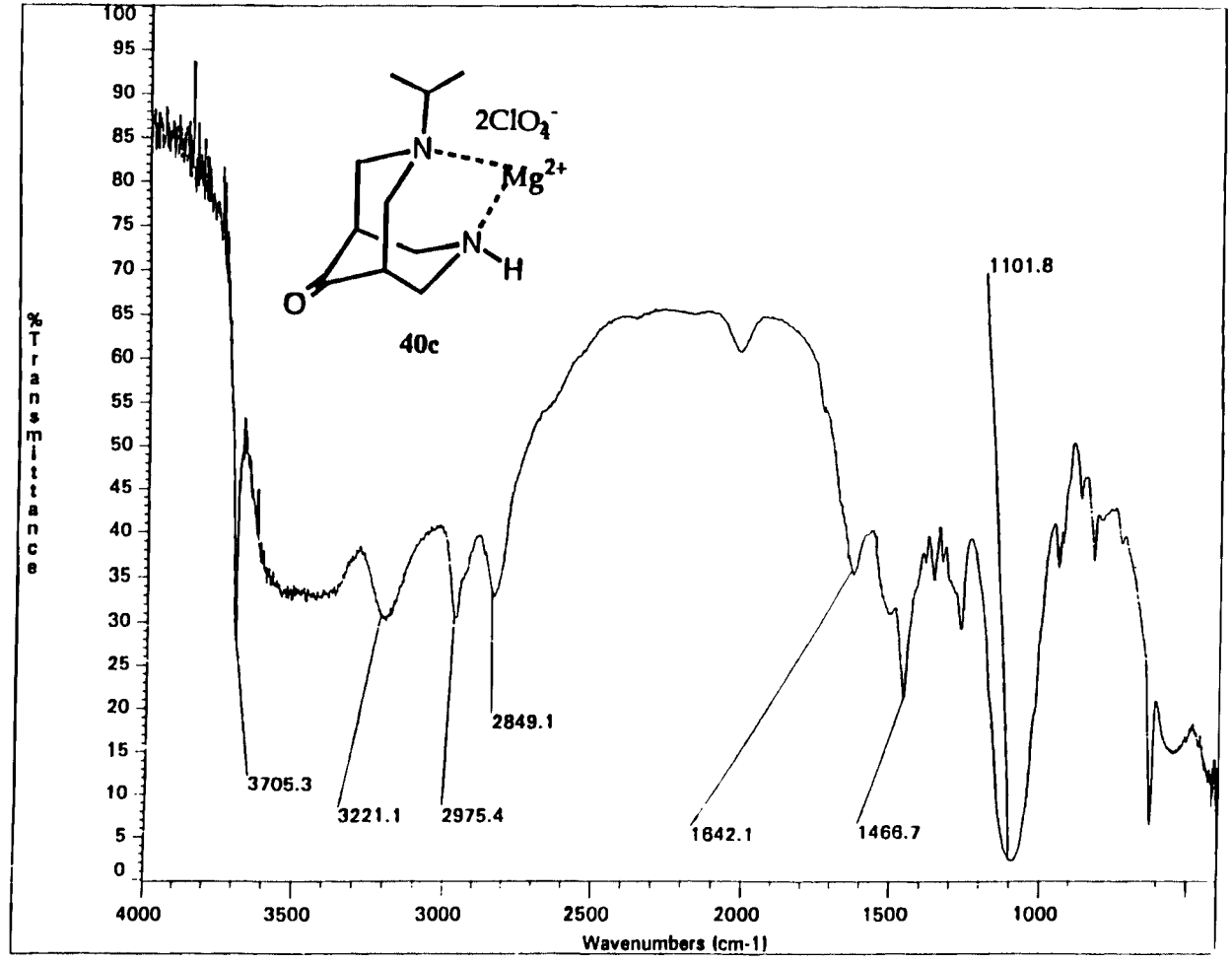
IR Spectrum of **40a**

Plate XXVII



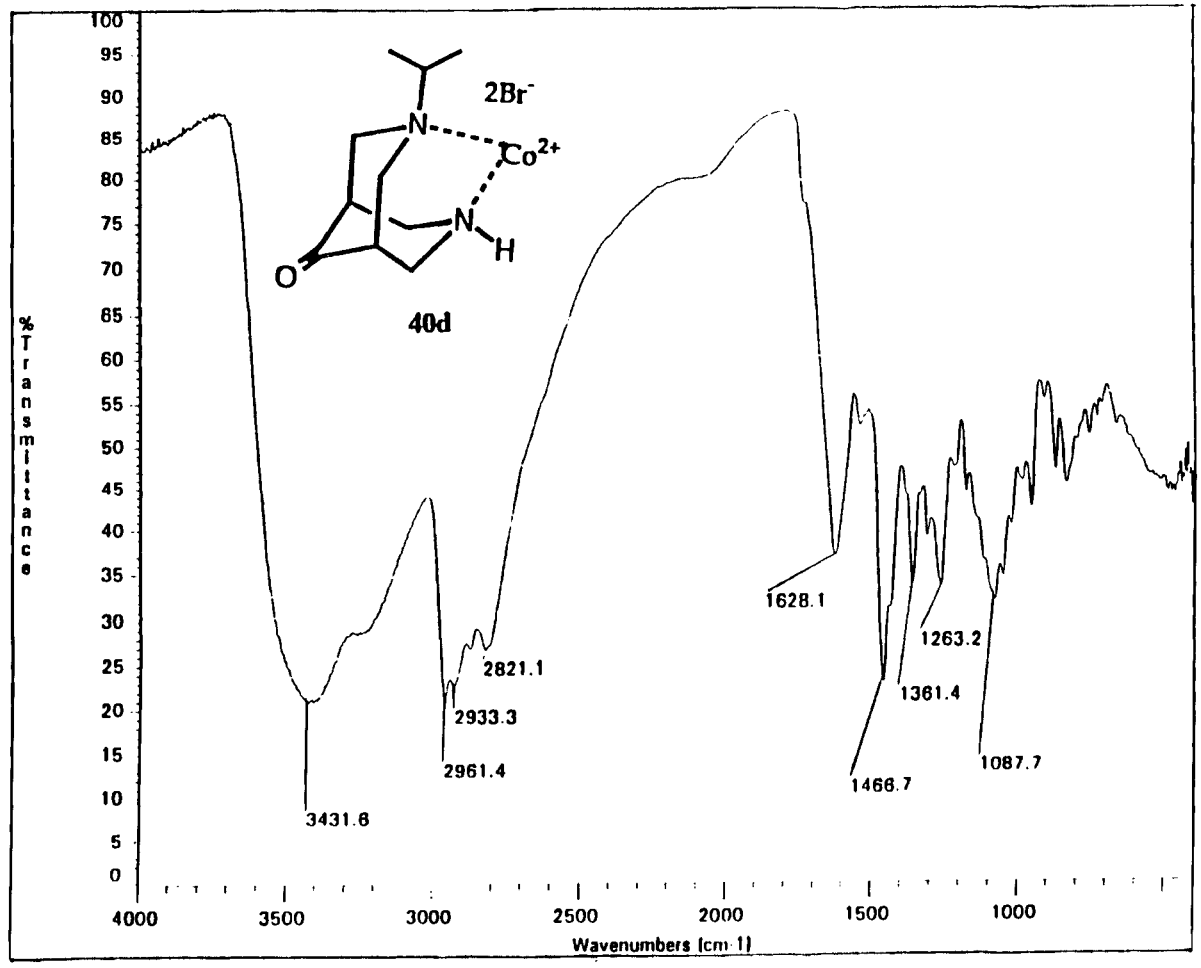
IR Spectrum of **40b**

Plate XXVIII



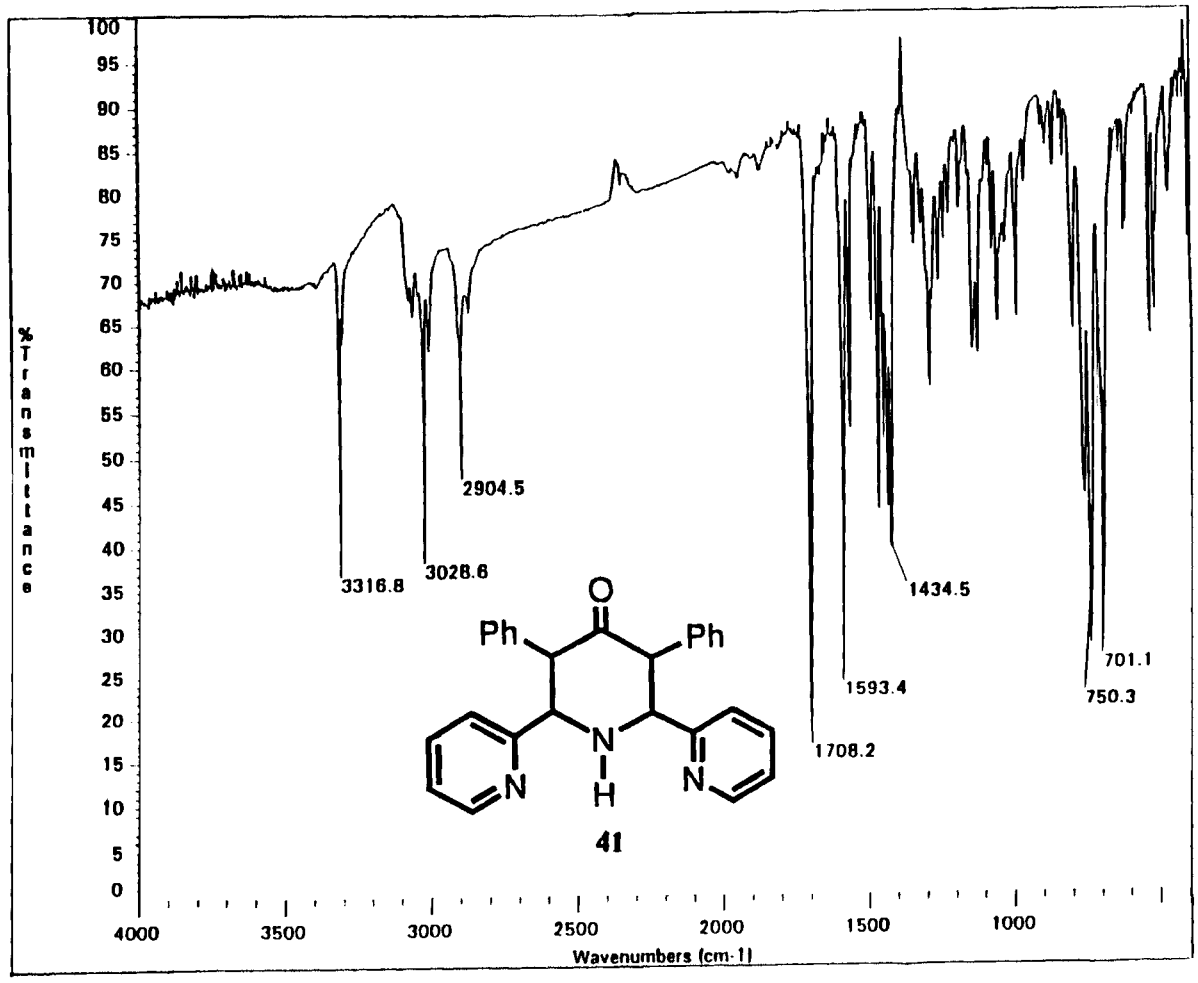
IR Spectrum of **40c**

Plate XXIX



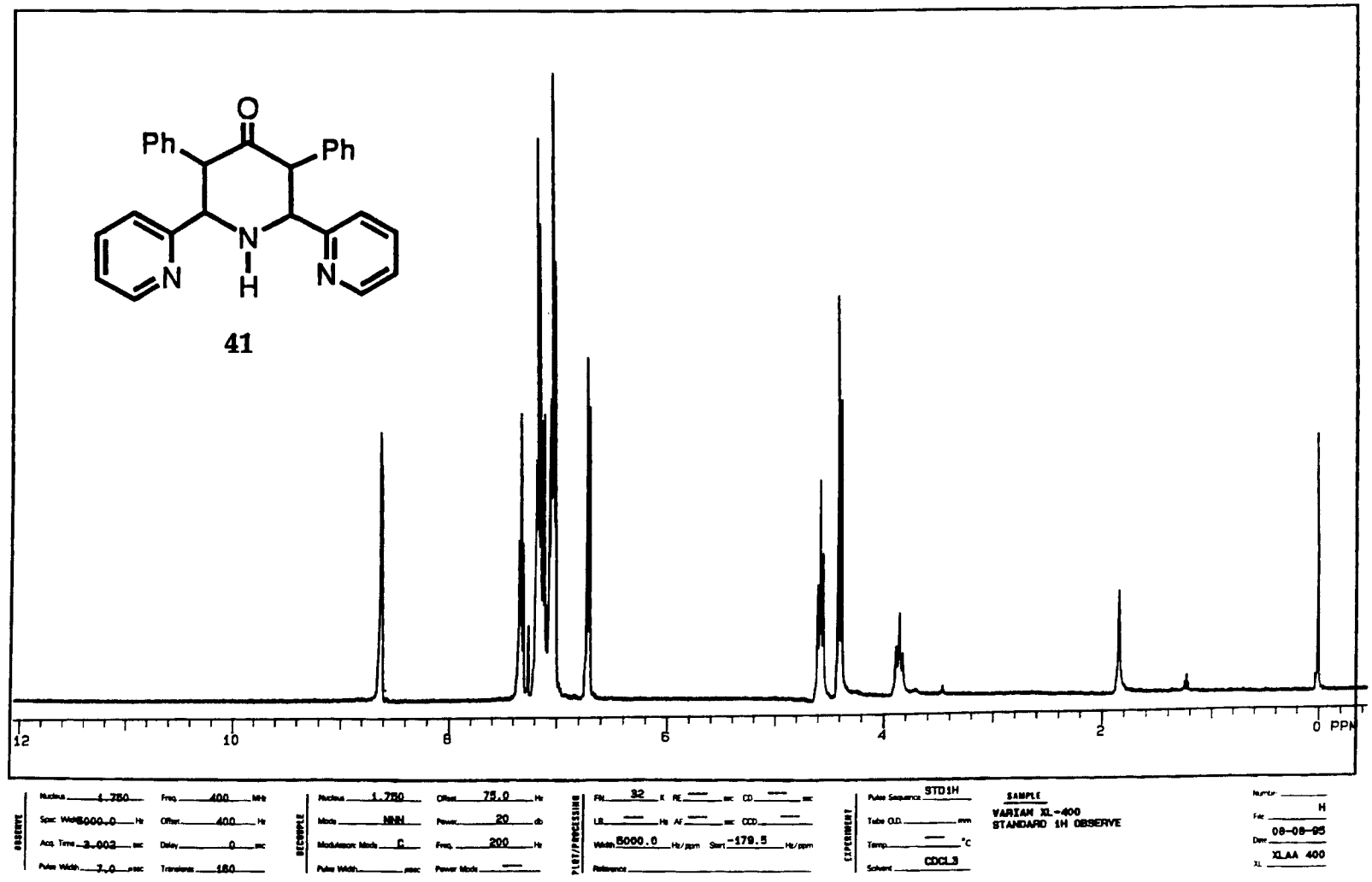
IR Spectrum of **40d**

Plate XXX

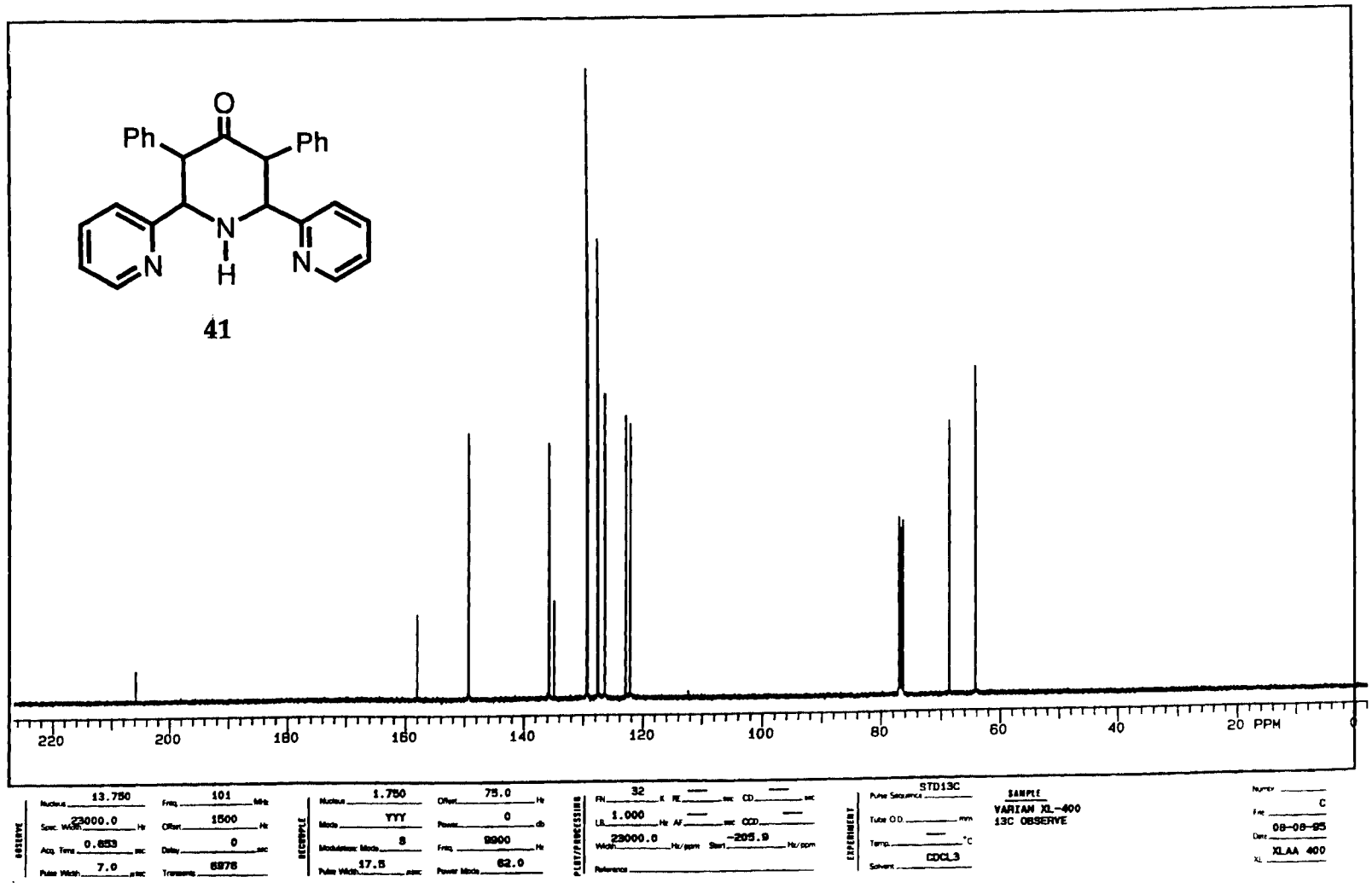


IR Spectrum of **41**

Plate XXXI

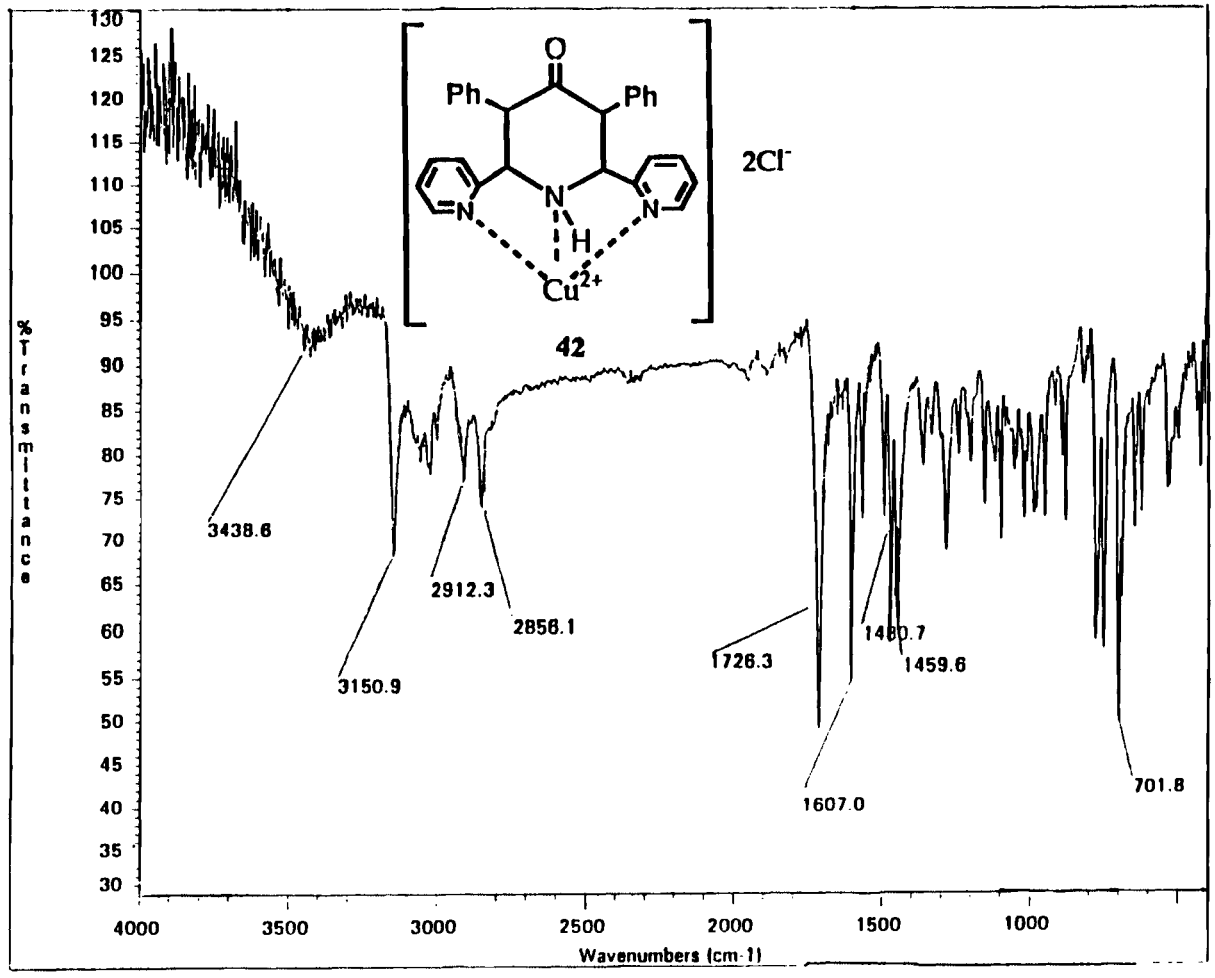


^{1}H NMR Spectrum of **41**



^{13}C NMR Spectrum of **41**

Plate XXXIII



IR Spectrum of **42**

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