Crystal and Molecular Structure of the Psychotropic Drug 2-(4-Ethyl-2,5-dimethoxyphenyl)-1-methylethylamine (4-Ethyl-2,5-dimethoxyamphetamine)

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The molecular conformation of the title compound was determined by *X*-ray diffraction analysis. The crystals are triclinic, $a = 7{\cdot}43(4)$, $b = 16{\cdot}73(4)$, $c = 5{\cdot}25(6)$ Å, $\alpha = 93° 30'$, $\beta = 87° 30'$, $\gamma = 96° 18'$, $P\bar{1}$, $Z = 2$. The structure was solved by direct methods. The molecular conformation resembles that of 2,4,5-trimethoxyamphetamine and differs from other substituted phenethylamines including dopamine hydrochloride and norepinephrine hydrochloride. This is the first determination of a free base in this class of compounds.

THE methoxylated amphetamine derivative DOET (2,5-dimethoxy-4-ethylamphetamine) is the ethyl homologue of the powerful hallucinogen DOM (2,5-dimethoxy-4-methylamphetamine).[1] DOET, however, unlike DOM at equivalent doses does not produce hallucinogenic effects in man.[2-4] In the dose range 0·7—4 mg DOET produced mild euphoria and a feeling of enhanced self-awareness and at the higher dosages a tendency to feel anxious; [2,3] DOET is apparently more potent than DOM in terms of the minimal dose required to produce subjective effects.[2,3]

It has been suggested [5] that in the free base hydrogen bonding between the hydrogen atom of the primary amine and the oxygen atom of the *ortho*-methoxy-group in substituted amphetamines could result in a simulation of part of lysergic acid diethylamide molecule, hence accounting for the hallucinogenic activity and cross-tolerance of these compounds. In order to evaluate this hypothesis we have determined the crystal and molecular structure of DOET. This is the first structure analysis of a free base of a substituted phenethylamine derivative, all other reported determinations having been carried out on salts or metal complexes (ref. 6 and references therein).

EXPERIMENTAL

Crystal Data.—$C_{13}H_{21}NO_2$, $M = 223$. Triclinic, $a = 7{\cdot}43(4)$, $b = 16{\cdot}73(4)$, $c = 5{\cdot}25(6)$ Å, $\alpha = 93° 30'$, $\beta = 87° 30'$, $\gamma = 96° 18'$, $U = 648{\cdot}3$ Å^3, $Z = 2$, $D_c = 1{\cdot}14$ g cm^{-3}, $F(000) = 244$. Space group $P1$ (No. 1) or $P\bar{1}$ (No. 2). The latter was confirmed by the successful refinement of the structure. Cu-K_α radiation, $\lambda = 1{\cdot}5418$ Å, μ(Cu-K_α) = 6·1 cm^{-1}.

The quality of the crystals was poor and in spite of attempts at recrystallisation we could not obtain better specimens. The crystals decomposed in air and for this reason they were sealed in capillary tubes under nitrogen prior to being mounted on the *X*-ray goniometer. Two crystals were used for data collection (dimensions 0·10 × 0·12 × 0·86 and 0·08 × 0·016 × 0·27 mm). The reflexions were streaky and had to be measured against a diffuse background. A total of 1014 reflexions were re-

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† External Staff, Medical Research Council.

[1] A. T. Shulgin, T. Sargent, and C. Naranjo, *Nature*, 1969, **221**, 537.

[2] S. H. Snyder, H. Weingartner, and L. A. Faillace, *Arch. Gen. Psychiat.*, 1971, **24**, 50.

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[5] S. H. Snyder and E. Richelson, *Proc. Nat. Acad. Sci. U.S.A.*, 1968, **60**, 206.

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corded with Cu-K_α radiation on Weissenberg photographs taken about two axes, hkn (n = 0—3) and hnl (n = 0—13). The intensities were originally measured by visual comparison and remeasured with a Nonius mark I microdensitometer and a double beam Joyce–Loebel densitometer. 408 Reflexions were classed as ' unobserved '. There was no significant difference between the three sets of measurements. After correction for spot-shape, Lorentz, and polarization effects, the intensities were correlated and put on a single scale. They were then reduced to normalized structure factors (E_{hkl}). No absorption corrections were applied.

Solution and Refinement.—The solution of the structure did not prove to be straightforward. The intensity statistics indicated the space group as $P\bar{1}$, and numerous attempts were made to solve the structure in this space group by direct methods using first the multisolution program TANFIZ [7] and subsequently an early version of the origin choice program.[8]

A solution was eventually found through a combination of direct and Patterson superposition methods [9] in space group $P1$. The first Karle map (E map) showed a distribution of peaks roughly corresponding to two independent molecules of DOET. The two molecules were approximately related by a pseudo-centre of symmetry.

The atomic positions deduced from this map were refined through several cycles of least squares calculations. The agreement between observed and calculated structure factors improved but the geometry of the benzene rings became increasingly distorted and R did not drop below 0·20. However, at this stage all but one hydrogen atom were found in a Fourier difference map close to those positions calculated from geometrical and steric considerations.

TABLE 1

Fractional co-ordinates ($\times 10^4$) and isotropic temperature factors (Å^2 $\times$ 10^3) with standard deviations in parentheses

Atom	x	y	z	U
C(1)	−803(19)	2756(8)	9228(29)	52(4)
C(2)	−959(19)	2102(8)	7537(29)	56(4)
C(3)	275(19)	1540(8)	7340(30)	55(4)
C(4)	1732(19)	1607(7)	8938(29)	50(4)
C(5)	1889(19)	2262(8)	10,606(28)	51(4)
C(6)	674(18)	2846(8)	10,826(28)	51(4)
C(7)	−2137(18)	3374(7)	9459(29)	52(4)
C(8)	−1951(18)	3962(8)	7303(29)	52(4)
N(9)	−137(16)	4432(7)	7292(24)	57(4)
O(10)	−2477(13)	2049(6)	6011(20)	65(3)
C(11)	−2711(19)	1414(8)	4072(27)	
C(12)	3035(20)	979(8)	8792(30)	64(5)
C(13)	2656(20)	398(8)	10,928(33)	
O(14)	3395(14)	2318(6)	12,136(22)	69(3)
C(15)	3656(20)	2956(8)	14,022(29)	
C(16)	−3353(22)	4539(9)	7600(34)	

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(11)	60(11)	65(10)	42(12)	6(8)	−23(8)	0(8)
C(13)	65(11)	68(10)	91(15)	33(9)	3(10)	18(8)
C(15)	66(11)	69(11)	55(13)	3(8)	−20(9)	2(9)
C(16)	94(14)	76(11)	73(15)	15(9)	−25(11)	24(10)

* In the form: $\exp[-2\pi(U_{11}a^{*2}h^2 + U_{22}b^{*2}k^2 + U_{33}c^{*2}l^2 + 2U_{12}a^*b^*hk + 2U_{13}a^*c^*hl + 2U_{23}b^*c^*kl)]$.

A fresh attempt at the refinement of the structure was made in space group $P\bar{1}$ with the origin of the unit cell shifted so as to coincide with the pseudo-centre already found between the two molecules. The isotropic refinement converged at R 0·14 for observed terms. Further cycles of refinement employing anisotropic thermal parameters for atoms C(11), C(13), C(15), and C(16) only, reduced R to its final value of 0·126. In view of the quality of the experimental data the refinement was terminated at this stage. During the last cycles all the hydrogen atoms, initially in their calculated positions, were allowed to refine but with positional parameters constrained such that respective vectors representing the C–H bonds retained their original magnitude and orientation. An overall isotropic temperature factor for all the hydrogen atoms had a final value of 0·043 Å^2. The final fractional co-ordinates and isotropic and anisotropic temperature factors are listed in Table 1 and the fractional co-ordinates and temperature factors for the hydrogen atoms in Table 2. Measured and calculated structure factors are listed in Supplementary Publication No. SUP 21020 (6 pp.).†

TABLE 2

Fractional co-ordinates ($\times 10^3$) for hydrogen atoms (U = 0·043 Å^2 throughout)

Atom	x	y	z
H(31)	11	106	602
H(61)	85	333	1212
H(71)	−195	370	1116
H(72)	−343	308	947
H(81)	−211	363	560
H(91)	92	416	714
H(92)	−3	500	744
H(111)	−282	86	488
H(112)	−162	146	278
H(113)	−388	147	315
H(121)	434	126	887
H(122)	289	65	708
H(131)	281	72	1266
H(132)	136	11	1086
H(133)	358	−2	1072
H(151)	257	293	1532
H(152)	378	350	1318
H(153)	482	290	1494
H(161)	−321	487	931
H(162)	−320	493	613
H(163)	−462	422	758

DISCUSSION

The conformation of the DOET molecule in the crystal structure and the numbering scheme used in the analysis are illustrated in Figure 1. The interatomic distances, bond angles, and torsion angles for the non-hydrogen atoms are listed in Table 3. C–H and N–H distances were set at 1·03 and 0·95 Å, respectively, during the constrained refinement. The deviation of atoms from the plane of the benzene ring is given in Table 4.

The benzene ring is planar within experimental error. The two methoxy-groups lie very nearly in the plane of the benzene ring, as has been observed in a number of related compounds. The ethyl group is staggered at an angle of 78° and is thus similar in orientation to the 4-methoxy-group in mescaline hydrobromide [10] where the

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† For details see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1973, Index issue. Items less than 10 pp. are supplied as full-size copies.

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[8] W. D. S. Motherwell and N. W. Isaacs, *Acta Cryst.*, 1971, **A27**, 713.

[9] C. Giacovazzo, to be published.

[10] S. R. Ernst and F. W. Cagle, jun., *Acta Cryst.*, 1973, **B29**, 1543.

corresponding torsion angle, computed by us from the published co-ordinates, is 85°.

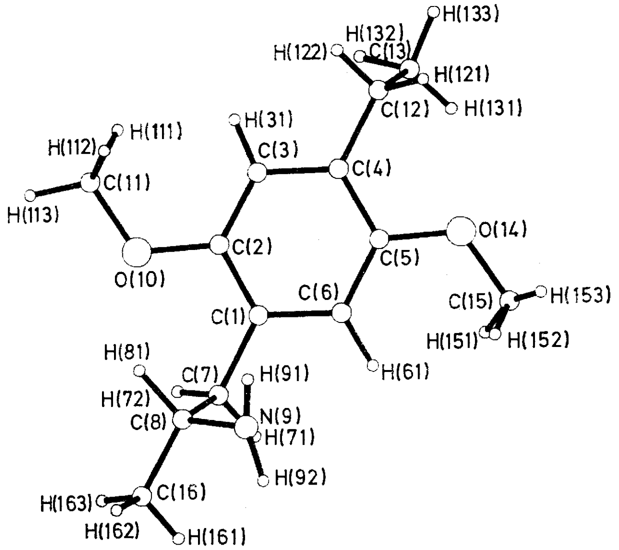

FIGURE 1 Projection of the DOET molecule normal to the benzene ring

The isopropylamine side chain is staggered at a similar angle of −76° to the plane of the benzene ring. This staggering is a general feature of the whole group of phenethylamine derivatives.[6] The torsion angle [τ_1 = C(8)–C(7)–C(1)–C(2)] about the exocyclic bond C(1)–C(7) ranges from 68° in the pseudoephedrin Cu complex [11] to 88° in mescaline hydrobromide.[10] The carbon of the isopropylamine side chain is fully extended with the α methyl group antiplanar [τ_4 = C(16)–C(8)–C(7)–C(1) = 178°]. In this orientation the nitrogen atom assumes the synclinal position [τ_3 = N(9)–C(8)–C(7)–C(1) = −62°]. The overall conformation is similar to 2,4,5-trimethoxyamphetamine hydrochloride (2,4,5-TMA) [6] where the corresponding angles are $\tau_1 = 70$, $\tau_3 = 50$, and $\tau_4 = 170°$, and to mescaline hydrobromide [10] where we compute $\tau_1 = -80$ and $\tau_3 = -55°$. It is interesting to note, however, that the torsion angles quoted in ref. 6 for mescaline hydrochloride are $\tau_1 = 88$ and $\tau_3 = 175°$ suggesting that the extended (antiplanar) and staggered (synclinal) orientations of the nitrogen atom may be equally favourable.

TABLE 3

Bond lengths (Å) and angles and principal torsion angles (deg.). Standard deviations are in parentheses

(*a*) Bond lengths			
C(1)–C(2)	1·37(2)	C(5)–C(6)	1·40(2)
C(1)–C(6)	1·41(2)	C(5)–O(14)	1·40(2)
C(1)–C(7)	1·51(2)	C(7)–C(8)	1·53(2)
C(2)–C(3)	1·38(2)	C(8)–N(9)	1·48(2)
C(2)–O(10)	1·41(2)	C(8)–C(16)	1·49(2)
C(3)–C(4)	1·39(2)	O(10)–C(11)	1·43(2)
C(4)–C(5)	1·36(2)	C(12)–C(13)	1·52(2)
C(4)–C(12)	1·50(2)	O(14)–C(15)	1·42(2)
(*b*) Bond angles			
C(6)–C(1)–C(2)	118(1)	O(14)–C(5)–C(4)	115(1)
C(7)–C(1)–C(2)	123(2)	O(14)–C(5)–C(6)	121(1)
C(7)–C(1)–C(6)	119(1)	C(5)–C(6)–C(1)	118(1)
C(3)–C(2)–C(1)	123(2)	C(8)–C(7)–C(1)	114(1)
O(10)–C(2)–C(1)	115(1)	N(9)–C(8)–C(7)	110(1)
O(10)–C(2)–C(3)	123(1)	C(16)–C(8)–C(7)	112(1)
C(4)–C(3)–C(2)	121(2)	C(16)–C(8)–N(9)	108(1)
C(5)–C(4)–C(3)	117(1)	C(11)–O(10)–C(2)	119(1)
C(12)–C(4)–C(3)	121(1)	C(13)–C(12)–C(4)	112(1)
C(12)–C(4)–C(5)	123(2)	C(15)–O(14)–C(5)	120(1)
C(6)–C(5)–C(4)	124(2)		
(*c*) Torsional angles			
C(11)–O(10)–C(2)–C(3)	−3·6	C(8)–C(7)–C(1)–C(2)	−75·5
C(15)–O(14)–C(5)–C(6)	2·8	C(16)–C(8)–C(7)–C(1)	178·0
C(13)–C(12)–C(4)–C(5)	78·5	N(9)–C(8)–C(7)–C(1)	−61·6

TABLE 4

Deviations (Å) of atoms from the mean plane of the benzene ring

Atom	Deviation	Atom	Deviation
C(1)	−0·00	N(9)	2·37
C(2)	−0·01	O(10)	−0·02
C(3)	0·01	C(11)	0·06
C(4)	−0·01	C(12)	−0·05
C(5)	0·00	C(13)	−1·45
C(6)	0·00	O(14)	0·01
C(7)	−0·02	C(15)	−0·03
C(8)	1·33	C(16)	1·24

All crystal structure determinations of the substituted phenethylamine class of compounds, with the exception of DOET, have been on salts or metal complexes, where it is probable that the conformation of the side chain is strongly influenced by geometrical requirements of the hydrogen bonding. This would generally favour an extended form so as to allow for co-ordination about the anion as in the case of the four independent molecules of amphetamine in amphetamine H_2SO_4.

The present investigation of DOET offers an opportunity of examining the conformation of a substituted phenethylamine molecule free from the influence of hydrogen bonding. The free base does not appear to form any intramolecular hydrogen bonds [5] since the distances between the amine nitrogen and the methoxy-oxygen atoms are N(9) · · · O(10) 4·30 Å and N(9) · · · O(14) 7·13 Å whereas the expected hydrogen bonded distance is *ca.* 2·9 Å. There is no evidence either, of any intermolecular hydrogen bonding. The closest distance between non-hydrogen atoms of neighbouring molecules is 3·14 Å. The molecules are thus held together in the crystal structure by van der Waals forces only.

We have recently developed a method [12,13] for analysing the pattern of molecular packing in crystal structures through calculations of the energy of interaction between neighbouring molecules using empirical atom–atom potentials.[14] A comparison of crystal structures analysed in this way may lead to an estimate of the conformation of the free molecules independent of crystal packing forces.

In the DOET structure the strongest interaction occurs between molecules related by a unit translation in the

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direction of the shortest (*c*) axis, and is of the order of 8·8 kcal mol^{-1}, which compares with 8—13 kcal mol^{-1} found in pyrimidine and purine structures [12,13] and *ca.* 8 kcal mol^{-1} in steroids.[15] There is no significance in the absolute values of these terms which serve only as a basis for comparison between different packing arrangements.

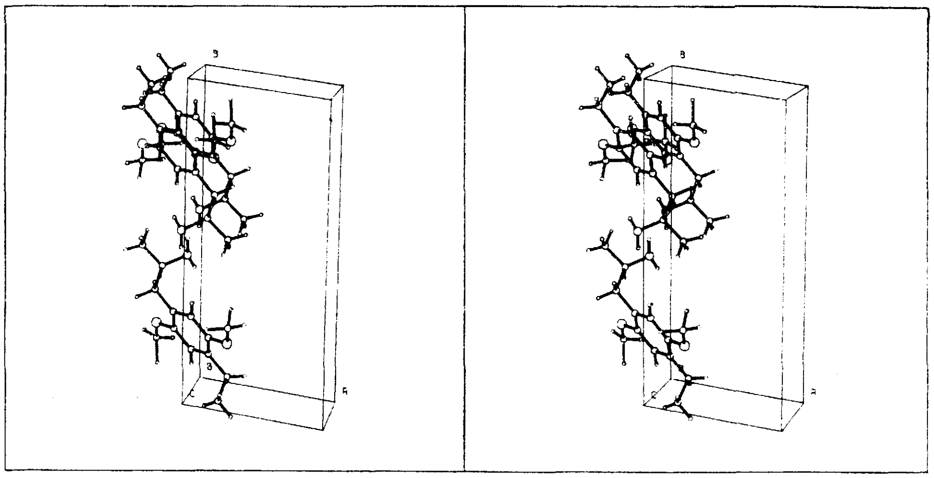

FIGURE 2 Packing diagram showing the association of molecules along the short crystallographic axis

The major interactions between neighbouring molecules are illustrated in a stereodiagram (Figure 2). This view also shows the comparatively short non-bonded contacts between the nitrogen atoms. These are not hydrogen bonded contacts as evidenced both by the distances between the nitrogen atoms (3·14 and 3·31 Å) and by the orientations of the attached hydrogen atoms which do not point in geometrically acceptable directions for hydrogen bonding. All other non-bonded distances are >3·5 Å.

Although our results to date [13] indicate that crystal packing forces have little influence on the conformation of the free molecule it would be unwise for us to attempt to correlate psychotropic effects with conformation on basis of the one structure determination free of hydrogen bonding or published determinations of salts and complexes. Further structural and theoretical studies are needed in developing our ideas of the conformation of hallucinogens at the receptor site.

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