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# Conformational Studies on Phenethylamine Hallucinogens: The Role of Alpha Alkyl Substitution

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## INTRODUCTION

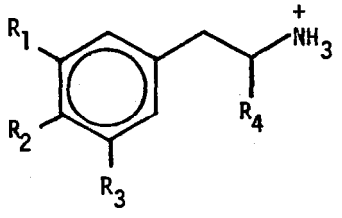
A large number of methoxyphenethylamine analogs have been synthesized (Shulgin 1970; Barfknecht and Nichols 1971) and evaluated in humans (Shwlgin, Sargent, and Naranjo 1969; Shulgin 1973) and animals (Aldous, Barrass, and Brewster 1974; Smythies, Bradley, and Johnston 1967) for psychotomimetic activity. The overall picture which emerges from these evaluations shows that small structural variations can produce drastic changes in the psychotropic potency of these compounds, making them particularly suitable for studies in structure activity relationships.

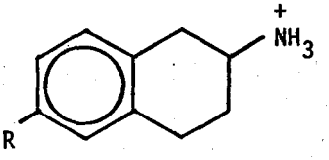
The dramatic effect that alpha alkyl substitution has on the pharmacological activity of these phenethylamines is of particular interest. It is thus well known (Shulgin 1970) that the presence of an alpha methyl group increases considerably the psychotomimetic potency of the corresponding phenethylamine. On the other hand, alpha ethyl substituted analogs are devoid of psychotomimetic activity and act as functional antagonists for their alpha methyl counterparts (Shulgin 1968; Standridge et al. 1976). Activity is recovered if the alpha ethyl group is tied back on the phenyl ring to give tetralin analogs which are weaker agonists (Violland, Violland-Duperet and Pacheco 1971; Nichols, Barfknecht et al. 1974).

In the present study we have used model methoxyphenethylamine analogs (1-5; figure 1) to study the effect of alpha alkyl substitution on the conformational properties of the phenethylamine component in these molecules. The information thus obtained was used to explain their observed divergent pharmacological properties.

The conformation of a drug is relevant to any consideration of its interaction with the receptor. Like many small molecules, phenethylamines and their alpha alkyl analogs are potentially flexible, and thus, may exist in solution in a number of conformations in equilibrium with one another. Of these, the most stable are the perfectly staggered conformations shown in figure 2, Since it is generally recognized that a flexible drug has only one *pharmacophoric conformation* in its complex with the receptor, the formation of this com-

FIGURE 1





1 $R_1, R_3, R_4$=H; $R_2$=$OCH_3$

2 $R_1, R_3$=H; $R_2$=$OCH_3$; $R_4$=$CH_3$

3 $R_1, R_2, R_3$=$OCH_3$; $R_4$=$CH_3$

4 $R_1$=H; $R_2, R_3$=$OCH_3$; $R_4$=$C_2H_5$

5 R=$OCH_3$

plex must involve a *conformational selection* which will influence the kinetics and energetics of complex formation. If the drug is present in more than one conformation, the extent to which the drug exists in the *pharmacophoric conformation* should influence its reactivity.

To study the conformational distribution of the model methoxyphenethylamine salts in solution, we used nuclear magnetic resonance (NMR) spectroscopy, which is clearly the experimental method of choice. We have also sought to obtain information on the role of the solvent in the conformational behavior of phenethylamines. by conducting our studies in two different solvents, $D_2O$ and $CDCl_3$, whenever possible. Because of its lower polarity, $CDCl_3$ can be expected to represent more accurately the hydrophobic environment of the nerve membrane.

It has been argued (Makriyannis 1974; Mautner 1974) that, in addition to conformation, molecular flexibility may play an important role during the drug-receptor interaction. To better evaluate the role that the conformational distribution of phenethylamine salts in solution plays on their biological activity, it is important to have information on the rate of conformational interconversion. If the compound exists predominantly in its *pharmacophoric conformation,* restricted flexibility will enhance its interaction with the receptor. On the other hand, if the predominant drug conformation is not the *pharmacophoric* one, the restricted rotation will hinder the conformational change necessary for the drug to achieve its proper conformation and will thus affect adversely the drug-receptor interaction. Such an observation (Gannelin 1973) served to explain the different pharmacological activities of histamine and 4-methylhistamine.

In this study, we have obtained a reasonable semiquantitative index for the molecular flexibility of phenethylamine salts in $D_2O$ solu-

tion by measuring the $^{13}C$ spin-lattice relaxation times ($T_1$) of individual carbon atoms. The information on molecular flexibility was then integrated into the results obtained from conformational analysis. The outcome was a more accurate dynamic picture for the conformational behavior of each molecule in solution. Such a picture gives us more insight into the possible mode of drug-receptor interaction (figure 3).

## METHODS

### A. Conformational Analysis

No single measurement can provide enough information for the unambiguous conformational analysis of potentially flexible molecules in solution. We have thus sought more than one criterion in our conformational assignments. As a result, we were able to clear. some remaining ambiguities existing in the literature related to the conformational analysis of alpha methylphenethylamines in solution (Neville et al. 1971).

#### 1. $^1H$ Coupling Constants

The measureument of vicinal $^1H$-$^1H$ coupling constants is the most direct and still the most important method used in the conformational analysis of small molecules in solution. The principle of this method is described in the Karplus equation (Karplus 1959) which states that the spin-spin coupling constant between proton attached to two adjacent carbon atoms is proportional to $\cos^2\phi$, the dihedral angle about the C-C band. In our system, the dihedral angle of interest is the one about the central Ar-C-C-N bond of the arylphenethylamine.

The two benzylic protons in the alpha alkylphenethylamine analogs (2, 3, 4) and those on the $C_1$ carbon of compound 5 constitute the AB portion of an ABC spin system. The four protons on the $ArCH_2CH_2CH_2N$ fragment of the phenethylamine analog are of the AA'BB' type. Initial estimates of the spectral parameters were obtained by standard methods (Pople, Schneider, and Bernstein 1969; Makriyannis et al. 1972) assuming that the corresponding spectra were approximately ABX and AA'XX'. The parameters were then refined by spectral simulation and iteration using Nicolet ITRCAL program.

The coupling constants thus obtained were considered to be averaged values arising from a mixture of three possible perfectly staggered rotamers. The relative population of each rotamer was then extracted from simple analogies which include $J_g$ and $J_t$ terms for the coupling constants of perfectly staggered *gauche* and *trans* vicinal protons.

While calculating the conformer distribution for the compounds under study, we made a special effort to consider the uncertainties inherent in the above method. The first of these uncertainties is the spectral assignment for each of the two benzylic protons in alpha alkylphenethylamines. Previous assignments (Neville et al. 1971; Bailey et al. 1971) in similar spin systems depended on pre-

dicting trends in the relative distribution of conformers among a series of analogs, based on stereochemical considerations. We have, in this study, provided additional spectral evidence which confirmed the previous assignments.

A second uncertainty is introduced with the choice of $J_g$ and $J_t$ values. to be used in our calculations. These values vary and to a large extent are dependent on the substituents of the C-C bond. They can thus either be obtained from model compounds in which the HCCH dihedral angle is fixed, or can be calculated from a number of semiempirical equations. In this study we have chosen those $J_g$ and $J_t$ values which gave results with the best internal consistency. We have used a combination of values (Table I, page ), some obtained from model compounds and others calculated from an empirical relationship between vicinal coupling constants and substituent electronegativities. This relationship (Abraham and Gatti 1969) has given us satisfactory results in the past (Makriyannis et al. 1972).

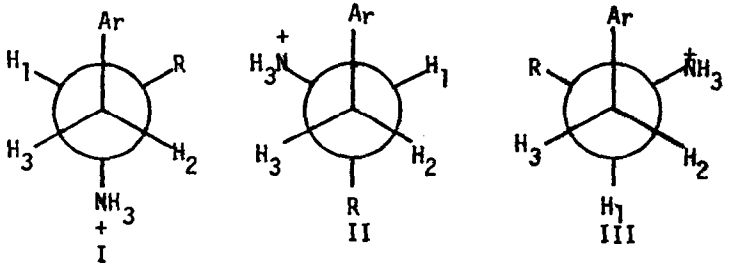
The final uncertainty considered here is related to the assumption that measured vicinal coupling constants with intermediate values, in between those of $J_g$ and $J_t$, are the result of the population-weighted average of the $J_g$ and $J_t$ values in three perfectly staggered rotamers. Although perfectly staggered rotamers are generally accepted as the most stable, the possibility must be considered that an off-staggered stable rotamer could exist in solution. The presence of such a conformer, with dihedral angles different from the usually assigned values of 60° and 180°, could lead to serious errors in our calculations. It could also mean that a single distorted conformer may account for observed coupling constants with intermediate values. Such a possibility is more likely in the case of sterically crowded compounds with large free energy differences among individual conformers.

In order to settle this uncertainty we undertook low temperature studies on compound 5 and other alpha ethylphenethylamine analogs. Since the coupling constants of a rotamer are usually minimally affected by temperature, a change in the observed vicinal coupling constants is an indication of a change in rotamer distribution. No change in the coupling constants with temperature indicates that, most probably, the compound exists solely in one conformation. Our low temperature experiments on alpha ethylphenethylamines in $CD_3OD$ and in $CDCl_3$ showed a considerable variation in the vicinal coupling constants with temperature, and indicated that these compounds exist in solution as an equilibrium mixture of two or more conformers. We shall report on these experiments in greater detail elsewhere. The results can be extrapolated to the other open chain phenethylamine analogs considered in this study and used as evidence against the presence of any of these compounds in solution as a single distorted conformer. Further evidence is, however, necessary to rule out the possibility that any of the compounds could exist as an equilibrium mixture of two or more off-staggered conformers.

## 2. Chemical Shifts

A careful examination of the $-CH_2CH-$ component in the $^1H$ NMR spec-

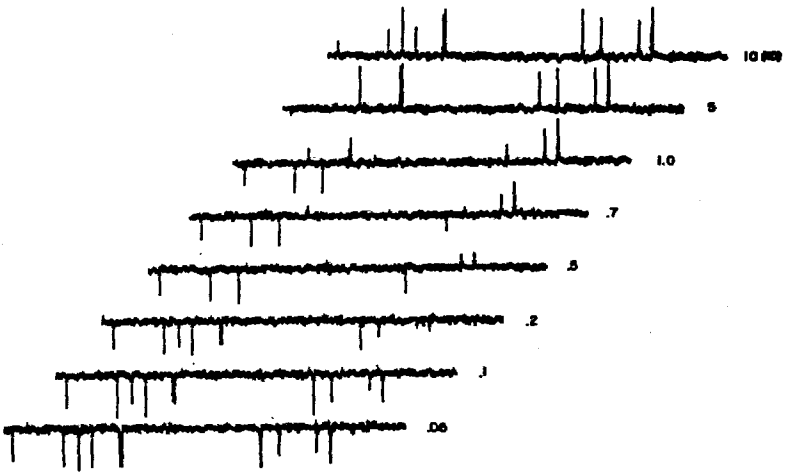
FIGURE 2




R = H, $CH_3$ or $C_2H_5$

Ar = 4-$OCH_3C_6H_5$; 3,4-di$OCH_3C_6H_5$; 3,4,5-tri$OCH_3C_6H_5$

FIGURE 3




Selected spectra from a $^{13}C$ spin-lattice relaxation tine ($T_1$) experiment on 2-amino-6-methoxytetralin hydrochloride. Determinations were made with complete $^1H$ decoupling using a $(-180°-\tau-90°-T-)_n$ inversion recovery pulse sequencewhere t is experimentally varied ($\tau$=0.05, .1, .2, .5, .7, 1.0, 5 and 10 sec) and T is equal to at least five times the longest $T_1$ to be measured.

trum of the alpha alkyl arylethylamines under consideration revealed that valuable information could be learned from the chemical shift differences between the two $H_2$, $H_3$ benzylic protons in this ABC system. These AB protons, which frequently give rise to two individual "quartets", have different chemical environments as a result of their different positions relative to their two vicinal substituents: the $NH_3$ and the alkyl groups. These substituents exert respectively deshielding and shielding influences with the more pronounced effects being experienced by the proton situated *gauche* to the substituent. The population-weighted average of these effects in the three possible rotamers determines the relative chemical shifts for each of the benzylic protons.

Additional useful information was gained by observing the spectra of the phenethylamine analogs in $D_2O$ and in $CDCl_3$ solutions. Solvent variation was usually accompanied by considerable changes in the chemical shifts and the coupling constants of the side chain protons. Chemical shift changes can be attributed to a reduction in the deshielding influence of the $NH_3$ group upon the neighboring *gauche* proton when $CDCl_3$ is replaced with $D_2O$. Such a modification of the deshielding influence of a charged nitrogen by solvent has been already reported (Reynolds and Priller 1968). The highly polar $D_2O$ presumably (Reynolds and Priller 1968) decreases the effect of the positive charge through direct solvation of the positive ion. The result is that, in the less polar $CDCl_3$, we observe a downfield shift relative to the chemical shift in $D_2O$. We have recently demonstrated (Makriyannis and Hite 1978), using a tropane derivative, that the magnitude of the chemical shift differences in the two solvents can be related to the relative distances between the protonated nitrogen and the neighboring protons. We were able to successfully apply this principle here, in the phenethylamine systems under investigation.

The information obtained from chemical shift measurements was used: a. to distinguish between the two diastereotopic $H_2$,$H_3$ benzylic protons in the spectra of the alpha alkylphenethyl analogs; b. to provide supporting evidence for the results on rotamer populations which were calculated from the vicinal coupling constants.

B. Molecular Dynamics

The method we have used to study the microdynamic behavior of the phenethylamine analogs in solution is based on the determination of effective correlation times ($\tau_{eff}$) for individu 1 carbon atoms which can be calculated from the corresponding $^{13}C$ spin-lattice relaxation times ($T_1$). The correlation times measure the period of molecular reorientation of a C-H vector through a given angular displacement. They can also serve as a measure for the motions of individual $^{13}C$ atoms and thus provide. a description of the molecule's dynamic behavior in solution. Such measurements allow us to make semiquantitative comparisons on the flexibility of closely related molecules in solution and also give us information about specific intramolecular interactions which affect their flexibility.

In intermediate sized molecules, spin-lattice relaxation, for carbons directly attached to protons, is usually dominated by the

$^{13}C$-H dipole-dipole mechanism. In such instances, the $T_1$ of a $^{13}C$ nucleus can be related to its effective correlation tine using the following equation (Allerhand et al. 1971) which assumes isotropic motion:

$$T^{-1} = mh^2\gamma_H\gamma_C r_{CH}^{-6} = n2.2065x10^{10}x\tau_{eff}$$

where n = number of protons directly attached on the $^{13}C$ nucleus under consideration. The only possible exceptim in our systems are fast rotating methyl groups where spin-rotation can be a contributing mechanism in the relaxation process. In such instances, the calculated $\tau_{eff}$ values should be considered only as upper limits.

## RESULTS AND DISCUSSION

The conformational and dynamic properties in solution for each of the compounds examined, are discussed, with special emphasis on the effects of alpha alkyl substitution. Chemical shifts, coupling constants and relaxation parameters are listed in tables I, II and III.

### 4-Methoxyphenethylamine hydrochloride (1)

This compound exists in solution as a mixture of two conformers. The conformational preference is slightly in favor of the *trans* conformer, which makes up slightly over me third of the total population. One third is the expected ratio for the *trans* conformer,if there is no conformational preference.

In p-nethoxyphenethylamine hydrochloride, the side chain carbons have similar correlation times indicating that both carbons are moving in unison. The movement of the side chain appears to be faster than the tumbling of the phenyl ring, as indicated by the longer correlation tine values for the phenyl carbons. This is an indicatim that rotation along the C-Ph bond is faster than along the C-C bond of the side chain. The methyl carbon in the para methoxy group has a $T_1$ value considerably longer than that of the rest of the protonated carbons and indicates very fast motion. Its calculated correlation time is probably only an upper limit, because of a possible contribution of spin-rotation in the relaxation of this carbon.

### 4-Methoxyamphetamine (2) and 3,4,5-trimethoxyamphetamine (3) hydrochlorides.

Amphetamines can occur as mixtures of two major (fig. 2, I. II) and one minor (fig. 2, III) conformers. In $D_2O$ compound 2 and compound 3 (which was included in this study because of its solubility in chloroform) occur as a mixture of equally populated conformers I and II with mly a modest cmtribution from conformer III. This last conformer has all three vicinal substituents *gauche* to one another and is, therefore, understandably not favored. When the solvent was changed to $CDCl_3$ in the trimethoxy analog 3) the conformational distribution was shifted strongly in favor of rotamer I which has the ammonium group *trans* and the methyl group *gauche* to the aromatic ring. This is an indication that hydrophobic media favor a *trans* phenethylamine configuration.

**TABLE I**

Proton Chemical Shifts[a] for the

Phenethylamine Hydrochloride Analogs

| Compound | Solvent | Chemical Shift (ppm) $H_1$ | $H_2$ | $H_3$ | $R_4[CH_2]$ | $[CH_3]$ | Difference[c] $V_3$-$V_2$ ($H_Z$) |
|---|---|---|---|---|---|---|---|
| 1 | $D_2O$[b] | 3.199 | 2.910 | | | | |
| 2 | $D_2O$[b] | 3.442 | 2.725 | | | 1.154 | 0 |
| 3 | $D_2O$[b] | 3.425 | 2.733 | | | 1.183 | 0 |
| | $CDCl_3$ | 3.573 | 2.816 | 3.166 | | 1.406 | 94.7 |
| 4 | $D_2O$ | 3.442 | 2.789 | 2.998 | (1.659,1.710) | 1.006 | 56.4 |
| | $CDCl_3$ | 3.375 | 2.880 | 3.183 | (1.708,1.727) | 1.092 | 81.7 |
| 5 | $D_2O$ | 3.449 | 2.639 | 2.962 | (1.667,2.020) | | 87.3 |
| | $CDCl_3$ | 3.613 | 3.044 | 3.266 | (2.041,2.379) | | 60 |

[a]Chemical shifts were measured from TMS which was used as an internal standard in the $CDCl_3$ solutions and as an external standard in a concentric tube in the $D_2O$ solutions. Unless stated otherwise spectra were obtained at 270 $MH_z$ using 0.10M solutions at an ambient temperature of 20°; [b]Spectra taken at 60 $MH_z$ using 0.30M solutions at 20°; [c]Frequency differences for spectra measured at 270 $MH_z$.

The accidental equivalence of the $H_2$ and $H_3$ benzylic protons in both amphetamine analogs when examined in $D_2O$ reflects the weighted deshielding influence of the ammonium group and the shielding influence of the methyl group on each of the two protons, in all three conformers. The net sum of these effects, in the above two examples, is apparently equal for both protons. The change to a hydrophobic solvent, in compound 3, is accompanied with a downfield shift for both $H_2$ and $H_3$ protons. This behavior reflects the increased deshielding influence of the positively charged nitrogen when going from aqueous to hydrophobic media. Furthermore, examination of the spectrum in $CDCl_3$ revealed that the $H_3$ proton undergoes a stronger downfield shift an the $H_2$ proton. he presence of the $H_2$-frequencies at higher field relative to the $H_3$ signal is compatible with the observed increase in the population of rotamer I. In this rotamer, the $H_2$ proton experiences the preferential shielding influence of the *gauche* methyl group. The above observed solvent effect is therefore evidence that the spectral assignments for the $H_2$ and the $H_3$ protons are correct.

The addition of an alpha methyl group on the side chain of the phenethylamine salt analog appears to slow down the overall movement of the molecule, as indicated by the general increase in the correlation times. In this amphetamine analog, the alpha methine carbon is the slowest moving carbon in the side chain and has a correlation time very similar to those of the ring carbons. The beta methylene carbon moves only slightly faster, indicating some flexibility around the C-Ph bond. Finally, the alpha methyl carbon ro-

tates cmsiderably faster than any other carbon on the side chain. Nevertheless, this methyl carbon has a correlation time at least three times as long as that of the freely rotating O-methyl group carbon. This indicates serious restriction in its rotation.

3,4-Dimethoxy-a-ethylphenethylamine Hydrochloride 4

This compound occurs in two principal conformations (I,II). Of these, the *trans* phenethylammonium conformation which has the ethyl group *gauche* to the aromatic ring is favored. As with the alpha methyl analog, the change to hydrophobic solvents enhances this conformation. The change of solvent also causes the signals for the $H_2$ and $H_3$ protons to shift to lower fields; the strongest effect is experienced by the $H_3$ proton. All of the above effects can be explained using the same arguments used for 4-methoxyamphetamine.

In this molecule (4), all but the three methyl carbons have very short relaxation times which correspond to long correlation times and indicate sluggish overall reorientation. Again the alpha methine carbon is the slowest, while the benzylic carbon has a slightly shorter correlation time. Such $\tau_{eff}$ values are compatible with slightly freer mobility around the C-Ph bond compared to the central C-C phenethylamine bond. The two carbons of the alpha ethyl substituent differ greatly in their dynamic behavior. While the methylene carbon is cmsiderably restricted, the methyl carbon has a very fast rotation, as shown by its very short correlation time. The free rotation of the above mentioned methyl group gives us some

TABLE II

Spin-Spin Coupling Constants and Conformational Distributions for the Phenethylamine Hydrochloride Analogs

| Compound | Solvent | $J_{1,2}$(Hz) | $J_{1,3}$(Hz) | $J_{2,3}$(Hz) | pI | pII | pIII |
|---|---|---|---|---|---|---|---|
| 2 | $D_2O$ | 7 | 7 | - | .47 | .47 | .06 |
| 3 | $D_2O$ | 7 | 7 | - | .47 | .47 | .06 |
| | $CDCl_3$[a] | 9.2 | 5.2 | 13.3 | .76 | .23 | .01 |
| 4 | $D_2O$[a] | 8.5 | 5.9 | 14.3 | .67 | .32 | .01 |
| | $CDCl_3$[a] | 9.3 | 5.1 | 13.4 | .77 | .21 | .01 |
| 5 | $D_2O$ | 9.5 | 4.6 | 15.5 | 1 | - | - |
| | $CDCl_3$ | 10.9 | 4.5 | 14.7 | 1 | - | - |
| 1 | $D_2O$[b] | 6.8($J_{AB}$) | 7.6($J_{AB'}$) | 13.5($J_{AA'}$) | .42 | .58 | |

[a] Conformer ratios were calculated assuming $J_t$=11.0Hz and $J_g$=3.5Hz; values were obtained from the model compound γ-1,2,5-trimethyl-4-phenyl-4-piperidinol (Casy 1971); [b] Conformer ratios were calculated assuming $J_t$=13.11 Hz and $J_g$=3.63 Hz (Abraham, and Gatti 1969).

TABLE III

Carbon-13 Spin-Lattice Relaxation Times[a] (sec) and Effective Correlation Times ($x10^{-12}$ sec) for Phenethylamine Hydrochloride Analogs

| Compound | $C_2$ | $C_3$ | $C_4C_5$ | $C_6$ | $C_\beta$ | $C_\alpha$ | $CH_2$ | $CH_3$ | $OCH_3$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1.76 | 1.76 | 1.76 | 1.76 | 1.02 | 1.02 | - | - | 2.31 |
| | (26) | (26) | (26) | (26) | (22) | (22) | | | (<6.5) |
| 2 | 1.07 | 1.04 | 1.04 | 1.07 | .58 | 1.04 | | .74 | 2.06 |
| | (42) | (44) | (44) | (42) | (39) | (44) | | (20) | (<7.7) |
| 4 | .34 | - | .39 | .33 | .27 | .44 | .40 | 1.33 | 0.93 .93 |
| | (133) | | (116) | (137) | (84) | (103) | (57) | (<11) | (<16)(<16) |
| 5. | - | .68($C_5$) | .80($C_7$).74($C_8$).42($C_1$).68($C_2$).41($C_3$).41($C_4$) | | | | | | 1.76 |
| | | (67) | (57) | (61) | (54) | (67) | (55) | (55) | (<8.6) |

[a] Measurements were made using .75M solutions of the compounds in $D_2O$. The results given are the average of three determinations.

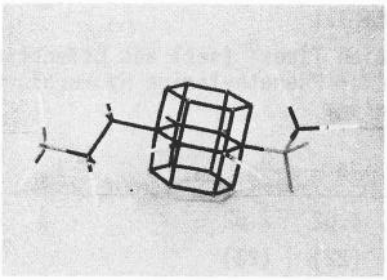
insight into the conformation around the HC-$CH_2CH_3$ bond. Of the three possible conformers, only one will allow the methyl group to experience free rotation. This conformer is one in which the methyl group is *gauche* to the ammonium group and *trans* to the benzylic methylene. According to the evidence, this conformation is the most favored. The chosen conformation is compatible with the downfield shift experienced by the methyl group when the solvent is changed from $D_2O$ to $CDCl_3$. The slightly increased value in the correlation tines of the two ortho O-methyl groups reflects some mutual interference in the rotation of the two groups.

2-Amino-6-methoxytetralin Hydrochloride (5)

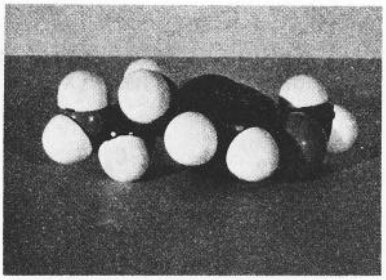
In addition to the coupling constants shown in table II, we have obtained approximate estimates for the vicinal coupling constants of the protons on carbon $C_3$ when coupling with the methine proton on carbon $C_2$ of this compound. These coupling constants were found to be equal to: $J_{vic}$=1OHz; 4Hz. The four vicinal coupling constants at hand are consistent with the two $H_{ax}$,-$H_{ax}$ and two $H_{ax}$-$H_{eq}$ couplings. Such coupling indicates that the saturated ring exists in a chair in which the methine proton on $C_2$ occupies an axial position and the ammonium group is equatorial.

The accurately measured vicinal coupling constants between the two benzylic protons on carbon Cl and the methine proton on $C_2$ indicate that this chair conformation is slightly deformed. If we assume that compound 5 exists in one dominant conformation in solution, we can then evaluate the ring distortion. This can be done by comparing the measured vicinal coupling constants with the coupling constants of

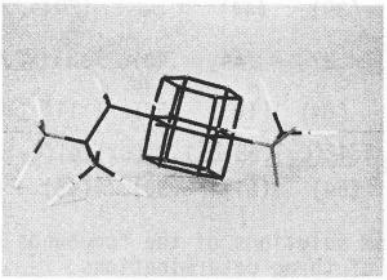
FIGURE 4



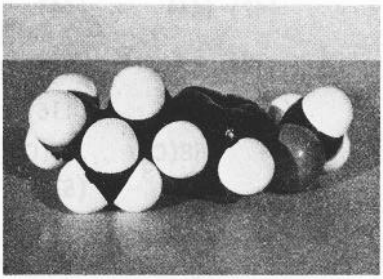
1a



1b



2a



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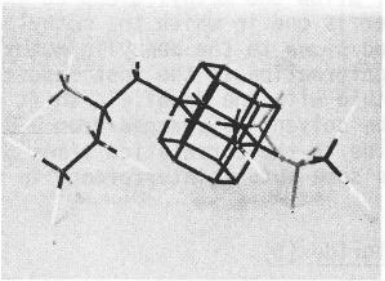
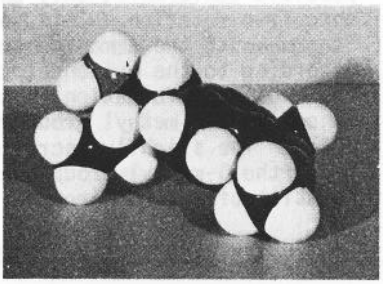
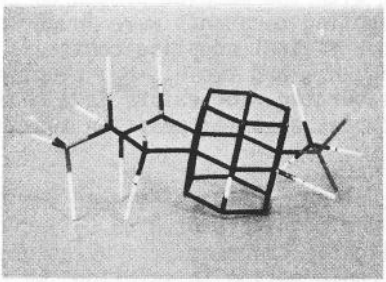


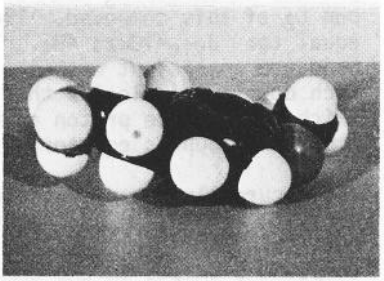
4a



4b



5a



5b

cyclohexane ($J_{ax,ax}$=13.31, $J_{ax\ eq}$=3.59; Abraham and Gatti 1969) which is considered to be a perfectly staggered chair. The following are the calculated dihedral angles for the $C_1H_2C_2H$ fragment of 2-amino-6-methoxytetralin hydrochloride in $D_2O$ and in $CDCl_3$ respectively: $\phi(H_{ax}C_1C_2H_{ax})$155°,158°; $\phi(H_{eq}C_1C_2H_{ax})$=55°, 56°.

The differing relaxation time values of the phenyl ring carbons in this tetralin analog are an indication of a certain degree of anisotropic motion. In this molecule, rotation appears to be favored around an axis which runs very near the $C_6$-O and the $C_2$-N bonds. The consistently shorter correlation times of the aliphatic carbons are an indication of some flexibility in the ring.

## CONCLUSION

Stick as well as space-filled models for compounds 1, 2, 4,and 5, in their preferred conformations, are shown in figure 4. The stick models provide a more accessible representation of the molecular conformation, while the space-filled models give a realistic portrayal of the structural features that may affect the drug-receptor interaction. The conformations around the C-O and the C-Ph bonds are only predicted conformations. Work is currently under progress for their experimental verification.

The evaluation of the results obtained in this study is given below:

1. This study has helped to put the conformational assignments for alpha alkylphenethylamine salts on more solid ground, with the use of variable temperature and solvent experiments. It was found that, in all of the compounds studied here, the *trans* phenethylammonium conformer makes up a sizeable portion of the total conformer population in solution.

2. The *trans* phenethylammonium conformer appears to be enhanced a) by the presence of a small alkyl group in the alpha position; b) by hydrophobic solvents.

3. The addition of alpha alkyl substituents introduces a considerable degree of rotational restriction. This restriction is more pronounced around the central C-C bond, while the C-Ph bond appears to maintain more rotational freedom in all the open chain compounds studied here. The deceased flexibility in the molecule allows a more important role to be played by the conformer distribution in the determination of the drug's biological activity.

4. It is tempting to suggest, on the basis of the evidence provided here, that the *trans* phenethylammonium conformation is essential for psychotomimetic activity. Such a suggestion is compatible with the finding that in the 2-(3.4,5-trimethoxyphenyl) cyclopropylamines, psychotomimetic activity resides with the *trans* isomer (Walters and Cooper 1968; Cooper and Walters 1972).

   No conclusions can be drawn from our experiments about the *pharmacophoric conformation* around the C-Ph bond.

This question will be investigated using ortho substituted phenethylamine analogs. A *trans pharmacophoric conformation* does not rule out the possibility that these drugs may produce their effects by interacting with more than me receptor.

5. The presence of an alpha methyl group *gauche* to the phenyl ring does not seem to obstruct the interaction of the phenethylammonium component with the receptor. On the contrary it may enhance its affinity through some hydrophobic interaction of the methyl group with the receptor site. The possibility of such a specific interaction is strengthened by the existing evidence about the stereospecific requirements of methoxyamphetamines for activity (Shulgin 1973; Standridge et al. 1976). When the alpha methyl is substituted with an ethyl group, the steric requirements of the receptor for productive interaction are not satisfied any longer. As can be seen from the models, the preferred conformation of the ethyl group is such,that the methyl group is protruding beyond the level of the ammonium group and probably obstructs its interaction with the receptor site. However,the molecule can still bind to the receptor although not productively because of its other structural features and therefore acts as an antagonist (probably competitive). The conformation of the alpha $CH_2CH_2$ chain is quite different in the tetralin analog. Such a conformation allows the interaction between the protonated nitrogen with the receptor site to occur and accounts for the psychotomimetic properties of this molecule.

We have currently extended our studies to include other phenethylamine analogs. We are seeking to understand how other structural modifications can affect the conformational properties of phenethylamines and how these conformational changes correlate with their psychotomimetic activity.

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