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NUCLEOPHILIC DISPLACEMENT AT THE 3-POSITION OF 1,2,3,6-TETRAHYDROPYRIDINES

WILLIAM ERNEST KRUEGER

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NUCLEOPHILIC DISPLACEMENT AT THE 3-POSITION OF 1,2,3,6-TETRAHYDROPYRIDINES

BY

WILLIAM ERNEST KRUEGER

B. S., University of Notre Dame, 1962

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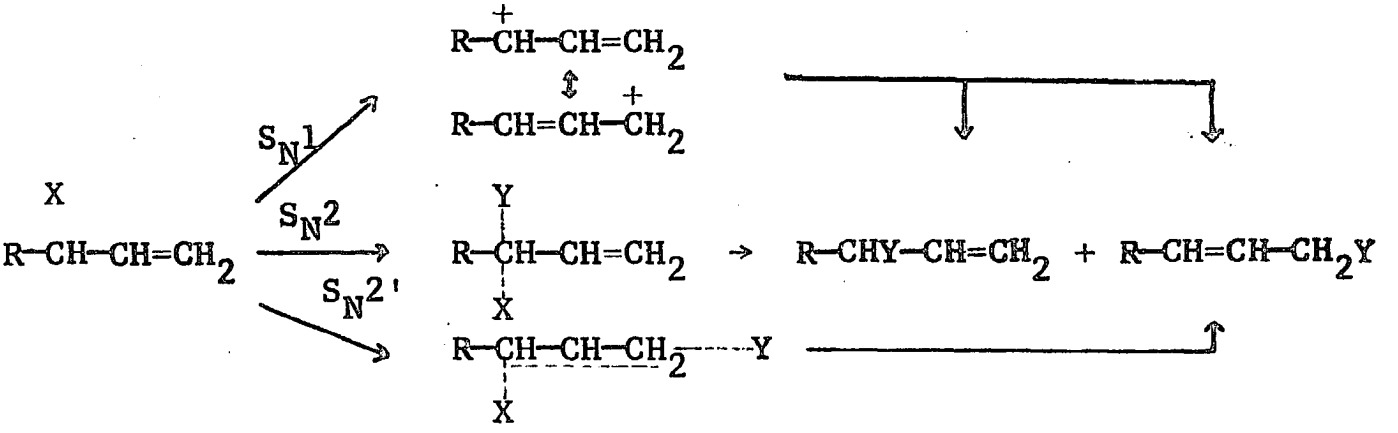
INTRODUCTION

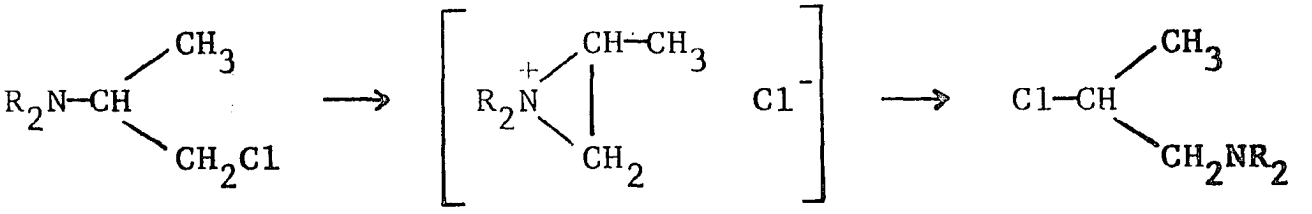
Nucleophilic displacement reactions on allylic systems have long been known to lead to rearrangement.[1] Reaction under S_N1 conditions has been shown to result in the formation of two electron deficient centers either of which may undergo reaction with the nucleophile. This was demonstrated by Catchpole and Hughes who showed that unsymmetrically substituted allyl groups underwent reaction with these conditions to give two products.[2] Reaction of an allyl compound under S_N2 conditions may also result in two products, one from the "normal" attack and the other from attack at the 3-position of the allyl system accompanied by rearrangement of the double bond.



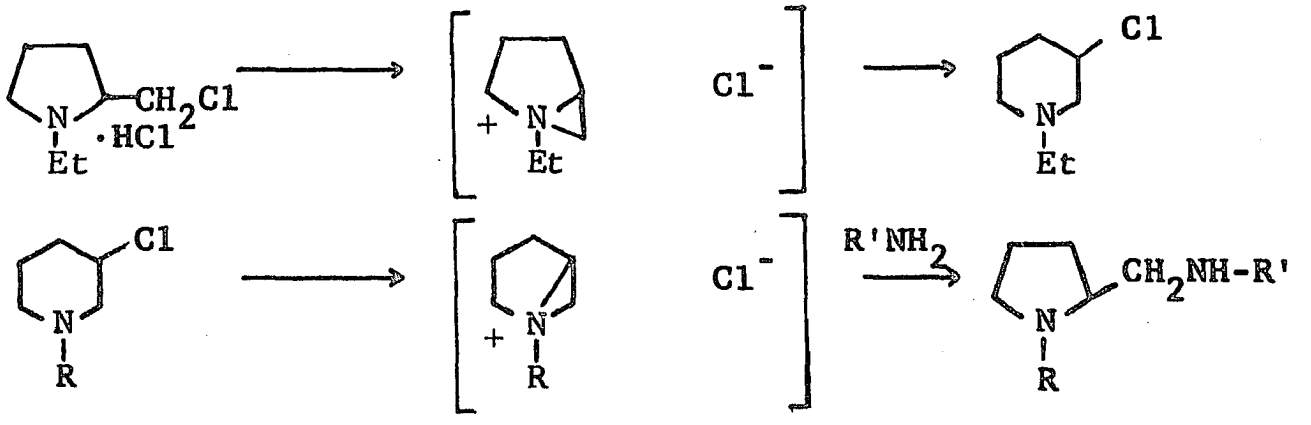
Similarly intramolecular nucleophilic displacements have been known for some time. The large number of atoms and functional groups which have been shown to behave as neighboring groups in these reactions include carbon, hydrogen, sulfur, oxygen, nitrogen, double bonds, and phenyl and cyclopropyl rings.[3] Of particular interest to this investigation is the ability of nitrogen to participate as a neighboring

group.

Early investigations of the nitrogen mustards indicated that the nitrogen atom, acting as a nucleophile, was capable of displacing a β-chlorine to form an aziridinium ion.[4] Further evidence for the participation of nitrogen via this ion was supplied by the independent studies of Zirkle[5] and Sprague[6] which reported the rearrangement of 1-chloro-2-dialkylaminopropanes to 1-dialkylamino-2-chloropropanes. At the same time numerous kinetic studies were advanced in support of such intermediates.[7]



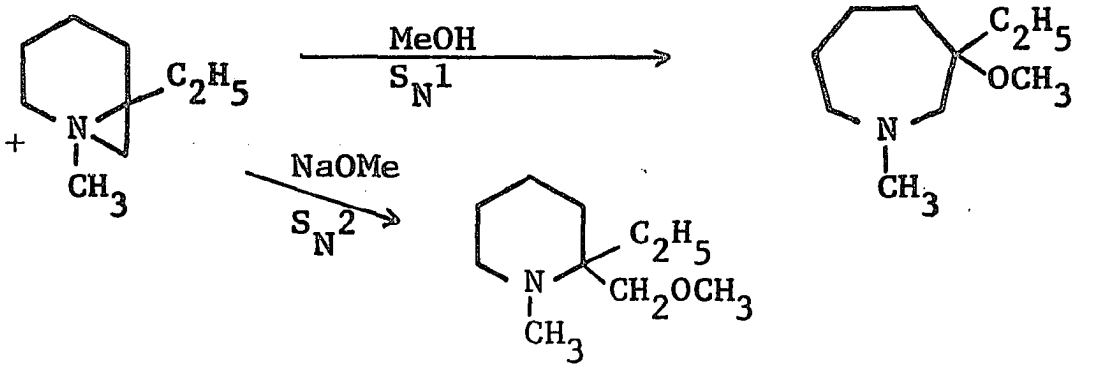
In 1949 Fuson and Zirkle observed that treatment of 1-ethyl-2-chloromethyl pyrrolidine hydrochloride with one equivalent of alkali gave a 3-chloropiperidine and not a pyrrolidine.[8] Almost simultaneously Reitsema reported the reverse reaction on treatment of 1-alkyl-3-chloropiperidines with a monosubstituted amine.[9] These results were rationalized on the basis of nitrogen participation and the formation of an aziridinium ion. Ring contraction of 3-halopiperidines or expansion of appropriately substituted pyrrolidines has also been



observed by Biel et al.[10], Smissman[11], and Mihta.[12]

Early attempts to trap aziridinium ions were complicated by the fact that most anions attack and open the three-membered ring.[13] However, Bergmann and coworkers succeeded in isolating a number of these ions as picrylsulfonates.[4a-d] Stable aziridinium ions were isolable if steric factors inhibited nucleophilic attack by the anion[14] or if low solubility facilitated isolation of the salt.[15] The first general method of trapping and preparing aziridinium ions was reported by Leonard who found that they were stable as their perchlorate or fluoroborate salts.[16]

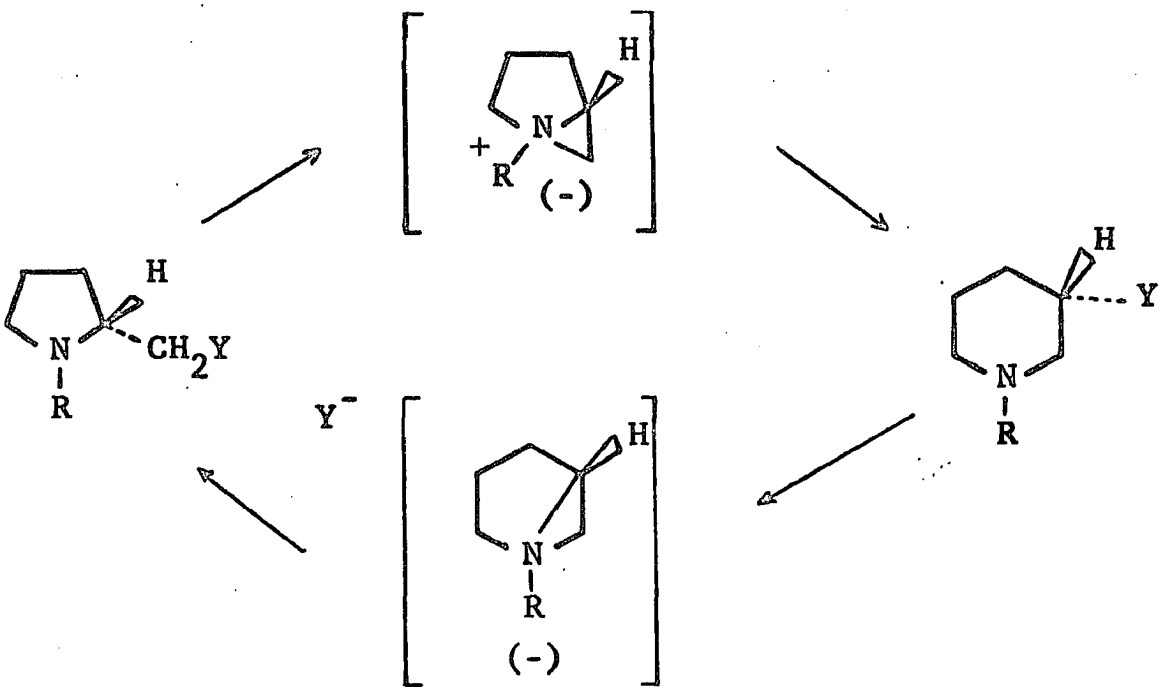
Leonard has further demonstrated that these ions undergo both S_N1 and S_N2 type reactions. Methanolysis of N-methyl-6-ethyl-azoniabicyclo[4.1.0]heptane perchlorate gave N-methyl-3-ethyl-3-methoxy-1-azacycloheptane, the product



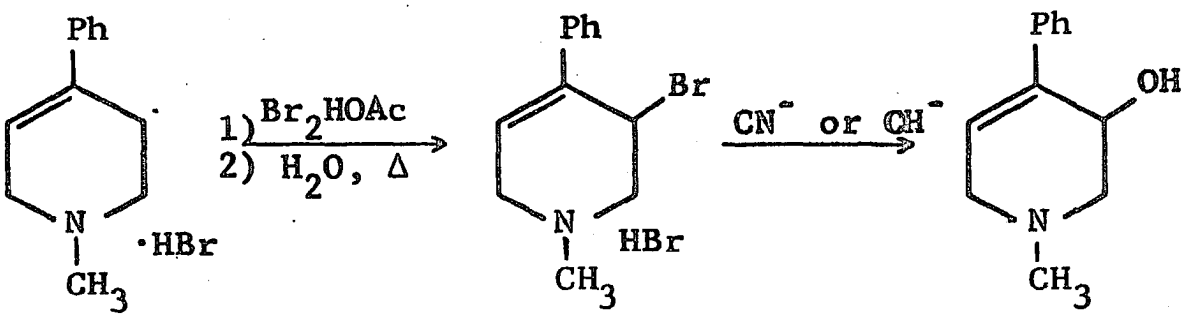
arising via the more stable carbonium ion. Treatment of this salt with sodium methoxide resulted in nucleophilic substitution at the less substituted carbon of the aziridinium ring to give N-methyl-2-ethyl-2-methoxymethyl piperidine.[17]

Recently Hammer and Heller reported a study of the stereochemistry of aziridinium ion formation.[18] (-)-N-alkyl-2-substituted methylpyrrolidines gave (-)-bicyclic intermediates which in turn gave the (+)-N-alkyl-3-substituted piperidines. The reverse reaction starting with the (+)-piperidine

gave the pyrrolidine with 85-100% overall retention of optical activity. These data were interpreted as requiring internal nucleophilic attack with inversion and as ruling out any free carbonium ion at the asymmetric center.[18]



Situations where allylic rearrangement and internal nucleophilic displacement have been in competition are rare. In 1950 McElvain and Safranski[19] reported that the reaction of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (1) hydrobromide with bromine followed by treatment with water gave 1-methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine hydrobromide (2). The reaction of the allylic bromide (2) with cyanide and hydroxide ions was reported to yield oils from which only one product was isolated in low yield. While the possibility of an aziridinium ion intermediate was considered, the tetrahydropyridine ring system was assigned to 3.

(1) 

1 2 3

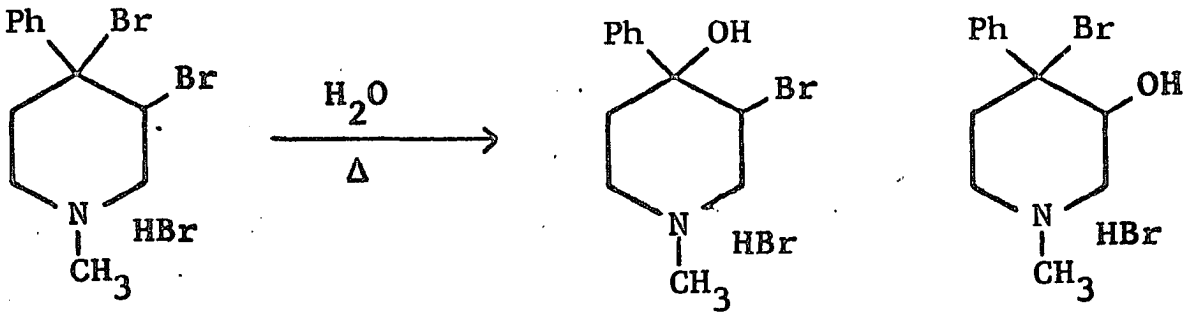
Because compound 2 is a 3-halopiperidine as well as an allylic bromide it appeared to be an ideal substrate to use to study the competition between rearrangement and internal displacement. This thesis reports the results of that study.

DISCUSSION

The Attempted Preparation of 1-Methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine Hydrobromide.

The reaction of bromine with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (1) hydrobromide in acetic acid followed by treatment with water was reported to give the allylic bromide, 2.[19] This halide was said to undergo a facile solvolysis with water in the presence of the stronger nucleophile, cyanide ion, to form the alcohol, 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3). The preparations of the allylic bromide and alcohol were attempted in this laboratory for the investigation of the displacement. Repetition of the bromination reaction gave a compound whose properties were inconsistent with the structure 2. The compound obtained after treatment of 1-methyl-4-phenyl-3,4-dibromopiperidine hydrobromide (4) with water exhibited a broad absorption band at 3400 cm^{-1} (Figure 2, Appendix) in the infrared spectrum, and the ultraviolet spectrum was consistent with the presence of a non-conjugated phenyl ring and not a substituted styrene system as required by 2. The nmr spectrum gave no evidence of a vinyl hydrogen, and the elemental analyses of the salt required one molecule of water more than structure 2.

There data suggested that the reaction of the dibromide, 4, with water resulted in hydrolysis of one of the bromine atoms to form either 5 or 6. The results of Schmidle and Mansfield, who treated 4-phenyl-4-bromopiperidine hydrobromide with water and alkali to get 4-phenyl-4-piperidinol[20], suggested 5 to be the more likely structure of the product of this reaction.



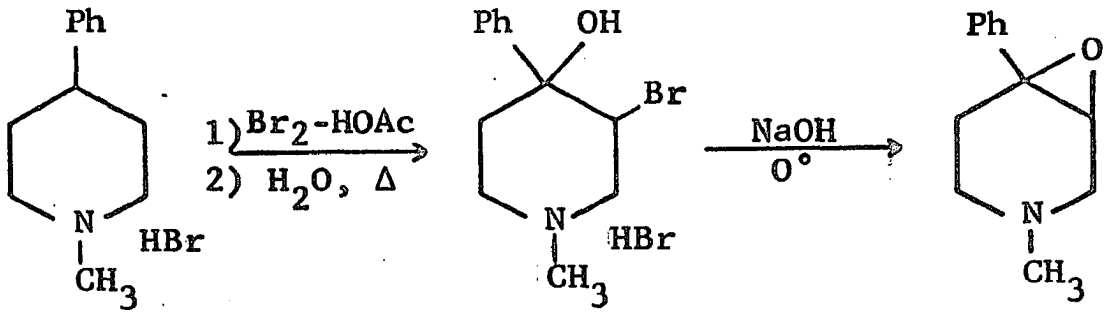
4 5 6

The reaction of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (1) hydrobromide with bromine-sodium bromide in water gave a white solid. The infrared and nmr spectra of this material were identical with those of the product obtained by treating 4 with water. A mixture melting point showed no depression. In view of the generally accepted mechanism for this reaction, these results also supported 5 rather than 6, as the product of 4 and water. This conclusion has been further substantiated by high dilution infrared studies of the free base which showed no evidence of intramolecular hydrogen bonding.[21] The position of the hydroxyl absorption band at 3612 cm^{-1} was typical of that of unbonded tertiary alcohols.[22]

The reaction of 1-methyl-3-bromo-4-phenyl-4-piperidinol hydrobromide (5) with base at 0° gave a solid product whose melting point corresponded with that reported for 3; however, the infrared spectrum (Figure 5, Appendix) showed no bands above 3150 cm^{-1} or in the carbonyl region and the nmr spectrum (Figure 36, Appendix) gave no evidence for a vinyl hydrogen. The ultraviolet absorption spectrum indicated an isolated aromatic ring and the elemental analyses were in agreement with the values required by 3. These data were con-

sistent only with a cyclic ether and indicate that scheme(1) should be amended to scheme(2).

(2)



1 5 7

Chemical Proof of the Structure of 1-Methyl-4-phenyl-3,4-epoxypiperidine.

Confirmation of the structure of the product of the reaction of 5 with base as the epoxide 7 was complicated by the fact that the reaction of 3-halopiperidines under solvolytic conditions often occurs with participation of the heterocyclic nitrogen to yield pyrrolidines.[9-13] The reaction of the suspected epoxide, 7, with lithium aluminum hydride gave an alcohol, cis-1-methyl-4-phenyl-3-piperidinol (8), which was not identical with 1-methyl-4-phenyl-4-piperidinol (10). It was, however, shown to be epimeric with trans-1-methyl-4-phenyl-3-piperidinol (9) (vide infra), prepared by the hydroboration of 1[23], thus confirming the ring structure of both 7 and 8.

The reaction of the epoxide 7 with 1 N hydrochloric acid gave 1-methyl-4-phenylpiperidine-3,4-diol (12). This glycol was also prepared directly from 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (1) by reaction with m-chloroperoxybenzoic acid. This further confirmed the presence of the piperidine ring system in 7. It is further evident from a

consideration of the nmr spectra of 5-8 (see Appendix) that these compounds contain a piperidine ring and not a pyrrolidine ring system. Thus no ring contraction due to nitrogen participation occurred during these reactions.

Eliel and coworkers have shown in a series of papers[24] that the reduction of unsymmetrically substituted epoxides with lithium aluminum hydride gave the more highly substituted alcohol. The mechanism of the reduction is known to involve a nucleophilic displacement[25a] of oxygen with inversion of configuration.[25a-c] It was, therefore, anticipated that the reduction of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) would give almost exclusively 1-methyl-4-phenyl-4-piperidinol (10). The reaction of 7 with lithium aluminum hydride, in fact, gave, in quantitative yield, a white solid that was neither 10 nor 9 as shown by infrared spectrum and mixture melting point. An infrared spectrum in solution indicated the presence of a hydoxyl group that was highly intramolecularly hydrogen bonded.[21] The infrared apsorption due to C-H stretching vibration (2800-3100 cm^{-1}) was virtually superimposible on that of 9. The nmr spectrum (Figure 38, Appendix) suggested a piperidine, rather than a pyrrolidine ring and the elemental analyses were in good agreement with the values required. Attempts to demonstrate the epimeric relationship of 8 with 9 by the equilibration methods of Eliel[26] and of Archer and Bell[27] were unsuccessful. This relationship was demonstrated, however, by the formation of both alcohols from the reduction of 1-methyl-4-phenyl-3-piperidone (11) with lithium aluminum hydride. The ketone 11 was prepared by the rearrangement of 7 with concentrated sulfuric acid.

The same alcohol, 8, was formed by cleavage of the oxygen ring of the epoxide, 7, by hydrogenation over Adam's catalyst. The anticipated stereochemistry[28] of hydrogenolysis

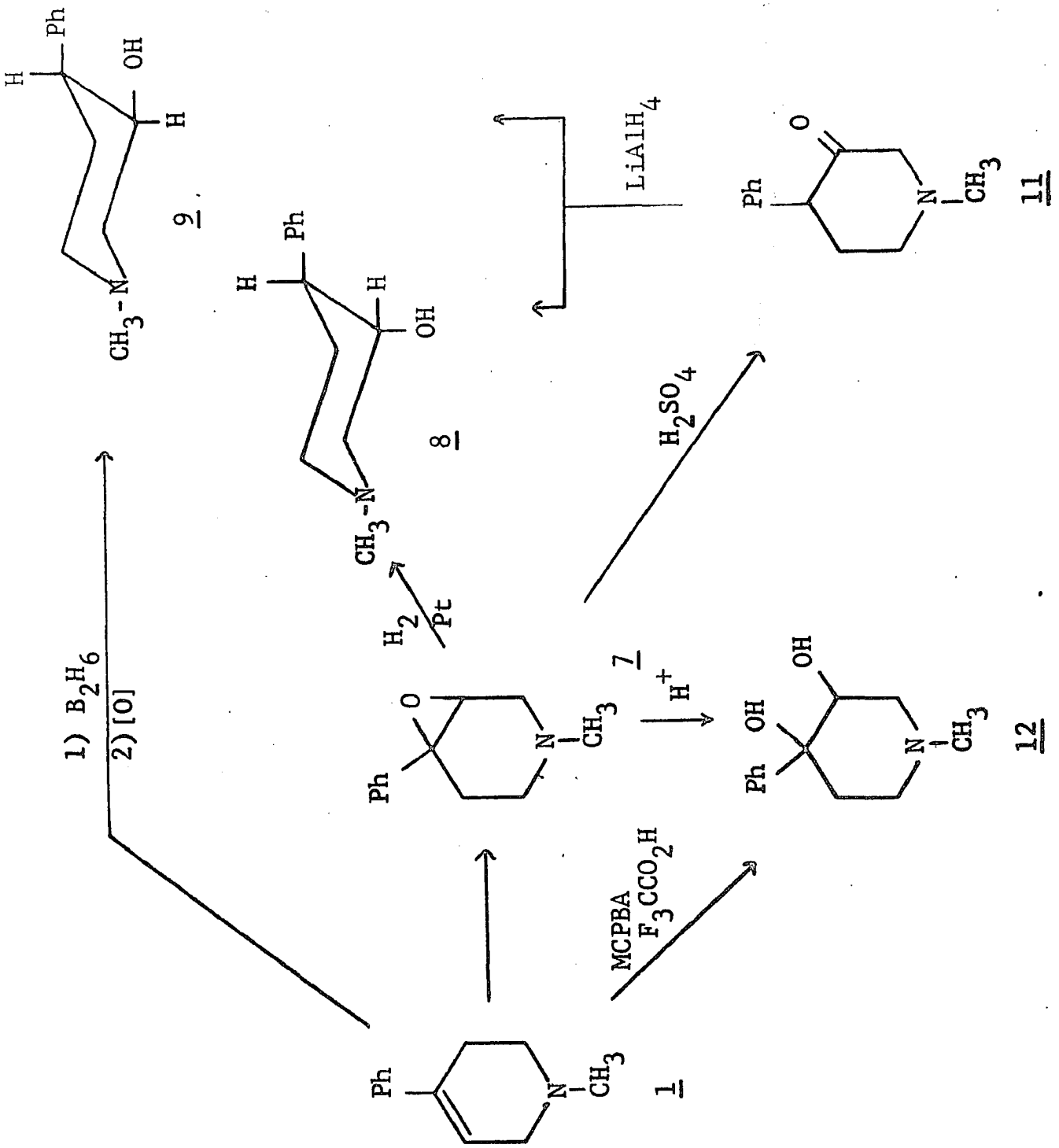


Figure I. Chemical Evidence for the Piperidine Ring System in Compounds 7-12

of an epoxide such as 7 is in agreement with the assignment of the structure of this product as cis-1-methyl-4-phenyl-3-piperidinol (8), and established the anomalous course of the reduction with lithium aluminum hydride.

Physical Evidence for the Structure of 1-Methyl-4-phenyl-3,4-epoxypiperidine. The Conformation of cis-1-Methyl-4-phenyl-3-piperidinol.

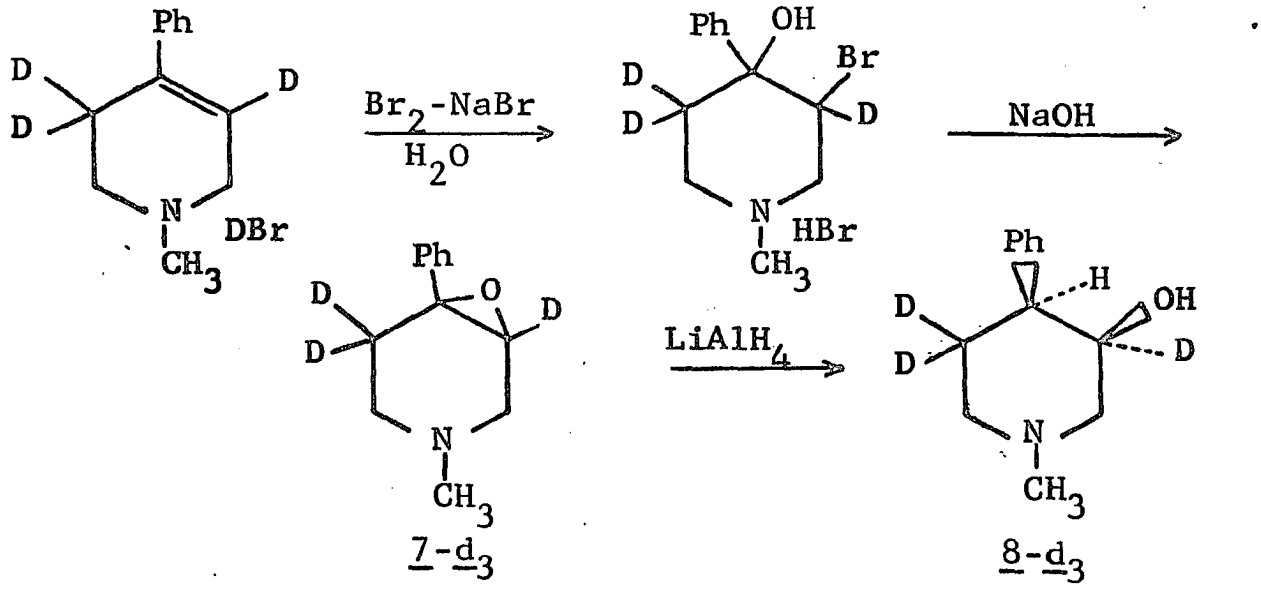
The protons of a methylene group adjacent to an asymmetric center may be magnetically nonequivalent and result in a signal typical of an AB, rather than an A_2 system.[29,30] An unsymmetrically substituted nitrogen atom may behave in the same manner. Frequently inversion of the nitrogen occurs so rapidly that the protons interchange environments and a singlet appears. But in certain cases, where inversion has been sterically inhibited or otherwise retarded, an AB pattern has been observed.[31] Finally, methylene nonequivalence may also occur from a slowed interconversion of the two chair forms of a six-membered ring.

In an effort to interpret the complex nmr spectra of 1-methyl-3-bromo-4-phenyl-4-piperidinol hydrobromide (5), 1-methyl-4-phenyl-3,4-epoxypiperidine (7), and cis-1-methyl-4-phenyl-3-piperidinol (8) and thus verify the presence of a piperidine skeleton in these compounds, this series was prepared with the 3- and 5-protons replaced by deuterium. The spectra of these compounds would be of interest because each compound contains all the requirements for nonequivalence of the 2-methylene and all but proximity to an asymmetric carbon for the 6-methylene protons.

1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine-3,5,5-d_3 deuteriobromide was prepared by the method of P. S. Anderson.[32] The introduction of deuterium into 1 was followed by observing

the disappearance of the band at 835 cm^{-1} in the infrared spectrum due to the out-of-plane deformation of the vinyl hydrogen. The nmr spectrum of the solid prepared by the method of Anderson exhibited only a very weak signal due to a vinyl proton and the integration of the signal indicated that incorporation of deuterium had occurred to at least 80%.

The deuterated analogues of 5, 7, and 8 were prepared from 1-d_3 by the reactions outlined below. The nmr spectra of these compounds are reproduced in part in Figures II and III (see Appendix for complete spectra), and the higher order AB patterns were treated according to the method outlined by Bible.[29] The results are summarized in Table I.



7-d_3 8-d_3

The spectrum of 1-methyl-3-bromo-4-phenyl-4-piperidinol-3,5,5-d_3 hydrobromide gave a broad signal at 6.35 τ assigned to the protons at C-6 and a pair of doublets centered at 5.95 τ due to the resonance of the 2-methylene protons. The observation of a single, though broadened, peak for the 6-protons indicated that in the protonated form inversion of conformation, as well as of nitrogen, was fast enough to produce an averaging effect. The coupling constant of the 2-protons

was J_{AB}= 14.5 cps and the chemical shift difference $\Delta\tau$ = 0.26.

Table I

Analyses of the AB Patterns of the 2-Methylene Groups

Compound	J_{AB}(cps)	τ_A	τ_B	$\Delta\tau$
5-d_3	14.5	6.08	5.83	0.26
7-d_3	13.4	7.41	6.93	0.48
8-d_3	11.5*	7.86	7.11*	0.75*

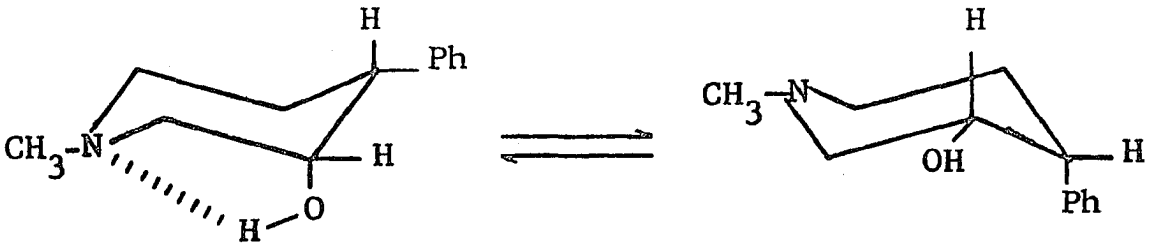
*These figures represent an average of the 2- and 6-protons.

The deuterated analogue of the epoxide 7 also gave a broad signal (7.60τ) for the 6-methylene and a pair of doublets, J_{AB}= 13.4 cps and $\Delta\tau$ = 0.48, for the 2-methylene. The broad singlet at 7.60 τ and the low $\Delta\tau$[34] for the 2-protons suggested that inversion of conformation was too rapid to permit observation of nonequivalence in the 6-protons.

The nmr of 8-d_3 gave a pair of doublets (4 protons) J_{AB}= 11.5 cps and $\Delta\tau$ = 0.75. It has been demonstrated independently by Hamlow[34a], Bohlmann[34b-c], and Lambert[33] that the protons α to nitrogen and trans-coplanar with the free pair are shifted upfield 0.80-0.93 ppm with respect to α-protons which are not in this configuration. On this basis the upfield doublet, the inside peak of which is overlapping with the N-methyl signal, has been assigned to the α-axial protons and the downfield doublet to the equatorial protons.

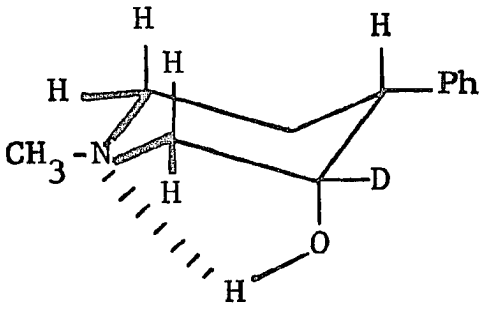
R. E. Lyle and coworkers[35] have found from nmr and hydrogen bonding studies of various 3-piperidinols that the

conformational preference of cis-1-methyl-4-phenyl-3-piperidinol lies about 99% in the direction of 8a. Thus the observation of nonequivalence for both the 2- and 6-positions of 8-d_3 is due to a retarded chair-chair equilibration.



8a 8b

When the spectrum of 8-d_3 was expanded by reducing the sweep width, the doublet assigned to the equatorial protons (part a, Figure III) at carbons 2 and 6 was shown to be an octet; but no change was observed in the signal of the axial protons (part b). A difference in the chemical shifts of the 2- and 6-equatorial protons as well as long range coupling can be shown to account for the observed pattern.



It is evident from an inspection of a model of 8-d_3 that the two equatorial protons experience different environments. Analysis of the pattern showed that the environmental difference resulted in a spacing of 3.3 cps. The analysis

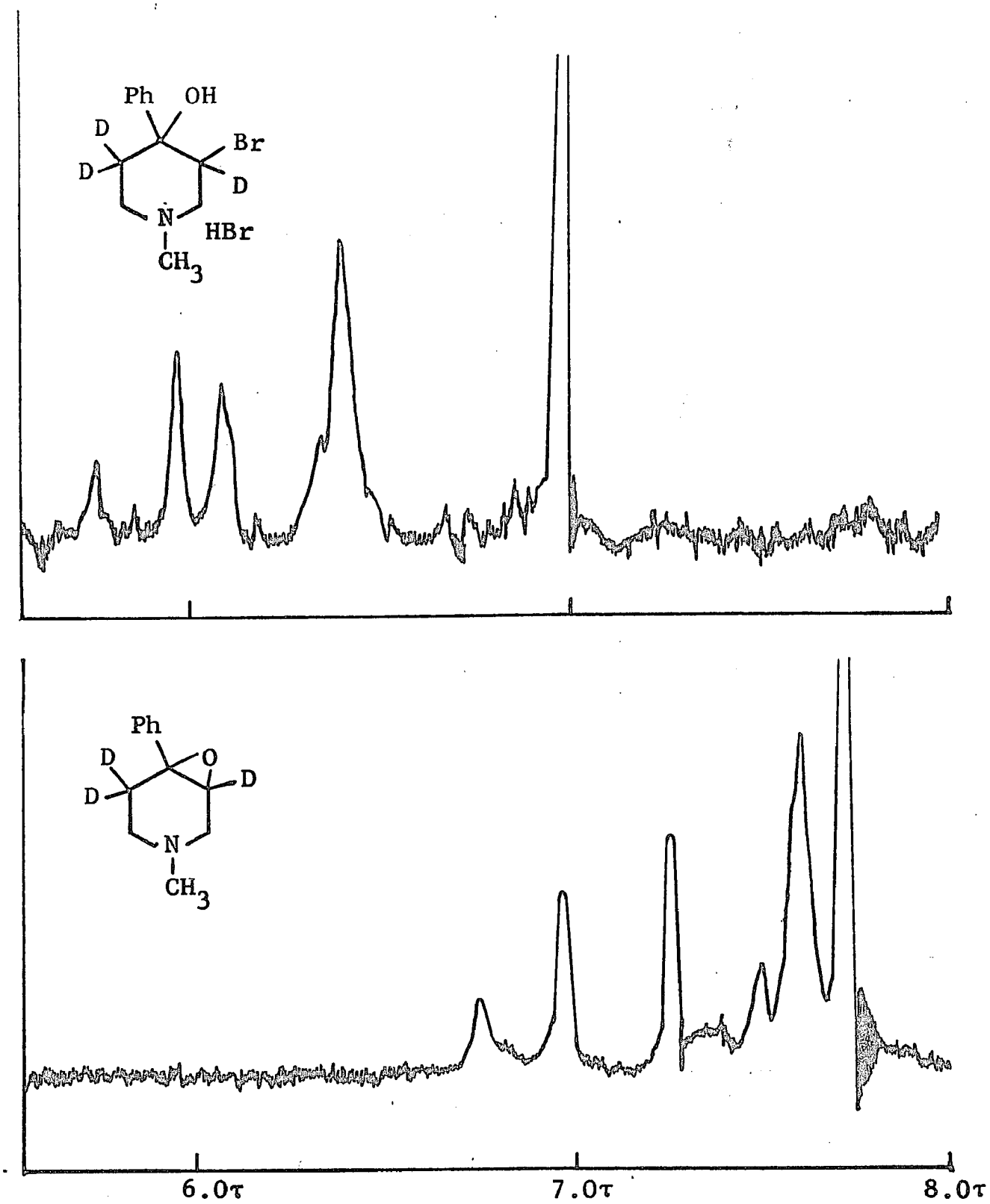


Figure II. The nmr Spectra of 5-d_3 and 7-d_3

also showed that the respective axial-equatorial coupling constants, J_{AB}=11.3 and 11.7 cps, were different. Thus the chemical shift and J_{AB} values reported in Table I are averages of two values.

Meinwald and coworkers have shown in a number of papers that long range coupling may occur where a "W" configuration permits a tail-to-tail interaction.[36] A consideration of the stereochemistry of 8-d_3 indicated that the equatorial protons on carbons 2 and 6 were indeed at the ends of a "W" as required. The value of $J_{2,6}$ was 1.8 cps.

The value of the long range coupling, J= 1.8 cps, is approximately that expected of a hydrogen-deuterium interaction. If it is assumed that such an interaction is responsible for the observed "fine structure", the magnitude of the coupling constant requires that the hydrogen and deuterium atoms be trans-diaxial. The evidence does not support an axial conformation for either the 2- or the 6-proton responsible for the signals downfield. First, the assignment of the downfield doublet as the signal of the axial protons contradicts the work of Hamlow[34a], Bohlmann[34b,c], and Lambert[33] cited above. Second, if this interaction is assumed, the spacing and symmetry of the observed pattern is difficult to rationalize. The so-called axial protons at carbons 2 and 6 would both be the B part of an AB pattern, but, since there is no axial deuterium at carbon 3 in 8a, only the doublet of the proton at C-6 would be split into a sextet by a hydrogen-deuterium interaction. This would lead to an unsymmetrical pattern which could have as many as eight peaks but in which two peaks would account for half the signal area. This was not the type of pattern observed (see a of Figure III). It is, therefore, unlikely that hydrogen-deuterium coupling is the cause of the fine splitting.

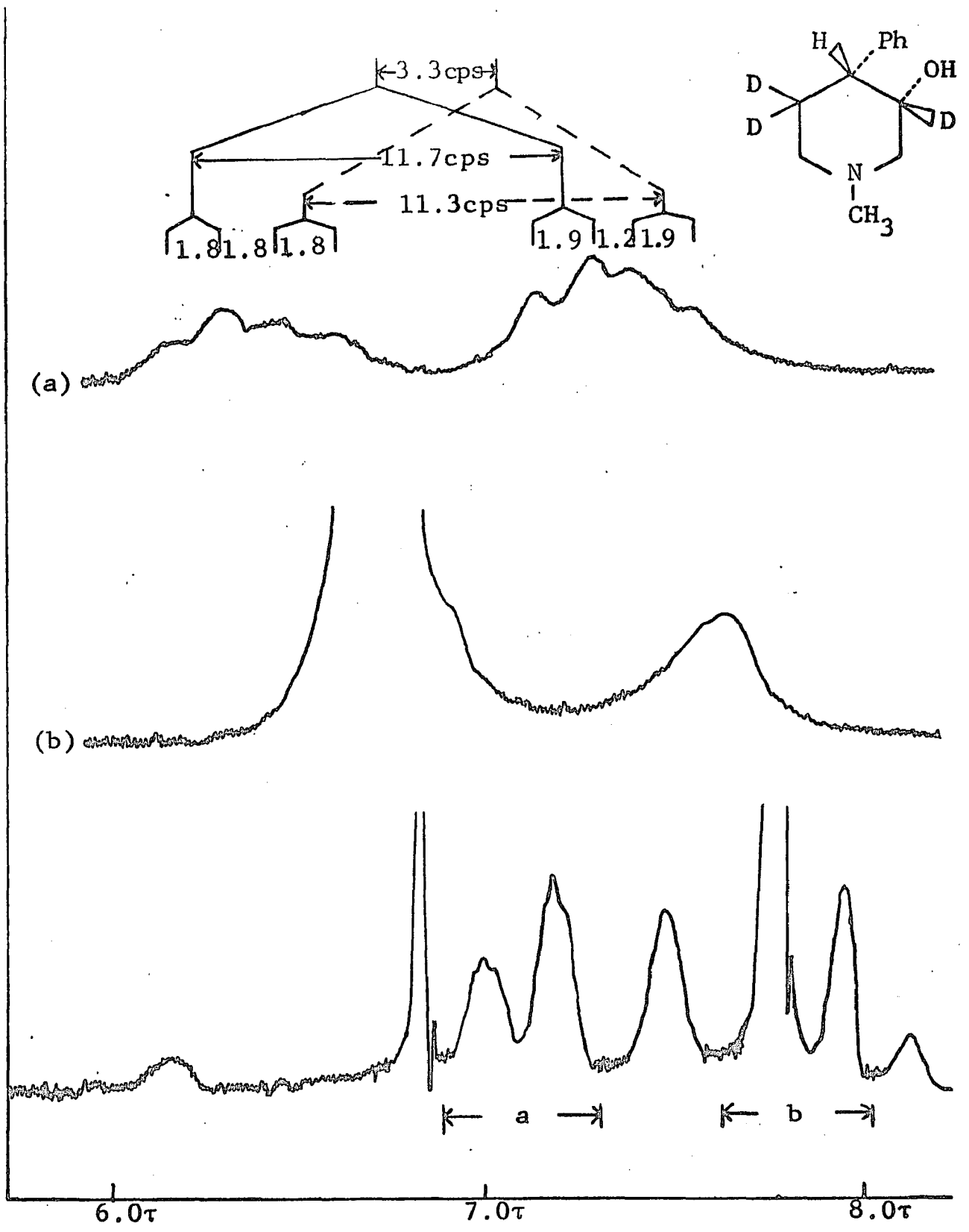


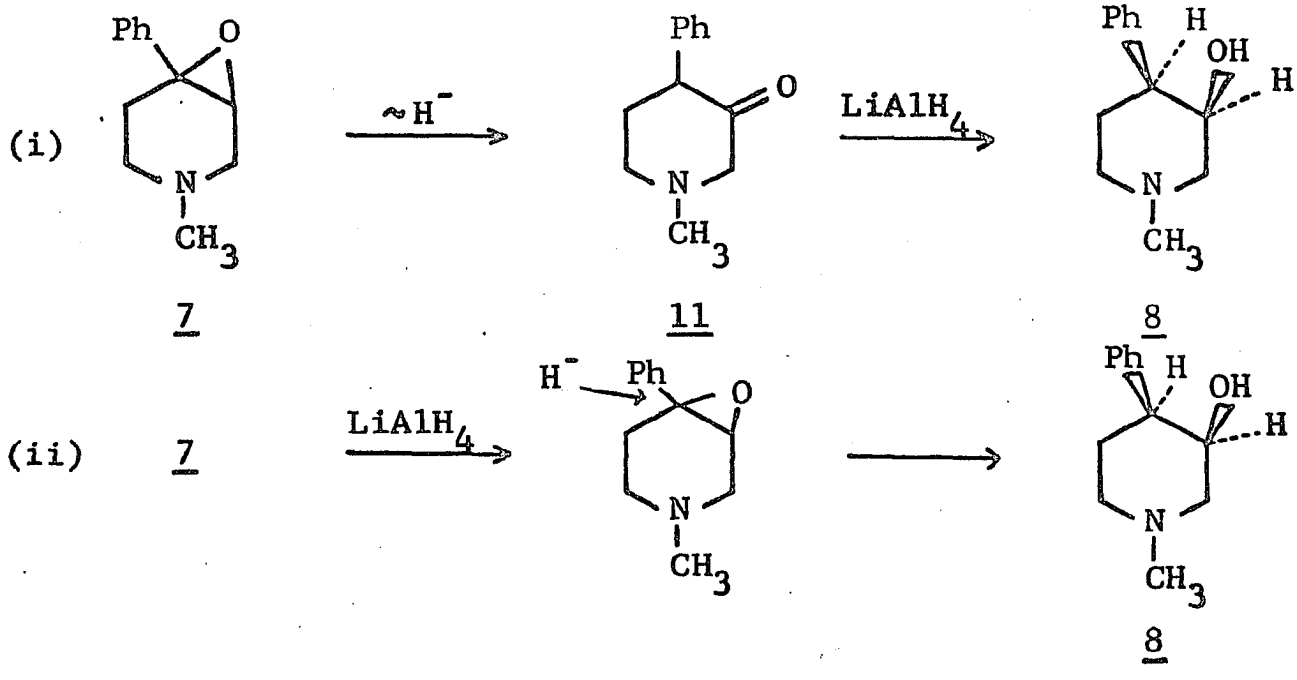
Figure III. The nmr Spectrum of cis-1-Methyl-4-phenyl-3-piperidinol-3,5,5-d_3

It is likely that each equatorial proton is the B part of AB pattern whose chemical shifts are different enough to permit the observation of four peaks and that each of the four is split in two by coupling across the piperidine ring.

The failure to observe "fine structure" in the signal of the axial protons must be attributed to a lack of long range coupling and a small difference in chemical shifts.

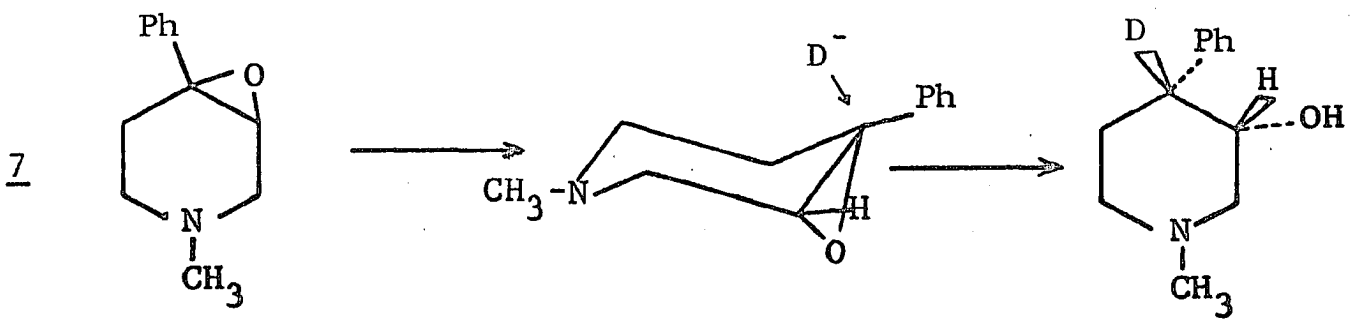
The Mechanism of the Reduction of 1-Methyl-4-phenyl-3,4-epoxypiperidine with Lithium Aluminum Hydride.

The reduction of 7 with lithium aluminum hydride could occur by either of two pathways. In mechanism (i) a shift of hydride from C-3 to C-4 leads to the piperidone (11) which subsequently undergoes reduction. Mechanism (ii) requires a simple nucleophilic displacement of the epoxide oxygen at C-4. Reaction paths (i) and (ii) were differentiated by a consideration of the products of the reaction of lithium aluminum hydride and piperidone (11), and by a study of the structure of the product of the reduction of 7 with lithium aluminum deuteride.



The reduction of 1-methyl-4-phenyl-3-piperidone (11) with lithium aluminum hydride gave 9 as the major product along with small amounts of 8. Since 8 was the exclusive product of reduction of the epoxide 7, it seemed unlikely that the piperidone 11 was an intermediate in this reaction.

The reduction of 7 with lithium aluminum deuteride further eliminated 11 as a possible intermediate. The gas phase chromatogram of the product showed it to be 8 uncontaminated by either 9 or 10 within the limits of detection. A comparison (Figure IV) of the nmr spectrum of unlabeled 8 with that of the product of the reduction by lithium aluminum deuteride indicated that the deuterium atom was on the 4-position. The signal at 6.02 τ, assigned to the carbinol proton, was the same in both compounds, but the signal assigned to the benzylic proton at carbon-4 (7.43τ) was absent in the product of the reduction with lithium aluminum deuteride. These results rule out mechanism (i) and are consistent with mechanism (ii). That this displacement occurs with inversion of configuration can be inferred from the stereochemistry of the product. Any mechanism proceeding with retention would produce the trans-piperidinol 9 not 8.



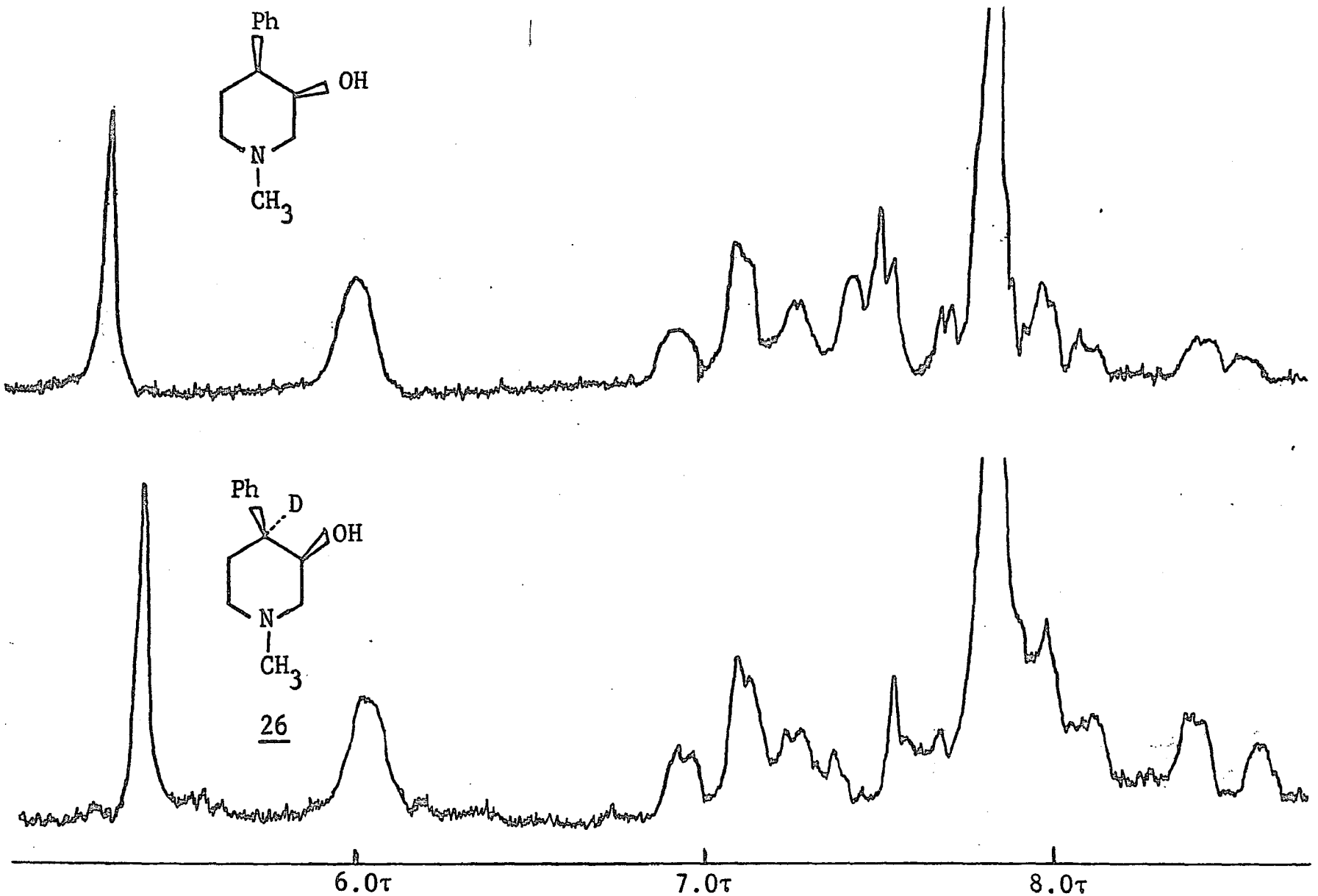
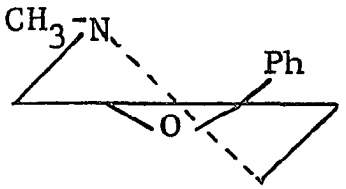


Figure IV. The nmr Comparison of 8 and the Product of 7 and Lithium Aluminum Deuteride

There remains the task of explaining the direction of epoxide opening. This apparently anomalous reduction may arise from conformational factors or from participation of the heterocycle nitrogen. The principle of diaxial ring opening has been known for some time. Nucleophilic reagents attack an epoxide ring from the axial side breaking the equatorial bond and leaving the oxygen in the axial position.[37] Thus, when 2β,3β-epoxytropane was treated with lithium aluminum hydride the sole product was 2β-tropanol.[38] However, in the case of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) the piperidine ring is conformationally mobile, and there is no reason to believe that transition state b would be considerably more stable than a. Thus, based on conformational considerations alone, axial attack may occur at C-3 or at C-4 (reaction scheme 3) giving a mixture of products. However, attack at C-3 would be reinforced by its steric accessibility, while attack at C-4 would be opposed by its relative inaccessibility. Thus a prediction from conformational factors

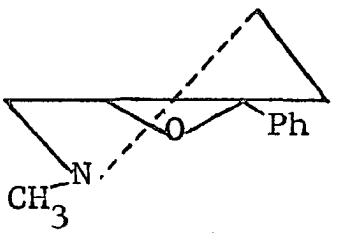
(3)



7a

axial attack at C-3

10



7b

axial attack at C-4

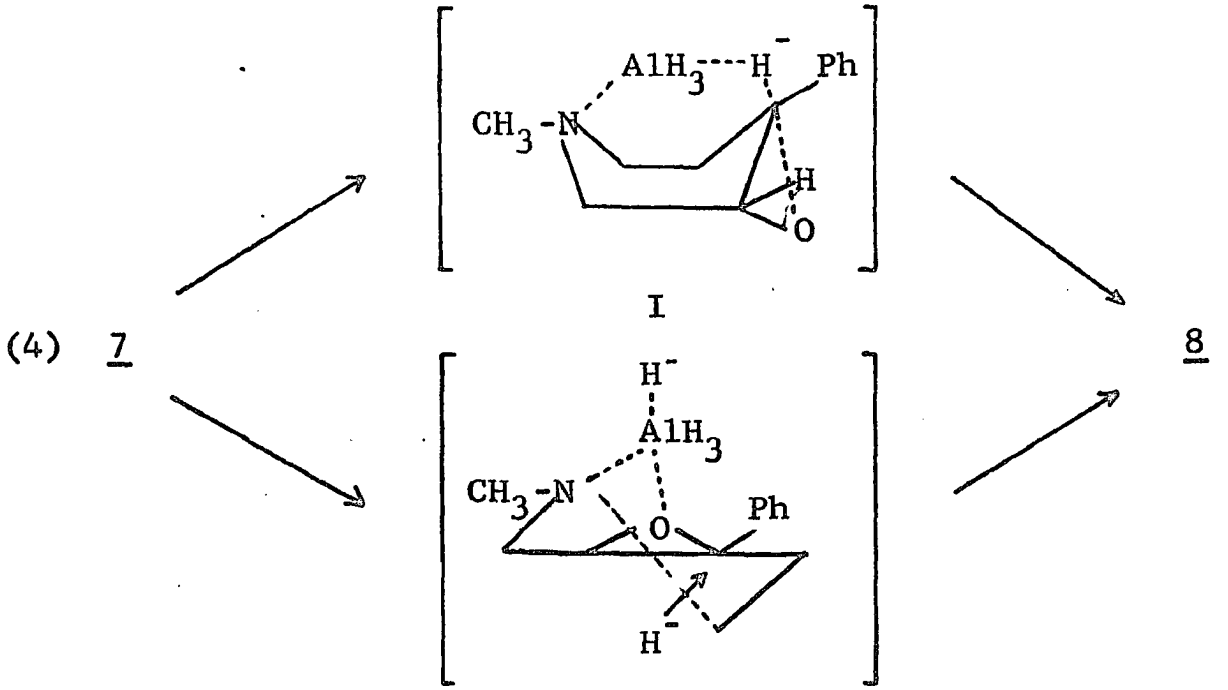
8

would require the presence of large amounts of 10 in the reaction mixture. The piperidinol 10 was not a product of the reaction of 7 with lithium aluminum hydride, so diaxial ring opening cannot be used to rationalize the course of this reduction.

The conclusion was supported by the results of the reaction of the carbocyclic analogue of 7, 1-phenylcyclohexene oxide, with lithium aluminum hydride. As predicted above, axial hydride attack occurs predominently at the sterically favored position to give 95% 1-phenylcyclohexanol and only 5% of 2-phenylcyclohexanol.

The failure of the carbocyclic analogue to give results comparable to those of 7 presents the likelihood that participation of the heterocyclic nitrogen is in some way responsible for the direction of epoxide cleavage. Transannular participation of nitrogen similar to that reported by Archer for nucleophilic displacement of 3-chlorotropanes[39] would be expected to proceed with retention of configuration at the 4-position and can be ruled out. The complex of aluminum hydride with the basic nitrogen, however, might determine the course of the reaction. The precedence for this type of coordination was reported in 1961 by Lansburg who observed that the basicity of lithium aluminum hydride in pyridine was enhanced compared to ether.[40] This effect was explained as resulting from the tendency of the pyridine to coordinate strongly with the incipient aluminum hydride and thus causing the tetrahydridoaluminum anion to release hydride more effectively. Analogously a more basic tertiary amine such as 7 would be expected to coordinate with the incipient aluminum hydride. Such a complex leading to transition state I would make reaction at C-4 favored by its proximity to the hydride ion being released and by allowing epoxide ring opening to

proceed in the preferred diaxial manner.



In transition state II the carbon oxygen bond at C-4 is partially polarized by coordination with the aluminum thus inviting reaction at carbon-4 by another hydride and allowing the cleavage to proceed in accordance with the principle of diaxial ring opening. Both I and II are consistent with the data available.

The importance of coordination of the nitrogen and aluminum hydride in determining the course of the reaction might be indicated by using an analogue in which complexing was prohibited by steric interference. 1,2,2,6,6-Pentamethyl-4-phenyl-3,4-epoxypiperidine was selected as the model compound and its synthesis was attempted.

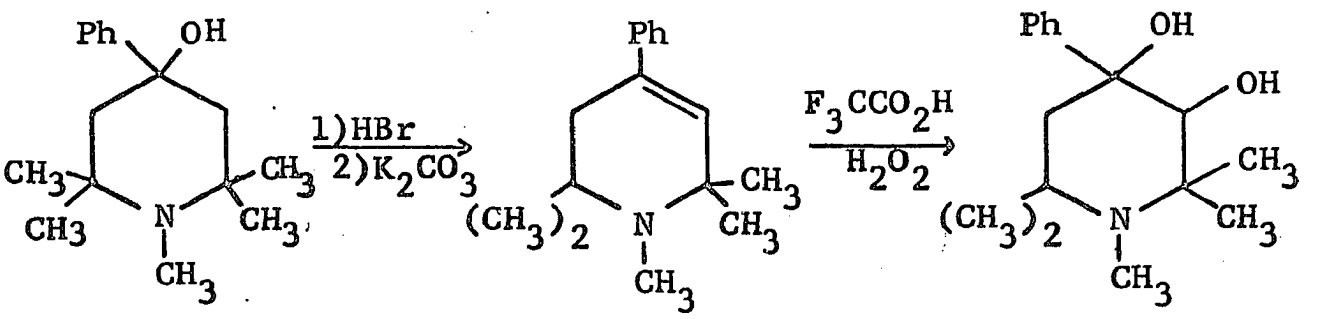
The reaction of 1,2,2,6,6-pentamethyl-4-piperidone[41]

with phenyl Grignard gave 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (13). This compound, when heated with an excess of 40% hydrobromic acid, gave a white solid. The infrared spectrum of the base (Figure 15, Appendix) had no absorption above 3100 cm^{-1}. The nmr spectrum (Figure 34, Appendix) showed the presence of one vinyl hydrogen and the ultraviolet spectrum was consistent with the presence of a substituted styrene system. These data indicate that 13 underwent a facile dehydration to form 1,2,2,6,6-pentamethyl-4-phenyl-1,2,5,6-tetrahydropyridine (14) hydrobromide. The elemental analyses were in agreement.

Attempts to prepare the epoxide via the bromohydrin were unsuccessful. The reaction of 14 with bromine-sodium bromide in water at room temperature resulted in an orange gum which smelled like bromine and gave back starting material when treated with acetone. The same reaction at 100° proceeded smoothly with decolorization of one equivalent of bromine. Evaporation of the water under reduced pressure and below 60° gave an orange oil mixed with a white solid (NaBr). The oil did not crystallize and slowly darkened. The gas chromatogram of the base showed peaks only for the starting material 14 and a number of more volatile compounds. On standing the base became heterogeneous. The solid formed was shown by infrared and mixture melting point to be the hydrobromide of 14. These results indicate that bromination occurred, but that the product was highly unstable probably due to the 2,4,6-triaxial substitution pattern.

Several attempts were made to synthesize the epoxide by direct oxidation. These were complicated by the fact that the heterocyclic nitrogen is also liable to oxidation. Reaction by the method of Fodor et al.[42], using trifluoroacetic acid to protect the nitrogen, resulted in a white solid whose

infrared spectrum (Figure 16, Appendix) had a band at 3500 cm^{-1}. The solubility properties of the solid were similar to those of 12[19] and the elemental analyses gave values in agreement with those required by 15. It is evident that the



13 14 15

double bond underwent oxidation while the nitrogen did not; however, in the acidic medium the resulting epoxide was cleaved to form 1,2,2,6,6-pentamethyl-4-phenylpiperidine-3,4-diol (15). This approach was abandoned.

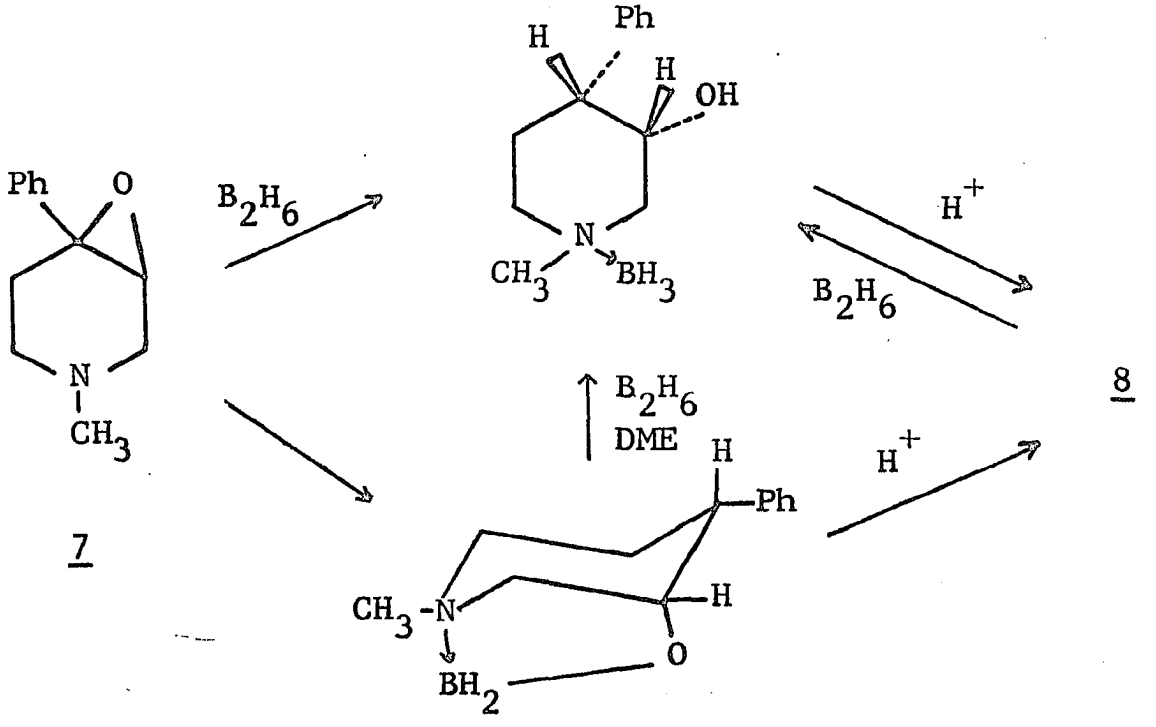
H. C. Brown has shown that epoxides undergo reaction with diborane to give alcohols[43a,b], and has reported that double bonds are more reactive towards diborane than is the epoxide group.[43b] C. K. Spicer has found in hydroboration studies of 1-methyl-1,2,5,6-tetrahydropyridine that formation of the amineborane occurs before reaction with the double bond.[23] This implies that the nitrogen of the amine is more reactive toward diborane than an epoxide linkage. In view of these findings it was anticipated that the reaction of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) with diborane would first form an amineborane thus resulting in an intermediate analogous to that proposed for the reaction of 7 with lithium aluminum hydride. If the mechanism in Scheme 4 obtains and if the analogy holds, further reaction of this intermediate

would be expected to cleave the epoxide linkage to give 8.

The reaction of a solution of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) in 1,2-dimethoxyethane with an excess of diborane, generated externally, gave, on evaporation of the solvent, a white solid. The infrared spectrum (Figure 13, Appendix) of this solid had a strong band at 3550 cm^{-1} and a multiplet between 2300 and 2450 cm^{-1}. Treatment of this compound with dilute hydrochloric acid gave 8. The reaction of 8 with diborane gave a white product that was identical by infrared with the amineborane obtained from the reaction of 7 with diborane. These data establish the structure as the amineborane of 8.

To show that an intermediate analogous to I in Scheme 4 was involved in this cleavage an effort was made to isolate the amineborane of 7.

The reaction of diborane with a solution of 7 in ether resulted in the precipitation of a white solid which



7

16

was shown to be different from the amineborane of 8 by infrared spectra, melting points, and mixture melting point. The infrared spectrum (Figure 14, Appendix) had no band above 3100 cm^{-1} and a multiplet from 2300 to 2450 cm^{-1}. Treatment of this solid with dilute hydrochloric acid gave 8. It is unlikely that the epoxide function was left intact by the diborane since the action of acid on the epoxide 7 has been shown to give the glycol 12, not 8.

Reaction of this solid with diborane in 1,2-dimethoxyethane gave the amineborane of 8. The elemental analysis for hydrogen was in agreement with the values required by 16. However, the analysis for carbon was low. This is consistent with the results of Letsinger and Wysocki who found that in the absence of a special catalyst, analyses for carbon were characteristically low.[44] While these data do not establish the structure of this compound, they are consistent with 16.

The unusual facility with which the cleavage of the epoxide linkage with diborane occurred prevented the isolation of the amineborane of 7 and suggested that the reduction proceeded at a rate comparable to that of coordination between nitrogen and boron. The reductions of 7 with lithium aluminum hydride and diborane were analogous in that they produced the same product. They also appear to proceed by similar mechanisms; however, any further analogy has not been demonstrated.

The Preparation and Reactions of 1-Methyl-4-phenyl-3-piperidone.[45]

The reaction of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) and boron trifluoride etherate under reflux gave a dark oil, whose infrared spectrum (Figure 9, Appendix) showed a moderate to weak band in the hydroxyl region and a strong

carbonyl band at 1730 cm^{-1}. The reaction of a sample of this crude product with hydroxylamine hydrochloride and base gave an oxime whose infrared spectrum (Figure 10, Appendix) had a strong, sharp band in the hydroxyl region and a weak but sharp band at 1680 cm^{-1}, and which gave the correct elemental analyses for 11-oxime. These data were interpreted as indicating that the epoxide 7 underwent reaction with boron trifluoride etherate to form 1-methyl-4-phenyl-3-piperidone (11).[45]

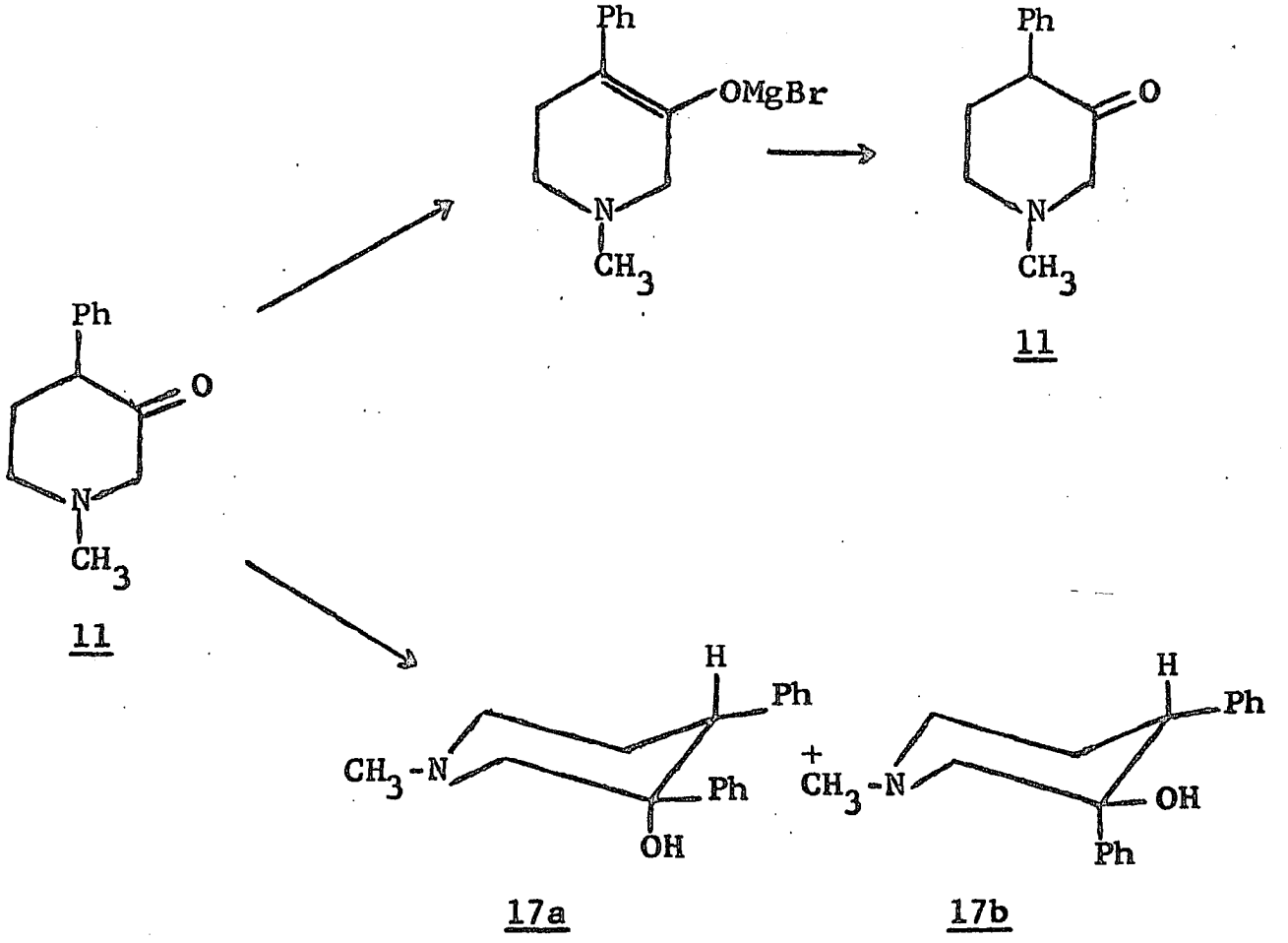
Treatment of 1-methyl-4-phenylpiperidine-3,4-diol (12) with concentrated sulfuric acid at 0° gave a product that was shown by infrared to be identical with 11 formed from 7 and boron trifluoride. Similarly, reaction of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) with sulfuric acid in the cold gave 11 in better than 70% yield. The crude product was shown by vpc analysis to contain trace amounts of two impurities. The high yield and purity of 11 make this procedure the method of choice.

Distillation of a sample of the piperidone 11 from 7 and boron trifluoride gave a fraction, b.p. 110-114°/0.1 mm., in 52% yield. Analysis of this oil by gas chromatography showed it to be 70-30 mixture of two compounds. The major component was shown by retention time and subsequent reactions to be piperidone 11. The minor component was isolated by chromatography over Florisil and identified as 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3) (vide infra) by infrared spectrum and vpc retention time.

The formation of the allylic alcohol 3 in this reaction can be rationalized from the normal course of boron trifluoride rearrangements of this type. The carbonium ion (III) initially formed can eliminate the proton next to the oxygen to form the enolate(IV) or a proton from C-5 to form the

alcoholate(V) (Figure V). The reactions of 12 and 7 with sulfuric acid undoubtedly proceed through a carbonium ion analogous to III. The absence of significant amounts of 3 in the product mixture when the temperature was carefully controlled indicates that the elimination of a proton from C-5 is favored by elevated temperatures.

The piperidone 11 resulted in a product obtained from boron trifluoride and phenylmagnesium bromide, which was shown by vpc analysis to be a 1:1:2 mixture of allylic alcohol 3, starting ketone 11, and addition products. Since an excess of the Grignard reagent was used, it is likely that the ketone 11 resulted from enolization caused by that reagent. If this is correct the ratio of enolization to addition is about 1:2.



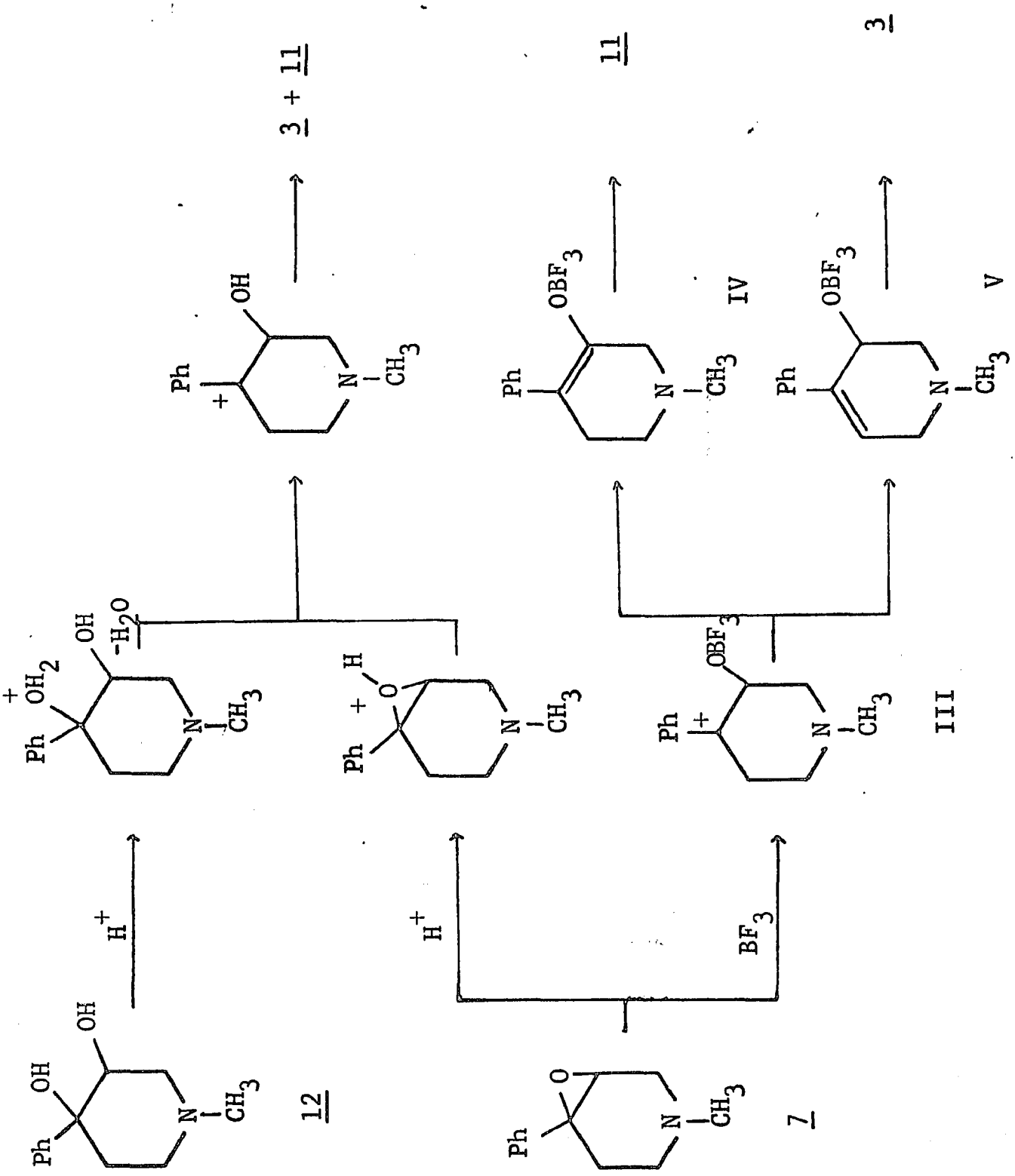
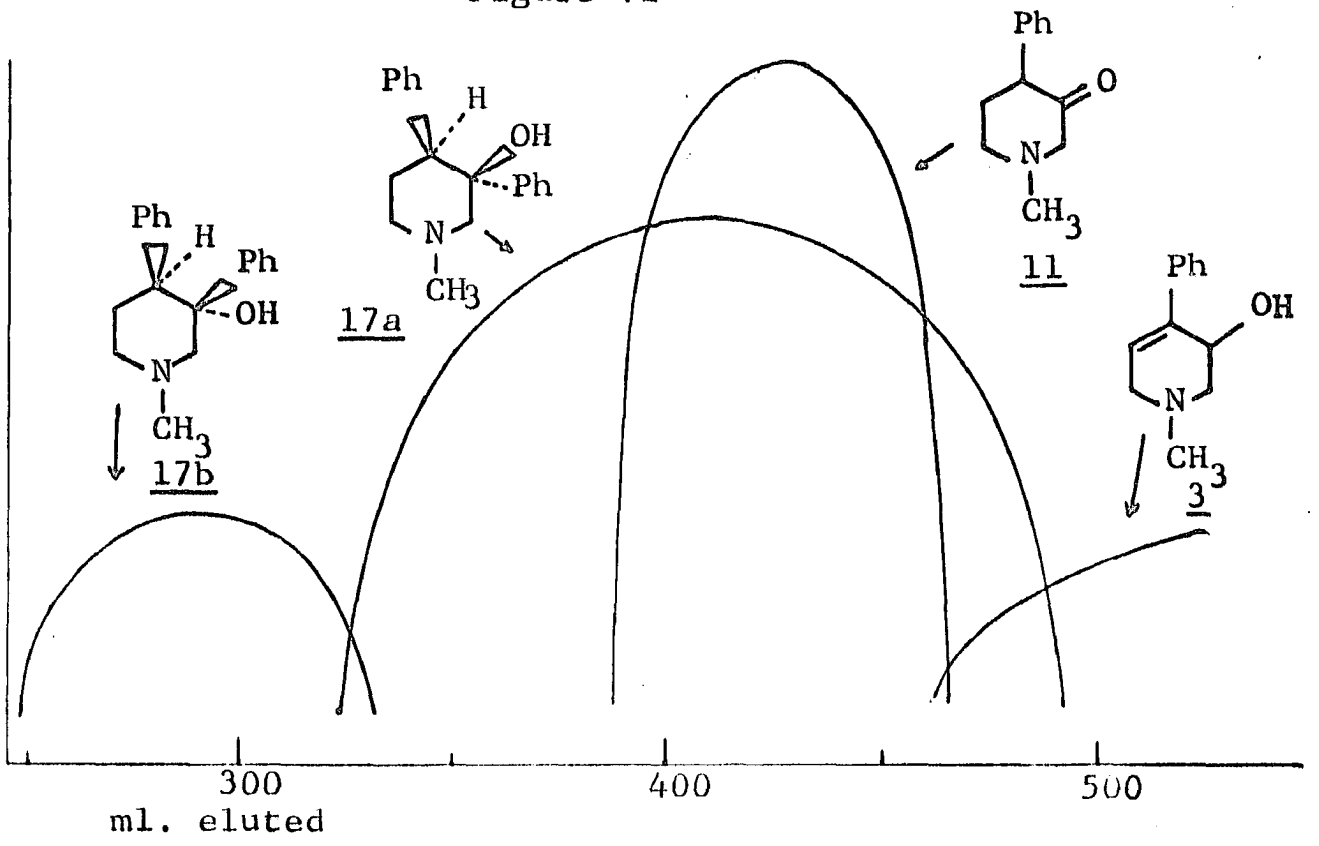


Figure V. The Mechanism of Formation of 1-Methyl-4-phenyl-3-piperidone

The crude product was then chromatographed over Florisil. The fractions were concentrated and compared by vapor phase chromatography on a 0.5 m. Carbowax 20M column (Figure VI). Under these conditions the addition products were resolved, demonstrating that both possible isomers, 17a and 17b, were formed in the reaction of 11 with phenyl Grignard. Since the yield of piperidinols was determined only after column chromatography, no meaningful ratio of formation of 17a and 17b was available.

Figure VI*



*The ordinate in this graph is peak height observed in the vpc analysis. The sample size was not reproduced so the areas under the curves are not a measure of the relative quantities of each component.

The fractions from 325 to 375 ml. were combined and the solvent was removed under reduced pressure to give an oily residue. Dissolution of the residue in acetone followed by treatment with hydrogen chloride resulted in a white solid. Its infrared spectrum (Figure 19, Appendix) had a strong, sharp band at 3400 cm^{-1} and a strong multiplet from 2500-2600 cm^{-1}. A high dilution infrared study of the free base indicated that the hydroxyl group was entirely intramolecularly hydrogen bonded to the nitrogen.[21] There was no evidence for a free hydroxyl group. These data suggested that the stereochemistry should be represented by 17a, rather than 17b. The elemental analyses of the hydrochloride were in agreement with the values required by this structure. It has been found that when one of two epimers exhibits significant hydrogen bonding, while the other does not, the intramolecularly bonded isomer will be eleuted first from a Carbowax 20M column.[46] Thus the fact that the base of the salt mentioned above had a retention time 1.9 min. shorter than its epimer further verifies the structure as 17a.

The fractions after 500 ml. were combined, and the solvent was removed by distillation. The residual oil solidified on standing and was shown by nmr and infrared spectra to be 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3).

1-Methyl-4-phenyl-3-piperidone (11) was reduced by the action of lithium aluminum hydride or sodium borohydride. Each reaction gave both possible epimers, cis- and trans-1-methyl-4-phenyl-3-piperidinol. The ratios of products are listed in Table II. A comparison with the results of the reduction of 2-phenylcyclopentanone with lithium aluminum hydride indicated that the heterocyclic nitrogen does not play a significant role in directing the course of this reaction. This conclusion cannot be extrapolated to the sodium borohydride

reduction. The increase in the percentage of the ratio of the cis isomer was anticipated in view of the smaller steric requirement of the tetrahydrido boride anion, but the magnitude of this change was greater than expected. It was, therefore, necessary to assume that some direction of the course of this reaction by nitrogen occurred.

Table II

The Reduction of 1-Methyl-4-phenyl-3-piperidone (11)

Compound	Reducing Agent	% cis	% trans
2-Phenylcyclopentanone[28]	$LiAlH_4$	35	65
11	$LiAlH_4$	30	70
11	$NaBH_4$	67	33

The Preparation of 1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol.

A study of the reaction of the epoxide 7 with organometallic reagents was initiated in order to determine whether or not the addition to the epoxide linkage would be stereospecific and if so to compare the course of the reaction with the stereospecificity observed for the reductions of 7 with complex metal hydrides. The study was also of interest since the product of the stereospecific addition of methyl lithium 7 would be the piperidinol precursor of β-prodine, the more active analgesic of the two racemates. These reactions would also constitute a new and specific route to this compound obtainable previously only as the minor component in a mixture

with the less active isomer. This mixture was obtained by treatment of 1,3-diemthyl-4-piperidone with phenyl lithium or phenyl Grignard.

Treatment of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) with methyl lithium, phenyllithium, or phenylmagnesium bromide, at room temperature, gave a white solid, m.p. 104-106°. The infrared spectrum of the product had a strong, broad band at 3400 cm^{-1}, and the ultraviolet spectrum was characteristic of a styryl chromophore. The nmr spectrum indicated the presence of one vinyl hydrogen and the elemental analyses were in agreement with the values required by 3. These data suggested that elimination rather than addition had occurred and that the product was 1-methyl-4-phenyl-1,2,-3,6-tetrahydro-3-pyridinol (3).

The several paths this reaction may take are outlined in Figure VII. The first, involving the abstraction of a proton α to the oxirane followed by elimination of the epoxide oxygen has been reported by Cope for the reaction of both cis- and trans-4-octene oxides with lithium diethyl amide.[47b] A similar reaction has been reported by Reeves[47a] and the trans nature of the elimination has been demonstrated by Hoeg.[47d] The second, involving the removal of the oxirane hydrogen, followed by a 1,2-hydride shift, was observed by Cope in the reactions of cis-cyclooctene oxide and cis-cyclodecene oxide.[47c] Small amounts of 1,2— migrations of carbon moieties have also been reported by Cope.[47b] The reaction of 7 with organometallic reagents undoubtedly involves the elimination mechanism to a large extent. However, small involvement of all the remaining pathways cannot be eliminated. The crude reaction mixture was highly colored, possibly due to the decomposition of 18. The vapor phase chromatogram of the product from 7 and n-butyl lithium and from 7 and 5-butyl

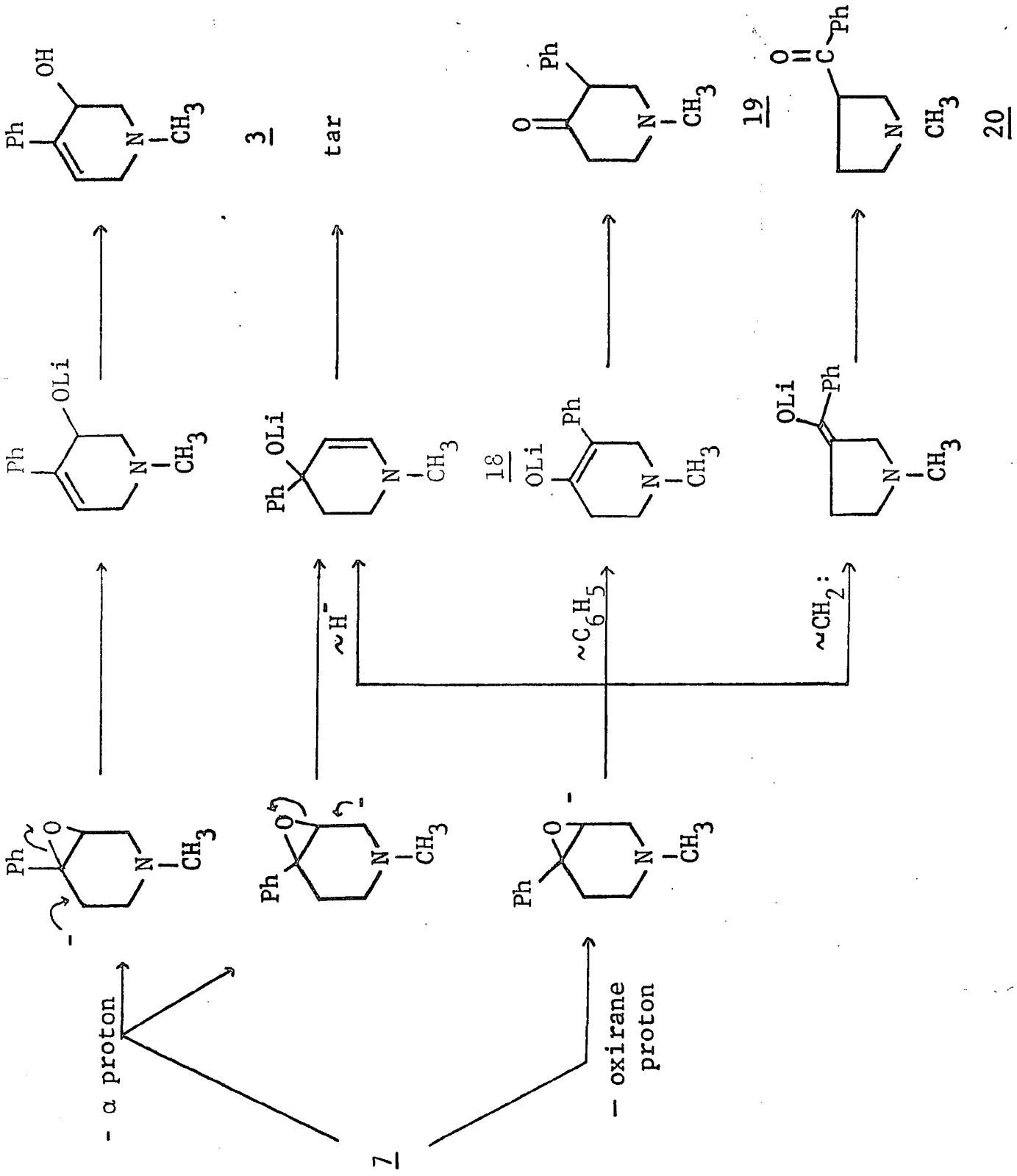


Figure VII. The Mechanism of the Reaction of 1-Methyl-4-phenyl-3,4-epoxypiperidine with Organometallic Reagents

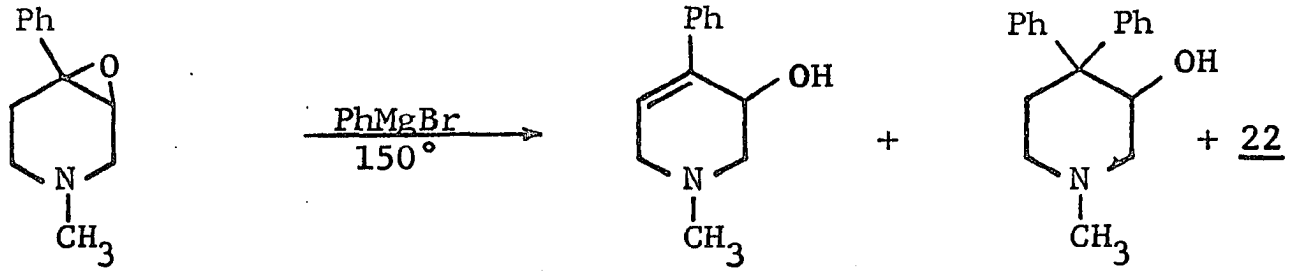
lithium had a small but definite peak of lower retention time than 3 . This product was not isolated or identified; thus the possibility that it is either 19 or 20 cannot be eliminated (Figure VII).

In the reactions of 7 with n-butyl lithium approximately 20% addition was observed. To find conditions under which addition might compete more favorably with elimination, 7 was treated with phenylmagnesium bromide in refluxing anisole. Analysis of the crude product by gas chromatography indicated that addition was favored over elimination by a ratio of 3:2 and demonstrated the presence of two distinct addition products.

The diphenyl piperidinols resulting from addition reactions were separated by chromatography over Florisil. The first compound which was eluted was a white solid, m.p. 157-9°, after recrystallization. The infrared spectrum of this solid (Figure 18, Appendix) had a band at about 3250 cm^{-1}. The results of high dilution infrared studies were discarded since an unexpected, inexplicable, strong, very broad absorption band was present at 3220 cm^{-1}. The nmr spectrum had a signal at 5.27τ, the area of which corresponded to one proton, using as standard either ten protons of the phenyl groups or the nitrogen methyl signal as three protons. However, it was not certain whether this signal was due to a hydroxyl or a carbinol proton. The elemental analyses were consistent with the values required for addition of C_6H_6 to 7. These data do not permit assignment of a structure to 22.

The second substance which was eluted solidified to give a white solid, m. p. 162-5°, after recrystallization. The infrared spectrum (Figure 17, Appendix) had a band above 3200 cm^{-1} which was assigned as an oxygen-hydrogen stretching vibration. The high dilution infrared spectrum[21] indicated a hydroxyl group partially bonded by an intramolecular hydrogen

bond to the heterocyclic nitrogen. The nmr spectrum showed a signal at 5.32 τ (quartet) due to a carbinol proton and the elemental analyses were correct for the values required by 21. These data are consistent with the assignment of 1-methyl-4,4-diphenyl-3-piperidinol[48] as the structure of this compound.



7 3 21

A consideration of the possible mechanisms for addition (Figure VIII) permits tentative assignment of the structure of 22. The first (i) involves a hydride shift to form the ketone 11 prior to reaction with the Grignard reagent. The second (ii) requires the migration of a moiety other than hydrogen to form a ketone which then undergoes reaction. The third (iii) requires that a molecule of the Grignard reagent first remove a proton from the epoxide 7 to form the elimination product, 3, which then adds a second molecule of Grignard reagent. Finally, pathway (iv) involves the addition of the Grignard reagent to the epoxide without rearrangement.

It was shown above that the reaction of the piperidone 11 with phenylmagnesium bromide gave 17a and 17b. These were shown to be different from 21 and 22 by vpc retention time and, in the case of 17a, by non-identity of the infrared spectra. Thus mechanism (i) can be ruled out. Since the migratory aptitude of hydrogen is generally considered to be superior to that of a methylene or of a phenyl group,[49] contribution from mechanism (ii) is unlikely in the absence of any evidence for

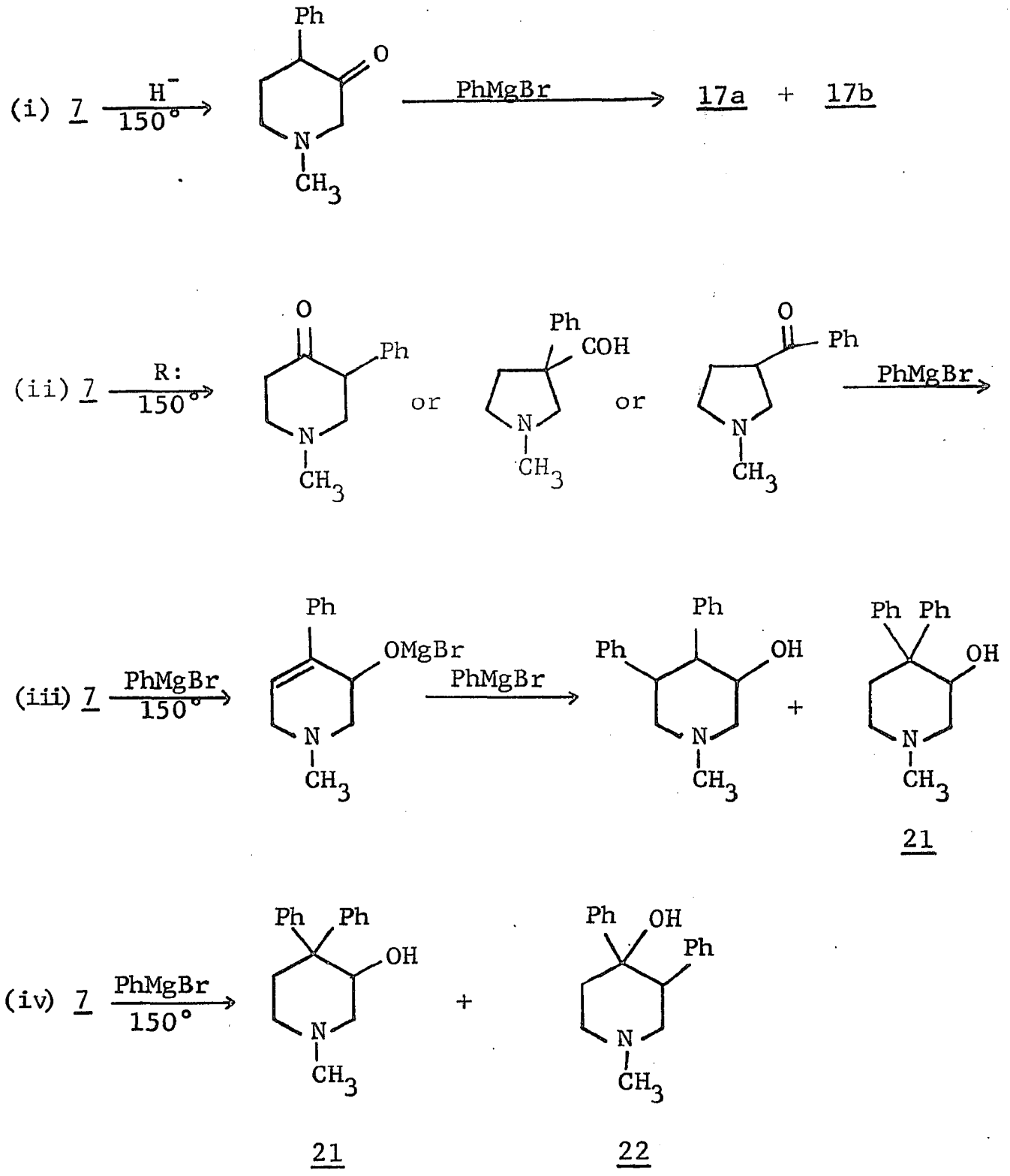
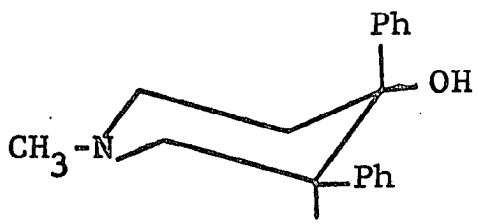


Figure VIII. The Possible Mechanisms of the Reaction of 1-Methyl-4-phenyl-3,4-epoxypiperidine with Phenylmagnesium Bromide at 150°

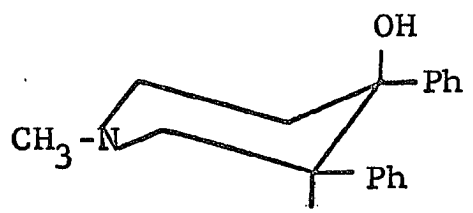
a hydride shift. Mechanism (iii) was eliminated as a possibility by a control reaction in which the allylic alcohol, 3, was treated with an excess of phenyl Grignard in refluxing anisole for extended periods of time. No addition was observed.

It is, therefore, probable that reaction of the epoxide 7 with phenyl Grignard at 150° involves normal addition to the epoxide linkage. This addition has often occurred with a multiplicity of products[49] and has been shown to occur with inversion of configuration.[50]

If it is correct to assume that mechanism (iv) holds in this case, the piperidinol 22 arises from attack of the Grignard reagent at C-3 and is, therefore, probably 1-methyl-3,4-diphenyl-4-piperidinol. Since the normal fission of the carbon-oxygen bond involves inversion of configuration, the stereochemistry of the product is more likely represented by 22a than 22b.[51]



22a



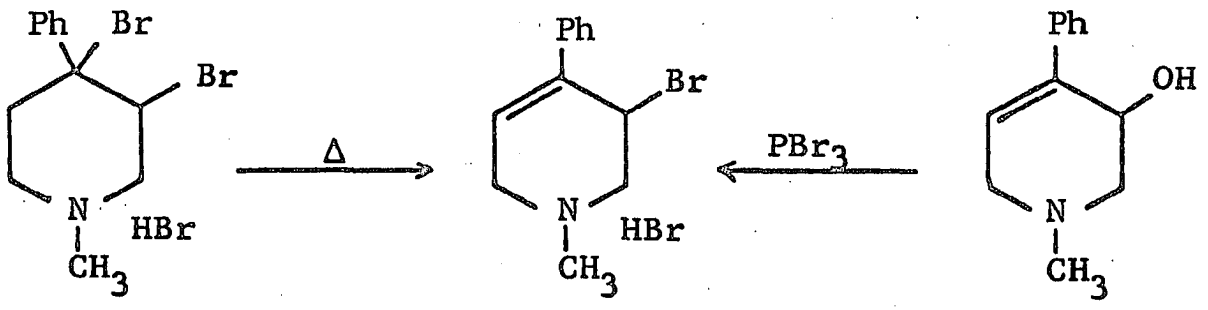
22b

The Preparation of Derivatives of 1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol.

The reaction of bromine with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (1) hydrobromide in acetic acid was reported to give the dibromide 1-methyl-3,4-dibromo-4-phenyl piperidine hydrobromide (4), m.p. 131-132°. This compound was said to isomerize on standing or heating to a second crystaline modifi-

cation, m.p. 188-191°.[19] Repetition of this isomerization resulted in a compound whose properties suggested that a chemical, rather than a physical change had taken place. The compound obtained on heating the dibromide exhibited a band at 243 mu in the ultraviolet spectrum which was consistent with the presence of a substituted styrene system and not an isolated phenyl chromaphore as required by 4. The nmr spectra (Figures 32, 33, Appendix) indicated the presence of one vinyl hydrogen, and the elemental analyses of the salt required one molecule of hydrogen bromide less than structure 4.

These data suggested that heating the dibromide 4 resulted in dehydrohalogenation, rather than a change in crystal structure and that the product of this reaction was 1-methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine hydrobromide (2). These results were verified when treatment of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3) with phosphorus tribromide gave a product which was shown by infrared and nmr spectra to be identical with the product obtained by heating 4.



4 2 3

Reaction of the hydrochloride of 3 in refluxing thionyl chloride gave a white solid. The infrared spectrum (Figure 23, Appendix) had no band above 3100 cm^{-1}, and the nmr spectra (Figures 30 and 31, Appendix) of the salt and base indicated the presence of one vinyl hydrogen. The ultraviolet spectrum was consistent with a substituted styryl group. These data were in agreement with the assignment of 1-methyl-3-chloro-4-phenyl-1,2,3,6-tetrahydropyridine (25) hydrobromide as the structure of this compound. The elemental analyses were correct for this structure.

An acetate was prepared by heating 3 in refluxing acetic anhydride. The infrared (Figure 26, Appendix), ultraviolet, and nmr spectra, as well as the elemental analyses, confirmed the structure to be 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol acetate hydrobromide.

To demonstrate the involvement of the double bond in the above reactions, the preparation of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol-5-d and 1-methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine-5-d was undertaken. The method of Lyle and coworkers[52] was used to prepare 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine-5-d hydrobromide (1-d_1). The bromination of this compound in acetic acid followed by heating the product on a steambath gave 1-methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine-d hydrobromide. An attempt to determine the location of the deuterium from the nmr spectrum indicated that it was distributed evenly at the 3- and 5-positions of the tetrahydropyridine ring (Figure IX). Since the intermediate dibromide was not isolated and characterized, it was uncertain whether scrambling of the deuterium occurred in the bromination or in the dehydrohalogenation step. The unexpected result precluded the direct preparation of a derivative of 3 with a deuterium label exclusively in the 5-position.

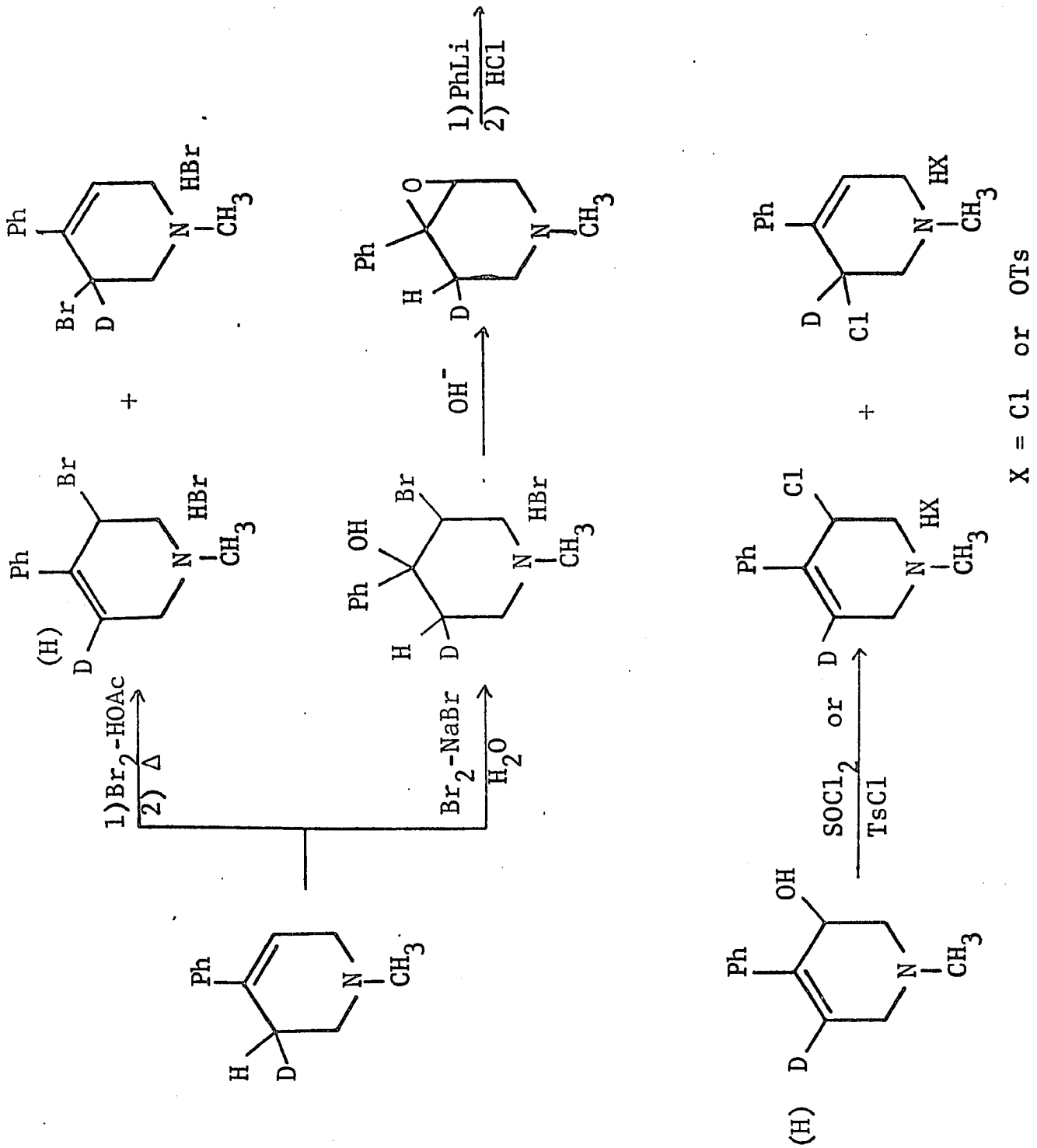


Figure IX. Deuterium Labeling Studies of the Solvolysis of 1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol and its Derivatives

The reaction of 1-d_1 with bromine-sodium bromide in water followed by treatment of the resulting solid with base gave 1-methyl-4-phenyl-3,4-epoxypiperidine-5-d. This epoxide and phenyl lithium at room temperature gave 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol-5-d as a white solid. Integration of the nmr spectrum showed that the ratio of the area of the signal of the vinyl proton to that of the carbinol proton was 1:2. Thus the elimination proceeded with no detectable isotope effect to give 3 with 50% of the vinyl hydrogen replaced by deuterium.

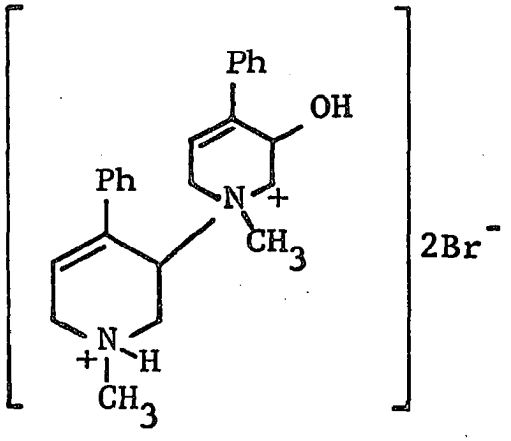
As anticipated, all attempts to derivatize 3-d_1 resulted in scrambling of the label over the 3- and 5-positions. The reaction of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol-5-d hydrochloride with thionyl chloride gave a material whose nmr spectrum showed that 50% of the deuterium was located at C-5 and 50% at C-3.

p-Toluenesulfonyl chloride and the hydrochloride of 3 in dimethylformamide gave a white solid. The infrared spectrum (Figure 24, Appendix) showed bands at 1170 cm^{-1} and 1040 cm^{-1} characteristic of a sulfonate anion[53a] and integration of the nmr spectrum indicated nine phenyl protons relative to one vinyl proton. The base gave a positive Beilstein test, and the infrared spectrum of the amine was identical with that of the free base of 25. These data were interpreted to require that the structure be the hydrotosylate of 25. The elemental analyses corroborated this assignment.

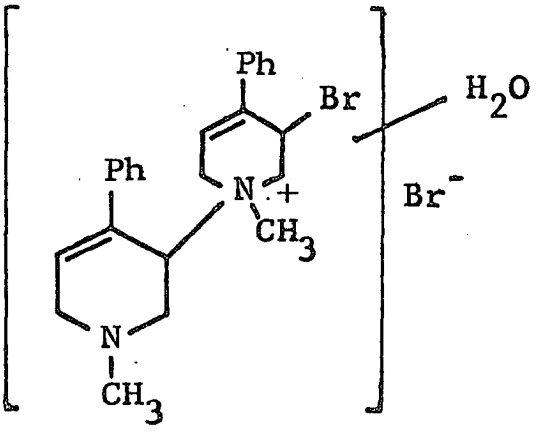
Repetition of this reaction using 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol-5-d hydrochloride resulted in a material whose nmr spectrum confirmed that the deuterium was distributed evenly over the 3- and 5-positions.

The Reaction of Derivatives of 1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol with Nucleophiles.

An ethereal solution of the base of 2 on standing overnight or evaporation to dryness gave a white solid which would not redissolve in ether. The infrared spectrum (Figure 27, Appendix) exhibited an absorption band at 3400 cm^{-1}. The solubility properties were characteristic of a quaternary salt and the ultraviolet absorption spectrum indicated the presence of a substituted styrene chromophore. These data suggested that the base quaternized with itself to form a dimer. The elemental analyses of this salt were correct for a dimer plus a molecule of water. Of the two structures considered below, 23a seemed the less likely due to the absence of a $\equiv\overset{+}{N}$-H stretching vibration in the infrared spectrum.



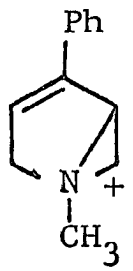
23a



23b

1-Methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine hydrobromide, when treated with an excess of aqueous sodium hydroxide at room temperature, underwent reaction to give a yellow solid. The vapor phase chromatogram of this solid indicated the presence of only one volatile component which was shown by its infrared spectrum to be 3. Under these conditions an aziridinium ion intermediate such as 24 would be expected to undergo nucleophilic attack at the less substituted carbon

of the three-membered ring to give an hydroxymethyl pyrrolidine.[17] Since there was no evidence for such a product in the reaction mixture, nucleophilic displacement of the bromine appeared to involve only the double bond.

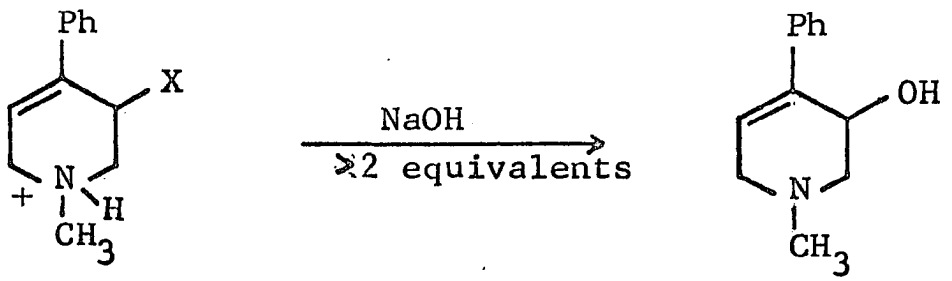


24

The reaction of 1-methyl-3-chloro-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride with more than two equivalents of aqueous alkali proceeded smoothly at 100°. The gas phase chromatographic analysis of the product mixture indicated the presence of only one volatile component which was identified by its infrared spectrum and melting point as 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3). The absence of a five-membered nitrogen heterocycle in the product mixture was assumed to rule out significant participation of the nitrogen in the displacement of chlorine. It is unlikely that an aziridinium ion intermediate such as 24 was involved.

In 1961 Smissman reported that the heating of some esters of 3-piperidinols resulted in ring contraction. In an attempt to determine whether an analogous reaction might occur, the acetate of 3 was distilled. The distillate was collected as one fraction which was shown by vapor phase analysis to be homogeneous. The infrared spectrum and melting point established the identity of this material with the starting material, the acetate of 3. There was no evidence of a thermal rearrangement involving nitrogen participation. That the acetate of 3 also underwent hydrolysis without formation

of an aziridinium ion was demonstrated by the isolation of 3 in good yield as the sole product on treatment of the acetate with excess sodium hydroxide.

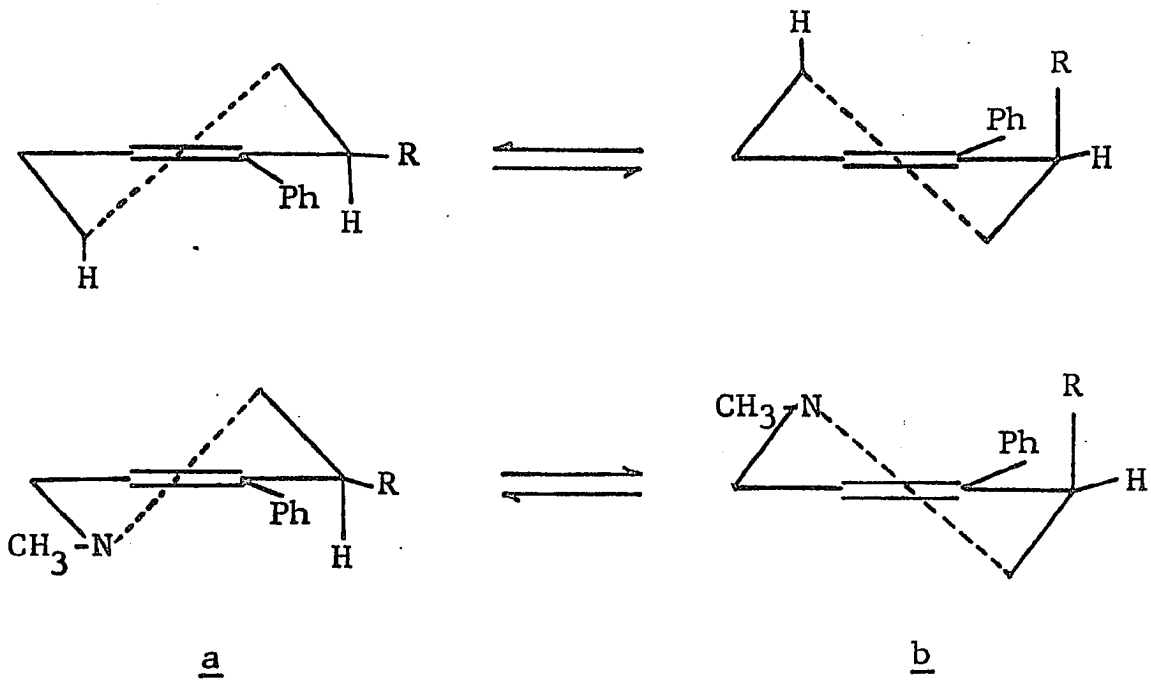


X = -OAc, Br, Cl

Whether the leaving group was acetate, bromide, or chloride ion, or whether the reactant was treated under conditions which would allow nucleophilic substitution or thermal rearrangement, no evidence was found for rearrangement and ring contraction. Therefore, it must be concluded that for the substrates studied the heterocyclic nitrogen does not compete with the 3,4-double bond in assisting nucleophilic displacement at the 3-position.

The Conformation of 3-Substituted-1-methyl-4-phenyl-1,2,3,6-tetrahydropyridines.

Garbisch[54] has shown by nmr spectroscopy that a suitably bulky substituent at the 6-position of a 1-phenylcyclohexene prefers an axial orientation. Johnson and Malhotra[55] suggested that the introduction of the 1,2-double bond causes a decrease in the dihedral angle between the 1- and 6-equatorial substituents and causes an increase in the Pitzer strain. Inversion of configuration from a to b was said to relieve this strain. Strain in b arises primarily from one 1,3-diaxial interaction between R and hydrogen.



a b

3-Substituted-1-methyl-4-phenyl-1,2,3,6-tetrahydropyridines are the nitrogen heterocyclic analogs of these cyclohexenes. Inversion from a to b in this case also relieves the repulsion between the 4-phenyl and 3-equatorial group in a, but now strain in b arises only from a 1,3-diaxial interaction between R and the free pair. The results of the nmr studies of these compounds are summarized in Table III.

It has been found in the cyclohexane series that the band width of an axial proton is generally broader than that of the corresponding equatorial proton. This principle has been successfully extended to cyclohexenes[54] and piperidines.[35] The separation of the terminal peaks of the carbinol protons of cis- and trans-1-methyl-4-phenyl-3-piperidinol have been reported as 8.1 cps and 23.9 cps respectively. These compounds are thought to be conformationally homogeneous[35] and were selected as models.

The small width at half-height (W_H $\leq$ 7.5) of the nmr signals for the 3-protons in the 1,2,3,6-tetrahydropiperidine

Table III

Conformational Preferences of 3-Substituted-1-methyl-4-phenyl-1,2,3,6-tetrahydropyridines

Compound	R	3-Hydrogen τ	3-Hydrogen W_H(cps)	5-Hydrogen τ	5-Hydrogen W_H(cps)	Conformational Preference of R
2	Br	4.81	6.4	3.92	7.4[a]	axial
2 - HBr	Br	4.50	6.0	3.93	7.4[b]	axial
3	OH	5.62	6.4	3.92	7.4[a]	axial
3 - HCl	OH	5.15	6.6	3.98	7.0[a]	axial
3-acetate	OAc	4.05	7.2	3.69	7.0[a]	axial
3-acetate-HBr	OAc	4.00	6.0	3.80	6.1[b]	axial
25	Cl	5.15	7.0	3.98	7.5[a]	axial
25 - HCl	Cl	4.74	6.6	3.98	7.2[a]	axial
8	OH	6.20	8.1[b]	–	–	axial

[a]Separation of the terminal peaks of a quartet.

[b]Separation of the terminal peaks of a multiplet.

is consistent with the assignment of the pseudo-equatorial conformation when compared with the value for the equatorial hydrogen of cis-1-methyl-4-phenyl-3-piperidinol. This indicates that without exception the 3-substituent prefers an axial orientation. This preference appears to be more pronounced in the heterocyclic examples, than in the cyclohexenes studied by Garbisch, since the acetoxy group showed no preference in 1-phenyl-6-acetoxycyclohexene[54a,b], but a very definite axial preference in cis-1-methyl-3-acetoxy-4-phenyl-1,2,3,6-tetrahydropyridine.

It should be pointed out that salt formation causes an unexpected downfield shift of the 3-hydrogen signal except when R = acetoxy. The cause of this shift is not fully understood, but it could result from the removal of a long-range shielding effect of the unbonded pair of electrons.

The conclusion that the 3-chloro, 3-bromo, and 3-acetoxy groups in this 1,2,3,6-tetrahydropyridine system prefer an axial orientation may offer a partial explanation for the failure to observe nitrogen participation in the nucleophilic displacement of these groups. In this conformation the leaving group does not have the proper stereochemistry to permit the nitrogen to assist its departure, while this conformation is favorable for participation of the double bond. That rearrangement of these 3-substituted-1,2,3,6-tetrahydropyridines was not observed probably resulted because conformation a, which would allow nitrogen participation, was energetically less favored than b.

EXPERIMENTAL

General

Melting Points. Melting points were determined using a Kofler Hot-stage melting point apparatus and are uncorrected.

Infrared Absorption Spectra. The infrared spectra were determined using a Perkin-Elmer Model 137B Infracord spectrophotometer equipped with sodium chloride optics or a Perkin-Elmer Model 337 grating infrared spectrophotometer. The spectra of liquids were determined as films and the spectra of solids as double mulls in Halocarbon oil, from 4000 cm^{-1} to 1300 cm^{-1} and in Nujol from 1300 cm^{-1} to 650 cm^{-1}. All spectra in the Appendix were determined using the Perkin-Elmer Model 137B. The Halocarbon oil was from Halocarbon Products Corp., Hackensack, N. J. and the Nujol was from Plough, Inc., San Francisco, Calif.

Ultraviolet Absorption Spectra. The ultraviolet absorption spectra were determined using a Perkin-Elmer Model 4000 spectracord recording spectrophotometer or using a Cary Model 15 recording spectrophotometer. The spectra determined using the Cary Model 15 are indicated by UV^{C}.

Nuclear Magnetic Resonance Spectra. The nuclear magnetic resonance spectra were determined using a Varian Model A-60 Spectrometer. Unless otherwise stated chemical shifts are reported as tau values from TMS as an internal standard. Solvents are indicated with each spectrum reproduced in the Appendix.

Gas Chromatographic Data. The gas chromatographic analyses were determined using a Perkin-Elmer Model 154 Vapor Fractometer or an Aerograph Autoprep Model A-700 using helium as the carrier gas. Mixtures were analyzed using a 1 m. column of Carbowax 20M Chromosorb W in series with a 1 m. column of silicone grease on Haloport F unless otherwise stated.

Elemental Analyses. Elemental analyses were determined by Schwartzkopf Microanalytical Laboratories, Woodside, New York, by Weiler and Strauss Microanalytical Laboratory, Oxford, England, or with a F and M Model 180 carbon, hydrogen, and nitrogen analyzer. The microanalyses determined by Weiler and Strauss are indicated by Found^{WS}; those determined using the F and M are indicated by Found^{FM} and are the average of two or more runs.

The Reaction of 1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine Hydrobromide with Bromine.

1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine (1) Hydrobromide. 1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine (1) hydrobromide was prepared in 51% yield by the method of Schmidle and Mansfield[56], m.p. 225-228°.

1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine-3,5,5-d_3 Deuteriobromide (1-d_3).[32] Dry hydrogen bromide was bubbled into a mixture of 5.0 g. (0.03 mole) of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (1) and 35 ml. of deuterium oxide until homogeneity was achieved and 6.5 g. of hydrogen bromide was dissolved. After the reaction had been standing for 24 hr., the deuterium oxide was removed by distillation under reduced pressure and the residue was dissolved in acetone. The solid which precipitated was collected by filtration and recrystallized from isopropyl alcohol to give 3.8 g. (52%) of (1-d_3) as a white solid, m.p. 222-224°. Deuterium incorporation was judged to be greater than 80% from the decrease in the infrared spectrum of the band at 835 cm^{-1} assigned to the out-of-plane deformation of the vinyl hydrogen. Integration, based on five phenyl protons, of the signal due to unexchanged vinyl protons in the nmr spectrum was in agreement this figure.

1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine-5-d Hydrobromide (1-d_1). Reduction of 4-phenylpyridine methiodide with sodium borohydride in deuterium oxide by the method of Lyle and Anderson[32,52] gave 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine-5-d hydrobromide (1-d_1) in 60% yield, m.p. 222-225°.

1-Methyl-3,4-dibromo-4-phenylpiperidine Hydrobromide (4). The reaction of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (1) hydrobromide[56] with bromine in acetic acid following the procedure of McElvain and Safranski[19] gave 80% of 1-methyl-3,4-dibromo-4-phenylpiperidine hydrobromide (4), m.p. 145-147°.

1-Methyl-3-bromo-4-phenyl-4-piperidinol Hydrobromide (5). (a) The reaction of 1-methyl-3,4-dibromo-4-phenylpiperidine hydrobromide (4), m.p. 145-147° (lit. m.p. 131-132°)[19] with water according to the method of McElvain and Safranski[19] gave 80% of 1-methyl-3-bromo-4-phenyl-4-piperidinol hydrobromide (5), m.p. 195-197°.

Anal. Calcd. for $C_{12}H_{15}Br_2NO$: C, 41.04; H, 4.89. Found: C, 41.16; H, 5.16.

IR Spectrum: See Figure 2, Appendix.

UV Spectrum: $\lambda_{max}^{H_2O}$ 250, 256, 261, 268 mu. (log ϵ 2.17, 2.22, 2.07, 1.77).

(b). A solution of 8.8 g. (0.025 mole) of 1 N hydrobromide in 100 ml. of water in a 500 ml. three-neck flask was treated with a solution of 10 g. of sodium bromide and 5.6 g. (0.028 mole) of bromine in 75 ml. of water added over a period of 1 hr. The solvent was removed at 70° under reduced pressure until precipitation occurred. Filtration and recrystallization from glacial acetic acid gave 11.7 g. (95%) of 5, m.p. 196-197°, identical with that prepared by method a above.

1-Methyl-3-bromo-4-phenyl-4-piperidinol-3,5,5-d_3 Hydrobromide (5-d_3). The reaction of 3.0 g. (0.009 mole) of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine-3,5,5-d_3 deuteriobromide (1-d_3) with bromine-sodium bromide in water according to method b above gave after recrystallization from glacial acetic acid 3.77 g. of 5-d_3 as a white solid, m.p. 199-202°.

IR and NMR Spectra: See Figures 3 and 35, Appendix.

1-Methyl-3-bromo-4-phenyl-4-piperidinol-5-d Hydrobromide (5-d_1). The reaction of 11.3 g. (0.045 mole) of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine-5-d hydrobromide (1-d_1) with sodium bromide-bromine in water according to method b above gave 14.1 g. (89%) of (5-d_1), m.p. 193-196°.

IR Spectrum: See Figure 4, Appendix.

The Preparation and Reactions of 1-Methyl-4-phenyl-3,4-epoxypiperidine.

1-Methyl-4-phenyl-3,4-epoxypiperidine (7). (a). A solution of 75 g. (0.21 mole) of 1-methyl-3-bromo-4-phenyl-4-piperidinol hydrobromide (5) in 800 ml. of water at 50° in a 2 l. flask was treated with 75 ml. of 6 N sodium hydroxide. The mixture was stirred for 0.5 hr. and cooled in an ice bath. Anhydrous potassium carbonate was added until the solution was saturated, and the insoluble solid which precipitated was collected by filtration to give 42.1 g. (104%) 1-methyl-4-phenyl-3,4-epoxypiperidine (7) contaminated by some inorganic salt. The mixture was heated with n-heptane, and the solution was filtered to remove the inorganic compound. The solution was cooled to -70° to give 37.4 g. (93%) of 7 as white crystals, m.p. 45-46.5°.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.16; H, 7.99. Found: C, 76.37; H, 8.05.

IR and NMR Spectra: See Figures 5 and 36, Appendix.

UV Spectrum: $\lambda_{max}^{i\text{-}PrOH}$ 253,258, 264 mu. (log ϵ 2.20, 2.27, 2.13).

(b). The procedure of McElvain and Safranski[19] for the reaction of 5 with base gave an oily product. The oil was

distilled under reduced pressure, and the fraction, b. p. 102-106° at 1.2 mm., 2.5 g. solidified on standing. Recrystallization of the solid from n-heptane gave white crystals which were shown by infrared spectrum and mixture melting point to be identical with the 7 isolated by method a.

(c). To a slurry of 0.75 g. (0.02 mole) of lithium aluminum hydride in 75 ml. of ether contained in a 200 ml. three-neck flask was added 2.0 g. (0.006 mole) of 5. The mixture was stirred for 6 hr. at room temperature, and the excess lithium aluminum hydride was decomposed with water. The precipitate which formed was removed by filtration and was washed carefully with two 10 ml. portions of ether. The combined ether solutions were dried over anhydrous potassium carbonate and evaporated to give 1.02 g. of a yellow oil. Crystallization of the yellow oil from n-heptane gave 0.92 g. (85%) of 7, m.p. 44-46°, identical by infrared spectrum and mixture melting point with that isolated by method a. The analysis of the crude oil by gas chromatography indicated that it contained 7 and the reduction product of 7, cis-1-methyl-4-phenyl-3-piperidinol (8) (vide infra), in a 15:1 ratio.

1-Methyl-4-phenyl-3,4-epoxypiperidine-3,5,5-d_3 (7-d_3). The reaction of 3.30 g. (0.01 mole) of 1-methyl-3-bromo-4-phenyl-4-piperidinol-3,5,5-d_3 hydrobromide (5-d_3) with sodium hydroxide according to method a above gave 7-d_3 was a white solid, m.p. 43-45°, in 86% yield.

IR and NMR Spectra: See Figures 6 and 37, Appendix.

1-Methyl-4-phenyl-3,4-epoxypiperidine-5-d (7-d_1). Treatment of 1-methyl-3-bromo-4-phenyl-4-piperidinol-5-d hydrobromide (5-d_1) with sodium hydroxide according to method a above gave 7-d_1 in 91% yield, m.p. 44-45°.

IR Spectrum: See Figure 7, Appendix.

1-Methyl-4-phenylpiperidine-3,4-diol (12). (a). A solution of 0.5 g. (0.003 mole) of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) 50 ml. 1 N hydrochloric acid was stirred for 10 hr. at room temperature. The mixture was saturated with potassium carbonate and the precipitate which formed was removed by filtration. Recrystallization of the precipitate from acetone gave 0.47 g. (86%) of 12, m.p. 157-159°. This compound appeared to be identical with the compound prepared by McElvain and Safranski[19] and identified as 12.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76. Found[FM]: C, 69.58; H, 8.32; N, 6.50.

IR Spectrum: See Figure 8, Appendix.

(b). To a solution of 3.5 g. (0.02 mole) of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (1) in 4.8 g. trifluoroacetic and 30 ml. acetic acids was added a solution of 5.2 g. of m-chloroperoxybenzoic acid in 25 ml. of acetic acid. The reaction was exothermic and the addition required 0.25 hr. After being stirred at room temperature for 8 hr., the reaction was cooled in an ice bath; 325 ml. of 20% sodium hydroxide was added while maintaining the temperature below 40°. The mixture was extracted four times with 100 ml. portions of ether, and the extracts were dried over potassium carbonate. The solvent was removed under reducted pressure to give 3.15 g. of an oily product. The residue was dissolved in acetone and deposited 1.35 g. (35%) of 1-methyl-4-phenylpiperidine-3,4-diol (12). After recrystallization from acetone, the product was shown by infrared spectroscopy, melting point, and mixture melting point to be identical with the 12 prepared by opening of the epoxide 7.

Reduction of 1-Methyl-4-phenyl-3,4-epoxypiperidine with Complex Metal Hydrides.

cis-1-Methyl-4-phenyl-3-piperidinol (8). (a). To a slurry of 0.75 g. (0.02 mole) of lithium aluminum hydride in 50 ml. of 1,2-dimethoxyethane in a 200 ml. three-neck flask was added 1.0 g. (0.003 mole) of 1-methyl-3-bromo-4-phenyl-4-piperidinol hydrobromide (5). The reaction mixture was heated under reflux for 2 hrs., and after cooling, the excess lithium aluminum hydride was decomposed with water. The precipitate was removed by filtration and was washed three times with 10 ml. portions of ether. The combined ether layers were dried over potassium carbonate and evaporated to give 0.5 g. of a yellow oil. Gas chromatographic analysis of the crude oil indicated that it was a mixture of 8 and trans-1-methyl-4-phenyl-3-piperidinol (9) or 1-methyl-4-phenyl-4-piperidinol (10) in a 3:1 ratio. Crystallization of the oil from n-heptane gave 0.29 g. (58%) of cis-1-methyl-4-phenyl-3-piperidinol (8), m.p. 95-97°.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96.
Found: C, 75.45; H, 8.98.

IR and NMR Spectra: See Figures 11 and 38, Appendix.

(b). A solution of 1.0 g. (0.005 mole) of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) in 10 ml. of ether was added dropwise to a slurry of 0.5 g. (0.013 mole) of lithium aluminum hydride in 50 ml. of anhydrous ether. The reaction was stirred at room temperature for 4 hr., and the excess lithium aluminum hydride was decomposed with water. The precipitate which formed was separated by filtration and washed with two 10 ml. portions of ether. The combined ether extracts were dried over potassium carbonate and evaporated to give as residue 1.0 g. (98%) of 8, m.p. 94-97°. After recrystallization from n-heptane,

the solid melted at 95-97° and was identical with 8 obtained from method a as shown by infrared spectrum and mixture melting point.

(c). A solution of 0.42 g. (0.002 mole of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) and one drop of perchloric acid in 25 ml. of methanol was hydrogenated over 0.023 g. of platinum oxide at room temperature and atmospheric pressure. After exposure to hydrogen for 24 hr., the reaction mixture was filtered, and the filtrate was dried over potassium carbonate and evaporated. The yellow residue was recrystallized from n-heptane to give 0.34 g. (81%) of 8, m.p. 95-97°. The product of this reaction was identical by infrared spectrum and gas chromatographic retention time with that obtained by methods a and b. A mixture melting point with 8 obtained from method a showed no depression.

cis-1-Methyl-4-phenyl-3-piperidinol-3,5,5-d_3 (8-d_3). The reaction of 0.70 g. (0.004 mole) of 1-methyl-4-phenyl-3,4-epoxypiperidine-3,5,5-d_3 (7-d_3) with lithium aluminum hydride according to method b above gave, after recrystallization from n-heptane, 0.66 g. (93%) of 8-d_3, m.p. 104-106°.

IR and NMR Spectra: See Figures 12 and 37, Appendix.

trans-1-Methyl-4-phenyl-3-piperidinol (9). The reaction of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (1)[56] with diborane according to the method of C. K. Spicer[23] gave trans-1-methyl-4-phenyl-3-piperidinol (9) in 30% yield, m.p. 78-82°, after recrystallization from n-heptane.

Attempts to Epimerize trans-1-Methyl-4-phenyl-3-piperidinol (9). (a). The treatment of 9 with aluminum isopropoxide according to the method of Eliel, McCay and Price[26]

resulted only in the recovery of starting material, trans-1-methyl-4-phenyl-3-piperidinol (9), as shown by gas chromatography and infrared spectrum.

(b). The treatment of trans-1-methyl-4-phenyl-3-piperidinol (9) with sodium and 3-pentanol according to the method of Bell and Archer[27] resulted only in the recovery of starting piperidinol (9) as shown by gas chromatography.

Attempts to Epimerize cis-1-Methyl-4-phenyl-3-piperidinol (8). Attempts to epimirize cis-1-methyl-4-phenyl-3-piperidinol (8) by the method of Bell and Archer[27] or by the method of Eliel, McCay and Price[26] resulted in the recovery of the unreacted starting piperidinol 8.

Reaction of 1-Methyl-4-phenyl-3,4-epoxypiperidine (7) with Lithium Aluminum Deuteride. A slurry of 0.31 g. (0.007 mole) of lithium aluminum deuteride in 10 ml. of anhydrous ether was prepared under nitrogen in a three-neck flask equipped with a gas inlet, pressure equalizing dropping funnel, and a condenser. The system was continually swept with nitrogen. A solution of 0.80 g. (0.004 mole) of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) in 20 ml. of anhydrous ether was added, and stirring was continued overnight. The excess lithium aluminum deuteride was hydrolyzed with water and the solid was separated by filtration. The filter cake was washed four times with 15 ml. portions of ether. The combined organic layers were dried over potassium carbonate and evaporated to dryness to give 0.79 g. (97%) of a white solid. Recrystallization of this solid from n-heptane gave 0.75 g. (92%) of 26 as white needles, m.p. 95-97°. The nmr spectrum of these needles had a signal at 6.02 τ (carbinol proton), but not at 7.43 τ (benzylic hydrogen). On this basis the structure of

this compound was assigned as cis-1-methyl-4-phenyl-3-piperidinol-4-d (26).

NMR Spectrum: See Figure IV, Discussion.

1-Phenylcyclohexene Oxide (27). A solution of 10 g. (0.06 mole) of 1-phenylcyclohexene[57] in 100 ml. benzene was placed in a three-neck flask. A solution of 12.4 g. (0.08 mole) of m-chloroperoxybenzoic acid in 100 ml. of benzene was added dropwise over 0.5 hr. The reaction mixture was stirred for 12 hr., during which time a voluminous white solid formed. The solid was removed by filtration. The benzene solution was washed twice with 20 ml. portions of 10% potassium carbonate solution and dried over magnesium sulfate. Evaporation of the solvent from the extracts gave 10.6 g. of a pale yellow oil as residue. Distillation of this oil gave 1-phenylcyclohexene oxide (27) as colorless fraction, 7.25 g. (66%), b.p. 98-101° at 1.0 mm. The infrared showed diagnostic epoxide bands[53b] at 1240, 905, and 820 cm^{-1}.

Reduction of 1-Phenylcyclohexene Oxide (27) with Lithium Aluminum Hydride. To a suspension of 1.0 g. (0.025 mole) of lithium aluminum hydride in 30 ml. of dry ether was added 1.0 g. (0.006 mole) of 1-phenylcyclohexene oxide (27). Stirring was maintained at room temperature for 3 hr. The excess lithium aluminum hydride was hydrolyzed with water and the solid which formed was separated by filtration. The filter cake was washed three times with 20 ml. portions of ether. The combined organic layers were dried over magnesium sulfate and evaporated to give a yellow oil which solidified on standing. Gas chromatographic analysis of the crude product using a 1 m. Carbowax 20M on Chromosorb W column showed

that it contained 1-phenylcyclohexanol and 2-phenylcyclohexanol in a 19:1 ratio. Recrystallization of the solid from n-heptane gave 0.78 g. (78%) of a white solid, m.p. 60-62°, whose infrared spectrum and vpc retention time were identical with that of 1-phenylcyclohexanol (28) prepared by the reaction of phenylmagnesium bromide with cyclohexanone.

Reaction of 1-Methyl-4-phenyl-3,4-epoxypiperidine (7) with Diborane. (a). A large excess of diborane generated externally by the method of H. C. Brown[58], was bubbled through a solution of 11.0 g. (0.06 mole) of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) in 150 ml. of 1,2-dimethoxyethane. The reaction was stirred for 6 hr. The solvent was removed under reduced pressure and the residue was dissolved in methanol. An equal volume of ether was added and the white solid that separated was collected by filtration. Recrystallization of the solid from toluene gave 7.5 g. (64%) of cis-1-methyl-4-phenyl-3-piperidinol (8) amineborane as a white solid, m.p. 137-140° dec.

Anal. Calcd. for $C_{12}H_{20}BNO$: C, 70.92; H, 9.91; N, 6.87. Found[FM]: C, 69.48; H, 10.16; N, 6.89.[44]

IR Spectrum: See Figure 13, Appendix.

Treatment of this compound with 6 N hydrochloric acid gave a white solid, m.p. 103-5°, which was shown to be identical to 8 by infrared spectra.

Treatment of 8 with an excess of diborane in tetrahydrofuran gave a white solid whose infrared spectrum was superimposible on the infrared spectrum of the solid obtained from the reaction of the epoxide 7 with diborane.

(b). A large excess of diborane generated as above was bubbled through a solution of 9.0 g. (0.05 mole) of

1-methyl-4-phenyl-3,4-epoxypiperidine (7) in anhydrous ether. The white solid that formed was collected by filtration. Recrystallization of the solid from ether-petroleum ether gave 5.2 g. (54%) of an amineborane, m.p.105-108°, not identical to the amineborane of 8 isolated from a.

Anal.Calcd. for $C_{12}H_{18}BNO$: C, 71.62; H, 9.00. Found[FM]: C, 70.81; H, 9.17.[44]

IR Spectrum: See Figure 14, Appendix.

Treatment of this compound with 6 N hydrochloric acid also gave cis-1-methyl-4-phenyl-3-piperidinol (8), m.p. 102-5°, which was shown by infrared spectra to be identical to 8 obtained from the reaction of 7 with lithium aluminum hydride.

1,2,2,6,6-Pentamethyl-4-phenyl-1,2,5,6-tetrahydropiperidine (14) Hydrobromide. A mixture of 4.8 g. (0.02 mole) of 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol[59] and 20 ml. of 40% hydrobromic acid were heated on the steambath for 0.5 hr. The water was removed under reduced pressure and the residual oil was dissolved in acetone. Precipitation was forced by the addition of ether. The white solid was collected by filtration and was recrystallized from water to give 4.8 g. (80%) of 14 hydrobromide 249-252°.

Anal. Calcd. for $C_{16}H_{24}BrN$: C, 61.96; H, 7.79. Found[FM]: C, 61.80; H, 7.83.

UV Spectrum: $\lambda_{max}^{H_2O}$ 243 mu (log ε 4.13)

IR and NMR Spectra: See Figures 15 and 34 (free bases), Appendix.

1,2,2,6,6-Pentamethyl-4-phenylpiperidine-3,4-diol (15).

A mixture of 3.7 g. (0.016 mole) of 1,2,2,6,6-pentamethyl-4-phenyl-1,2,5,6-tetrahydropyridine (14) and 2.7 g. (0.024 mole) of trifluoroacetic acid was placed in a 50 ml. three-neck flask along with 0.1 g. of sodium tungstate. A 30% solution of hydrogen peroxide was added and stirring was maintained for 6 hr. The cooled solution was neutralized with 6 N sodium hydroxide solution and the product was salted out with potassium carbonate. The mixture was extracted four times with 25 ml. portions of ether and the organic layers were combined, dried over potassium carbonate, and evaporated to give a yellow oil which partially crystallized on standing. The oil was taken up in cold n-heptane and the solid was collected by filtration. Recrystallization of the solid from n-heptane gave 0.6 g. (12%) of 15 as white needles, m.p. 184-186°.

Anal. Calcd. for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57. Found^{FM}: C, 73.10; H, 9.70.

IR Spectrum: See Figure 16, Appendix.

Attempts to Brominate 1,2,2,6,6-Pentamethyl-4-phenyl-1,2,5,6-tetrahydropyridine (14) Hydrobromide. (a). A solution of 2.0 g. (0.006 mole) of 1,2,2,6,6-pentamethyl-4-phenyl-1,2,5,6-tetrahydropyridine (14) hydrobromide in 100 ml. of water was treated with bromine-sodium bromide in water according to the method of Lyle and Lyle.[60] The addition of the bromine solution caused the formation of an orange gum. The gum was triturated in acetone. The resulting solid was collected by filtration and shown by infrared spectra to be unreacted starting material, the hydrobromide of 14.

(b). A solution of 5.0 g. (0.016 mole) of 14 hydrobromide in 75 ml. of water was heated under reflux. A solution

of bromine-sodium bromide in water was added over 1 hr. The mixture was allowed to cool to 50° and the water was removed under reduced pressure to leave a white solid (sodium bromide) and an orange oil as residue. The oil was dissolved in acetone and separated from the sodium bromide by filtration. Atempts to crystallize the oil from acetone, acetone-ether, and acetonitrile were unsuccessful. The oil decomposed on standing.

The Preparation and Reactions of 1-Methyl-4-phenyl-3-piperidone.

1-Methyl-4-phenyl-3-piperidone (11). A solution of 2.5 g. (0.013 mole) of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) in 25 ml. of ether was placed in a 200 ml. three-neck flask and 35 ml. of boron trifluoride etherate was added over a period of 5 min. The mixture was heated under reflux for 8 hr., cooled, and neutralized with 70 ml. of 6 N sodium hydroxide. Stirring was continued for 1 hr. The layers were separated and the water layer was extracted with four 50 ml. portions of ether and four 50 ml. portions of chloroform. The organic layers were combined, dried over potassium carbonate, and evaporated to give 1.62 g. (65%) of crude 1-methyl-4-phenyl-3-piperidone (11).[45]

The product was characterized as the oxime which was prepared by heating an aqueous methanolic solution of crude 11, 1.04 g. of hydroxylamine hydrochloride, and 0.06 g. of sodium hydroxide. Concentration of the reaction mixture by evaporation gave 0.60 g. (38%) of 11-oxime, m.p. 166-168°, after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90. Found: C, 70.65; H, 8.11.

IR Spectrum: See Figure 10, Appendix.

Distillation of a 10.0 g. sample of the crude oil obtained from method a gave a fraction, 5.2 g. (52%), b.p. 110-4° at 0.1 mm. The gas chromatographic analysis of this fraction using a 1 m. Carbowax 20M column showed that it was a 70/30 mixture of piperidone 11 and 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3).

(b). Concentrated sulfuric acid, 25 ml., was placed in a 50 ml. round-bottom flask and was cooled to below 5° in an ice bath. To this was added 0.95 g. (0.005 mole) of solid 1-methyl-4-phenyl-3,4-epoxypiperidine (7). Stirring was continued for 0.5 hr. The mixture was poured over 100 g. of ice and neutralized in the cold with 50% sodium hydroxide solution. The basic mixture was extracted five times with 50 ml. portions of ether. The combined organic layers were dried over potassium carbonate and evaporated to give 0.7 g. (74%) of a pale yellow oil. Gas chromatographic analysis of this oil using a 1 m. Carbowax 20M column indicated that the product was piperidone 11 and that it was at least 95% pure. The oil was shown by vpc retention time to be identical with 11 prepared by method a.

IR Spectrum: See Figure 9, Appendix.

(c). The reaction of 1-methyl-4-phenylpiperidine-3,4-diol (12) with sulfuric acid using method b gave an oil in 25% yield. This oil was shown by its infrared spectrum to be identical with 11 prepared by method b.

Reduction of 1-Methyl-4-phenyl-3-piperidone (11) with Lithium Aluminum Hydride. A solution of 5.0 g. (0.026 mole) of 1-methyl-4-phenyl-3-piperidone (11) in 15 ml. of 1,2-dimethoxyethane. The reaction mixture was heated under reflux for 1 hr. and the excess lithium aluminum hydride was hydrolyzed with water. The resulting precipitate was separated by

filtration and washed with two 10 ml. portions of ether. The combined ether extracts were dried over potassium carbonate and evaporated to give 3.1 g. (76%) of a yellow oil. Gas chromatographic analysis of the crude oil indicated that it contained cis- and trans-1-methyl-4-phenyl-3-piperidinol in a ratio of 2:5.

A picrate, m.p. 224-230°, isolated from the crude oil, had an infrared spectrum identical with that of the picrate of trans-1-methyl-4-phenyl-3-piperidinol (9), m.p. 226-229°.

The Reduction of 1-Methyl-4-phenyl-3-piperidone (11) with Sodium Borohydride. A solution of 0.25 g. of 1-methyl-4-phenyl-3-piperidone (11) in 10 ml. of 1,2-dimethoxyethane was added to a solution of 0.25 g. of sodium borohydride in 15 ml. of 1,2-dimethoxyethane in a 50 ml. three-neck flask. The mixture was heated under reflux for 2 hr. The excess sodium borohydride was decomposed with 12 ml. of 6 N sodium hydroxide. The water layer was drawn off and extracted three times with 25 ml. portions of ether. The combined ether layers were dried over potassium carbonate and evaporated to give 0.23 g. (90%) of a yellow oil as residue. Gas chromatographic analysis of the crude product indicated that it contained cis- and trans-1-methyl-4-phenyl-3-piperidinol in a ratio of 2:1.

The Reduction of 1-Methyl-4-phenyl-3-piperidone (11) with Diborane. A solution of 0.7 g. of 1-methyl-4-phenyl-3-piperidone (11) in 20 ml. of ether was placed in a three-neck flask equipped with a gas inlet and fitted with a rubber septum. The system was flushed with nitrogen. A syringe was used to add 6 ml. of a 1 M solution of diborane in tetrahydrofuran. The yellow solid which separated was collected by

filtration and hydrolyzed with an excess of 3 N hydrochloric acid. The solution was neutralized with 50% sodium hydroxide and extracted three times with 25 ml. portions of ether. The combined organic layers were dried over potassium carbonate and evaporated under reduced pressure to give 0.6 g. (85%) of a yellow oil. The gas chromatographic analysis of the oil indicated that cis- and trans-1-methyl-4-phenyl-3-piperidinol had been formed in a 1:1 ratio.

The reaction of 1-Methyl-4-phenyl-3-piperidone (11) with Phenylmagnesium Bromide. A solution of 11.8 g. (0.075 mole) of bromobenzene in 100 ml. of ether was added to 1.8 g. (0.075 mole) of magnesium turnings. After all the magnesium had undergone reaction, and ether solution of 4.8 g. (0.025 mole) of 1-methyl-4-phenyl-3-piperidone (11) obtained from method a was added. Stirring was maintained at room temperature for 6 hr. The reaction mixture was poured over 50 g. of ice and 100 ml. of 4 N hydrochloric acid. The water layer was drawn off and the ether layer was extracted twice with 25 ml. portions of 4 N hydrochloric acid. The combined acid layers were neutralized with 50% sodium hydroxide solution and saturated with potassium carbonate. The resulting mixture was extracted four times with 50 ml. portions of ether. The combined ether extracts were dried over potassium carbonate and evaporated to give 4.5 g. (70%) of a dark oil. Gas chromatographic analysis using a 1 m. Silicone GE XE-60 column showed that the ratio of addition products to unreacted starting material was 1:1. It was shown from the retention times of known compounds that under these conditions the starting piperidone 11 and its contaminant, 3, were unresolved. The peak assumed to be addition product was also unresolved.

Analysis using 1 m. Carbowax 20M column resolved the

unreacted starting material but the addition products were not eluted. The ratio of piperidone 11 to tetrahydropyridine 3 was 1:1. These data indicate that the ratio of addition to enolization was 2:1.

Analysis using a 0.5 m. Carbowax 20M column resolved the addition products. Thus the reaction of 11 with phenylmagnesium bromide formed both 17a and 17b. No ratio was determined.

The dark oil was chromatographed over a 40 cm. column of Florisil using ether as the eluent. Fractions were collected every 25 ml., concentrated and analyzed using a 0.5 m. Carbowax 20M column. All fractions containing a single component of similar retention time were combined. The fractions from 325-375 ml., on evaporation, gave a dark oil as residue. The oil was dissolved in acetone and treated with hydrogen chloride. The solid which separated was collected by filtration and recrystallized from ethanol to give 1-methyl-3,4-diphenyl-3-piperidinol (17) hydrochloride, m.p. 262-5°.

Anal. Calcd. for $C_{18}H_{22}ClNO$: C, 71.15; H, 7.30; N, 4.61. Found: C, 71.12; H, 7.35; N, 4.70.

IR Spectrum: See Figure 19, Appendix.

The fractions after 500 ml. gave an oil which solidified on standing. Recrystallization from acetone gave a white solid, m.p. 102-4°. This compound was shown by nmr to be 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-piperidinol (3).

Reaction of 1-Methyl-4-phenyl-3,4-epoxypiperidine with Organometallic Reagents

1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3).

(a). A suspension of 0.30 g. (0.04 mole) of freshly cut lithium ribbon in ether was placed in a 500 ml. three-neck

flask. The system was flushed thoroughly with nitrogen and methyl bromide was bubbled in until all the lithium had undergone reaction. Excess methyl bromide was removed by heating and sweeping with nitrogen for 0.5 hr. A solution of 4.0 g. (0.02 mole) of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) in ether was added dropwise over a period of 0.5 hr., and the mixture was heated under reflux for an additional 12 hr. The unreacted methyllithium was hydrolyzed with water, and the organic material was salted out with potassium carbonate. The water layer was drawn off and extracted three times with 50 ml. portions of ether. The combined organic layers were dried over potassium carbonate and evaporated to give 2.4 g. (60%) of a dark oil. The oil was taken up in an equal volume of n-heptane, and on standing a white solid separated. Recrystallization of the solid from n-heptane gave 1.8 g. (45%) of 3 as white needles, m.p. 104-106°.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.16; H, 7.99. Found: C, 76.31; H, 8.18.

IR and NMR Spectra: See Figures 20 and 28, Appendix.

UV Spectrum: $\lambda_{max}^{i\text{-}PrOH}$ 244 mu (log ϵ 4.06).

Treatment of an acetone solution of the crude product obtained from 5.0 g. (0.03 mole) of 7 with dry hydrogen chloride gave, after recrystallization of the salt from wet isopropyl alcohol, 4.35 g. (73%) of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3) hydrochloride, m.p. 211-214°.

Anal. Calcd. for $C_{12}H_{16}ClNO$: C, 63.85; H, 7.14; N, 6.21. Found [WS]: C, 63.61; H, 7.02; N, 6.30.

IR and NMR Spectra: See Figures 21 and 29, Appendix.

UV Spectrum: $\lambda_{max}^{H_2O}$ 242 mu (log ϵ 4.21).

(b). A solution of 3.1 g. (0.02 mole) of bromobenzene in 15 ml. of ether was added dropwise to a suspension of

0.32 g. (0.04 mole) of freshly cut lithium ribbon in 15 ml. of ether. After all the lithium had undergone reaction, a solution of 2.0 g. (0.01 mole) of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) in ether was added over the period of 0.5 hr. Stirring was maintained at room temperature overnight. The reaction was worked up as in Part a above to give a pale yellow solid. Recrystallization of the yellow material from n-heptane gave 0.90 g. (45%) of a white solid, m.p. 103-105°, identical by infrared spectrum with 3 prepared by method a.

(c). A solution of 3.1 g. (0.02 mole) of bromobenzene in ether was added to 0.5 g. (0.02 mole) of magnesium turnings. As the reaction mixture darkened an additional 30 ml. of ether was added. After all the magnesium had undergone reaction, a solution of 1.9 g. (0.01 mole) of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) in ether was added. Stirring was maintained under reflux overnight. The reaction mixture was cooled and poured over 100 ml. of 4 N hydrochloric acid and 50 g. of ice. The water layer was removed, and the ether layer was extracted twice with 25 ml. portions of 2 N hydrochloric acid. The combined acid layers were neutralized with 50% sodium hydroxide solution and saturated with potassium carbonate. The resulting mixture was extracted four times with 50 ml. portions of ether. The combined ether extracts were dried over potassium carbonate and evaporated to give a dark solid. Recrystallization of this solid from n-heptane gave 1.05 g. (52%) of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3) identical in melting point and infrared spectrum with 3 prepared by methods a and b.

(d). A solution of 0.5 g. (0.0025 mole) of 1-methyl-4-phenyl-3,4-epoxypiperidine (7) in 25 ml. of ether was placed

in a three-neck flask, equipped with a gas inlet and fitted with a rubber septum. The system was flushed with nitrogen, and 2 ml. of 1.6 M solution of n-butyl lithium[61] was added from a syringe. The resulting mixture was stirred at room temperature for 3 hr. and hydrolyzed with water. The water layer was extracted twice with 20 ml. portions of ether. The combined organic layers were dried over potassium carbonate and evaporated to give 0.55 g. of a dark oil. Analysis of the oil by gas chromatography using a 1 m. Silicone GE XE-60 column indicated that the ratio of elimination to presumed addition was 3:1.

(e). The same reaction using t-butyl lithium[62] as the organometallic reagent gave 0.45 g. of a dark oil. Gas chromatographic analysis of this oil indicated that the ratio of elimination to presumed addition was greater than 9:1.

1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol-5-d (3-d_1). The reaction of 1-methyl-4-phenyl-3,4-epoxypiperidine-5-d (7-d_1), m.p. 44-45°, with phenyl lithium as in method b above gave 3-d_1 hydrochloride in 58% yield. Integration of the nmr spectrum indicated 0.5 protons in the vinyl position relative to five phenyl protons. Thus no observable deuterium isotope effect was involved in the elimination process.

The Reaction of 1-Methyl-4-phenyl-3,4-epoxypiperidine (7) with Grignard Reagents at Elevated Temperatures.
(a). A solution of 14.9 g. (0.09 mole) of bromobenzene in 100 ml. of anisole was treated with 2.2 g. (0.09 mole) of magnesium turnings at 150°. After all the magnesium had unergone reaction, an anisole solution of 5.7 g. (0.03 mole) of 1-methyl-4-phenyl-3,4-piperidine (7) was added. The solution was heated under reflux for 5 hr. and cooled to 50° before

being poured over 200 ml. of 4 N hydrochloric acid and 50 g. of ice. The acidic water layer was removed and the organic layer was extracted twice with 50 ml. portions of 2 N hydrochloric acid. The combined acidic water layers were made basic with 50% sodium hydroxide and an excess of potassium carbonate was added. The basic solution was extracted four times with 100 ml. portions of ether. The combined organic layers were dried over potassium carbonate and evaporated to give 6.25 g. of a dark oil. Analysis of the dark oil by gas chromatography using a 1 m. Silicone GE XE-60 column indicated the presence of at least two addition products, together with 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3), the product of elimination. The ratio of addition to elimination was 3:2. Crystallization of the oil from 5 ml. of n-heptane gave a yellow solid. Recrystallization of this solid from ethanol gave 2.1 g. (30%) of a white solid, m.p. 128-135°.

The solid was chromatographed using a 30 cm. column of Florisil with acetone as the eluent. Fractions of 25 ml. were collected, concentrated, and analyzed using a 1 m. Silicone GE XE-60 Column. All fractions containing a single component of similar retention time were combined. The fractions from 325 ml. to 425 ml. gave a white solid. Recrystallization from acetone gave 22 as white crystals, 157-159°. This compound was probably 1-methyl-3,4-diphenyl-4-piperidinol.

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found[WS]: C, 80.81; H, 8.02; N, 5.13.

IR Spectrum: See Figure 18, Appendix.

The fractions after 500 ml. also gave a white solid. Recrystallization from acetone gave 1-methyl-4,4-diphenyl-3-piperidinol (21) as white crystals, m.p. 162-165°; reported m.p. 158-159°.[48]

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found [WS]: C, 80.50; H, 7.93; N, 5.41.

IR Spectrum: See Figure 17, Appendix.

(b). The reaction of 7 with phenylmagnesium bromide at 80° in refluxing 1,2-dimethoxyethane as in a above gave a dark oil. Gas chromatographic analysis of this oil indicated that the ratio of elimination to addition was 3:2.

Control Experiment with 1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3). A solution of 4.71 g. (0.03 mole) of bromobenzene in 50 ml. of anisole was added to 0.73 g. of magnesium turnings and heated to 150°. When all the magnesium had reacted, a solution of 1.90 g. (0.01 mole) of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3) in 25 ml. of anisole was added and stirring was continued for 12 hr. The reaction mixture was cooled and poured over 50 g. of ice and 100 ml. of 4 N hydrochloric acid. The water layer was drawn off and the organic layer was extracted twice with 25 ml. portions of 2 N hydrochloric acid. The combined acid layers were made basic with 50% sodium hydroxide and extracted three times with 75 ml. portions of ether. The combined ether layers were dried over potassium carbonate and evaporated to give 1.80 g. of a yellow solid. This solid was shown by gas chromatography to contain only one component, and a recrystallized sample was shown by its infrared spectrum to be unreacted tetrahydropyridinol, 3. The 1.80 g. represented 95% recovery of 3.

The Hydrogenation of 1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3). (a). A solution of 0.20 g. (1 mmole) of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3) and a drop of perchloric acid in 25 ml. of ether was hydrogenated over 0.022 g. of platinum oxide at room temperature and

atmospheric pressure. After exposure to hydrogen for 36 hr., the reaction mixture was filtered, and the filtrate was dried over potassium carbonate and evaporated to give a yellow oil in virtually quantitative yield. Gas chromatographic analysis of the crude material using a 1 m. Carbowax 20M column indicated that cis- and trans-1-methyl-4-phenyl-3-piperidinol had been formed in a 1:1 ratio.

(b). A solution of 0.1 g. (0.5 mmole) of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridiniol (3) in 10 ml. of 1 N hydrochloric acid was hydrogenated over 0.023 g. of platinum oxide at room temperature and atmospheric pressure. After exposure to hydrogen for 24 hr., the reaction mixture was filtered. The filtrate was saturated with potassium carbonate and extracted four times with 10 ml. portions of ether. The combined ether extracts were dried over potassium carbonate and evaporated to give an oil which gave no evidence of an aromatic ring. The nmr spectrum suggested the presence of a cyclohexyl group and the infrared spectrum gave no indication of a phenyl substituent. The product was probably 1-methyl-4-cyclohexyl-3-piperidinol.

NMR Spectrum: No signal below 6.00 τ; 6.26 τ, carbinol proton; 7.55 τ, hydroxyl; 7.78 τ, N-methyl; 8.00-9.50 τ, methylene plateau. Overall integration showed 23 protons.

Derivatives of 1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol

1-Methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine Hydrobromide (2). (a). A solution of 2.5 g. (7 mmole) of 1-methyl-3,4-dibromo-4-phenylpiperidine hydrobromide (4) in 20 ml. of glacial acetic acid was heated on a steambath under reduced pressure. Heating was continued until the acetic acid had been removed and the molten residue had become solid, about 0.75 hr. Recrystallization of the solid from glacial acetic

acid gave 1.2 g. (60%) of 2, m.p. 186-188°.

Anal. Calcd. for $C_{12}H_{15}Br_2N$: C, 43.27; H, 4.54; N, 4.21. Found[WS]: C, 43.87; H, 4.87; N, 4.11.

IR and NMR Spectra: See Figures 25, 32, and 33, Appendix.

UV Spectrum: λ_{max}^{EtOH} 243 mu. (log ε 4.09).

(b). Phosphorus tribromide, 20 ml., was cooled to 5° and 1.90 g. (0.01 mole) of solid 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3) was added. After 1 hr. at 5° the reaction mixture was allowed to warm to room temperature and to stand overnight. Ether was added to force precipitation and the solid was collected by filtration. The crude material was triturated in methanol, isolated by filtration, and recrystallized from glacial acetic acid to give 2.6 g. (78%) of 2 as a white solid, m.p. 185-188°. This solid was shown by infrared spectrum and mixture melting point to be identical with 2 prepared by method a.

The Reaction of 1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine-5-d Hydrobromide with bromine by the method of McElvain and Safranski[19] followed by heating as in a above gave a white solid, m.p. 185-188°. The nmr spectrum of this solid was similar to that of undeuterated 2 prepared by method a above. However, integration of this spectrum showed approximately 0.75 protons at both the 3- and the 5-position. Thus the deuterium was distributed evenly over the two positions involved.

1-Methyl-3-chloro-4-phenyl-1,2,3,6-tetrahydropyridine (25) Hydrochloride. A solution of 12.25 g. (0.05 mole) of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3) hydrochloride in 100 ml. of thionyl chloride was heated under reflux

for 5 hr. The thionyl chloride was removed under reduced pressure and 40 ml. of n-heptane was added and removed by distillation. Crystallization of the residue from acetone gave 11.2 g. (85%) of [illegible] hydrochloride of 25, and recrystallization from dimethylformamide gave 10.1 g. (76%) of 25 hydrochloride as white crystals, m.p. 198-199°.

Anal. Calcd. for $C_{12}H_{15}Cl_2N$: C, 59.02; H, 6.19. Found[FM]: C, 59.58; H, 6.37.

IR and NMR Spectra: See Figures 23, 30, and 31, Appendix.

UV Spectrum. $\lambda_{max}^{H_2O}$ 243 mu. (log ϵ 4.09).

The Reaction of 1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol-5-d Hydrochloride with thionyl chloride by the method above gave 1-methyl-3-chloro-4-phenyl-1,2,3,6-tetrahydropyridine-d hydrochloride in 69% yield. Integration of the nmr spectrum of the free base indicated that the deuterium label was divided evenly between the 3- and 5-positions.

1-Methyl-3-chloro-4-phenyl-1,2,3,6-tetrahydropyridine (25) Hydrotosylate. A solution of 4.5 g. (0.02 mole) of 3 hydrochloride in 150 ml. of dimethylformamide was heated at 50° overnight with 9.5 g. of p-toluenesulfonyl chloride. After cooling, the mixture was poured into 500 ml. of ether. The solid which formed was separated by filtration and recrystallized from isopropyl alcohol to give the hydrotosylate of 25 as a white solid, m.p. 199-202°.

Anal. Calcd. for $C_{19}H_{22}ClNO_3S$: C, 60.06; H, 5.83. Found[FM]: C, 60.15; H, 5.99.

Treatment of 25 hydrotosylate with base gave a yellow oil whose infrared spectrum was identical with that of the free base obtained on treating the hydrochloride of 25 with

base.

IR Spectrum: See Figure 24, Appendix.

The Reaction of 1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol-5-d (3) Hydrochloride with p-toluenesolfonyl chloride by the method above gave 1-methyl-3-chloro-4-phenyl-1,2,3,6-tetrahydropyridine-d hydrotosylate. Recrystallization of this solid from wet isopropyl alcohol gave white plates, m.p. 202-203°. Integration of the nmr spectrum of the free base indicated that the deuterium label was divided evenly between the 3- and 5-positions.

1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3) Acetate Hydrobromide. A solution of 8.5 g. (0.045 mole) of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3) and 1.5 g. of sodium acetate in 60 ml. of acetic anhydride was heated under reflux for six hr. and cooled in an icebath. The mixture was made basic with an excess of potassium carbonate and the water layer was extracted three times with 50 ml. portions of ether. The combined organic layers were dried over potassium carbonate and evaporated to give a dark oil. Dissolution of this oil in acetone followed by treatment with hydrogen bromide gave, in three crops, 11.5 g. (81%) of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3) acetate hydrobromide. Recrystallization from ethanol gave an analytical sample, m.p. 230-232°.

Anal. Calcd. for $C_{14}H_{18}BrNO_2$: C, 53.86; H, 5.81; N, 4.49. Found[WS]: C, 53.88; H, 5.87; N, 4.74.

IR Spectrum: See Figure 26, Appendix.

UV Spectrum. $\lambda_{max}^{H_2O}$ 240 mu. (log ϵ 4.07).

The Solvolysis of 1-Methyl-3-chloro-4-phenyl-1,2,3,6-tetrahydropyridine (25) Hydrobromide. A solution of 0.8 g. (0.02 mole) of sodium hydroxide in 10 ml. of water was added to 1.0 g. (4 mmole) of 25 hydrochloride in 10 ml. of water. The mixture was heated at 80° for 1 hr., cooled and extracted four times with 50 ml. portions of ether. The combined organic layers were dried over potassium carbonate and evaporated to give 0.75 g. (100%) of a yellow solid. Gas chromatographic analysis of this solid on a 1 m. Carbowax 20M column indicated that it contained only one volatile component. Recrystallization of this solid from n-heptane gave 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3), m.p. 101-103°, as shown by vpc retention time and infrared spectrum.

The Solvolysis of 1-Methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine Hydrobromide (2). (a). A solution of 0.5 g. (0.5 mmole) of 2 in 15 ml. of water was heated on a steam-bath for 0.5 hr. The solution was cooled, neutralized with excess potassium carbonate, and extracted with three 20 ml. portions of ether. The combined ether extracts were dried over potassium carbonate and evaporated to give 0.27 g. (95%) of a yellow solid. Gas chromatographic analysis on a 1 m. Carbowax 20M column indicated the presence of only one volatile compound in the reaction mixture. Recrystallization of the solid from n-heptane gave 0.23 g. (83%) of 3, m.p. 101-103°, as shown by infrared spectrum and vpc retention time.

(b). A solution of 0.3 g. (8 mmole) of sodium hydroxide in 5 ml. of water was added to a solution of 1.0 g. (3 mmole) of 2 in 50 ml. of water and stirring was maintained at room temperature for 2 hr. The mixture was extracted five times with 25 ml. portions of ether. The combined extracts were dried over potassium carbonate and evaporated to give 0.40 g. (70%) of a pale, yellow solid. Analysis of the crude

product by vapor phase chromatography indicated the presence of only one volatile component. Recrystallization of the solid from n-heptane gave 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3), m.p. 99-102°, as shown by vpc retention time and infrared spectrum.

The Reaction of 1-Methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine Hydrobromide Under Apparent S_N1 Conditions. To a mixture of an aqueous solution of potassium carbonate and ether was added 1.0 g. (3 mmole) of 1-methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine hydrobromide (2). The mixture was shaken until, on standing, both layers were homogeneous. The water layer was drawn off and the ether layer was dried over potassium carbonate. The organic layer was evaporated and the solid residue was triturated with acetone. Recrystallization from water gave 0.2 g. (18%) of a white solid, m.p. 238-241°. The infrared spectrum of the solid had a broad band at 3400 cm^{-1}: the elemental analyses were correct for a dimer plus a molecule of water, and the ultraviolet spectrum indicated the presence of two isolated styryl groups. A likely structure for this compound is 1-methyl-1-[5-(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridyl)]-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridinium bromide monohydrate (23).

Anal. Calcd. for $C_{24}H_{30}Br_2N_2O$: C, 55.19; H, 5.79; N, 5.36; Br, 30.60. Found[WS]: C, 54.92; H, 5.96; N, 4.73. Found(Mohr Method): Br, 30.85.

IR Spectrum: See Figure 27, Appendix.

UV Spectrum: $\lambda_{max}^{H_2O}$ 245 mu. (log ε 4.34).

The Attempted Thermal Rearrangement of 1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol Acetate. A sample of the acetate of 3, m.p. 78-80°, was distilled under aspirator pressure. The distillate was collected as a single fraction

with the largest amount boiling from 177-179°. The product was identified by its vpc retention time and infrared spectrum as the unrearranged acetate of 3. The analysis by gas chromatography showed that within the limits of detection no rearrangement had occurred.

The Hydrolysis of 1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3) Acetate. A mixture of 1.1 g. (5 mmole) of the acetate of 3 and water was heated above the melting point of the organic material and a solution of 0.8 g. of sodium hydroxide in 5 ml. of water was added. The mixture was heated under reflux for 24 hr. and cooled to 10° in an icebath. The solid which separated was collected by filtration, dissolved in ether, and dried over potassium carbonate. The vapor phase chromatographic analysis of this solution indicated the presence of only one volatile component which was identified by its retention time as 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3). Evaporation of the ether gave a white solid, m.p. 101-104°, after recrystallization from n-heptane. This solid was shown by infrared spectrum to be 3.

SUMMARY

1. 1-Methyl-3,4-dibromo-4-phenylpiperidine hydrobromide (4), m.p. 131-132°, was reported to isomerize to a higher melting form, m.p. 189-191°. Repetition of this reaction in this laboratory indicated that a chemical, not a physical change was involved and that dehydrohalogenation had occurred to give 1-methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine hydrobromide (2).

2. Treatment of the dibromide 4, m.p. 131-132°, 1-methyl-3-bromo-4-phenyl-4-piperidinol hydrobromide with water gave (5), not 2, as previously reported, and the reaction of 5 with base gave 1-methyl-4-phenyl-3,4-epoxypiperidine (7), not 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3), as previously reported. The nmr, infrared, and ultraviolet spectra supported these assignments.

3. The piperidine ring structure in these compounds was established by relating them to compounds of known structures or to materials synthesized unambiguously from other six-membered nitrogen heterocycles.

4. In contrast to the reduction of 1-phenylcyclohexene oxide, the reduction of the epoxide 7 with lithium aluminum hydride involved nucleophilic displacement of oxygen from carbon-4 rather than from carbon-3. The exclusive product of this reduction was cis-1-methyl-4-phenyl-3-piperidinol (8).

5. Analogs of 1-methyl-3-bromo-4-phenyl-4-piperidinol hydrobromide (5); 1-methyl-4-phenyl-3,4-epoxypiperidine (7); and cis-1-methyl-4-phenyl-3-piperidinol (8) were prepared in which the 3- and 5-positions had been replaced by

deuterium. The nmr spectrum of each exhibited an AB pattern assigned to the protons of the 2-methylene. The signal of the two protons at C-6 was a broad singlet in the case of both 1-methyl-3-bromo-4-phenyl-4-piperidinol hydrobromide (5) and 1-methyl-4-phenyl-3,4-epoxypiperidine (7), but in the case of cis-1-methyl-4-phenyl-3-piperidinol (8), and AB pattern was observed. The magnetic nonequivalence of the 6-methylene group of 8 was attributed to a hydrogen bonded retardation of the chair-chair equilibrium. In this rigid conformation the equatorial hydrogens at carbons-2 and -6 occupy the ends of a "W" and long range coupling was observed.

6. The reaction of 7 with organometallic reagents at room temperature gave only the elimination product, 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3), although some addition was observed at higher temperatures.

7. The bromo, chloro, and acetate derivatives of 3 were prepared and reacted with base under S_N2 conditions. In each case careful analysis of the product mixtures failed to show the presence of a pyrrolidine, and thus no evidence for the intermediacy of an aziridinium ion was found. An attempted thermal rearrangement of the acetate also failed to give any evidence of nitrogen participation. It was concluded that the heterocyclic nitrogen does not compete effectively with the 4,5-double bond in assisting displacement at the 3-position of 1,2,3,6-tetrahydropyridines. This result was explained, in part, by unfavorable conformational features in 3-substituted-4-phenyl-1,2,3,6-tetrahydropyridines.

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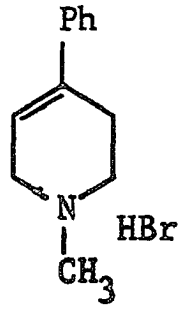
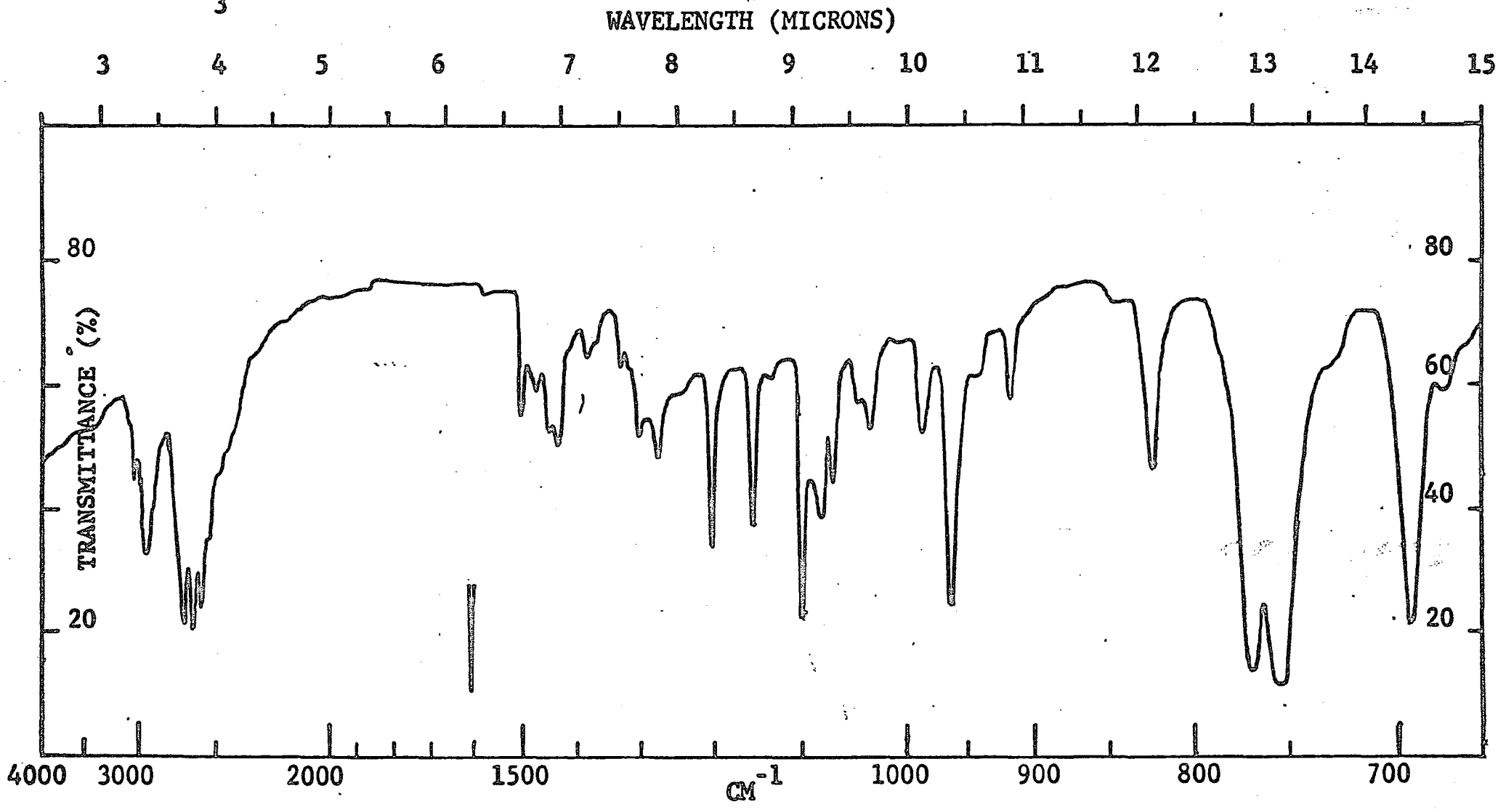


Figure 1

1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine (1) Hydrobromide



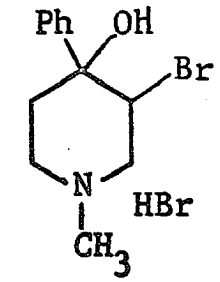
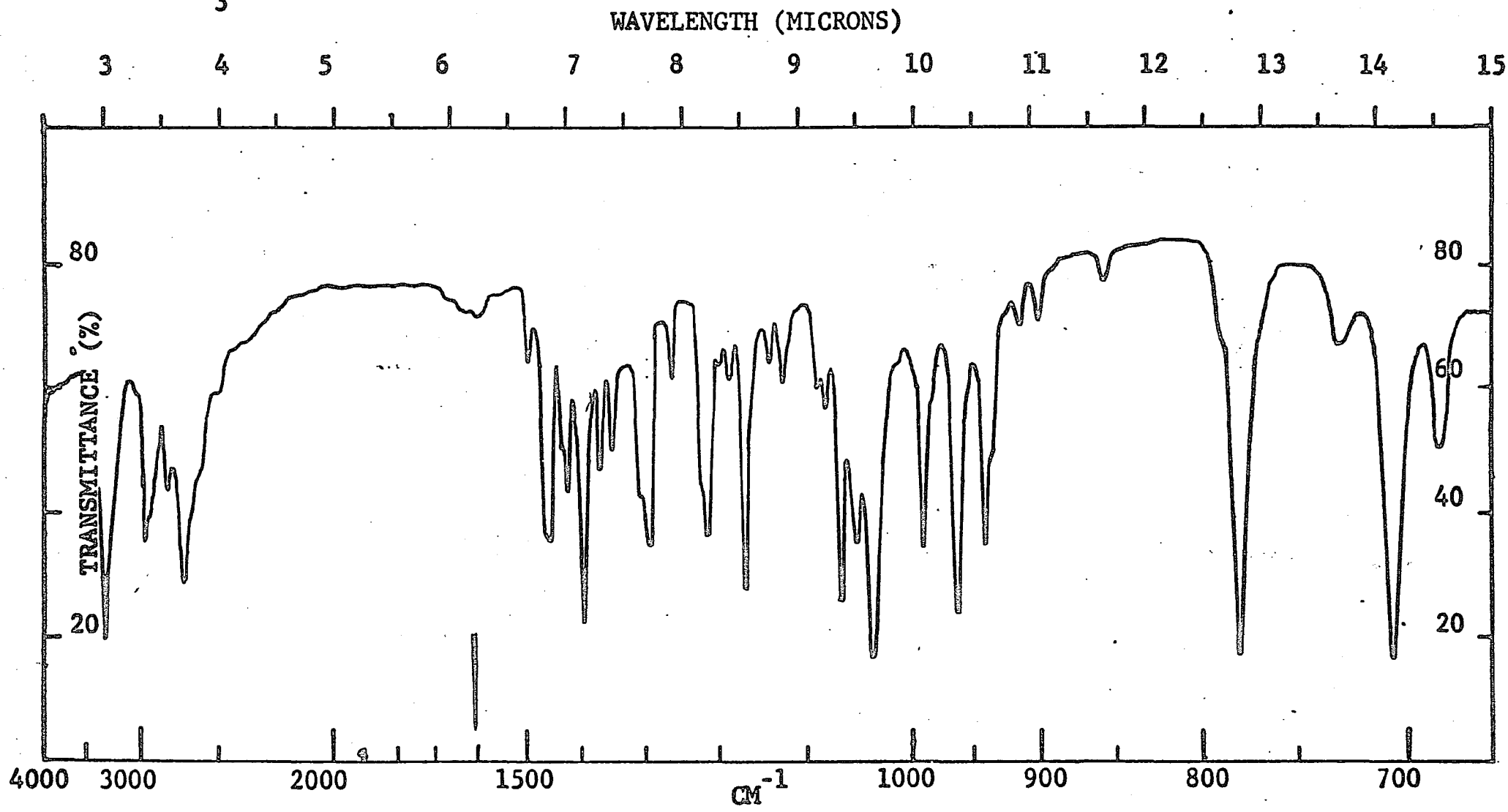


Figure 2

1-Methyl-3-bromo-4-phenyl-4-piperidinol

Hydrobromide (5)



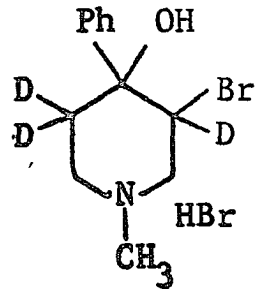
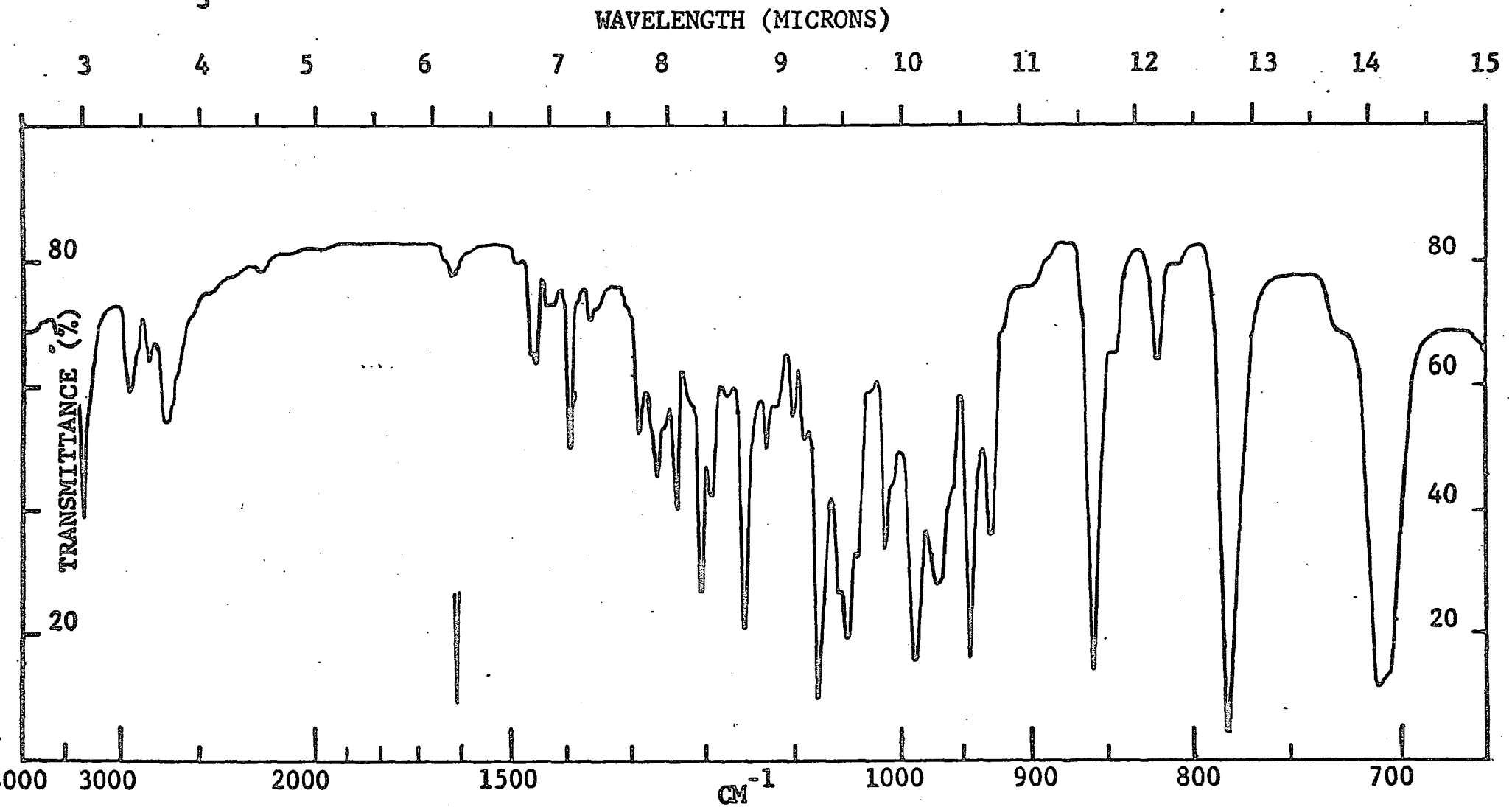


Figure 3

1-Methyl-3-bromo-4-phenyl-4-piperidinol-3,5,5-d_3 Hydrobromide ($\underline{5}$-$\underline{d}_3$)



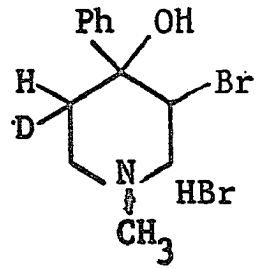


Figure 4

1-Methyl-3-bromo-4-phenyl-4-piperidinol-5-d_1

Hydrobromide (5-d_1)

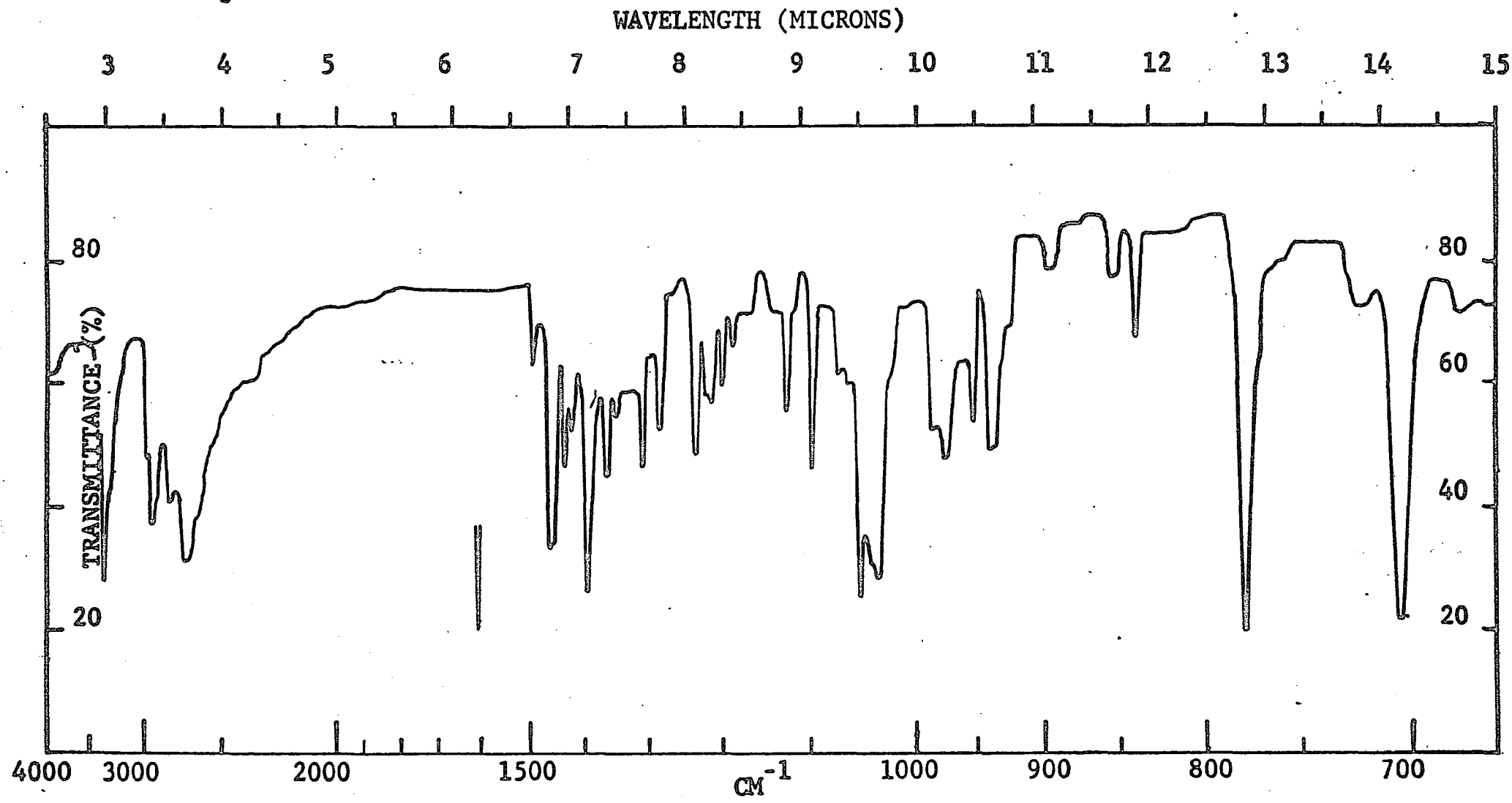
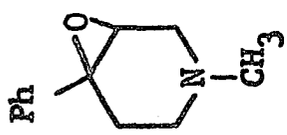


Figure 5

1-Methyl-4-phenyl-3,4-epoxypiperidine (7)



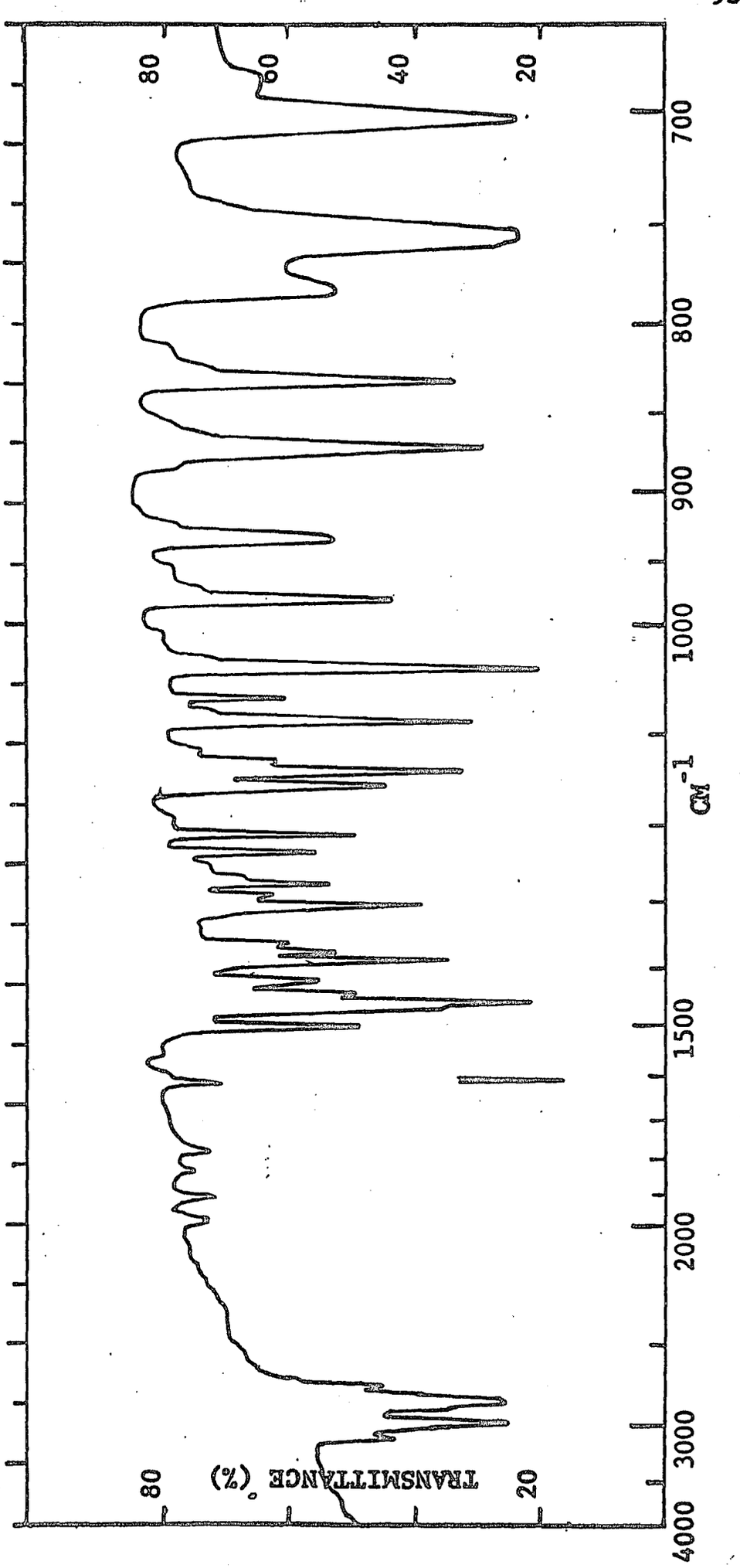
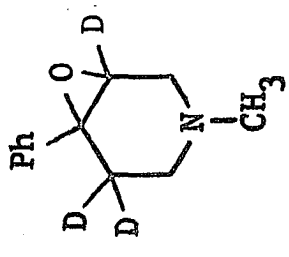


Figure 6

1-Methyl-4-phenyl-3,4-epoxypiperidine-3,5,5-d_3 (7-d_3)



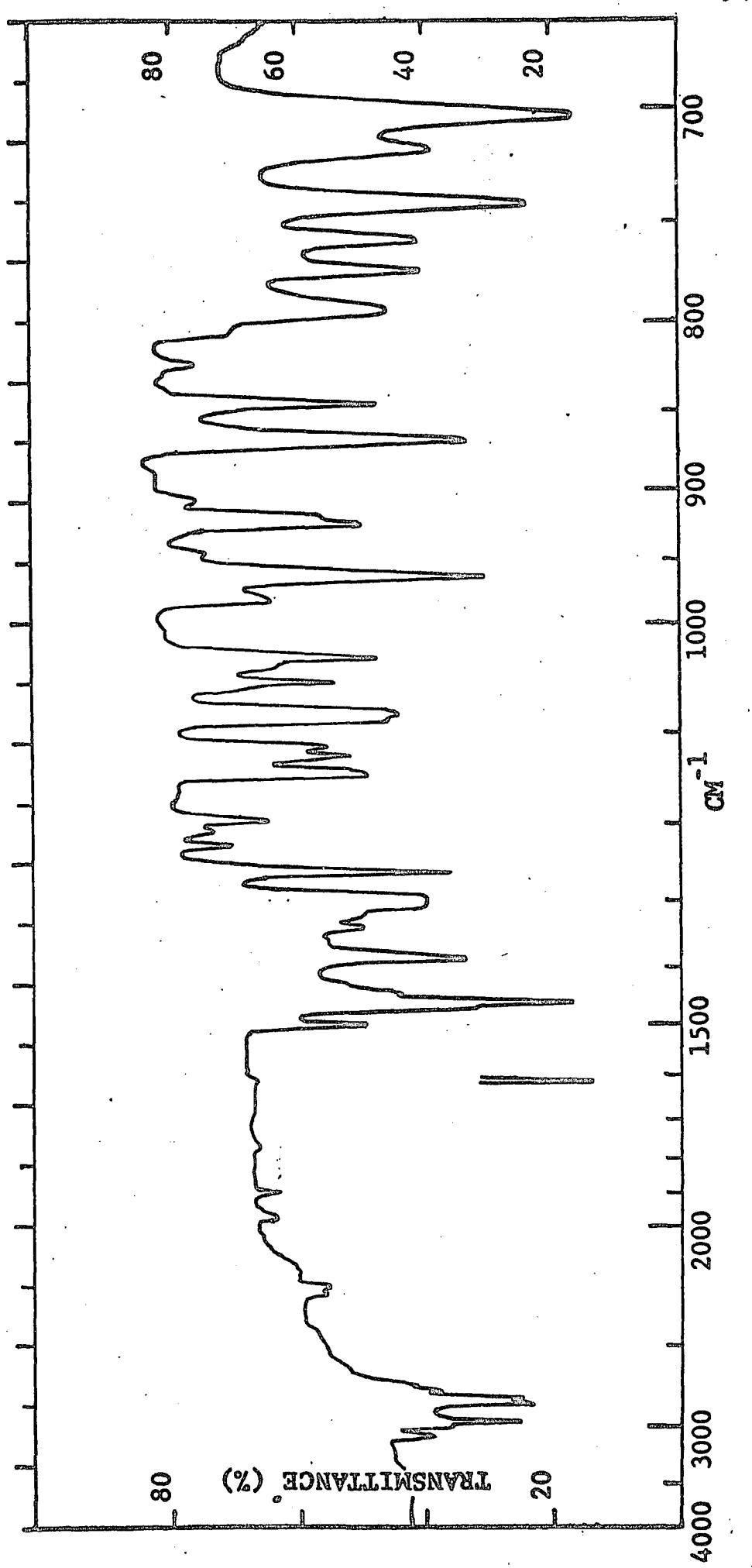
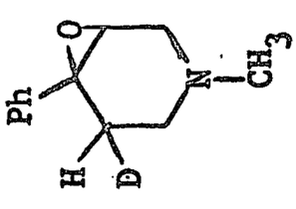
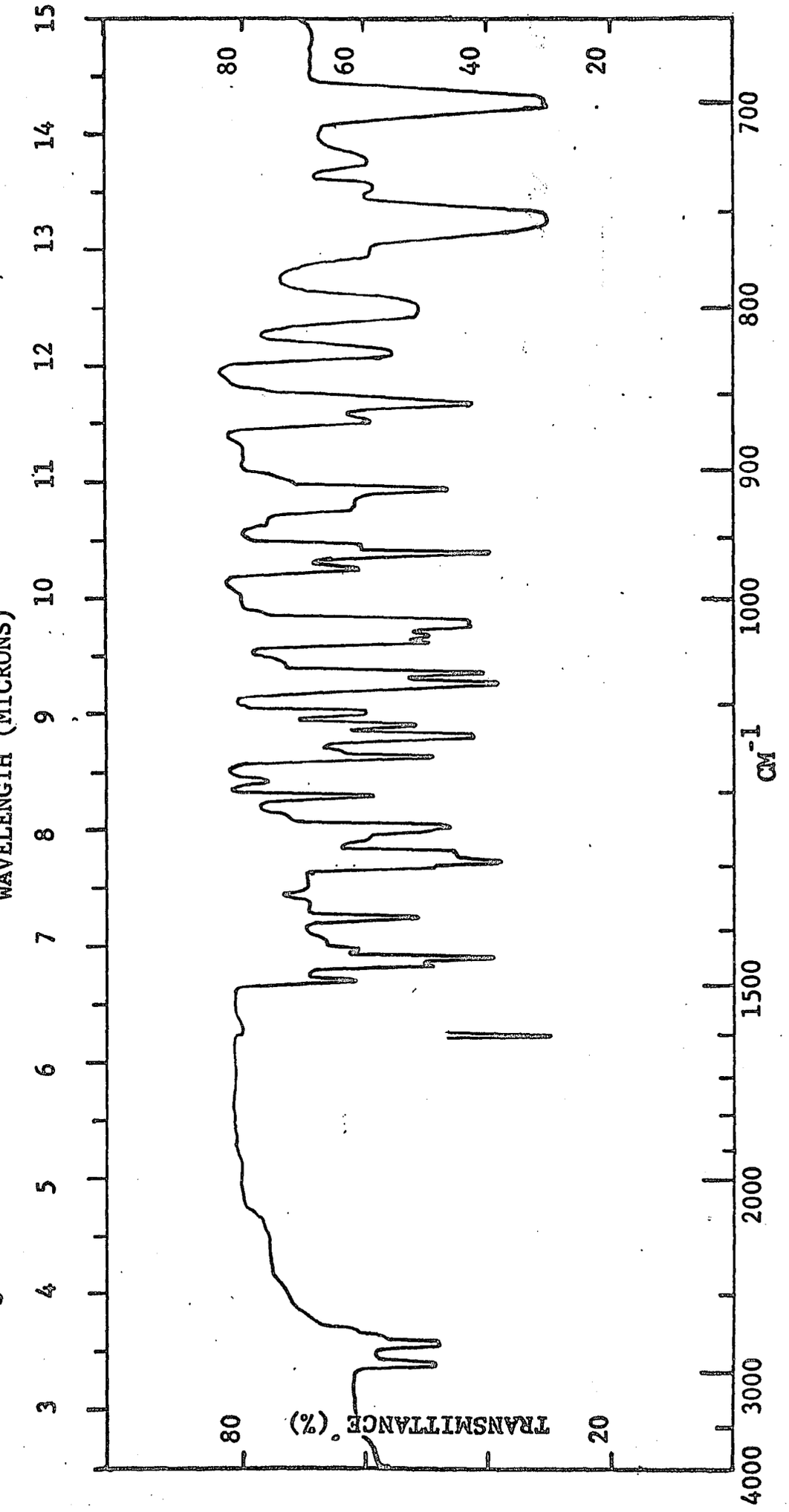


Figure 7

1-Methyl-4-phenyl-3,4-epoxypiperidine-5-d ($\underline{7}$-d_1)





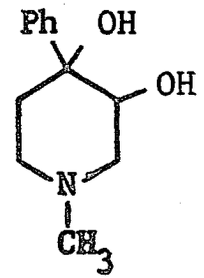


Figure 8

1-Methyl-4-phenylpiperidine-3,4-diol (12)

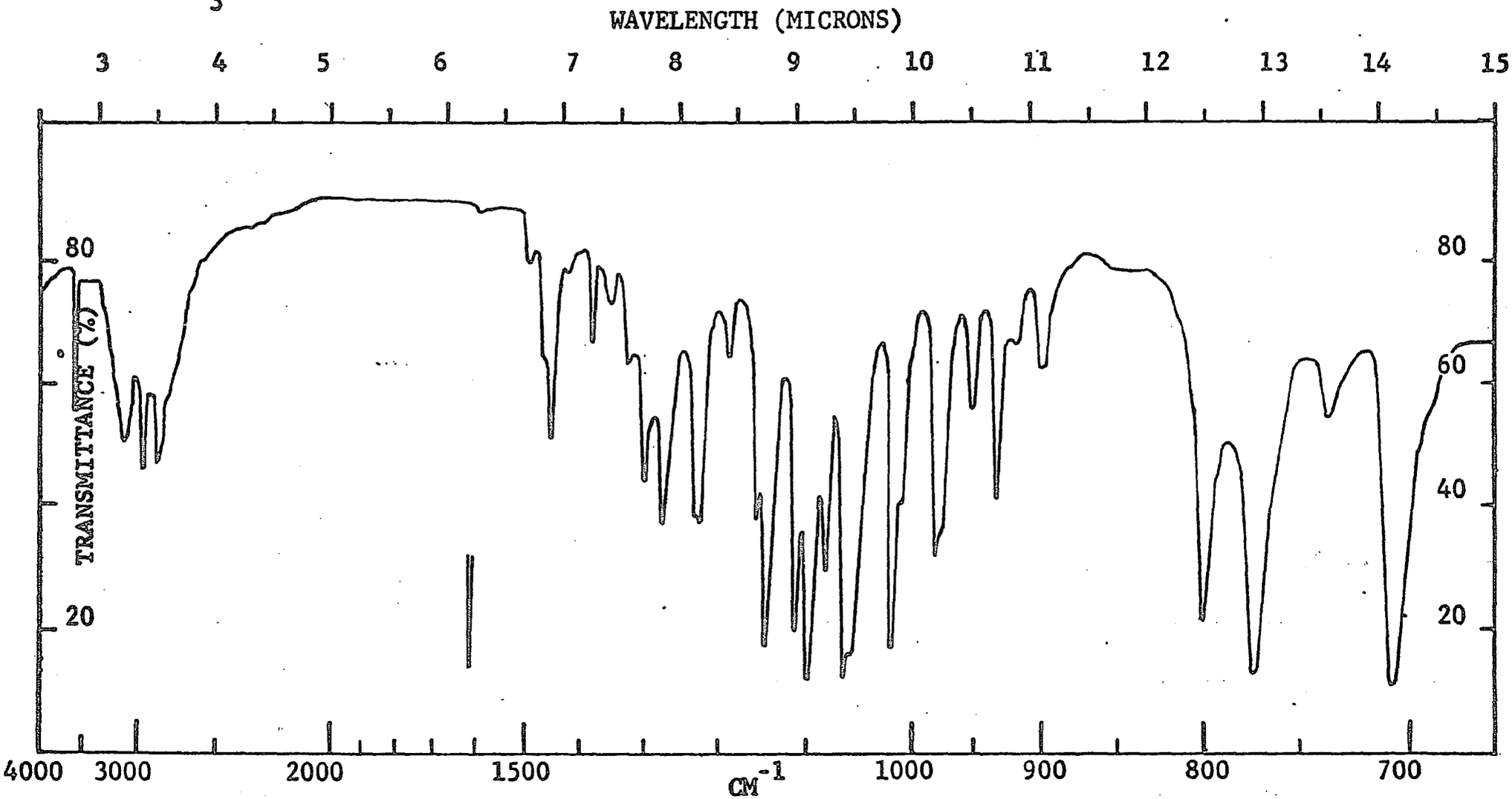
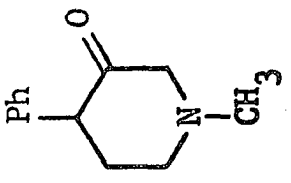
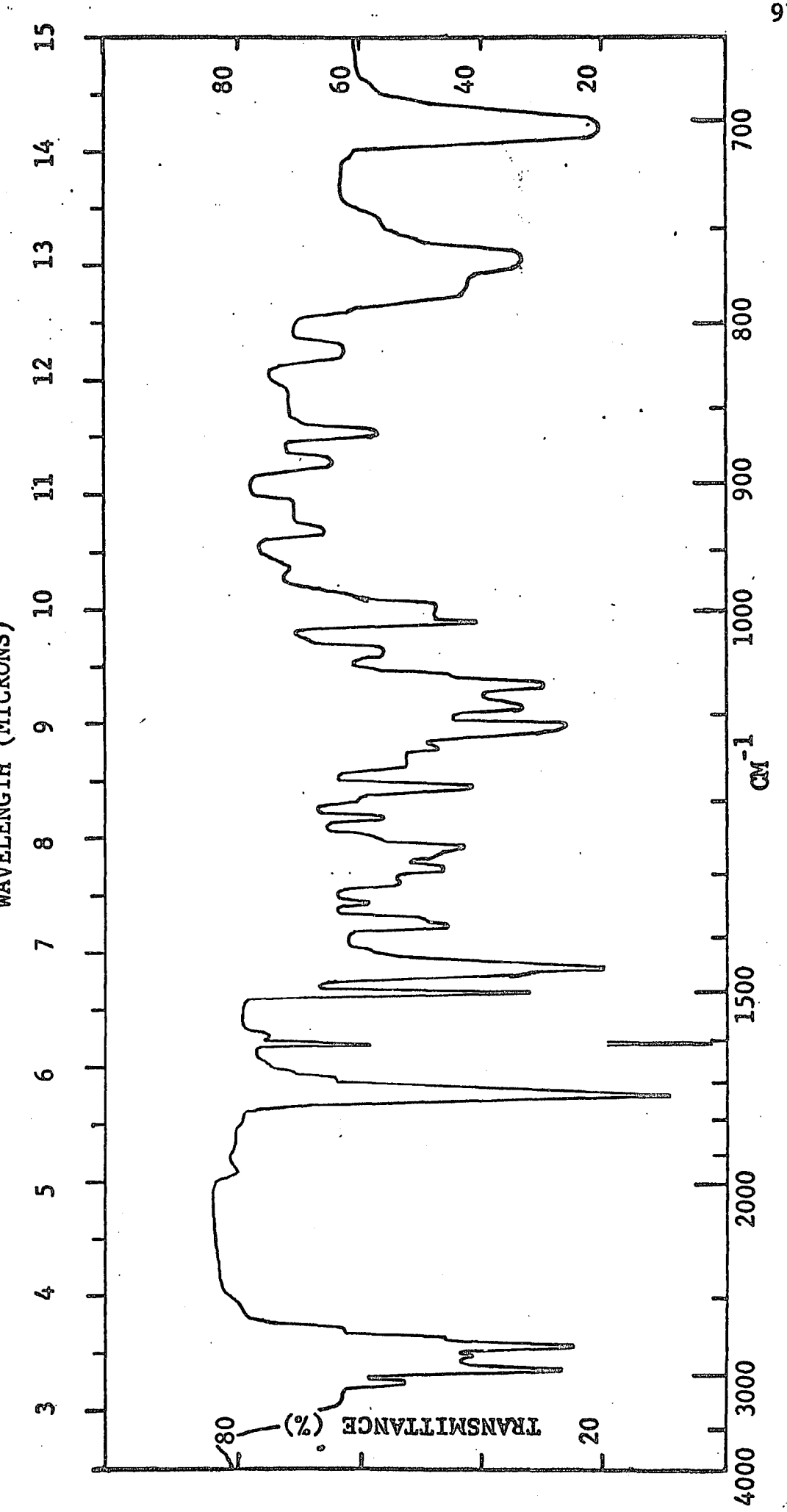


Figure 9

1-Methyl-4-phenyl-3-piperidone (11)





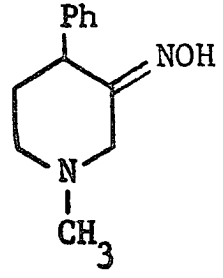


Figure 10

1-Methyl-4-phenyl-3-piperidone Oxime

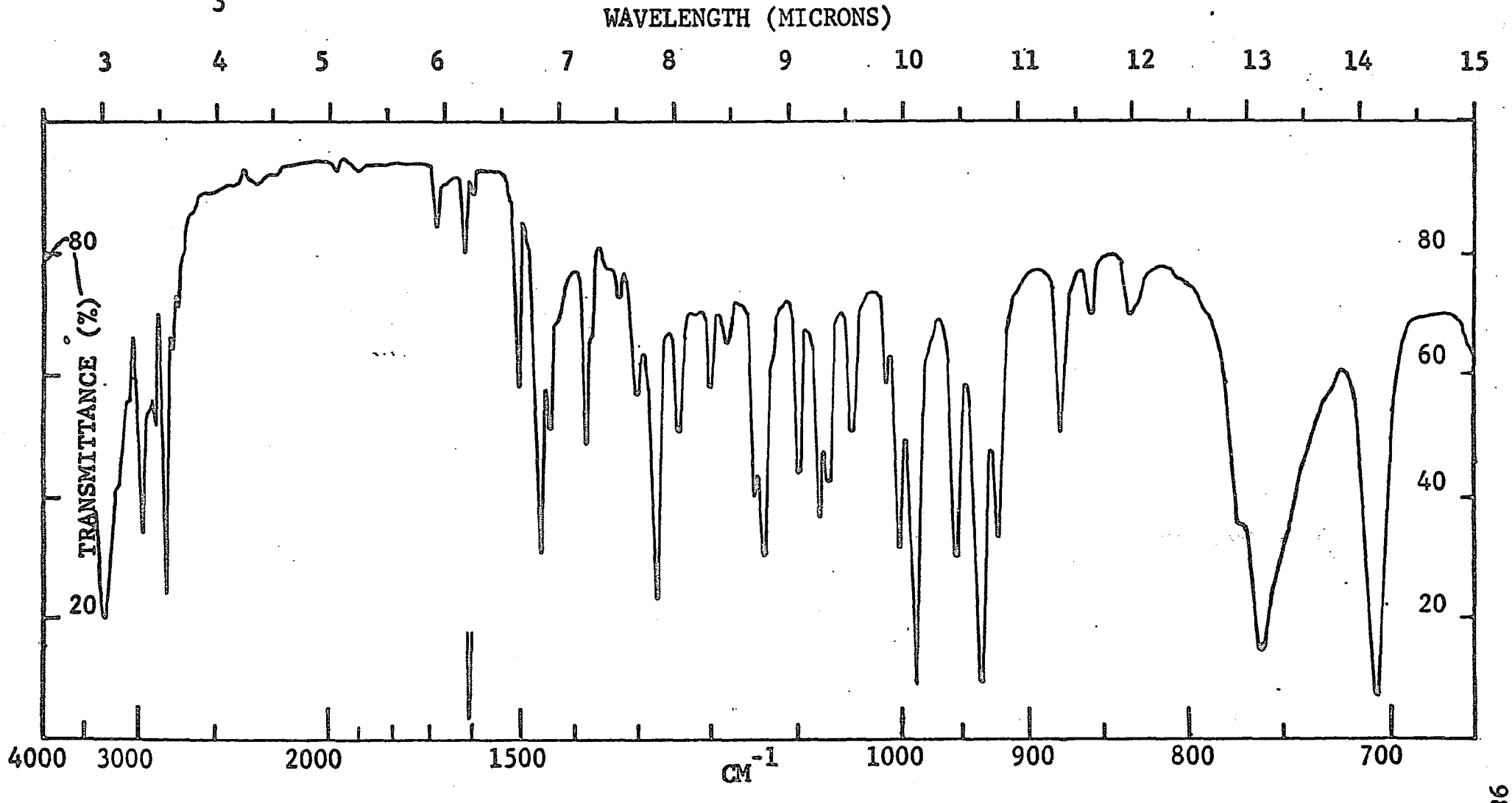
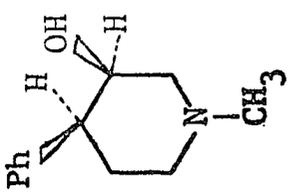
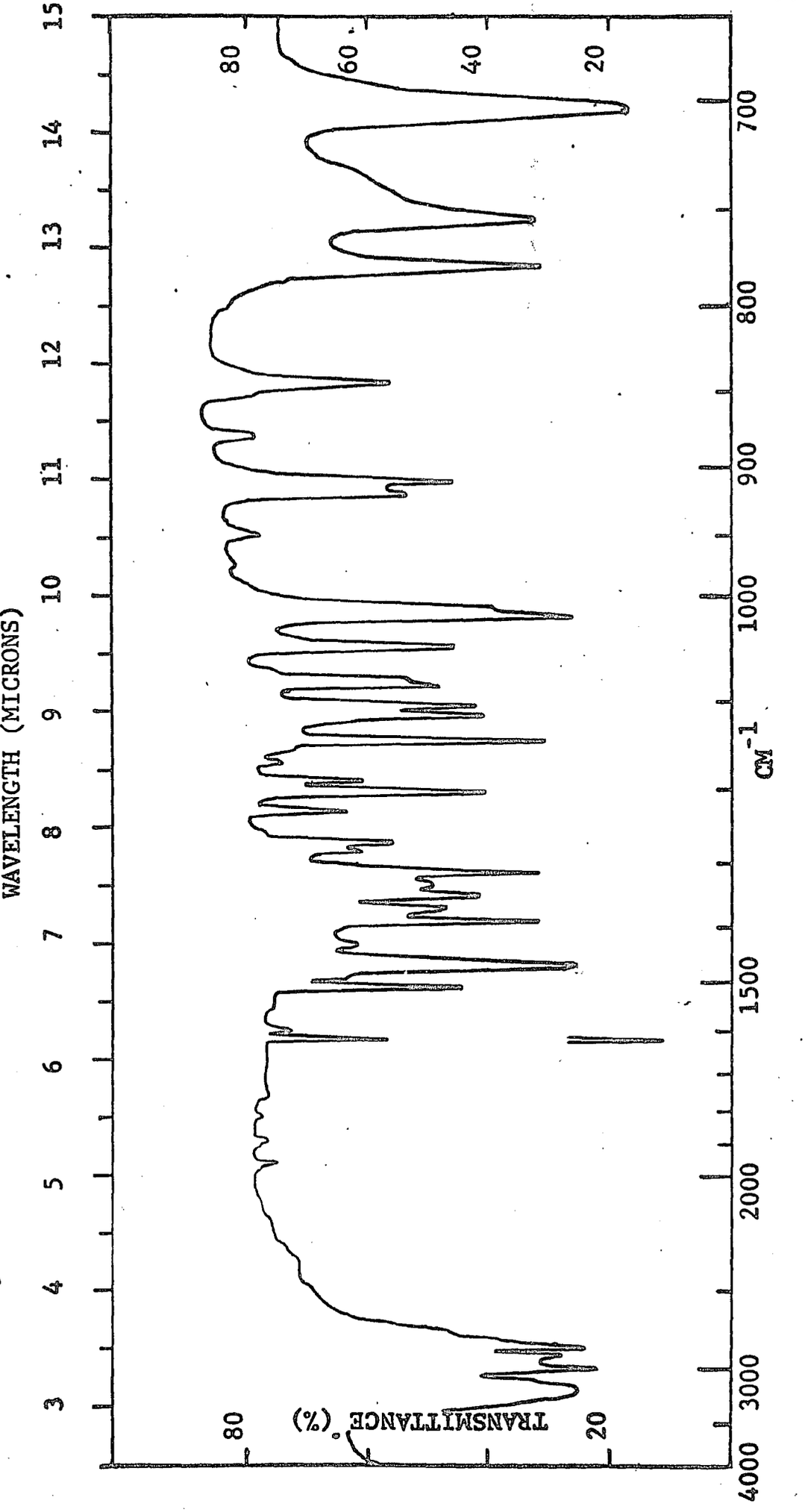


Figure 11

cis-1-Methyl-4-phenyl-3-piperidinol (8)





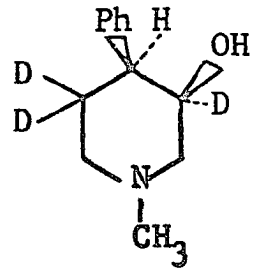
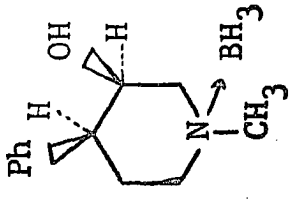


Figure 12

cis-1-Methyl-4-phenyl-3-piperidinol-3,5,5-d_3 (8-d_3)

Figure 13

cis-1-Methyl-4-phenyl-3-piperidinol Amineborane



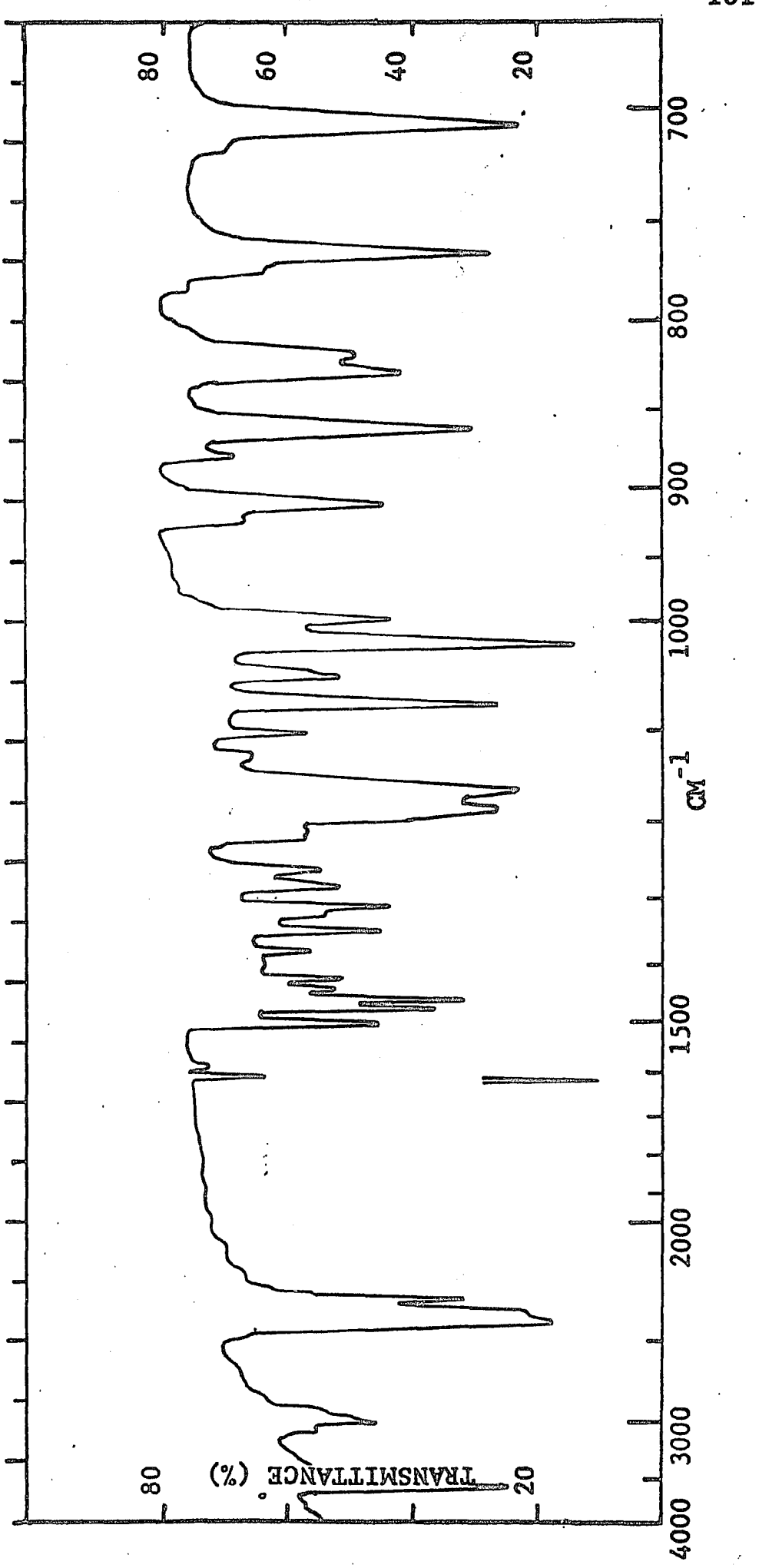
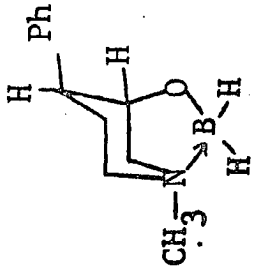


Figure 14

Dehydrato-cis-1-methyl-4-phenyl-3-piperidinolatoboron (16)



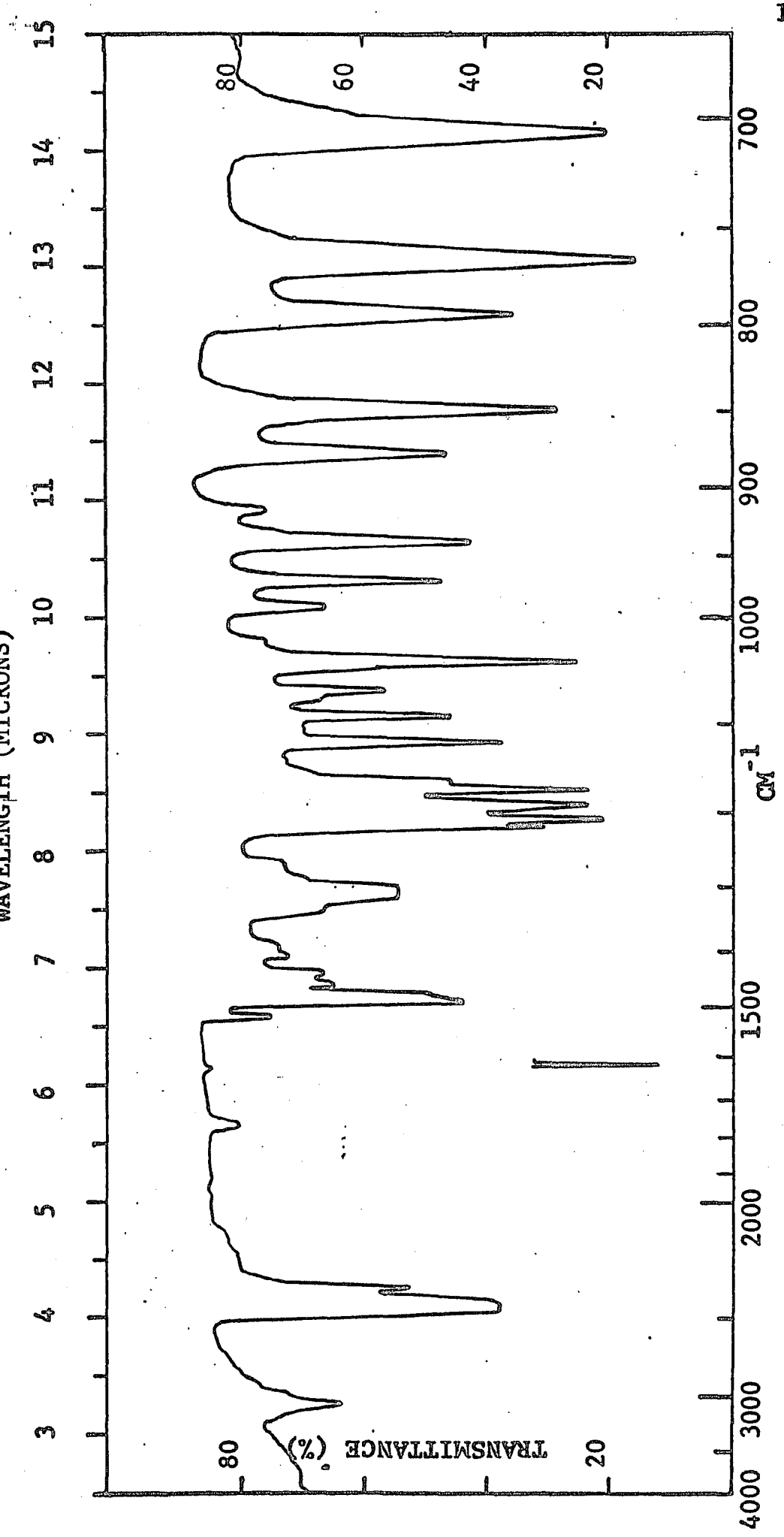
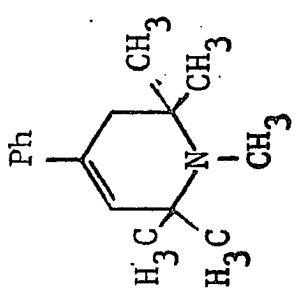


Figure 15

1,2,2,6,6-Pentamethyl-4-phenyl-1,2,5,6-tetrahydropyridine (14)



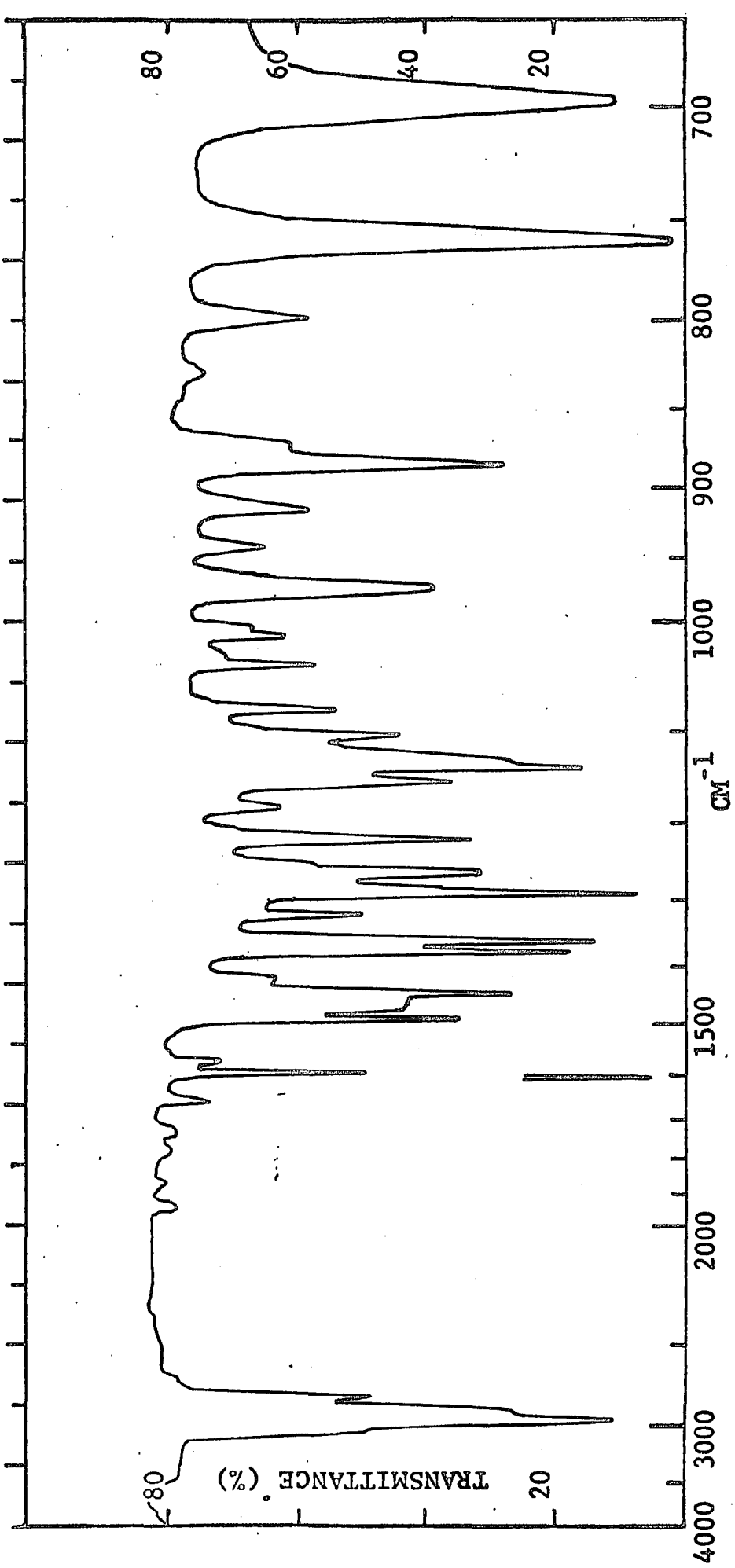
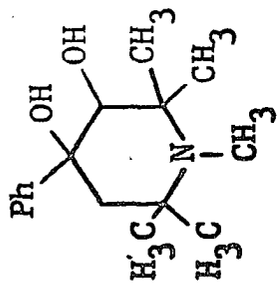


Figure 16

1,2,2,6,6-Pentamethyl-4-phenylpiperidine-3,4-diol (15)



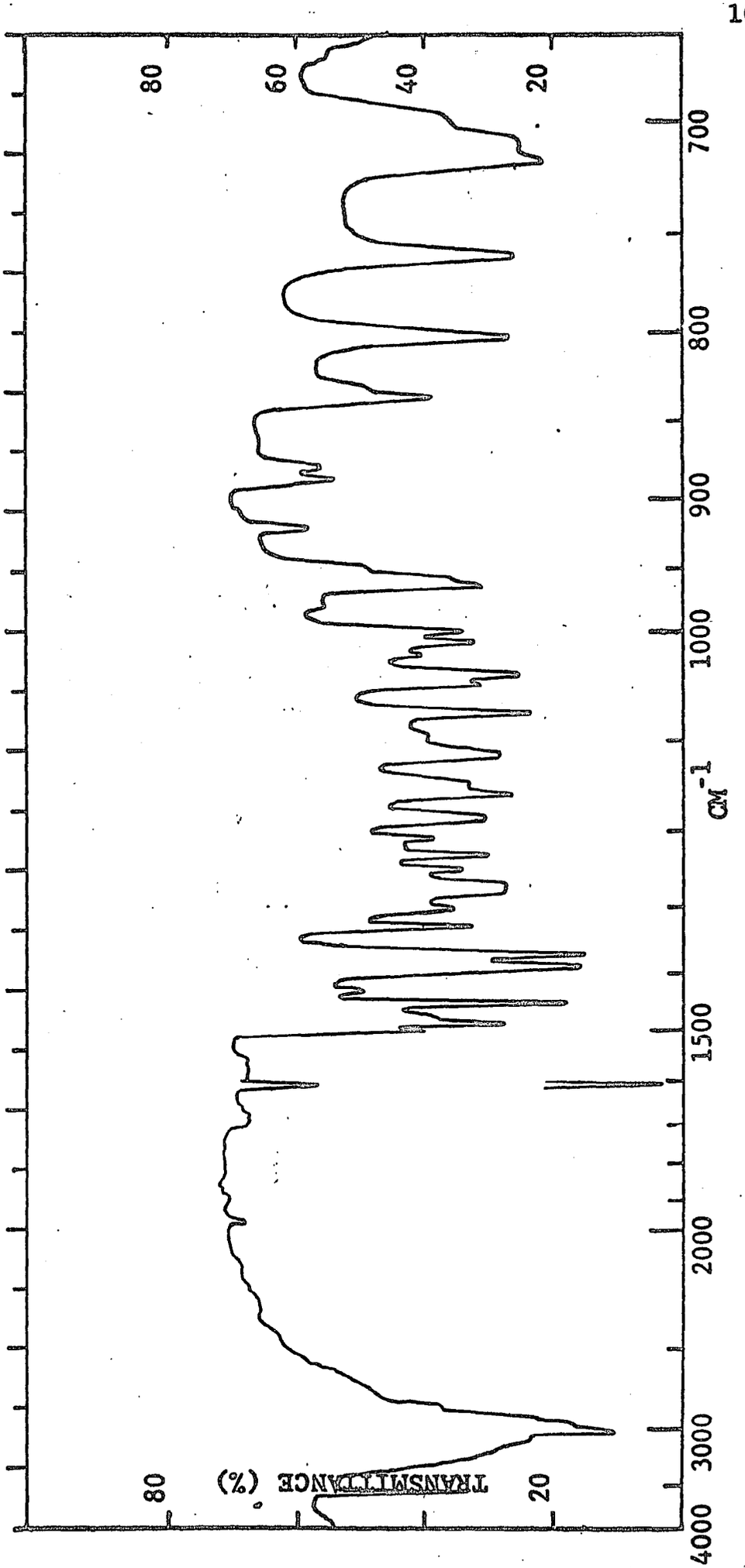
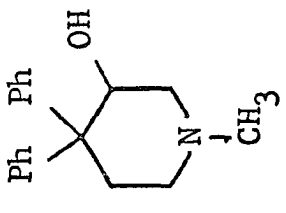


Figure 17

1-Methyl-4,4-diphenyl-3-piperidinol (21)



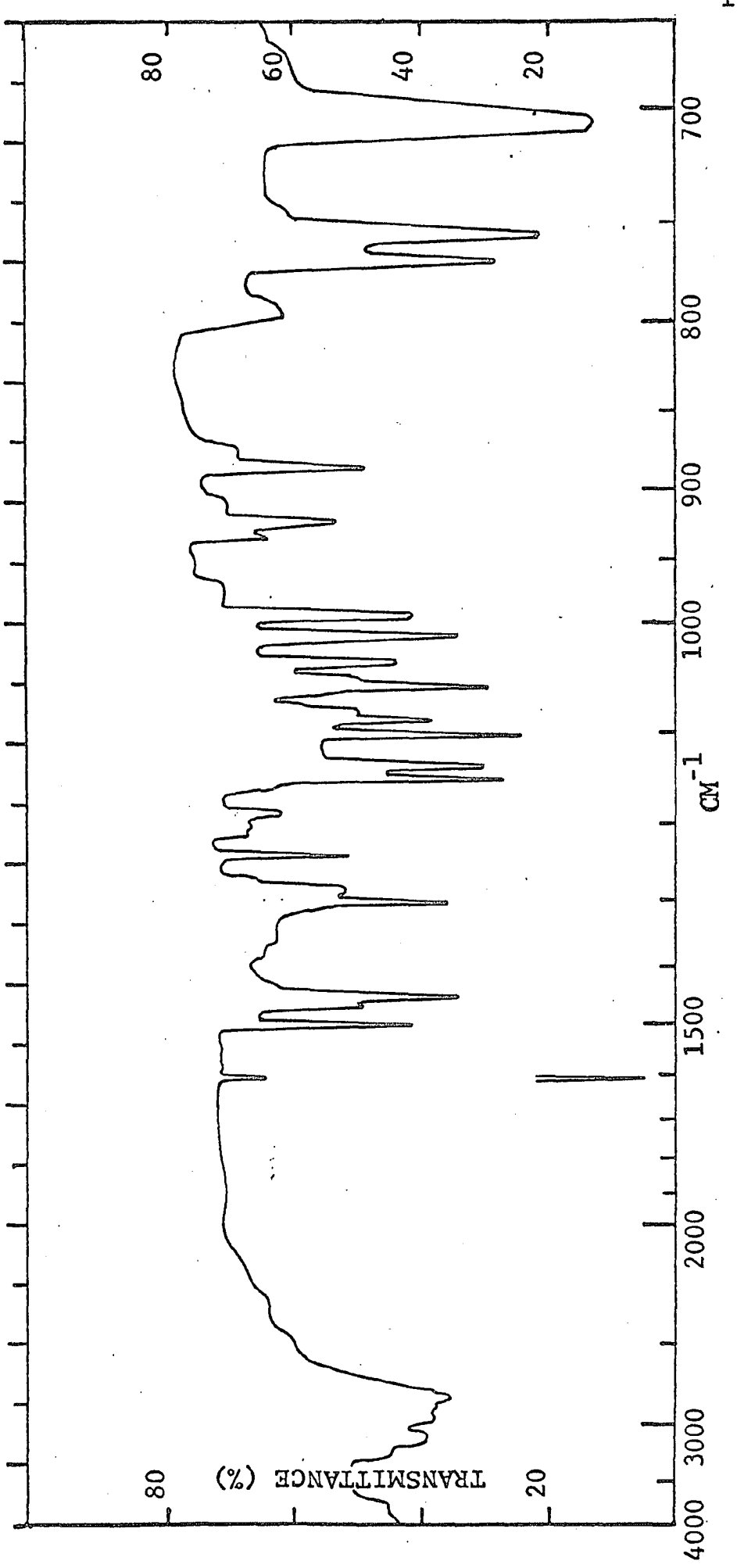
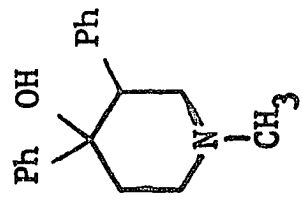


Figure 18

1-Methyl-3,4-diphenyl-4-piperidinol (22)



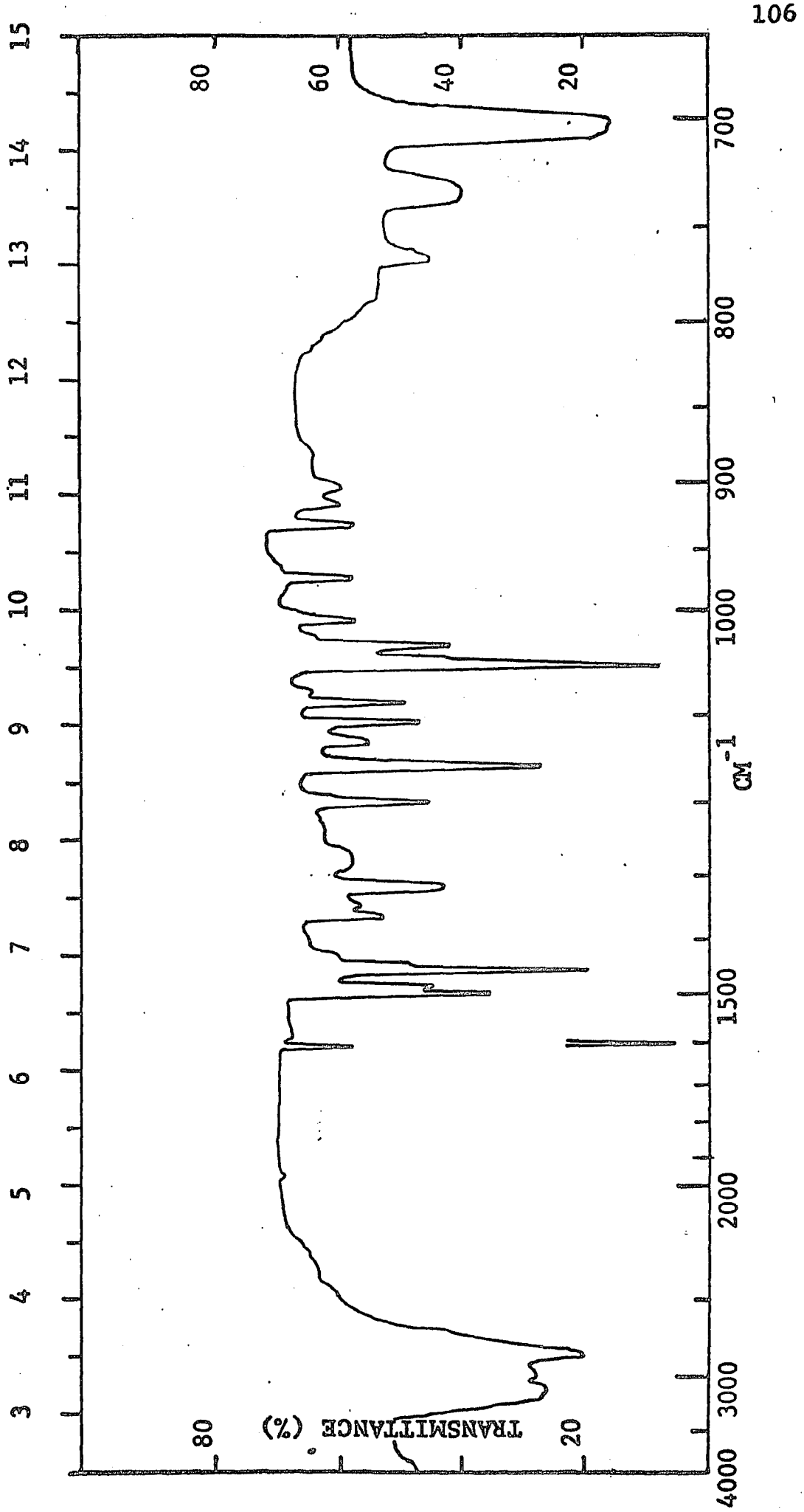
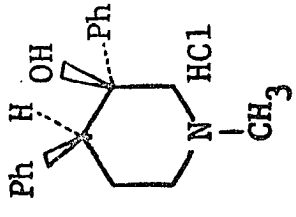


Figure 19

1-Methyl-3,4-diphenyl-3-piperidinol Hydrochloride (17)



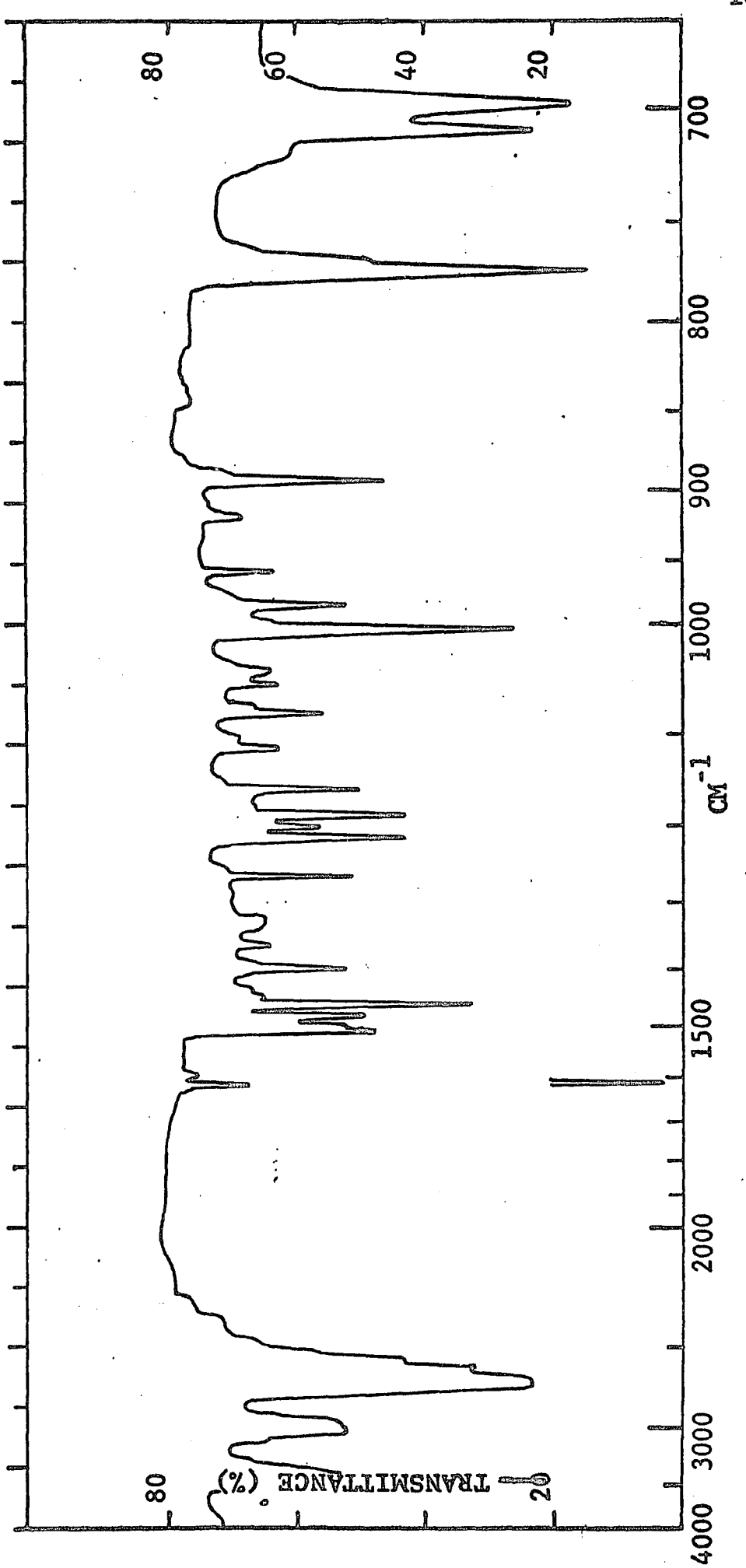
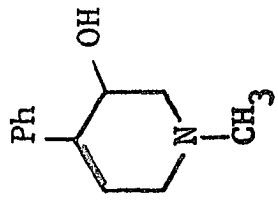


Figure 20

1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3)



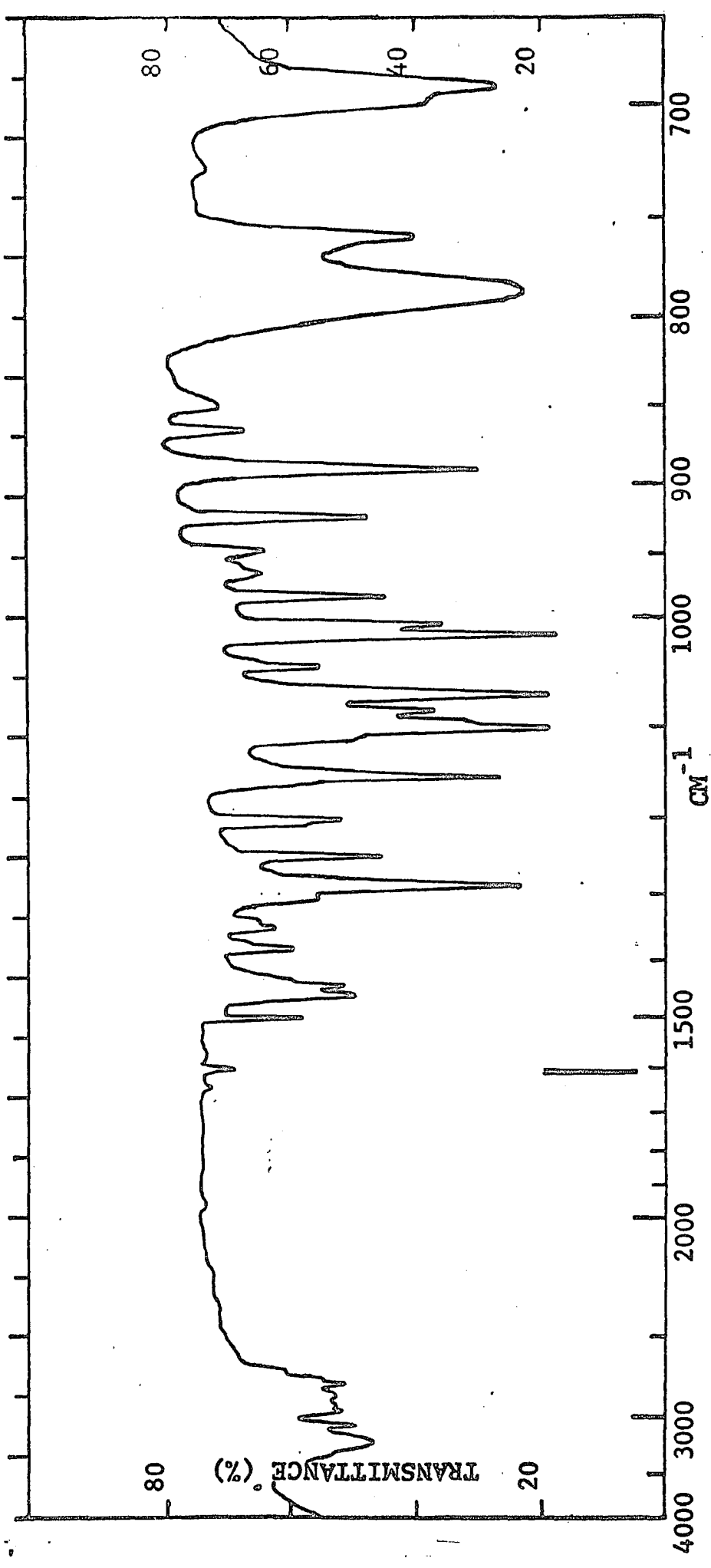
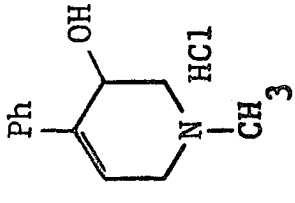


Figure 21

1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3) Hydrochloride



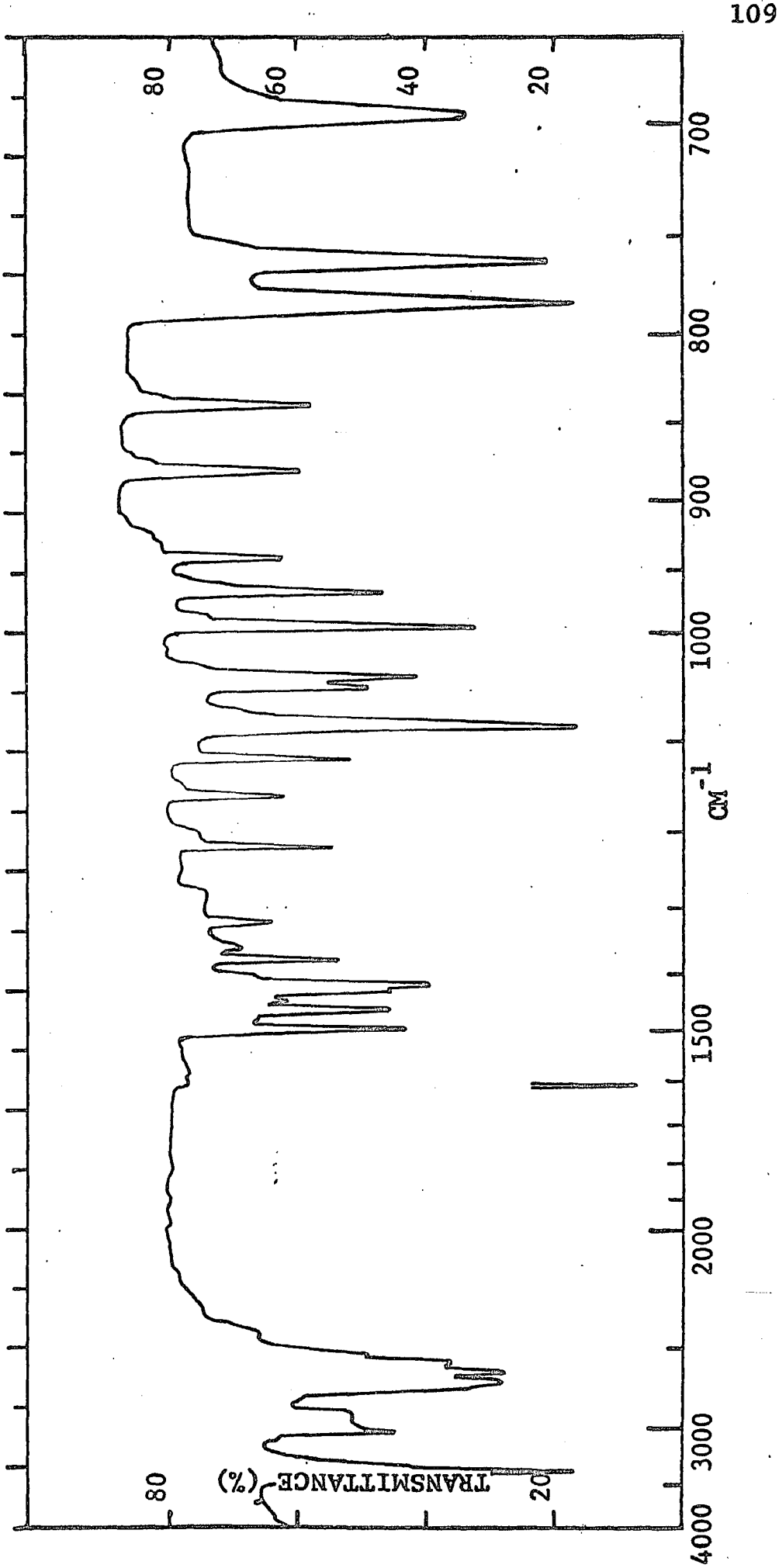
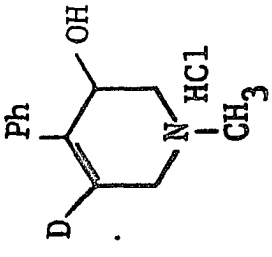


Figure 22

1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol-5-d Hydrochloride



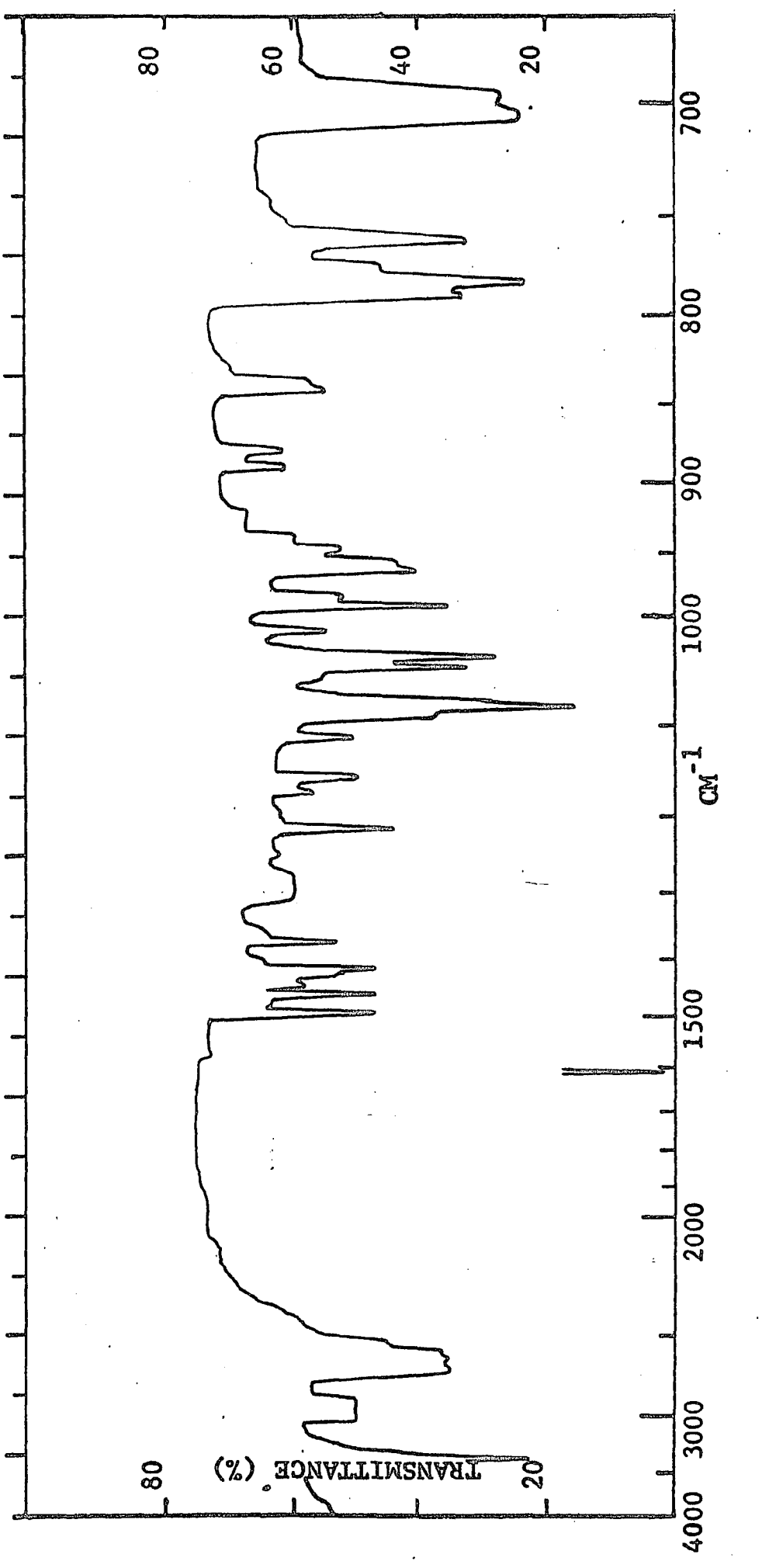
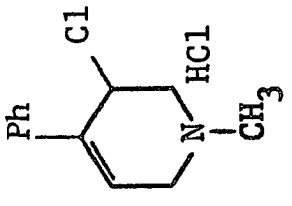


Figure 23

1-Methyl-3-chloro-4-phenyl-
1,2,3,6-tetrahydropyridine (25) Hydrochloride



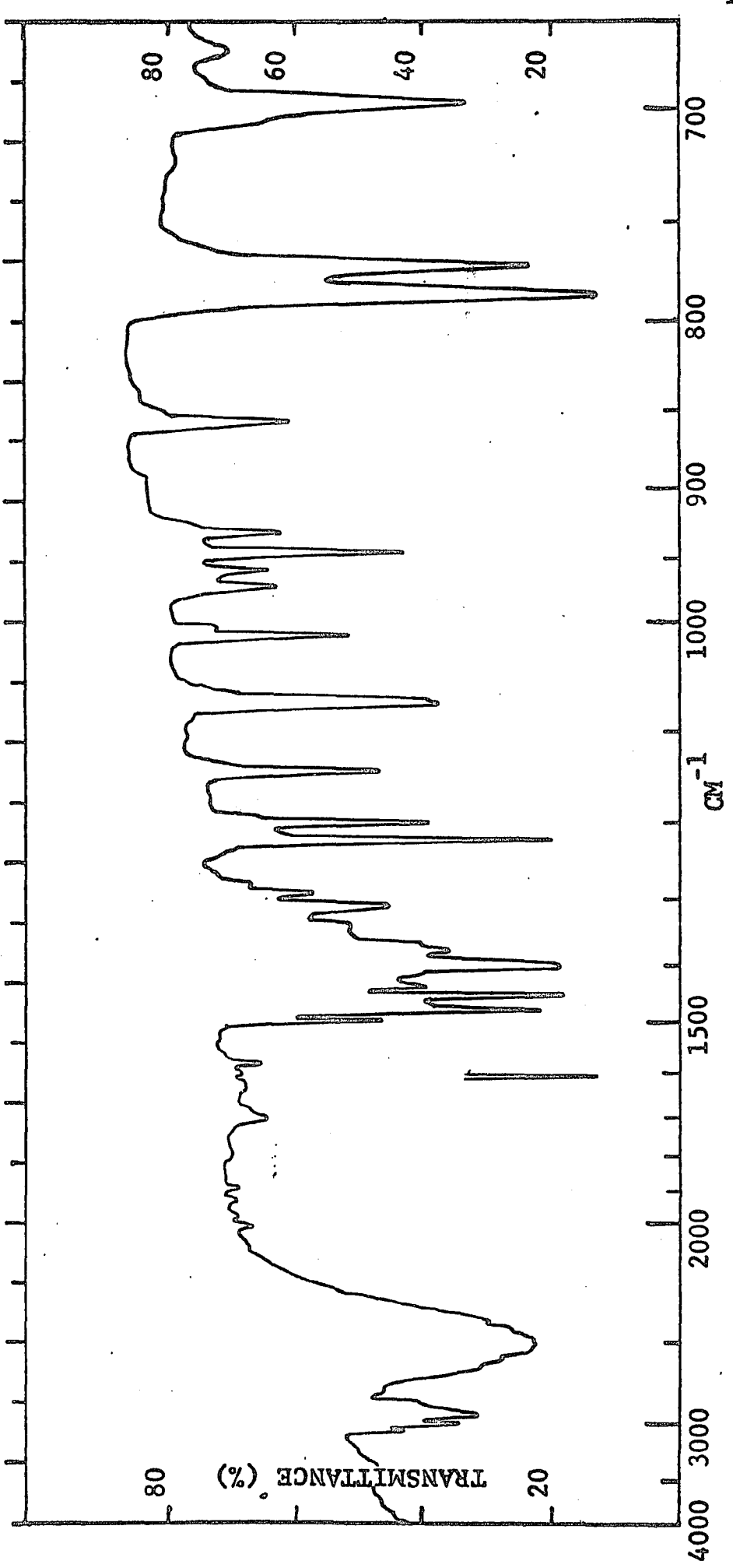
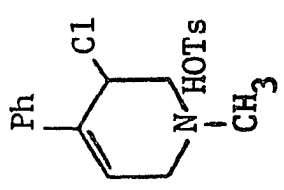


Figure 24

1-Methyl-3-chloro-4-phenyl-
1,2,3,6-tetrahydropyridine (25) Hydrotosylate



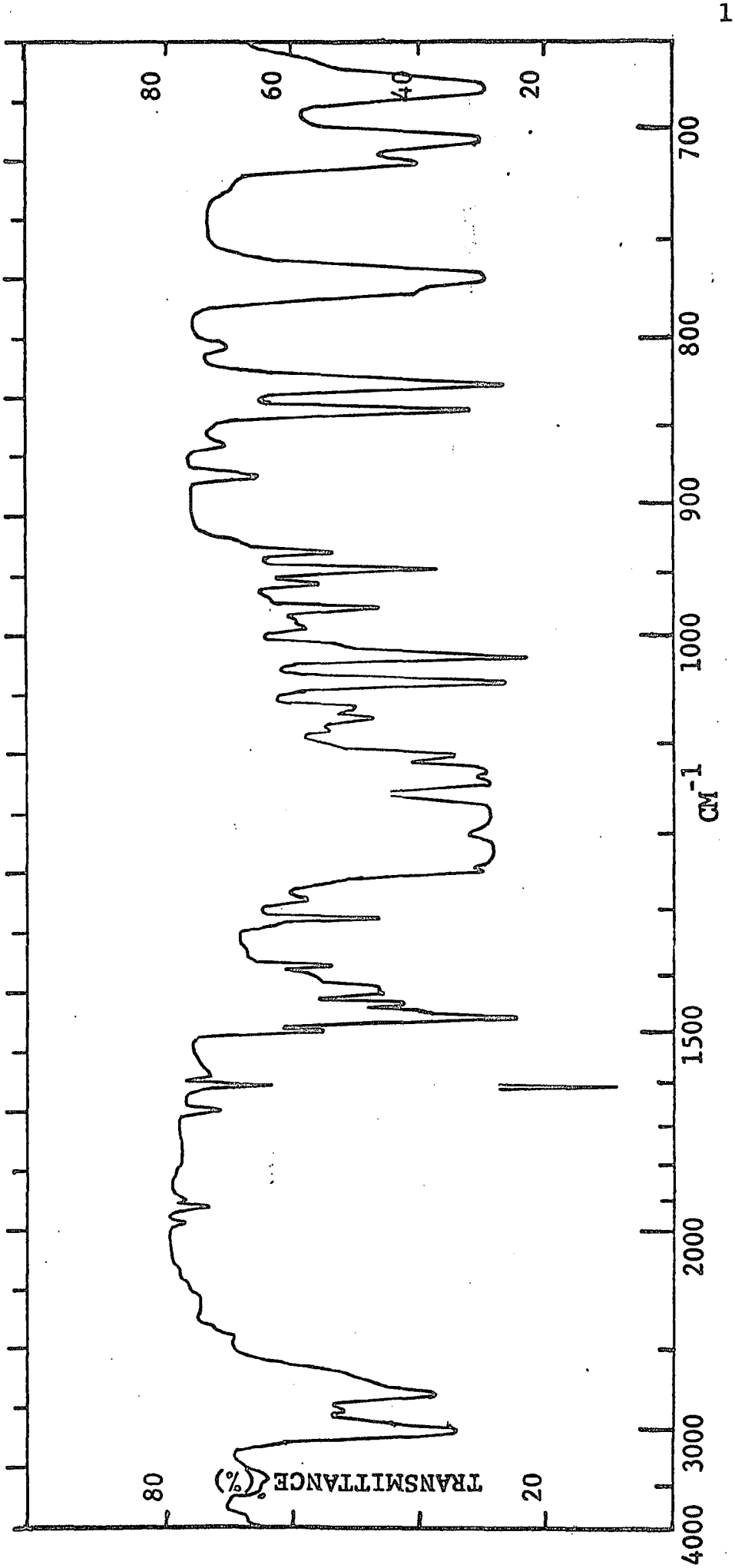
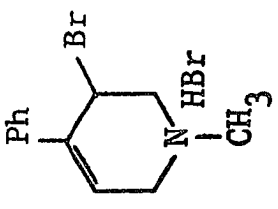


Figure 25

1-Methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine Hydrobromide (2)



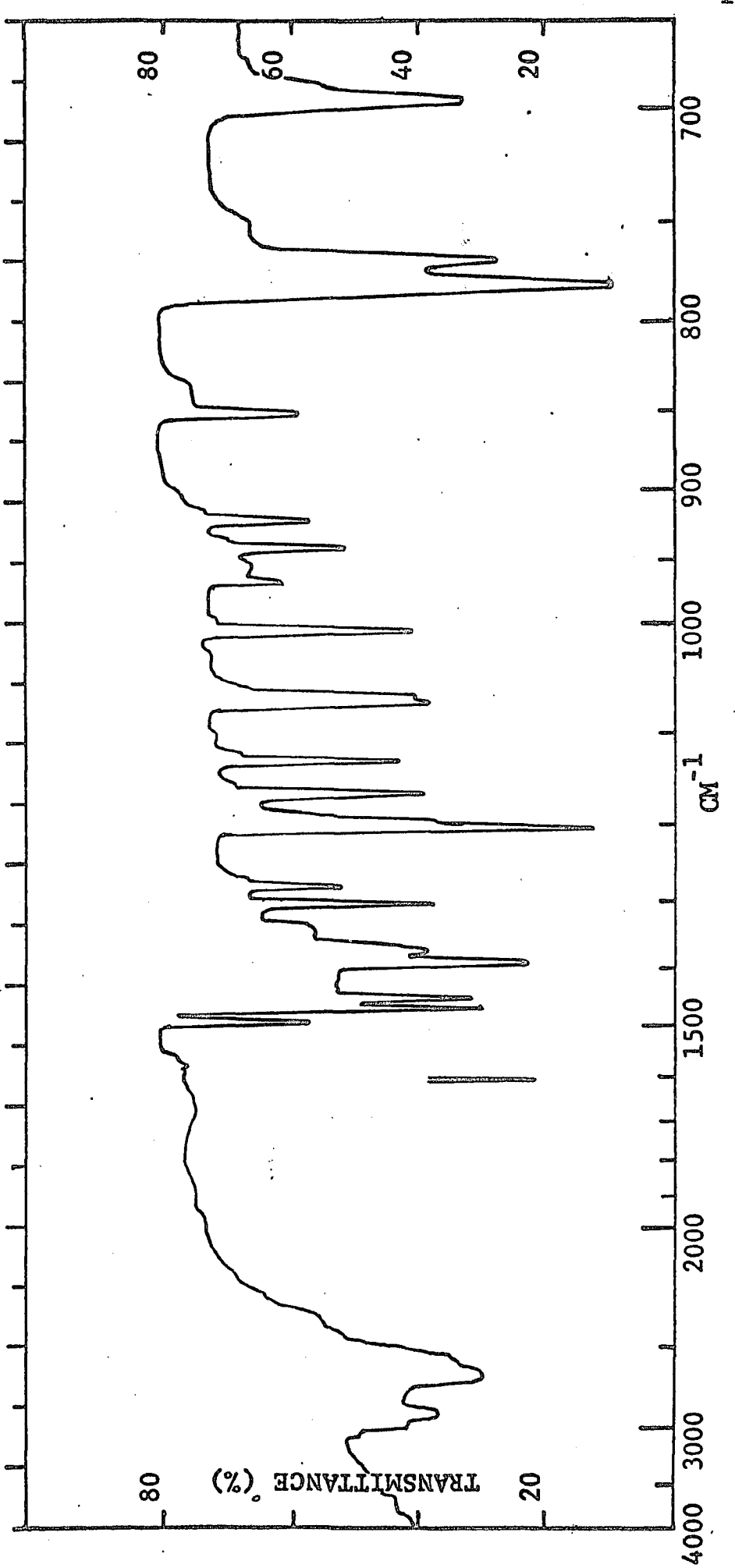
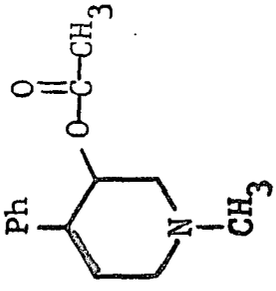
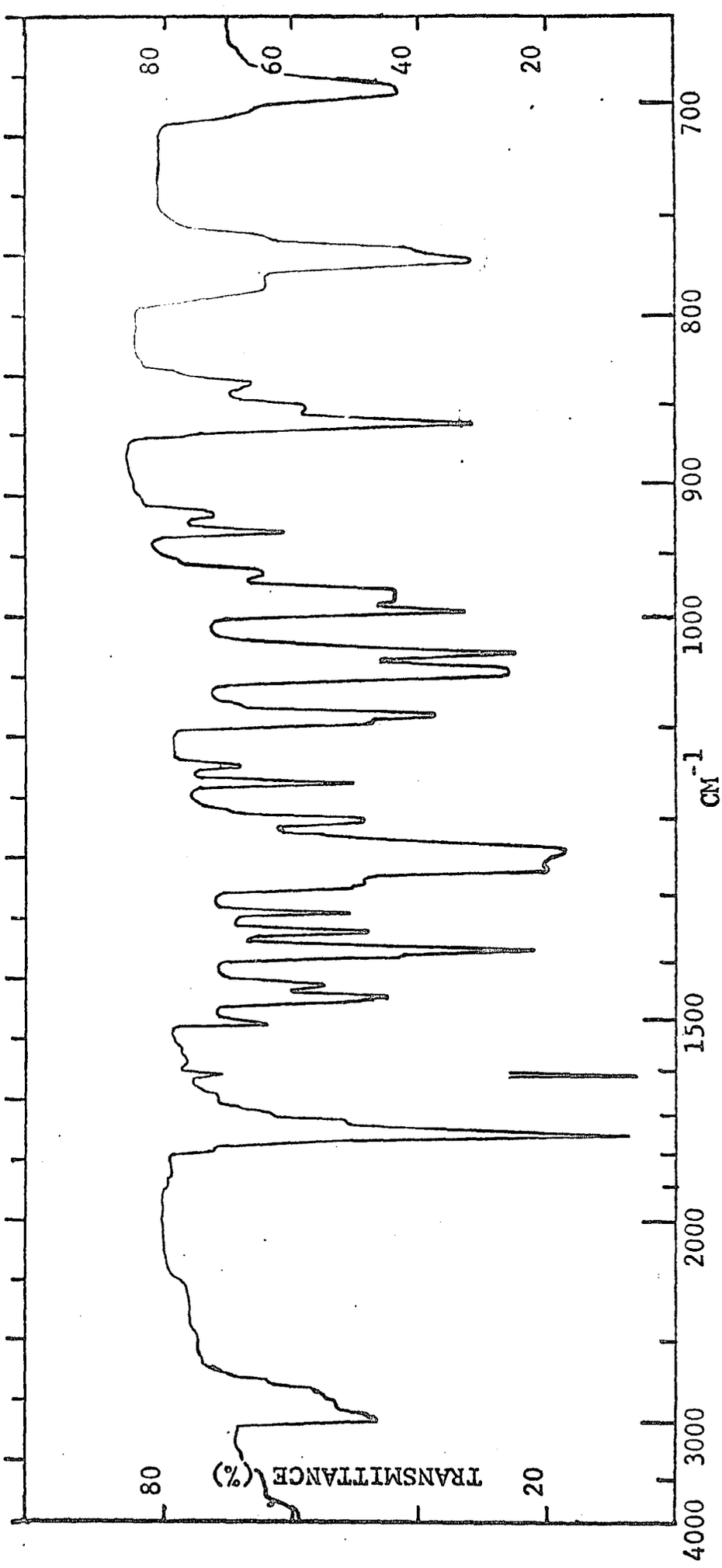
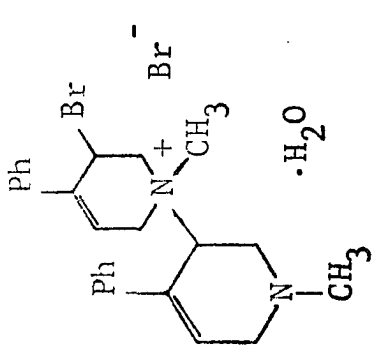


Figure 26

1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3) Acetate



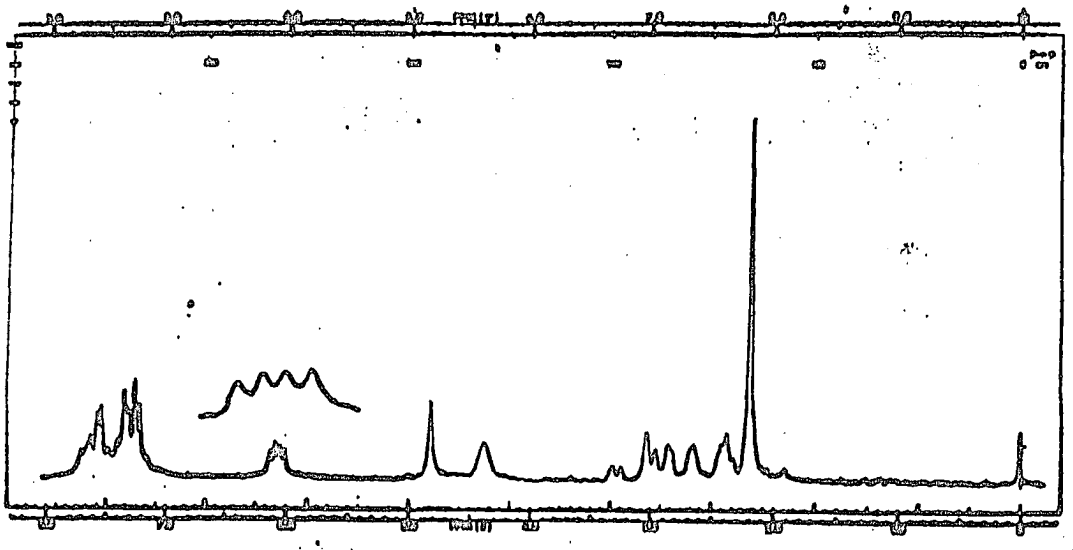




·H_2O

Figure 27

1-Methyl-1-[3-(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridyl)]-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridinium Bromide Monohydrate



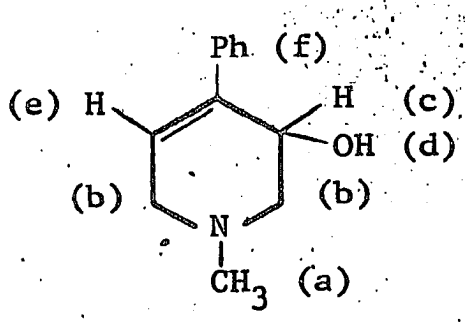
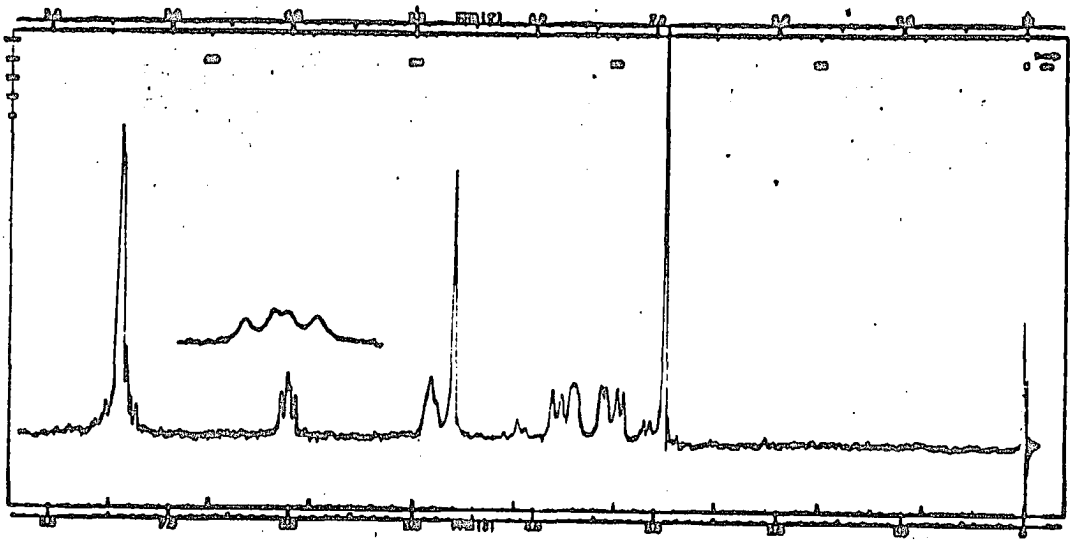


Figure 28. 1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (3) in $DCCl_3$

a. 7.90
b. 7.70-6.60
c. 5.62
d. 5.18
e. 3.93
f. 2.57



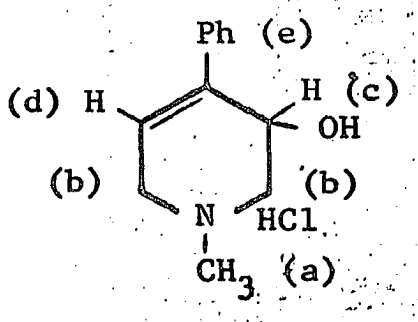
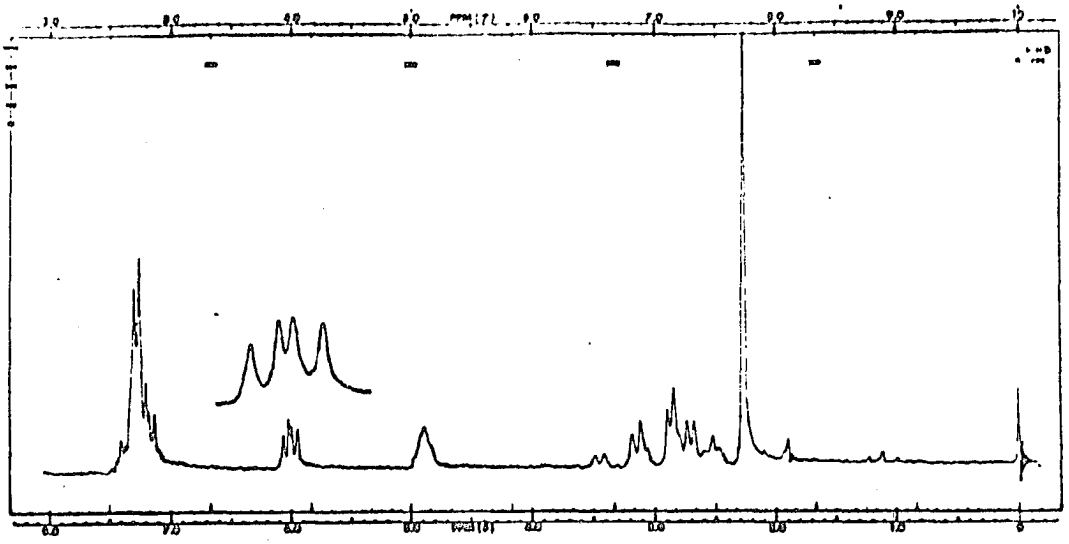


Figure 29. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-3-ol (3) Hydrochloride in D_2O with TMS as an external standard

a. 7.08
b. 7.00-5.70
c. 5.15
d. 3.98
e. 2.60
f. 5.33 (HDO)



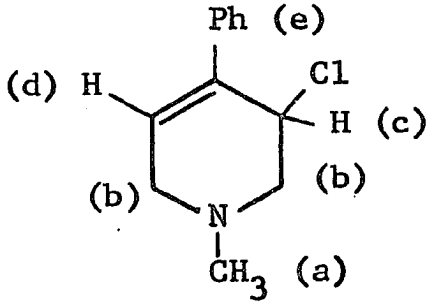
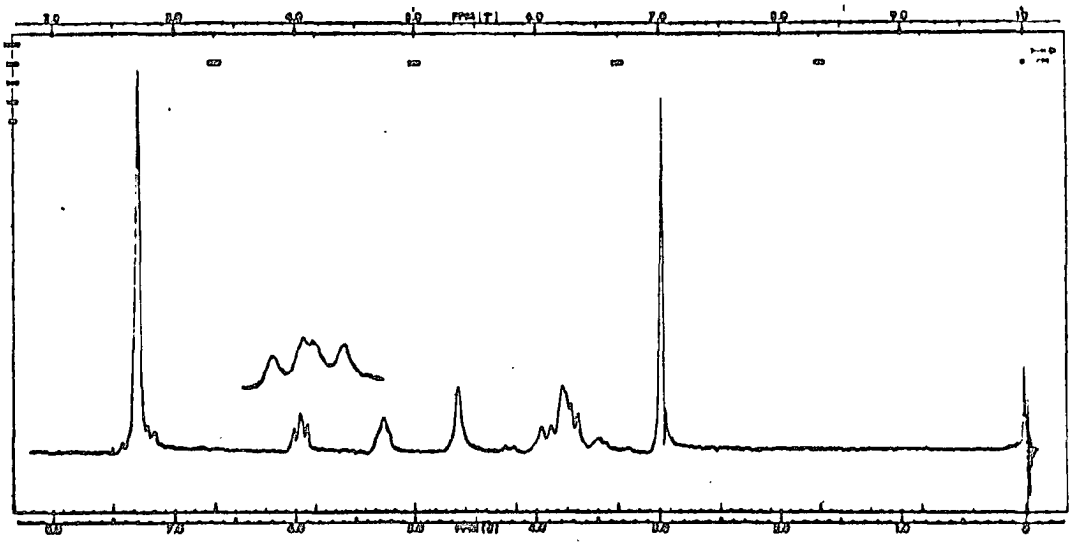


Figure 30. 1-Methyl-3-chloro-4-phenyl-1,2,3,6-tetrahydropyridine (25) in $DCCl_3$

a. 7.72
b. 7.60-6.40
c. 5.15
d. 3.98
e. 2.72



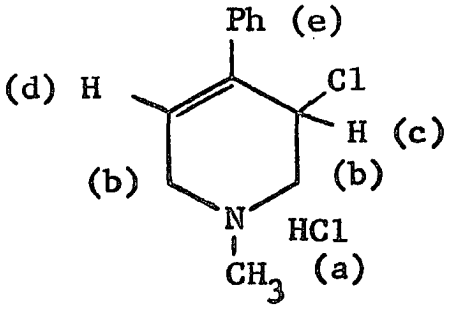
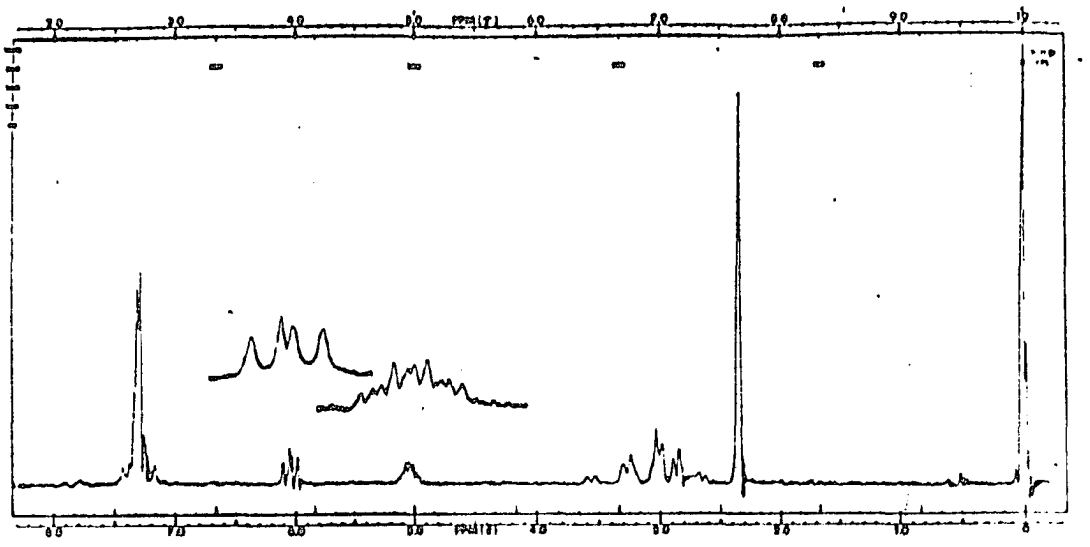


Figure 31. 1-methyl-3-chloro-4-phenyl-1,2,3,6-tetrahydropyridine (25) Hydrochloride in D_2O with TMS as an external standard

a. 7.05
b. 6.80-5.70
c. 4.74.
d. 4.05
e. 2.72
f. 5.62 (HDO)



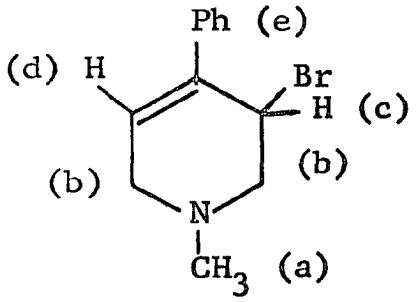
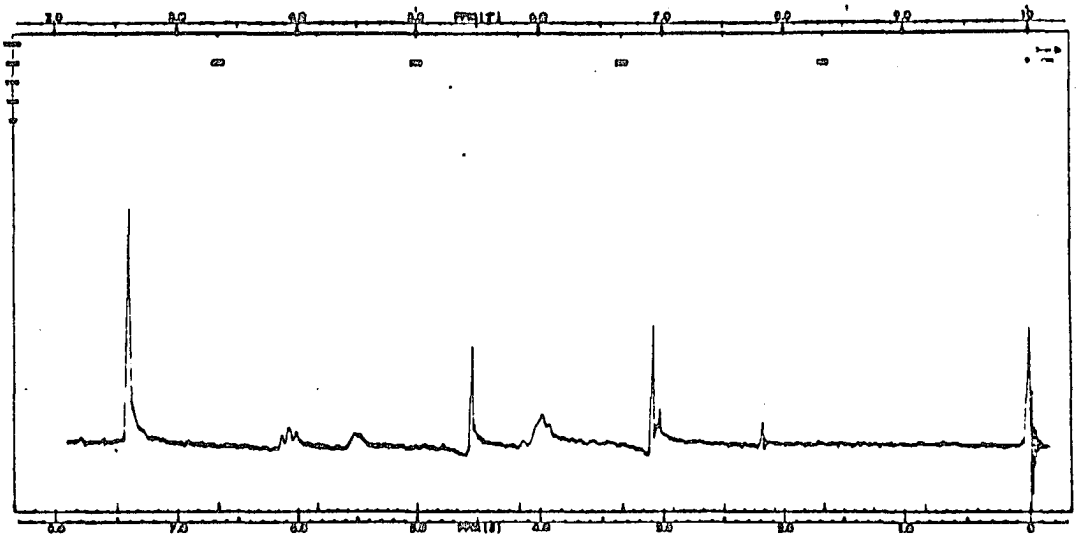


Figure 32. 1-Methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine in CCl_4

a. 7.65
b. 7.50-6.30
c. 4.95
d. 3.95
e. 2.72



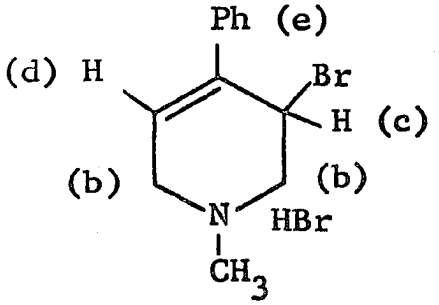
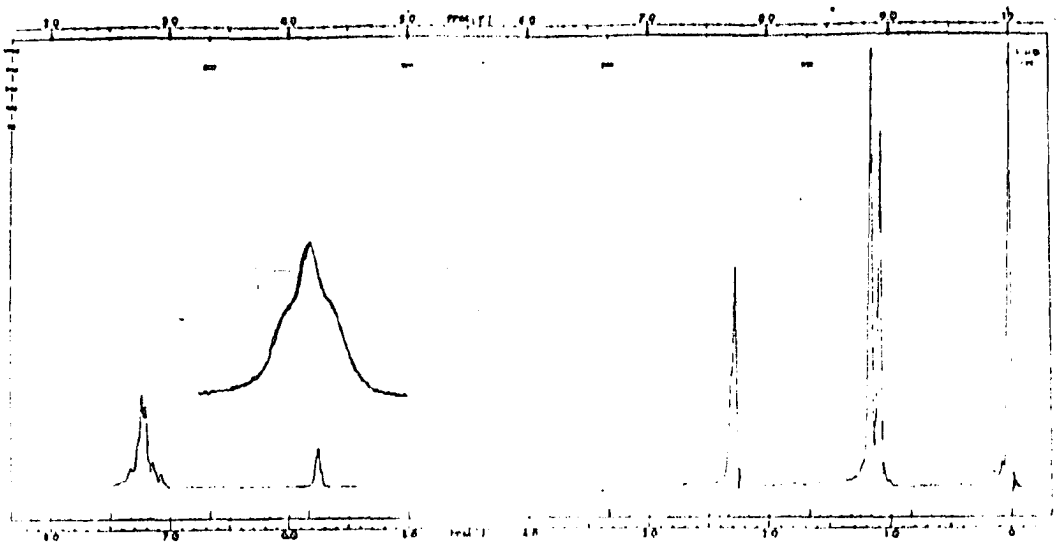


Figure 33. 1-Methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine Hydrobromide (2) in D_2O with TMS as an external standard

a. 6.92
b. 6.20-5.80
c. 4.50
d. 3.93
e. 2.58
f. 5.45(HDO)



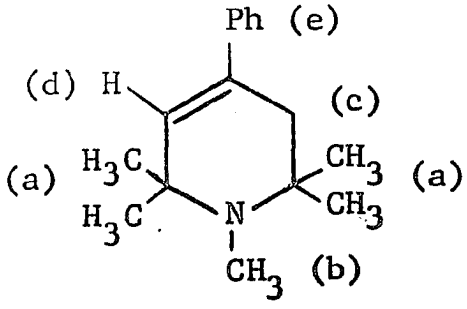
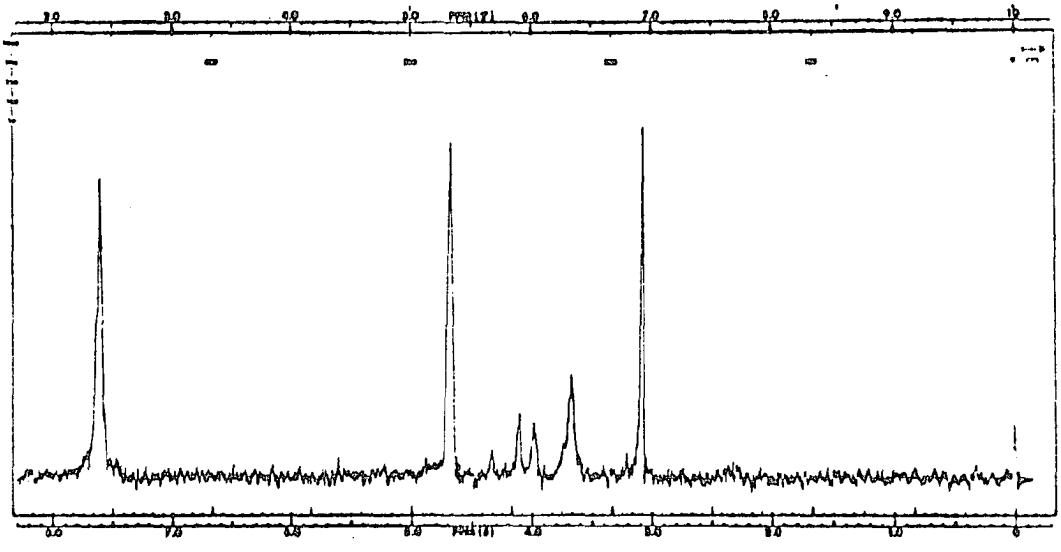


Figure 34. 1,2,2,6,6-pentamethyl-4-phenyl-1,2,5,6-tetrahydropyridine (14) neat

a. 8.94 & 8.82
b. 7.73
c. 7.73
d. 4.27, J=0.9 cps
e. 2.78



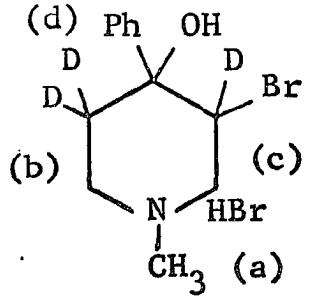
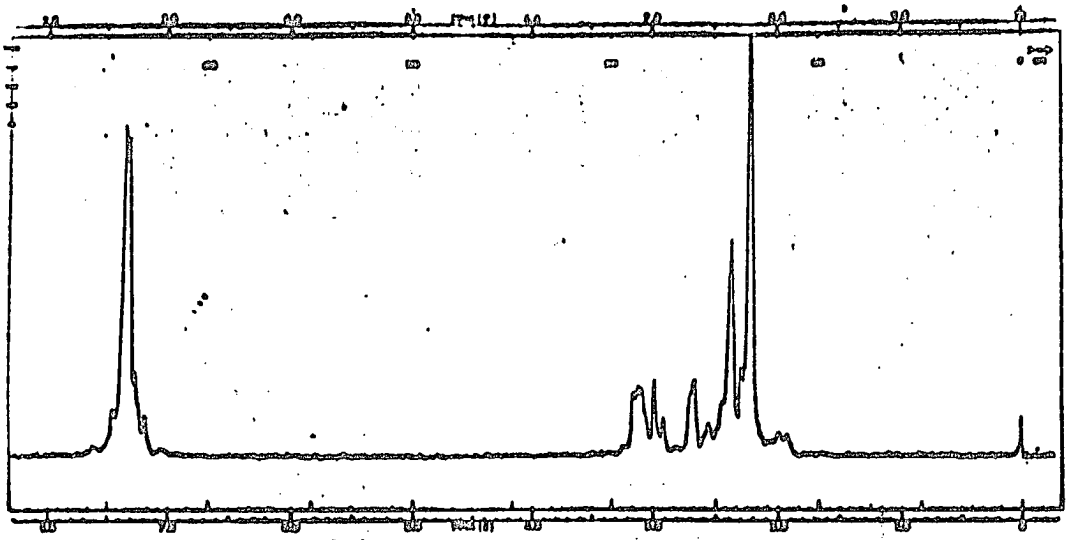


Figure 35. 1-Methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine-3,5,5-d_3 Hydrobromide in D_2O with TMS as an external standard

a. 6.92
b. 6.33
c. 5.95, J=14.5 cps
d. 2.38
e. 5.32 (HDO)



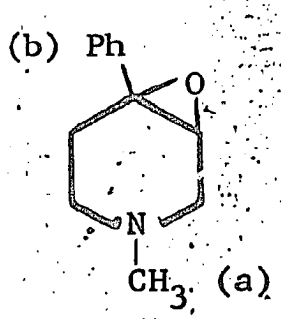
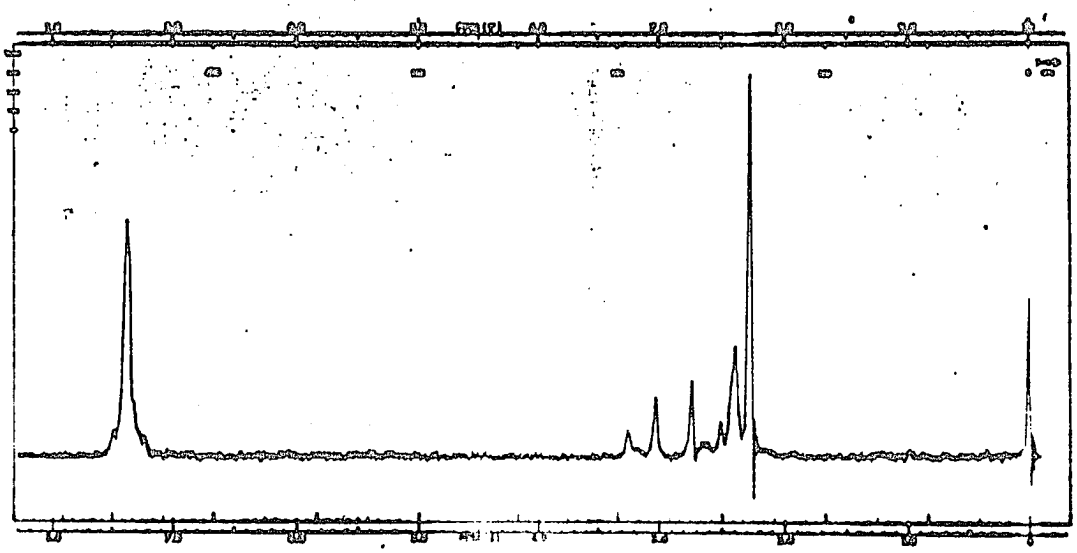


Figure 36. 1-Methyl-4-phenyl-3,4 epoxypiperidine (7) in $DCCl_3$

a. 7.80
b. 2.68
c. ring protons 8.05-6.60



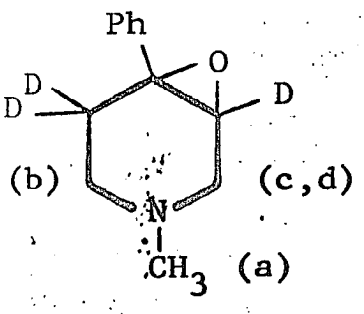
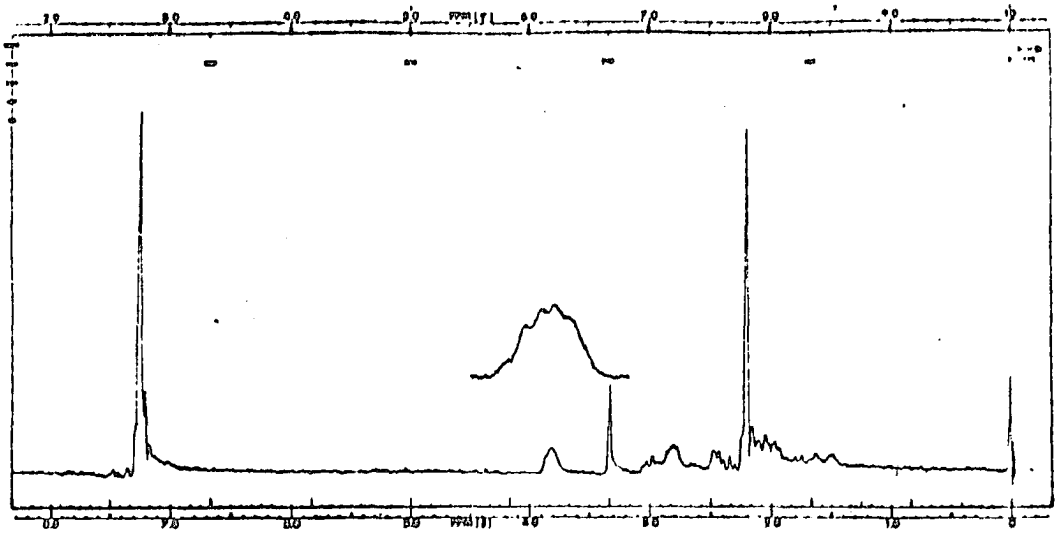


Figure 37. 1-Methyl-4-phenyl-3,4-epoxypiperidine-3,5,5-d_3 in $DCCl_3$

a. 7.73 e. 2.61
b. 7.60
c,d. 7.36,6.88 J=13.4 cps



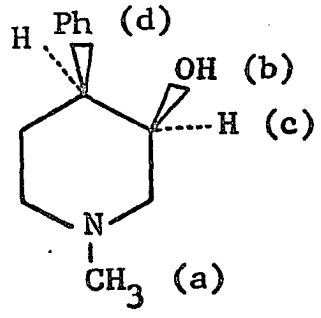
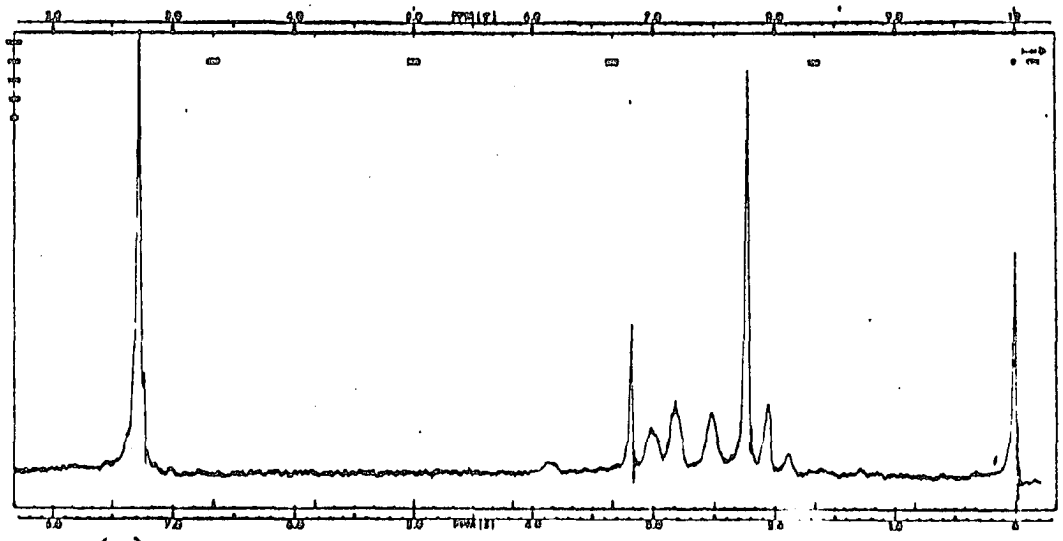


Figure 38. cis-1-Methyl-4-phenyl-3-piperidinol (8) in $DCCl_3$

a. 7.80
b. 6.68
c. 6.20
d. 2.77
e. 8.60-6.90, ring protons



(a)

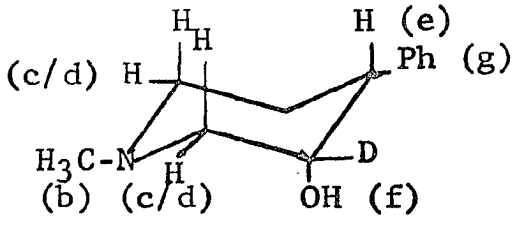


Figure 39. cis-1-Methyl-4-phenyl-3-piperidinol-3,5,5-d_3 in $DCCl_3$

a. 7.86, J=11.3-11.7 cps
b. 7.78
c/d. 7.50/7.45; $J_{a\text{-}c/d}$=11.3/11.7 cps, $J_{c,d}$=1.8 cps
f. 6.87
g. 2.27
h. 8.13 and 6.14 unexchanged protons at 3 and 5

BIOGRAPHICAL DATA

Name: William Ernest Krueger

Date of Birth: June 26, 1940

Place of Birth: St. Louis, Missouri

Secondary education: St. Louis University High School

Collegiate institutions attended:	Dates	Degree
University of Notre Dame	1958-1962	B.S.

Publications:

"The Preparation and Reactions of 1-Methyl-4-phenyl-3,4-epoxypiperidine," with R. E. Lyle, J. Org. Chem., 30, 394 (1965).

"Mechanism of Sodium Borohydride Reduction of Pyridinium Ions. III. Formation of Piperidines," with P. S. Anderson and R. E. Lyle, Tetrahedron Letters, No. 45, 4011 (1965).

"Hydrogen Bonding and Conformational Analysis of 3-Piperidinol Derivatives," J. Org. Chem., 31, in Press (1966).