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Molecular Structures of Hallucinogenic Substances: Lysergic Acid Diethylamide, Psilocybin, and 2,4,5-Trimethoxyamphetamine

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SUMMARY

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X-ray diffraction structure analyses of the hallucinogenic substances lysergic acid diethylamide *o*-iodobenzoate monohydrate, *N*,*N*-dimethyl-4-phosphoryloxytryptamine monoethanolate (psilocybin), and 2,4,5-trimethoxyamphetamine hydrochloride are reported. They reveal some relationships among the relative structural arrangements of possible pharmacodynamic groups of these substances.

INTRODUCTION

Similarities in effect and cross-tolerances among the most potent hallucinogenic substance known, lysergic acid diethylamide (1), the hallucinogenic-substituted tryptamines, and the methoxy-substituted amphetamines (2) indicate that the mechanisms of action of these drugs *in vivo* are similar. Several attempts have been made recently to predict the conformations of these substances and to compare and relate these predicted conformations. The proposals of Snyder and Richelson (3), based on model building, involved a comparison of possible ring system similarities of the molecules. Those of Chothia and Pauling (4), based primarily on known crystal structures of functional groups, led to a somewhat different comparison of the steric relationships of possible functional groups. Kang and Green (5) have considered other conformations as relevant to biological action. We report here the crystal structures of lysergic acid diethylamide, the tryptamine derivative psilocybin, and a trimethoxyamphetamine.

EXPERIMENTS

Crystals of lysergic acid diethylamide *o*-iodobenzoate monohydrate are monoclinic, space group $P2_1$, $a = 1421(2)$, $b = 765(1)$, $c = 1324(2)$ pm, $\beta = 115.53(5)$ degrees, $Z = 2$ formula units per unit cell, $\rho_{obs} =$

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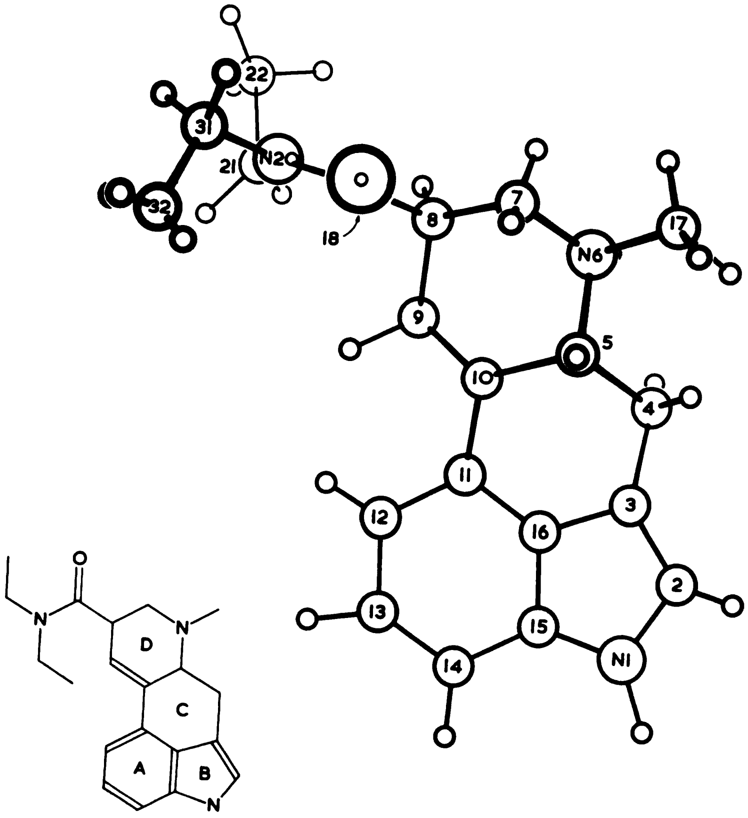

FIG. 1. *Conformation of lysergic acid diethylamide observed in crystals of the o-iodobenzoate, projected on plane of indole ring*

1470(10), ρ_{calc} = 1510 kg m^{-3}. Three-dimensional diffraction data measured on a Hilger and Watts linear diffractometer, using graphite monochromatized MoK_α radiation, resulted in 1448 symmetry-independent observed [$I \geqq 3\sigma(I)$] diffraction maxima. The structure was solved by heavy atom and Fourier methods and refined by full-matrix least-squares analysis to a residual of R = 0.039, using anisotropic thermal parameters for the non-hydrogen atoms and an over-all isotropic thermal parameter for the hydrogen atoms. All hydrogen atom positions of the molecule have been determined from difference syntheses, as has also one of the hydrogen atoms of the water molecule of crystallization, which forms hydrogen bonds to the oxygen atoms of the iodobenzoate anions. The observed conformation in the absolute configuration of the active enantiomer is shown in Fig. 1, projected on the plane of the indole ring. Certain torsion angles (6)[1] of the observed conformation and distances from the plane are listed in Table 1, and interatomic distances of the major groups, in Table 2. The conformation of lysergic acid diethylamide, accepting values for bonded interatomic distances and angles, lower limits of nonbonded interatomic distances, and other accepted stereochemical principles, has been discussed by Chothia and Pauling (4) as a five-parameter problem. In view of the rigidity of the ring structure, the torsion angles given are sufficient to describe completely the observed

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[1] The torsion angle of the bonded group *A—X—Y—B* is the angle between the plane *AXY* and the plane *XYB*. It is positive 0 → 180 degrees if clockwise from the nearer bond *AX* to the further bond *YB*. Values of 0, ±60, ±120, and 180 degrees are termed syn(peri)planar, ± synclinal, ± anticlinal, and anti(peri)planar, respectively (6).

TABLE 1

Distances of all non-hydrogen atoms from least-squares plane of indole ring of lysergic acid diethylamide, and torsion angles sufficient to describe fully the observed conformation, accepting observed coplanarity of indole ring

Atom	Distance	Group	Torsion angle[a]
	pm		*degrees*
N_1	0	$N_1—C_2—C_3—C_4$	−177
C_2	0	$C_2—C_3—C_4—C_5$	−150
C_3	−4	$C_3—C_4—C_5—N_6$	−174
C_4	−12	$C_4—C_5—N_6—C_{17}$	−61
C_5	60	$C_4—C_5—N_6—C_7$	177
N_6	43	$C_5—N_6—C_7—C_8$	−69
C_7	107	$N_6—C_7—C_8—C_9$	47
C_8	26	$C_7—C_8—C_9—C_{10}$	−12
C_9	−4	$C_8—C_9—C_{10}—C_{11}$	170
C_{10}	15	$C_8—C_9—C_{10}—C_5$	−5
C_{11}	6	$C_9—C_{10}—C_{11}—N_{12}$	−11
C_{12}	−2	$C_5—C_{10}—C_{11}—N_{12}$	164
C_{13}	−4	$C_{10}—C_{11}—C_{12}—C_{13}$	−177
C_{14}	0	$C_{17}—N_6—C_7—C_8$	168
C_{15}	6	$N_6—C_7—C_8—C_{18}$	166
C_{16}	−1	$C_7—C_8—C_{18}—O$	−24
C_{17}	102	$C_7—C_8—C_{18}—N_{20}$	156
C_{18}	114	$C_{10}—C_9—C_8—C_{18}$	−130
O	233	$C_9—C_8—C_{18}—O$	96
N_{20}	47	$C_9—C_8—C_{18}—N_{20}$	−84
C_{21}	−97	$C_8—C_{18}—N_{20}—C_{21}$	1
C_{22}	−168	$C_{18}—N_{20}—C_{21}—C_{22}$	−108
C_{31}	136	$C_8—C_{18}—N_{20}—C_{31}$	−178
C_{32}	188	$C_{18}—N_{20}—C_{31}—C_{32}$	−83

[a] The torsion angle of the bonded group *A—X—Y—B* is the angle between the plane of *A—X—Y* and that of *X—Y—B*. It is positive 0 → +180 degrees if clockwise from *A—X/Y* to *X/Y—B* and negative 0 → −180 degrees if counterclockwise, viewed from *A* (6).

conformation, which is identical with that predicted by Chothia and Pauling (4).

The constraints involved in the linked ring system lead to small departures from normal bond and torsion angles. The conformation observed here in protonated lysergic acid diethylamide is similar to that observed in ergotamine, both as a free base and as the brosylate salt.[2] That the observed conformations are similar in three derivatives indicates that the conformation of lysergic acid diethylamide reported here is the preferred one. Methyl substitution at position 8, however, leads to a change of conformation[2] and loss of hallucinogenic activity, as observed in 1,8-dimethyl-*d*-lysergic acid *p*-bromoanilide.[2] Carbon 7 is found below the plane of ring D, and the amide group is axial instead of equatorial as observed in lysergic acid diethylamide and the two ergotamines.

Crystals of psilocybin monoethanolate (*N*,*N* - dimethyl - 4 - phosphoryloxytryptamine) are monoclinic, space group $P2_1/c$, $a = 1216(1)$, $b = 2905(2)$, $c = 883(1)$ pm, $\beta = 107.37(3)$ degrees, $Z = 8$ formula units per unit cell, including 8 molecules of ethanol of crystallization. Three-dimensional diffraction data were measured on a four-circle diffractometer, using MoK_α radiation with balanced filters, and resulted in 4026 symmetry-independent observed diffraction maxima $[I \geqq 3\sigma(I)]$. The structure was solved by direct methods, using symbolic addition, and refined by block-diagonal least-squares analysis to a current value of the residual $R = 0.041$, using anisotropic thermal parameters for the non-hydrogen atoms and isotropic thermal parameters for the hydrogen atoms. The positions of the hydrogen atoms were determined from difference syntheses. The observed conformation of psilocybin is shown in Fig. 2, projected on the plane of the indole ring. Certain torsion angles and distances from the plane are listed in Table 3. Interatomic distances of the major groups are given in Table 4. The two molecules in the asymmetrical unit are nearly, but not quite, identical. The molecule shown in the figure has an angle of 66 degrees between the plane of the indole ring and the ethylamine chain, inclined toward the phosphoryloxy group. In the other molecule this angle is 97 degrees, with the ethylamine chain inclined slightly away from the phosphoryloxy group. The observed conformations are similar to those proposed on stereochemical principles (4). There has been much discussion (3, 4) about the possibility of forming a hydrogen bond between the ammonium nitrogen atom and an oxygen atom of the 4-phosphoryloxy group of the indole ring, to form a ring analogous to ring C of lysergic acid diethylamide. No such hydrogen bond is formed in psilocybin or in any

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[2] H. P. Weber, unpublished observations.

TABLE 2

Some interatomic distances of lysergic acid diethylamide observed in crystals of the o-iodobenzoate

C_{17}	147								
A[a]	553	650							
B[b]	495	558	232						
DB[c]	263	401	352	423					
N_1	603	657	291	145	528				
O	410	497	688	740	367	844			
N_{20}	489	607	716	797	383	902	557		
C_{22}	604	719	855	928	525	1035	700	249	
C_{32}	668	782	772	890	518	983	602	237	426
	N_6	C_{17}	A	B	DB	O	N_{20}	N_{20}	C_{22}

[a] A, to the center of ring A, is defined as the arithmetic mean of the distances to C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, and C_{16}.

[b] B, to the center of ring B, is defined as the arithmetic mean of the distances to N_1, C_2, C_3, C_{15}, and C_{16}.

[c] DB, to the middle of the $C_9{=}C_{10}$ double bond, is defined as the arithmetic mean of the distances to C_9 and C_{10}.

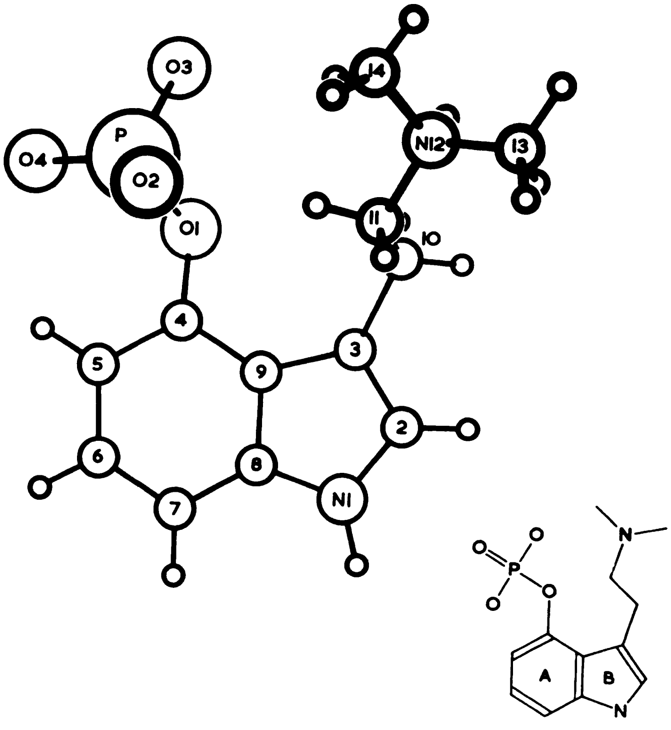

FIG. 2. *Observed conformation of 1 of the 2 molecules in the asymmetrical unit of psilocybin, projected on plane of indole ring*

The conformation of the other molecule in the asymmetrical unit is similar.

TABLE 3

Distances of all non-hydrogen atoms from plane of indole ring of both molecules of psilocybin in the asymmetrical unit and some observed torsion angles

Atom	Atom distance		Group	Torsion angle	
	A	B		A	B
	pm			*degrees*	
N_1	−3	−3	$N_1—C_2—C_3—C_{10}$	175	171
C_2	2	0	$C_8—C_9—C_3—C_{10}$	−174	−175
C_3	2	3	$C_4—C_9—C_3—C_{10}$	8	11
C_4	−3	−2	$C_2—C_3—C_{10}—C_{11}$	−107	−72
C_5	0	−2	$C_9—C_3—C_{10}—C_{11}$	65	98
C_6	3	2	$C_3—C_{10}—C_{11}—N_{12}$	174	−165
C_7	0	2	$C_{10}—C_{11}—N_{12}—C_{13}$	144	84
C_8	−2	0	$C_{10}—C_{11}—N_{12}—C_{14}$	−91	−155
C_9	0	1	$C_3—C_9—C_4—O_1$	5	3
C_{10}	18	26	$C_6—C_5—C_4—O_1$	175	176
C_{11}	154	168	$C_8—C_9—C_4—O_1$	−173	−176
N_{12}	179	213	$C_9—C_4—O_1—P$	−140	−148
C_{13}	260	254	$C_5—C_4—O_1—P$	44	34
C_{14}	243	330	$C_4—O_1—P—O_2$	55	50
P	60	55	$C_4—O_1—P—O_3$	171	166
O_1	−16	−11	$C_4—O_1—P—O_4$	−63	−78
O_2	211	195			
O_3	28	46			
O_4	22	−34			

other known tryptamine derivative. Psilocybin is hydrolyzed in the organism to psilocin (*N*,*N*-dimethyl-4-hydroxytryptamine), and psilocin is considered to be the likely active metabolite (1).

Available crystal structure analyses suggest no definite conclusions about the preferred conformation of biologically active derivatives of tryptamine (Table 5) although there are generally consistent relationships among the hallucinogenic tryptamines. The hallucinogenic *N*,*N*-dimethyl-5-methoxytryptamine HCl (13) is nearly planar, as is the neurotransmitter 5-hydroxytryptamine (serotonin) in crystals of the creatinine sulfate monohydrate (8). In the picrate monohydrate (9), however, 5-hydroxytryptamine has $\tau_1 = -115$ degrees (Table 5) and $\tau_3 =$ 67 degrees, similar to the observed conformations of tryptamine HCl (7) and 5-methoxytryptamine (10). Six observed independent conformations of the hallucinogenic substances *N*,*N*-dimethyltryptamine (11), bufotenine (12), and psilocybin are consistent, in that τ_1 and τ_2 [$\tau_1 + (-\tau_2) = 180$ degrees if the indole system is strictly planar] are 90 ± 20 degrees and τ_3 is approximately 180 degrees. It is only this conformation of tryptamine derivatives which corresponds with the rigid conformation of lysergic acid diethylamide.

Of the seven observations of *N*,*N*-dimethyltryptamine, six are consistent: four are bases and two are ethanolates, a large organic anion. The one inconsistent observed conformation is a hydrochloride and forms an N—H ··· Cl hydrogen bond (13).

Shulgin, Sargent, and Naranjo (2) have synthesized and tested a large number of substituted amphetamines for hallucinogenic activity. There are no clear-cut conclusions about activity as a function of location of substituents on the benzene ring. We have analyzed the structure of 2,4,5-trimethoxyamphetamine, the most potent of the trimethoxyamphetamines. A commonly

TABLE 4

Observed interatomic distances of psilocybin in crystals of the iodide

Molecules A and B are the two molecules in the asymmetrical unit of the crystal.

Molecule A							
C_{13}	148						
C_{14}	148	245					
A^a	600	652	697				
B^b	501	594	565	256			
P	463	430	606	413	502		
O_1	432	453	567	296	360	161	
N_1	589	688	635	290	144	604	461
	N_{12}	C_{13}	C_{14}	A	B	P	O_1
Molecule B							
C_{13}	151						
C_{14}	150	243					
A	604	605	716				
B	495	548	593	256			
P	513	423	643	407	505		
O_1	456	413	595	297	360	161	
N_1	577	642	658	293	145	607	462
	N_{12}	C_{13}	C_{14}	A	B	P	O_1

[a] A, to the center of the 6-membered indole ring, is defined as the arithmetic mean of the six distances to C_4, C_5, C_6, C_7, C_8, and C_9.

[b] B, to the center of the 5-membered indole ring, is defined as the arithmetic mean of the five distances to N_1, C_2, C_3, C_8, and C_9.

used hallucinogenic amphetamine is a congener having a 4-methyl group instead of a 4-methoxy group.

Crystals of 2,4,5-trimethoxyamphetamine hydrochloride are orthorhombic, space group Pbca, $a = 2016.5(5)$, $b = 1707.0(5)$, $c = 829.8(8)$ pm, $Z = 8$ formula units per unit cell. Three-dimensional diffraction data collected on a computer-controlled, four-circle diffractometer, using graphite monochromatized MoK_α radiation, resulted in 513 symmetry-independent observed $[I \leqq 3\sigma(I)]$ diffraction maxima. The structure was solved by the heavy atom method, using the chlorine atom, and refined by full-matrix least-squares analysis to the value of the residual $R = 0.040$, using anisotropic thermal parameters for all atoms except hydrogen and an over-all isotropic thermal parameter for the hydrogen atoms. The hydrogen positions were determined from difference syntheses and refined. The conformation of the molecule as observed in crystals of the hydrochloride is shown in Fig. 3, projected on the plane of the benzene ring. Certain torsion angles and distances from the plane are given in Table 6. Interatomic distances of the major groups are given in Table 7. The observed conformation is unusual; for all other known structures of phenylethylamine derivatives (excepting amino acids) the nitrogen atom is antiplanar with respect to C_1 about the C_7—C_8 bond, and the angle between the planes of the ethylamine chain and the benzene ring is approximately 90 degrees, as seen in Table 8. In the observed structure of 2,4,5-TMA[3] the angle between the planes defined by C_8—C_7—C_1 and the benzene ring is similar to the other compounds, but the α-methyl group is antiplanar and the nitrogen atom is synclinal with respect to C_1. This unusual crystallographic conformation (Table 8) may be due to the crystal packing of the compound, which involves an N—H ··· Cl and two N—H ··· O hydrogen bonds.

This observed unusual conformation of 2,4,5-TMA in crystals of the hydrochloride illustrates one of the dangers of interpreting face-value results of diffraction analyses. For labile molecules such as derivatives of phenylethylamine and tryptamine it is essential to have several observed structures available to determine possible and probable conformations relevant to drug action. We do not consider the unusual conformation observed for 2,4,5-TMA to be responsible for the hallucinogenic effects of this and related compounds. On the basis of the correlation with lysergic acid diethylamide, it is the usually observed conformation of derivatives of phenylethylamine (Table 8) which is relevant to drug and transmitter action. It is the methoxy or other substitution, not changes in conformation, that alters the properties of

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[3] The abbreviation used is: 2,4,5-TMA, 2,4,5-trimethoxyamphetamine HCl.

TABLE 5

Observed conformations in terms of torsion angles of derivatives of tryptamine

For a review of all known structures of indole derivatives, see ref. 14.

Compound	τ_1[a]	τ_2[b]	τ_3[c]	Reference
		degrees		
Tryptamine HCl	−111	69	60	7[d]
5-Hydroxytryptamine creatine sulfate H_2O	−9	167	−173	8
5-Hydroxytryptamine picrate H_2O	−115	67	67	9
5-Methoxytryptamine	−116	63	55	10
N,*N*-Dimethyltryptamine				
a	−102	79	−176	11
b	−90	89	172	
5-Hydroxy-*N*,*N*-dimethyltryptamine (bufotenine)				
a	−87	89	−175	
b	−72	102	−170	12
5-Methoxy-*N*,*N*-dimethyltryptamine HCl	−17	161	−179	13
4-Phosphoryloxy-*N*,*N*-dimethyltryptamine monoethanolate (psilocybin)				
a	−107	65	174	
b	−72	98	−165	

[a] τ_1 is torsion angle $C_2—C_3—C_{10}—C_{11}$.
[b] τ_2 is torsion angle $C_9—C_3—C_{10}—C_{11}$.
[c] τ_3 is torsion angle $C_3—C_{10}—C_{11}—C_{12}$.
[d] Coordinates from Professor K. Tomita.

the compounds, although in the case of the methoxy-substituted amphetamines no clear-cut relationship between activity and position of substitution is evident (2).

As in psilocybin, there is no evidence for an intramolecular hydrogen bond between the ammonium nitrogen atom and the oxygen atom in position 2. In the observed conformation the nitrogen atom is on the side of the chain away from oxygen atom O_2 rather than toward it ($N—O_2 = 392$ pm). The methoxy groups are in the plane of the benzene ring, as is invariably observed (4) except where some neighboring atom interferes, as in mescaline (3,4,5-trimethoxyphenylethylamine), where the methyl of the 4-methoxy group is forced out of the plane by steric hindrance with the two neighboring methoxy groups (4).[4]

DISCUSSION

These observed conformational results are not generally consistent with the proposals of Snyder and Richelson (3) and Kang and Green (5), but are in accord with the proposals of Chothia and Pauling (4).

Given the observed conformations of lysergic acid diethylamide and psilocybin and the conformation of hallucinogenic amphetamines as those normally observed in derivatives of phenylethylamine, there are approximate but not exact relationships between what may be pharmacodynamic groups essential for hallucinogenic activity. These approximate relationships are best seen with the aid of Corey-Pauling-Koltun atomic models. The relationships between the aromatic ring system and the charged nitrogen atom (N_6 in lysergic acid diethylamide, N_{12} in psilocybin, and N_{10} in 2,4,5-TMA) are nearly the same in the three molecules,

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[4] C. de Rango, C. Zelwer, G. Tsoucaris, R. Panthasarathy, and F. Cole, manuscript in preparation.

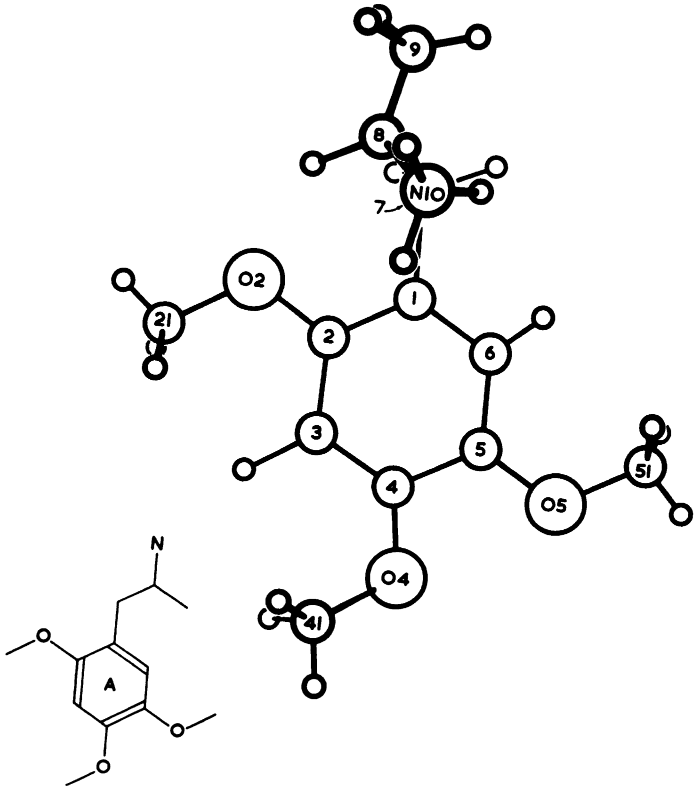

FIG. 3. *Conformation of 2,4,5-trimethoxyamphetamine observed in crystals of the hydrochloride, projected on plane of benzene ring*

TABLE 6

Observed distances of all non-hydrogen atoms from plane of benzene ring and certain torsion angles in 2,4,5-trimethoxyamphetamine hydrochloride

Atom	Distance	Group	Torsion angle
	pm		*degrees*
C_1	0	$C_3—C_2—C_1—C_7$	179
C_2	0	$C_5—C_6—C_1—C_7$	−179
C_3	−1	$C_2—C_1—C_7—C_8$	68
C_4	2	$C_6—C_1—C_7—C_8$	−114
C_5	−1	$C_1—C_7—C_8—N$	50
C_6	0	$C_1—C_7—C_8—C_9$	170
O_2	−2	$C_3—C_2—O_2—C_{21}$	−1
C_{21}	−4	$C_3—C_4—O_4—C_{41}$	−12
O_4	0	$C_6—C_5—O_5—C_{51}$	4
C_{41}	23		
O_5	−5		
C_{51}	1		
C_7	−1		
C_8	133		
C_9	135		
N_{10}	260		

particularly if one does not try to obtain an exact atom-by-atom fit of the 6-membered aromatic rings. There are also approximate relationships among the 9,10 double bond of lysergic acid diethylamide, the 4-hydroxyl group of psilocin, and the 2-methoxy group of 2,4,5-TMA and among the ring nitrogen atoms N_1 of lysergic acid diethylamide and psilocybin and the 5-methoxy group of 2,4,5-TMA although these latter relationships are not very convincing. These relationships are shown diagrammatically in Fig. 4.

At the level of precision of conformation presented here, it is impossible to find exact relationships among the groups (see tables). However, exact relationships may not be essential for the related activities of the substances.

ACKNOWLEDGMENTS

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TABLE 7

Observed interatomic distances of 2,4,5-trimethoxyamphetamine

In the conformation considered relevant to biological action, in which the methyl group at C_9 and the nitrogen atom are interchanged, the distances to C_9 and N are interchanged.

N	246							
A[a]	537	407						
O_2	444	392	294					
C_{12}	570	513	381	145				
O_4	797	626	292	487	508			
C_{14}	870	698	377	511	493	138		
O_5	717	553	294	553	634	259	396	
C_{15}	712	562	383	637	737	403	540	144
	C_9	N	A	O_2	C_{12}	O_4	C_{14}	O_5

[a] A, to the center of the 6-membered ring, is defined as the arithmetic mean of the distances to C_1, C_2, C_3, C_4, C_5, and C_6.

TABLE 8

Observed conformations in terms of torsion angles of derivatives of phenylethylamine

For a review of the known structures of derivatives of phenylethylamine, see ref. 15.

Compound	τ_1[a]	τ_2[b]	τ_3[c]	Reference
Phenylethylamine HCl	73	−113	−171	16
Ephedrine HCl				
I	81	−103	−162	17
II	81	−98	−164	18
Dopamine HCl	79	−99	174	19
Norepinephrine HCl	82	−97	176	20
Amphetamine H_2SO_4				
a	71	−109	−175	21
b	77	−107	−173	
c	69	−114	−172	
d	81	−100	−166	
Mescaline HCl	88	−90	175	—[d]
Pseudoephedrine Cu complex				
a	74	−96	−163	22[e]
b	68	−106	−179	
c	74	−103	−172	
6-Hydroxydopamine HCl	83	−94	−175	23
2,4,5-Trimethoxyamphetamine HCl	70	−111	50	

[a] τ_1 is torsion angle $C_2—C_1—C_7—C_8$.

[b] τ_2 is torsion angle $C_6—C_1—C_7—C_8$.

[c] τ_3 is torsion angle $C_1—C_7—C_8—N$.

[d] Coordinates from Dr. George Tsoucaris.

[e] Coordinates from Dr. Pamela M. Bailey.

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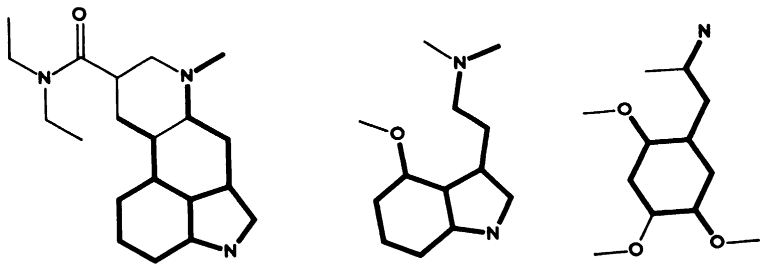

FIG. 4. *Diagrammatic representations of conformations of lysergic acid diethylamide, psilocybin, and 2,4,5-trimethoxyamphetamine, showing possible structural correlations*

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