MOLECULAR PHARMACOLOGY, 9, 640–648

Theoretical Studies on the Conformations of Psilocin and Mescaline

SUNGZONG KANG, CARL L. JOHNSON, AND JACK P. GREEN

Department of Pharmacology, Mount Sinai School of Medicine, City University of New York, New York, New York 10029, and Herbert M. Singer Laboratory of Neurosciences and Addictive Diseases, Morris J. Bernstein Institute, Beth Israel Medical Center, New York, New York 10003

(Received March 2, 1973)

SUMMARY

KANG, SUNGZONG, JOHNSON, CARL L., AND GREEN, JACK P.: Theoretical studies on the conformations of psilocin and mescaline. *Mol. Pharmacol.* **9,** 640–648 (1973).

Molecular orbital calculations and classical potential function calculations were carried out to examine the proposal that the conformations of the hallucinogenic tryptamines and phenylalkylamines are such that their 6-membered aromatic rings and their alkylamino nitrogens are congruent with the A ring and N(6) nitrogen atom of lysergic acid diethylamide (the nitrogen of the D ring). The congruent conformation of psilocin is $\psi\{C(9)—C(3)—C(\beta)—C(\alpha)\} = 46 \pm 10$ degrees, $\varphi\{C(3)—C(\beta)—C(\alpha)—N\} = 230 \pm 20$ degrees, $\theta_1\{C(\beta)—C(\alpha)—N—C(1N)\} = 180 \pm 10$ degrees, and $\theta_2\{C(\beta)—C(\alpha)—N—C(2N)\} = 300 \pm 10$ degrees; that of mescaline is $\psi\{C(2)—C(1)—C(\beta)—C(\alpha)\} = 147 \pm 10$ degrees and $\varphi\{C(1)—C[\beta]—C(\alpha)—N\} = 160 \pm 20$ degrees. These results show that congruence of psilocin and mescaline with lysergic acid diethylamide is energetically permissible.

INTRODUCTION

Certain *N*,*N*-dimethyltryptamines (e.g., psilocin) and methoxylated phenylalkylamines (e.g., mescaline) are hallucinogenic and show cross-tolerance with *d*-lysergic acid diethylamide (1–7) that is not attributable to metabolic disposition (7) but rather suggests activity at the same or a similar site in the nervous system. In a paper from this laboratory (8) it was suggested that the conformations of the hallucinogenic tryptamines and phenylalkylamines at the receptor were such that their 6-membered aromatic rings and their alkylamino nitrogens are congruent with the A ring and N(6) of lysergic acid diethylamide (Fig. 1). The lone pair electrons (or the proton) of the nitrogen would be below the plane in the same way as that of lysergic acid diethylamide. This proposed conformation, which explains the inactivities of *l*-lysergic acid diethylamide and *d*-isolysergic acid diethylamide (9), has received support from radioimmunoassay studies (10), from observations on the mescaline-like activity of the *trans* isomer of the cyclopropylamine analogue of mescaline (11), from observations on the mescaline-like activities of the *R* forms of hallucinogenic phenylisopropylamines (12, 13), and from the observed (and predicted) mescaline-like activity of 2-amino-7-hydroxytetralin (14). Another proposed conformation (15) cannot account for all these laboratory findings. That the conformation proposed by us was not observed in crystals (16) does not pre-

This research was supported by Grant MH-17489 from the National Institute of Mental Health.

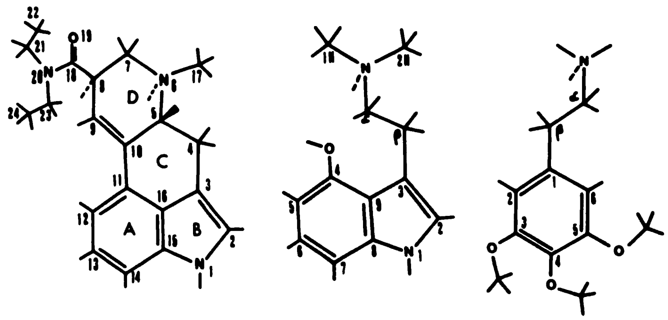

FIG. 1. *Numbering scheme for lysergic acid diethylamide, psilocin, and mescaline*

clude their occurrence at the biological site of action: more than one conformation can be observed in a unit cell of a single crystal (16, 17); and the conformation in crystals is influenced by the free energy of crystal packing, which is not a consideration in a biological system. The unknown effects of a receptor on the molecule require that evidence of all kinds be considered in inferring the conformation, including information obtained from molecular orbital studies. The conformation that we proposed (8) was based on stereochemical models because the exact atomic coordinates of lysergic acid diethylamide were not known at the time. With the availability of these coordinates (16),[1] the proposed conformations of mescaline and psilocin were examined by both classical potential function calculations and molecular orbital calculations. The results of this work are presented here.

METHODS

Molecular geometry and stereochemical definition. Standard bond lengths and bond angles (18) were used to define the geometry of mescaline and psilocin. The dihedral angles of mescaline and psilocin are given in Table 1. Positive rotation means clockwise rotation of the far bond with respect to the near bond, as proposed by Klyne and Prelog (19).

TABLE 1

Definition of dihedral angles of mescaline and psilocin (see Fig. 1)

Compound	Notation	Dihedral angle
Mescaline	φ	N(alkyl)—C(α)—C(β)—C(1)
	ψ	C(α)—C(β)—C(1)—C(2)
Psilocin	θ_1	C(1N)—N(alkyl)—C(α)—C(β)
	θ_2	C(2N)—N(alkyl)—C(α)—C(β)
	φ	N(alkyl)—C(α)—C(β)—C(3)
	ψ	C(α)—C(β)—C(3)—C(9)

Methods of energy calculations. The molecular orbital method at the intermediate neglect of differential overlap level of approximation (20) and the classical Lennard-Jones 6–12 potential function, including an electrostatic term (21–23), were used to calculate the conformational energy. In the classical calculations the energy of the nonbonded interaction is given by

$$E_{ij} = \frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} + 332.0 \times \frac{q_i q_j}{D \cdot r_{ij}}$$

where r_{ij} is the distance between atoms i and j. B_{ij} is given by the Slater-Kirkwood equation

$$B_{ij} = \frac{\frac{3}{2}\, e(\hbar/m^{1/2})\alpha_i \alpha_j}{(\alpha_i/N_i)^{1/2} + (\alpha_j/N_j)^{1/2}}$$

where α_i and α_j are the atomic polarizabilities, and N_i and N_j are the effective numbers of outer shell electrons on atoms i and j, respectively. A_{ij} is given by the expression

$$A_{ij} = \tfrac{1}{2} B_{ij} r_{\min}^{6}$$

where $r_{\min}$ is the sum of the intramolecular van der Waals (24) radii for atoms i and j. D is the dielectric constant and assumed to be 1.0 for these calculations. q_i and q_j are the net atomic charges on atoms i and j, cal-

---

[1] P. Pauling, personal communication.

culated by the INDO[2] molecular orbital method, for mescaline cation with $\varphi = 180$ degrees and $\psi = 90$ degrees, and for psilocin cation with $\theta_1 = 60$ degrees ($\theta_2 = 180$ degrees), $\varphi = 180$ degrees and $\psi = 90$ degrees. Calculations of the net atomic charges on all atoms of the molecule in different conformations (48 for mescaline cation and 168 for psilocin cation) showed that the charges did not significantly vary with alteration of the conformation, changing only in the fourth decimal except where there was hydrogen bonding, as between the phenolic hydroxyl group of psilocin and the side chain amino group. The orientations of the hydroxyl group of psilocin and the methoxy groups of mescaline are shown in Fig. 1. It was observed that the orientation of the methoxy group does not influence the conformational energy diagram. Other constants used in these calculations are given elsewhere (24).

RESULTS

Mescaline. The total molecular orbital energies of the molecule were calculated by simultaneously rotating φ and ψ in increments of 30 degrees. The values of the energy at 5-degree intervals were estimated by plotting the energy against φ and ψ and drawing curves through the points. Values of the energy at 5-degree intervals were estimated from the curves and used to construct a contour diagram (Fig. 2) with a CDC-6600 digital computer plotting program. The contour diagram, as well as the molecule, has S_2 symmetry (rotation-reflection) along the $\psi = 90$ degrees or $\varphi = 180$ degrees symmetry axis; thus the conformer of $\varphi\, 30 =$ degrees and $\psi = 60$ degrees is identical with the conformer of $\varphi = 330$ degrees and $\psi = 120$ degrees. As a result, two minimal energy conformations were observed: $\varphi = 60$ degrees and $\psi = 90$ degrees and $\varphi = 180$ degrees and $\psi = 90$ degrees. Similar results were obtained for phenylethylamines by another method (25), perturbative configuration interaction using localized orbitals (PCILO). X-ray crystallographic analyses of phenylethylamines (16, 26) showed two conformations that fall in the two energy minima (Fig. 2).

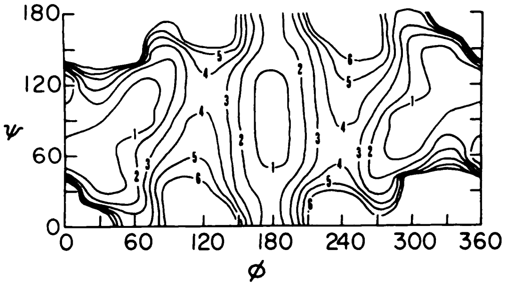

FIG. 2. *Conformational energy contour diagram (ψ-φ map) of mescaline cation, calculated by the INDO molecular orbital method*

The lowest energy conformer, $\psi = 60$ degrees and $\varphi = 30$ degrees, was set to zero. The numbers inside the diagram are given in kilocalories per mole. Since the diagram has S_2 symmetry (rotation-reflection) along the $\psi = 90$ degrees or $\varphi = 180$ degrees axis, the left and right side energy minima are identical.

Psilocin. Because of the bulky N,N-dimethyl groups the rotation of the dihedral angle θ of psilocin becomes important; thus the complete conformational energy calculations require simultaneous rotations of θ, φ, and ψ. Complete calculation by the INDO molecular orbital method is at present impractical. Therefore the energies of the molecule were calculated by the simultaneous rotations of φ and ψ in increments of 30 degrees (and, when appropriate, 15 degrees), while θ_1 was fixed either at 60 degrees ($\theta_2 = 180$ degrees) or at 180 degrees ($\theta_2 = 300$ degrees), respectively (see Table 1). The conformer of $\theta_1 = 60$ degrees and $\theta_2 = 180$ degrees is the *gauche-trans* form; the conformer of $\theta_1 = 180$ degrees and $\theta_2 = 300$ degrees is the *trans-gauche* form. The *gauche-gauche* form ($\theta_1 = 300$ degrees and $\theta_2 = 60$ degrees) was not calculated, since molecular models showed that this form would be less stable than the other two forms because of steric hindrance, a conclusion supported by crystallographic studies (16, 17). The values of the energy at 5-degree intervals were obtained by the graphic method as described above for mescaline and were used to construct the contour diagram shown in Fig. 3.

The results (Fig. 3) show that in the *gauche-trans* form of the θ angle three energy minima were observed: $\varphi = 30$ degrees, $\psi = 45$ degrees; $\varphi = 180$ degrees, $\psi = 45$ degrees; and $\varphi = 270$ degrees, $\psi = 120$ degrees. The lower

---

[2] The abbreviation used is: INDO, intermediate neglect of differential overlap.

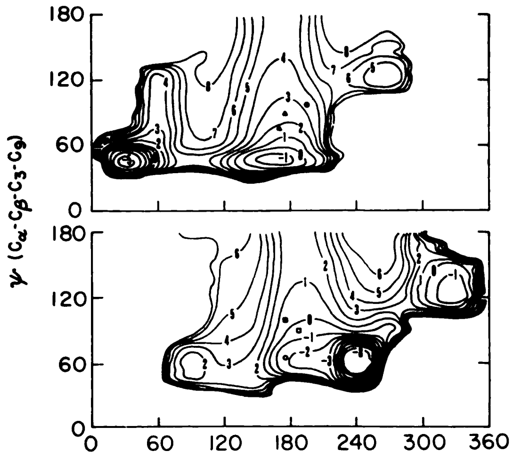

FIG. 3. *Conformational energy diagrams (ψ-φ map) of psilocin, calculated by the INDO molecular orbital method*

In the upper diagram the angle of the molecule was fixed such that θ_1 = 60 degrees and θ_2 = 180 degrees. In the lower diagram the angle was fixed such that θ_1 = 180 degrees and θ_2 = 300 degrees (*tg* form). The energy of the conformer of θ_1 = 180, φ = 180, and ψ = 90 degrees was set to zero. The numbers inside the diagram are given in kilocalories per mole. The experimentally observed conformations are: ○ and ●, psilocybin; △ and ▲, *N*,*N*-dimethyl-5-hydroxytryptamine; □ and ■, *N*,*N*-dimethyltryptamine.

energy at φ = 30 degrees and ψ = 45 degrees is probably due to hydrogen bonding between the hydrogen of the alkylamino nitrogen and O(4): the distance between N(alkyl) and O(4) is 2.8 A, and that between H(*N*-alkyl) and O(4) is 2.4 A. Such a hydrogen bond is unlikely in physiological solution, owing to the energetically more favorable solute-water hydrogen bonding, as often observed (e.g., ref. 27). Another local minimum, at φ = 270 degrees and ψ = 120 degrees, has relatively high energy compared with other minima and would not be preferred.

In the *trans-gauche* form of the θ angle three energy minima were also observed: φ = 90 degrees, ψ = 60 degrees; φ = 240 degrees, ψ = 60 degrees; and φ = 300 degrees, ψ = 120 degrees. The especially low energy at φ = 240 degrees and ψ = 60 degrees is due to the hydrogen bonding between the hydrogen of the alkylamino nitrogen and O(4): the distance between N(alkyl) and O(4) is 2.5 A, and that between H(*N*-alkyl) and O(4) is 1.6 A. Again, such hydrogen bonding is unlikely in physiological solution, on account of the energetically more favorable solute-water hydrogen bonding (e.g., ref. 27). In the absence of such a hydrogen bond the energy minimum at φ = 240 degrees and ψ = 60 degrees shifts to φ = 180 degrees and ψ = 60 degrees. Crystals of hallucinogen tryptamines have been described with conformations that fall in the region of φ = 180 degrees and ψ = 60 degrees (16, 17).

In order to define further the importance of the θ rotation, the classical energy calculations were performed by simultaneously rotating θ and φ at a fixed ψ value or θ and ψ at a fixed φ value in increments of 5 degrees. Figure 4 shows that at ψ = 60 degrees the preferred conformational energy range is φ = 180 degrees and θ_1 = 60–180 degrees. At ψ = 90 degrees the preferred conformational energy range is near φ = 180 degrees and θ_1 = 60–180 degrees. However, the preferred energy range at ψ = 90 degrees is wider than that at ψ = 60 degrees (Fig. 5). The θ-ψ energy contour diagram at φ = 180

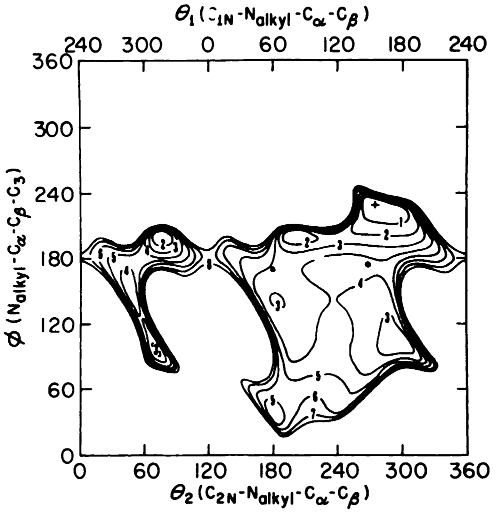

FIG. 4. *φ-θ energy map at ψ = 60 degrees, calculated by the classical method*

+ denotes the zero-energy point. The experimentally observed conformations are: ○, psilocybin; ▲, *N*,*N*-dimethyl-5-hydroxytryptamine. The numbers inside the diagram are given in kilocalories per mole.

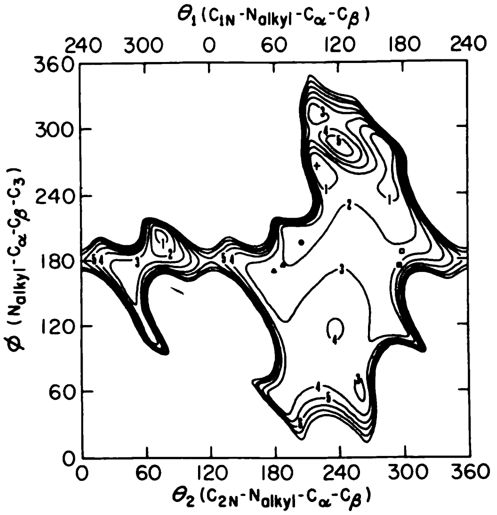

FIG. 5. *φ-θ energy map at ψ = 90 degrees, calculated by the classical method*

+ denotes the zero-energy point. The experimentally observed conformations are: ●, psilocybin; △ and ▲, N,N-dimethyl-5-hydroxytryptamine; □ and ■, N,N-dimethyltryptamine.

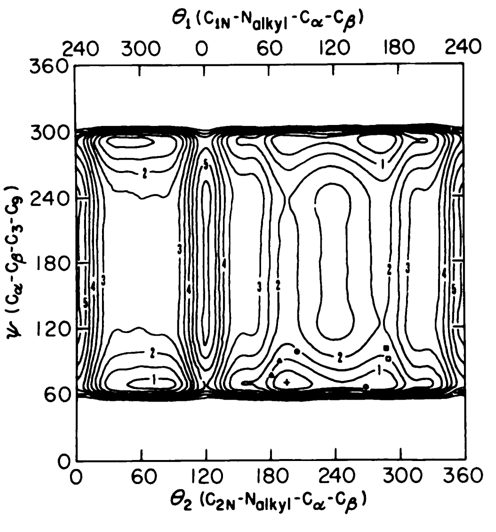

FIG. 6. *ψ-θ energy map at φ = 180 degrees, calculated by the classical method*

+ denotes the zero-energy point. The experimentally observed conformations are: ○ and ●, psilocybin; △ and ▲, N,N-dimethyl-5-hydroxytryptamine; □ and ■, N,N-dimethyltryptamine. The contour level is 0.5 kcal/mole. The numbers inside the diagram are given in kilocalories per mole.

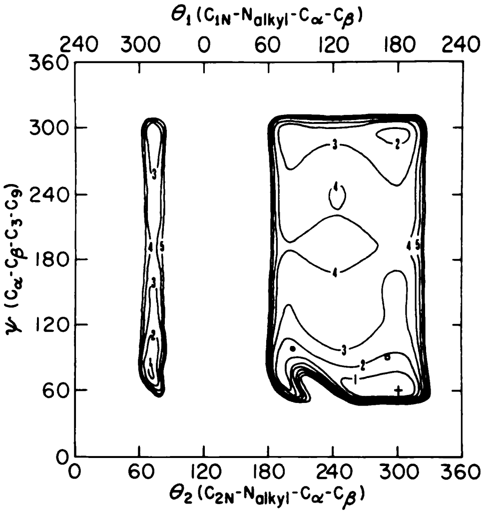

FIG. 7. *ψ-θ energy map at φ = 210 degrees, calculated by the classical method*

+ denotes the zero-energy point. The experimentally observed conformations are: ●, psilocybin; □, N,N-dimethyltryptamine. The numbers inside the diagram are given in kilocalories per mole.

degrees shows two energy minima: ψ = 65 degrees and θ_1 = 300 degrees, and ψ = 60 degrees and θ_1 = 60–180 degrees (Fig. 6). At φ = 210 degrees the θ-ψ diagram showed one major minimum, at ψ = 60 degrees and θ_1 = 180 degrees (Fig. 7). Since the θ-ψ diagram at ψ = 60 degrees (Fig. 4) is a continuation of that at ψ = 90 degrees (Fig. 5) along the ψ angle, the preferred conformational ranges at ψ = 60 degrees and ψ = 90 degrees are identical. The same is true for the θ-ψ diagrams at φ = 180 degrees and φ = 210 degrees.

DISCUSSION

The proposed conformations (8) of tryptamines and phenylalkylamines, as congruent with d-lysergic acid diethylamide, have not been observed by crystallographic studies (13). Availability of the atomic coordinates of this drug provided an opportunity to examine more rigorously the possibility that these conformations can exist. Because the X-ray crystallographic data on lysergic acid diethylamide (16) showed, surprisingly, that the indole ring is out of plane, we optimized slightly in order to put the indole ring in plane, consonant with other studies (17). If it is assumed that C(11), C(12), and C(13) of the A ring of lysergic acid diethylamide have (x, y, z) coordinates (in Angstrom units) of C(11) = (0, 0, 0), C(12) = (0, 0, 1.39), and C(13) = (1.23, 0, 2.06), then N(6) of lysergic acid diethylamide has the coordinate value of (-2.15, 0.42, -3.01). When the ring of mescaline is superimposed on the A ring of lysergic acid diethylamide and φ and ψ are simultaneously rotated in increments of 1 degree, the most congruent position (-2.21, 0.41, -3.01) of the alkylamino nitrogen of mescaline with N(6) of lysergic acid diethylamide is $\psi = 147$ degrees and $\varphi = 160$ degrees. The congruent position (-1.93, 0.43, -3.06) of psilocin gives the value of $\psi = 46$ degrees and $\varphi = 230$ degrees. The deviation from exact congruency within a small volume element, e.g., $(\pm 0.2)^3$, should not prevent an interaction, and we may still expect the conformation of $\psi = 147 \pm 10$ degrees and $\varphi = 160 \pm 20$ degrees for mescaline, and of $\psi = 46 \pm 10$ degrees and $\varphi = 230 \pm 20$ degrees for psilocin, to be congruent with lysergic acid diethylamide.

Figure 2 shows that the conformation of mescaline congruent with lysergic acid diethylamide is within 2 kcal/mole of the global minimum, which could well permit interaction with the receptor.

Because of the bulky *N*,*N*-dimethyl groups of psilocin, the φ-ψ map varies with the orientation of the θ angle. For *N*,*N*-dimethyltryptamines the conformation of the θ angle is as important as the φ and ψ conformations, because the θ angle determines the position of the nitrogen lone pair electrons or the incoming proton. Thus θ_1 of psilocin corresponds to the dihedral angle C(4)—C(5)—N(6)—C(7) of lysergic acid diethylamide, and θ_2 corresponds to the dihedral angle C(4)—C(5)—N(6)—C(17). The X-ray crystallographic data show that the dihedral angle C(4)—C(5)—N(6)—C(7) of lysergic acid diethylamide is 178 degrees and that the dihedral angle C(4)—C(5)—N(6)—C(17) is 300 degrees (16). The *trans-gauche* ($\theta_1 = 180$ degrees, $\theta_2 = 300$ degrees) form of the θ angle of psilocin is therefore congruent with lysergic acid diethylamide (lower diagram of Fig. 3). Figures 3–7 show that the conformation of psilocin congruent with lysergic acid diethylamide is within 3 kcal/mole of the global minimum, which could well permit interaction with the receptor.

The molecular orbital calculations indicate that although the conformations of psilocin and mescaline that are congruent with lysergic acid diethylamide are not necessarily the most stable ones, only small energy differences—less than the energy of a hydrogen bonding—need to be overcome in order to attain the congruency. These energy differences, however, could result in a relatively small amount of the appropriate conformer being available (Boltzmann distribution) to the receptor, which could account for the relatively low potencies of these compounds compared with *d*-lysergic acid diethylamide.

Consistent with these proposed conformations of psilocin and mescaline are observations that it is the *R* forms of the hallucinogenic phenylisopropylamines that are active (12, 13), and that 2-amino-7-hydroxytetralin is mescaline-like (14). Both these observations were explicitly predicted in a previous paper (8), both in the text and in Fig. 1 of that paper. These proposed conformations also account for the inactivities of *l*-lysergic acid diethylamide (ref. 8 and Fig. 8) and of *d*-isolysergic acid diethylamide (Fig. 8).

The inactivity of *d*-isolysergic acid diethylamide could rest solely on the fact that its diethylamide group at C(8) is axial. In this case the bulky diethylamide group is oriented below the plane and sterically hinders the approach of the lone pair of the N(6) nitrogen to the receptor; alternatively the axial orientation may not be stable, and the D ring may be puckered so that the lone pair of the N(6) nitrogen is not oriented below the plane (the conformation of the D ring of *d*-isolysergic acid diethylamide is not known). In addition, the diethylamide group itself may react with the receptor, and an equatorial orientation may be necessary for the reaction; it is known that the dimethylamide analogue of lysergic acid diethylamide has lower activity than the latter and that lysergic acid has little or no biological activity (9).

Chothia and Pauling (15) proposed a conformation of tryptamines and phenylalkylamines in which $\psi = \pm 90$ degrees and $\varphi = \pm 180$ degrees for both compounds; the coordinate positions of the alkylamino nitrogen (if it is assumed that the benzene ring is congruent with the A ring of lysergic acid diethylamide) are (−0.84 ±1.45, −4.67) for

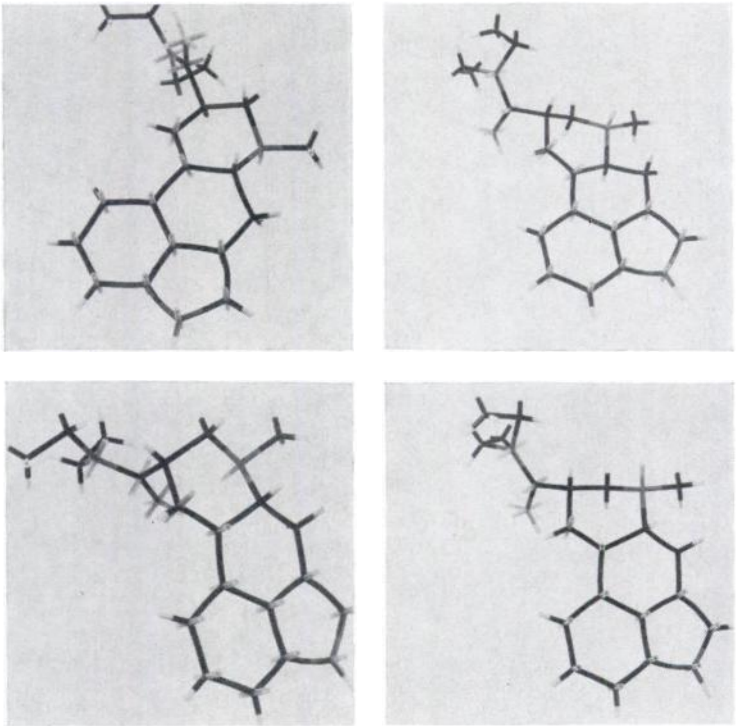

FIG. 8. *Structures of lysergic acid diethylamide isomers*

Upper left, *d*-lysergic acid diethylamide (5*R*,8*R*); upper right, *l*-lysergic acid diethylamide (5*S*,8*S*); lower left, *d*-isolysergic acid diethylamide (5*R*,8*S*); lower right, *d*-isolysergic acid diethylamide (5*R*,8*S*) with the D ring puckered.

TABLE 2

Proposed coordinates in mescaline and psilocin compared with coordinates of d-lysergic acid diethylamide obtained by X-ray diffraction analysis

It is assumed that the benzene rings of psilocin and mescaline are superimposed on the A ring of *d*-lysergic acid diethylamide.

Compound	Atom	Coordinates (in Angstrom units)			Reference
		x	*y*	*z*	
Lysergic acid diethylamide	C_{11}	0	0	0	16
	C_{12}	0	0	1.39	
	C_{13}	1.23	0	2.06	
	N_6	−2.15	0.42	−3.01	
Mescaline	N_6	−2.21	0.41	−3.01	This paper
	N_6	−3.03	±1.45	−1.75	15
Psilocin	N_6	−1.93	0.43	−3.06	This paper
	N_6	−0.84	±1.45	−4.67	15

TABLE 3

Conformations of N,N-dimethyltryptamines as observed in crystals

The angles θ_1 and θ_2 were calculated in this work.

Compounds	Symbol[a]	ψ	φ	θ_1	θ_2	Reference
		degrees				
Psilocybin						
A molecule	○	65	174	144	269	16
B molecule	●	98	195	84	205	16
5-Hydroxy-*N*,*N*-dimethyltryptamine						
A molecule	△	−89	175.7	67.8	188.7	17
B molecule	▲	−102	170.4	58.9	180.2	17
N,*N*-Dimethyltryptamine						
A molecule	□	−89	188.2	166.8	289.3	17
B molecule	■	−79	175.8	165.6	288.2	17

[a] Symbols used in Figs. 3–7.

tryptamines and $(-3.03 \pm 1.45, -1.75)$ for phenylalkylamines. In this model the alkylamino nitrogen is far away from N(6) of lysergic acid diethylamide (Table 2). The model cannot explain why *l*-lysergic acid diethylamide and *d*-isolysergic acid diethylamide are inactive. Nor does it explain the activities of the *R* form of phenylisopropylamines (12, 13) and 2-amino-7-hydroxytetralin (14). A subsequent model (15) not only has these deficiences but also cannot explain cross-tolerance between mescaline and lysergic acid diethylamide (Fig. 4 of ref. 16).

It is interesting that there is little or no energy barrier between the *gauche-trans* (θ_1 = 60 degrees, θ_2 = 180 degrees) form and the *trans-gauche* (θ_1 = 180 degrees, θ_2 = 300 degrees) form, but a large energy barrier between the *gauche-gauche* (θ_2 = 300 degrees, θ_2 = 60 degrees) form and the *gauche-trans* form, or between the *gauche-gauche* form and the *trans-gauche* form (Table 3 and Figs. 4–7). Interestingly, both the *gauche-trans* and *trans-gauche* forms are observed in crystals (16, 17) (see Table 2). The observed hydrogen bonding of $O(4) \cdots H—N(CH_3)_2—CH_2—$ (Fig. 3) is unlikely to exist in physiological solution, but in a nonpolar environment, with the amino group deprotonated, hydrogen bonding of the type $O(4)H \cdots N(CH_3)_2CH_2—$ could exist.

ACKNOWLEDGMENT

We thank Mr. Marian Strelczyk for technical assistance.

REFERENCES

1. A. Balestrieri and D. Fontanari, *Arch. Gen. Psychiat.* 1, 279–282 (1959).
2. D. X. Freedman and G. K. Aghajanian, *Fed. Proc.* **18**, 390 (1959).
3. A. B. Wolbach, Jr., H. Isbell, and E. J. Miner, *Psychopharmacologia* 3, 1–14 (1962).
4. J. R. Smythies, E. A. Sykes, and C. P. Lord, *Psychopharmacologia* **9**, 434–446 (1966).
5. J. B. Appel and D. X. Freedman, *Psychopharmacologia* 13, 267–274 (1968).
6. M. T. Silva, E. A. Carlini, U. Claussen, and F. Korte, *Psychopharmacologia* **13**, 332–340 (1968).
7. J. C. Winter, *J. Pharmacol. Exp. Ther.* **178**, 625–630 (1971).
8. S. Kang and J. P. Green, *Proc. Nat. Acad. Sci. U. S. A.* 67, 62–67 (1970).
9. H. Isbell, E. J. Miner, and C. R. Logan, *Psychopharmacologia* **1**, 20–28 (1959).
10. H. Van Vunakis, J. T. Farrow, H. B. Gjika, and L. Levine, *Proc. Nat. Acad. Sci. U. S. A.* **68**, 1483–1487 (1971).
11. P. D. Cooper and G. C. Walters, *Nature New Biol.* **238**, 96–98 (1972).
12. A. T. Shulgin, *J. Pharm. Pharmacol.* **25**, 271–272 (1973).
13. F. Benington, R. D. Morin, J. Beaton, J. R. Smythies, and R. J. Bradley, *Nature New Biol.* **242**, 185–186 (1973).
14. J. P. Green, K. P. Dressler, and N. Khazan, *Life Sci.* **12**, 475–479 (1973).
15. C. Chothia and P. Pauling, *Proc. Nat. Acad. Sci. U. S. A.* **63**, 1063–1070 (1969).
16. R. W. Baker, C. Chothia, P. Pauling, and H. P. Weber, *Mol. Pharmacol.* **9**, 23–32 (1973).
17. G. Falkenberg, Dissertation, The Molecular Structure of Some Psychoactive Indoleal-

kylamines and Related Substances. Tryckeri Balder AB, Stockholm, 1972.

18. J. A. Pople and M. Gordon, *J. Amer. Chem. Soc.* **89**, 4253–4261 (1967).
19. W. Klyne and V. Prelog, *Experientia* 16, 521–523 (1960).
20. J. A. Pople, D. L. Beveridge, and P. A. Dobosch, *J. Chem. Phys.* **47**, 2026–2033 (1967).
21. H. A. Scheraga, *Advan. Phys. Org. Chem.* **6**, 103–184 (1968).
22. E. W. Gill, *Progr. Med. Chem.* **4**, 39–85 (1965).
23. M. Froimowitz and P. J. Gans, *J. Amer. Chem. Soc.* **94**, 8020–8025 (1972).
24. C. L. Johnson, S. Kang, and J. P. Green, *Proc. Int. Symp. Conformation of Biological Molecules and Polymers (Jerusalem Symp.)*. In press.
25. B. Pullman, J.-L. Coubeils, P. Courrière, and J.-P. Gervois, *J. Med. Chem.* **15**, 17–23 (1972).
26. R. Bergin, Dissertation, The Molecular Structure of Some Sympathomimetic Amines and Related Substances. Tryckeri Balder AB, Stockholm, 1971.
27. J. Pitha, *Biochemistry* **9**, 3678–3683 (1970).