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STEREOCHEMICAL ANALYSIS OF N-BENZYL, N-ISOPROPYL, AND N-BENZOYL HETEROCYCLES USING MAGNETIC NONEQUIVALENCE OF DIASTEREOTOPIC PROTONS

LONDON NORWOOD PRIDGEN

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NONEQUIVALENCE OF DIASTEREOTOPIC PROTONS

by

LONDON NORWOOD PRIDGEN

B.S., Morgan State College, 1967  
M.S., State University College at Fredonia, 1969

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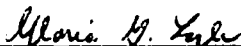
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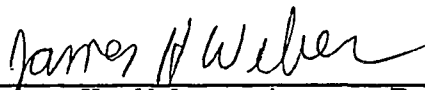
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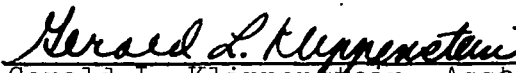
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## ABSTRACT

### STEREOCHEMICAL ANALYSIS OF N-BENZYL, N-ISOPROPYL, AND N-BENZOYL HETEROCYCLES USING MAGNETIC NONEQUIVALENCE OF DIASTEREOTOPIC PROTONS

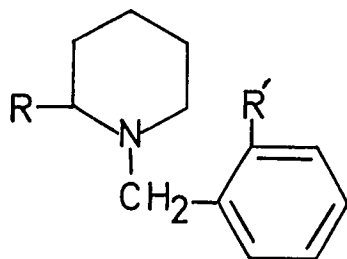
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LONDON NORWOOD PRIDGEN

In order to prepare desired N-benzyl substituted piperidines for conformational study, several substituted pyridines had to be made by alkylation of the pyridine ring with both nucleophilic and electrophilic reagents. 2-Methyl-4-substituted pyridines were prepared by nucleophilic addition of methyllithium to the 2-position of the 4-substituted pyridine. The 2-methyl-5-substituted pyridines were prepared by the reaction of methyllithium with pyridine to form a 1,2-dihydropyridine which was subsequently alkylated at the 5-position with alkyl halides. The 3-substituted pyridines were formed by alkylation of lithium tetrakis (dihydropyridyl) aluminate with alkylhalides.

The stereochemistry of the products formed from reduction of those pyridines of their N-Benzyl pyridinium salts was investigated. The assignment of isomers was made using the magnitude of the nonequivalence or equivalence of the N-benzyl protons. This method of evaluation was based on the postulate that proximity of an equatorial 2-substituent to the benzylic protons, will cause substantial perturbation of

the magnetic environment of these protons. The proximity of the 2-substituent is determined by rotational and conformational preferences. The latter was evaluated by considering the number of unfavorable butane gauche interactions present in each piperidine conformer of 1-benzyl 2,3-, 2,4-, 2,5-, 3,4-, and 3-substituted piperidines. Rotational preference was investigated by preparing two series of N-benzyl piperidines; one with substituents at the ortho-position of the phenyl ( $R' = \text{NH}_2$ , NAc,  $\text{NO}_2$ , OAc, and OH) and the other with different substituents at the 2-position on the piperidine ring ( $R = \text{CH}_3$ ,  $\text{Ph-CH}_2$ , and Ph).



N-Isopropyl piperazines were prepared in order to see if the diastereotopic methyl groups would be nonequivalent in a flexible ring system. N-benzyl quinolines were prepared to determine if analogous conclusions concerning stereochemical assignments could be drawn relative to the piperidines.

A paramagnetic shift study using  $\text{Eu}(\text{THD})_3$  was performed on cis-1-benzyl-2,4-dimethylpiperidine to determine the conformation of the piperidine ring.

## CHAPTER I

### INTRODUCTION

The discovery that two diastereotopic hydrogens, two hydrogens not capable of being interchanged by reflection through a mirror plane, could be detected by their signal in the proton magnetic spectrum has provided a convenient probe for the study of the stereochemistry of cyclic amines. Benzyl derivatives of pyrrolidines <sup>1</sup>, indanes <sup>2</sup>, isoquinolines <sup>3</sup>, aza-steroids <sup>4</sup>, thio-cyclopentanes <sup>5</sup>, sulfenamides <sup>6</sup>, sulf-oxides <sup>7</sup>, and various alkaloids <sup>8</sup> have been used in the study of the stereochemistry of derivatives of their ring systems <sup>9</sup>.

Diastereotopic hydrogens as defined above must be in theory capable of magnetic nonequivalence. This could be evident in observed differences in the chemical shifts of the signals for the two hydrogens or might be observed by differences in the magnitude of the coupling constants of these protons with a third proton. Although all diastereotopic hydrogens in a methylene group of the type  $\text{ArCH}_2\text{X}$  must be considered to be stereochemically "nonequivalent", experimentally the criteria of non identity of the chemical shifts or coupling constants may not be detectable. In this discussion "magnetic nonequivalence" will be used to describe diastereotopic hydrogens which show different chemical shifts in the proton magnetic resonance spectrum.

The protons of a methylene group removed by one or more bonds from a center of chirality are diastereotopic and

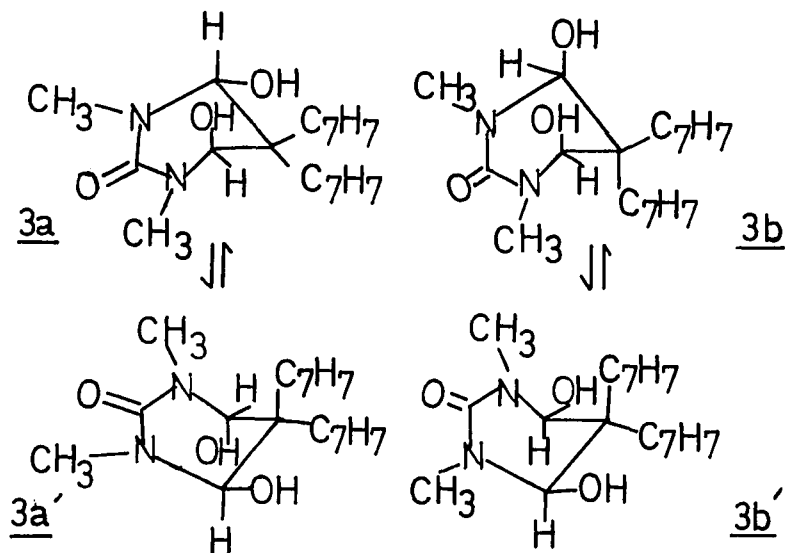
may be magnetically nonequivalent and display AB-type nuclear magnetic resonance spectra. Although the existence of preferred rotational conformations about the bond connecting the methylene group to the chiral center has often been considered to be necessary for the magnetic nonequivalence, such preferred conformations are not a theoretical prerequisite for observable nonequivalence<sup>10</sup>.

It should be emphasized that in this discussion the relative importance of rotational preference and "intrinsic" asymmetry is not the question at issue, but rather approximately how much can be attributed to each. It should also be understood that as the "intrinsic" asymmetry increases the rotational preference increases. There seems little doubt that conformational preference with respect to the asymmetric center will in general lead to a major contribution to the magnetic nonequivalence. "A better understanding of the structural requirements which lead to observable nonequivalence of geminal protons should permit this physical measurement to be used as a probe for conformational as well as configurational chirality"<sup>11</sup>.

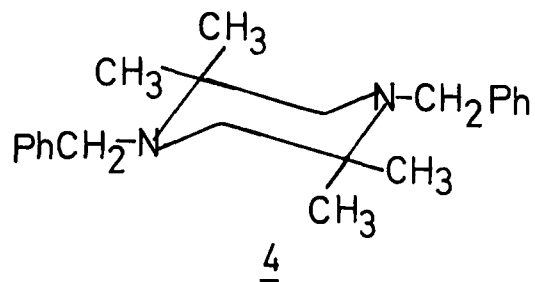
A series for which it is difficult to predict the magnetic nonequivalence or lack of it, are the dibenzylbarbiturates prepared by Dudley<sup>12</sup> below. "Due to the conformational uncertainties of, a difference of substituents at the chiral center in, and the questionable rotamer dispositions of seemingly hindered 5,5-dibenzyl groups in the barbiturate reduction products, no conclusions have been drawn regarding the magnetic



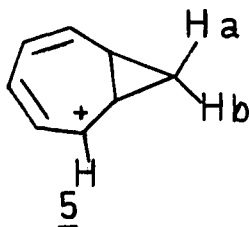




A possible explanation for the magnetic equivalence of the benzylic protons in the trans isomer 3a could be the presence of a  $C_2$  axis<sup>10</sup> which, because of fast rotation at room temperature, renders the benzylic protons equivalent. A comparison can then be made with 4 in which a singlet is observed for the benzylic protons at room temperature<sup>13</sup>.

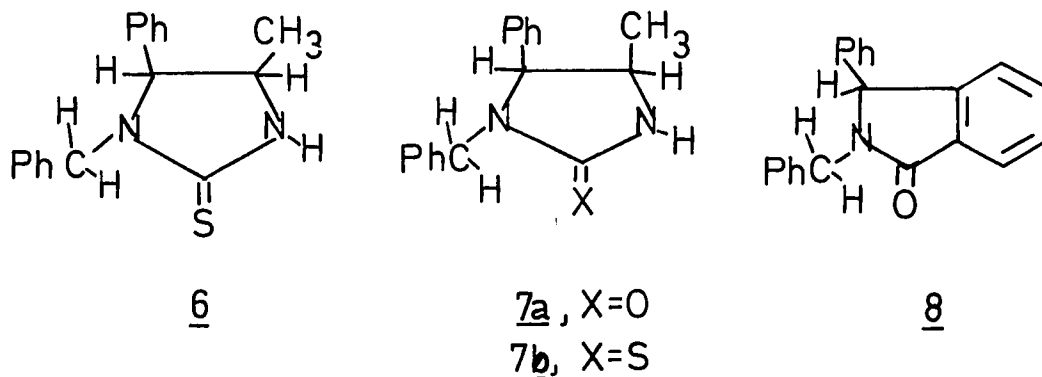


What is probably an extreme case of a conformational influence on the magnetic nonequivalence of a methylene group was reported by Rosenberg<sup>14</sup> for 5. The observed chemical shift difference between Ha and Hb was 5.8 ppm. Ha (-0.6 $\delta$ ), being over the seven membered ring, was shielded by the system while Hb (5.2 $\delta$ ), which lay almost coplanar with the ring, was deshielded by the same system.

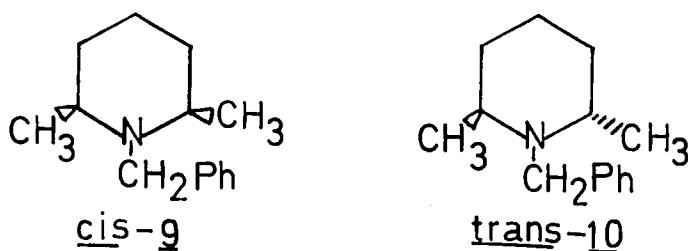


The proximity of one of the methylene hydrogens of a benzyl group to a substituent which exhibits a large magnetic anisotropic effect will greatly affect the magnitude of any chemical shift differences between the two protons of the methylene groups. The observation of a substantial nonequivalence is favored by a strong conformational preference, hindered rotation, or both. This can be illustrated in a study conducted by Milliman<sup>15</sup> where he found in the imidazolinine system a shift difference of nearly 2 ppm between the methylene protons of the benzyl group on 6. The shift difference of the benzyl protons of 7a is 1.3 ppm which approaches the 1.75 ppm observed by Lewin<sup>16</sup> for 8. The chemical shift difference was shown to be very large when the oxygen was replaced by sulfur, as in 7b, which has a  $\Delta\nu$  of 1.85 ppm. Clearly, the change from a carbonyl group to a thiocarbonyl has resulted in shielding

or deshielding effect confined largely to one proton of the geminal pair.

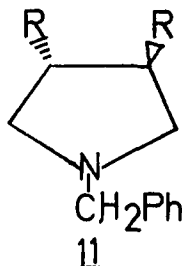


Utilizing a similar system in which the chiral center was near one of the benzylic substituents, Hill<sup>17</sup> showed that the configuration of 2,6-disubstituted piperidines could be assigned by this method. The cis isomer 9 gave a singlet (since the geminal benzylic protons would not be diastereotopic) while the trans isomer 10, in which they are diastereotopic, gave an AB quartet for the methylene with a  $\Delta\delta$  of 31 Hz.



A study of trans-3,4-disubstituted pyrrolidine (11) gave disappointing results: the N-benzyl methylene showed no signs of splitting and magnetic nonequivalence even though the protons were diastereotopic. The assumption was made that the asymmetry of the  $\beta$ -carbon atoms was too far removed from

the benzylic protons to perturb their magnetic environment.<sup>17</sup>



To explain observed benzylic nonequivalence in N-benzyl piperazines and piperidines, Lyle and co-workers<sup>11</sup> postulated that rotational preference about the benzyl-N bond was also an important requirement for observed nonequivalence. The three represented rotamers (Figure 1) of the benzyl-N bond should represent energy minima. Thus Rotamer c should contribute little and rotamer b should be of considerably lower energy than rotamer a<sup>17</sup>. Rotamer b should be present in largest amount and the magnetic environment of the two hydrogens being very different leads to an AB quartet with a large  $\Delta\delta$ . When the methyl is axial the difference in energy of the rotamers a and b is negligible and the rotamers are equally populated. The pseudo-enantiomeric nature of the two conformers leads to identical chemical shifts for the two hydrogens. One therefore could have a means of measuring the extent of conformational equilibrium. The inherent error in this method of analysis is the assumption that rotational preference and magnetic anisotropy are not dependent on the substituents.

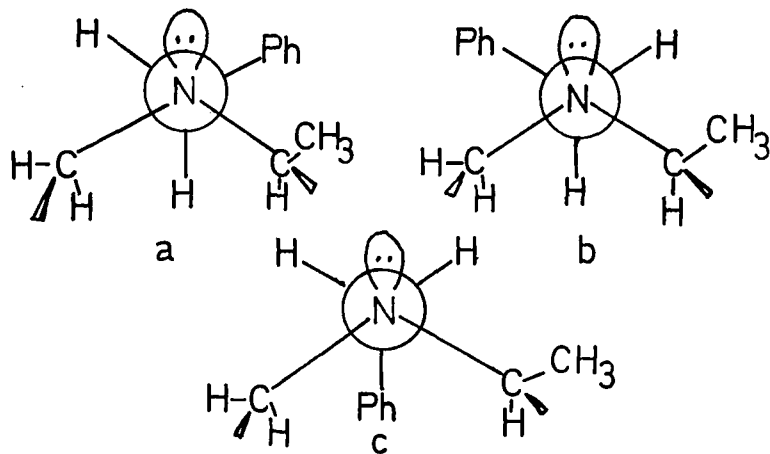


Figure 1. The three rotamers of the benzyl-N bond which should represent energy minima.

It was observed that for the cis-1-benzyl-2,5-dimethylpiperazine (12), which is conformationally mobile, the pmr signal for the benzylic methylene protons was a singlet (See Figure 2). This suggested that because of steric interactions of the benzyl and equatorial 2-methyl, conformer 12a would have a higher energy and be present in smaller amounts in the conformational equilibrium. The "intrinsic" asymmetry in this case is not close enough to perturb the equivalent magnetic environment of the benzylic protons.

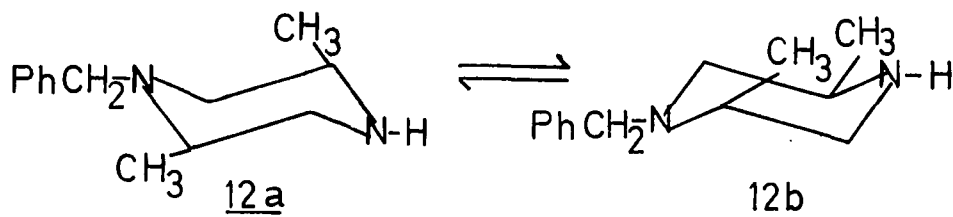


Figure 2. The Conformational Equilibrium of cis-1-Benzyl-2,5-dimethylpiperazine (12).

The benzylic protons of cis-1,4-dibenzyl-2,5-dimethylpiperazine 13 gave an AB quartet with a  $\Delta \delta$  of 21.6 Hz at room temperature. At  $-81^\circ$  this original AB quartet was transformed into an AB quartet of 1.2 ppm with a singlet in the middle <sup>17</sup>. Apparently at room temperature the interconversion between conformers is rapid and a time averaged benzylic signal was observed (See Figure 3). At low temperature, the mobile conformational interconversion was slowed sufficiently to allow the difference in proximity of the benzyl hydrogens to the equatorial and axial methyls to be detectable. The equatorial methyl caused the AB quartet for the nmr signal of the adjacent benzyl group and the axial methyl led to the singlet.

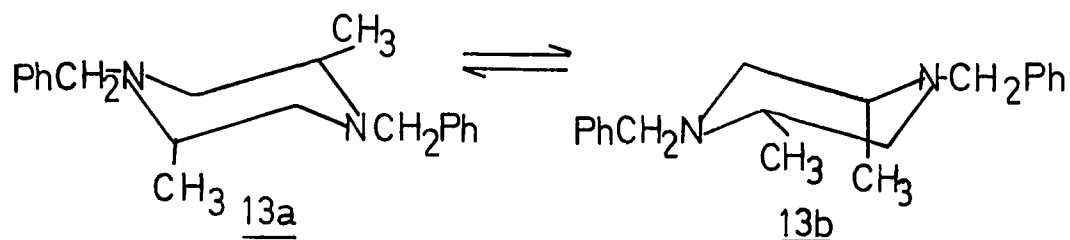


Figure 3. The Conformational Equilibrium of cis-1,4-Dibenzyl-2,5-dimethylpiperazine (13).

It was the purpose of this research to use the observable nonequivalence of the diastereotopic methylene protons of benzyl groups or the diastereotopic methyl groups of isopropyl substituents to:

1. Develop a quantitative method for estimating the conformational equilibrium of cis and trans isomers of piperidines, piperazines, and quinolines;

2. Determine the effect of the nature of the substituent on the ring on the "intrinsic" asymmetry;

3. Determine to what extent substituents in the  $\beta$ -position affect the observable nonequivalence; and

4. Assess the effect that substituents on the phenyl ring of the N-benzyl have on rotational preference of the phenyl methylene bond and the effect of this change on the magnitude of the  $\Delta\delta$  of any AB quartet.

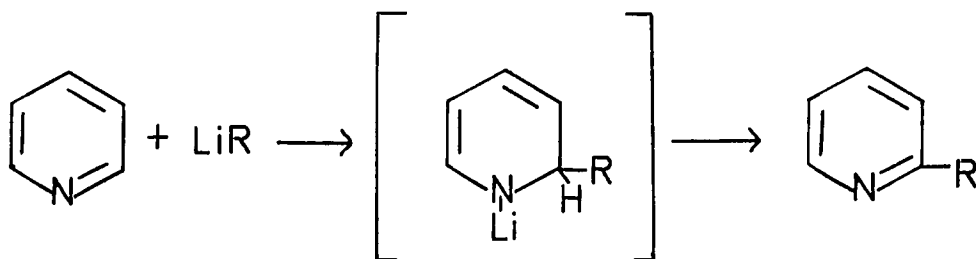


## CHAPTER II

## DISCUSSION

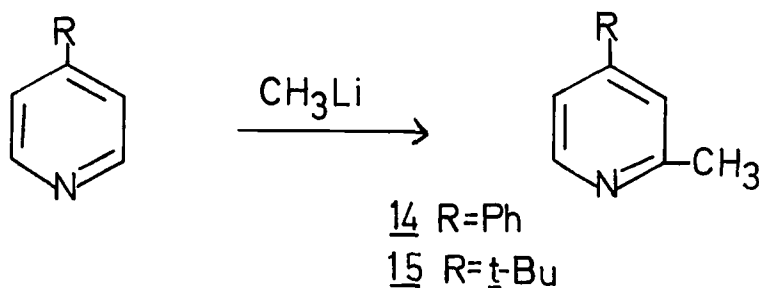
Preparation and Reduction of Pyridines  
and Pyridinium SaltsSynthesis of Pyridine Derivatives

The study of the nmr spectra of diastereotopic protons of N-benzyl heterocycles required a series of substituted piperidines. In general these compounds were not available commercially and were prepared by hydrogenation of the corresponding pyridines or their salts. The pyridines which were not available were obtained by nucleophilic substitution of pyridines. The 3-substituted piperidines were prepared from 3-piperidones, or by alkylation of the enamine intermediate from the nucleophilic addition to pyridine.



Nucleophiles such as lithium and magnesium alkyls and aryls should add primarily to the pyridine nucleus at the 2- or 4-position because of the lower electron densities at these positions <sup>18</sup>. The formation of a 4-substituted pyridine has not been reported in such reactions except in those cases where the 2- and 6-positions of the pyridine ring are blocked <sup>19-23</sup>. A lithio intermediate is formed first

and this on heating loses lithium hydride to give the 2-substituted pyridine. It is clear, therefore, that the addition of 1 mole of the lithium reagent to a 2- or 4-substituted pyridine can lead only to the formation of one compound <sup>24,25</sup>. Using methyllithium, 2-methyl-4-phenylpyridine (14) and 2-methyl-4-t-butylpyridine (15) were prepared in 77% and 73% yield, respectively, from the corresponding 4-substituted pyridines following the procedure of Abramovitch <sup>25</sup>.



Giam <sup>26</sup> used phenyllithium as the nucleophile for reaction with pyridine, and at 0°C in the THF he was able to isolate in 80% yield the intermediate adduct 1-lithio-2-phenyl-1,2-dihydropyridine (16), which was characterized by nmr (See Figure 4a). This dihydropyridine has been termed a cyclic enamine <sup>27</sup> and was shown to undergo reaction with electrophiles such as alkyl halides. Giam was able to alkylate the 5-position with appropriate halides and thus obtained 2,5-disubstituted pyridine in an average yield of 45% after hydrolysis <sup>28</sup>.

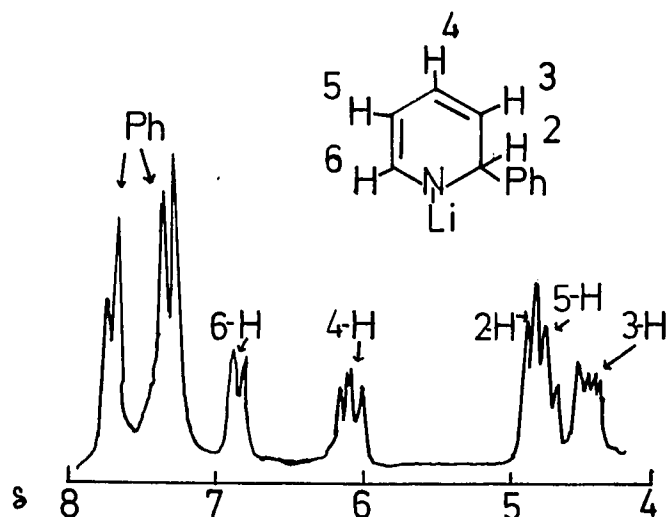


Figure 4a. The NMR Spectrum of 1-Lithio-2-phenyl-1,2-dihydropyridine (16).

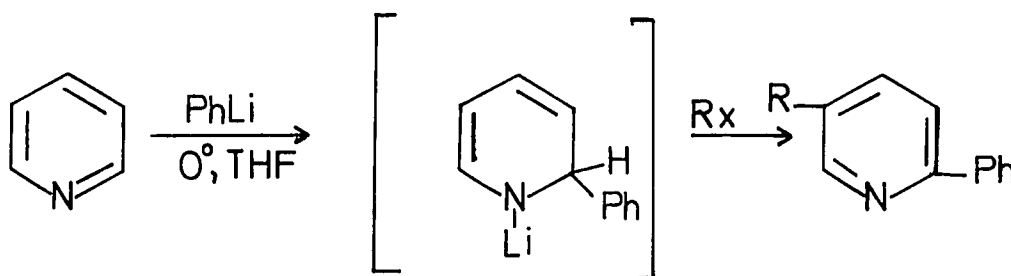
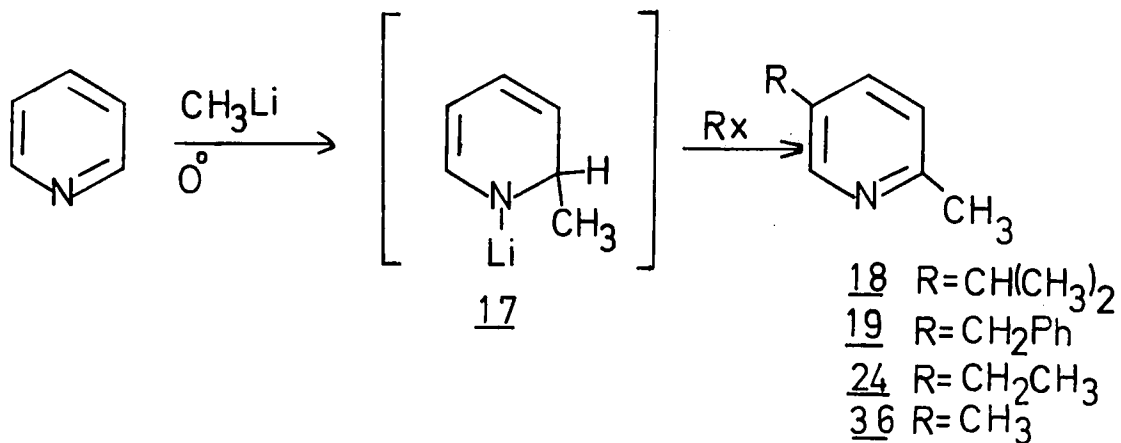


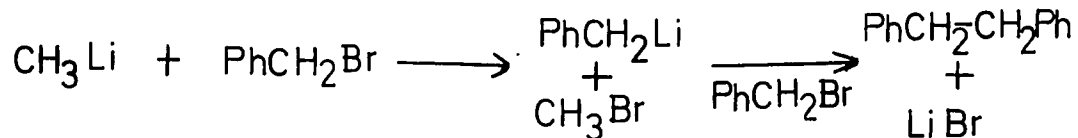
Figure 4b. The Preparation of 2-Phenyl-5-substituted Pyridines.

Using Giam's procedure <sup>28</sup>, dry pyridine was treated with methyllithium to form the 1-lithio-2-methyl-1,2-dihydropyridine (17) intermediate. The appropriate iodides, methyl or ethyl, and bromides, isopropyl or benzyl, were added to give 50, 66, 38 and 33% of the 2,5-disubstituted pyridines 36, 24, 18, and 19, respectively. The reaction temperature had to be increased from 0°C <sup>28</sup> to room temperature or to the temperature of refluxing ether in order to get maximum yields of the

2,5-disubstituted pyridines. At temperatures lower than zero degrees, the reaction with methyllithium and benzyl bromide gave only dibenzyl.  $\alpha$ -Picoline could not be detected by nmr. This suggested that methyllithium did not add to the pyridine nucleus at this low temperature but gave metal-halogen exchange with the benzyl bromide to form the coupling product, dibenzyl.



It was reported by Gilman<sup>29</sup> that methyllithium was not effective in causing metal-halogen exchange. Since Gilman reported the formation of dibenzyl from benzyl chloride in his attempts to prepare benzyl lithium with lithium ribbon<sup>30</sup>, it is evident that if benzyl lithium formed it would immediately be converted to dibenzyl.



To prepare 3-substituted pyridines, another procedure of Giam's <sup>31</sup> was used that took advantage of the cyclic enamine character of dihydropyridine system of lithium tetrakis (N-dihydropyridyl) aluminate (LDPA) <sup>32</sup> illustrated in Figure 5.

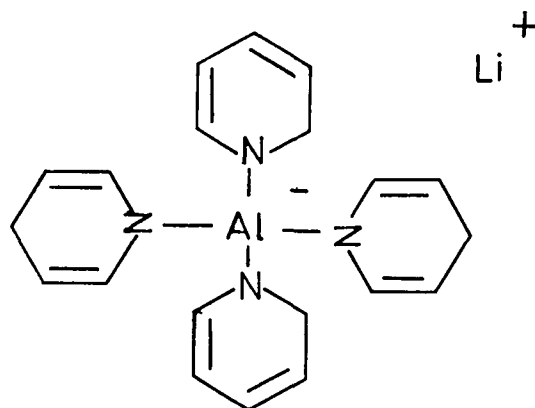
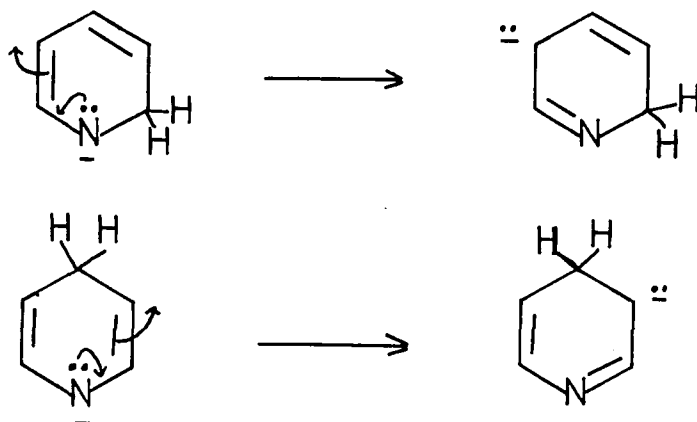


Figure 5. Lithium Tetrakis (N-dihydropyridyl) Aluminate (LDPA).

The 3-positions of both 1,4- and 1,2-dihydropyridines are activated for electrophilic attack by participation of the electron pair on nitrogen in the total resonance of the dihydropyridines. The electrophiles used were the alkyl halides isopropyl and ethyl bromides.



Hydrolysis of the aluminum complex yielded 13% and 11% of 3-isopropylpyridine (20) and 3-ethylpyridine (21), respectively, compared with the average yield of 80% for the alkylations reported by Giam<sup>31</sup>.

The pyridine derivatives purchased from Aldrich Chemical Co. were: 4-phenylpyridine (22), 3-hydroxy-6-methylpyridine (23), 2-methyl-5-ethylpyridine (24), 3-acetylpyridine (25), 1-benzyl-3-piperidone (26). Those obtained from Reilly Tar and Chemical Corp. as gifts were: 2,4-dimethylpyridine (27), 2-benzylpyridine (28), 3,4-dimethylpyridine (29), 3-ethyl-4-methylpyridine (30), 4-t-butylpyridine (31), 3-methyl-4-ethylpyridine (32), and 2-methylpiperidine (34). In addition 2,3-dimethylpyridine (35) was purchased from K & K Laboratories, Inc., and 2,5-dimethylpyridine (36) was purchased from Matheson, Coleman and Bell, 2-phenylpiperidine (33) was obtained from J. K. Kaminski, and 3-chloromethylpyridine hydrochloride (37) from J. Bristol.

The Reduction of Pyridines and N-Benzylpyridinium Salts

The N-benzylpiperidines studied were prepared by reduction of pyridinium salts by catalytic hydrogenation <sup>33</sup> or by NaBH<sub>4</sub> in methanol as described by Lyle and Anderson <sup>34</sup>. Catalytic hydrogenation of the pyridine to the piperidine gave a secondary amine that was alkylated with benzyl bromide.

When disubstituted pyridine or pyridinium salts are reduced to disubstituted piperidines, a pair of cis and trans isomers are produced. The accepted mechanism of catalytic hydrogenation predicts cis addition to the unsaturated double bond from the less hindered side <sup>25</sup>. For instance, catalytic reduction of 1-benzyl-2,3-dimethylpyridinium bromide (38) would be expected to give cis-1-benzyl-2,3-dimethylpiperidine (39) as the major product rather than trans-1-benzyl-2,3-dimethylpiperidine (40) (See Figure 6).

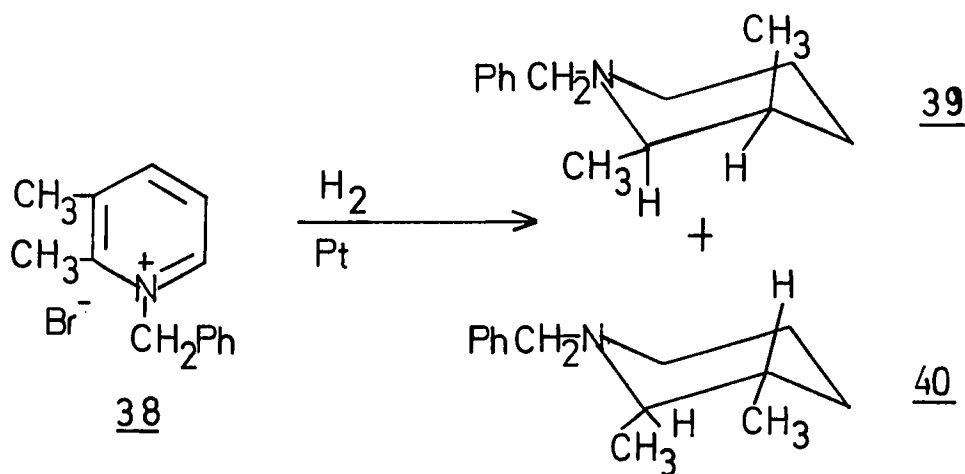


Figure 6. The Hydrogenation of 1-Benzyl-2,3-dimethylpyridinium bromide (38).

Catalytic hydrogenation of 2,4-dimethylpyridine (27) or 1-benzyl-2,4-dimethylpyridinium bromide (41) with PtO<sub>2</sub> gave only the expected cis-1-benzyl-2,4-dimethylpiperidine (42), whereas catalytic hydrogenation of 1-benzyl-2,5-dimethylpyridinium bromide (43) gave a 50:50 cis-trans isomeric mixture of cis-1-benzyl-2,5-dimethylpiperidine (44) and trans-1-benzyl-2,5-dimethylpiperidine (45). The catalytic hydrogenation of all 2,5-disubstituted N-benzylpyridinium salts gave nearly equal amounts of the cis and trans isomers (See Table I), with the exceptions of 1-benzyl-2-methyl-5-benzylpyridinium bromide (49) and 1-benzyl-2-methyl-5-*t*-butylpyridinium bromide (159) which gave mostly the cis and trans isomer, respectively.

TABLE I

cis-trans Ratios of N-Benzyl-disubstituted Piperidines  
Obtained by the Catalytic Hydrogenation of N-  
Benzylpyridinium Bromides<sup>a</sup>

N-Benzyl Pyridinium Bromides	<u>cis</u> % ( <sup>±</sup> 5%)	<u>trans</u> %
2,3-dimethyl ( <u>38</u> )	100	0
2,4-dimethyl ( <u>41</u> )	100	0
3,4-dimethyl ( <u>46</u> )	100	0
2,5-dimethyl ( <u>43</u> )	50	50
2-methyl-5-ethyl ( <u>47</u> )	47	53
2-methyl-5-isopropyl ( <u>48</u> )	53	47
2-methyl-5-benzyl ( <u>49</u> )	74	26
3-ethyl-4-methyl ( <u>50</u> )	90	10
3-methyl-4-ethyl ( <u>51</u> )	100	0
2-methyl-5- <i>t</i> -butyl ( <u>159</u> )	18	82

<sup>a</sup>Reaction conditions are 50 psi of hydrogen with 2% Pt(w/w) in 95% ethanol. Integrations of the benzyl or methyl protons provided the analysis for the isomer ratios.



The hydrogenation of 2,3-lutidine (35) in acetic acid rather than ethanol produced a 75:25 cis to trans isomeric mixture. It was stated by Tsuda <sup>36</sup> that the cis-trans ratios obtained in hydrogenation must be kinetically controlled, since prolonged contact with the Pt catalyst caused isomerization of the less stable isomer. The ratios obtained in the catalytic isomerizations should therefore reflect the relative thermodynamic stability of the cis and trans isomers <sup>37</sup>. The formation of the trans isomer from the reduction of 35 in acetic acid indicated that some equilibration was occurring, for the hydrochloride of 2,3-lutidine 35 gave only the cis isomer on reduction in ethanol. The acetic acid would be expected to coordinate less strongly with the 2,3-lutidine nitrogen than HCl, thereby making the Pt catalyst less effective in promoting reduction <sup>33</sup> thus requiring a longer reaction time during which some equilibration occurred.

Reductions by  $\text{NaBH}_4$  in methanol followed by catalytic hydrogenation of the tetrahydropyridine always gave a mixture of cis and trans isomers (See Table II).

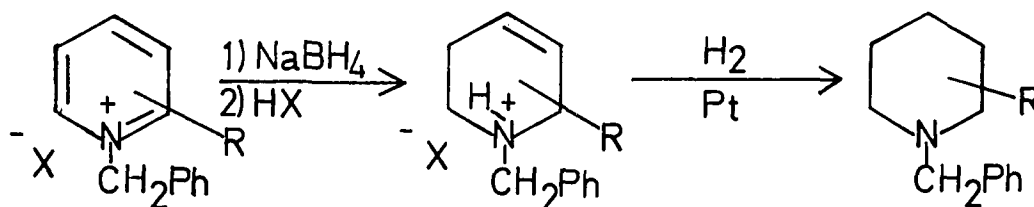


TABLE II

cis-trans Isomer Ratios of Products from  
Reduction by  $\text{NaBH}_4$  then Hydrogenation<sup>a</sup>

N-Benzyl Pyridinium Bromides	<u>cis%</u>	( $\pm 5\%$ )	<u>trans%</u>
2,3-dimethyl ( <u>38</u> )	75		25
3-methyl-4-ethyl ( <u>50</u> )	73		27
2-methyl-4-phenyl ( <u>52</u> )	70		30
2-methyl-4- <u>t</u> -butyl ( <u>53</u> )	60		40

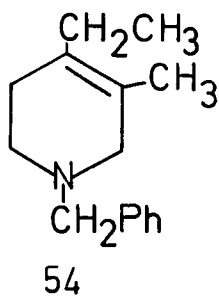
<sup>a</sup>For reaction conditions see the experimental section. Integration of the benzyl or methyl protons was used to determine the isomer ratio.

The reaction of sodium borohydride with substituted pyridinium salts has been shown to yield di- and tetrahydro-pyridines as the major products. The dienamine system formed by the initial attack of the hydride on the pyridinium ion undergoes reaction with a proton from the solvent to give an immonium salt. This is reduced further by  $\text{NaBH}_4$  to give the tetrahydropyridine <sup>38</sup>.

The reaction of hydride ion, from a metal hydride, with an unsaturated heterocyclic ring is an irreversible reaction. Thus the isomer ratio reflects the relative rates of the reactions to form the isomers and the stereochemistry of the reaction being kinetically controlled <sup>38</sup>. Since the hydride ion reductions occur by addition in solution, the products of kinetic control may be different in stereochemistry from the products of kinetic control in catalytic hydrogenation which

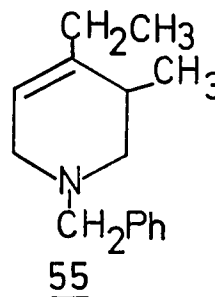
usually produce a predominance of the cis isomer by a heterogeneous reaction.

The stereochemistry of the final reduction product of 1-benzyl-3-methyl-4-ethylpyridinium bromide (50), 1-benzyl-2-methyl-4-phenylpyridinium bromide (52), and 1-benzyl-2-methyl-4-t-butylpyridinium bromide (53) is determined by the last step, the catalytic hydrogenation. In the transition state of catalytic hydrogenation the double bond must approach the catalytic surface as closely as possible. Under the conditions used for reduction (50 psi) the hydrogen apparently adds to the side of the double bond which is opposite the 2-methyl substituent thus leading to a high percentage of cis products from 52 and 53. Cis addition is expected to be the major pathway on catalytic hydrogenation of the tetrahydropiperidine 54, formed on  $\text{NaBH}_4$  reduction of 50, but the tetrahydropiperidine 55 also formed from the  $\text{NaBH}_4$  reduction could presumably give a large percentage of the trans product.



1-Benzyl-3-methyl-4-ethyl-  
1,2,5,6-tetrahydropiperidine  
(54)

1,2,5,6-tetrahydropiperidine  
(54)



1-Benzyl-3-methyl-4-ethyl-  
1,2,3,6-tetrahydropiperidine  
(55)

Stereochemical Studies of N-Benzoyl, N-Isopropyl,  
And N-Benzyl Heterocycles by NMR Spectroscopy

Nonequivalence of N-Benzyl Piperidines

The number of diastereomers formed and their cis and trans relationship were determined by interpretation of the nmr spectra of the reaction mixtures. These assignments were based on the postulate of Lyle and co-workers<sup>11</sup>. The isomer with the larger  $\Delta\nu$  for the AB quartet for the pmr signal of the benzylic proton was assigned the trans configuration for the 2,3- and 2,5-disubstituted derivatives and the cis configuration for the 2,4-disubstituted derivative. These assignments were made on the basis that the predominant conformer of the trans 2,3- and 2,5- and the cis 2,4-disubstituted derivatives would have the 2-methyl equatorial, thus causing substantial benzyl nonequivalence<sup>11</sup>.

Catalytic hydrogenation of 1-benzyl-2,3-dimethylpyridinium bromide (38) yielded only one isomer identified as cis-1-benzyl-2,3-dimethylpiperidine (39) by nmr analysis of the benzylic region (See Figure 7). The resonance signals assigned to the methyl protons appeared as two doublets at 0.90 $\delta$ , further substantiating the isomeric purity of 39.

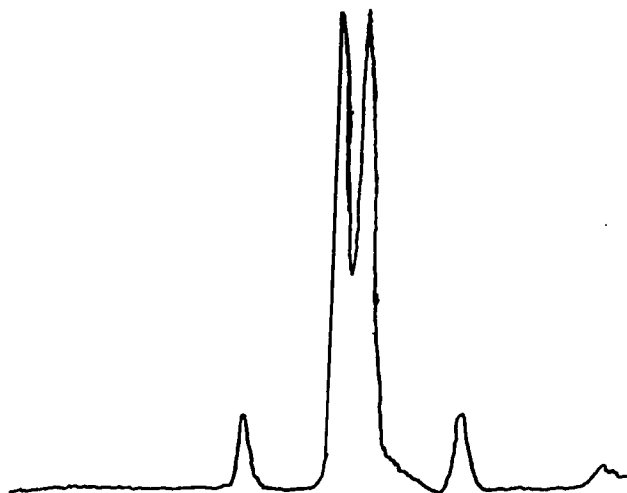


Figure 7. The NMR Signal of the Benzylic Methylene Protons of cis-1-Benzyl-2,3-dimethylpiperidine (39).

A similar reduction of 1-benzyl-2,5-dimethylpyridinium bromide (43) gave a mixture of isomers 44 and 45 as evidenced by the AB pattern of the methylene signals in the benzylic region of the nmr spectrum (See Figure 8).

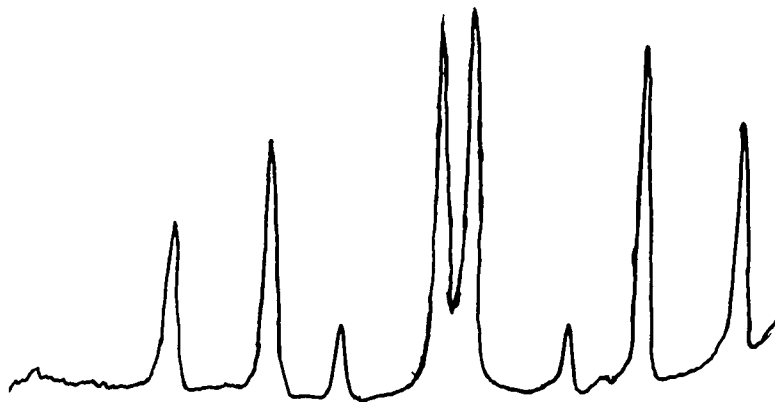


Figure 8. The Methylene Signals in the NMR Spectrum of a Mixture of cis and trans-1-Benzyl-2,5-dimethylpiperidines (44 and 45).

According to the proposal put forth by Lyle *et al.*,<sup>11</sup> where proximity of the chiral center, conformational preference, and rotational preference are considered, the analysis of the system for trans-1-benzyl-2,5-dimethylpiperidine (45) readily led to the assignment of the larger AB quartet to the preferred conformer and rotamer (See Figure 9). The observed nonequivalence of the methylene protons of the benzyl group of cis-1-benzyl-2,3-dimethylpiperidine (39) and cis-1-benzyl-2,5-dimethylpiperidine (44), required some modification of the relationship derived from piperazines, for these isomers would have been expected to give singlets for the methylene protons. The previous results had shown that the equatorial-equatorial interaction of the N-benzyl and 2-methyl of an unbiased 6-membered cyclic system gave a preference of the conformer with the 2-methyl axial. This in turn led to a lack of rotational preference of the N-benzyl bond.

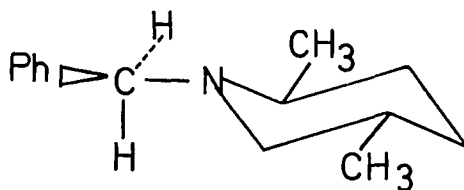


Figure 9. The Preferred Conformation of trans-1-Benzyl-2,5-dimethylpiperidine (45).

If the energetically preferred rotamer is one which has the phenyl farthest away from the 2-methyl group when the 2-methyl is predominantly equatorial, the methylene protons

of the benzyl group should have a large chemical shift separation (See Figure 1). The methylene protons of the benzyl group will be situated as if they were axial and equatorial at the 2-position of a piperidine <sup>11</sup>. The resonance signals for these protons have been shown to differ in chemical shift by more than 1 ppm <sup>39</sup>. However if the preferred conformation has the 2-methyl axial, the benzylic protons should show a minimal chemical shift separation. For example, if a comparison is made between the energy differences of the conformers of cis-1-benzyl-2,3-dimethylpiperidine (39a and 39b) by comparing the number of butane gauche interactions <sup>40</sup>, it would appear that the energy difference between the two would be very small (See Figure 10).

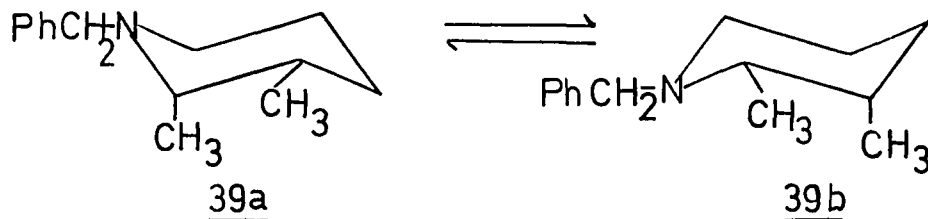


Figure 10. The Conformational Equilibrium of 1-Benzyl-2,3-dimethylpiperidine (39).

The total enthalpy of interaction for each conformer of these derivatives can be estimated, assuming that one gauche interaction between a substituent methyl group and the residual part of the molecule is approximately 0.9 kcal/mol, a 1,3-diaxial methyl-methyl interaction is an additional 1.9 kcal/mol <sup>41</sup>, the benzyl-methyl interaction is the equivalent

of a gauche methyl-methyl interaction with the benzyl spending the majority of its time in the equatorial position, and two methyl-hydrogen interactions are 1.7 kcal/mol<sup>40</sup>.

After applying this method of evaluation of energy differences to the two conformers of cis-1-benzyl-2,3-dimethylpiperidine (39a and 39b), it was seen that theoretically there was no difference. Table III shows the calculated results.

TABLE III  
Conformations and Enthalpies of 1-Benzyl-  
dimethylpiperidines

Compound	Conformation	No. of <u>Gauche</u>	Interac- tions 1,3- dimethyl	Calculated Interaction Energy <sup>a</sup>
<u>39</u>	a	4	0	3.5 kcal/mol
	b	4	0	3.5 (2.7) kcal/mol
<u>44</u> <sup>b</sup>	a	3	0	2.6 kcal/mol
	b	3	0	2.6 (1.8) kcal/mol
<u>45</u> <sup>b</sup>	a	5	0	4.3 (2.6) kcal/mol
	b	1	0	0.9 kcal/mol

<sup>a</sup>Gauche interactions are 0.9 kcal/mol and syn 1,3-dimethyl interactions are 1.9 kcal/mol<sup>41</sup>. Values in parentheses are obtained using 0.93 kcal/mol for the total axial methyl-lone pair-hydrogen interactions. The benzyl-methyl interaction is treated as a gauche interaction.<sup>b</sup> See Figure 11.

For 39b the 2-methyl will be in close proximity to the benzyl protons. If it is in a fixed conformation, the benzyl protons would exhibit an AB quartet with a chemical shift on the order of 1 ppm (60Hz), while the benzyl protons in 39a should show only a singlet if they are fixed in the depicted conformation. According to Table III, the size of the benzylic methylene nonequivalence should be between these two limits



at about 30 Hz since the conformational equilibrium should be composed of 50% of each conformer. The observed separation of the benzylic quartet was 7.9 Hz.

Katritzky reported a value of 0.93 kcal/mol for an axial methyl interaction with a lone pair and a hydrogen. This value was arrived at by configurational equilibrium of cis- and trans-1-t-butyl-3,5-dimethyl-4-piperidones (56) and (57)<sup>42</sup>. Using this value of (0.93 kcal/mol) as the energy of interaction of the axial methyl with the axial hydrogen and the axial lone pair, the values in parenthesis in Table III were obtained. This value predicted that conformer 39b would be favored by 0.9 kcal/mol. Thus, the small  $\Delta\nu$  (7.9 Hz) of the benzylic protons for cis-1-benzyl-2,3-dimethylpiperidine (39) was unexpected if conformer 39b was favored, since the 2-methyl was now in close proximity to the N-benzyl. An alternative explanation for the small  $\Delta\nu$  of cis-1-benzyl-2,3-dimethylpiperidine (39) might be a larger sterically repulsive interaction than anticipated between the 2-methyl and N-benzyl, thus making 39a with its axial 2-methyl and equatorial N-benzyl much more highly favored than 39b with its equatorial N-benzyl and equatorial 2-methyl.

A similar calculation of the enthalpy energies can be done for cis- and trans-1-benzyl-2,5-dimethylpiperidines (44 and 45) (See Figure 11).

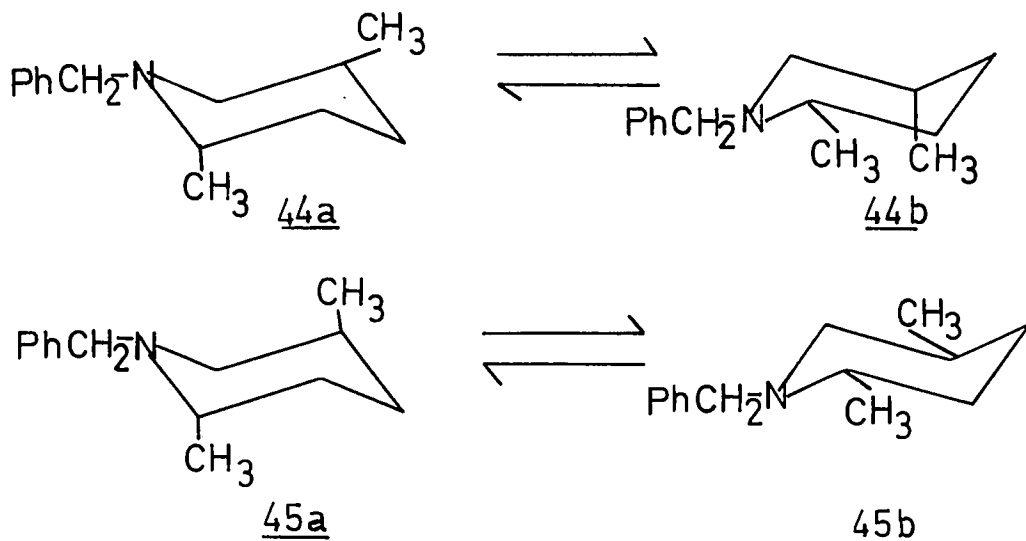


Figure 11. The Conformational Equilibria of cis- and trans-1-Benzyl-2,5-dimethylpiperidine (44 and 45).

The observed difference in chemical shifts for the protons in the AB quartet for 44 was 10.5 Hz. Using the same arguments as presented for cis-1-benzyl-2,3-dimethylpiperidine (39), it appears as if the conformer 44a is favored. Since Table III shows no energy calculation that could favor this conformer, the steric interaction between the equatorial 2-methyl and N-benzyl group must be large, favoring conformer 44a just as postulated for 39a.

trans-1-Benzyl-2,5-dimethylpiperidine (45) agrees more nearly with the theoretical calculation in that the conformer 45b (favored by 3.5 (2.7) kcal/mol) appears to be the major conformer from evaluation of its AB benzylic chemical shift difference of 54.6 Hz. This value approaches the

maximum reported value of 1 ppm. The percentage of the equatorial 2-methyl conformer 45b must be substantially higher than 45a.

A sample of cis-1-benzyl-2,3-dimethylpiperidine (39) in an nmr tube was cooled down to  $-44^{\circ}$  ( $\pm 3^{\circ}$ ) at which temperature the AB quartet of the benzylic methylene had coalesced to a singlet. The nmr spectrum of a sample of cis-1-benzyl-2,5-dimethylpiperidine (44) behaved similarly in the same temperature region,  $-47$  ( $\pm 3^{\circ}$ ) (See Figure 12). The chemical shift difference of the methylene protons in the benzyl group of the trans isomer becomes greater; compare Figure 12b with Figure 8. At  $-80^{\circ}$  ( $\pm 5^{\circ}$ ) the separation has increased to 84 Hz. This would indicate that at low temperatures the conformers 39a, 44a, and 45b are indeed the more stable form of each corresponding set and each is the predominant conformer at room temperature on the basis of the size of the benzylic methylene's AB quartet.

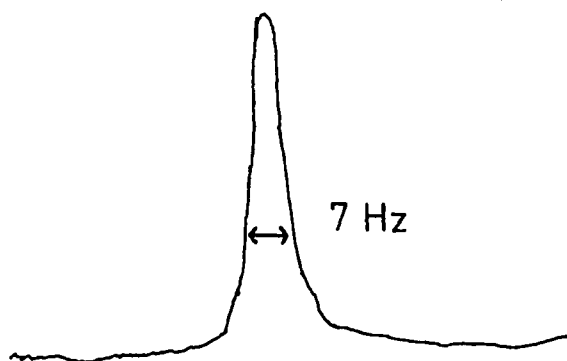


Figure 12a. The NMR Spectrum of the Benzyl Methylene Protons at  $-44^{\circ}$  of cis-1-Benzyl-2,3-dimethylpiperidine (39)

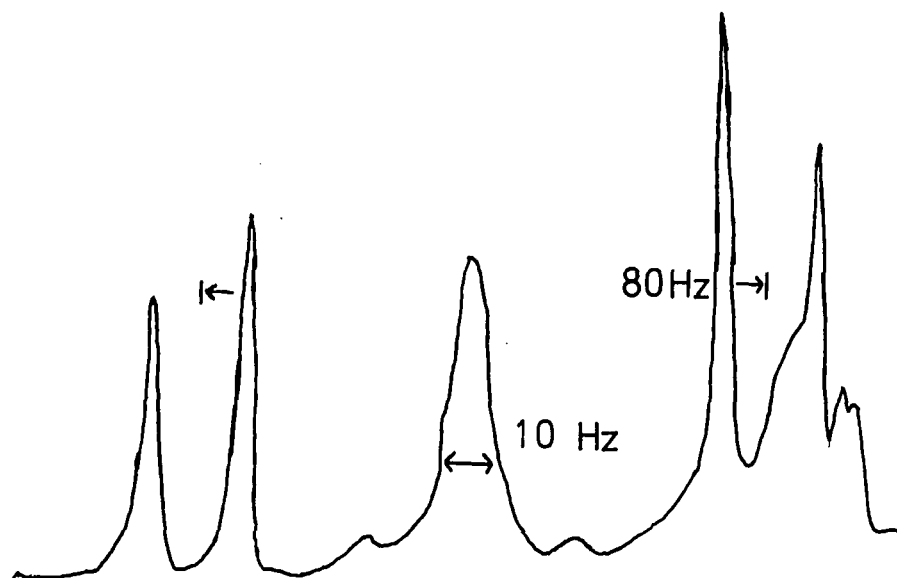


Figure 12b. The NMR Spectrum of the Benzyl Methylene Protons at  $-47^{\circ}$  of cis and trans-1-Benzyl-2,5-dimethylpiperidines (44 and 45)

The changes in the system cis-1-benzyl-2,3-dimethylpiperidine (39) which were observed on conversion of the base to the salt included a separation of overlapping doublets at 0.90 ppm for the methyls of the base to two distinct doublets at 0.90 ppm ( $J=6.5$  Hz) and 1.33 ppm ( $J=6.5$  Hz) for the hydrobromide. The signal for the methylene protons of the benzyl group of cis-1-benzyl-2,3-dimethylpiperidine (39) hydrobromide appeared as a singlet at 4.73 ppm. The hydrochloride of cis-1-benzyl-2,5-dimethylpiperidine (44) gave similar differences in the nmr spectrum as compared with that of the base. The doublet for the  $\text{CH}_3\text{-C}$  resonance at 1.02 ppm was shifted downfield to 1.35 ppm ( $J=6.4$  Hz) in the salt while the  $\text{CH}_3\text{-C}$  doublet at 0.94 ppm ( $J=6.0$  Hz) in 44 was found slightly

upfield at 0.85 ppm in the hydrochloride. The methylene protons of the benzyl group in this case also appeared as a singlet.

trans-1-Benzyl-2,5-dimethylpiperidine (45) exhibited a doublet at 1.45 ppm ( $J=6.0$  Hz) for one  $\text{CH}_3$ -C resonance in the hydrochloride instead of 1.12 ppm as found in the base. The second methyl doublet was observed at 0.60 ppm ( $J=5.8$  Hz) in the salt slightly upfield from the chemical shift of 0.68 ppm shown in the base. The benzylic methylene protons appeared as a smaller AB quartet ( $\Delta\nu=29.6$  Hz,  $J_{\text{AB}}=12.6$  Hz) at 4.25 ppm in the salt than the base. In each case the downfield shift of the nmr signal of the 2-methyl on protonation of the nitrogen must result from the proximity of the  $\text{CH}_3$  to the positively charged nitrogen of the salt. Since there was also a change in solvent from  $\text{CDCl}_3$  (for the base) to  $\text{D}_2\text{O}$  in obtaining the nmr spectra of the hydrohalides, these changes may reflect a large entropy difference in the two sets of conformers.

An upper limiting value of  $\Delta\nu$  was desired for the AB quartet of the diastereotopic protons in a six-membered ring system containing an equatorial 2-methyl and an N-benzyl group so that some attempt to correlate the value of  $\Delta\nu$  of the benzylic methylene protons and the conformational equilibrium of the ring could be made. Due to the high preference of a t-butyl group for the equatorial position in the cyclohexane ring ( $-\Delta G = \text{kcal/mol}$ )<sup>40</sup>, cis-1-benzyl-2-methyl-4-t-butylpiperidine (58) was prepared. The nmr spectrum exhibited a  $\Delta\delta$  of 59.0 Hz for the diastereotopic benzylic protons. Similarly cis-1-benzyl-2-methyl-4-phenylpiperidine (59) and another piperidine, cis-1-benzyl-2,4-dimethylpiperidine (42),

showed large chemical shift separations of their benzylic protons, 61.0 Hz and 60.5 Hz respectively (For complete nmr spectra of the latter three compounds see Figures A-9, A-11, and A-12 in the appendix).

Because of the large unfavorable steric interaction between syn-diaxial 2- and 4-substituents, contribution from conformer a of Figure 13 should be negligible in the conformational equilibrium<sup>40</sup>. Thus the maximum  $\Delta\nu$  to be expected for the benzylic methylene protons in a system with rotational bias produced by a 2-equatorial methyl would be about 1.0 ppm.

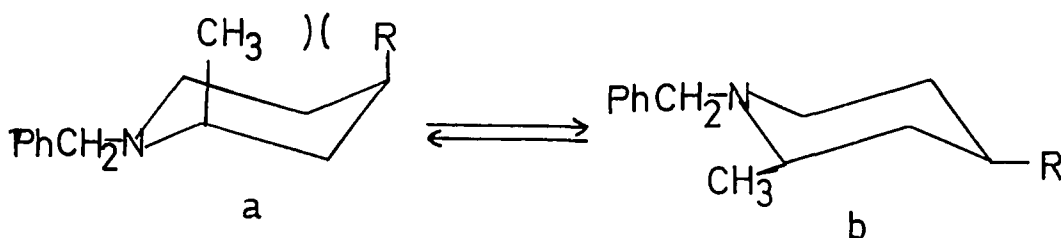


Figure 13. The Conformational Equilibrium of cis-1-Benzyl-2-methyl-4-substituted Piperidine.

The trans-1-benzyl-2-methyl-4-phenylpiperidine (60) and trans-1-benzyl-2-methyl-4-t-butylpiperidine (61) gave singlets for their benzylic methylene protons in the nmr as expected, for now the more favored or predominant conformer would be expected to have an axial 2-methyl and an equatorial 4-substituent. This assignment was supported by analogy to work done by Johnson<sup>44</sup> who showed that a methyl group in the axial position was coupled more strongly to the adjacent ring proton by about 1-2 Hz than was a methyl that was equatorial

(See Table IV). While the results are not conclusive, it is evident that the axial methyl in the cases cited does have a slightly larger coupling constant.

TABLE IV  
Correlation of the 2-Methyl Coupling Constant  
with Axial or Equatorial Assignment

Compound	J(Hz <sup>±.2</sup> ) <sup>a</sup>	Assignment	Equatorial or Axial
<u>58</u>	6.1	Equatorial	
<u>59</u>	6.1	Equatorial	
<u>42</u>	6.0	Equatorial	
<u>60</u>	6.75	Axial	
<u>61</u>	6.75	Axial	

<sup>a</sup>Obtained at a sweep width of 50 Hz on the Varian A-60 in CDCl<sub>3</sub>.

After evaluation of the 2,4-disubstituted series, a study of a 2,5-disubstituted series was desired for comparison. This would allow immediate comparison of the effect of steric size at the 5-position on the conformer preference by determining through the magnitude of the  $\Delta\nu$  of the benzylic methylene nonequivalence (See Figure 14). As noted in Table I, catalytic hydrogenation of 2,5-disubstituted pyridinium salts gave a mixture of cis and trans isomers. The results of the nmr studies are listed in Table V.

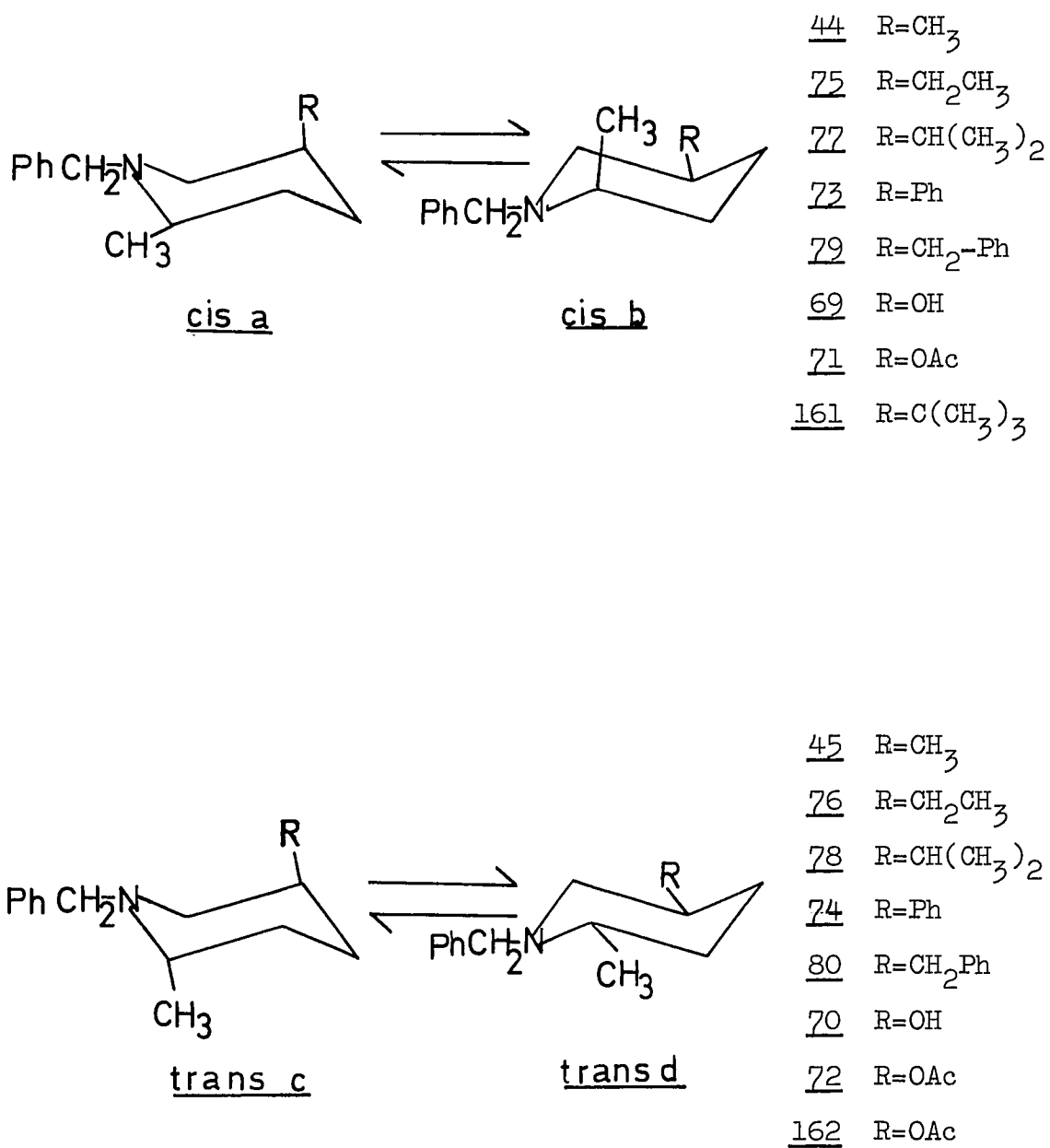


Figure 14. The Conformational Equilibria of cis- and trans-1-Benzyl-2-methyl-5-substituted Piperidines.



TABLE V  
NMR Parameters of 1-Benzyl-2,5-disubstituted  
Piperdines

Compound #	5-Substituent	$\Delta\nu$ ( $\pm 2$ Hz)	$J_{AB}$ ( $\pm .5$ Hz)	$J_{2-CH_3}$ ( $\pm .5$ Hz)
<u>cis</u>				
<u>44</u>	methyl	10.5	12.6	6.4
<u>75</u>	ethyl	17.5	12.5	--- <sup>a</sup>
<u>77</u>	isopropyl	12.9	13.5	---
<u>73</u>	phenyl	singlet	---	6.5
<u>79</u>	benzyl	24.0	13.5	6.3
<u>69</u>	hydroxyl	13.5	13.0	6.5
<u>70</u>	acetoxyl	23.2	14.0	6.5
<u>161</u>	<u>t</u> -butyl	7.5	13.2	---
<u>trans</u>				
<u>45</u>	methyl	54.6	12.8	5.6
<u>76</u>	ethyl	53.0	13.0	---
<u>78</u>	isopropyl	52.9	13.3	---
<u>74</u>	phenyl	53.7	13.5	5.5
<u>80</u>	benzyl	45.6	13.3	6.3
<u>71</u>	hydroxyl	46.0	13.5	6.1
<u>72</u>	acetoxyl	47.1	13.8	6.0
<u>162</u>	<u>t</u> -butyl <sup>96</sup>	52.4	13.2	5.4

<sup>a</sup>These dotted lines indicate hidden signals.

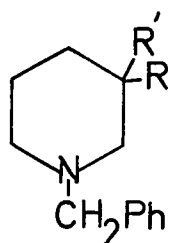
From Table V it is seen that the  $\Delta\nu$  values for the benzylic protons for the trans derivatives are similar in magnitude. The large size of  $\Delta\nu$  for this series substantiates the fact that trans d should be the major conformer.

The data for the cis series were less easily understood, for as the steric size of the 5-substituent increased it was anticipated that the contribution of conformer cis b to the equilibrium would also increase. This should lead to a singlet for the nmr signal of the benzylic methylene protons in all cases in which the 5-substituent was larger than methyl. Quite the contrary was observed. For example, cis-1-benzyl-2-methyl-5-phenylpiperidine (73) with the large phenyl ( $-\Delta G$ -3kcal/mol) gave a singlet as expected, but cis-1-benzyl-2-methyl-5-ethyl-piperidine (75) with the large ethyl group ( $-\Delta G$ -1.8 kcal/mol)<sup>40</sup> gave an AB quartet with a  $\Delta\nu$  of 17.5 Hz. Both substituents, phenyl and ethyl, would be expected to maintain the equatorial conformation, and the benzyl methylene protons would be expected to have an nmr signal of a singlet because the 2-axial methyl group of conformer cis b of Figure 14 should not cause rotamer bias.

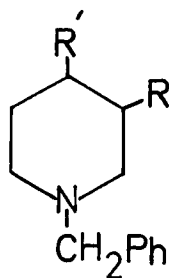
The relative  $\Delta\nu$ 's are more reasonable if one notes that the axial 5-substituent has only one syn-axial hydrogen interaction and one interaction with the nitrogen free pair. The 5-alkyl group would prefer the axial conformation as compared with the 2-methyl; however, the electronic interaction of an axial phenyl with the lone pair would be strongly repulsive<sup>42b</sup>.

These data suggested that the symmetry of the magnetic field experienced by the benzyl protons was being perturbed to some extent by the axial 5-substituent. To evaluate the nature of this long range effect, a series of 1-benzyl-3-substituted and 1-benzyl-3,4-disubstituted piperidines were studied (See Table VI).

The following compounds were then prepared by the procedures described in the experimental section:



<u>81</u>	R=CH <sub>3</sub> , R'-H <sup>45</sup>	<u>91</u>	R=OH, R'-H <sup>46</sup>
<u>83</u>	R=CH <sub>2</sub> CH <sub>3</sub> , R'-H	<u>86</u>	R=Ph, R'-OH <sup>46</sup>
<u>85</u>	R=CH(CH <sub>3</sub> ) <sub>2</sub> , R'-H	<u>87</u>	R=Ph, R'-OAc
<u>88</u>	R=Ph, R'-H	<u>92</u>	R=CH <sub>2</sub> CH <sub>3</sub> , R'-OH <sup>46</sup>
<u>90</u>	R=CH <sub>2</sub> Ph, R'-H	<u>93</u>	R=CH <sub>2</sub> CH <sub>3</sub> , R'-OAc <sup>46</sup>
		<u>160</u>	R=C(CH <sub>3</sub> ) <sub>3</sub>



	<u>cis</u>	<u>trans</u>	
<u>95</u>	R=CH <sub>3</sub> , R'-CH <sub>2</sub> CH <sub>3</sub>	<u>100</u>	R=CH <sub>3</sub> , R'-CH <sub>2</sub> CH <sub>3</sub>
<u>97</u>	R = CH <sub>2</sub> CH <sub>3</sub> , R'-CH <sub>3</sub>		
<u>99</u>	R=CH <sub>3</sub> , R'-CH <sub>3</sub>		

TABLE VI

NMR Parameters of 1-Benzyl-3-substituted and  
1-Benzyl-3,4-disubstituted Piperidines<sup>a</sup>

Compound #	Substituents	( $\pm$ 1 Hz)	$J_{AB}$ ( $\pm$ .25 Hz)
<u>81</u>	3-CH <sub>3</sub>	singlet <sup>45</sup>	---
<u>83</u>	3-CH <sub>2</sub> -CH <sub>3</sub>	singlet	---
<u>85</u>	3-CH(CH <sub>3</sub> ) <sub>2</sub>	6.65	13.2
<u>88</u>	3-Ph	singlet	---
<u>90</u>	3-CH <sub>2</sub> Ph	12.9	13.0
<u>91</u>	3-OH	singlet	---
<u>87</u>	3-OAc, Ph	singlet	---
<u>93</u>	3-OAc, CH <sub>2</sub> CH <sub>3</sub>	7.15	13.3
<u>86</u>	3-OH, Ph	singlet <sup>46</sup>	---
<u>92</u>	3-OH, CH <sub>2</sub> CH <sub>3</sub>	singlet <sup>46</sup>	---
<u>95</u>	3-CH <sub>3</sub> -4-CH <sub>2</sub> CH <sub>3</sub>	12.2	13.5
<u>97</u>	3-CH <sub>2</sub> CH <sub>3</sub> -4-CH <sub>3</sub>	10.4	13.3
<u>99</u>	3,4-CH <sub>3</sub>	10.0	13.5
<u>100</u>	3-CH <sub>3</sub> -4-CH <sub>2</sub> CH <sub>3</sub>	singlet	---
<u>160</u>	3-t-butyl	12.95 <sup>96</sup>	13.2

<sup>a</sup>Spectra were determined using a Jeol MH 100 spectrometer expanded to a sweep width of 270 Hz.

The nmr data in Table VI show that the 3-substituent must influence the magnetic environment of the N-benzyl protons. For the entries 93, 95, 97, 99 and 160, a small quartet was noted in each case. This perturbation of the benzylic environment must be from an axial 3-substituent since the equatorial substituents of 81, 83, 88, and 91 showed no effect on the N-benzyl nonequivalence. Conformer b (Figure 15) would be expected to contribute significantly to the conformational equilibrium since R is syn axial to only one hydrogen.

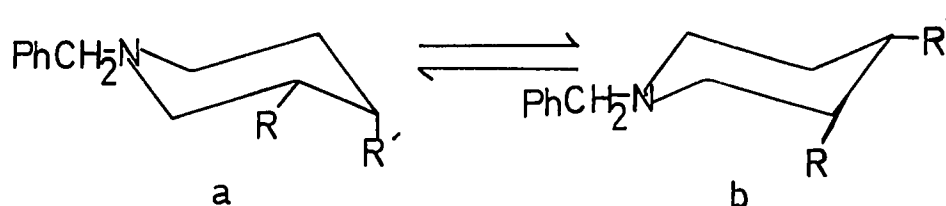


Figure 15. The Conformational Equilibrium of cis-1-Benzyl-3,4-disubstituted Piperidines.

The assignment of the cis configuration to these isomers was made on the basis of the assumption that the cis product would be the major isomer formed on catalytic hydrogenation of the disubstituted pyridine<sup>35</sup>. The trans-1-benzyl-3-methyl-4-ethylpiperidine (100) exhibited a singlet for the benzyl methylene protons. Since the diequatorial conformer is expected to be highly favored the observed results are in agreement with the axial 3-substituent causing the observed benzylic nonequivalence.

For the mono  $\beta$ -substituted series only the isopropyl 85, benzyl 90, and t-butyl 160 groups showed any effect on the diastereotopic benzyl methylene. This must be due to the steric size of the isopropyl, t-butyl, and benzyl groups which was detected in the form of nonequivalent N-benzyl protons. This effect appears to be comparable to that of an axial methyl (See Table VI).

In 93 it was observed that a small  $\Delta\nu$  of 7.15 Hz for an AB quartet was exhibited for the N-benzyl protons, while in 92 the N-benzyl protons were a singlet. Since the  $\beta$ -acetoxy group of 93 should be axial<sup>40</sup>, the carbonyl group present must create a substantial magnetic field perturbation which the methylene protons can detect. A similar effect was noted by Iorio<sup>47</sup>; however, this effect was not observed for 87.

The diastereotopic protons of the methylene group of an N-benzyl substituent on a six-membered heterocycle appear as an AB quartet if (1) it is adjacent to an equatorial substituent or (2) if the N-benzyl group is  $\beta$  to an axial substituent. The former condition probably causes an unequal population of C-N rotamers because of steric interaction. To determine to what extent the effect that substituents at the ortho-position of the phenyl ring would have on rotational preference and the magnitude of  $\Delta\nu$ , a series of N-(ortho-substituted)-benzyl-2-methyl and 2,4-dimethylpiperidines were prepared (See Table VII).

TABLE VII

NMR Spectral Data of Substituted N-Benzyl-2-methyl and cis-2,4-Dimethylpiperidines<sup>a</sup>

Compound	$\Delta\nu(\pm 2\text{Hz})$	$J(\pm .5\text{Hz})$
1-( <u>o</u> -Nitrobenzyl)-2-methylpiperidine ( <u>101</u> )	45.4	15.5
<u>cis</u> -1-( <u>o</u> -Nitrobenzyl)-2,4-dimethylpiperidine ( <u>102</u> )	67.0	16.0
1-(2,6-Dichlorobenzyl)-2-methylpiperidine ( <u>103</u> )	35.6	12.2
1-( <u>o</u> -Acetamidobenzyl)-2-methylpiperidine ( <u>104</u> )	64.5	13.7
<u>cis</u> -1-( <u>o</u> -Acetamidobenzyl)-2,4-dimethylpiperidine ( <u>105</u> )	83.5	13.3
1-( <u>o</u> -Acetoxybenzyl)-2-methylpiperidine ( <u>106</u> )	56.4	13.2
1-( <u>o</u> -Hydroxybenzyl)-2-methylpiperidine ( <u>107</u> )	53.1	14.2
1-( <u>o</u> -Aminobenzyl)-2-methylpiperidine ( <u>108</u> )	68.9	12.85
<u>cis</u> -1-( <u>o</u> -Aminobenzyl)-2,4-dimethylpiperidine ( <u>109</u> )	88.6	12.2

<sup>a</sup>Spectral Data obtained at a sweep width of 500 Hz in  $\text{CDCl}_3$ .

The effect that the ortho-substituent has on the magnitude of the  $\Delta\nu$  probably resulted from a change in the preferred rotational conformation of the aryl to methylene bond. This is an unpredictable relationship. From Table VII you will note that the smallest  $\Delta\nu$  was observed for the most hindered system, the 2,6-dichloro derivative 103.

The introduction of an o-nitro group on the benzyl group of 1-benzyl-2,4-dimethylpiperidine (42) caused an increase in the magnitude of  $\Delta\nu$  of 6.5 Hz in cis-(o-nitrobenzyl-2,4-dimethylpiperidine (102)). This increase probably results from a different rotamer population about the Ar-CH<sub>2</sub> bond.

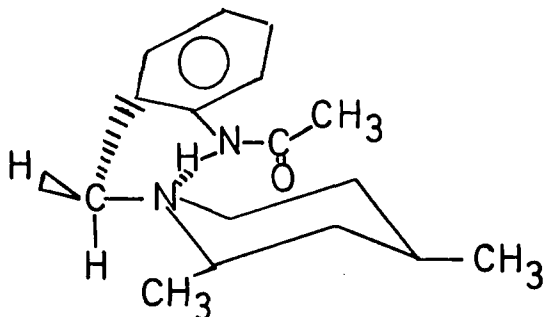


Figure 16. Intramolecular Hydrogen Bonded cis-(o-Acetamidobenzyl)-2,4-dimethylpiperidine (105).

It was generally noted that if protons exchangeable by D<sub>2</sub>O were present on the ortho-substituents, the value of  $\Delta\nu$  was large. The exception to this was the o-hydroxy derivative 107 which may exist to a large extent as a zwitterion. An explanation for the large  $\Delta\nu$  when exchangeable hydrogens



are present is that intramolecular hydrogen bonding can occur leading to restricted rotation about the aryl-methylene bond (See Figure 16). The benzylic protons are in distinctly different magnetic environments due to the anisotropic current of the aromatic ring. The difference of 20.3 Hz between the values of 1-(o-Aminobenzyl)-2-methylpiperidine (108) and cis-1-(o-Aminobenzyl)2,4-dimethylpiperidine (109) may be a reflection of the contribution of the conformation having a 2-axial group (Figure 17) to the equilibrium of 108. The equatorial-equatorial interaction of the 1-benzyl and 2-methyl substituents in the chair conformation 108b is unfavorable and results in a significant contribution of 108a to the conformational equilibrium (See Figure 17). Since 109 has more of the

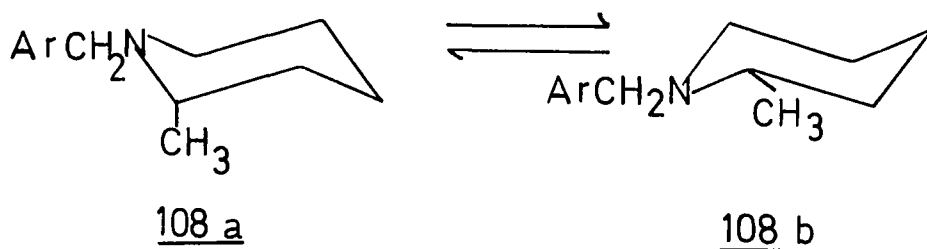


Figure 17. The Conformational Equilibrium of N-(o-Substituted)-2-methylpiperidines.

conformer with the equatorial 2-methyl than does 108, it would be expected to show the larger chemical shift separation of the benzylic methylene protons.

While this research was in progress, Chow<sup>48</sup> reported that for N-benzyl-2-methyl piperidines, as the electro-

negativity of the p-phenyl substituent increased,  $J_{AB}$  increased. For example, p-OCH<sub>3</sub> gave a  $J_{AB}$  of 13.1 Hz while p-NO<sub>2</sub> gave 14.5 Hz. The coupling constants ( $J_{AB}$ ) in Table VII, followed the trend reported by Chow for the mono-substituted phenyls. The o-hydroxybenzyl-2-methylpiperidine (107) was exceptional for the coupling constant was larger than would be predicted for an electron-releasing group such as hydroxyl<sup>49-51</sup>.

In order to investigate further the contributions of each rotamer to the methylene nonequivalence in the piperidine ring system, 1-(2,2-diphenylethyl)-2-substituted piperidines were made (See Figure 18). The 1-methylene (A) and methine (B) protons gave rise to a spectral pattern ( $\alpha_1, \alpha_2, \beta$ ) approximating the ABX for a system undergoing fast rotation but with unequal population of rotamers<sup>52,53</sup>.

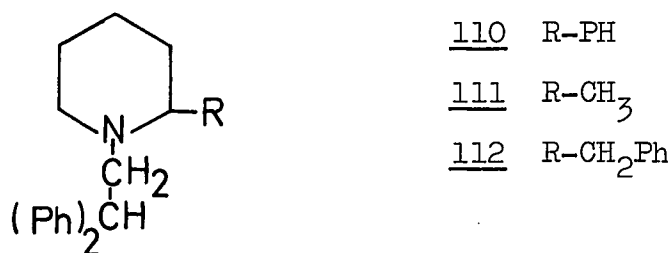


Figure 18. N-(2,2-diphenylethyl)-2-substituted Piperidines.

Assuming that compounds 110, 111, and 112 exist in a dynamic equilibrium among the three classically staggered rotamers A, B, and C having mole fractions a, b, and c

respectively, the coupling constant can be related to the mole fraction of the rotamer (See Figure 19). If all the couplings between gauche protons in Figure 19 are equal, the mole fractions of each rotamer can be calculated using the following equations<sup>52</sup>:

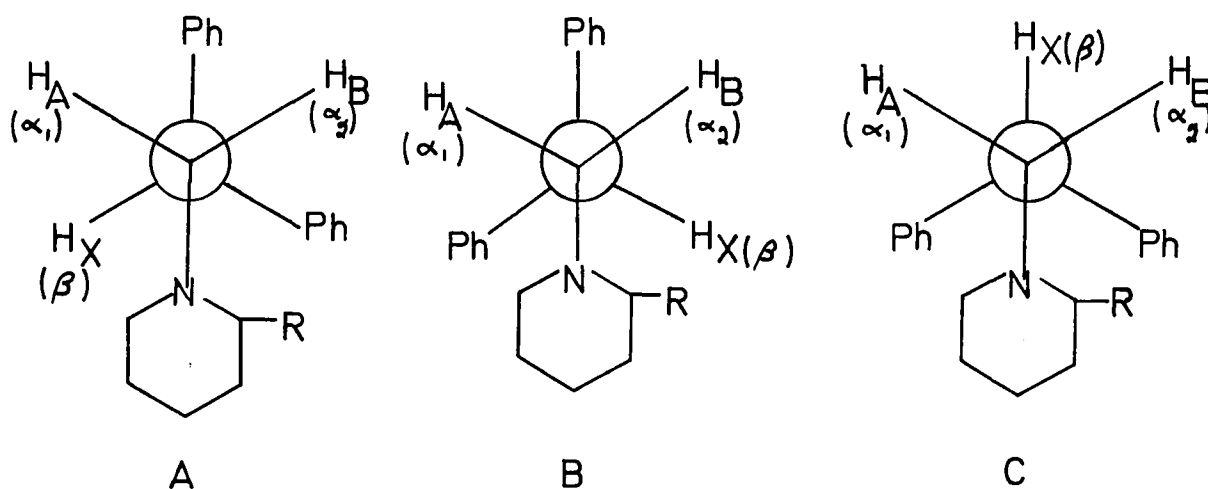


Figure 19. Representations of Three Rotamers of N-(2,2-diphenylethyl)-2-substituted Piperidines.

$$a = \frac{J_{\alpha_2\beta} - J_g}{J_t - J_g}$$

$$b = \frac{J_{\alpha_1\beta} - J_g}{J_t - J_g}$$

$$c = \frac{J_t + J_g - (J_{\alpha_1\beta} + J_{\alpha_2\beta})}{J_t - J_g}$$

Only if the two  $\beta$  groups are different on the 1-substituent would the gauche coupling be expected to be different because of the difference in electronegativities of these two groups<sup>52</sup>. There are no suitable models from which to choose  $J_{\underline{t}}$  and  $J_{\underline{g}}$ , but in order to give some estimate the values  $J_{\underline{t}}=14$  and 13 Hz and  $J_{\underline{g}}=2.0$  Hz were taken for trial calculations (See Table VIII for results).

The assignment of the protons  $H_A$  and  $H_B$  to the diastereotopic protons in Figure 19 was arbitrary, and thus the structure of rotamers A and B may be reversed. It seems probable, however, that the change in chemical shift of the proton at higher field in the AB quartet of 111 from 2.9 ppm with a 2-methyl to 2.4 ppm in 110 with a 2-phenyl reflects the shielding effect of the 2-phenyl on the hydrogen of closest proximity ( $H_B$ ). This proton also showed the smaller coupling with the methine proton. Thus rotamer B should be the major contributor to the system at room temperature.

The effect of the 2-substituent on the  $\Delta\nu$  in the 1-diphenyl-ethyl series showed the same trend as that observed for the 1-benzyl-2-substituted piperidines. The 2-phenyl gave the largest  $\Delta\nu$  (37.0 Hz, 111), and the 2-benzyl was smallest (15.2 Hz, 112). The values for the 1-benzyl series are as follows:  $\Delta\nu = 61.5$  Hz for 1-benzyl-2-phenylpiperidine (113),  $\Delta\nu = 49.1$  Hz for 1-benzyl-2-methylpiperidine (114)<sup>48</sup> and for 1,2-dibenzylpiperidine (115) a  $\Delta\nu$  of 34.9 Hz was observed.

TABLE VIII  
The Effect of Choice of  $J_t$  and  $J_g$  on Calculated  
Rotamer Populations<sup>a</sup>

		$J_t$	$J_g$	Observed $J_{\alpha,\beta} = 10.3$ , $J_{\alpha_2\beta} = 4.7$ Hz		
				a	b	c
<u>110</u> (R-Ph)	14	2	.225	.695	.083	
	13	2	.246	.755	0	
	13	3	.170	.730	.110	
				Observed $J_{\alpha,\beta} = 8.18$ , $J_{\alpha_2\beta} = 6.5$ Hz		
				a	b	c
<u>111</u> (R-CH <sub>3</sub> )	14	2	.375	.515	.116	
	14	2	.41	.56	.12	
	13	3	.35	.518	.122	
				Observed $J_{\alpha,\beta} = 7.3$ , $J_{\alpha_2\beta} = 7.3$ Hz		
				a	b	c
<u>112</u> (R-CH <sub>2</sub> PH)	14	2	.441	.441	.117	
	13	2	.481	.481	.127	
	13	3	.390	.390	.140	

<sup>a</sup> $J_{\alpha,\beta}$  and  $J_{\alpha_2\beta}$  are the equivalent of  $J_{AX}$  and  $J_{BX}$  respectively and were determined from their nmr spectra and verified by calculation using the equations of Pople<sup>54</sup>.

#### N-Benzyl and N-Isopropyl Nonequivalence of Piperazines and Quinolines

Several N-isopropylpiperazines were prepared in order to study the effect of the 2-substituted heterocycles on the chemical shifts of diastereotopic methyl groups (See Figure 20).

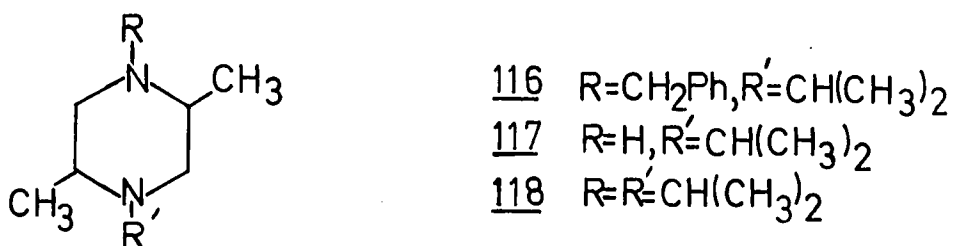


Figure 20. cis-1,4-Disubstituted-2,5-dimethylpiperazines.

The spectral data obtained from the piperazine derivatives 116-118 were disappointing. Nonequivalence of the isopropyl methyls was observed but the separation in chemical shift was small (< 4 Hz). Positive distinction between the signals for the methyls of the isopropyl group and those on the ring could not be made, so a quantitative measurement of any difference was not possible. Not unexpectedly, the benzyl protons of 116 gave a  $\Delta\nu$  of 33.0 Hz<sup>11</sup>.

A large difference in chemical shift ( $\Delta = .33$  ppm) between the diastereotopic methyl groups of trans-1-isopropyl-2,5-dimethyl-4-piperidone (119) was reported by Casy<sup>55</sup>. This is in contrast with the chemical shift identity of the methyls of the isopropyl in 1-isopropyl-3-methyl-4-piperidone (120). These observations suggest that the preferred orientation in 119 of the N-substituent with respect to the piperidine ring is that depicted in Figure 21a. In this conformation (which avoids methyl-methyl interactions with the equatorial substituent at C-2), the two isopropyl methyl groups differ in their magnetic environment, one being gauche and the other trans to

the nitrogen lone pair. In 120 the isopropyl methyls are symmetrically disposed about the lone pair orbital<sup>55</sup> (See Figure 21b).

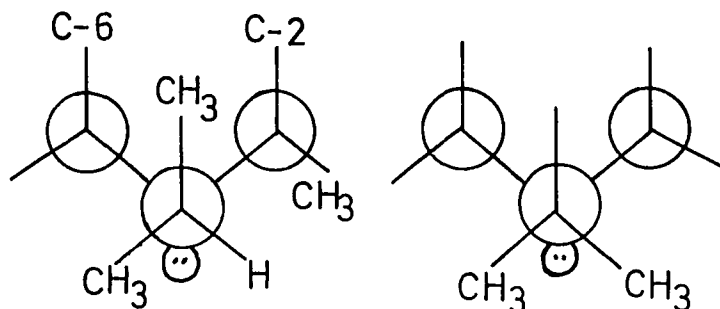


Figure 21. The Preferred Rotamers of trans-1-Isopropyl-2,5-dimethyl-4-piperidone (119) and 1-Isopropyl-3-methyl-4-piperidone (120), a and b respectively.

The pmr spectrum of 1-isopropyl-2-methylpiperidine (121) showed a small separation (4 Hz) of the methyl signals of the isopropyl group. This small separation of the isopropyl methyls in 121 must result from contribution of both chair conformers of the piperidine ring to the conformational equilibrium, thereby minimizing the 2-methyl-isopropyl methyl interaction.

The possibility of observing the nonequivalence of the diastereotopic benzyl methylene protons in 1-benzyl-2-methyl-1,2,3,4-tetrahydroquinoline (124) (Figure 22) was investigated. In this bicyclic system, the aromatic ring of the quinoline was expected to enhance the magnetic nonequivalence of the benzyl protons. The conformer 124b of Figure 22 would

be expected to be the more stable because of the equatorial methyl substituent, and this should also affect the benzyl methylene protons' magnetic environment. Surprisingly the benzyl methylene protons appeared as a singlet showing accidental magnetic equivalence.

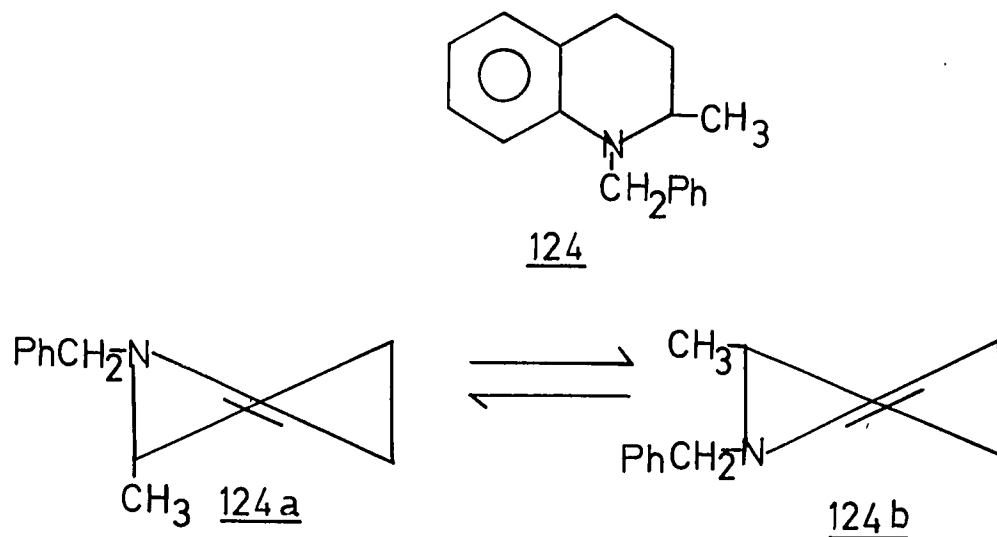


Figure 22. The Conformation Equilibrium of 1-Benzyl-2-methyl-1,2,3,4-tetrahydroquinoline (124).

The cis-1-benzyl-2-methyl-decahydroquinoline (126) also gave a singlet in the nmr for the benzyl methylene protons. The cis stereochemistry was assigned to this isomer because this would be the expected product from the catalytic hydrogenation of 2-methylquinoline (122)<sup>33</sup>.



Determination of the Conformation of the Benzamide of 2-Substituted Piperidines, Piperazines, and Quinolines

The study by Johnson<sup>44, 56</sup> of the conformation of alkylpiperidine amides suggested that a 2-substituent on the piperidine ring preferred the axial orientation in the amides in order to minimize the steric interaction with the carbonyl of the amide group. This research was intended to explore the generality of this concept and utilize additional physical data to test the hypothesis of Johnson. It was desirable to know if the unfavorable energy encountered by the carbonyl group with an equatorial 2-substituent was greater than the syn-diaxial interaction encountered when the piperidine ring was substituted by cis groups at the 2- and 4-position. From the value of the coupling constant of the 2-methyl with the ring proton, the multiplicity of the furthest downfield aliphatic proton signal, and from a europium chemical shift study of cis-1-benzoyl-2,4-dimethylpiperidine (127), further evidence on this question was sought (Table IX).

It was reported by Nagarujan<sup>57</sup> that the 1-benzoyl-2-methyl-1,2,3,4-tetrahydroquinoline (123) gave a septet for the nmr signal at 4.8 ppm ( $J=6.5-7.0$  Hz) for the 2-proton. He concluded from this that 123 was held in a single conformation with the 2-methyl group axial, for the equatorial proton at the 2-position was coupled almost equally with the protons at the 3-position and those attached to the 2-methyl group.

On examination of the nmr spectrum of cis-1-benzoyl-2,4-dimethylpiperidine (127) at 100 MHz, it was found that the signal for the 2-proton was also a septet, and the assignment of this signal was verified by decoupling studies. It must

be concluded by analogy with 123 that 127 also exists as a conformer having an axial 2-methyl. As to whether the conformations of the other amides listed in Table IX also have the 2-methyl in an axial conformation has not been determined definitely. The previous discussion in relating coupling constants with conformation (p.32) suggests that the arrangement of the 2-methyls may be indicative of the ring conformation as shown in Figure 23 or a distorted form of this structure.

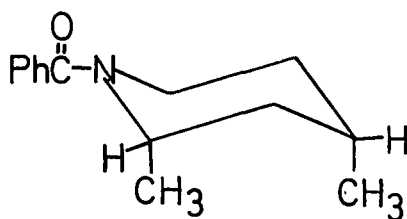


Figure 23. cis-1-Benzoyl-2,4-dimethylpiperidine (127).

cis-1-Benzoyl-4-isopropyl-2,5-dimethylpiperazine (132) gave a chemical shift separation for the isopropyl methyls of 13Hz. This probably means that the preferred conformation in this cis-2,5-dimethylpiperazine has the 2-methyl axial and the 5-methyl equatorial causing nonequivalence of the isopropyl methyls near the same magnitude as that observed by Casy<sup>55</sup> for the 4-piperidone 119.

The possibility of utilizing first order analysis of the coupling of the 2- and 6-protons of the piperidine and piperazine amides as a means for determining the ring conformation was not generally possible. Only amides 123 and 127

TABLE IX  
NMR Parameters of Cyclic Substituted Benzamides

Compound	Most Downfield Aliphatic Signals ( $\delta$ )	Multiplicity and No. of Hydrogens	$J_{C_2-CH_3}$ ( $\pm 0.5$ Hz)
<u>cis</u> -1-Benzoyl-2,4-dimethylpiperidine(127)	4.2(st,1H)		6.5 <sup>a</sup>
<u>cis</u> -1-Benzoyl-2,3-dimethylpiperidine(128)	4.4-3.5(m,2H)		6.8 <sup>a</sup>
<u>cis</u> -1-Benzoyl-2-methyl-4-phenylpiperidine(129)	4.3-3.8(m,1H)		6.2
<u>cis</u> -1-Benzoyl-2-methyl-4- <u>t</u> -butylpiperidine(130)	3.5-2.7(m,3H) <sup>b</sup>		6.2
<u>cis</u> -1-Benzoyl-4-isopropyl-2,5-dimethylpiperazine(132)	4.9-3.7(m,2H)		6.5 <sup>a</sup>
1-Benzoyl-2-methyl-1,2,3,4-tetrahydroquinoline(123)	4.83(st,1H) <sup>57</sup>		6.5-7.0
<u>cis</u> -1-( <u>o</u> -Nitrobenzoyl)-2,4-dimethylpiperidine(133)	4.2-3.9(m,1H)		6.8

<sup>a</sup>Determined at a sweep width of 50 Hz where the error should be now  $\pm 0.1$ Hz. <sup>b</sup>Analyzed as a mixture of cis and trans isomers.

gave nmr spectra in which the protons to the nitrogen could be identified. Even these could not be used to provide an unequivocal assignment of conformation.

Lanthanide ions have been used successfully as paramagnetic shift reagents by several workers.<sup>58-64</sup> This means that protons in the vicinity of a site for complexation of the metal complex will show a larger displacement of the nmr signal than those further away. It has been shown that this

technique can be utilized for assigning conformations provided there is some knowledge of the site of interaction of the shift reagent and the substrate. Assuming that the amide 127 has a rigid conformation as shown in Figure 23 with little rotation about the C-N bond and no conformational changes (subsequent plots of the europium shifts obtained versus  $\frac{1}{R^3}$  eliminated all other possible rotameric forms and the diequatorial conformation) the McConnell-Robertson equation can be used to correlate the paramagnetic shift of each proton with its distance from (R) and angle to ( $\theta$ ) the lanthanide ion using the relationship:

$$\frac{\Delta\nu}{\nu} = \frac{3(\cos^2\theta - 1)}{R^3}$$

In this study tris-(dipivalomethanato) europium III<sup>59</sup>, commonly known as  $\text{Eu}(\text{DPM})_3$ , was used as the shift reagent. In the model, europium ion was assumed to be  $3.5 \text{ \AA}$ <sup>61</sup> above the carbonyl oxygen.<sup>61, 60b</sup> The distance to the surrounding protons was measured from Dreiding Models and plotted against the molar ratio of europium to the amide cis-1-benzoyl-2,4-dimethylpiperidine (127). Figure 24 shows the plot of the data from Table X as fitted by least-squares computation.

The angle ( $\theta$ ) in the McConnell Equation has been defined as the angle between the assumed symmetry axis of the lanthanide chelate and the vector from lanthanide to proton<sup>61</sup>. The  $(3\cos^2\theta - 1)$  term would be positive for the more prevalent angles from  $0^\circ$  to  $54.7^\circ$  and from  $125.2$  to  $180^\circ$  but negative between  $54.7$  and  $125.2^\circ$ . For angles in the latter range a positive  $\Delta\nu$ , a shift to higher field, should be observed<sup>62-64</sup>.

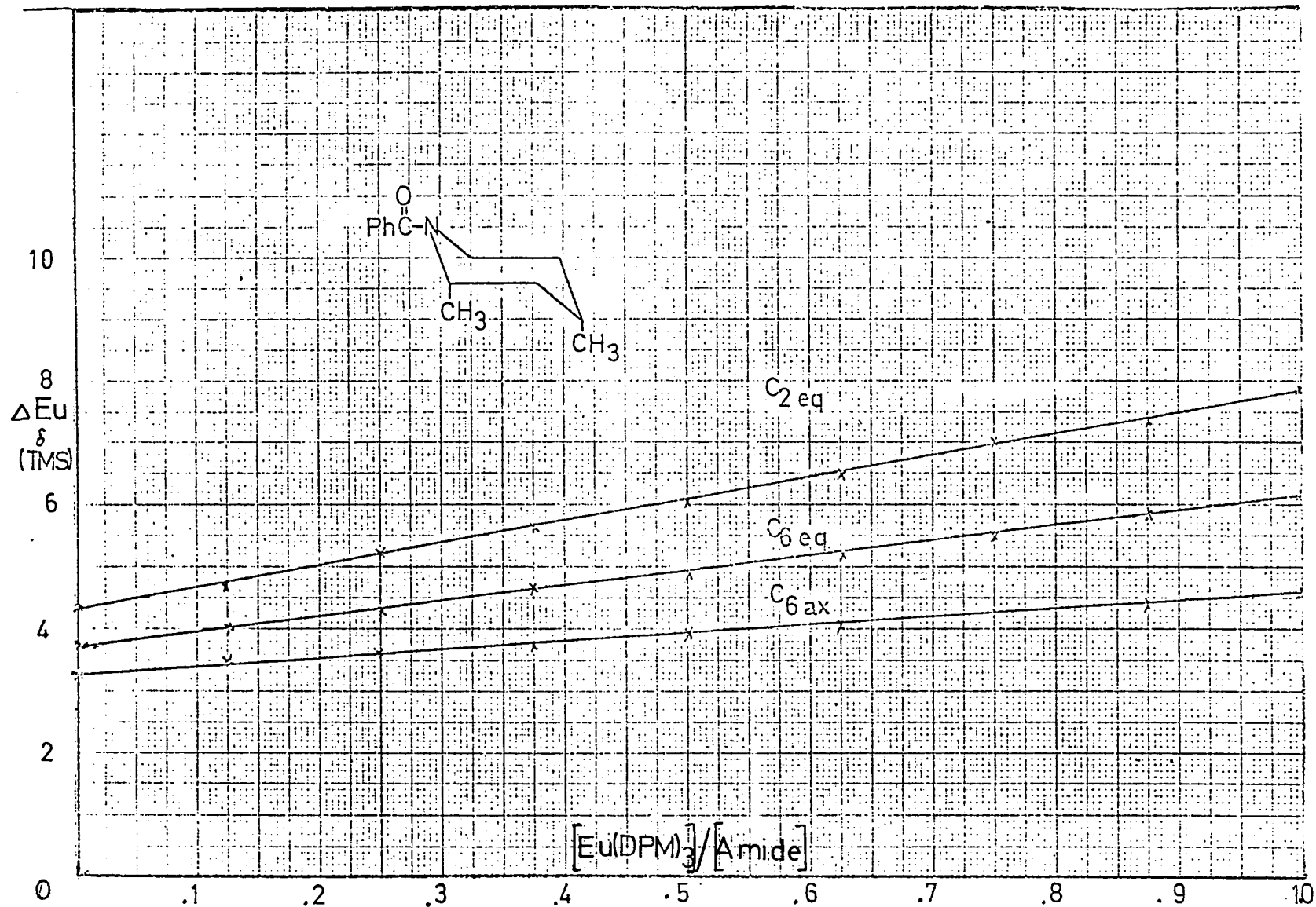


Figure 24. A Plot of the Paramagnetic Shift Against the Molar Ratio of Europium to the Amide (127).

The magnitude of the shift is determined by consideration of both the europium-hydrogen angle ( $\theta$ ) and the distance between the nuclei (R).

The best plot of the paramagnetic shift versus  $\frac{1}{R^3}$  was obtained when the europium of the complex was located at a distance  $3.5 \text{ \AA}$  away from the carbonyl oxygen<sup>61,65</sup> and arranged so that the symmetry vector and the vector connecting the oxygen and europium gave an angle of  $90^\circ$ . This places the europium  $5.0 \text{ \AA}$  from the  $C_2$ -equatorial proton and located the symmetry vector pointing toward the phenyl ring.

The  $(3 \cos^2\theta - 1)$  factor was shown to affect the signs of the shifts of the phenyl protons (See Table X). The shifts were positive for the meta- and para- protons which lie in the range of  $\theta=90-120^\circ$  and were negative for the ortho-protons which are closer and are at more acute angles,  $\theta=40.60^\circ$ . Similar measurements for the  $C_{2eq}$ ,  $C_{6ax}$ ,  $C_2$ -methyl, and  $C_4$ -methyl gave values of  $\theta \approx 30, 60, 50, 145,$  and  $130^\circ$  respectively, and all but the  $C_{6eq}$  had positive angle factors (See Table XI).

From Figure 24 it is readily observed that the  $C_2$ -proton (assigned by decoupling experiments as discussed on p. 51) moved the farthest downfield as the concentration of the shift reagent was increased. The slope of the plot of the shift of the  $C_2$ -proton was 3.52 compared to 2.39 and 1.23 for the  $C_6$ -equatorial and axial protons respectively. Thus Figure 24 serves as an indication that the europium ion was closer to the  $C_2$ -proton and the  $C_6$ -equatorial protons than to the  $C_6$ -axial proton or to the  $C_2$ - and  $C_4$ -methyls.

TABLE X

Results of Paramagnetic Induced Shifts( $\delta$ ) Using Tris(dipivalomethanato) Europium III

Conc. of Eu(DPM) <sub>3</sub>	[Eu] [Amide] <sup>a</sup>	1-Benzoyl- <u>cis</u> -2,4-dimethylpiperidine (127)						
		$\delta_{eq}$	$\delta_{C_{6ax}}$	$\delta_{C_{2eq}}$	$\delta_{C_2\text{-methyl}}$	$\delta_{C_4\text{-methyl}}$	$\delta_{Ph_{m-p}}$	$\delta_{Ph_o}$
0		3.8(3.65) <sup>c</sup>	3.3(3.22) <sup>c</sup>	4.40(4.27) <sup>c</sup>	1.40(1.30) <sup>c</sup>	1.12(1.06) <sup>c</sup>	7.5(7.47) <sup>c</sup>	7.5(7.81) <sup>c</sup>
.25x10 <sup>-4</sup> mol(.12)		4.03(3.95)	3.43(3.38)	4.81(4.69)	1.41(1.38)	.98(.998)	7.4(7.40)	7.65(7.66)
.5x10 <sup>-4</sup> mol(.25)		4.23(4.27)	3.53(3.54)	5.12(5.15)	1.41(1.46)	.92(.94)	7.3(7.32)	7.88(7.91)
.75x10 <sup>-4</sup> mol(.375)		4.47(4.58)	3.67(3.70)	5.45(5.59)	1.47(1.54)	.85(.88)	7.2(7.25)	8.08(8.16)
1x10 <sup>-4</sup> mol(.50)		4.70(4.89)	3.70(3.87)	5.80(6.03)	1.58(1.62)	.80(.82)	7.13(7.17)	8.27(8.41)
1.25x10 <sup>-4</sup> mol(.625)		5.13 (5.21)	3.98(4.03)	6.37(6.47)	1.66(1.71)	.75(.76)	7.13(7.04)	8.63(8.66)
1.5x10 <sup>-4</sup> mol(.75)		5.55(5.52)	4.25(4.19)	7.00(6.91)	1.79(1.79)	.70(.70)	7.10(7.02)	9.07(8.91)
1.75x10 <sup>-4</sup> mol(.875)		5.90(5.82)	4.35(4.36)	7.41(7.35)	1.89(1.87)	.61(.64)	6.93(6.95)	9.23(9.16)
2.0x10 <sup>-4</sup> mol(1)		6.27(6.15)	4.61(4.52)	7.90(7.79)	2.07(1.96)	.65(.58)	6.85(6.87)	9.35(9.41)
b								
$\Delta$ Eu at 1 Molar Concentration		-2.47	-1.31	-3.50	-.67	+.47	+.65	-1.70
Correlation Coefficient		.991	.983	.994	.956	.973	.984	.991

a The amide, 44mg(2x10<sup>-4</sup>mol) was dissolved in .4ml of CCl<sub>4</sub>. b The difference in resonance position for a given solute proton when dissolved in inert CDCl<sub>3</sub> from that when an equimolar amount of Eu(DPM)<sub>3</sub> is present in the same solvent, i.e.,  $Eu = \delta_{CDCl_3} - \delta_{Eu(DPM)_3}$ .<sup>61</sup> c Data in parentheses was computed by the method of least-squares using a STATPACK program.

TABLE XI

The Relationship Between Bond Distances  
and Paramagnetic Induced Shifts of  
Eu(DPM)<sub>3</sub> on the Amide 127

Proton Assignment	R(A°) <sup>a</sup>	$\frac{1}{R^3} \times 10^{-3}$	$\Delta E^b$
C <sub>2eq</sub>	5.0	8.0(7.43) <sup>c</sup>	-3.50
C <sub>6eq</sub>	5.60	5.7(5.87)	-2.47
C <sub>6ax</sub>	6.70	3.3(3.12)	-1.31
C <sub>2</sub> -CH <sub>3</sub>	7.00	2.9(3.15)	- .67
C <sub>4</sub> -CH <sub>3</sub>	7.80	2.1(1.43)	+ .47

<sup>a</sup>Determined by direct measurement from a Dreiding Model of Figure 23. <sup>b</sup>See Table X. <sup>c</sup>Data in parentheses was computed by the method of least-squares using a STATPACK program.

In an attempt to check the assumed location of the europium ion with respect to the piperidine ring, a plot was made of  $\Delta E$  versus  $\frac{1}{R^3}$ , where  $\Delta E$  is the paramagnetic shift and R is the distance in A° of the proton in question from the lanthanide ion (See Table XI and Figure 25). The correlation coefficient is .967 and the slope is .550. The correlation of the proton distance from the europium with the magnitude of the paramagnetic shift is illustrated by Figure 25. Along with the decoupling data discussed on p. 51 these experiments appear to provide ample evidence that the amide cis-1-benzoyl-2,4-dimethylpiperidine (127) exists in a conformation with the 2- and 4- methyl groups axial. However, when the McConnell equation is converted to the form  $\log \Delta \nu$



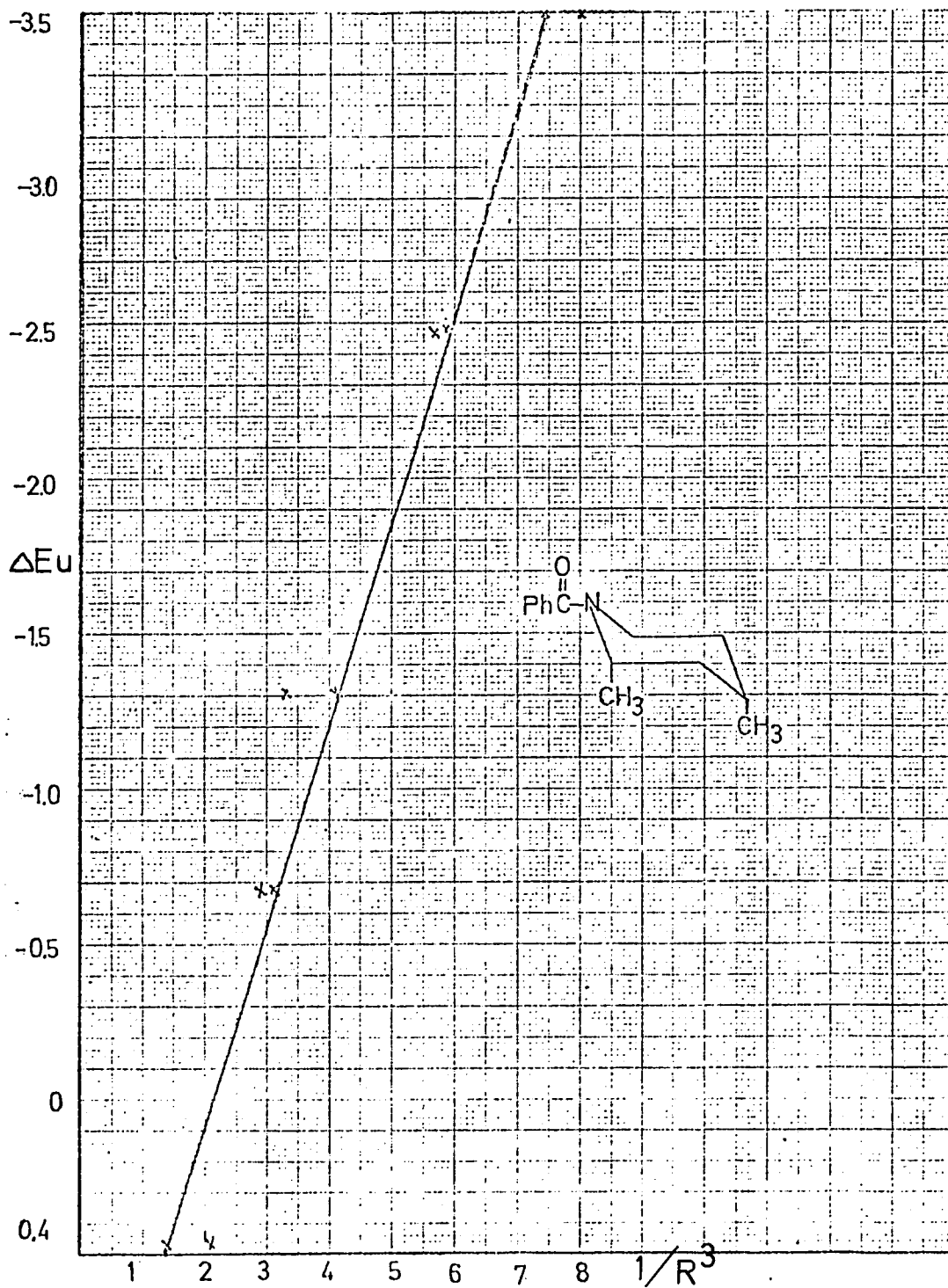


Figure 25. A Plot of  $\Delta E_u$  Against  $1/R^3(\text{\AA}^3)$ . The points not connected are the observed, not least-squares derived.

$= -3 \log R + \log k$  and  $\log \Delta\nu$  is plotted against  $\log R$  a slope of  $-3$  should be obtained (See Table XII and Figure 26). The data plotted in Figure 26 utilized the computer calculated least-squares points for the values of  $R(A^\circ)$ . The correlation coefficient is .980. The slope obtained averaged  $-4.87$ . The upfield shift of the  $C_4$ -methyl led to a smaller value for the slope. The large deviation of the observed slope from  $-3.0$  may be due to complexation of more than 1 molecule of the europium or to the inaccurate positioning of the europium complex relative to the protons shifted. This incorrect positioning could result from a conformational distortion of the piperidine ring or the presence of both cis and trans rotameric forms of the amide 127.

TABLE XIIA

Logarithmic Data of Eu and  $R(A^\circ)$ 

$\Delta E^a$ (log $\Delta E$ )	$R(A^\circ)$ (logR)	Computed Log $R^b$
3.50 (.541)	5.0 (.699)	.709
2.47 (.390)	5.6 (.748)	.741
1.131 (.053)	6.7 (.826)	.811
.61 (-.17)	7.0 (.845)	.857

<sup>a</sup>  $\Delta E$  and  $R(A^\circ)$  are obtained from Table XI. <sup>b</sup> Computed by the method of least-squares using a STATPACK program

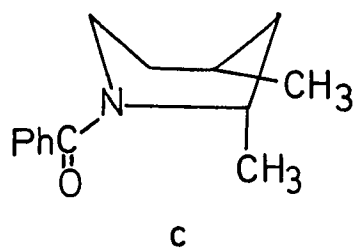
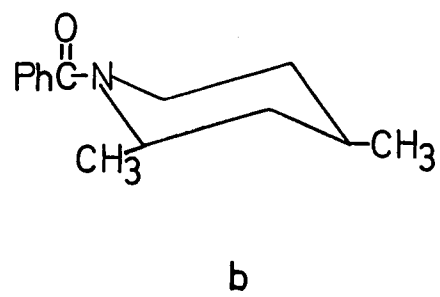
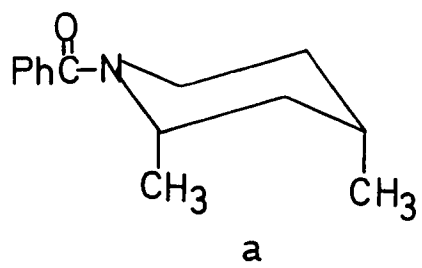
The correlation of the observed shifts in proton resonance in amide 127 on addition of the europium complex (Eu (DPM)<sub>3</sub>) was found to be better with conformation a, having two axial methyl groups, than b; however, to determine as closely as possible the extent of the distortion of the ring of cis-1-benzoyl-2,4-dimethylpiperidine (127) the boat conformation c with the 2-methyl in an axial position was studied. From a plot of  $\Delta E$  versus  $1/R^3$ , a least-squares analysis of the data in Table XIII gave a correlation coefficient of .962. When  $\log \Delta E$  was plotted against  $\log R$  a slope of -3.89 was obtained and the correlation coefficient was .934. It is evident from the data obtained in this Eu(DPM)<sub>3</sub> study that a definitive assignment of the conformation of the amide 127 would be difficult. But it is certain that the 2-methyl group is axial.

TABLE XIIB

Logarithmic Data of  $\Delta E$  and  $R(A^\circ)$   
From the Boat Conformation

$\Delta E^a$ (log $\Delta E$ )	$R(A^\circ)^b$	Log R	$1/R^3$
3.5 (.541)	4.0	.602	.015
2.47 (.390)	5.0	.699	.008
1.13 (.053)	5.6	.748	.005
.67 (-.17)	6.0	.778	.004
-.47 ----	8.4	----	.001

<sup>a</sup>  $\Delta E$  was obtained from Table XI. <sup>b</sup> Obtained by measurement from a Dreiding model.



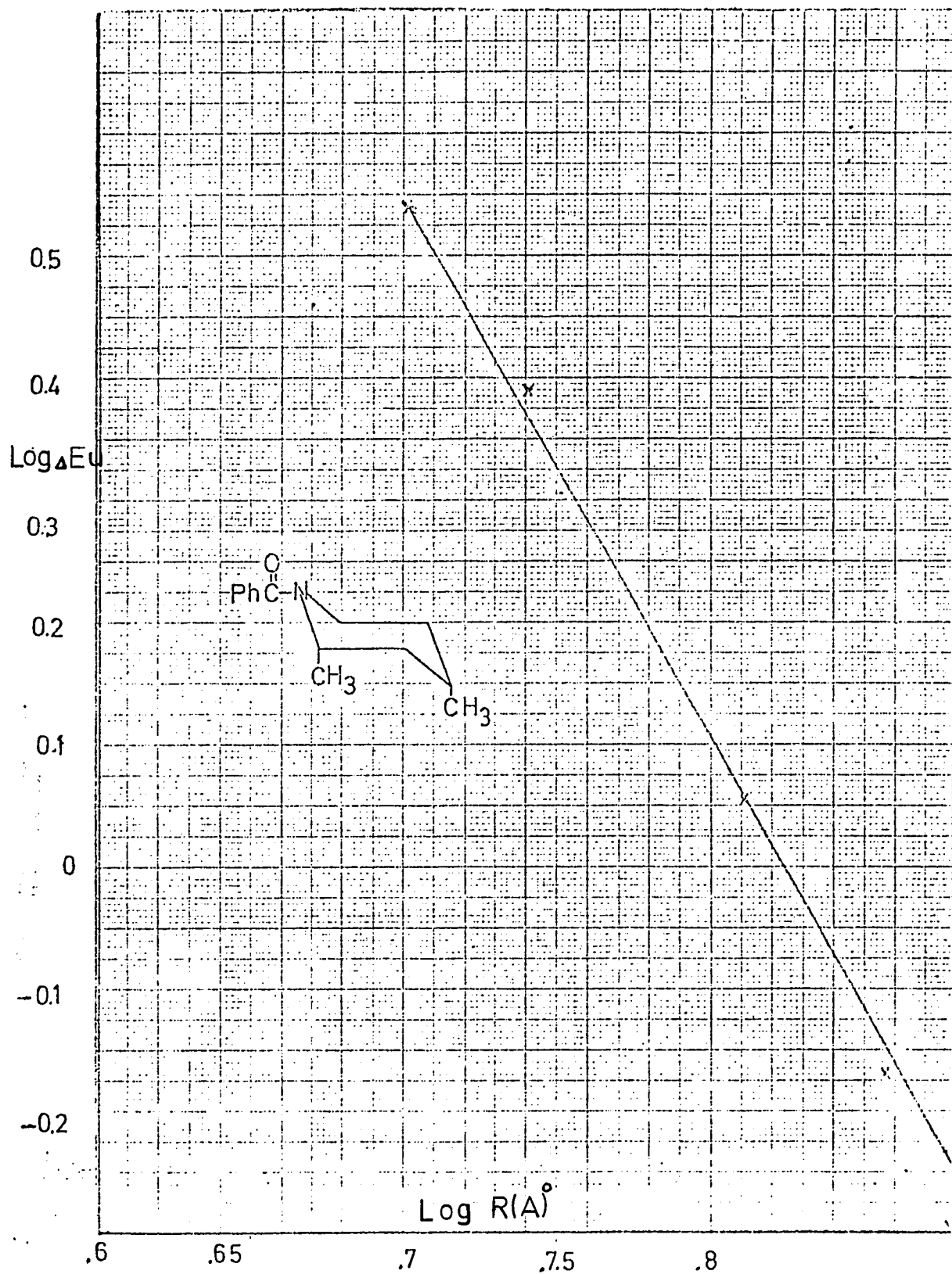


Figure 26. A Plot of  $\log \Delta Eu$  Against  $\log R(A^\circ)$ .

## CHAPTER III

## EXPERIMENTAL

General

Melting Points. Melting points were determined using either a Mel-Temp melting point apparatus or a Thomas Hoover capillary melting point apparatus. All melting points were uncorrected.

Infrared Absorption Spectra. The infrared absorption spectra were determined using a Perkin-Elmer Model 337 grating infrared spectrometer. The spectra of liquids were determined as films, and the spectra of solids were determined as mulls in Nujol. The intensity of the bands are indicated by (s), strong; (m), medium; (w), weak; (b), broad; and the location of the bands are given in frequency units,  $\text{cm}^{-1}$ .

Nuclear Magnetic Resonance Spectra. The nuclear magnetic resonance spectra were determined using either a Varian Model A-60, Varian Model HA-100, or JNM-MH100 proton resonance spectrometer. The spectra were determined in a 20%(v/v)  $\text{CDCl}_3$  solution using a sweep width of 500 Hz unless otherwise specified. The chemical shifts are given in ppm relative to tetramethylsilane as an external standard. The probe temperature was maintained at approximately  $33^\circ\text{C}$ . The multiplicity of the signal assignments were indicated as (s), singlet; (d), doublet; (t), triplet; (d,d), double doublet; (q), quartet; (st), sextet; (ht), heptet; (h), hidden; and (b), broad.

Variable temperature spectra were obtained with a V-6057 variable-temperature controller and probe. Temperatures were checked before and after each spectrum by measuring the chemical shift difference in the absorption peaks of methanol at low temperature and ethylene glycol at high temperature. Temperature-dependent spectra are reproducibly reversible in all cases.

Materials. Lithium reagents were either obtained as gifts from Foote Mineral Co.<sup>65</sup> or prepared by Gilman's method;<sup>66</sup> concentration was determined by the method of Watson.<sup>67</sup> Diethylether (anhydrous grade), benzene, and toluene used as solvents were stored over sodium wire. Tetrahydrofuran was distilled from potassium hydroxide and stored over molecular sieves. Pentane was purified by the method of Vogel.<sup>68</sup> Pyridine was distilled from potassium hydroxide and stored over anhydrous barium oxide. Other solvents and materials were reagent grade.

Analytical Data. Microanalyses were determined by either Jack Gunther, Ingo Hartmann, or Linda Heavner on a F & M Model 185 carbon, hydrogen, and nitrogen analyzer.

#### General Procedure for Preparation of 1-Benzyl Pyridinium Salts(I)

Three methods were used for preparation of the pyridinium salts. Method A was most commonly used and usually provided crystalline material. Methods B and C were used only if salt formation proved to be difficult by Method A. Tabulated

preparation and analytical data are given in Tables XIII and XIV, respectively.

Method A. To a solution of the substituted pyridine in acetone or anhydrous ether was added an equal molar amount of benzyl bromide or chloride also dissolved in ether or acetone. The resulting mixture was heated under reflux for 2-12 hr and then filtered. The solid was washed with ether and allowed to dry in air. The filtrate was concentrated; the residue crystallized on standing at room temperature or on cooling. After washing with ether, the solid was collected and the process repeated until the residual oil from the filtrate no longer gave solid precipitate.

Method B. To an ethanolic solution of the substituted pyridine was added an equal molar amount of benzyl bromide or chloride. On standing for 12-24 hr the solution was concentrated and crystallization was effected with addition of ether.

Method C. To neat substituted pyridine was added an equal molar amount of benzyl bromide. The solution was allowed to stand at room temperature until recrystallization occurred or heated with an oil bath at 100° until a crystalline mass was obtained. Recrystallization was effected from ethanol-ether.

#### General Procedure of Preparation of 1-Benzyl Piperidines(II)

Four methods of preparation of the 1-benzylpiperidines were studied. Method B was used the most often when the



pyridine or pyridinium salt was resistant to catalytic hydrogenation as was the case with 2-methyl-4-t-butylpyridine (15). Method C was used when the amide was desired for study. Method D was used when the piperidine was available and the amide was not desired. The yields in all four cases were comparable. Tables XV and XVI in the Appendix provide preparation and analytical data respectively for the benzylpiperidines.

Method A. The pyridinium salt was dissolved in 75-100 ml of 95% ethanol and platinum oxide (2%w/w) was added. The suspension was flushed three times with hydrogen then kept under a blanket of hydrogen, either at atmospheric conditions using the Fieser reduction set-up<sup>69</sup> or under 50 psi using a Parr low pressure reduction apparatus. The latter was found to give better yields. When the calculated amount of hydrogen was absorbed, the platinum was removed by filtration. The filtrate was concentrated to dryness under reduced pressure and the residue was basified with aqueous potassium carbonate and then extracted several times with ether. The ether extracts were combined and dried over either magnesium sulfate, potassium carbonate, or sodium sulfate. The N-benzylpiperidine residue after concentration was purified by distillation.

Method B. The pyridinium salt was dissolved in 50 ml of methanol and cooled with ice-water to 0-5°. A two molar excess of sodium borohydride was added portionwise with stirring. After the addition was complete, the reaction mixture was stirred at room temperature for .5 hr and then acidified with dilute hydrochloric acid. The mixture was concentrated

under reduced pressure and dissolved in 75-100 ml of 95% ethanol. Any insoluble material was removed by filtration and platinum oxide (2% w/w) was added to the reduction vessel which was kept under 50 psi of hydrogen (after flushing three times) until the calculated amount of hydrogen was absorbed (12 hr). The platinum was removed by filtration, and the filtrate was concentrated to dryness. The residue was made basic with aqueous potassium carbonate and extracted with ether. The ether extracts were combined and dried over either magnesium sulfate, potassium carbonate, or sodium sulfate. The N-benzylpiperidine residue after concentration was purified by distillation.

Method C. The pyridine was dissolved in 75-100 ml of 95% ethanol contained in a Parr reduction vessel and platinum oxide (2% w/w) was added. The solution was made distinctly acidic with concentrated hydrochloric acid, flushed three times with H<sub>2</sub> and kept under an atmosphere of hydrogen at 50 psi until the calculated amount of hydrogen was absorbed. The platinum was removed by filtration, and the filtrate was evaporated to dryness. The residue was basified with aqueous potassium carbonate and extracted with ether several times. The combined ether extracts were dried over either magnesium sulfate, potassium carbonate, or sodium sulfate. The piperidine residue obtained after concentration was purified by distillation.

To an Erlenmeyer flask containing 10 ml of ether was added the piperidine and 10 ml of 20% sodium hydroxide to

form a suspension. An equimolar amount of benzoyl chloride in 5 ml of ether was added dropwise with stirring. After the addition and stirring at room temperature for 6-12 hr, the suspension was extracted with ether and the ether extracts were dried over sodium sulfate or potassium carbonate. Upon concentration of the ether layer the benzamide obtained was purified by recrystallization from hexane followed by sublimation or distillation.

To 30 ml of anhydrous ether under dry nitrogen in a three necked flask was added lithium aluminum hydride with stirring. At room temperature to this slurry was added a .5 molar amount (relative to the lithium aluminum hydride) of the benzamide dissolved in 10 ml of anhydrous ether. When the addition was completed, the suspension was heated to reflux temperature and stirred for 12 hr under nitrogen. The suspension was cooled and hydrolyzed using 15% sodium hydroxide in the Fieser <sup>70</sup> manner. After drying the ether layer over either magnesium sulfate, potassium carbonate, or sodium sulfate, concentration of the ether solution and distillation of the residue gave the pure N-benzylpiperidine.

Method D. To a 50 ml solution of benzyl bromide in benzene was added slowly a 10-20% molar excess of the secondary piperidine. After the addition the reaction mixture was heated under reflux for 6-12 hr. The cooled reaction mixture was concentrated to dryness, basified with aqueous potassium carbonate, and extracted with ether. After drying the ether solution over either magnesium sulfate, sodium sulfate, or

potassium carbonate, it was evaporated to dryness and the N-benzylpiperidine residue was purified by distillation.

### Preparation of Pyridines

2-Methyl-4-t-butylpyridine (15). - To 15g (.11 mol) of 4-t-butylpyridine (31) in 100 ml of anhydrous ether under a nitrogen atmosphere using the method of Abramovitch <sup>71</sup>, methyl-lithium (.11 mol, prepared in the standard manner from methyl bromide and lithium ribbon <sup>66</sup>) was added slowly under ether reflux. When the addition was complete, the ether was removed by distillation while an equal volume of dry toluene was added. The temperature of the black reaction mixture was slowly raised to 110° and kept there for 7.5 hr. The mixture was cooled, and cautiously treated with water (the mixture then turned light yellow) and extracted with ether. The ether extracts were combined, dried over potassium hydroxide and concentrated to yield 12g (80 mmol, 73%) of the pyridine 15, bp 120 (25mm), Lit<sup>72</sup> bp 94-6(5mm); ir (film, #11491) 2970, 1605, 1300, 895, 835 cm<sup>-1</sup>; nmr (CDCl<sub>3</sub>, #10811) δ 8.24(d, 1, J= 5.0Hz, H<sub>6</sub>), 6.9(m, 2, H<sub>3</sub> and H<sub>5</sub>), 2.35(s, 3, CH<sub>3</sub>), 1.1(s, 9(CH<sub>3</sub>)<sub>3</sub>).

For Analysis see Table XIII of the Appendix.

2-Methyl-4-phenylpyridine (14). - Using the above method of Abramovitch, <sup>71</sup> 30g (.18 mol) of 4-phenylpyridine (22) was added to 200 ml of ether under nitrogen at room temperature. Slowly at reflux temperature methyl-lithium (.2 mol) <sup>66</sup> was added. After the addition, the ether was distilled while an equal volume of toluene was added. The black

reaction mixture was heated under reflux at  $110^{\circ}$  for 7 hr, hydrolyzed cautiously with water (the reaction mixture then turned light yellow) and extracted several times with ether. The ether extracts were combined, dried over potassium hydroxide and concentrated. The oily residue was distilled twice to yield 22g (.13 mol, 72%) of the pyridine 14, bp  $120^{\circ}$  (.2mm), mp  $48.5-50^{\circ}$ ; ir (film, #11492) 3100-3000, 2900, 1605, 1545, 840, 765,  $695\text{ cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ , #10202)  $\delta$  8.15(d,1,J=5.0Hz,  $\text{H}_6$ ). 7.1(m,7), 2.23(s,3, $\text{C}_2\text{-CH}_3$ ).

Anal. (#30) Calcd. for  $\text{C}_{12}\text{H}_{11}\text{N}$ : C, 85.17; H, 6.55; N, 8.27. Found: C, 85.40; H, 6.61; N, 8.28.

2-Methyl-5-t-butylpyridine (137). - Methylolithium<sup>65</sup> (50 mmol) was added slowly at room temperature to a solution of 5g (37 mmol) of 3-t-butylpyridine (135) in 20 ml of dry ether under nitrogen. The ether was distilled and simultaneously 100 ml of toluene was added. The black solution was heated under reflux 7 hr and cooled. Water (20 ml) was added to the flask to hydrolyze the reaction mixture which was basified with potassium hydroxide pellets, and extracted with ether. The ether extracts were combined, dried over potassium hydroxide-potassium carbonate, and concentrated. The residue was distilled, bp 100-102 (25mm), to yield 2.6g (17.5 mmol, 48%) of a mixture of the pyridine 137 and 2-methyl-3-t-butylpyridine (136) in a ratio of 86:14<sup>71</sup> respectively by nmr analysis; nmr ( $\text{CCl}_4$ , #14717)  $\delta$  8.30 (d,1,J=2.5Hz, $\text{H}_6$ ), 7.32 (dd,1,J=2.5Hz, J=8.0Hz, $\text{H}_4$ ), 6.78 (d,1,J=8.0Hz, $\text{H}_3$ ), 2.3 (s,3, $\text{C}_2\text{-CH}_3$ ), 1.15 (s,9, $\text{C}(\text{CH}_3)_3$ ), 2.55 (singlet of the  $\text{C}_2\text{-CH}_3$  of (136)).

For preparation and analysis of the N-benzylpyridinium bromide see TABLES XIII and XIV.

2-Methyl-5-isopropylpyridine (18). - Following the procedure of Giam<sup>73</sup>, methyllithium<sup>65</sup> (50ml, 80mmol) in dry diethylether at room temperature was added to 8 ml of dry pyridine (100mmol). The black solution was stirred for 1 hr under nitrogen and cooled to 0°C, and isopropyl bromide (8.6g, 70mmol) in 10 ml of dry tetrahydrofuran was added slowly. The solution was allowed to warm to room temperature, stirred for .5 hr, and heated under reflux for .5 hr. Water (20ml) was added and the yellow aqueous solution was extracted with ether several times. The ether extracts were combined, dried over potassium carbonate and concentrated. The residue was distilled to yield 3.5g(30mmol, 38%, based on methyllithium) of the pyridine 18, bp 78-88°(25mm).

For analysis, see Table XIII of the Appendix.

2-Methyl-5-ethylpyridine (24). - To a stirred solution of 20 ml of dry ether and 5 ml (63 mmol) of dry pyridine was added slowly with stirring at room temperature 30 ml (45 mmol) of methyllithium. The black solution was stirred for 15 min then 7.2 g (46 mmol) of ethyl iodide was added slowly over 45 min. The solution was stirred for 1 hr, and then hydrolyzed with 20 ml of water. The yellow aqueous layer was extracted several times with ether. The ether extracts were combined, dried over potassium hydroxide and concentrated. The residue was distilled to yield 2.4 g (20 mmol, 66%), bp 90°(25mm), Lit<sup>74</sup> bp 174-176° (7.60mm). The distilled sample

was still contaminated (by nmr and tlc) with an impurity. When the ethyl iodide was added at  $-60^{\circ}$  over 45 min to the reaction mixture instead of at room temperature, the impurity was still present after isolation of the product.

For the preparation of an analytical sample of the N-benzylpyridinium bromide, see Tables XIII and XIV in the Appendix.

2,5-Dimethylpyridine (36). - To a stirred solution of 20 ml of dry ether and 5 ml (63 mmol) of dry pyridine was added slowly with stirring at room temperature 30 ml (45 mmol) of methyllithium. The black solution was stirred 15 min then 6.5 g of methyl iodide (46 mmol) was added slowly over .5 hr. The solution was stirred 1 hr then hydrolyzed with 20 ml of water. The yellow aqueous layer was extracted several times with ether. The ether extracts were combined, dried over potassium hydroxide and concentrated. The residue was distilled to yield 1.6 g (15 mmol, 50%) of the pyridine, bp  $50-60^{\circ}$  (25 mm), Lit<sup>75</sup> bp  $159-160^{\circ}$  (760 mm) . The distilled sample was still contaminated (by nmr and tlc) with an impurity.

For the preparation of an analytical sample of the N-benzylpyridinium bromide, see Tables XIII and XIV in the Appendix.

2-Methyl-5-benzylpyridine (19). - Using the above procedure, 8 ml of dry pyridine (100 mmol) was added to a stirred solution of methyllithium (80 mmol) in dry diethyl-ether at room temperature. The mixture was stirred for 1 hr under nitrogen and benzyl bromide (13.5g, 80 mmol) in 10 ml

of dry tetrahydrofuran was added to the black solution. After stirring for 5 min water (20 ml) was added to the solution and the yellow aqueous layer was extracted several times with ether. The ether extracts were combined, dried over potassium hydroxide, and concentrated. The residue was distilled four times through a 12 cm Vigreux column to remove a low boiling impurity to yield 4.5g (24 mmol, 33%) of the pyridine 19, bp 100-106° (.5mm), mp (picrate) 139-141° .

For analysis see Table XIII in the Appendix.

Attempted preparation of 2-methyl-5-phenylpyridine (94). - Using the procedure above, 40 mmol of iodobenzene or diphenyliodonium chloride <sup>76</sup> was used as the phenylating agent. On hydrolysis only about 10% (by nmr) of the pyridine was alkylated. Purification was not attempted.

3-Isopropylpyridine (20). - Following the procedure of Giam <sup>75</sup>, 12 ml of isopropyl iodine was added slowly to suspension of 50 mmol of lithium tetrakis (N-dihydropyridyl) aluminate (LDPA) in an Erlenmeyer flask while the contents were stirred and cooled by ice-water. After 1-2 hr, the reaction mixture was hydrolyzed with 50 ml of water, basified with 20% sodium hydroxide and repeatedly extracted with ether. The ether extracts were combined, concentrated to dryness to remove excess pyridine, and acidified with 75% hydrochloric acid. After standing 15 min the acidic layer was neutralized with solid sodium carbonate, made basic with sodium hydroxide pellets, and extracted several times with ether. The ether extracts were combined and dried over potassium carbonate.



Concentration of the ether extracts and distillation of the residue gave 18 g (6.6 mmol, 13%) of the desired pyridine 20, bp 74-76° (20 mm), Lit<sup>78</sup> 179(744 mm) ; mp (picrate) 127°, Lit<sup>78</sup> 138.1-138.6°.

3-Ethylpyridine (21). - Using the method above for alkylation of LDPA, ethyl iodide (.11 mol) was used as the alkylating agent. On hydrolysis of the complex and distillation of the pyridine residue at 30-40° (25 mm), 0.6 g (5.4 mmol, 11%) of the 3-ethylpyridine, shown by nmr analysis to be slightly contaminated with some impurities, was obtained. No attempt was made to purify the pyridine, but the crude product was benzylated as it was obtained.

See TABLE XIII of the Appendix for analysis.

Attempted preparation of 3-phenylpyridine (139). - Using the above method of attempted phenylation of LDPA with iodobenzene and diphenyliodonium chloride<sup>76</sup>, gave only the starting material.

3-Benzylpyridine (63). - To a solution of 8.2 g (5.0 mmol) of 3-chloromethylpyridine hydrochloride (37), mp 139-142°, Lit<sup>79</sup> 142-145°, in 70 ml of dry benzene was added with shaking and stirring 13.5 g aluminum trichloride. The mixture turned dark brown and was heated under reflux 5 hr, then poured into ice-water, and diluted with benzene. The two phase solution was basified with solid sodium hydroxide to dissolve the aluminum hydroxide and extracted with chloroform several times. The chloroform extracts were

combined, dried over potassium hydroxide and concentrated. The residue was distilled to yield 7.2 g (4.3 mmol, 85%) of the pyridine 63, bp  $90^{\circ}$  (.4 mm), mp  $33-35^{\circ}$ , Lit.<sup>80</sup> mp  $34^{\circ}$ .

#### Preparation of Piperidines

1-Benzyl-2-methyl-5-benzoxypyridinium bromide (66). - To 2 g (18 mmol) of 3-hydroxy-6-methylpyridine (23) in 30 ml of glyme was added a 25% excess of sodium hydride (.55 g, 23 mmol). The suspension was heated under reflux for 2-3 hr, then 3.9 g (23 mmol) of benzyl bromide in 10 ml of ether was added, and the suspension was again heated under reflux for 3 hr. The dark brown suspension was diluted with 50 ml of ether and filtered. The filtrate was concentrated and 20 ml of acetone was added. To this acetone solution was added 3 ml of benzyl bromide and boiling was maintained for 2 hr. The solution was evaporated to dryness. The solid precipitate was removed by filtration, washed with ether, and dried to yield 3.6 g (70%) of 66, mp  $195-197^{\circ}$ .

Anal. (#50) Calcd. for  $C_{20}H_{26}BrNO$ : C, 64.87; H, 5.44; N, 3.80. Found: C, 64.78; H, 5.32; N, 3.75.

1-Benzyl-2-methyl-5-benzoxy-1,2,3,6-tetrahydropyridine (67). - To 5 g (13.5 mmol) of the pyridinium bromide 66 in 50 ml of methanol was added with stirring at  $0^{\circ}C$ , 1g (27 mmol) of sodium borohydride portionwise. After stirring for .5 hr at room temperature, the solution was concentrated, and the residue was basified with aqueous potassium carbonate, and extracted with ether. After drying the combined ether extracts over potassium carbonate the ether solution was

concentrated. The residue that remained (3.9 g, 13.3 mmol) was the piperidine 67, which was used without further purification: ir (film, #19001) 3100-3000, 2920(b), 1695 (s), 1510, 1470, 1390, 1190, 725, 695  $\text{cm}^{-1}$  (Ph-H), ( $\text{CDCl}_3$ , #12319A)  $\delta$  7.20(s,5,Ph-H), 4.7(bs,3), 3.65(q,2, $J_{AB}=13.1$ ,  $\text{CH}_2\text{-Ph}$ ), 3.2-2.1(m,5), 1.25(d, $J=6.0\text{Hz}$ ,  $\text{C}_2\text{-CH}_3$ ).

1-Benzyl-2-methyl-5-piperidone (68). - A solution of 3.9 g (13.3 mmol) of the tetrahydropyridine 67 in 10 ml of concentrated hydrochloric acid and 4 ml of water was heated under reflux for 14 hr. The solution was extracted with ether, after cooling, to remove the benzyl alcohol and the aqueous layer was basified with potassium carbonate. The aqueous phase was extracted several times with ether. The ether extracts were combined, dried, and concentrated to yield 2.6 g (12.8 mmol) of the piperidone 68: ir (film, #19002) 3100-3000, 2950, 2800, 1730 (s), 1120, 1065, 1025, 740, 705  $\text{cm}^{-1}$  (Ph-H); nmr ( $\text{CDCl}_3$ , #12319)  $\delta$  7.05(s,5,Ph-H), 3.5(q,2, $J_{AB}=12.8\text{Hz}$ ,  $\Delta\tau = 22.1\text{Hz}$ ,  $\text{CH}_2\text{-Ph}$ ), 3.0-1.4(m,7), 1.2(d, $J=6.0\text{Hz}$ ,  $\text{C}_2\text{-CH}_3$ ).

The hydrobromide was obtained as a white solid by precipitation from ether and recrystallization from ethanol-ether, mp (HBr) 159-169 $^\circ$ .

Anal. (#53) Calcd. for  $\text{C}_{13}\text{H}_{18}\text{BrNO}$ : C, 54.94; H, 6.38; N, 4.92. Found: C, 54.64; H, 6.42; N, 4.80.

cis- and trans-1-Benzyl-2-methyl-5-hydroxypiperidine (69) and (70), respectively. - To 10 mmol of lithium aluminum hydride in ether was slowly added 1.5 g (5 mmol) of the piperidone 68. The suspension was stirred for 12 hr at reflux

temperature followed by hydrolysis in the Fieser manner <sup>70</sup> with 15% sodium hydroxide. Concentration of the ether solution gave a quantitative yield (1.3 g) of the alcohols 69 and 70, bp 150 (.5 mm), as a 42:58 cis-trans isomeric mixture: ir (film, #18988) 3480 (b), 3100-3000 (Ph-H), 2930, 2795, 1500, 1460, 1145, 1070, 1035, 905, 735, 695  $\text{cm}^{-1}$  (Ph-H); nmr ( $\text{CDCl}_3$ , #12312),  $\delta$  7.28 (s, Ph-H), 4.1-3.0 (2 superimposed AB quartets for the cis- and trans- benzylic protons, cis-  $J_{AB}=13.0\text{Hz}$ ,  $\Delta\nu=13.5$ , trans-  $J_{AB}=13.5\text{Hz}$ ,  $\Delta\nu=46.0\text{ Hz}$ ), 3.55 (m, CH-OH), 3.0-1.3 (m), 1.3-1.0 (dd,  $J = 6.5\text{ Hz}$  and  $6.1\text{ Hz}$ ).

Anal. (#70) Calcd. for  $\text{C}_{13}\text{H}_{19}\text{NO}$ : C, 76.05; H, 9.32; N, 6.82. Found: C, 76.80; H, 9.20; N, 6.50.

cis- and trans- 1-Benzyl-2-methyl-5-acetoxypiperidines (71) and (72) respectively. - To .75 g of the isomeric mixture of piperidinols 69 and 70 in 50 ml of chloroform was added 2 ml of acetyl chloride in 10 ml of chloroform. The solution was stirred at room temperature for 12 hr, concentrated, and the residual oil was basified with aqueous potassium carbonate. The aqueous solution was extracted with ether. The ether extracts were combined, dried, and concentrated to yield the acetylated 43:57 cis-trans piperidinol mixtures 71 and 72, bp 170 (.5mm), ir (film, #18998) 3100-3000, 2900, 2795, 1750(s), 1510, 1470, 1390, 1240 (b), 1030, 740, 700  $\text{cm}^{-1}$  (Ph-H); nmr ( $\text{CDCl}_3$  #12310)  $\delta$  7.30 (s, Ph-H), 4.10 (bm, CH-OAc), 4.2-3.1 (2 superimposed AB quartets trans-  $J_{AB}=13.8\text{ Hz}$ ,  $\Delta\nu=47.1\text{ Hz}$ , cis-  $J_{AB}=14.0\text{ Hz}$ ,  $\Delta\nu=23.2\text{ Hz}$ ), 3.1 and 1.3 (m), 1.95 and 1.90 (2s, CH<sub>3</sub>-C), 1.2 (dd,  $J=6.0\text{ Hz}$  and  $6.5\text{ Hz}$ ).

Anal. (#72) Calcd. for  $C_{15}H_{21}N_1O_2$ : C, 72.84; H, 8.55; N, 5.66. Found: C, 73.05; H, 8.52; N, 5.76.

cis- and trans-1-Benzyl-2-methyl-5-phenylpiperidines  
(73) and (74) respectively. - To 1.6 g (7.8 mmol) of the piperidone 68 in 20 ml of dry ether was added 60 ml of .25 N phenyllithium (15 mmol) <sup>66</sup> slowly with stirring under nitrogen. The solution was stirred without heating for 12 hr and then hydrolyzed with water, extracted several times with ether, and the extracts were dried over magnesium sulfate. Concentration of the ether extracts gave 2.2 g (7.8 mmol) of residue which was dissolved in 17 ml of concentrated hydrochloric acid and 31 ml of glacial acetic acid and heated under reflux for 12 hr. The reaction mixture was concentrated under reduced pressure. The residual hydrochloride was dissolved in 75 ml of 95% ethanol and placed in a hydrogenation bottle. Adam's catalyst was added, and the bottle was kept under 50 psi of hydrogen for 18 hr. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residual brown oil was basified with aqueous potassium carbonate and the aqueous solution was extracted several times with ether. The ether extracts were combined, dried over potassium carbonate, and concentrated to yield 1.7 g (6.5 mmol, 86%) of a 63:37 cis-trans isomeric mixture of the piperidines 73 and 74, bp 170 (.5mm); ir (film, #19232) 3100-3000, 2920, 2780, 1500, 1460, 1145, 750  $cm^{-1}$ ; nmr ( $CDCl_3$ , #12502)  $\delta$  7.15(m, Ph-H), 3.55 (q,  $J_{AB}=13.5$  Hz,  $\Delta\nu=53.7$  Hz, trans isomer), 3.55 (s,  $CH_2$ -Ph, cis isomer), 1.2 (d,  $J=5.3$  Hz,  $C_2$ -methyl of trans isomer),

1.05 (d, J=6.5 Hz, C<sub>2</sub>-methyl of cis isomer), see A-10, Appendix).

The major cis isomer was isolated and purified by recrystallization of its hydrobromide salt, mp 200-201.5°, from ethanol-ether.

Anal. (#62) Calcd. for C<sub>19</sub>H<sub>24</sub>BrN: C, 65.89; H, 6.98; N, 4.04. Found: C, 66.09; H, 7.05; N, 4.11.

1-Benzyl-3-hydroxy-3-phenylpiperidine (86). - To 2 g (10 mmol) of 1-benzyl-3-piperidone (26) dissolved in anhydrous ether was slowly added 60 ml (16 mmol) of .26 M phenyllithium under a nitrogen atmosphere. The solution was stirred at room temperature for 17 hr, heated under reflux for 1 hr, and allowed to cool to room temperature. The solution was hydrolyzed with water and extracted with ether. The ether extracts were combined, dried over potassium carbonate, and concentrated to yield 24 g (9 mmol, 90%) of the impure piperidinol 86 which was recrystallized from hexane to give an analytical sample, mp 64-67°, Lit.<sup>81</sup> 68-71° .

1-Benzyl-3-phenylpiperidine (88). - To 2.4 g (9 mmol) of the piperidinol 86 was added 17 ml of concentrated hydrochloric acid and 31 ml of glacial acetic acid. The solution was heated under reflux for 12 hr and then concentrated to dryness. The residue was dissolved in 100 ml of 95% ethanol and 20 mg of platinum oxide was added. The suspension was kept under 50 psi of hydrogen for 18 hr and filtered. The filtrate was concentrated, and the residue basified with aqueous potassium carbonate. The aqueous solution was extracted several times with ether. The ether extracts were combined,

dried over potassium carbonate and concentrated to yield 1.8 g (.7 mmol, 77%) of the piperidine 88, mp (HCl) 204-206°, Lit<sup>82</sup> 210° .

1-Benzyl-3-acetoxy-3-phenylpiperidine (87). - A solution of 1 g (4 mmol) of the piperidinol 86 in 3 ml of dry pyridine and 6 ml of acetic anhydride was heated under reflux for 3 hr. After distillation of all the volatile materials, the residue was dissolved in ether and filtered through basic alumina. After concentration and distillation of the residue; .7 g (62%) of the acetate was obtained as an oily residue, bp 170-190° (.4 mm); ir (film, #19135) 3100-3000, 2930, 2800, 1745 (s), 1230 (b), 730, 695 cm<sup>-1</sup> (Ph-H); nmr (CDCl<sub>3</sub>, #12548) δ 7.30(s, 5, Ph-H), 3.52(s, 2, CH<sub>2</sub>-Ph), 3.0(q, 2, J<sub>AB</sub>=12.0 Hz, Δν=34.5 Hz, C<sub>2</sub>-methylene), 2.7-0.7 (m, 6), 1.95(s, 3, CH<sub>3</sub>-C).

The hydrobromide was obtained as a white solid by precipitation from ether and recrystallization from ethanol-ether, mp 178-179°.

Anal. (#65) Calcd. for C<sub>20</sub>H<sub>24</sub>BrO<sub>2</sub>N: C, 61.54; H, 6.19; N, 3.58. Found: C, 61.39; H, 6.17; N, 4.25.

α,α-Dimethyl-3-pyridine methanol (142). - To a solution of 19 g (.16 mol) of 3-acetylpyridine (25) in dry ether was added with stirring at -10° 120 ml (.16 mol) of methyl-lithium. The reaction mixture was heated under reflux for 4 hr, and then the reaction was decomposed by cautiously pouring the yellow ethereal suspension into a mixture of 20 ml (.33 mol) of glacial acetic acid and 1 liter of cracked ice. The aqueous solution was extracted with chloroform. The chloroform

layer was removed and the product was distilled through a 12 cm Vigreux column to yield 11.8 g (50%) of the pyridine 142, bp 92-94° (.4mm), mp (picrate) 142-145°, Lit<sup>78</sup> bp 126 (8mm), Lit<sup>78</sup> mp (picrate) 149-150°.

3-Isopropenylpyridine (143). - To 4.6 g of the  $\alpha,\alpha$ -dimethyl-3-pyridine methanol (142) in 50 ml of glacial acetic acid was added 13 ml of concentrated sulfuric acid. The solution was heated under reflux .5 hr and then concentrated under reduced pressure to give the sulfate salt as residue. This was basified with aqueous potassium carbonate and the aqueous layer was extracted with ether. The ether residue was distilled to give 2.0 g (50% yield) of the 3-propenylpyridine (143), mp (picrate) 152-154°, Lit<sup>78</sup> mp (picrate) 155.5-156°.

1-Benzyl-3-isopropylpiperidine (85) from 3-Isopropenylpyridine (143). - To 4 g (.017 mol) of 1-benzyl-3-isopropenylpyridinium bromide (134) (see Tables XIII and XIV of the Appendix for method of preparation, physical constants, and analysis) in 100 ml of 95% ethanol was added 20 mg of platinum oxide. The suspension was kept under hydrogen at 50 psi until the calculated amount of hydrogen was absorbed. The piperidine was isolated as described in Method A of general procedure II to yield 2.3 g (91%) of 1-benzyl-3-isopropylpiperidine (85). The ir and nmr spectra were identical to the spectral data of the product obtained from catalytic hydrogenation of 84.



o-Nitrobenzylbromide (64). - A 250 ml flask containing 10.0 g (74 mmol) of o-nitrotoluene, 12.0 g (67 mmol) of N-bromosuccinimide, 1 g of dibenzoyl peroxide, and 50 ml of carbon tetrachloride was fitted with a reflux condenser. The mixture was heated under reflux until all the solid had floated to the surface (6-8 hr). The hot mixture was filtered through a Büchner funnel into a 500 ml suction flask. The solid in the funnel was washed with two 50 ml portions of carbon tetrachloride and the solvent was removed from the filtrate under reduced pressure. The residual lachrymatory oil was collected, weighed, and used without further purification<sup>83</sup>, 13.5 g (89%).

1-(o-Nitrobenzyl)-2-methylpiperidine (101). - A solution of 5 g (23 mmol) of o-nitrobenzyl bromide (64) and 10 ml of 2-methylpiperidine (34) in 60 ml of benzene was heated under reflux for 3-4 hr and the solvent was removed by distillation. The residual brown oil was basified with aqueous potassium carbonate, 30 ml of ether was added, and the two phase suspension was stirred for 1 hr. The aqueous layer was extracted four times with 100 ml portions of ether, and the ether extracts were combined and dried over potassium carbonate and sodium sulfate. Concentration of the ether layer yielded a residue which after distillation gave 3.0 g (12.8mmol, 56%) of the pyridine 101, bp 125 (.7mm); ir (film, #10961) 3120-3040, 2940 (s), 2850, 1530 (s,NO<sub>2</sub>), 1350 (s, NO<sub>2</sub>), 780, 725 cm<sup>-1</sup>; nmr (CDCl<sub>3</sub>, #10093) δ 7.2-7.8(m,4,Ar-H), 3.75 (q,2,Δν=45.4 Hz, J<sub>AB</sub>=15.5 Hz, CH<sub>2</sub> Ar), 2.2-1.0(m,9), 0.93(d,3,J=6.3 Hz, C<sub>2</sub>-CH<sub>3</sub>).

The hydrobromide was obtained as a white solid by precipitation from ether and recrystallization from ethanol-ether, mp 169-171°.

Anal. (#11A) Calcd. for  $C_{13}H_{19}BrN_2O_2$ : C, 49.53; H, 6.07; N, 8.88. Found: C, 49.53; H, 6.06; N, 8.70.

1-(o-Aminobenzyl)-2-methylpiperidine (108). - The 1-(o-nitrobenzyl)-2-methylpiperidine (101) (0.43 g) was dissolved in 10 ml of 95% ethanol and 10 mg of platinum oxide was added. The mixture was stirred for 2 hr under a hydrogen pressure of 40 psi and then filtered. The ethanol was removed by distillation to yield 0.36 g (83%) of the amino compound 108, bp 130-140° (1 mm), mp 50-52°; ir (film, #10437) 3400 and 3300 (m, NH<sub>2</sub>) 3100-3020 (Ph-H), 2930 (s), 2850 (m), 2800 (m), 1600 (s), 1500 (s), 760 (s), 730 (w)cm<sup>-1</sup>; nmr (CDCl<sub>3</sub>, #9803) δ 7.2-6.4 (m, 4, Ar-H), 4.6 (b, 2, NH), 3.5 (q, 2, Δν=68.9 Hz, J<sub>AB</sub>=12.85 Hz, CH<sub>2</sub>-Ar), 2.7-1.1 (m, 9), 1.05 (d, J=6.2 Hz, C<sub>2</sub>-CH<sub>3</sub>).

Anal. (#19B) Calcd. for  $C_{13}H_{20}N_2$ : C, 76.41; H, 9.86; N, 13.70. Found: C, 76.72; H, 9.49; N, 13.72.

1-(o-Acetamidobenzyl)-2-methylpiperidine (104). - To 0.865 g (4 mmol) of the 1-(o-aminobenzyl)-2-methylpiperidine (108) in 50 ml of chloroform was added a 2 molar excess of acetyl chloride, and the mixture was stirred 6 hr. The chloroform was evaporated, and the residual salt was basified with aqueous potassium carbonate. After extraction with ether several times, the combined ether extracts were dried over potassium carbonate and the ether was distilled to yield 0.88 g (96%) of amide 104, mp 85-87°; ir (film, #10530) 3350-3100

(broad, NH), 3100-3000, 2930, 2850, 2840, 1695 (s, C=O), 1600 (s), 1540 (s), 1450 (s),  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ , #10084)  $\delta$  8.25 (d, 1,  $J=7.8$  Hz,  $\underline{\text{m-Ar-H}}$ ), 7.35-6.9 (m, 3,  $\text{Ar-H}$ ), 3.70 (q, 2,  $\Delta\nu=64.5$  Hz,  $J_{\text{AB}}=13.7$  Hz,  $\underline{\text{CH}_2\text{-Ar}}$ ), 2.9-1.3 (m, 4), 2.18 (s, 3,  $\underline{\text{CH}_3\text{-C}}$ ), 1.18 (d, 3,  $J=6.2$  Hz,  $\text{C}_2\text{-CH}_3$ ).

Anal. (#14A) Calcd. for  $\text{C}_{15}\text{H}_{22}\text{N}_2$ : C, 73.13, H, 9.00; N, 11.37. Found: C, 72.86; H, 9.14; N, 11.30.

1-(o-Hydroxybenzyl)-2-methylpiperidine (107). - To 1.65 g (106 mmol) of freshly distilled salicylic acid chloride 86 in 50 ml of benzene was added 1 ml of 2-methylpiperidine (34). The product was isolated as described previously in Method C of general procedure II to give 1.8 g (85 mmol, 80%) of the benzamide which showed strong absorption at  $1620\text{ cm}^{-1}$  in the infrared spectrum. This material was added without further purification to 25 ml of dry ether which was then added to a stirred suspension of 1.2 g of lithium aluminum hydride in 25 ml of ether under nitrogen. The reaction mixture was heated under reflux for 12 hr and then was hydrolyzed in the Fieser<sup>70</sup> manner and filtered. The ethereal filtrate was dried and concentrated to yield 1.65 g (78 mmol, 91%) of the piperidine 107, bp  $50\text{-}60^\circ$ ; ir (film, #10963) 3500-3000 (broad, OH), 2930, 2825, 2800, 1600 (s), 1255, 750 (s)  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ , #10091)  $\delta$  7.25 (s, 1, OH), 7.15-6.7 (m, 4,  $\text{Ar-H}$ ), 3.7 (q, 2,  $\Delta\nu=53.1$  Hz,  $J_{\text{AB}}=14.2$  Hz,  $\underline{\text{CH}_2\text{-Ar}}$ ), 2.9-1.2 (m, 9), 1.10 (d, 3,  $J=6.3$  Hz,  $\text{C}_2\text{-CH}_3$ ), see A-7, Appendix).

Anal. (#12) Calcd. for  $\text{C}_{13}\text{H}_{20}\text{BrNO}$ : C, 54.55; H, 7.04; N, 4.89. Found: C, 54.74; H, 6.98; N, 4.88.

1-(o-Acetoxybenzyl)-2-methylpiperidine (106). - A solution of 5 g (2.3 mmol) of the hydroxyl derivative 107 and 2 ml of acetyl chloride in 50 ml of chloroform was stirred for 12 hr, and the chloroform was removed by distillation under reduced pressure. The residue was dissolved in water and basified with potassium carbonate. The aqueous layer was extracted three times with ether, and the combined ether layers were dried over potassium carbonate-magnesium sulfate. The ether was distilled under reduced pressure to yield 0.5 g (82%) of 1-(o-acetoxybenzyl)-2-methylpiperidine (106), bp 80° (.2 mm); ir (film, #10692) 3100-3020 (w, Ph-H), 2940, 2875, 2800, 1760 (s, C=O), 1200 (s), cm<sup>-1</sup>; nmr (CDCl<sub>3</sub>, #10081) δ 7.65-6.9 (m, 4, Ar-H) 3.6 (q, 2, Δν=56.4 Hz, J<sub>AB</sub>=13.2 Hz, CH<sub>2</sub>Ar), 2.9-1.3 (m, 9), 2.4 (s, 3, CH<sub>3</sub>-C-), 1.25 (d, 3, J=6.0 Hz, C<sub>2</sub>-CH<sub>3</sub>), see A-8 Appendix).

Anal. (#16A) Calcd. for C<sub>15</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: C, 72.84, H, 8.55, N, 5.66. Found: C, 72.97; H, 8.63; N, 5.58.

1-(2,6-Dichlorobenzyl)-2-methylpiperidine (103). - To 5 g (25 mmol) of α,2,6-trichlorotoluene was added 5 g (50 mmol) of 2-methylpiperidine (34) in benzene. The solution was heated under reflux for 36 hr (6 hr gave no reaction and the trichlorotoluene was recovered). The basic solution was stirred with ether for 2 hr and after separating the layers the aqueous layer was then extracted three times with ether. After drying over potassium carbonate, the combined ether extracts were distilled to yield 2.1 g (7.7 mmol, 30%) of the N-benzylpiperidine 103, bp 120-130°; ir (film, #10583)

3100-3020, 2930, 2850, 2740, 1580 (w), 1430 (s), 768 (s)  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ , #10073)  $\delta$  7.55-6.9 (m,3,Ar-H), 3.8 (q,2,  $\Delta\nu=35.6$  Hz,  $J_{AB}=12.2$  Hz,  $\text{CH}_2\text{-Ph}$ ), 2.8-1.3 (m,9), 1.20(d,3,  $J=6.3$  Hz,  $\text{C}_2\text{-CH}_3$ ).

The hydrobromide was obtained as a white solid, mp 191-193 $^\circ$ , by precipitation from ether and recrystallization from ethanol-ether.

Anal. (#13A) Calcd. for  $\text{C}_{13}\text{H}_{18}\text{BrCl}_2\text{N}$ : C, 46.04; H, 5.35; N, 4.13. Found: C, 46.05; H, 5.53; N, 4.07.

cis-1-(o-Nitrobenzoyl)-2,4-dimethylpiperidine (133). - To an ethereal solution of 2.0 g (18 mmol) of cis-2,4-dimethylpiperidine (149) was added with stirring at room temperature, 40 ml of 20% sodium hydroxide solution and an ethereal solution of 3.0 g (16 mmol) of o-nitrobenzoylchloride. The suspension was stirred 6 hr and then was extracted with ether. The ether solution was washed with 15% hydrochloric acid, sodium bicarbonate solution and water, and then it was dried over magnesium sulfate. After concentration of the ether layer the residue was distilled to yield 3.1 g (11.7 mmol, 66%) of the amide 133, bp 180-190 $^\circ$  (air-bath temperature, 3 mm); ir (film, #17338) 3100 (Ph-H), 2950, 2860, 1640 (C=O), 1520 (-O), 1440, 1350 (N-O), 1245, 1120, 1000, 850, 760, 785, 740  $\text{cm}^{-1}$ , nmr ( $\text{CDCl}_3$ , #11768)  $\delta$  8.1-7.1 (m,4,Ph-H), 4.2-3.9 (m,1), 3.2-2.9 (m,2), 2.1-1.15(m,s), 1.1 (d,3, $J=6.8$  Hz,  $\text{C}_2\text{-methyl}$ ), 0.98 (d,3, $J=6.0$  Hz,  $\text{C}_4\text{-methyl}$ ).

Anal. (#39) Calcd. for  $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_3$ : C, 64.09; H, 6.91; N, 10.68. Found: C, 63.55; H, 6.83; N, 10.58.

cis-1-(o-Nitrobenzyl)-2,4-dimethylpiperidine (102) -

To 3 g (22 mmol) of cis-2,4-dimethylpiperidine (149) dissolved in 30 ml of dry benzene was added 3.1 g (22 mmol) of o-nitrobenzylbromide (64) <sup>80</sup>. The solution was stirred under reflux for 12 hr and worked up in the manner described in Method D of general procedure II to yield 1.4 g (27%) of the N-benzylpiperidine 102, bp 150° (.4mm); ir (film, #17352) 3080 (Ph-H), 2950, 2800, 1540 (N-O), 1360 (N-), 1190, 1140, 860 (Ph-H), 730 cm<sup>-1</sup> (Ph-H); nmr (CDCl<sub>3</sub>, #11777) δ 7.8-7.2 (m,4,Ph-H), 3.9 (q,2,J<sub>AB</sub>=16.0 Hz,Δν=67.0 Hz, CH<sub>2</sub>-Ph), 2.8-1.1 (m,8), 1.05 (d,3,J=6.0Hz, C<sub>2</sub>-methyl), 0.83 (d,3,J=4.0 Hz, C<sub>4</sub>-methyl), see A-6, Appendix).

Anal. (#44) Calcd. for C<sub>14</sub>H<sub>21</sub>BrN<sub>2</sub>O<sub>2</sub>: C, 51.07; H, 6.42; N, 8.50. Found: C, 51.06; H, 6.58; N, 8.27.

cis-1-(o-Aminobenzyl)-2,4-dimethylpiperidine (109). -

To 0.8 g (6 mmol) of the above nitro derivative 102 in 6 ml of 95% ethanol was added 0.1 g of platinum oxide. The suspension was stirred for 2 hr at room temperature under hydrogen at atmospheric pressure. The mixture was filtered and the solution evaporated. The white solid amino piperidine 109 was purified by sublimation to give 0.8 g (quantitative yield) of the piperidine 109, mp 57-60°; ir (Nujol, #17363) 3400 (N-H), 3300 (N-H), 3030 (Ph-H), 2940, 2800, 1610 (N-H), 1350, 1180, 1130, 1095, 1060, 1025, 820, 750, 730 cm<sup>-1</sup> (Ph-H); nmr (CDCl<sub>3</sub>, #11826) δ 7.1-6.3 (m,s,Ph-H), 4.75 (bs,2,NH), 3.6 (q,2,J<sub>AB</sub>=12.2 Hz,Δν=83.6 Hz, CH<sub>2</sub>-Ph), 3.9-0.80 (m,8), 1.3 (d,3,J=6.0 Hz, C<sub>2</sub>-CH<sub>3</sub>), 0.95 (d,3,J=4.3 Hz, C<sub>4</sub>-CH<sub>3</sub>), see A-3, Appendix.

cis-1-(o-Acetamidobenzyl)-2,4-dimethylpiperidine (105). -

To 1 g (4.5 mmol) of the o-aminocompound 109, in 50 ml of chloroform was added 1 ml of acetyl chloride. The solution was stirred at room temperature for 12 hr and then concentrated to dryness. The hydrochloride was basified with aqueous potassium carbonate and extracted with ether to yield 1 g (4.1 mmol, 91%) of the acetamide 105, bp 120° (.4mm), mp 54-56°; ir (film, #17366) 3300 (N-H), 2950, 2800, 1695 (C=O), 1600 (N-H), 780-750 (Ph-H); nmr (CDCl<sub>3</sub>, #11794)  $\delta$  8.28 (d, 1, J=7.5 Hz, o-Ph-H), 7.4-6.9 (m, 3, Ph-H), 3.7 (q, 2, J<sub>AB</sub>=13.3 Hz,  $\Delta\nu$ =83.5 Hz, CH<sub>2</sub>-Ph), 2.9-1.0 (m, 8), 2.1 (s, 3, CH<sub>3</sub>-C), 1.12 (d, 3, J=6.0 Hz, C<sub>2</sub>-CH<sub>3</sub>), 0.90 (d, J=4.8 Hz, C<sub>4</sub>-CH<sub>3</sub>), see A-5, Appendix).

The hydrobromide was obtained as a white solid by precipitation from ether and recrystallization from ethanol-ether, mp 203-204°.

Anal. (#43) Calcd. for C<sub>16</sub>H<sub>25</sub>BrN<sub>2</sub>O: C, 56.30; H, 7.38; N, 8.20. Found: C, 56.20; H, 7.54; N, 8.12.

cis-1-Benzoyl-2,3-dimethylpiperidine (128). - To 5 g (40 mmol) of cis-2,3-dimethylpiperidine (144), was added 6 g (40 mmol) of benzoyl chloride in 10 ml of ether and 10 ml of 20% sodium hydroxide. Using the same procedure as outlined in Method C of general procedure II, 2.0 g (22%) of the amide 128 was isolated and purified by distillation, bp 140 (.2 mm); mp 49-52°; ir (film, #11496) 3100-3020 (Ph-H), 2940, 2870, 1635 (C=O), 1430, 1270, 1090, 780, 700 cm<sup>-1</sup> (Ph-H); nmr (CDCl<sub>3</sub>, #10747)  $\delta$  7.3 (s, 5, Ph-H), 4.4-3.5 (m, 2, C<sub>6</sub>-H), 3.15-2.5 (m, 1, C<sub>2</sub>-H), 2.0-2.1 (m, 5), 1.02 (d, 3, J=6.8 Hz, C<sub>2</sub>-CH<sub>3</sub>), 0.78 (d, 3, J=6.4 Hz, C<sub>3</sub>-CH<sub>3</sub>).

Anal. (#74) Calcd. for  $C_{14}H_{19}NO$ : C, 77.37; H, 8.81; N, 6.44. Found: C, 77.36; H, 8.90; N, 6.37.

cis- and trans-1-Benzoyl-2,5-dimethylpiperidines (147) and (148) respectively. - To 12 g (0.1 mol) of a mixture of cis- and trans-2,5-dimethylpiperidines (145) and (146) respectively, was added 15 g (0.1 mol) of benzoyl chloride in 10 ml of ether and 10 ml of 20% sodium hydroxide. Using the same procedure as outlined in Method C of general procedure II, the isomeric amide mixture was isolated and purified by distillation to give 2.3 g (80%) of 147 and 148, bp 145-150° (.3 mm); ir (film, #11494) 3100-3020 (Ph-H), 2940, 2850, 1640 (C=O), 1430, 1270, 785, 760, 695  $cm^{-1}$  (Ph-H); nmr ( $CDCl_3$ , #10837)  $\delta$  7.28 (s, 5, Ph-H), 3.35 (q, 2,  $J_{AB}=13.5$  Hz,  $\Delta\nu=33.6$  Hz,  $C_6$ -H), 2.0-0.7 (m, 11).

Anal. (#36) Calcd. for  $C_{14}H_{19}NO$ : C, 77.37; H, 8.81; N, 6.44. Found: C, 77.68; H, 8.72; N, 6.30.

cis-1-Benzoyl-2,4-dimethylpiperidine (127). - To 0.5 g (4 mmol) of cis-2,4-dimethylpiperidine (149) was added 0.6 g (4 mmol) of benzoyl chloride in 10 ml of ether and 10 ml of 20% sodium hydroxide. Following the procedure as outlined in Method C of general procedure II, the amide was isolated and purified by sublimation to give 0.8 g (80%) of the benzamide 127, mp 64-65°; ir (Nujol, #11534) 3100-3030 (Ph-H), 1640 (C=O), 1350, 1160, 1110, 995, 780 (Ph-HO), 730 (Ph-H), 690  $cm^{-1}$  (Ph-H); nmr ( $CDCl_3$ , #11729)  $\delta$  7.2 (s, 5, Ph-H), 4.2 (st, 1,  $J=6.5$  Hz,  $C_2$ -H), 3.8-2.9 (m, 2,  $C_6$ -H), 2.2-1.6 (m, 5), 1.35 (d, 3,  $J=6.5$  Hz,  $C_2$ -CH<sub>3</sub>), 1.1 (d, 3,  $J=6.2$  Hz,  $C_4$ -CH<sub>3</sub>)<sup>84</sup>.



Anal. (#29) Calcd. for  $C_{14}H_{19}NO$ : C, 77.37; H, 8.81; N, 6.44. Found: C, 77.58; H, 8.74; N, 6.53.

Debenzylation of cis- and trans-1-Benzyl-2-methyl-4-t-butylpiperidines (58) and (61) respectively. - To 5 g (20 mmol) of the isomeric mixture of N-benzylpiperidines 58 and 61 (See Table XV in the Appendix) was added 100 ml of anhydrous ether. Anhydrous hydrogen chloride gas was bubbled through the solution to form the hydrochloride salt. The salt was separated by filtration and was dissolved in 75 ml of 95% ethanol. The solution together with 1 g of palladium-on-charcoal was placed on the medium pressure hydrogenator for 48 hr at 150 psi. At the end of this time the suspension was concentrated to dryness and basified with aqueous potassium carbonate. The solution was extracted with ether and the ether extracts were combined and dried over sodium sulfate-potassium carbonate. The residue obtained after concentration of the ether was purified by a short path distillation to yield 3.2 g (33%) of the cis- and trans-2-methyl-4-t-butylpiperidines, (150) and (151) respectively, bp  $120^{\circ}$  (25 mm); ir (film, #11538) 3400 (N-H).

Debenzylation of 1-Benzyl-cis- and trans-2-methyl-4-phenylpiperidines (59) and (60) respectively. - To 14 g of the isomeric mixture of N-benzylpiperidines 59 and 60 (See Table XV in the Appendix) was added 110 ml of anhydrous ether. Anhydrous hydrogen bromide gas was bubbled in the solution to form the hydrobromide salt. The salt was dissolved in 100 ml of 95% ethanol, 2 g of palladium-on-charcoal was added, and the

mixture was placed under 160 psi on the medium pressure hydrogenator for 36 hr. At the end of this time the suspension was concentrated to dryness and basified with aqueous potassium carbonate. The aqueous solution was extracted several times with ether. The ether extracts were combined, dried over sodium sulfate-potassium carbonate and was concentrated to yield 1.7 g (20%) of the cis- and trans-2-methyl-4-phenylpiperidine (152) and (153) respectively, bp 78-85° (.5 mm), Lit.<sup>85</sup> bp 128° (10.5 mm) ; ir (film, #11545) 3480-3160 (-H).

The hydrobromide of the major cis isomer was obtained as a white solid by precipitation from ether and recrystallization from ethanol-ether, mp 221-223°.

cis-1-Benzoyl-2-methyl-4-phenylpiperidine (129). -

To a suspension of 1.2 g (6.8 mmol) of cis- and trans-2-methyl-4-phenylpiperidines (152) and (153) respectively, in 10 ml of ether and 10 ml of sodium hydroxide was added 0.9 g (6.8 mmol) of benzoyl chloride in 10 ml ether. The suspension was stirred for 6 hr and worked up in the manner previously described in Method C of general procedure II to give 1 g (3.2 mmol, 50%) of the benzamide 129, bp 170° (0.2 mm); ir (film, #11595) 3100-3020 (Ph-H), 2940, 2875, 1640 (C=O), 1450, 1260, 1210, 1170, 1110, 780, 760, 700 cm<sup>-1</sup> (Ph-H); nmr (CDCl<sub>3</sub>, #10993)  $\delta$  7.25 (s,5,Ph-H), 7.05 (s,5,Ph-H), 4.3-3.8 (m,1,C<sub>2</sub>-H), 3.6-2.4 (m,2,C<sub>6</sub>-H), 2.1-1.2 (m,5), 1.1 (d,3,J=6.2 Hz, C<sub>2</sub>-CH<sub>3</sub>). Only one isomer could be detected. Assignment was made on the basis that the major isomer was the cis isomer in the N-benzylpiperidine 59. (See Table XVIII in the Appendix).

Anal. (#29) Calcd. for  $C_{14}H_{19}NO$ : C, 77.37; H, 8.81; N, 6.44. Found: C, 77.58; H, 8.74; N, 6.53.

cis- and trans-1-Benzoyl-2-methyl-4-t-butylpiperidine (130) and (131) respectively. - To 1 g of mixture of cis- and trans-2-methyl-4-t-butylpiperidines (150) and (151) respectively, in 10 ml of ether and 10 ml of 20% sodium hydroxide was slowly added an ethereal solution of 0.9 g (6.5 mmol) of benzoyl chloride. The suspension was stirred for 6 hr and worked up in the manner previously described in Method C of general procedure II to give 1.3 g (5.6 mmol, 80%) of the benzamide 130, bp  $160^{\circ}$  (.2 mm); ir (film, #11522) 3060 (Ph-H), 2930, 2845, 1640 (C=O), 1210, 1170, 1040, 1010, 995, 700  $cm^{-1}$  (Ph-H); nmr ( $CDCl_3$ , #10290)  $\delta$  7.3 (s, 5, Ph-H), 3.5-2.7 (m, 3), 2.1-1.0 (m, 5), 1.25 (d, 3, J=6.2 Hz,  $C_2$ -methyl of the cis isomer), 1.08 (partially hidden,  $C_2$ -methyl of the trans isomer).

Anal. (#37) Calcd. for  $C_{17}H_{25}NO$ : A satisfactory analysis could not be obtained.

1-(2,2-Diphenylethyl)-2-methylpiperidine (111). - Using the procedure in Method C of general procedure II for preparation of amides, 5 g (22 mmol) of diphenylacetic acid chloride, prepared by the method of Fieser<sup>86</sup>, was added to a 4 molar excess of 2-methylpiperidine (34) in 10 ml of benzene. The amide, 6.3 g (21 mmol), was isolated as a solid (C=O,  $1650\ cm^{-1}$ ) that melted at  $69-72^{\circ}$ . The crude amide was dissolved in 20 ml of dry ether and added to a suspension of 44 mmol of lithium aluminum hydride in ether. This suspension was stirred for 12 hr under reflux under nitrogen then hydrolyzed

in the Fieser<sup>70</sup> manner. The filtrate was dried over sodium sulfate and concentrated to yield 6.0 g (20 mmol) of the piperidine 111, bp 148 (.5 mm); ir (film, #10905) 3100-3020, 2930 (s), 2855 (m), 2785 (m), 1600 (w), 1500 (m), 750 (m), 700 (s)  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ , #10119)  $\delta$  7.22 (m, 10, Ph-H) 4.16 (dd, 1,  $J_{\text{BX}}=6.5$  and  $J_{\text{AX}}=8.2$  Hz,  $\text{CH}-(\text{Ph})_2$ ), 3.6-2.5 (m, 2,  $J_{\text{AB}}=13.1$  Hz,  $\Delta\nu=31.7$  Hz,  $\text{CH}_2-\text{CH}$ ), 2.5-1.0 (m, 9), 0.90 (d,  $J=6.2$  Hz,  $\text{C}_2-\text{CH}_3$ )<sup>86</sup>, see A-19, Appendix).

Anal. (#19) Calcd. for  $\text{C}_{20}\text{H}_{25}\text{N}$ : C, 85.96; H, 9.01; N, 5.01. Found: C, 85.94; H, 9.14; N, 4.82.

1-(2,2-Diphenylethyl)-2-benzylpiperidine (112). -

Using the procedure described in Method C of general procedure II for preparation of amides, 5.0 g (28 mmol) of diphenylacetyl chloride<sup>86</sup> was treated with a 3 molar excess of 2-benzylpiperidine (62) in 10 ml of benzene. Extraction with ether yielded 11 g of crude amide ( $\text{C}=\text{O}$ ,  $1630 \text{ cm}^{-1}$ ) which melted at  $89-93^\circ\text{C}$ . The white solid was added without further purification to 20 ml of dry ether. This solution was then added to a suspension of 60 mmol of lithium aluminum hydride in ether and stirred under nitrogen for 12 hr at ether reflux. The reaction mixture was hydrolyzed in the Fieser manner<sup>70</sup> and the filtrate was dried over sodium sulfate. Concentration of the ether solution gave 4.7 g (26 mmol, 93%) of the piperidine 112, bp  $155^\circ$  ( $< 1 \text{ mm}$ ); ir (film, #10986) 3100-3000, 2920, 2850, 1600, 1500, 1450, 1120, 740, 695  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ , #10221)  $\delta$  7.28 (m, 15, Ph-H), 4.18 (t, 1,  $J=7.3$  Hz,  $\text{CH}-(\text{Ph})_2$ ),

3.4-2.8 (m, 2,  $J_{AB}$ -13.0 Hz,  $\Delta\nu$ =15.2 Hz,  $\text{CH}_2$ -CH), 2.8-0.7 (m, 11)<sup>87</sup>  
see A-17, Appendix).

Anal. (#17) Calcd. for  $\text{C}_{26}\text{H}_{29}\text{N}$ : C, 87.83; H, 8.22;  
N, 3.94. Found: C, 87.80; H, 8.83; N, 3.96.

1-(2,2-Diphenylethyl)-2-phenylpiperidine (110). -

Using Method C of general procedure II for the preparation of amides, 2.5 g (10.5 mmol) of diphenylacetyl chloride<sup>86</sup> was added to 3.5 g (21 mmol) of 2-phenylpiperidine (33) in 10 ml of benzene. The amide was isolated as an oil ( $\text{C}=\text{O}$ ,  $1640\text{ cm}^{-1}$ ) which was added to 20 ml of dry ether. This ether solution was added to a suspension of 30 mmol lithium aluminum hydride under nitrogen, and the mixture was heated under reflux for 12 hr. Hydrolysis was accomplished in the Fieser manner<sup>70</sup> and the filtrate was dried over sodium sulfate. Concentration of the ether solution gave 0.13 g (0.5 mmol, 5.2%) of the piperidine 110, bp 150 ( $\leq$  1mm); ir (film, #10966) 3110-3030, 2930, 1600 (w), 1500 (m), 1450 (m), 1215, 1120, 760, 700  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ , #10348) 7.14 (m, 15, Ph-H) 4.15 (dd, 1,  $J_{AX}$ =10.3 and  $J_{BX}$ =4.7 Hz,  $\text{CH}(\text{Ph})_2$ ), 2.8-2.25 (octet, 2,  $J_{AB}$ =12.6 Hz,  $\Delta\nu$ =37.0 Hz,  $\text{CH}_2$ - $(\text{Ph})_2$ ), 3.5-0.9 (m, 9),<sup>87</sup> (see A-18, Appendix).

Anal. (#18) Calcd. for  $\text{C}_{25}\text{H}_{27}\text{N}$ : C, 87.92; H, 7.96;  
N, 4.10. Found: C, 87.60; H, 8.26; N, 4.02.

1-(Triphenylacetyl)-2-methylpiperidine (154). - To

2 g (6.5 mmol) of triphenylacetyl chloride<sup>88</sup>, prepared from triphenylacetic acid<sup>89</sup> in 87% yield, was added 1 ml of 2-methylpiperidine (34) (14.5 mmol) in 50 ml of benzene. The suspension was stirred for 12 hr and then filtered under reduced pressure. The benzene solution was dried over sodium

sulfate and concentrated to yield 2.0 g (5.4 mmol, 83%) of the amide 158, mp 192-194<sup>o</sup>; ir (Nujol) 3010-3030, 1625 (2,C=O), 748 (s), 695 (s) cm<sup>-1</sup>; nmr (CDCl<sub>3</sub>, #10062) δ 7.25 (s,15,Ph-H), 3.3-1.2 (m,9), 1.1 (d,J=7.0 Hz, C<sub>2</sub>-CH<sub>3</sub>).

Anal. (#21) Calcd. for C<sub>26</sub>H<sub>27</sub>NO: C, 84.51; H, 7.36; N, 3.79. Found: C, 84.34; H, 7.39; N, 3.79.

Attempted Preparation of 1-(2,2,2-triphenylethyl)-2-methylpiperidine (155). - All attempts to reduce the amide 154 with lithium aluminum hydride, aluminum hydride<sup>90</sup>, or diborane in ether or tetrahydrofuran were unsuccessful and lead only to recovery of starting material, mp 190<sup>o</sup>C (C=O, 1625). Attempts to perform a nucleophilic displacement of 1-(2,2,2-triphenylethyl)-tosylate (156) with 2-methylpiperidine (34) or 1-lithio-2-methylpiperidine (157), prepared from n-butyllithium and 2-methylpiperidine (34) in tetrahydrofuran lead to recovery of the tosylate 160, mp 127<sup>o</sup>, Lit.<sup>91</sup> 106.

1-Isopropyl-2-methylpiperidine (121). - To 7 g (71 mmol) of 2-methylpiperidine (34) in 30 ml of dry benzene was added a solution of 6 g (35 mmol) of 2-iodopropane in 10 ml of dry benzene. The mixture was heated under reflux over a steam bath for 12 hr and then concentrated to dryness. The residue was basified with aqueous potassium carbonate and extracted with ether. The ether extracts were combined, dried over potassium carbonate and concentrated to yield 6.0 g (28.5 mmol, 81%) of the piperidine 121, bp 80<sup>o</sup> (25 mm); ir (film, #11064) 2950, 2800, 1460, 1380, 1270, 1215, 1180, 1145, 1160, 1060 cm<sup>-1</sup>; nmr (CDCl<sub>3</sub>, #10390) δ 3.2 (ht,1,J=6.4 Hz, CH(CH<sub>3</sub>)<sub>2</sub>),

2.9-1.2 (m,9), 1.15-0.70 (overlapping doublets, 9, CH- $\underline{\text{CH}_3}$ ).

Anal. (#27) Calcd. for  $\text{C}_9\text{H}_{20}\text{BrN}$ : C, 48.65; H, 9.07; N, 6.30. Found: C, 48.83; H, 9.39; N, 6.31.

#### Preparation of Piperazines

cis-1-Isopropyl-2,5-dimethylpiperazine (117). - To 2 g (16.8 mmol) of cis-2,5-dimethylpiperazine (98) in 30 ml of anhydrous benzene was added a solution of 2.86 g (16.8 mmol) of isopropyl iodide in 10 ml of dry benzene. The mixture was heated under reflux on a steam bath for 12 hr and then concentrated to dryness. The residue was basified with aqueous potassium carbonate and extracted with ether. The ether extracts were combined, dried over potassium carbonate and concentrated to yield 1.6 g (10 mmol, 62%) of the piperazine 117, bp  $32^\circ$  (.2 mm); ir (film, #11085) 3380 (N-H), 2080, 2800, 1460, 1380, 1160, 1040, 870, 790,  $750\text{ cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ , #10405)  $\delta$  3.1-1.8 (m,7), 1.55 (s,1, N-H), 1.15-0.80 (overlapping doublets, 12, CH- $\underline{\text{CH}_3}$ ).

cis-1-Isopropyl-2,5-dimethyl-4-benzoylpiperazine (132). - To 2 g (12.8 mmol) of cis-1-isopropyl-2,5-dimethylpiperazine (117), prepared above, was added 1.8 g (12.8 mmol) of benzoyl chloride in 40 ml of acetone. The solution was allowed to stir for 6 hr. The solid which precipitated was separated by filtration and basified with aqueous potassium carbonate. The aqueous solution was then extracted several times with chloroform. The chloroform extracts were combined, dried over potassium carbonate and concentrated to dryness. An attempt to distill the residue was unsuccessful; however, column

chromotography over basic aluminum with petroleum ether-chloroform (20:1) yielded 1.1 g (4.2 mmol, 33%) of a pure sample of the benzamide 132, mp 66-68°; ir (film, #11090) 3120-3020(Ph-HO), 2965, 2810, 1640, 1430, 1255, 1175, 1110, 1060, 790, 750, 670 cm<sup>-1</sup> (Ph-H); nmr (CDCl<sub>3</sub>, #11980) δ 7.4 (s,5,Ph-H), 4.9-3.7 (bm,2), 3.35 (ht,1,J=6.5 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 3.05-2.2(m,4), 1.40-1.05(dd,6,J=6.6 Hz, ring methyls), 1.05-0.82(dd,6,J=6.5 Hz, CH(CH<sub>3</sub>)<sub>2</sub>)<sup>84</sup> (see A-21, Appendix).

The hydrobromide was obtained as a white solid, 209-210°, by precipitation from ether after recrystallization from ethanol ether.

Anal. (#26) Calcd. for C<sub>16</sub>H<sub>25</sub>BrN<sub>2</sub>O: C, 56.30; H, 7.38; N, 8.20. Found: C, 56.39; H, 7.30; N, 8.20.

cis-1,4-Diisopropyl-2,5-dimethylpiperazine (118). - From the above attempted distillation of 132, was isolated 30 mg of cis-1,4-diisopropyl-2,5-dimethylpiperazine (118) along with 200 mg of the cis-1,4-dibenzoyl-2,5-dimethylpiperazine (140), mp 145-147, Lit.<sup>92</sup> 145-145.5°. An analytical sample of the piperazine 118 was obtained by recrystallization of its hydrobromide from ethanol-ether, mp 264-266°. The spectral data for the oil are ir (film, #11152) 2970, 2820, 1460, 1380, 1205, 1175, 760 cm<sup>-1</sup>; nmr (CDCl<sub>3</sub>, #10538) δ 3.2-2.2 (m,8), 1.2-0.90 (overlapping doublets, 12, CH<sub>3</sub>-CH).

Anal. (#23) Calcd. for C<sub>16</sub>H<sub>28</sub>N<sub>2</sub>Br<sub>2</sub> (H<sub>2</sub>O): C, 38.10; H, 7.99; N, 7.40. Found: C, 37.99; H, 8.06; N, 7.68.

cis-1-Isopropyl-2,5-dimethyl-4-benzylpiperazine (116). - An ethereal solution of 1.6 g (6 mmol) of cis-1-isopropyl-2,5-



dimethyl-4-benzoylpiperazine (132) was added slowly under nitrogen to a well stirred suspension of 1.5 g of lithium aluminum hydride in 40 ml of ether. The suspension was stirred at room temperature for .5 hr and then heated at reflux for 2 hr. The mixture was decomposed with 15% sodium hydroxide in the Fieser manner<sup>70</sup>. The filtrate was dried over potassium carbonate-sodium sulfate for 12 hr and concentrated to yield 1.1 g of a 2:1 mixture of cis-1-isopropyl-2,5-dimethyl-4-benzylpiperazine (116) and cis-1-benzyl-2,5-dimethylpiperazine (141). The ir spectrum of the mixture showed absorption at  $3300\text{ cm}^{-1}$  (N-H). Column chromatography over basic alumina (pet. ether-chloroform, 20:1) gave a pure sample of 116, bp  $90^{\circ}$  (.2 mm); ir (film, #11171)  $3120$  (Ph-H),  $2990$ ,  $2800$ ,  $1465$ ,  $1380$ ,  $1200$ ,  $1150$ ,  $1065$ ,  $730$ ,  $695\text{ cm}^{-1}$  (Ph-H); nmr ( $\text{CDCl}_3$ , #10608A)  $\delta$  7.3 (s, 5, Ph-H), 3.55 (q, 2,  $J_{AB}=13.1\text{ Hz}$ ,  $\Delta\nu=33.0\text{ Hz}$ ,  $\text{CH}_2\text{Ph}$ ), 3.05-2.26 (m, 6), 1.30-0.85 (m, 12,  $\text{CH}_2\text{CH}$ ).

The hydrobromide was obtained as a white solid by precipitation from ether and recrystallization from ethanol-ether, mp  $194-197^{\circ}$ .

Anal. (#28) Calcd. for  $\text{C}_{16}\text{H}_{28}\text{N}_2\text{Br}_2(2\text{H}_2\text{O})$ : C, 43.26; H, 7.26; N, 6.30. Found: C, 43.64; H, 7.14; N, 6.34.

#### Preparation of Quinolines

1-Benzoyl-2-methyl-decahydroquinoline (125). - To 5 g (35 mmol) of 2-methylquinoline (122) dissolved in 100 ml of glacial acetic acid was added 300 mg of platinum oxide. The reaction mixture was placed in a Parr reduction vessel and kept at 53 psi of hydrogen pressure until the uptake of

hydrogen had ceased; about 18 mmol were absorbed. After filtration and concentration of the mixture, the residual acetate salt was neutralized with aqueous potassium carbonate. The basic solution was extracted with ether and the combined extracts were concentrated to yield 4 g (28 mmol, 80%) of 2-methyldecahydroquinoline (138)<sup>93</sup> which was distilled at 100° (25 mm) and used without further purification.

To 0.8 g of the decahydroquinoline 138 suspended in 20% sodium hydroxide was added 0.8 g of benzoyl chloride dissolved in 10 ml of ether. The suspension was stirred 2 hr, and the ether layer was separated and dried. Concentration of the solution gave 1.5 g of an oil which gave an analytical sample on distillation followed by crystallization and recrystallization from hexane of the white solid 125, mp 65-68°; ir (film, #17511) 3100-3030 (Ph-H), 2940, 2860, 1640 (C=O), 1420, 1370, 1250, 1175, 1040, 780, 755, 705, 660 cm<sup>-1</sup>, nmr (CDCl<sub>3</sub>, #12011) δ 7.05 (s, 5, Ph-H), 4.2-3.2 (m, 2), 2.3-1.0 (m, 17, containing two methyl doublets, 6.4 and 6.6 Hz).

Anal. (#45) Calcd. for C<sub>17</sub>H<sub>23</sub>NO: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.25; H, 9.10; N, 5.40.

1-Benzyl-2-methyldecahydroquinoline (126). - To 0.5 g (0.13 mol) of lithium aluminum hydride in 50 ml of ether was added slowly with stirring under nitrogen 1 g (40 mmol) of the benzamide 125. After stirring for 12 hr at ether reflux, the reaction mixture was quenched in the Fieser<sup>70</sup> manner with 15% sodium hydroxide then filtered. The ethereal filtrate after drying was concentrated to yield 0.9 g (36 mmol, 90%)

of the 1-benzyl-2-methyldecahydroquinoline (126), bp 152-153° (1.5 mm), Lit.<sup>94</sup> 170° (3 mm); ir (film, #17448) 3100-3030, 2930, 2840, 1500, 1200, 1160, 1130, 730, 700 cm<sup>-1</sup> (Ph-H); nmr (CDCl<sub>3</sub>, #11893) 7.05 (m, 5, Ph-H), 3.3 (s, 2, CH<sub>2</sub>-Ph), 2.4-1.1 (m, 15), 1.1 (d, J=6.1 Hz, CH-CH<sub>3</sub>).

2-Methyl-1,2,3,4-tetrahydroquinoline (163). - To 5 g (35 mmol) of 2-methylquinoline (122) in 10 ml of ethanol (95%) was added 0.2 g of platinum oxide. The suspension was kept under hydrogen at 50 psi until about 70 mmol of hydrogen was absorbed. The mixture was filtered, and the filtrate was concentrated to yield 4.5 g (90%) of the 2-methyl-1,2,3,4-tetrahydroquinoline (163), bp 60-66° (.2 mm), Lit.<sup>94</sup> 102-103 (.5 mm) .

1-Benzoyl-2-methyl-1,2,3,4-tetrahydroquinoline (123). - To 1 g (7 mmol) of 2-methyl-1,2,3,4-tetrahydroquinoline (163) suspended in 10 ml of ether and 20 ml of 20% sodium hydroxide was added slowly a solution of 1 ml of benzoyl chloride in 5 ml of ether. The suspension was stirred for 6 hr and then extracted with ether. Concentration of the ether solution gave 1.5 g (6 mmol, 85%) of the amide 123, mp 112-115° Lit<sup>94</sup> 118-119°; ir (Nujol, #17482) 3100-3030, 1640, 1500, 1460, 1400, 790, 760, 750, 700, 660 cm<sup>-1</sup>; nmr (CDCl<sub>3</sub>, #11969) 7.25 (s, 5, Ph-H), 7.2-6.5 (m, 4, Ar-H), 4.83 (st, 1, J=6.5 Hz, C<sub>2</sub>-H), 3.1-2.1 (m, 3), 1.9-1.2 (d, J=6.4 Hz, C<sub>2</sub>-CH<sub>3</sub>).

1-Benzyl-2-methyl-1,2,3,4-tetrahydroquinoline (124). - To .5 g (.13 mol) of lithium aluminum hydride suspended in ether was added a solution of 1.0 g (40 mmol) of 1-benzoyl-2-

methyl-1,2,3,4-tetrahydroquinoline (123) in 10 ml of dry ether. The suspension was heated under reflux for 12 hr and hydrolyzed with sodium hydroxide in the Fieser manner<sup>70</sup>. Ether was added and the mixture was filtered. The ether layer was separated and dried over potassium carbonate. After concentration the oily residue was distilled to give 0.3 g (12.5 mmol, 32%) of 124, bp 130 (.3 mm); ir (film, #17473) 3110-3030, 2950, 2850, 1600, 1505, 1470, 750, 700  $\text{cm}^{-1}$  (Ph-H); nmr ( $\text{CDCl}_3$ , #11934)  $\delta$  7.0 (s, 5,  $\text{CH}_2$ -Ph), 6.80-6.10 (m, 4, Ar-H), 4.35 (s, 2,  $\text{CH}_2$ -Ph), 3.45 (1, m), 2.70 (1, m), 1.80 (1, m), 1.1 (d, 3,  $J=6.1$  Hz,  $\text{C}_2$ - $\text{CH}_3$ ), see A-20, Appendix). The oil turned a bluish-green color on prolonged contact with the atmosphere.

Anal. (#46) Calcd. for  $\text{C}_{17}\text{H}_{19}\text{N}$ : C, 86.03; H, 8.07; N, 5.90. Found: C, 85.42; H, 8.73; N, 5.77.

## CHAPTER IV

## SUMMARY

1) The N-benzyl piperidines studied were prepared by benzylation of the pyridine bases, which in some cases were prepared by alkylation with methyllithium or by a combination of methyllithium followed by reaction with the appropriate alkyl halide. The piperidines were then formed by reduction of the N-benzyl pyridinium halide.

2) The reductions of the N-benzyl pyridinium bromides were accomplished by catalytic hydrogenation over platinum or by a sodium borohydride reaction followed by catalytic hydrogenation. Catalytic hydrogenation of the 2,3- and 2,4-substituted pyridinium salts gave only the cis isomer while nearly equal amounts of the cis and trans isomers were obtained from the 2,5-isomers. The exceptional reactions of 1-benzyl-2-methyl-5-benzylpyridinium bromide (49) and 1-benzyl-2-methyl-5-t-butylpyridinium bromide (159) gave a large excess of the cis and trans isomer respectively. The sodium borohydride reduction procedure always gave a mixture of isomers with the cis isomer being produced in the major amount.

3) In evaluation of the conformational equilibrium for the 2,3-, 2,4- and 2,5-disubstituted sets it was found that the magnitude of the chemical shift differences of the nmr signal for the benzyl methylene protons was different for the two isomers in each set and varied with substituents within a set but always approached an upper limit of 60 Hz. The trans-2,3-, cis-2,4,- and trans-2,5-isomers gave the

largest values of  $\Delta\nu$  for their corresponding set.

It was also observed that when the methyl group was axial it had a slightly larger methine coupling than when it was equatorial.

4) Rotational preference about the benzyl-nitrogen bond was evaluated using a piperidine ring system with an ortho-substituted N-benzyl group and a N-(2,2-diphenylethyl)-2-substituted piperidine ring system. For the former system it was found that the N-benzyl methylene nonequivalence increased as the intramolecular hydrogen bonding ability of the ortho-substituents increased. For the latter system the  $\beta$  proton of the N-(2,2-diphenylethyl) group was the X part of an ABX system and its coupling to the A and B protons varied with the 2-substituent (e.g.,  $\text{CH}_3$ ,  $\text{CH}_2\text{-Ph}$ , and Ph).

5) An N-benzyl-3,4-disubstituted series was prepared in which it was found that for the cis isomer a small separation of the benzyl protons was observed. This was explained in terms of the conformer with the axial 3-methyl being favored and influencing the magnetic environment of the benzyl protons.

6) For the N-benzyl-3-substituted series, nonequivalence of the benzyl protons was observed when the 3-substituent was large (e.g., benzyl, isopropyl, and t-butyl). This was believed to be caused by the steric size of the equatorial 3-substituent which exerted an effect on the N-benzyl protons comparable to an axial 3-methyl.

7) The diastereotopic methyl groups of N-isopropyl piperidine and a piperazine ring system were studied but the

observable nonequivalence in the nmr was less than expected. The expected nonequivalence was shown to be more pronounced for cis-1-isopropyl-4-benzoyl-2,5-dimethyl-piperazine (132) where the piperazine ring system should be quite rigid.

8) The stereochemistry of cis-1-benzoyl-2,4-dimethyl-piperidine (127) was evaluated using  $\text{Eu}(\text{DPM})_3$ . It was found from a consideration of the paramagnetic shifts of the 2- and 6- ring protons and the ring methyls that the 2-methyl was axial but a definitive determination of the remainder of the ring conformation was not possible.

## BIBLIOGRAPHY

1. C. G. Overberger, M. Valentine, and J. P. Anselme, J. Amer. Chem. Soc., 91, 687 (1969).
2. I. L. Imbach, G. Haury, and N. H. Cromwell, Bull. Soc. Chem. Fr., 3889 (1969).
3. C. O. Bender and R. Bonnett, J. Chem. Soc. C., 2186 (1968).
4. J. P. Kutney, G. Eigendorf, and J. E. Hall, Tetrahedron, 24, 845 (1968).
5. E. W. Abel, R. P. Rush, and F. J. Harpon, Trans. Faraday Soc., 3277 (1966).
6. M. Raban, F. B. Jones, Jr., G. W. Kenney, Jr., Tetrahedron Lett., 5055 (1968).
7. T. Durst, R. Viau, and M. R. McClory, J. Amer. Chem. Soc., 93, 3077 (1971).
8. N. Ueda, T. Tokuyama, and T. Suka, Bull. Chem. Soc. Jap., 39, 2012 (1966).
9. For a review on magnetic nonequivalents see: M. von Garkon and G. Hall, Quart. Rev., 22, 14 (1968).
10. K. Mislow and M. Raban, in "Topics in Stereochemistry", Vol. 1, N. Allinger and E. Eliel Eds., Wiley (Interscience), New York, N. Y., 1967, Chapter 1.
11. R. E. Lyle, J. J. Thomas, D. A. Walsh, in "Conformational Analysis", Vol. 21, G. Chiurdoglu, Ed., Academic Press, New York, 1971, pp. 157-164.
12. K. Dudley, J. J. Davis, D. Kim, and F. Ross, J. Org. Chem., 35, 147 (1970).
13. Barry M. Trost, "Problems in Spectroscopy", 1st ed., W. A. Benjamin, Inc., New York, N. Y., 1967, #28.
14. J. L. Rosenberg, Jr., J. E. Muhler, and R. Pettit, J. Amer. Chem. Soc., 84, 2842 (1962).
15. P. L. Southwick, J. A. Fitzgerald, and G. E. Milliman, Tetrahedron Lett., 1247 (1965).
16. A. H. Lewin, J. Lipowitz, and T. Cohen, Tetrahedron Lett., 1241 (1965).
17. R. K. Hill and T. H. Chan, Tetrahedron, 21, 2015 (1965).



18. R. M. Acheson, "Heterocyclic Compounds", 2nd ed., Interscience Publishers, New York, N. Y. 1967, Chapter 5.
19. K. Ziegler and H. Zeiser, Chem. Ber., 63, 1847 (1930).
20. J. Evans, C. Allen, Org. Synthesis, Coll. Vol. II, 517 (1942).
21. R. A. Abramovitch and C. S. Giam, Can. J. Chem., 213 (1962).
22. J. Palacek, K. Vondra, and J. Kuthan, Collect. Czech. Chem. Commun., 34, 2991 (1969).
23. U. Eisner and J. Kuthan, Chem. Rev., 72, 1 (1972).
24. R. A. Abramovitch in "Kirk-Uthner Encyclopedia of Chemical Technology", Vol. 16, Wiley, New York, N. Y. 1968, p. 780.
25. R. A. Abramovitch, C. S. Giam, and A. D. Notation, Can. J. Chem., 38, 761 (1960).
26. C. S. Giam and J. L. Stout, J. Chem. Soc., D., 142 (1969).
27. A. G. Cook, "Enamines: Synthesis, Structure, and Reactions", 1st ed., Macel Dekker, Inc., New York, N. Y., 1969.
28. C. S. Giam and J. L. Stout, J. Chem. Soc., D., 479 (1970).
29. R. C. Jones and H. Gilman, "Organic Reactions," Vol. 6, Wiley, 1951, p. 339.
30. H. Gilman and R. D. Gorsich, J. Amer. Chem. Soc., 77, 3134 (1955).
31. C. S. Giam and S. D. Abbott, J. Amer. Chem. Soc., 93, 1294 (1971).
32. P. T. Lansbury and J. O. Peterson, J. Amer. Chem. Soc., 83, 3537 (1961).
33. R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, Inc., New York, N. Y., 1965.
34. P. S. Anderson, Ph.D. Thesis, University of New Hampshire, Durham, New Hampshire, 1963.
35. H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Inc., New York, N. Y., 1965, Chapter 1.
36. Y. Kawazoe, M. Tsuda, and T. Horie, Chem. Pharm. Bull., 19, (2), 429(1971).
37. N. L. Allinger and J. L. Coke, J. Amer. Chem. Soc., 81, 4080 (1959).

38. R. E. Lyle and P. Anderson, in "Advances in Heterocyclic Chemistry," Vol. VI, A. Katritzky, ed., Academic Press, Inc., New York, N. Y.
39. H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Lett.*, 2553 (1964).
40. E. Eliel, N. Allinger, S. Angyal, G. Morrison, "Conformational Analysis," J. Wiley and Sons, Inc., New York, N. Y., 1967, Chapter 2.
41. M. Tsuda and Yutaku Kawazoe, *Chem. Pharm. Bull.*, 18(12), 2499 (1970).
42. (a) P. J. Brignell, K. Brown, and A. R. Katritzky, *J. Chem. Soc., B*, 1462 (1968).  
(b) E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, 88, 5347 (1966).  
(c) For a review on Heterocyclic Conformational Analysis see: F. G. Ridell, *Chem. Rev.*, 21, 364 (1967).
43. M. D. Brown, M. J. Cook, G. Desimoni, and A. R. Katritzky, *Tetrahedron*, 26, 5281 (1970).
44. R. A. Johnson, *J. Org. Chem.*, 33, 3627 (1967).
45. Y. L. Chow and C. J. Colon, *Can. J. Chem.*, 45, 2559 (1967).
46. D. McMahon, Ph.D. Thesis, University of New Hampshire, N.H. 1967.
47. M. A. Iorio, P. Ciuffa, and G. Damia, *Tetrahedron*, 26, 5519 (1970).
48. Y. L. Chow, S. Black, J. E. Blier, and M. M. Tracy, *Can. J. Chem.*, 48, 2134 (1970).
49. M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, 85, 1899 (1963).
50. J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, 42, 1339 (1965).
51. R. N. Fraser, P. Hanbury, and C. Reyes-Zamora, *Can. J. Chem.*, 45, 2481 (1967).
52. K. Baily, A. W. By, K. C. Graham, and D. Vernier, *J. Can. Chem.*, 49, 3143 (1971).
53. F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y. 1969.
54. J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Inc., New York, 1959, Chapter 5.

55. M. M. Hassan and A. F. Casy, *Tetrahedron*, 26, 4517 (1970).
56. W. E. Stewart and T. H. Sidall, *Chem. Rev.*, 70, 517 (1970).
57. K. Nagarujan, M. Nair, and P. M. Pillai, *Tetrahedron*, 23, 1683 (1967).
58. C. C. Hinckley, *J. Amer. Chem. Soc.*, 91, 5160 (1969).
59. P. V. Demarco, *J. Amer. Chem. Soc.*, 92, 5734 (1970).
60. (a) J. K. M. Sanders and D. H. Williams, *Tetrahedron Lett.*, 2813 (1971).  
(b) R. Cory and A. Hassner, *Tetrahedron Lett.*, 1245 (1972).  
(c) K. K. Andersen and J. J. Uebel, *Tetrahedron Lett.*, 5253 (1970).
61. M. R. Willcott, III and R. E. Lenkinski, *J. Amer. Chem. Soc.*, 94, 1742 (1962).
62. B. L. Shapiro, J. R. Hlubucek, G. R. Sullivan, and L. F. Johnson, *J. Amer. Chem. Soc.*, 93, 3281 (1971).
63. R. R. Fraser and Y. Y. Wigfied, *Chem. Commun.*, 1471 (1970).
64. J. Briggs, F. A. Hart, and G. P. Moss, *Chem. Commun.*, 1506 (1970).
65. Methyllithium (1.6 M in diethylether) and n-butyllithium (1.6 M in hexane).
66. H. Gilman, Z. E. Zoellner, and W. M. Selby, *J. Amer. Chem. Soc.*, 55, 1252 (1933).
67. S. Watson and J. Eastam, *J. Organometal. Chem.* 9, 165 (1967).
68. Arthur I. Vogel, "Practical Organic Chemistry," 3rd ed. Wiley, New York, N. Y., 1956, p. 173.
69. L. F. Fieser, "Organic Experiments," 2nd ed., Raythem Education Co., 1968, Chapter 16.
70. L. Fieser and M. Fieser, "Reagent for Organic Synthesis," Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1967, pp. 503-584.
71. (a) R. A. Abramovitch, C. S. Giam, and A. D. Notation, *Can. J. Chem.*, 38, 761 (1960);  
(b) R. A. Abramovitch and C. S. Giam, *Can. J. Chem.* 41, 3127 (1963).  
(c) H. E. Podall, *Anal. Chem.*, 29, 1423 (1957).

72. T. Nakushima, *Yakugaku Zasshi*, 77, 698-700 (1957); *Chem. Abstr.* 51 16462g.
73. C. S. Giam and J. L. Stout, *J. Chem. Soc., D.*, 478 (1970).
74. F. Fichter and H. P. Labhardt, *Chem. Ber.*, 42, 4714 (1909).
75. G. Errera, *Chem. Ber.*, 34, 3698 (1901).
76. F. M. Beringer, E. J. Geering, I. Kuntz, and M. Mausne, *J. Phys. Chem.*, 60, 141 (1956).
77. C. S. Giam and S. D. Abbott, *J. Amer. Chem. Soc.*, 93, 1294 (1971).
78. H. C. Brown and W. A. Murphey, *J. Amer. Chem. Soc.*, 73, 3308 (1951).
79. H. S. Mosher and J. E. Tessieri, *J. Amer. Chem. Soc.*, 73, 4925 (1951).
80. J. Dietrich, *Chem. Ber.*, 93, 2966 (1960).
81. D. H. McMahon, Ph.D. Thesis, University of New Hampshire, Durham, N. H., 1967.
82. A. V. El'tsov, A. G. Chigarev, and N. T. Starykh, *Biol. Aktivn. Soedin., Aknd. Nauk, SSSR*, 109 (1965); *Chem. Abstr.*, 63, 16299h, (1965).
83. A. Kalir, "Organic Synthesis," 46, 81 (1966).
84. These nmr structural assignments were determined by decoupling on a Varian HA-100, courtesy of Dr. R. Stolow, Tufts University.
85. Hans Henecka, German Patent 904, 532(1954); *Chem. Abstr.*, 52, 9222d (1958).
86. L. Fieser and M. Fieser, "Reagents for Organic Synthesis," 1st ed., J. Wiley and Sons, New York, N. Y., 1967, p. 1153.
87. ABX coupling constants were calculated using the formulas of George Slump, *Applied Spectroscopy Reviews*, 2(2), 263 (1969).
88. J. F. Norris and A. Cresswell, *J. Amer. Chem. Soc.*, 56, 423 (1954).
89. H. Gilman and B. J. Gaj, *J. Org. Chem.*, 28, 1725 (1963).
90. H. C. Brown and N. M. Yoon, *J. Amer. Chem. Soc.*, 88, 1464 (1966).
91. S. Winstein, *J. Amer. Chem. Soc.*, 74, 1113 (1952).

92. J. J. Thomas, Ph.D. Thesis, University of New Hampshire, 1966.
93. G. Buchmann and Rudi Schmuck, Z. Chem., 2, 11-15 (1962); Chem. Abstr., 57 16555b (1962).
94. L. G. Yudin, A. W. Kost, E. Kh. Zolotaves, and A. N. Mirza, Fiz. i Khim., 13, 169-176 (1958); Chem. Abst., 53, 8135b (1959).
95. M. Shamma and P. Rosenstock J. Org. Chem., 26, 718 (1961).
96. The starting material (3-t-butylpyridine (135)) was generously donated by Dr. H. C. Brown and Gary Kramer of Purdue University.

APPENDIX

TABLE XIII

## PREPARATION AND PHYSICAL CONSTANTS OF PYRIDINIUM SALTS

<u>1-Benzyl-Pyridinium Salts</u>	<u>Yield</u>	<u>M.P.</u>	<u>Procedure</u>
1-Benzyl-2,3-dimethyl pyridinium bromide ( <u>38</u> )	69%	156-159°	A
1-Benzyl-2,5-dimethyl pyridinium bromide ( <u>43</u> )	90.3%	170-171°	A
1-Benzyl-2,4-dimethyl pyridinium bromide ( <u>41</u> )	85%	168-169°	A
1-Benzyl-2-methyl-4-phenyl pyridinium bromide ( <u>52</u> )	--- <sup>a</sup>	225-226°	C
1-Benzyl-2-methyl-4-t-butyl pyridinium bromide ( <u>53</u> )	--- <sup>a</sup>	196-199°	C
1-Benzyl-2-methyl-5-isopropyl pyridinium bromide ( <u>48</u> )	--- <sup>a</sup>	218-219°	B
1-Benzyl-2-methyl-5-benzyloxy pyridinium bromide ( <u>66</u> )	70%	195-197°	A
1-Benzyl-2-methyl-5-ethyl pyridinium bromide ( <u>47</u> )	95%	132-135°	A
1-Benzyl-3-ethyl-4-methyl pyridinium bromide ( <u>50</u> )	79%	161-163°	B
1-Benzyl-3-methyl-4-ethyl pyridinium bromide ( <u>51</u> )	84%	144-146°	B
1-Benzyl-3-isopropyl pyridinium bromide ( <u>84</u> )	67%	158-160°	B
1-Benzyl-3,4-dimethyl pyridinium bromide ( <u>46</u> )	84%	200-201.5°	A
1-Benzyl-3-ethyl pyridinium bromide ( <u>82</u> )	88%	150-152°	A
1-Benzyl-3-isopropenyl pyridinium bromide ( <u>134</u> )	64%	124-126°	A
1-Benzyl-2-methyl-5-benzyl pyridinium bromide ( <u>49</u> )	87%	218-221°	A
1,3-Dibenzyl pyridinium bromide ( <u>89</u> )	82%	117-119°	A
1-Benzyl-3-t-butylpyridinium bromide ( <u>158</u> )	95%	115-118°	A
1-Benzyl-2-methyl-5-t-butyl pyridinium bromide ( <u>159</u> )	84%	225-226°	A

<sup>a</sup>Not determined

TABLE XIV

## ANALYSES OF PYRIDINIUM SALTS

Comp. No.	Formula	Anal. Calcd.			Found			Anal. No.
		C	H	N	C	H	N	
<u>38</u>	$C_{14}H_{16}BrN_1$	60.44	5.79	5.03	60.46	5.72	4.94	1A
<u>43</u>	$C_{14}H_{16}BrN$	60.44	5.79	5.03	60.65	6.00	4.92	15
<u>41</u>	$C_{14}H_{16}BrN$	60.44	5.79	5.03	60.72	5.76	4.94	24A
<u>52</u>	$C_{19}H_{19}BrN$	66.86	5.61	4.10	67.10	5.52	4.07	31
<u>53</u>	$C_{17}H_{23}BrN(H_2O)$	60.35	7.15	4.14	60.71	7.05	4.22	34
<u>48</u>	$C_{16}H_{20}BrN$	62.75	6.58	4.57	62.72	6.52	4.60	47
<u>66</u>	$C_{20}H_{20}BrN$	64.87	5.44	4.32	64.78	5.32	3.75	50
<u>47</u>	$C_{15}H_{18}BrN$	61.65	6.20	4.79	61.53	6.24	4.78	51
<u>50</u>	$C_{15}H_{18}BrN$	61.65	6.20	4.79	61.74	6.24	4.88	55
<u>51</u>	$C_{15}H_{18}BrN$	61.65	6.20	4.79	61.70	6.06	4.84	56
<u>84</u>	$C_{15}H_{18}BrN$	61.65	6.20	4.79	61.32	6.14	4.98	59
<u>46</u>	$C_{14}H_{16}BrN$	60.44	5.79	5.03	60.65	5.86	5.07	61
<u>82</u>	$C_{14}H_{16}BrN$	60.44	5.79	5.03	60.52	5.86	5.20	68
<u>134</u>	$C_{15}H_{16}BrN(H_2O)$	58.45	5.88	4.54	58.30	5.92	4.58	73
<u>49</u>	$C_{20}H_{20}BrN$	67.80	5.68	3.95	67.87	5.57	3.98	69
<u>89</u>	$C_{19}H_{18}BrN(H_2O)$	66.17	5.40	4.06	66.34	5.29	4.12	77
<u>158</u>	$C_{16}H_{20}BrN(H_2O)$	59.26	6.83	4.31	59.33	6.59	4.40	81
<u>159</u>	$C_{17}H_{22}NBr$	63.75	6.92	4.37	63.78	6.91	4.40	82



TABLE XV  
 PREPARATION AND PHYSICAL CONSTANTS OF  
 1-BENZYLPIPERIDINE

1-Benzylpiperidines	Yield <sup>a</sup>	M.P.	Procedure
<u>cis</u> -1-Benzyl-2,3-dimethyl piperidine (39)	78%	186-188°(HBr)	B <sup>b</sup> , C <sup>c</sup>
<u>cis</u> -1-Benzyl-2,5-dimethyl piperidine (44)	38%	177-179°(HCl)	A <sup>d</sup>
<u>trans</u> -1-Benzyl-2,5-dimethyl piperidine (45)	38%	204-205°(HCl)	A
<u>cis</u> -1-Benzyl-2,4-dimethyl piperidine (42)	78%	174-176°(HBr)	A, C
<u>cis</u> -1-Benzyl-2-methyl-4-phenyl piperidine (59)	75%	176-178°(HBr)	B <sup>b</sup> , C <sup>e</sup>
<u>cis</u> -1-Benzyl-2-methyl-4-5-butylpiperidine (58)	66%	142-144°(HBr)	B <sup>f</sup> , b, D
<u>cis</u> - and <u>trans</u> -1-Benzyl-2-methyl-5-isopropylpiperidines (77) and (78)	62%	---	A <sup>g</sup>
<u>cis</u> - and <u>trans</u> -2-methyl-5-ethylpiperidines (75) and (76)	46%	---	A <sup>g</sup>
<u>cis</u> -1-Benzyl-3-ethyl-4-methylpiperidine (97)	81%	147-149°(HBr)	A <sup>b</sup>
<u>cis</u> -1-Benzyl-3-methyl-4-ethylpiperidine (95)	20%	142-144°(HBr)	A, B <sup>h</sup>
1-Benzyl-3-isopropylpiperidine (85)	56%	---	A
1-Benzyl-3-methylpiperidine (81) <sup>45</sup>	73%	---	C
1-Benzyl-2-phenylpiperidine (113)	54%	75-82 [Lit. <sup>95</sup> 78-82]	C
1-Benzyl-2-benzylpiperidine (115)	---	196-198°(HBr)	C
<u>cis</u> -1-Benzyl-3,4-dimethylpiperidine (99)	45%	160-162°(HBr)	A
1-Benzyl-3-ethylpiperidine (83)	60%	---	A
<u>cis</u> - and <u>trans</u> -1-Benzyl-2-methyl-5-benzyl piperidines (79) and (80)	69%	202-203°(HBr)	A <sup>b</sup>
1,3-Dibenzylpiperidine (90)	89%	194-197°(HBr)	A
1-Benzyl-3-t-butylpiperidine (160)	80%	200-205°(HBr)	A
<u>cis</u> - and <u>trans</u> -1-Benzyl-2-methyl-5-t-butylpiperidine (161)	60%	244-245°(HBr)	A <sup>g</sup>

<sup>a</sup>The product has been distilled and the yield is based on the corresponding pyridine. The yield is for the first procedure given.

<sup>b</sup>In these cases a cis-trans isomeric mixture resulted which corresponded to the following ratios by averaged nmr integration: 39 and 40 (70/30); 59 and 60 (70/30); 58 and 61 (60/40); 97 and 95 (90/10); 79 and 80 (74/26). The major isomer in each case was separated and purified by recrystallization of its hydrobromide salt.

<sup>c</sup>The corresponding pyridine was reduced under 50 psi of pressure using acetic acid as solvent with P<sub>2</sub>O<sub>5</sub> as catalyst in 75% yield to give the piperidine in a (75/25) cis-trans ratio.

<sup>d</sup>Separated by column chromatography over Florasil using 1/9-ether: Hexane. The enriched samples were purified by recrystallization of their hydrochloride salts.

<sup>e</sup>A hydrogen pressure of 400-500 psi was necessary to reduce the corresponding pyridine. The final product 59 was obtained in 50% yield.

<sup>f</sup>Care had to be exercised in acidifying the sodiumborohydride reaction mixture. A too acidic medium lead to extensive decomposition, the Ph should be kept near 5 or 6.

<sup>g</sup>See Table XVIII for the isomeric ratios.

<sup>h</sup>By Method B the yield increased to 79% giving a (73/27) cis-trans mixture.

TABLE XVI

## ANALYSES OF 1-BENZYLPIPERIDINES

Comp. No.	Formula	Anal. Calcd.			Found			Anal. No.
		C	H	N	C	H	N	
<u>39</u>	$C_{14}H_{22}BrN$	59.15	7.80	4.92	59.31	7.85	4.95	2
<u>44</u>	$C_{14}H_{22}ClN$	70.12	9.24	5.84	70.49	9.20	5.85	6
<u>45</u>	$C_{14}H_{22}ClN$	70.12	9.24	5.84	70.38	9.39	5.84	5
<u>42</u>	$C_{14}H_{22}BrN$	59.15	7.80	4.92	58.96	7.84	4.86	25
<u>59</u>	$C_{19}H_{24}BrN$	65.89	6.98	4.04	65.56	6.98	4.13	32
<u>58</u>	$C_{17}H_{28}BrN$	62.56	8.64	4.29	62.52	8.75	4.44	35
<u>77&amp;78</u>	$C_{16}H_{25}N$	83.05	10.89	6.05	83.37	11.67	6.15	47A
<u>75&amp;76</u>	$C_{15}H_{23}N$	82.88	10.66	6.44	83.17	11.65	6.54	75
<u>97</u>	$C_{15}H_{24}BrN$	60.40	8.11	4.69	60.41	8.31	4.74	
<u>95</u>	$C_{15}H_{24}BrN$	60.40	8.11	4.69	60.09	8.09	4.79	57
<u>85</u>	$C_{15}H_{23}N$	82.89	10.58	6.44	82.94	11.54	6.41	63B
<u>115</u>	$C_{19}H_{24}BrN$	65.89	6.98	4.04	66.18	6.89	4.03	18B
<u>99</u>	$C_{14}H_{22}BrN$	59.15	7.80	4.92	58.87	7.87	4.91	64
<u>83</u>	$C_{14}H_{21}N$	82.70	10.41	6.90	82.78	11.71	6.92	71
<u>79&amp;80</u>	$C_{20}H_{25}N$	85.96	9.01	5.01	83.57	9.11	4.87	76
<u>90</u>	$C_{19}H_{24}BrN$	65.89	6.98	4.04	66.12	7.07	4.12	77
<u>79</u>	$C_{20}H_{26}BrN$ ( $H_2O$ )	58.60	7.07	3.41	58.42	7.40	5.18	80
<u>160</u>	$C_{17}H_{28}BrN$	62.56	8.64	4.29	62.20	8.58	4.44	83
<u>161</u>	$C_{16}H_{26}BrN$	61.53	8.39	4.48	61.22	8.98	4.44	84

TABLE XVII

## INFRARED ABSORPTION BANDS OF 1-BENZYLPIPERIDINES

Compound No. (I.R. No.)	Frequency Range		
	4000-1500	1499-1100	1100
<u>39</u> (9749)	3054-3150 (w) 2950 (s) 2800 (m) 1500 (m)	1460 (m) 1360 (m) 1150 (m) 1100 (m)	1050 (m) 745 (m) 730 (s) 695 (s)
<u>44</u> (10007)	3050-3150 (w) 2950 (s) 2810 (m) 1560 (m)	1460 (m) 1360 (m) 1150 (m)	1060 (m) 730 (s) 690 (s)
<u>45</u> (10008)	3020-3100 (w) 2930 (s) 2795 (m) 1500 (m)	1450 (m) 1370 (m) 1140-1120 (m)	725 (s) 690 (s)
<u>42</u> (11162)	3020-3120 (m) 2950 (s) 2795 (m) 1500 (m)	1450 (m) 1460 (m) 1380 (m) 1180 (m) 1140 (m)	1065 (m) 1040 (m) 955 (w) 730 (s) 695 (s)
<u>59</u> (11532)	3020-3100 (w) 2925 (s) 2870 (m) 2795 (m) 1500 (m)	1450 (m) 1380 (m) 1150 (m) 1130 (m)	1060 (m) 1025 (w) 750 (m) 730 (s) 690 (s)
<u>58</u> (11621)	3025-3120 (w) 2980 (s) 2880 (m) 2800 (m) 1500 (m)	1460 (m) 1360 (m) 1240 (w) 1150 (m)	1070 (w) 730 (s) 690 (s)
<u>77</u> and <u>78</u> (19022)	3020-3120 (w) 2960 (s) 2880 (s) 2800 (m) 1500	1475 (m) 1380 (m) 1220 (w) 1180-1100 (m)	1030 (m) 730 (s) 690 (s)

TABLE XVII (cont.)

## INFRARED ABSORPTION BANDS OF 1-BENZYLPIPERIDINES

Compound No. (I.R. No.)	Frequency Range		
	4000-1500	1499-1100	1100
<u>75</u> and <u>76</u> (19023)	3020-3120 (w) 2930 (s) 2850 (s) 2790 (m) 1500 (m)	1450 (m) 1380 (m) 1330 (w) 1210 (w) 1170-1120 (m)	1065 (m) 1025 (m) 730 (s) 690 (s)
<u>97</u> and <u>96</u> (19020)	3040-3120 (w) 2940 (s) 2800 (m) 1500 (m)	1470 (m) 1380 (m) 1170 (m) 1125 (m)	1070 (m) 1030 (m) 900 (w) 835 (w) 790 (w) 730 (s) 695 (s)
<u>95</u> (19021)	3040-3120 (w) 2920 (s) 2800 (m) 1500 (s)	1460 (s) 1380 (m) 1200 (w) 1170 (m) 1120 (m)	1090 (m) 1065 (m) 1025 (w) 815 (w) 730 (s) 695 (s)
<u>85</u> (19092)	3020-3100 (w) 2930 (s) 2880 (m) 2790 (m) 1500 (m)	1460 (m) 1360 (m) 1150 (m) 1125 (m)	1125 (m) 1075 (m) 1025 (m) 730 (s)
<u>81</u> (19037)	3025-3110 (w) 2925 (s) 2800 (s) 1500 (m)	1470 (s) 1370 (m) 1320 (w) 1155 (w) 1120 (m)	1075 (m) 1030 (m) 970 (m) 735 (s) 695 (s)
<u>113</u> (10970)	3030-3100 (w) 2940 (s) 2860 (m) 2800 (m) 1500 (w)	1460 (m) 1310 (w) 1110 (m)	1045 (w) 1020 (w) 840 (w) 750 (s) 695 (s)

TABLE XVII (cont.)

## INFRARED ABSORPTION BANDS OF 1-BENZYLPIPERIDINES

Compound No. (I.R. No.)	Frequency Range		
	4000-1500	1499-1100	1100
<u>115</u> (10969)	3030-3100 (w) 2940 (s) 2860 (m) 2800 (m) 1500 (m)	1460 (m) 1365 (w) 1120 (m)	1070 (w) 1025 (w) 730 (s) 695 (s)
<u>99</u> (19137)	3030-3100 (w) 2930 (s) 2850 (m) 2890 (m) 1600 (w) 1500 (m)	1455 (m) 1475 (m) 1150 (m)	1025 (m) 905 (m) 730 (s) 695 (s)
<u>79</u> and <u>80</u> (19962)	3030-3100 (w) 2930 (s) 2850 (m) 2890 (m) 1600 (w) 1500 (m)	1455 (m) 1375 (m) 1150 (m)	1025 (m) 905 (m) 730 (s) 695 (s)
<u>90</u> (20026)	3110-3020 (m) 2940-2750 (s) 1505 (w)	1470 (m) 1150 (m)	1095 (w) 1070 (w) 1025 (w) 740 (s) 695 (s)
<u>83</u> (20027)	3100-3020 (w) 2940 (s) 2860 (m) 2800 (m)	1475 (m) 1290 (w) 1160 (w)	1075 (w) 1025 (w) 735 (s) 695 (s)
<u>160</u> (20126)	3100-3300 (w) 2940-2860 (s) 2800-2760 (s) 1500 (w)	1480-1440 (m) 1370 (m) 1160 (m) 1100 (m)	735 (s)
<u>161</u> (20134)	3100-3030 (w) 2950-2870 (s) 2800 (m)	1500 (m) 1475 (m) 1360 (m)	733 (s) 695 (s)

TABLE XVIII  
NUCLEAR MAGNETIC RESONANCE ASSIGNMENTS

U.N.H. Spec. No.	Compound	Chemical shift (p.p.m.)	No. of Protons	Pat-tern	J(Hz)	As-sign-ment
5028 A-4	 39	7.30 3.45 2.95-1.10 0.90	5 2 8 6	m q m dd	--- $J_{AB}=13.8, \Delta\nu=7.9$ --- 6.8	b a d c
9135 A-1	 44	7.26 3.45 3.05-1.05 1.02 0.94	5 2 8 3 3	m q m d d	--- $J_{AB}=12.6, \Delta\nu=10.5$ --- 6.4 5.0	b a d c e
9136 A-2	 45	7.20 3.50 2.8-0.90 1.12 .68	5 2 8 3 3	m q m d d	--- $J_{AB}=12.8, \Delta\nu=54.6$ --- 5.6 5.2	b a d c e
10557 A-11	 42	7.2 3.55 2.83-1.0 1.1 0.8	5 2 8 3 3	s q m d d	--- $J_{AB}=12.5, \Delta\nu=60.5$ --- 6.0 <sup>a</sup> 4.5 <sup>a</sup>	b a d c e
10857 A-9	 59	7.1 & 7.2 3.5 3.0-1.3 1.12	10 2 8 3	2s q m d	--- $J_{AB}=13.5, \Delta\nu=61.0$ --- 6.1 <sup>a</sup>	b a d c
1196 A-12	 58	7.34 3.60 3.0-1.0 1.27 0.88	5 2 8 3 9	s q m d s	--- $J_{AB}=13.3, \Delta\nu=59.0$ --- 6.1 <sup>a</sup> ---	b a d c e

TABLE XVIII (cont.)

## NUCLEAR MAGNETIC RESONANCE ASSIGNMENTS

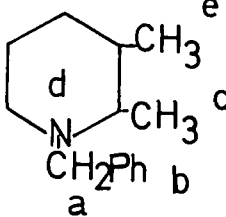
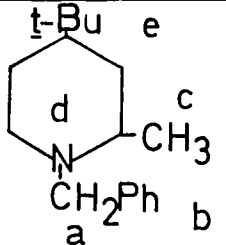
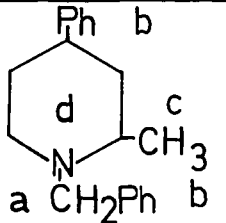
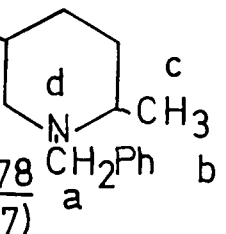
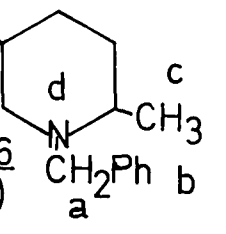
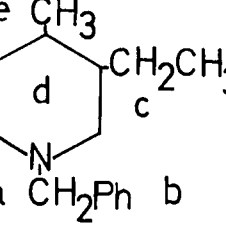
U.N.H. Spec. No.	Compound	Chemical shift (p.p.m.)	No. of Protons	Pattern	J(Hz)	Assignment
9047 A-4		7.28 3.6 3.0-1.0 1.30 1.0	5 2 8 3 3	s q m d hidden	--- $J_{AB}=13.5, \Delta\tau=43.0$ --- 6.0 ---	b a d c e
<u>40</u>						
1196A		7.34 3.6 3.0-1.0 1.0 0.88	5 2 8 3 9	s s m d s	--- --- --- $6.75^a$ ---	b a d c e
<u>61</u>						
10857A		7.1 & 7.2 3.5 3.0-1.3 .95	10 2 8 3	s s m d	--- --- --- 6.75	b a d c
<u>60</u>						
12286 <sup>b</sup> A-13		7.20 3.6(cis) 3.2-1.4 1.5-0.85 3.6(trans)	5 2 8 10 -	s q m m q	--- $J_{AB}=13.5, \Delta\tau=12.9$ --- --- $J_{AB}=13.5, \Delta\tau=52.9$	b a d c a
<u>77 and 78</u> (53/47)						
12356 <sup>b</sup> A-14		7.2 3.62(cis) 2.9-1.4 1.4-0.8 3.62(trans)	5 2 8 8 ---	s q m m q	--- $J_{AB}=12.5, \Delta\tau=17.5$ --- --- $J_{AB}=13.0, \Delta\tau=53.0$	b a d c a
<u>75 and 76</u> (43/57)						
12414 <sup>b</sup>		7.0 3.38(cis) 3.0-0.80 0.85 3.48(trans)	5 2 13 3 -	s q m d s	--- $J_{AB}=13.3, \Delta\tau=12.2$ --- 5.5 ---	b a d e a
<u>97 and 96</u> (90/10)						

TABLE XVIII (cont.)

## NUCLEAR MAGNETIC RESONANCE ASSIGNMENTS

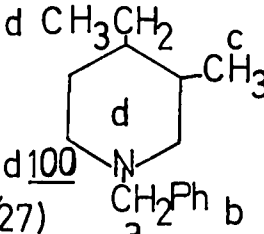
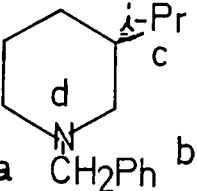
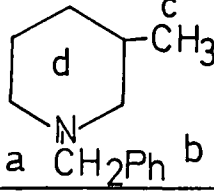
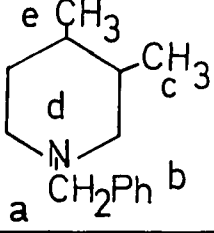
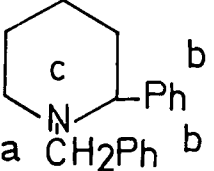
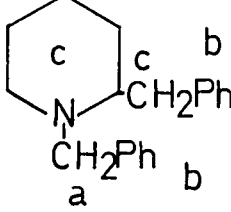
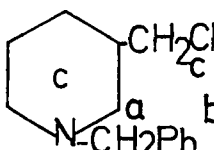
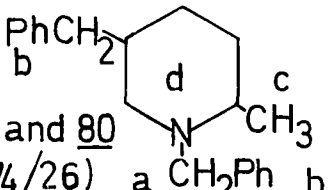
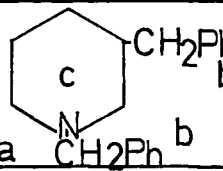
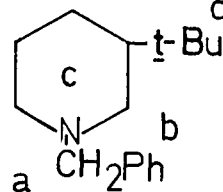
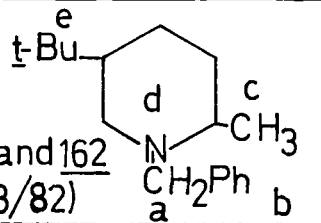
U.N.H. Spec. No.	Compound	Chemical shift (p.p.m.)	No. of Protons	Pattern	J(Hz)	Assignment
12413 <sup>b</sup> A-15		7.05 3.40(cis) 2.9-0.75 0.90 3.53(trans)	5 2 13 3 -	s q m d s	--- $J_{AB}=13.5, \Delta\nu=12.2$ --- 6.2 ---	b a d c a
12443		7.30 3.55 3.1-1.1 0.98	5 2 10 6	s q m d	--- $J_{AB}=13.2, \Delta\nu=6.65$ --- 5.2	b a d c
12423		7.04 3.35 1.4-2.9 0.82	5 2 9 3	s s m d	--- --- --- 5.2	b a d c
12552		7.40 3.6 2.9-1.5 1.0	5 2 8 6	s q m dd	--- $J_{AB}=3.5, \Delta\nu=10.0$ --- 5.0 6.5	b a d e c
10171		7.10 3.25 3.4-0.90	10 2 9	bs q m	--- $J_{AB}=14.0, \Delta\nu=61.5$ ---	b a c
10203		7.3 & 7.4 3.75 3.3-1.2	10 2 11	2(s) q m	--- $J_{AB}=13.5, \Delta\nu=34.85$ ---	b a c



TABLE XVIII (cont.)  
NUCLEAR MAGNETIC RESONANCE ASSIGNMENTS

U.N.H. Spec. No.	Compound	Chemical shift (p.p.m.)	No. of Protons	Pat-tern	J(Hz)	As-sign-ment
12624		7.20 3.40 2.9-0.50	5 2 9	s s m		b a c
14538		7.3-6.8 3.6(cis) 2.9-1.3 1.08 3.6(trans)	10 2 10 2 -	m q m d q	$J_{AB}=13.5, \Delta\nu=24.0$ $J=6.2$ Hz $J_{AB}=13.25, \Delta\nu=45.6$	b a d c a
14512		7.08 3.4 2.9-0.70	10 2 11	2(s) q m	$J_{AB}^c=13.0$ Hz, $\Delta\nu=12.9$	b a c
14723		7.30 3.50 3.1-1.0 0.87	5 2 9 9	s q m s	$J_{AB}=13.2, =12.95$	b a c
14761		0.88(cis) 7.30 3.60(trans) 3.0-1.0 1.2 0.80	- 5 2 8 3 9	small singlet s q m d s	$J_{AB}=13.8, =52.4$ $J=5.4$	e b a d c e

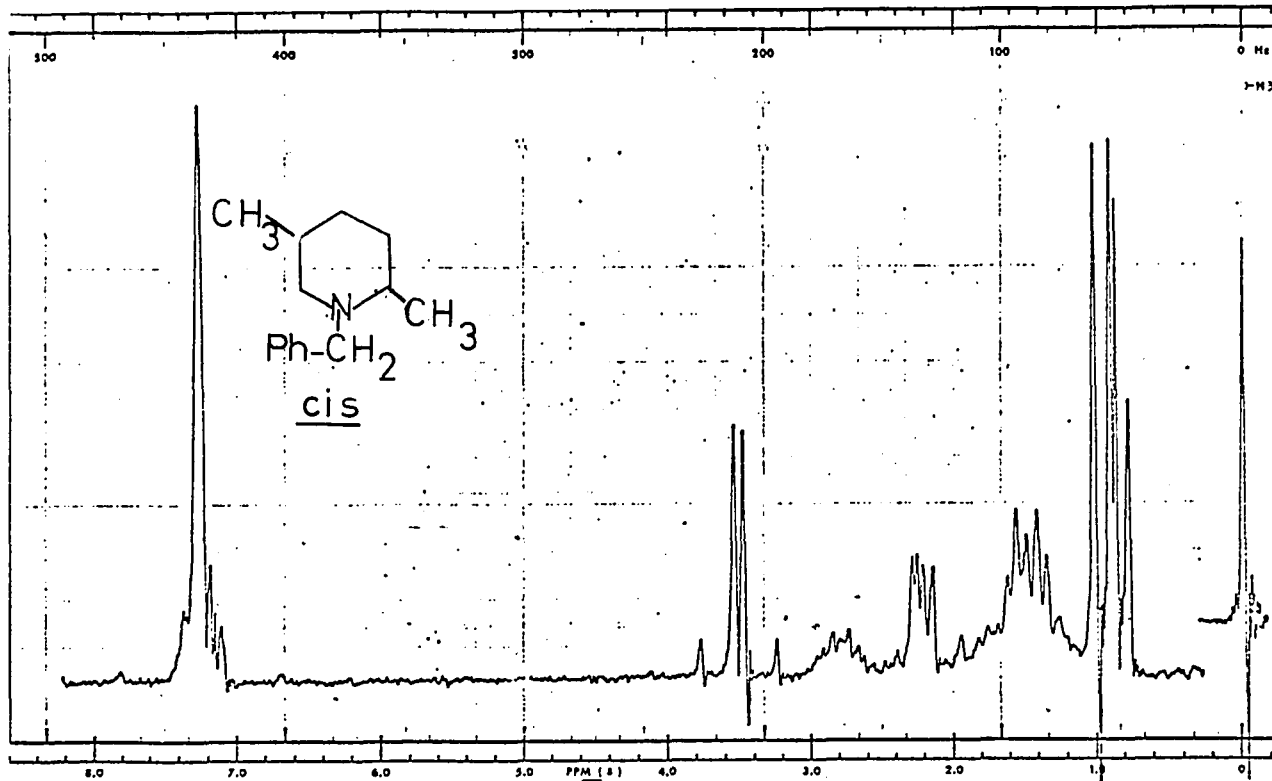
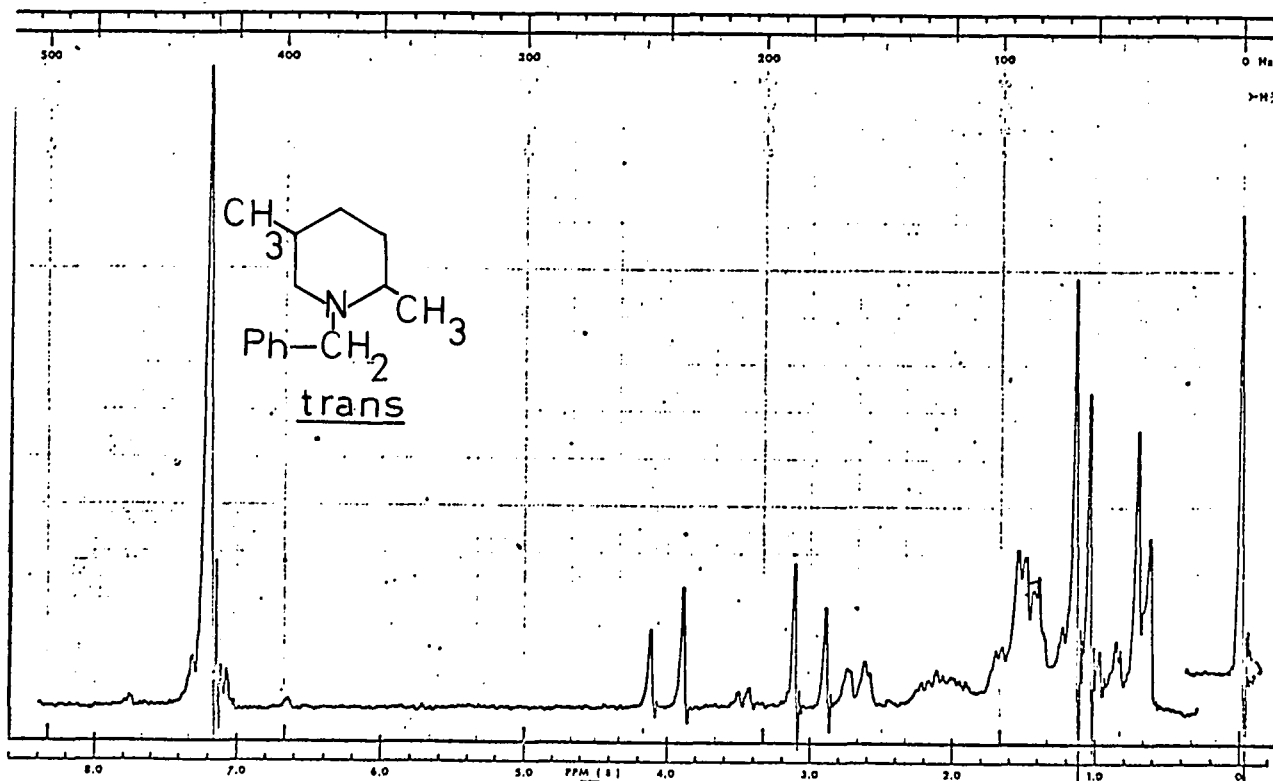
<sup>a</sup>A sweep width of 50 Hz was used to determine these coupling constants.

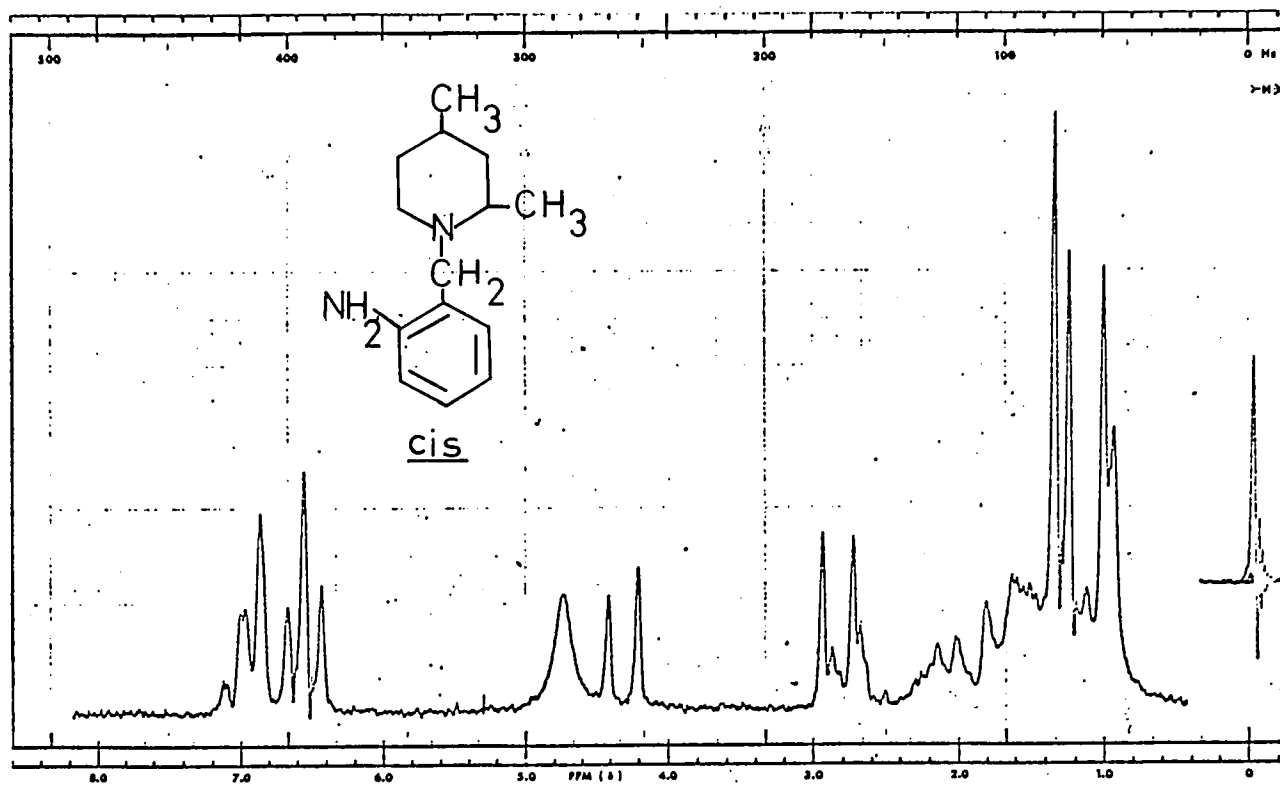
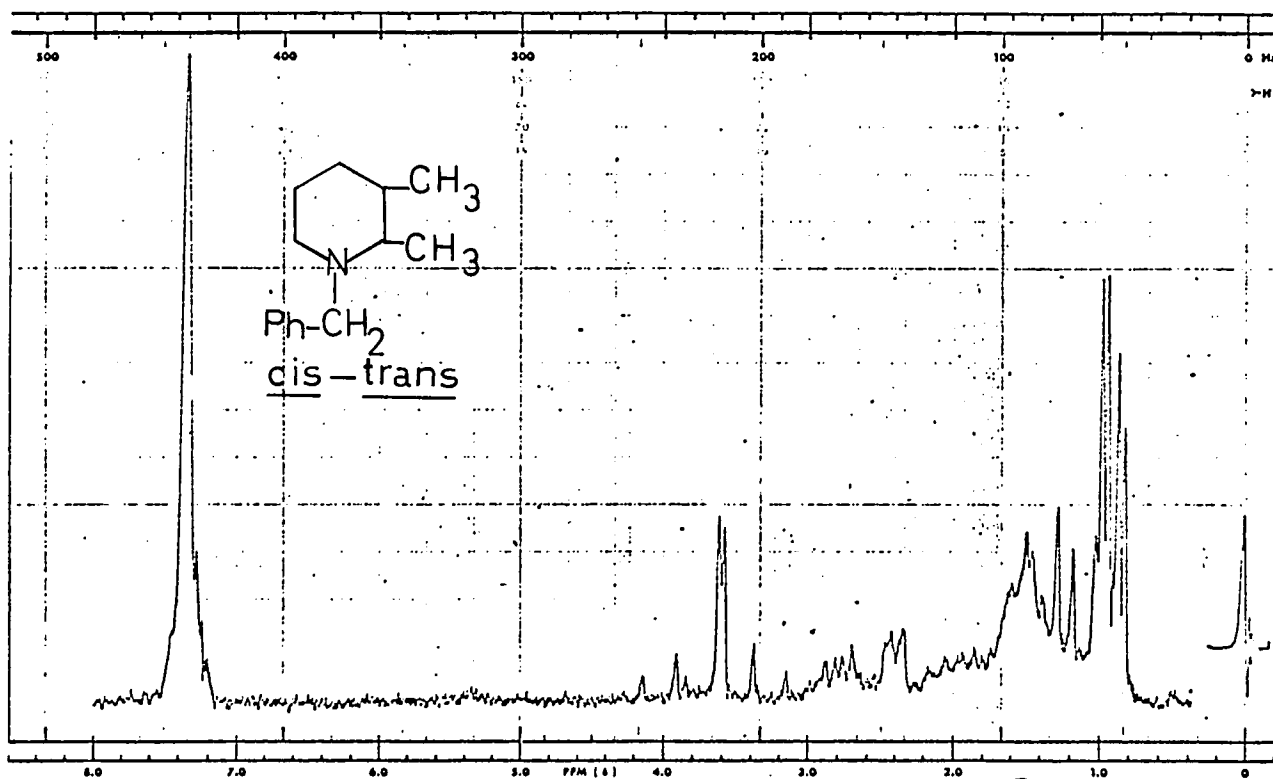
<sup>b</sup>In cases involving isomers where separations were not performed, the ratio of isomers in an isomeric mixture was determined by electronic integration of the benzylic or methyl protons.

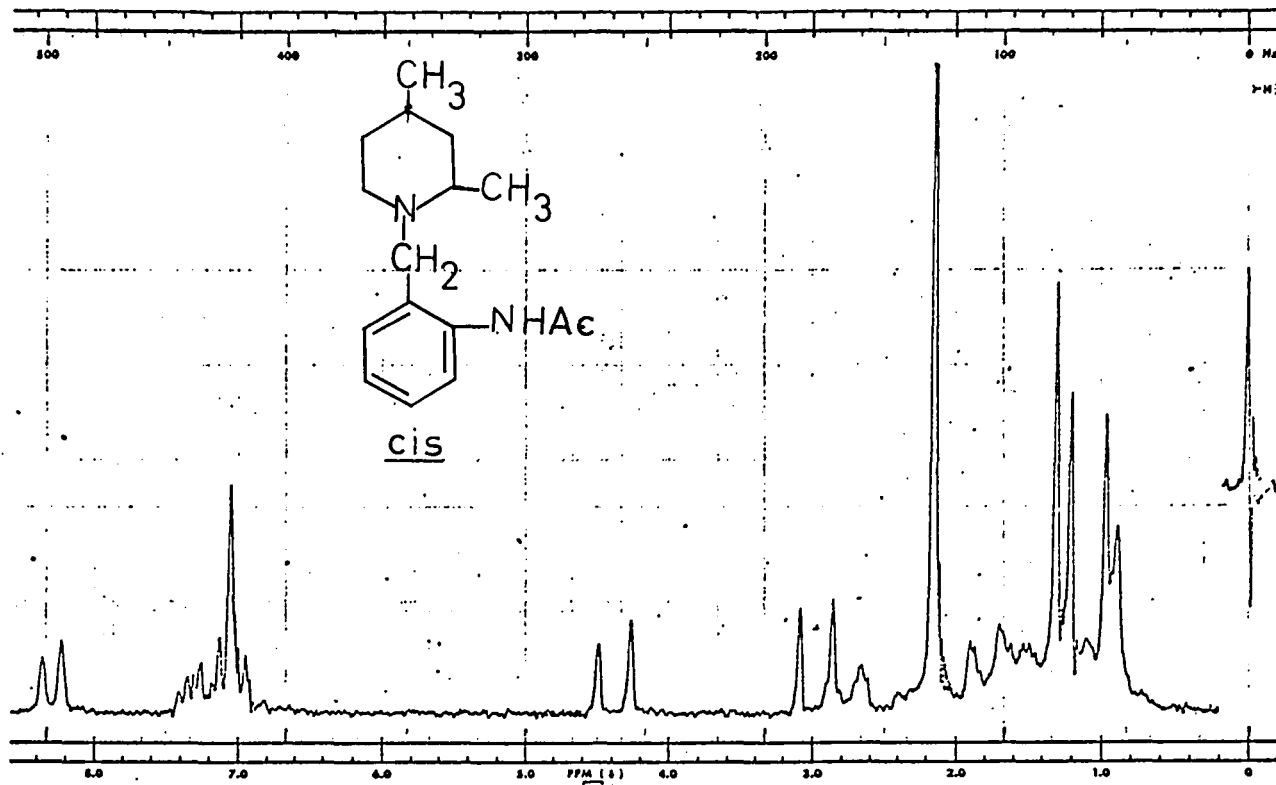
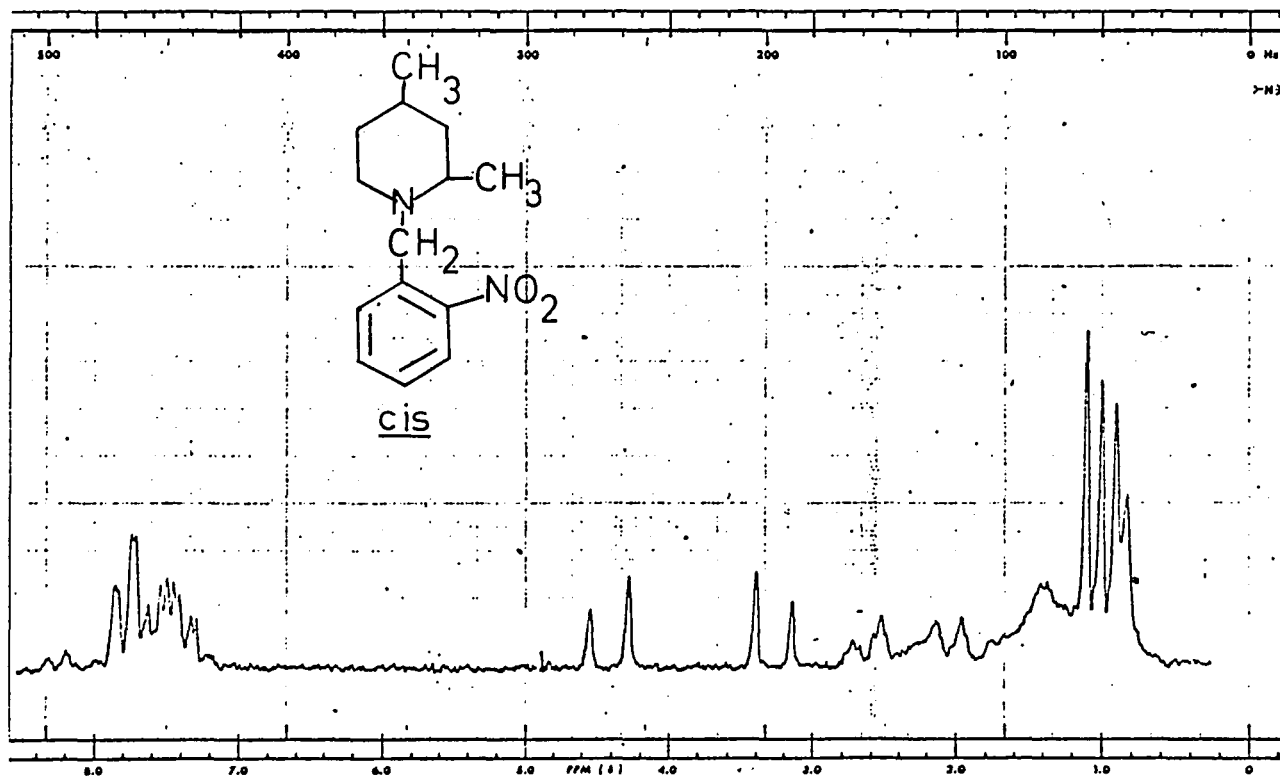
<sup>c</sup>Spectra were obtained from the JHM-MH100 spectrometer.

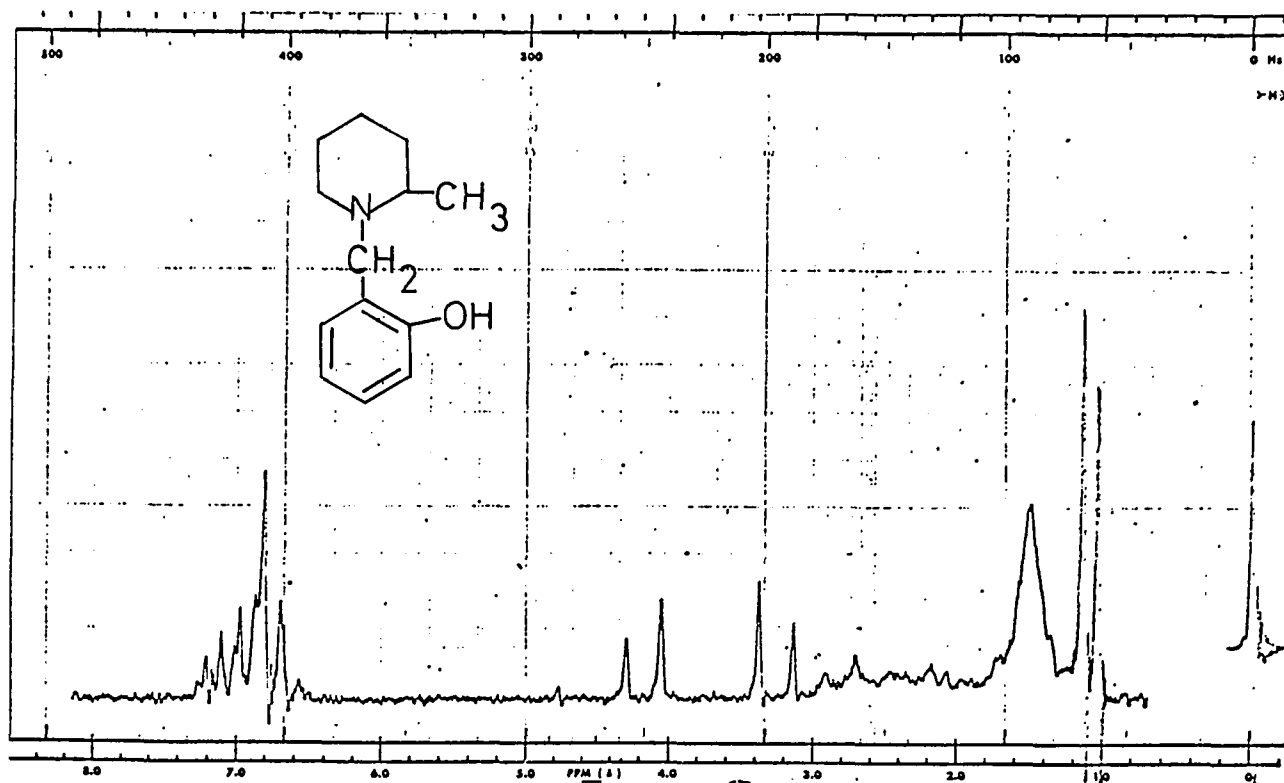
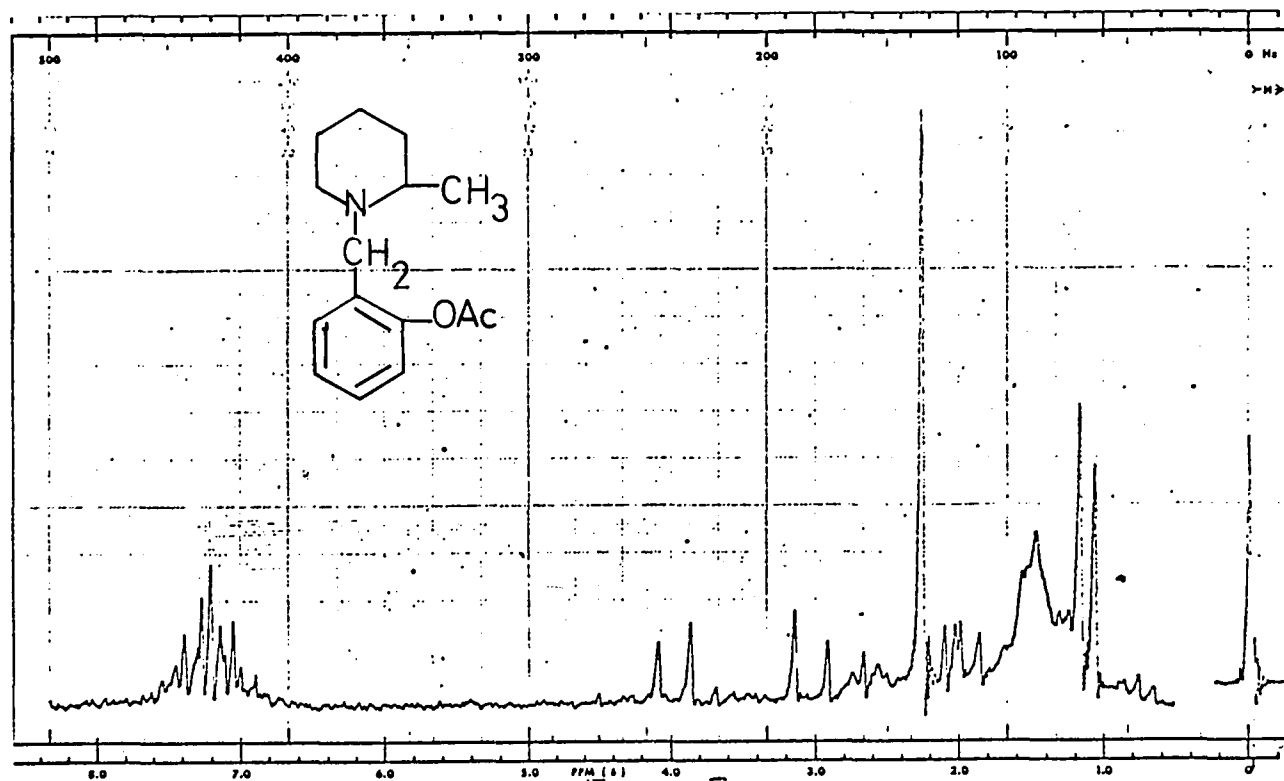
<sup>d</sup>The designation within the ring denotes ring protons.

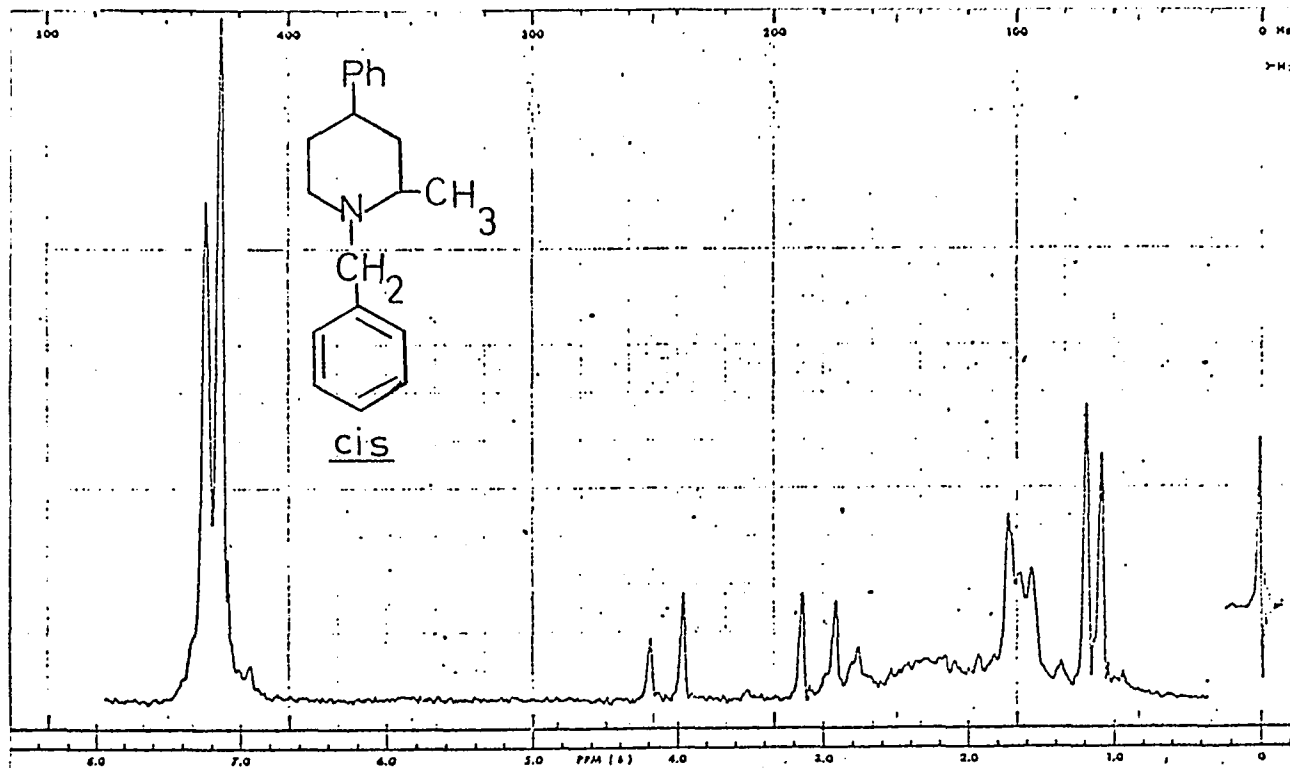
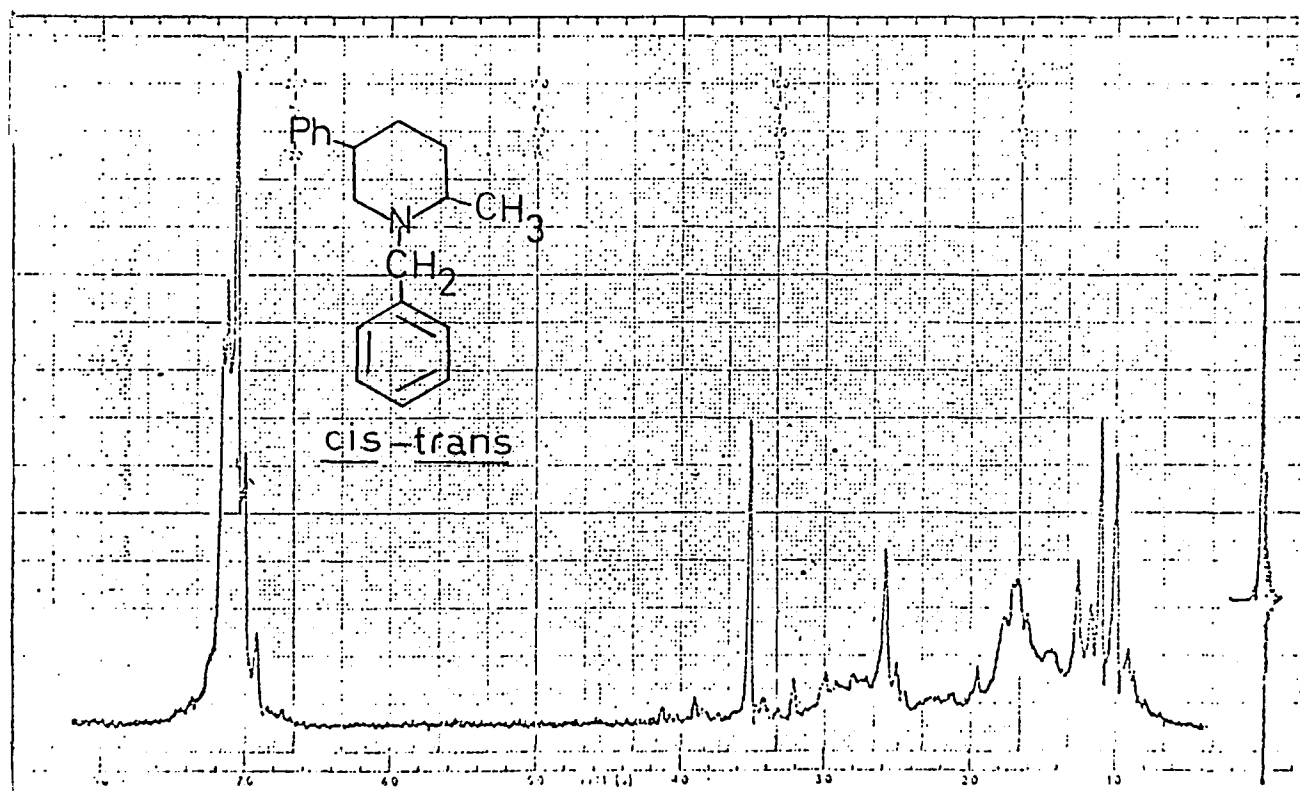
8

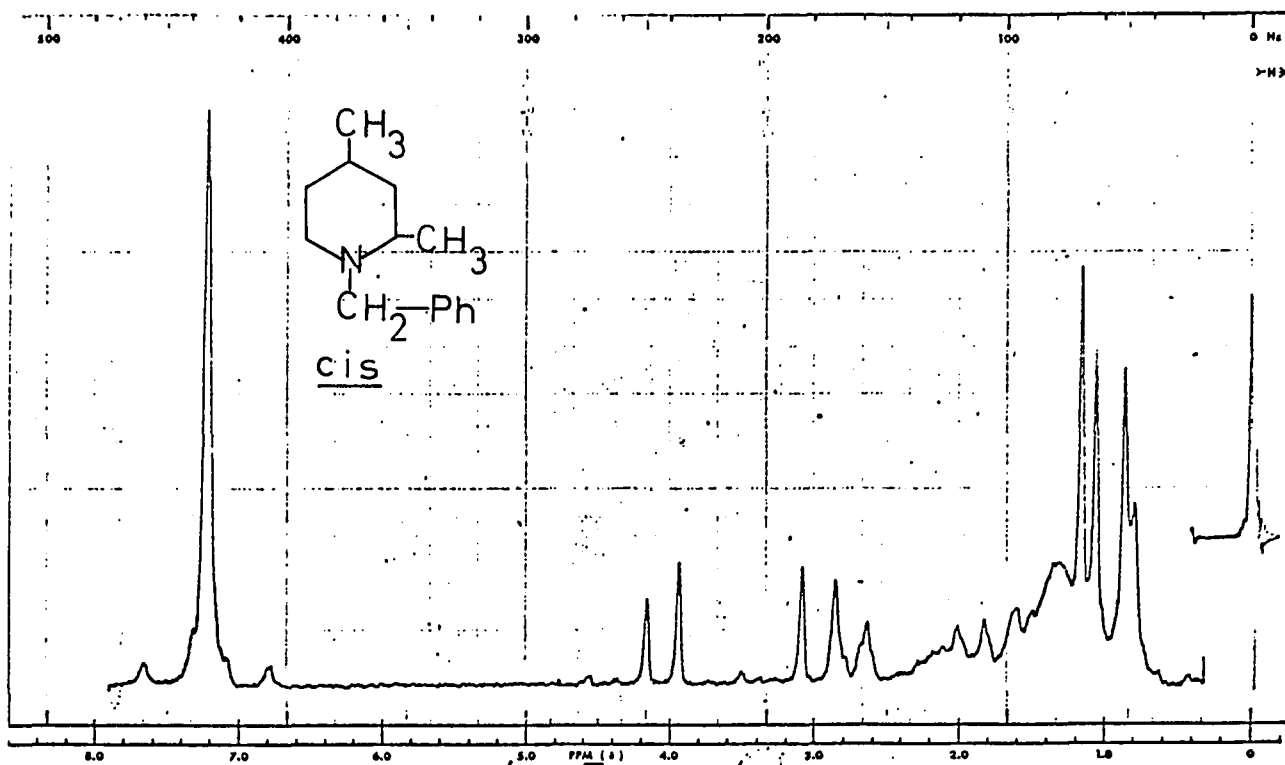
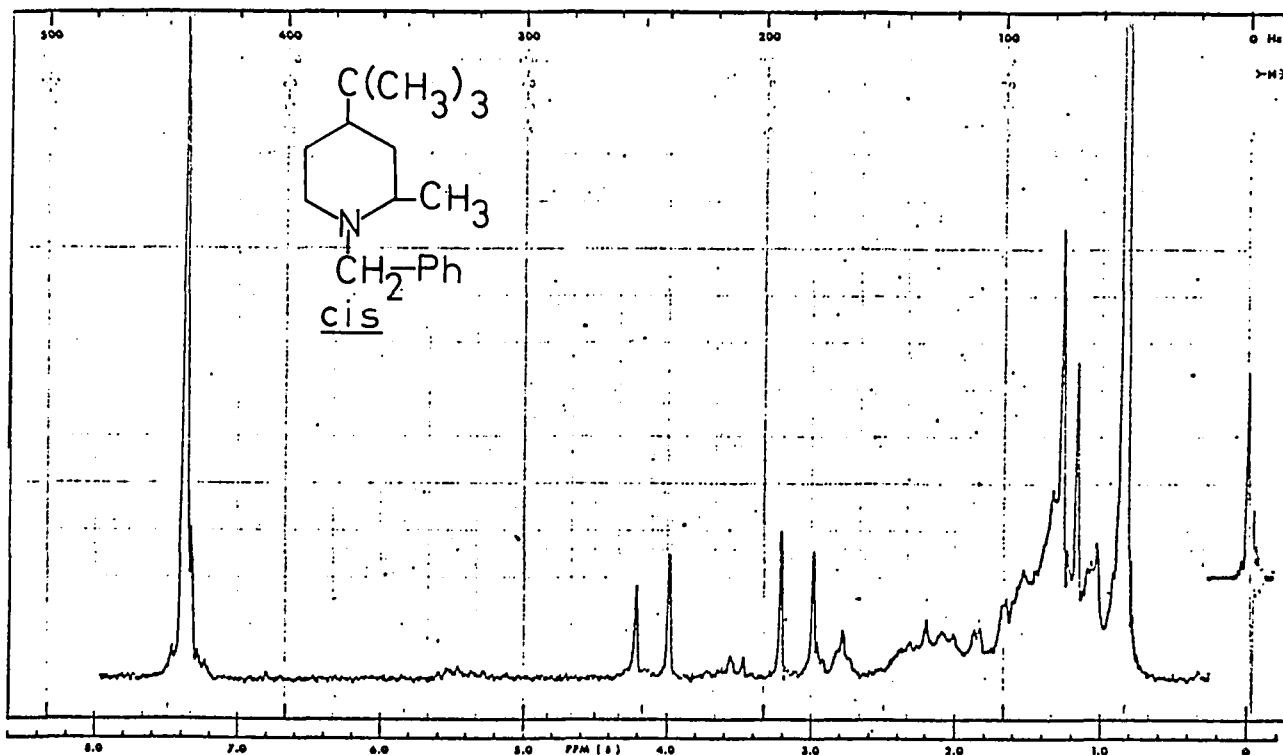
A-1 cis-1-Benzyl-2,5-dimethylpiperidine (44)A-2 trans-1-Benzyl-2,5-dimethylpiperidine (45)

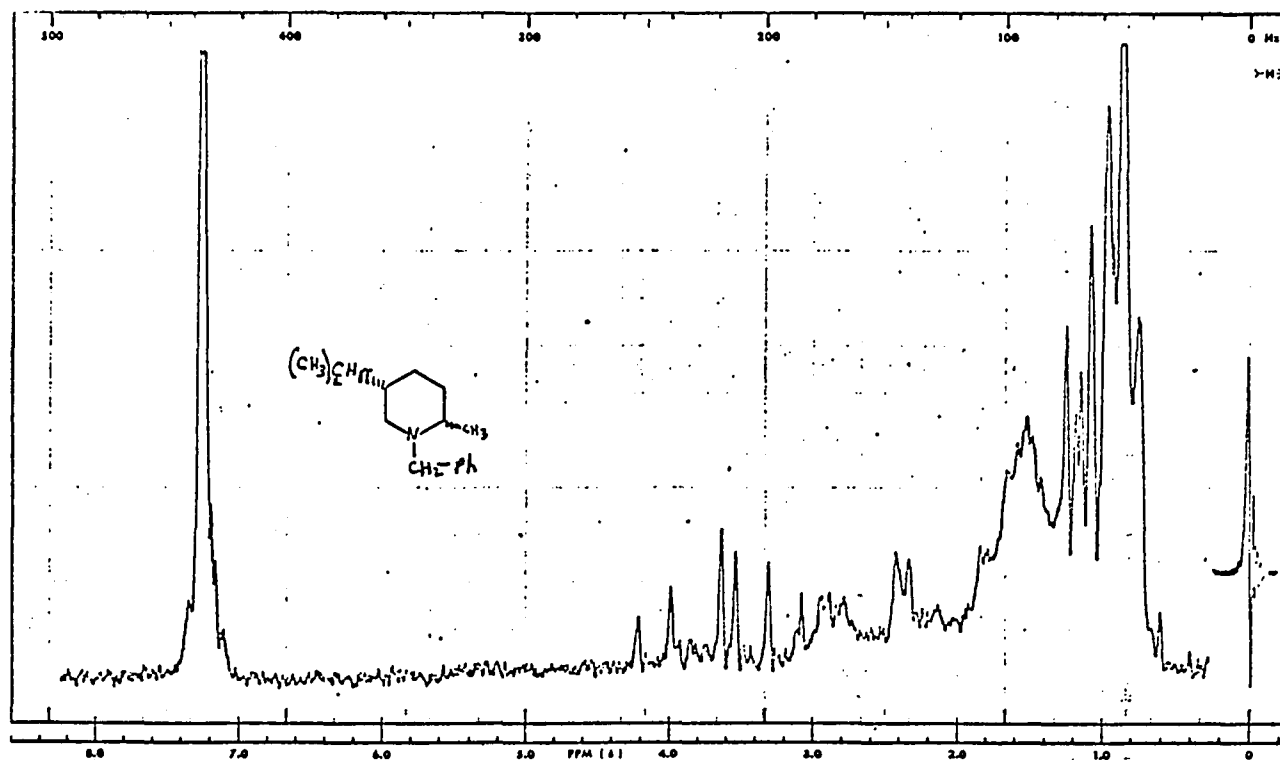
A-3 cis-1-(o-Aminobenzyl)-2,4-dimethylpiperidine (109)A4 cis- and trans-1-Benzyl-2,3-dimethylpiperidines (39) and (40)

A-5 cis-(o-Acetamidobenzyl)-2,4-dimethylpiperidine (105)A-6 cis-1-(o-Nitrobenzyl)-2,4-dimethylpiperidine (102)

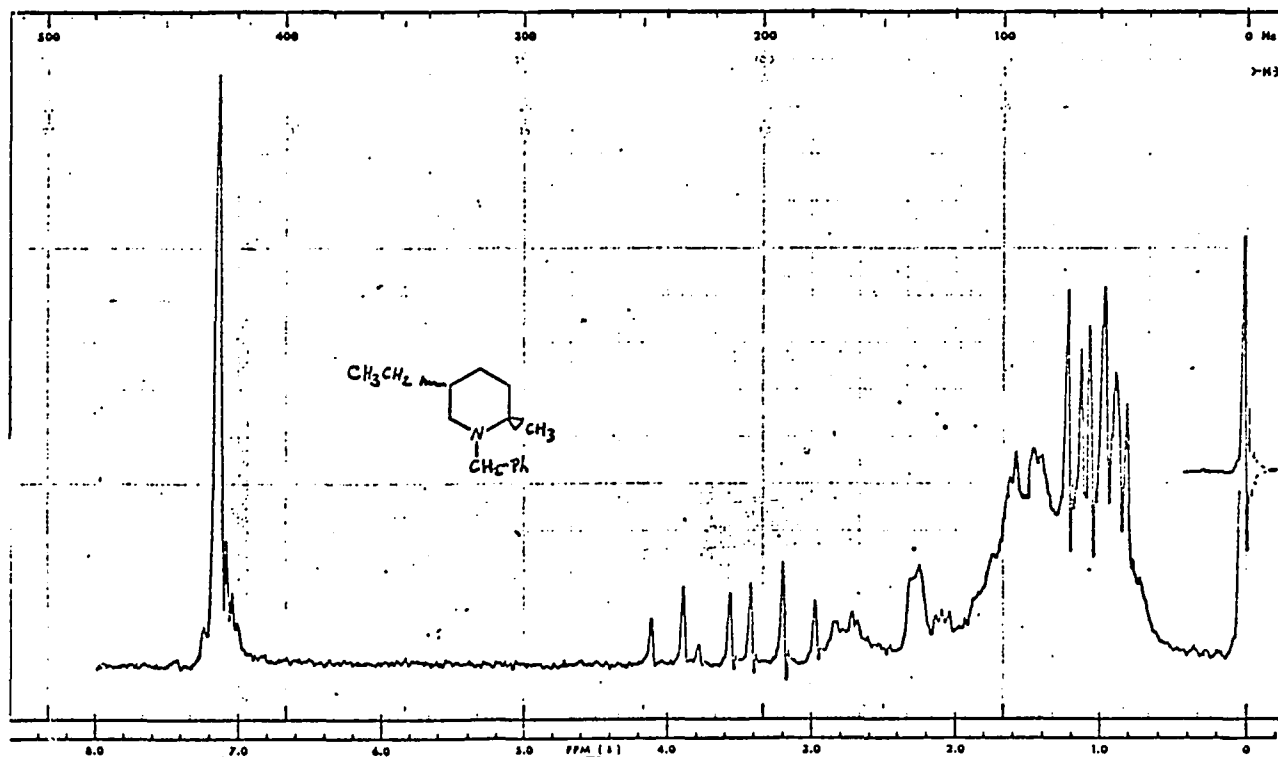
A-7 1-(o-Hydroxybenzyl)-2-methylpiperidine (107).A-8 1-(o-Acetoxybenzyl)-2-methylpiperidine (106)

A-9 cis-1-Benzyl-2-methyl-4-phenylpiperidine (59)A-10 cis- and trans-1-Benzyl-2-methyl-5-phenylpiperidines (73) and (74)

A-11 cis-1-Benzyl-2,4-dimethylpiperidine (42)A-12 cis-1-Benzyl-2-methyl-4-t-butylpiperidine (58)

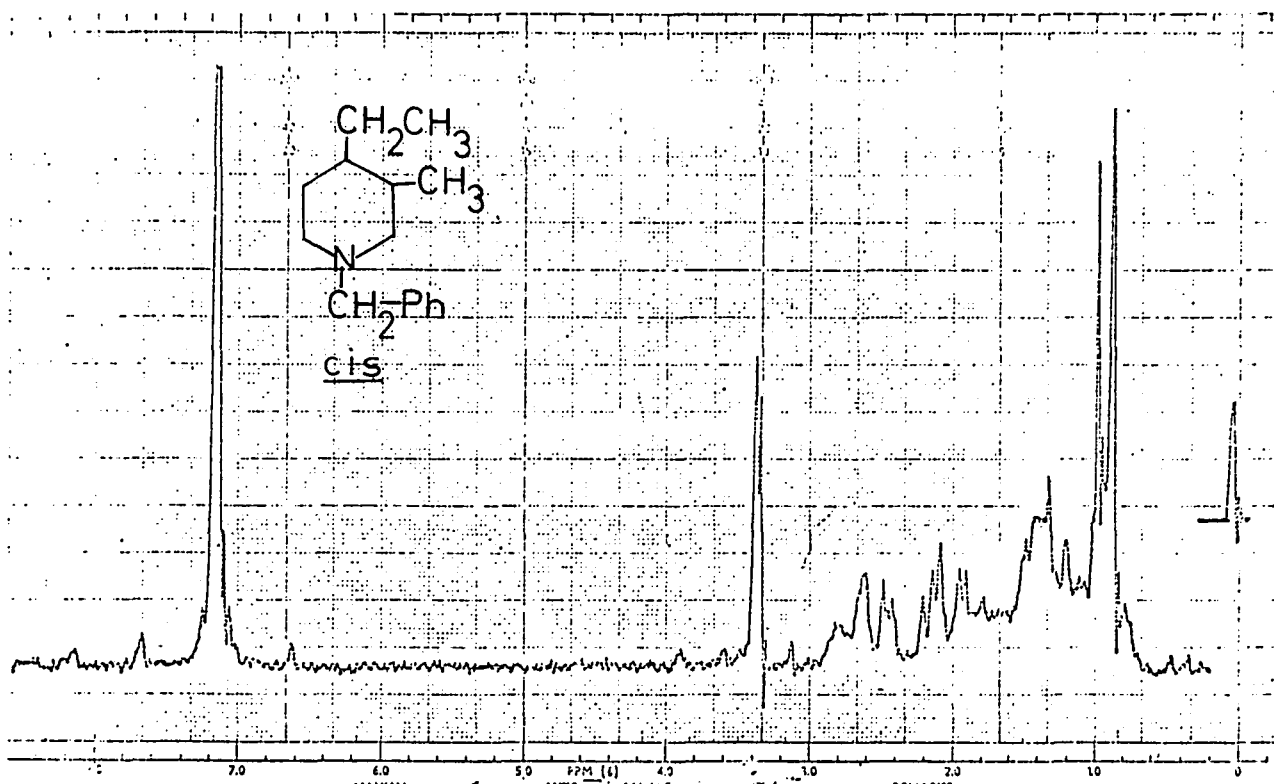


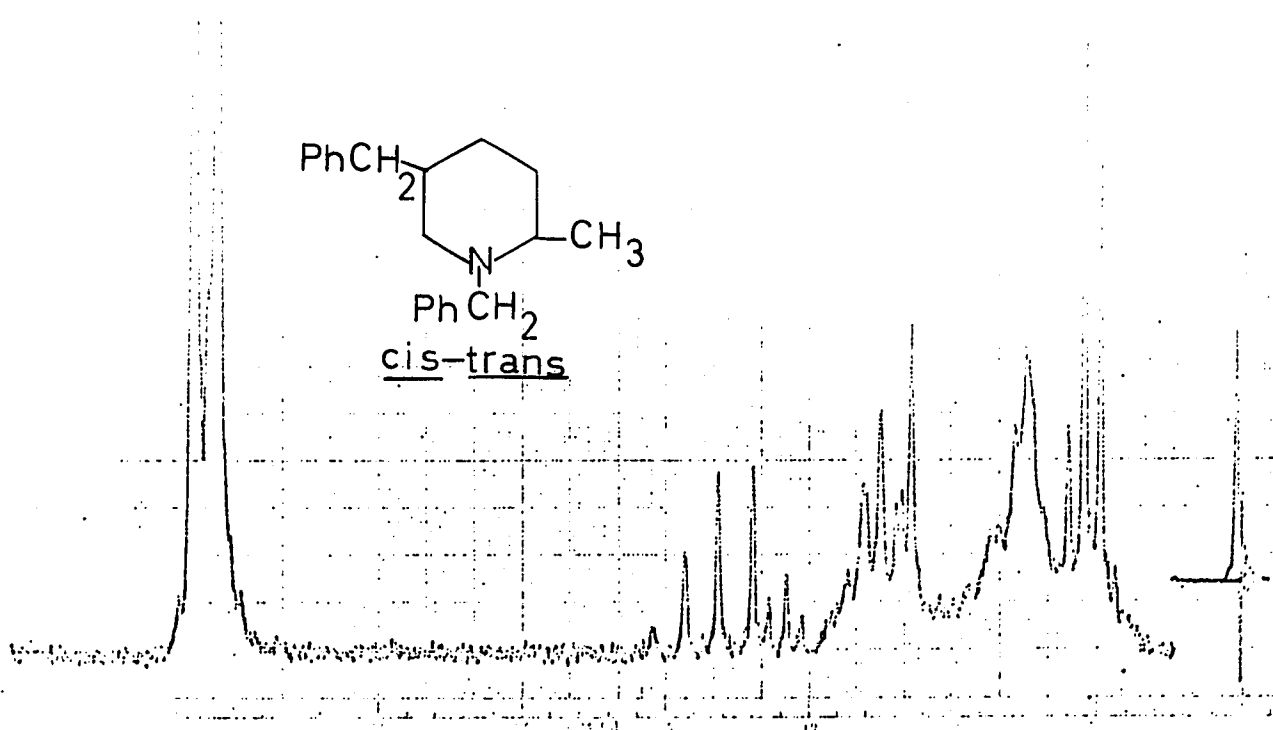
A-13 cis- and trans-1-Benzyl-2-methyl-5-isopropylpiperidines (77) and (78)



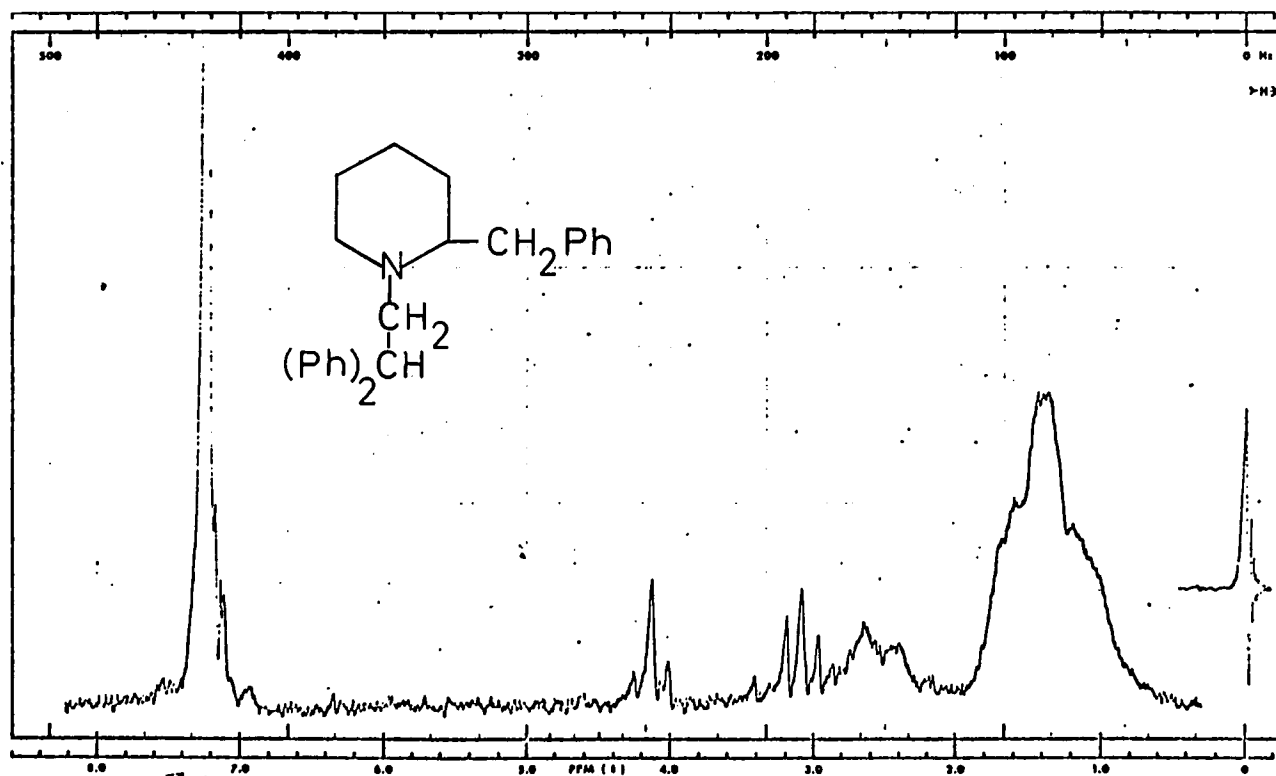
A-14 cis- and trans-1-Benzyl-2-methyl-5-ethylpiperidines (75) and (76)



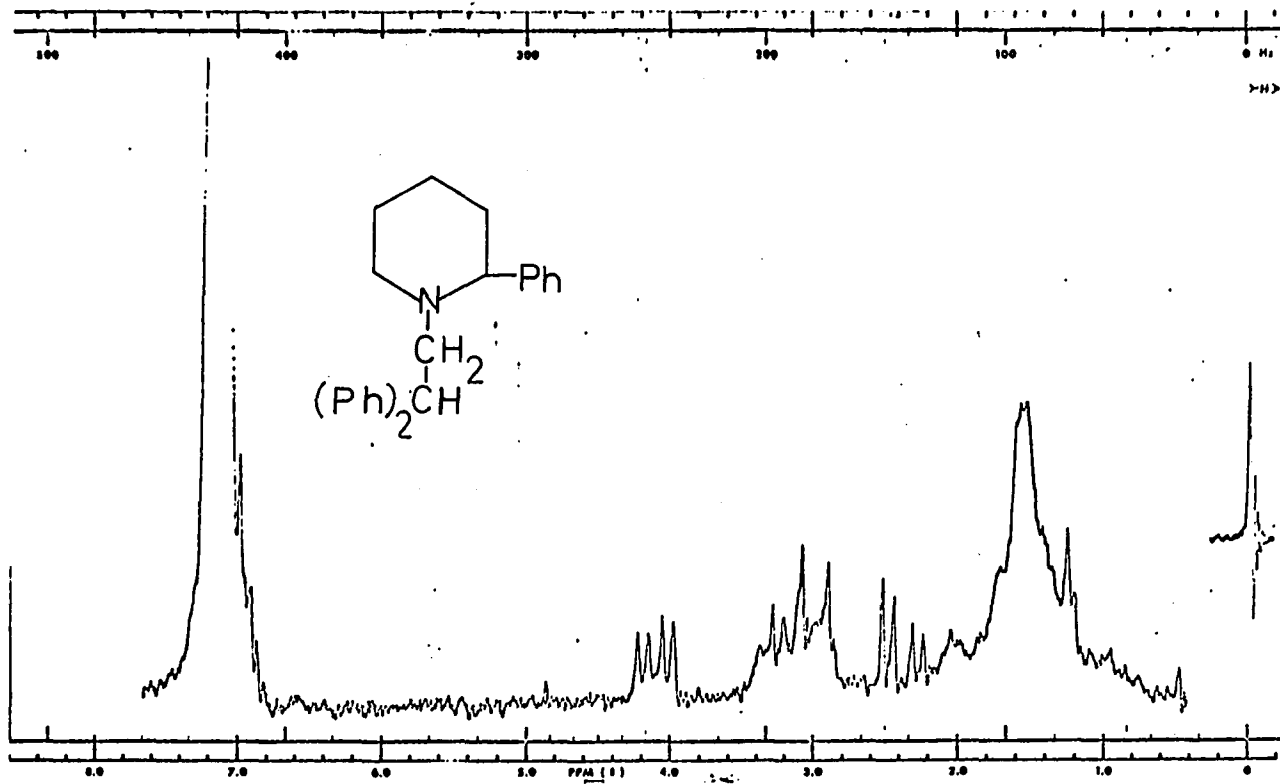
A-15 cis-1-Benzyl-3-methyl-4-ethylpiperidine (95)



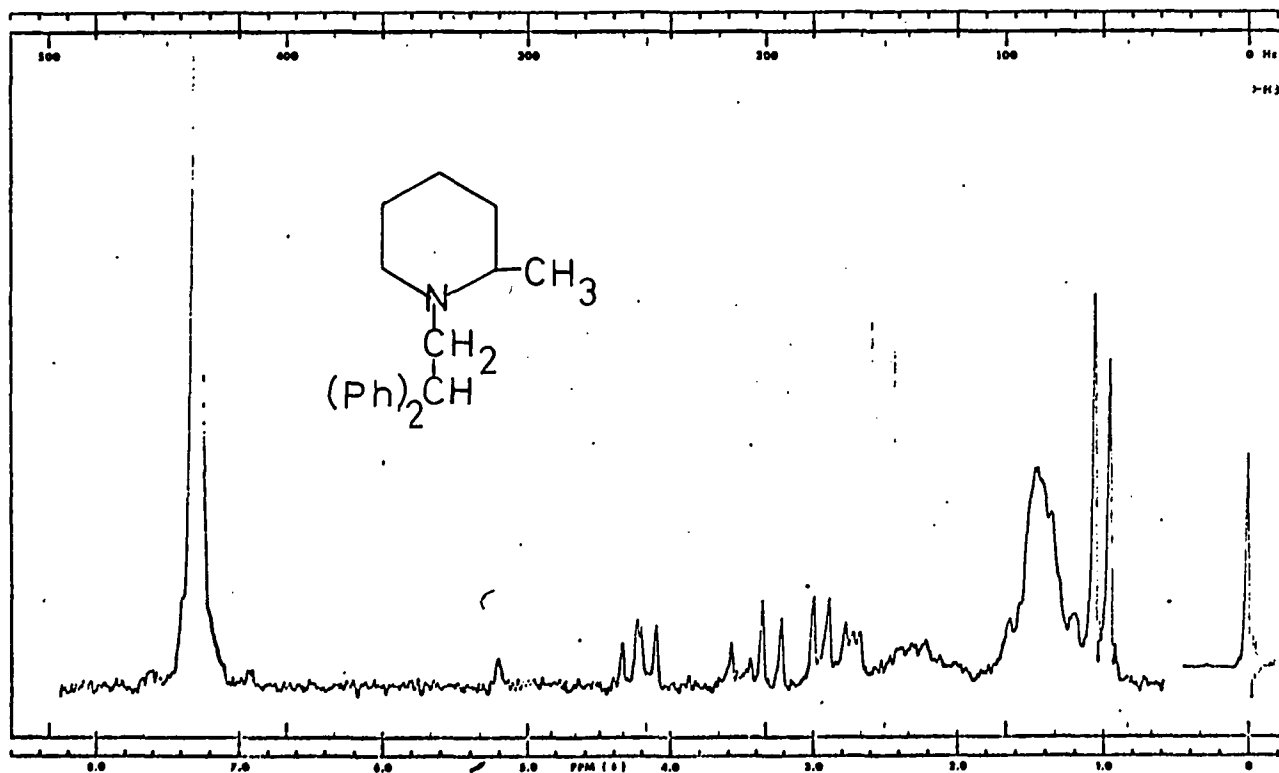
A-16 cis- and trans-1-Benzyl-2-methyl-5-benzylpiperidines (79) and (80)



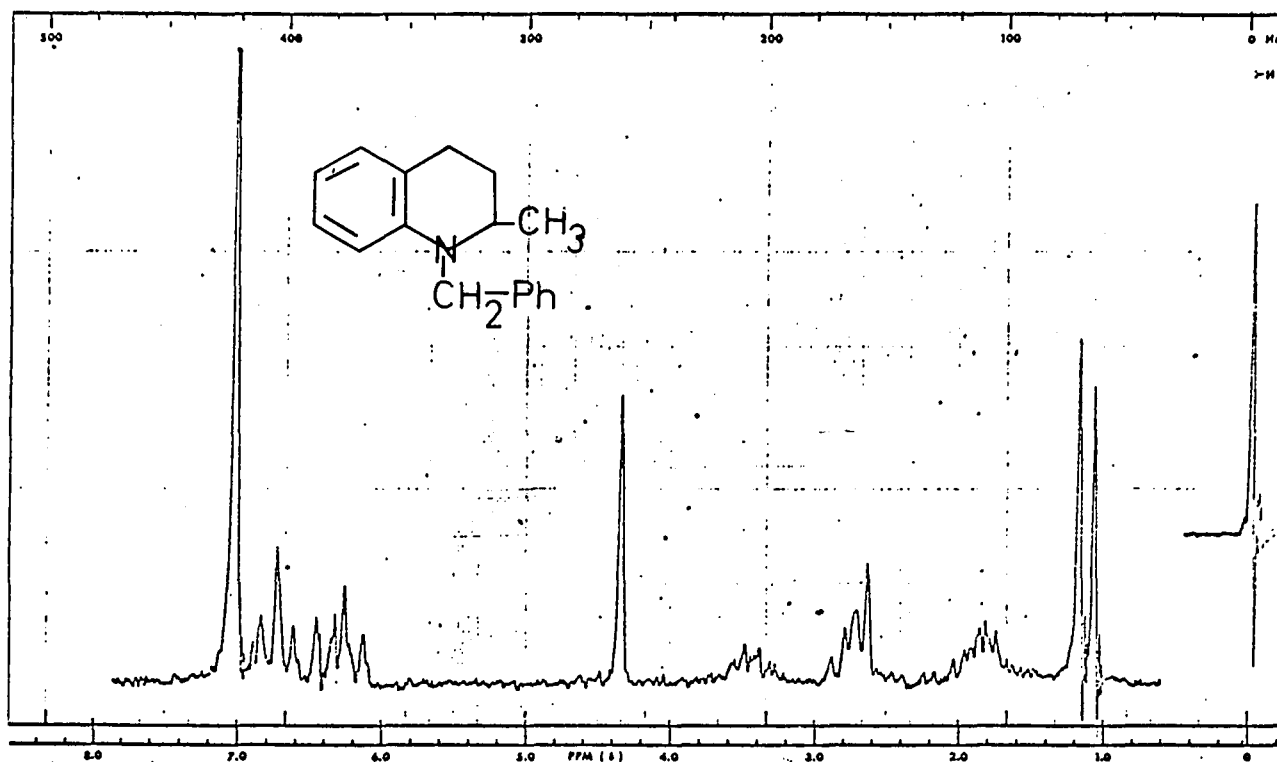
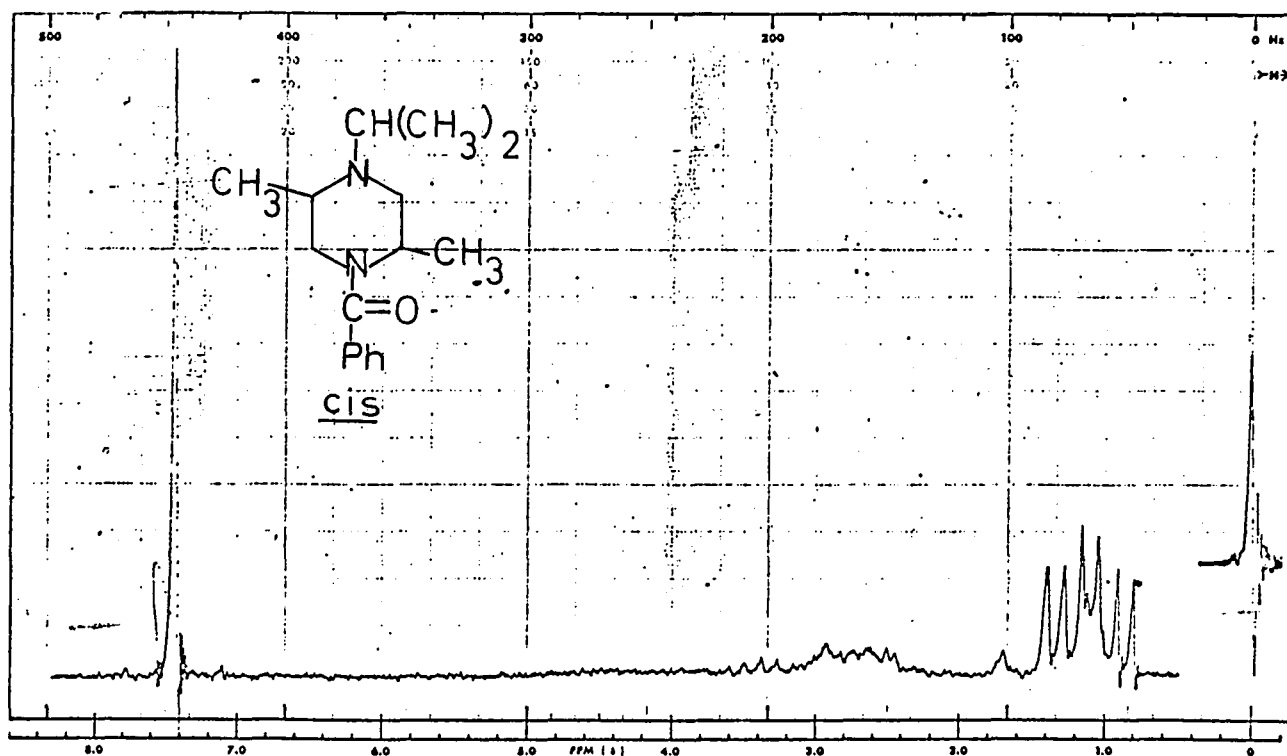
A-17 1-(2,2-Diphenylethyl)-2-benzylpiperidine (112)

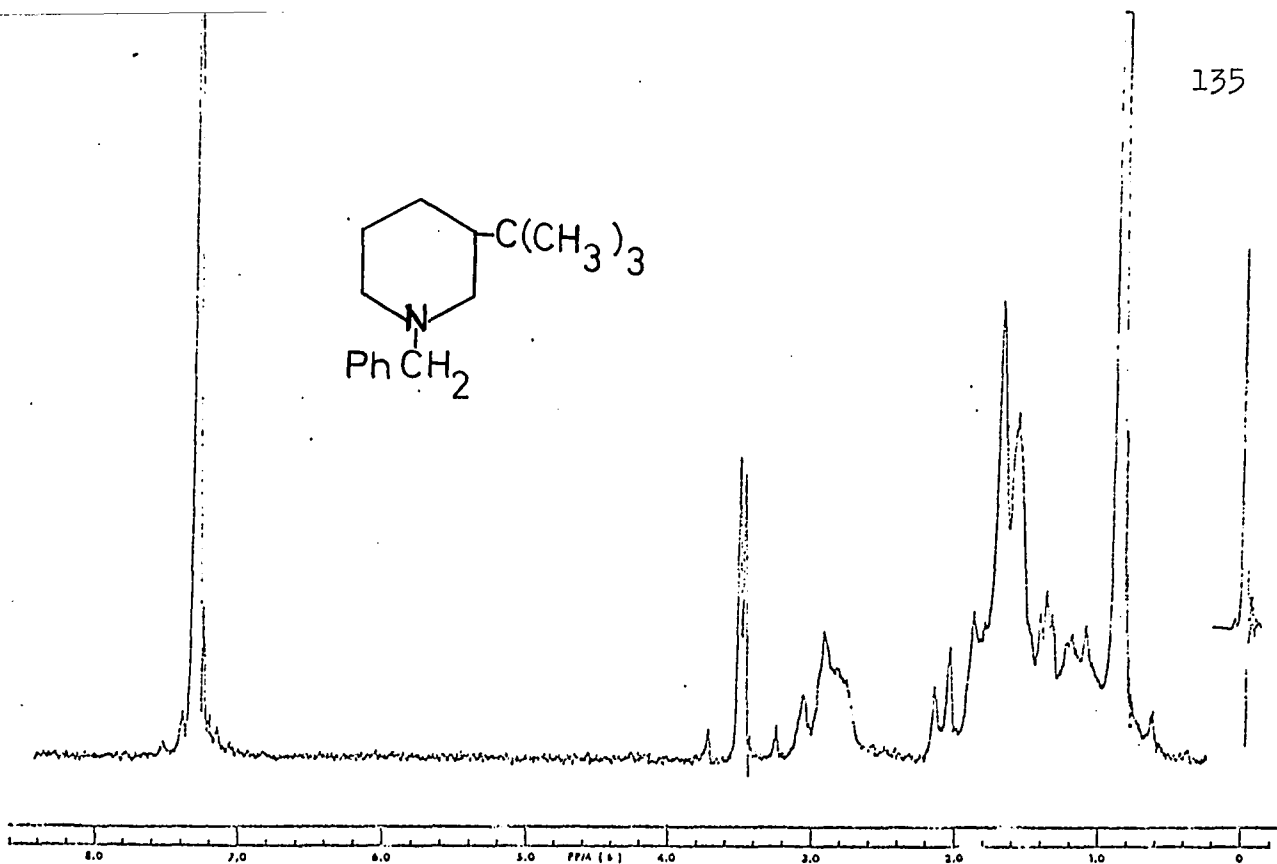
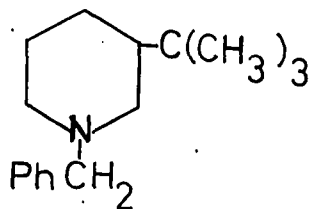
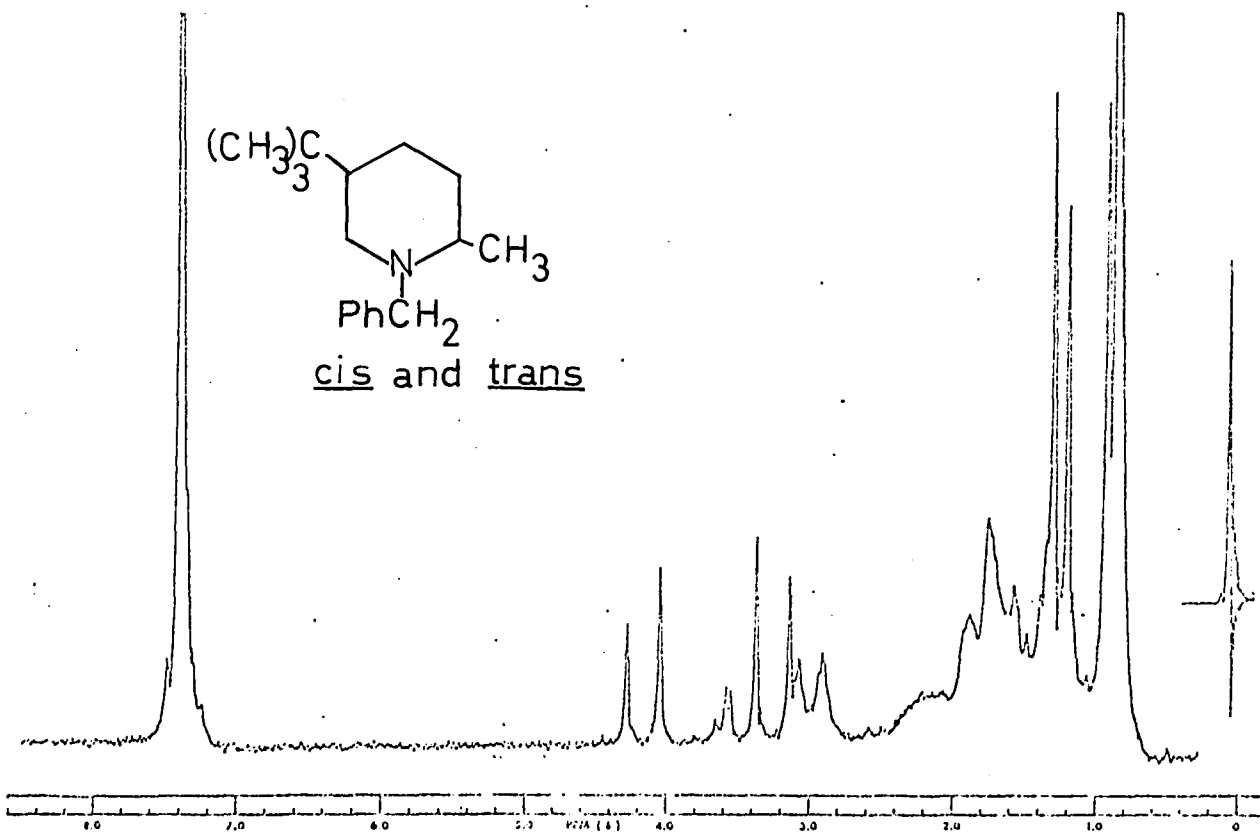
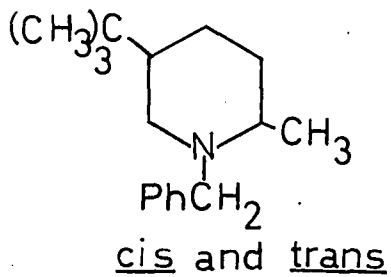


A-18 1-(2,2-Diphenylethyl)-2-phenylpiperidine (110)



A-19 1-(2,2-Diphenylethyl)-2-methylpiperidine (111)

A-20 1-Benzyl-2-methyl-1,2,3,4-tetrahydroquinoline (124)A-21 cis-1-Isopropyl-2,5-dimethyl-4-benzoylpiperazine (132)

A-22 1-Benzyl-3-t-butylpiperidine (160)A-23 cis- and trans-1-Benzyl-2-methyl-5-t-butylpiperidines (161)  
and (162)

## BIOGRAPHICAL DATA

Name: Lendon Norwood Pridgen

Date of Birth: September 25, 1945

Place of Birth: Whiteville, North Carolina

Secondary Education: Central High School  
Whiteville, North Carolina

Collegiate Institutions Attended:	Dates	Degrees
Morgan State College Baltimore, Maryland	1963-1967	B.S.
State University College Fredonia, New York	1967-1969	M.S.

Publications: "Conformational Analysis of Disubstituted Tropanes," with J. H. Supple and J. J. Kaminski, Tetrahedron Lett., 1829 (1969).

"Observable Magnetic Non-Equivalence of Diastereotopic Protons as a Probe for Conformational Analysis of Substituted Piperidines," with R. E. Lyle, G. A. Heavner, J. J. Kaminski, Abstracts, 163rd National Meeting of the American Chemical Society, Boston, Mass., April, 1972, No. 0119.