Quantum Mechanical Study of the Conformational Properties of Phenethylamines of Biochemical and Medicinal Interest†

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The quantum-mechanical MO method PCILO (perturbative configuration interaction using localized orbitals) is applied to the study of the conformational aspects of a series of phenethylamines of biochemical and medicinal significance: phenethylamine, tyramine, dopamine, norepinephrine, norephedrine, epinephrine, ephedrine, and amphetamine. The compounds unsubstituted at the ethylamine side chain exhibit 3 practically equivalent stable conformations, one trans and two gauche ones. Their number is reduced to 2, one trans and one gauche in derivatives containing an α-OH group, the trans form having a slightly greater stability or probability of existence. In amphetamine the folded form is slightly more probable. Since some of the molecules considered are involved in α-sympathomimetic activity, the evaluation of interatomic distances in the preferred conformations, between centers frequently considered to be implicated in the interactions of these drugs with their receptors, suggests possible features for the receptor. Because of its known α-sympathomimetic activity the study has also been extended to naphazoline. The most stable conformation of this drug corresponds to a perpendicular orientation of two rings: naphthalene and imidazole.

Phenethylamine (I) is a basic skeleton for a series of compounds of biological and medicinal interest. Outstanding among them are the neurotransmitter, norepinephrine, the mediators, epinephrine and dopamine, the sympathomimetics, ephedrine and amphetamine, and the hallucinogen, mescaline, etc.

A pioneering effort of utilizing quantum-mechanical procedures for the study of the conformational and electronic characteristics of molecules of medicinal interest was carried out recently by Kier[1-4] and involved, among others, the examination of norepinephrine (II), ephedrine (III), and dopamine (IV) by the Extended Hückel Theory.[5,6] The aim of this paper is an extension and a refinement of the work in this field by enlarging the number of compounds studied and utilizing a more elaborate quantum-mechanical procedure. The compounds included in our computations involve, besides I-IV, tyramine (V), norephedrine (VI), epinephrine (VII), and amphetamine (VIII). One of the basic problems studied is the influence of substituents fixed on the phenylethylamine skeleton upon its conformational properties.

Experimental Section

The method utilized in this work is a refined all-valence-electrons procedure, designated as the PCILO method,[7] developed recently in our laboratory and which has been used successfully in the study of conformational problems concerning a large number of biomolecules: the amino acid residues of proteins,[8-13] nucleosides, and nucleotides,[14] steroids,[15] disaccharides[16] retinals,[17] etc., and more recently of a number of compounds of medicinal interest: serotonin,[18] histamine,[19] cholinergic drugs,[20] etc.

The designation PCILO stands for perturbative configuration interaction using localized orbitals. Details of the method are to be found in the original papers. Only its broad principles are outlined here. A larger summary is presented in reference 13.

The method belongs to the all-valence-electrons procedures, studying, therefore, simultaneously the σ and π electrons. It takes into account interelectronic repulsions and goes beyond the self-consistent field approximation in the calculation of the ground-state energy by incorporating an appreciable fraction of the correlation energy. Its fundamental idea is to choose a set of reasonable bonding and antibonding orbitals localized on the chemical bonds. Such a set may be constructed on a basis of hybridized atomic orbitals (χ_i), the bond orbitals being obtained as linear combinations of distinct hybrids taken two by two, each bonding orbital Φ_i being associated with an orthogonal antibonding orbital Φ_i^*.

$$\Phi_i = C_{i1}\chi_{i1} + C_{i2}\chi_{i2}$$

$$\Phi_i^* = C_{i2}\chi_{i1} - C_{i1}\chi_{i2}$$

A localized orbital representing a lone pair is described by a single hybrid orbital.

The bonding orbitals are then used to construct a fully localized Slater determinant. This determinant represents the zero-order wave function for the ground state of the system. The antibonding orbitals are utilized to build the excited states and a configuration interaction matrix is considered to be constructed on such a basis of configurations. Then, the lowest eigenvalue and eigenstate, *i.e.*, the energy and the wave function of the ground state of the system are obtained by a Rayleigh-Schrödinger perturbation expansion truncated after the third order.

As a technical simplification, the principal working hypotheses of the CNDO/2 procedure have been retained, in particular the hypothesis of complete neglect of differential overlap as well as the general parametrization of this procedure.[21,22]

The study consists, in the first place, of constructing the conformational energy maps by varying the torsion angles τ (this was done in increments of 30°). Bear in mind that the torsion angle τ of the bonded atoms A–B–C–D is the angle between the planes ABC and BCD. Viewed from the direction of A, τ is positive for clockwise and negative for anticlockwise rotations. The value τ = 0° corresponds to the planar-cis arrangement of the bonds AB and CD. Values of τ = 0°, 60°, 120°, and 180° are termed syn-planar, syn-clinal, anti-clinal and anti-planar, respectively. Unless otherwise stated the geometrical input data (bond lengths and bond angles) correspond to standard values. Secondly, some essential electronic characteristics, in particular the significant interatomic distances between groups frequently considered as involved in the activity of the molecules studied, were evaluated for the most stable conformation(s).

Results

Phenethylamine (I). This molecule, representing the fundamental skeleton studied here, contains 3 torsion angles: $\tau_1(C_5\text{–}C_6\text{–}C_7\text{–}C_8)$, $\tau_2(C_6\text{–}C_7\text{–}C_8\text{–}N_9^+)$, and τ_3 $(C_7\text{–}C_8\text{–}N_9^+\text{–}H_{10})$. In fact, the essential angles are τ_1 and τ_2. Following previous evidence based on the study of serotonin, histamine, and the cholinergic drugs[18-20] the N^+H_3 group may be considered as adopting a staggered position with τ_3 = 60°, 180°, and 300°.

The conformational energy map of I is presented in Figure 1. It contains 3 practically equivalent energy minima corresponding all to $\tau_1 = 90°$ and to τ_2 equal, respectively, to 180°, 60°, and –60°. While the combination $\tau_1 = 90°$, $\tau_2 = 180°$ corresponds to an extended all-trans form, the 2 combinations $\tau_1 = 90°$, $\tau_2 = 60°$, and $\tau_1 = 90°$, $\tau_2 = -60°$ correspond to folded enantiomorphs in which the terminal

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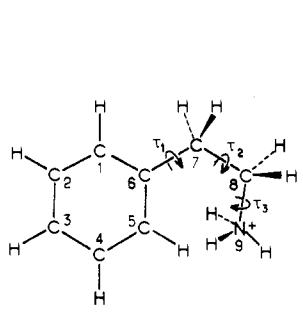
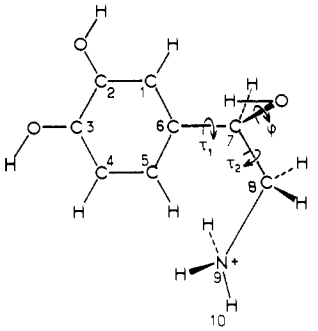
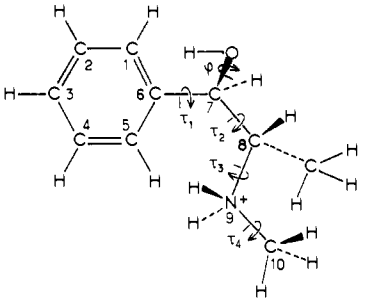


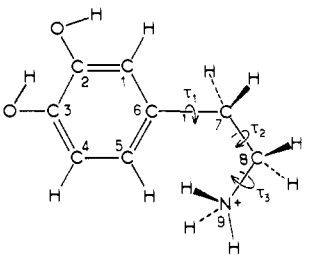
I. PHENETHYLAMINE



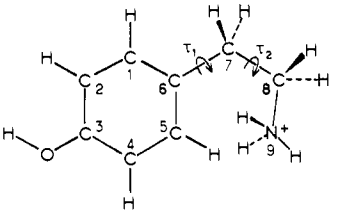
II. NOREPINEPHRINE



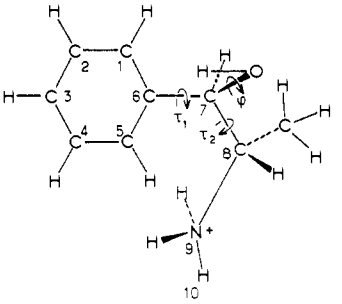
III. EPHEDRINE



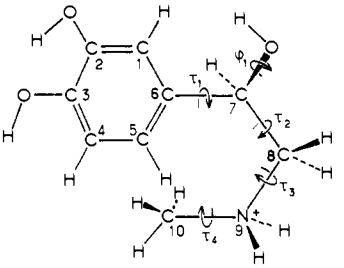
IV. DOPAMINE



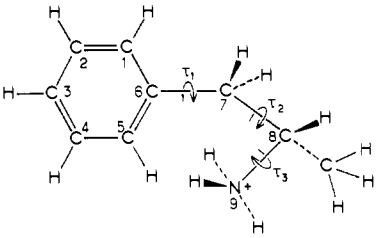
V. TYRAMINE



VI. NOREPHEDRINE



VII. EPINEPHRINE



VIII. AMPHETAMINE

quaternary ammonium group points in the direction of the aromatic ring. For reasons of symmetry τ_1 may also take the value $-90°$, corresponding to the same conformations. Both the energy minima and the surfaces of the low isoenergy contours being practically equivalent the 2 types of conformers have nearly equal probabilities of existence *in vacuo*.

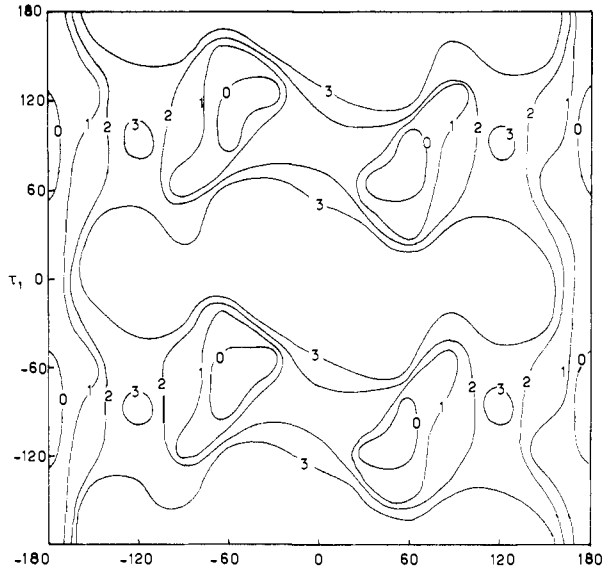


Figure 1. Conformational energy map (kcal/mole with respect to the global minimum) of phenethylamine (I).

In the crystal of phenethylamine only the extended form seems to be observed.[23] This preference must be attributed to the action of intermolecular forces. Fundamentally it is not astonishing that such forces should favor this form which enables the interaction of the side chain of one molecule with the aromatic ring of its neighbor.

Tyramine (V). This molecule differs from I only by the presence of an OH group at the para position. By fixing this group in the plane of the ring, the problem may again be reduced to the evaluation of the conformational stability as a function of the torsion angles τ_1 and τ_2.

The corresponding conformational energy map is given in Figure 2. It is similar to that of Figure 1 having also 3 practically equivalent minima for the same values of τ_1 and τ_2. For symmetry reasons, we find identical minima corresponding to negative values of τ_1. They refer to the same form because, in fact, there is free rotation of the OH group and no optical isomers are observed (τ_1 and $\tau_1 + 180°$ correspond to the same configuration).

Dopamine (IV). This molecule differs from the preceding one by having one more OH group on the benzene ring. In this particular case the geometrical input data were taken from the X-ray study of the crystal of dopamine·HCl.[24] In spite of the differences in details the conformational energy map for dopamine (Figure 3) indicates again the existence of 3 practically equivalent minima corresponding to 1 ex-

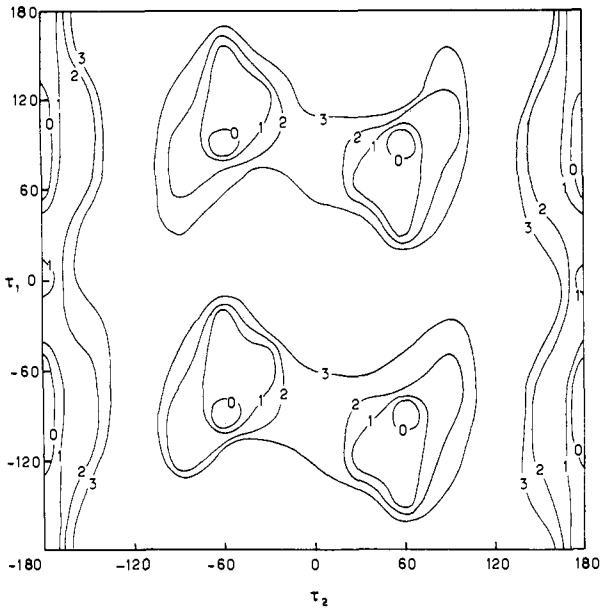


Figure 2. Conformational energy map (kcal/mole with respect to the global minimum) of tyramine (V).

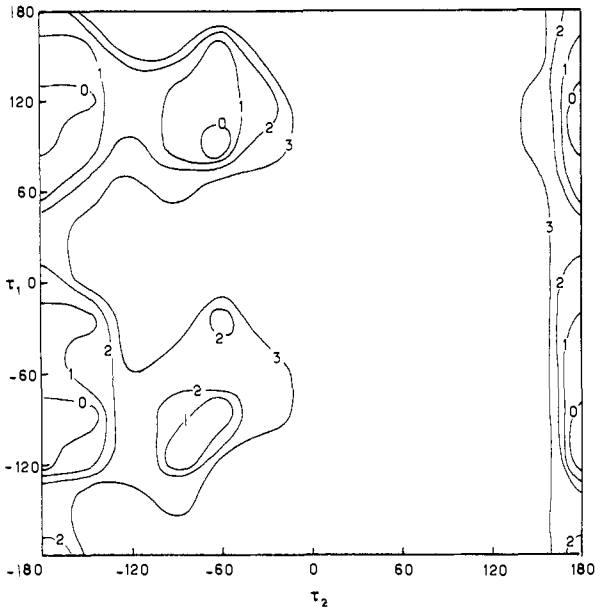


Figure 4. Conformational energy map (kcal/mole with respect to the global minimum) of norepinephrine (II).

tended and 2 folded conformers. The 0 kcal/mole contours for the extended form englobes the coordinates of the crystallographic form ($\tau_1 = 101°$, $\tau_2 = 186°$), which correspond to a trans (extended) conformation. We may remark that the EHT treatment of Kier[3] predicted that gauche (folded) conformers ($\tau_1 = 90°$, $\tau_2 = 60°$, $\tau_1 = 90°$, $\tau_2 = -60°$, $\tau_1 = 150°$, $\tau_2 = -60°$, and $\tau_1 = 30°$, $\tau_2 = 60°$) should be the most stable ones for this compound.

Norepinephrine (II). This molecule contains two OH groups at the phenyl ring at the meta and para positions and a third OH group in the side chain in the α position. We have again considered the N^+H_3 group in the staggered arrangement and fixed the 2 phenolic OH groups in the plane of the ring as indicated in H.

We are thus left with 3 rotational angles τ_1, τ_2, and φ (C_6-C_7-O-H). Three conformational energy maps were constructed corresponding to $\varphi = -60°$, 60°, and 180° and on varying τ_1 and τ_2 in the usual way. The geometrical input data were taken from the crystallographic results of Carlström and Bergin,[25] on the norepinephrine·HCl on symmetrizing, however, the positions of the 3 hydrogens of the quaternary ammonium group.

The 3 conformational energy maps are extremely similar in their general aspects. The maps corresponding to $\varphi = 60°$ and $\varphi = 180°$ have, however, their global minima located, respectively, 2.6 and 2.2 kcal/mole above the global minimum of the map corresponding to $\varphi = -60°$. We have therefore considered this last map as representing the most stable arrangement and it is this map which is reproduced in Figure 4.

The results indicate the existence of two energetically equivalent global minima located at (1) $\tau_1 = 120°$, $\tau_2 = 180°$; (2) $\tau_1 = 90°$, $\tau_2 = -60°$; and of 2 secondary minima, about 1 kcal/mole above the global ones, at (3) $\tau_1 = -120°$, $\tau_2 = 180°$; (4) $\tau_1 = -90°$, $\tau_2 = -60°$.

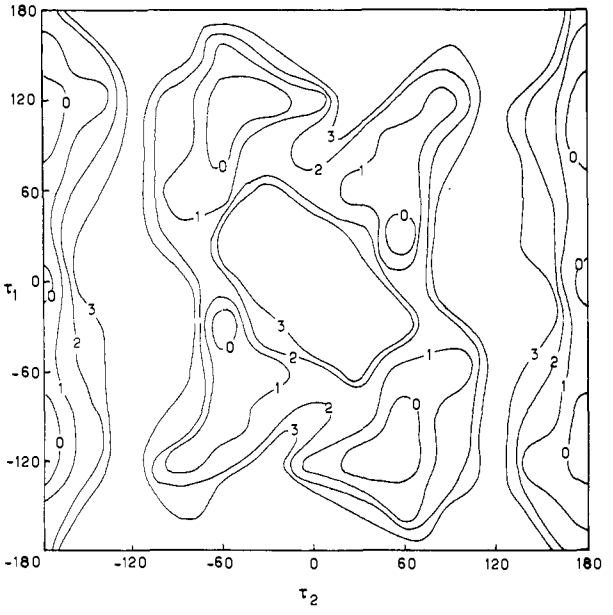


Figure 3. Conformational energy map (kcal/mole with respect to the global minimum) of dopamine (IV).

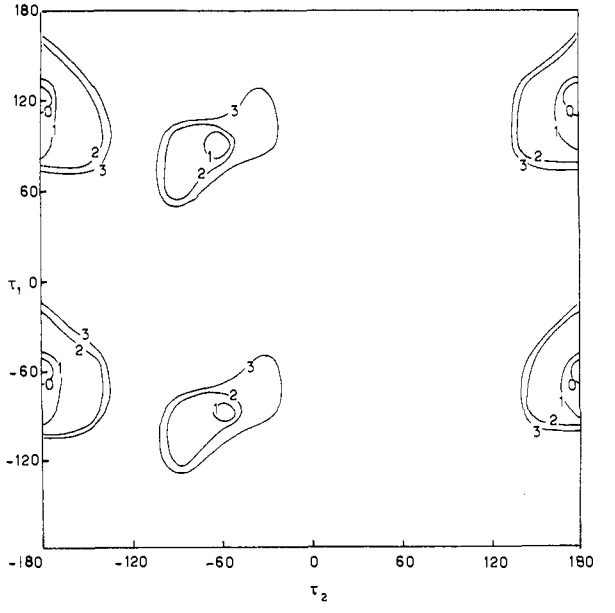


Figure 5. Conformational energy map (kcal/mole with respect to the global minimum) of norephedrine (IV).

The first global minimum which represents an extended conformation and which seems to have a higher *probability* than the second minimum corresponds to the crystalline form observed by Carlström and Bergin[17] and is close to the conformation predicted by Kier[2] using the Extended Hückel Theory. The second equivalent global minimum represents a folded conformation in which the N^+H_3 group is oriented toward the benzene ring. This conformation is also depictable in the Extended Hückel computations where it is, however, predicted to be somewhat less stable than the extended one.

The 2 secondary minima correspond to a variation of 180° in τ_1, *i.e.*, to the rotation of the ring by 180°.

Norephedrine (VI). This molecule does not contain any OH group in the ring. On the other hand it contains an OH and a Me group on adjacent carbons of the side chain. Both this CH_3 group and the terminal N^+H_3 group have been fixed in a staggered position. Moreover by analogy with the results for norepinephrine a value of −60° has been adopted for the torsion angle φ. In these conditions the conformational energy map represented in Figure 5 indicates the existence of 2 regions of stability: (1) a global minimum located at $\tau_1 = 120°$ and $\tau_2 = 180°$ corresponding to an extended conformation and (2) a local minimum, about 1 kcal/mole above the global one, at $\tau_1 = 90°$, $\tau_2 = -60°$ corresponding to a folded form.

One notes also, of course, conformations $\tau_1 = -60°$, $\tau_2 = 180°$ and $\tau_1 = -90°$, $\tau_2 = -60°$ corresponding to the rotation of the ring by 180°.

Epinephrine (VII). The molecule contains two OH groups in the ring, at positions para and meta, and 2 substituents on the side chain, an α-OH group, and a CH_3 group at the amino N. Using for the 3 OH groups the same assumptions as in the case of VI ($\varphi = -60°$, the 2 phenolic OH groups in the plane of the ring), and selecting on the basis of explicit calculations $\tau_3 = 180°$ as the preferred value for this torsion angle, the conformational energy map (Figure 6) indicates the existence of a global minimum at $\tau_1 = 120°$, $\tau_2 = 180°$ corresponding to an extended conformation and of 2 local minima both at $\tau_2 = -60°$ but associated with $\tau_1 = -30°$ and $\tau_1 = 100°$, respectively, and representing 2 folded conformations.

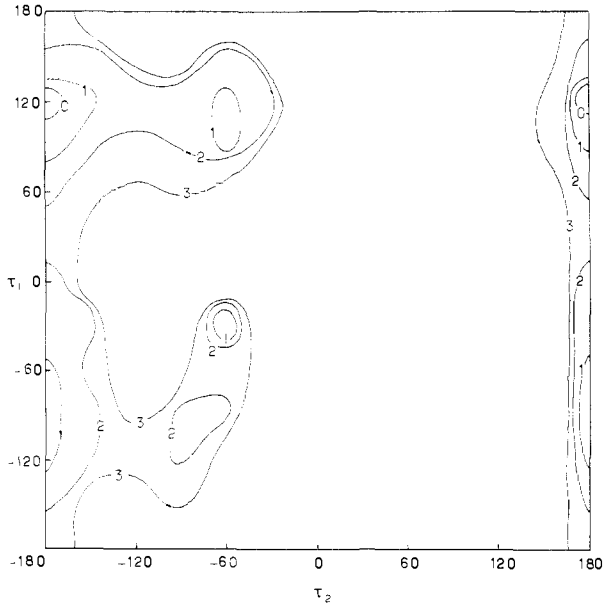


Figure 6. Conformational energy map (kcal/mole with respect to the global minimum) of epinephrine (VII).

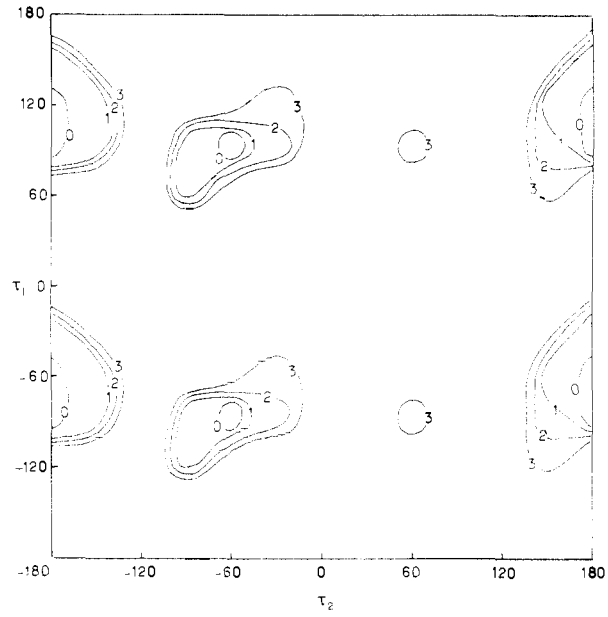


Figure 7. Conformational energy map (kcal/mole with respect to the global minimum) of ephedrine (III).

Ephedrine (III). This molecule does not contain any substituent on the ring, but it carries 3 substituents on the ethylamine side chain: an OH group at the C atom adjacent to the ring and two methyl groups at positions β and γ (NMe). Assuming again $\varphi = -60°$ and a staggered arrangement for the 2 Me groups, the calculations show for τ_3 a preferred value of 180° and the conformational energy map yields the results presented in Figure 7, pointing to the existence of 2 energetically nearly equivalent minima, one at $\tau_1 = 120°$, $\tau_2 = 180°$ and the other at $\tau_1 = 90°$, $\tau_2 = -60°$, of which the first corresponds to an extended and the second to a folded conformation. The zone covered by the 0 kcal/mole contour or by the 1 kcal/mole contour is greater for the extended than for the folded form indicating a somewhat greater probability of occurrence of the former. The first minimum corresponds to the experimental value of ephedrine·HCl[26] and to the calculation of Kier.[1]

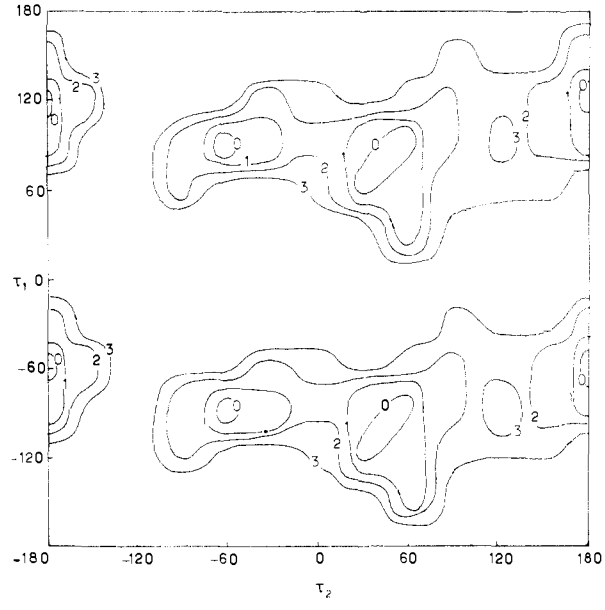


Figure 8. Conformational energy map (kcal/mole with respect to the global minimum) of amphetamine (VIII).

Amphetamine (VIII). This molecule, which has no substituent on the ring, carries a single additional Me group at the β-carbon. Its conformational energy map, presented in Figure 8 resembles that of the molecules devoid of an OH substituent on the α-C in the sense that it presents 3 energetically equivalent minima associated one with the extended conformation ($\tau_1 = 120°$, $\tau_2 = 180°$) and the other 2 ($\tau_1 = 90°$, $\tau_2 = -60°$, and $\tau_1 = 90°$, $\tau_2 = 60°$) with 2 folded conformations. The low isoenergy curves cover a somewhat broader area in the case of the last folded conformation thus indicating that it may have a somewhat greater probability of existence.

General Discussion and Conclusions

The overall conformational problem centers on the preference toward an extended (trans) or a folded (gauche) conformation. In the first case the terminal amino group points away from the ring, in the second it is rotated toward the ring.

Altogether all the molecules studied exhibit one local energy minimum corresponding to an extended form with the plane of the side chain approximately perpendicular to the plane of the ring and 1 or 2 folded conformations. More precisely, the following observations can be made.

(1) The 3 molecules with no substituent at the ethylamine side chain, namely phenethylamine, tyramine, and dopamine, present 3 equivalent energy minima associated one with the extended form and 2 with folded forms. The presence of 1 or 2 OH groups on the ring para or meta with respect to the side chain, apparently does not have a visible influence on the relative stability of these fundamental conformers.

(2) The molecules carrying an OH group at the α-C of the side chain, independently of whether they carry also or do not carry an OH group in the ring (norepinephrine, epinephrine, norephedrine, and ephedrine), manifest generally only 2 stable local energy minima: the presence of the OH group at the side chain eliminates or greatly decreases the relative stability of one of the folded forms, the one corresponding to $\tau_2 \approx 60°$, leaving in competition the extended conformation and the remaining folded one (preferred over the eliminated one because of the tendency of the positively charged quaternary ammonium group to be attracted by the negatively charged alcoholic OH group). The stabilities of the two remaining forms are comparable, however, with a slight advantage on the energy scale or on the probability scale for the extended one.

(3) Amphetamine is an example of a phenethylamine without an OH substituent at the α-C but with a substituent (Me) at the β-C. The removal of the substituent further away from the ring has the effect of favoring the reappearence of 3 energy minima, implying 1 extended and 2 folded conformations, as in the case of the compounds carrying no substituent at the side chain. In contrast to this last case in which the 3 minima are quite equivalent, there appears for amphetamine on the probability scale, a slight preference for one of the folded forms, the one centered on $\tau_1 = 90°$, $\tau_2 = 60°$.

Altogether it is evident that the molecules studied here do not have very striking preferences among their possible extended or folded conformations. It can also be seen from Figures 1-8 that the energy barriers separating these conformations are frequently relatively low, of the order of a few kcal/mole. It may therefore be expected that external conditions (solvent effects or crystal packing forces) will have an important influence on the selection of the observable form. In the 4 cases for which X-ray data are available, phenethylamine, ephedrine, dopamine, and norepinephrine, the crystal structure favors the extended form.‡

Finally, a number of compounds studied in this paper (phenethylamine, tyramine, norephedrine) exert α-sympathomimetic activity; we have considered possible analogies between some characteristics of these molecules and those of norepinephrine, the apparent mediator liberated under the influence of appropriate stimulations at the neuroeffector sites of the sympathetic nervous system. According to Ahlquist[28,29] the sympathomimetics are generally divided into two classes, α- and β-sympathomimetics.

The similarity in the location of the minima on the conformational energy maps of the above cited molecules suggests analogies in the spatial distribution of centers which may play a role in the interaction of α-sympathomimetic drugs with their receptor. (Caution must, of course, be taken with respect to the obvious possibility that conformations calculated for molecules in their free state need not be the same as those of the molecules bound to their receptors or present in solutions or in crystals. In the latter case, the comparison of experimental and theoretical data shows that it is nevertheless frequently so.) Among the centers those which have most frequently been implicated in such interactions are the quaternary N, the alcoholic OH of the side chain, and the Ph ring. We have evaluated therefore the following distances in the stable conformers of these molecules: D_1: the distance between the center of the Ph ring and the O atom of the alcoholic OH; D_2: the distance between the center of the Ph ring and the quaternary N; D_3: the distance between the alcoholic O and the quaternary N; D_4: the distance between the alcoholic O and the plane of the ring; D_5: the distance between the quaternary N and the plane of the ring.

The results are summarized in Table I. They point to a few common features. Thus, in their extended form all the compounds have their N atom situated at a distance 1.2-1.4 Å above the plane of the aromatic ring. The distance of that N from the center of the aromatic ring is 5.11-5.13 Å in the different substituted phenethylamines. The distance between the N and the alcoholic O atom of the side chain in norepinephrine and norephedrine is 2.85 Å and the distance of that O from the center of the Ph ring 3.6-3.7 Å.

Although it possesses a molecular structure which at first sight differs appreciably from that of the above-discussed molecules, we have carried out calculations also for naphazoline (IX), a well-known α-sympathomimetic. This molecule, composed of a naphthalene ring linked to an imidazole ring through CH_2, may be looked upon as containing an enlarged benzene ring and an N atom separated from that ring by 2 C atoms.

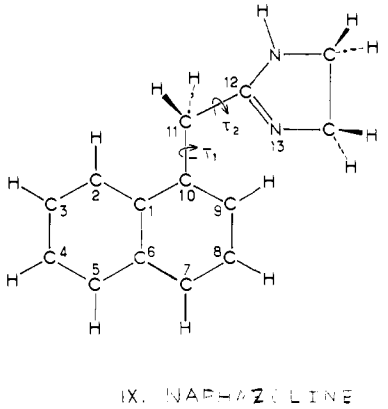
The presence of the 2 rings imposes on the molecule a certain degree of rigidity. There are essentially two torsion angles, $\tau_1 = (C_9\text{-}C_{10}\text{-}C_{11}\text{-}C_{12})$ and $\tau_2 = (C_{10}\text{-}C_{11}\text{-}C_{12}\text{=}N_{13})$. The conformational energy map, presented in Figure 9, indicates the existence of a global minimum at $\tau_1 = 0$, $\tau_2 = -90$ (and of an enantiomorph at $\tau_1 = 0$, $\tau_2 = 90$) corresponding to a mutually perpendicular orientation of the 2 rings. There are a few local minima at 1 or 2 kcal/mole above the global one.

The values of 3 significant interatomic distances: D_5': the distance between the NH of the imidazole ring and the

‡Note Added in Proof. It has been shown recently by nmr studies that the same is true for amphetamine in aqueous solution.[27]

Table I. Interatomic Distances (Å) in Different Stable Conformations of α-Sympathomimetics

	τ_1	τ_2	D_1		D_2		D_3		D_4		D_5		
Phenethylamine													
Extended	90	180			5.11						−1.43		
Folded	90	60				3.82						−2.14	
Folded	90	−60					3.82						−2.14
Tyramine													
Extended	120	180			5.11						−1.24		
Folded	90	60				3.82						−2.14	
Folded	90	−60					3.82						−2.14
Norepinephrine													
Extended	120	180	3.68		5.11			2.85		0		−1.32	
Folded	90	−60		3.69			3.79		2.88		0.67		−2.16
Norephedrine													
Extended	120	180	3.63		5.13			2.84		0		−1.24	
Folded	90	−60		3.64			3.83		2.84		0.66		−2.14



plane of the naphthalene ring; D_5'': the distance between the N of the imidazole ring and the plane of the naphthalene ring; D_5''': the distance between the nitrogens of the imidazole ring and the center of the naphtalene ring; are indicated in Table II.

Possible features which could be postulated on the basis of Tables I and II for the α-adrenergic receptor are illustrated in Figure 10. This model is not fundamentally different from that postulated by Kier.[2,4,30] It cannot, of course, be considered as more than a speculative basis for further investigations. The preparation and trial on isolated organs of rigid analogs corresponding to the predicted stable

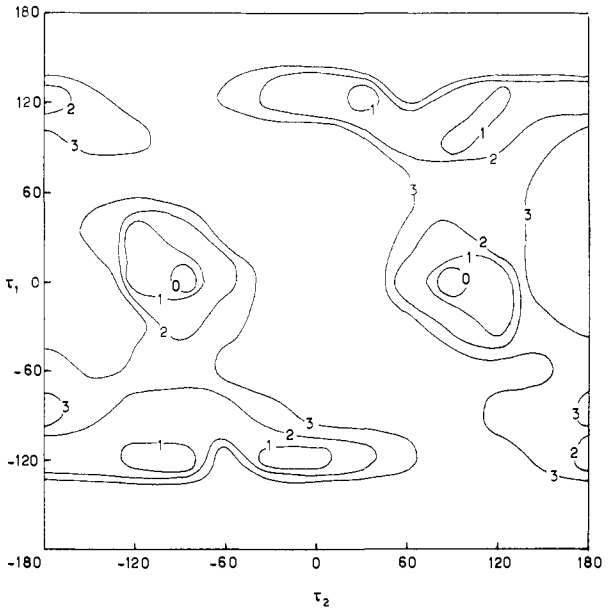


Figure 9. Conformational energy map of naphazoline (IX).

Table II. Interatomic Distances (Å) in Naphazoline

	D_5'	D_5''	D_5'''
1st minimum	+1.33	−1.16	5.25
Its enantiomorph	−1.33	+1.16	5.25

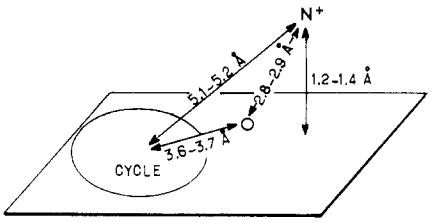


Figure 10. Postulated α-adrenergic receptor features.

conformations could perhaps indicate whether the active site has a configuration close to that suggested by the model.

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Phenethylamine in a Rigid Framework. 2,3-Substituted *cis*- and *trans*-6-Amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols†

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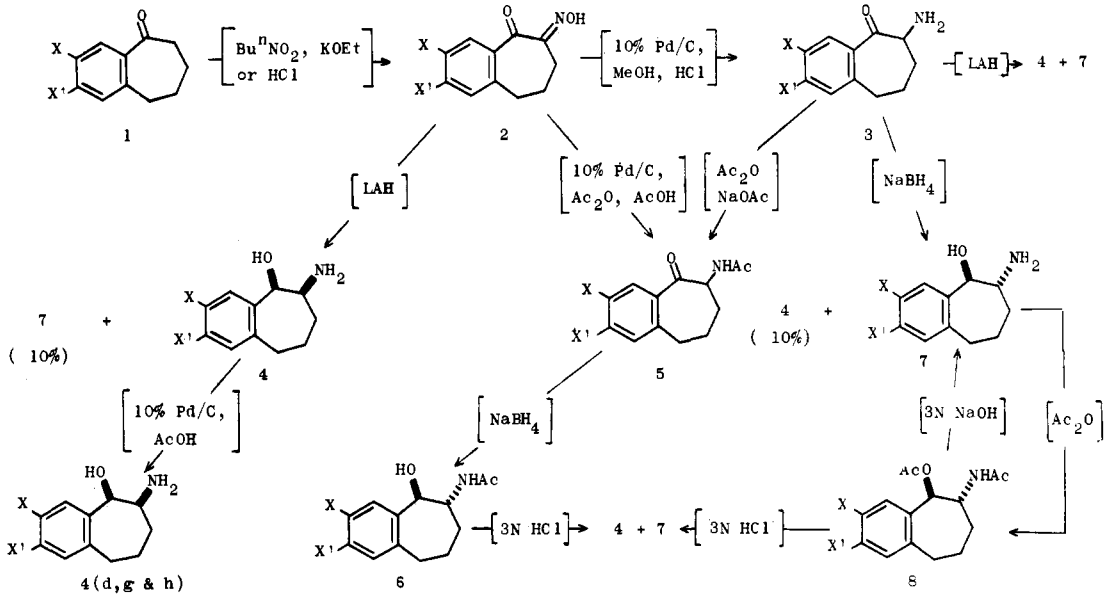
The synthesis and biological activity of 2,3-substituted *cis*- and *trans*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols are described; *cis*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol exhibited significant tranquilizing activity, while *cis*-2,3-dihydroxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol showed marked sympathomimetic activity.

Rigid models of prototypes, having a limited number of permissible conformations, have been useful in receptor analysis. In continuing our study of compounds having the phenethylamine moiety in a rigid framework, 1-aminomethylisochromans[1] and *cis*- and *trans*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols[2] were reported earlier. In this paper we report the synthesis and biological evaluation of *cis*-2-hydroxy-, -3-hydroxy- and -2,3-dihydroxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols and some related 2,3-disubstituted analogs.

The scheme of synthesis is described in Scheme I. Most of the 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones (**1**) required as starting materials were known compounds and were prepared by literature methods.[3-7] 2-Hydroxy- and 2,3-dihydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones (**1g**, **1d**) were prepared by demethylation of the corresponding methoxy ketones using Py · HCl or $AlCl_3$–C_6H_6, and the corresponding benzyl ethers **1e** and **1c** were synthesized by treating the phenols with $PhCH_2Cl$–K_2CO_3 in Me_2CO. 2,3-Diacetoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (**1l**) was prepared by heating **1d** with Ac_2O. The oximino ketones **2** were obtained by treating the ketones **1** with *n*-BuONO in the presence of dry HCl, NaOEt, or KOEt.

The catalytic reduction of oximino ketones, **2**, was found to depend on the activity of the catalyst and the nature of the substituents in the benzene ring (Scheme II). The catalytic reduction of 2-methoxy and 2,3-dimethoxy oximino ketones **2a** and **2j** in MeOH–HCl using dry 10% Pd/C stopped at the stage of the amino ketone **3**, while 3-methoxy and the unsubstituted oximino ketones gave the corresponding aminoheptenols **4** under the same conditions. The same re-

Scheme I



(a) X = X' = OMe
(b) X = X' = Me
(c) X = X' = OCH_2Ph
(d) X = X' = OH
(e) X = H, X' = OCH_2Ph
(f) X = OCH_2Ph, X' = H
(g) X = H, X' = OH
(h) X = OH, X' = H
(i) XX' = $-(CH_2)_4-$
(j) X = H, X' = OMe
(k) X = OMe, X' = H
(l) X = X' = OAc

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