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The Crystal and Molecular Structure of 5,6-Dimethoxy-2-methyl-3-[2-(4-phenyl-1-piperazinyl)ethyl]indole Hydrobromide Sesquihydrate, Oxypertine.HBr.$1\frac{1}{2}H_2O$

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Crystals of oxypertine hydrobromide sesquihydrate ($C_{23}H_{30}N_3O_2.HBr.1\frac{1}{2}H_2O$) are monoclinic, space group $P2_1/c$, with $a = 9.969$ (2), $b = 16.790$ (3), $c = 14.361$ (3) Å, $\beta = 94.88$ (2)°. Calculated and observed densities are 1·351 and 1·362 g cm^{-3}, respectively, for $Z = 4$. The intensity data were collected on an automated diffractometer using Nb-filtered Mo $K\bar{\alpha}$ radiation and the structure was solved by the heavy-atom technique. Full-matrix least-squares refinement yielded an R value of 0·11 for 2099 observed reflections. The accuracy of the resulting structure is affected by disorder in the Br atom position. The plane defined by the ethylamine side chain is nearly perpendicular to the indole nucleus and the chain itself is almost fully extended {torsion angle τ_2 [C(3)–C(10)→C(11)–N(12)] is 163°}.

Introduction

Oxypertine is a tranquilizer used experimentally in the treatment of schizophrenia. It resembles serotonin with respect to its indole nucleus, and shares several features in common with other neuroleptic drugs, especially the ethylpiperazine group. Oxypertine appears to be capable of stimulating the release and antagonizing the action of norepinephrine (Wylie & Archer, 1962). The drug has been reported to activate the depressed as well as to quiet the overactive individual (Skarbek & Jacobsen, 1965). It was of interest to investigate the three-dimensional structure of oxypertine in order to compare its conformation to those of other neuroleptic drugs.

Experimental

A sample of oxypertine, supplied by Sterling–Winthrop, was crystallized as the hydrobromide salt from a mixture of acetone and water. The crystals were colorless rectangular plates elongated about the c^* axis, with a^* being the plate normal. Weissenberg and precession photographs indicated the crystals to be monoclinic; the space group $P2_1/c$ was determined by the systematic absences $0k0$ with k odd and $h0l$ with l odd. A crystal with approximate dimensions 0·1 × 0·2 × 0·4 mm was mounted on an Oak Ridge computer-controlled diffractometer and accurate cell dimensions (see abstract) were obtained by least-squares refinement of the angular positions of nine Mo $K\alpha_1$ reflections (Busing, Ellison, Levy, King & Roseberry, 1968). The measurements were made at 26 ± 1 °C. The intensities of 2678 unique reflections with $\sin\theta/\lambda < 0.60$ Å^{-1} were measured with Nb-filtered Mo $K\bar{\alpha}$ radiation using the θ–2θ scan technique. Of these, 2099 had intensities $>1\sigma$ and were used in the subsequent analysis. Absorption and extinction corrections were not applied. Each intensity was assigned a variance $\sigma^2(I)$ based on counting statistics plus a term $(0.04I)^2$ where I is the net intensity.

The position of the Br atom was determined from a three-dimensional Patterson function. A three-dimensional Fourier synthesis phased on the Br atom allowed the determination of the positions of all non-hydrogen atoms. One water molecule was also located, and there is evidence of a second partially occupied water site. Full-matrix least-squares refinement of the positional and isotropic thermal parameters of the non-hydrogen atoms reduced the R value $(= \sum||F_o| - |F_c||/\sum|F_o|)$ to 0·23. The calculated positions for most H atoms were used in subsequent refinements. The H atoms attached to N(12) and C(26) were located from a three-dimensional difference Fourier map. The H atoms attached to the remaining methyl C atoms and the water molecules could not be located with any certainty.

Difficulty arose during refinement concerning the accurate representation of the electron density for the Br atom. From a three-dimensional difference Fourier map, it appeared that the Br atom could be represented as two half Br atoms, separated by approximately 0·5 Å. The apparent shift in the Br position may be compensated by the absence of the second water molecule [O(27)] in approximately 50% of the sites.

In subsequent refinements, all heavy atoms, except the Br, were given isotropic thermal parameters and the H atoms were held fixed at calculated positions. Refinement of a single anisotropic Br resulted in a cigar-shaped ellipsoid elongated in the a direction. A three-dimensional difference Fourier map about the Br contained a positive peak of 1·1 e Å^{-3} and a negative peak of $-0{\cdot}9$ e Å^{-3}. This refinement resulted in an R factor of 0·109. When the Br was represented as two anisotropic half Br atoms, refinement resulted in the coalescence of the two. This refinement also resulted in the lowest R factor obtained, $R = 0{\cdot}10$. When represented as two isotropic half Br atoms, the sites did not coalesce and remained separated by 0·67 Å. This refinement, taken as the final representation, yielded an R value of 0·11. The area near these Br sites still suffers from some disorder which may also be affected by the partially occupied water site nearby. In this representation, the standard deviation of an observation of unit weight, defined as $[\sum w|\Delta F|^2/(n-p)]^{1/2}$ where n is the number of observations and p the number of adjusted parameters, was 2·14. The largest parameter shift during the last cycle of refinement was 30% of the estimated standard deviation.

Scattering factors for the non-hydrogen atoms were taken from Cromer & Mann (1968) and for the H atoms from Stewart, Davidson & Simpson (1965). Values for the real and imaginary parts of the dispersion correction of the atomic scattering factor for the Br were taken from Cromer (1965). All calculations were performed with the XRAY system (Stewart, Kruger, Ammon, Dickinson & Hall, 1972).

Table 1. *Positional* ($\times 10^4$) *and thermal* ($\times 10^2$) *parameters for non-hydrogen atoms*

The isotropic temperature factor is $\exp[-8\pi^2 U(\sin\theta/\lambda)^2]$. Standard deviations in units of the last significant digits are given in parentheses.

	x	y	z	U (Å^2)
Br(1)*	−1544 (3)	696 (2)	1120 (2)	4·9 (1)
Br(2)*	−892 (4)	790 (2)	1171 (2)	7·3 (1)
C(24)	−2338 (12)	4946 (7)	1733 (8)	4·9 (3)
C(25)	−4602 (16)	915 (9)	−734 (11)	8·0 (4)
C(26)	−5561 (13)	3413 (8)	−3035 (9)	5·8 (3)
O(28)	−502 (10)	4059 (6)	3961 (7)	8·5 (3)
O(27)*	2161 (26)	800 (14)	515 (18)	11·9 (8)
N(1)	−3393 (8)	4502 (5)	164 (5)	3·4 (2)
C(2)	−2834 (11)	4322 (6)	1045 (7)	3·7 (3)
C(3)	−2859 (10)	3503 (6)	1147 (7)	3·4 (3)
C(4)	−3823 (10)	2417 (6)	−29 (7)	3·3 (3)
C(5)	−4435 (10)	2311 (6)	−909 (7)	3·5 (3)
C(6)	−4744 (10)	2974 (6)	−1502 (7)	3·5 (3)
C(7)	−4406 (10)	3731 (6)	−1206 (7)	3·3 (3)
C(8)	−3812 (10)	3831 (6)	−312 (7)	3·2 (3)
C(9)	−3480 (10)	3185 (6)	298 (7)	3·2 (3)
C(10)	−2396 (10)	3059 (6)	2024 (7)	3·4 (3)
C(11)	−906 (10)	2851 (6)	2060 (7)	3·4 (3)
N(12)		2653 (4)	3011 (5)	2·8 (2)
C(13)	−1031 (10)	1992 (6)	3483 (7)	3·5 (3)
C(14)	−374 (11)	1844 (6)	4454 (7)	3·6 (3)
N(15)	1043 (8)	1637 (5)	4442 (5)	2·8 (3)
C(16)	1782 (11)	2267 (7)	3993 (8)	4·3 (2)
C(17)	1171 (11)	2428 (7)	3024 (8)	4·5 (3)
C(18)	1655 (10)	1312 (6)	5274 (6)	2·9 (2)
C(19)	2954 (11)	1516 (6)	5646 (8)	3·7 (3)
C(20)	3531 (11)	1173 (7)	6467 (8)	4·3 (3)
C(21)	2844 (11)	631 (6)	6940 (6)	4·3 (3)
C(22)	1578 (11)	404 (6)	6588 (7)	4·2 (3)
C(23)	969 (10)	737 (6)	5763 (7)	3·3 (2)
O(5)	−4832 (8)	1597 (5)	−1312 (5)	5·4 (2)
O(6)	−5367 (7)	2788 (4)	−2369 (5)	4·8 (2)

* Occupancy fixed at 0·5.

The final atomic parameters, along with their standard deviations, estimated from the inverse of the normal-equations matrix, are given in Table 1.*

Discussion

A drawing of the crystal structure is shown in Fig. 1. The molecules in the crystal are held together by two hydrogen bonds. One is N(12)–H(12)···O(28) (the N–O distance is 2·74 Å and the N–H–O angle is 177°). A second possible hydrogen bond involves the H atoms of O(28) and the bromide ion; however, these H atoms could not be located with any confidence.

Least-squares planes were calculated through the indole nucleus, the ethylamine chain, the C atoms of the piperazine ring and the phenyl group. Perpendicular distances of relevant atoms from each plane along with the equations of the planes are given in Table 2. The indole nucleus is essentially planar with the dihedral angle between the planes calculated for the pyrrole and benzene moieties of the indole nucleus being 0·7°. C(10) attached to the pyrrole ring at C(3) was found to be 0·05 Å out of the indole plane. The exocyclic O(5) and O(6) deviate less than 0·03 Å from the indole plane.

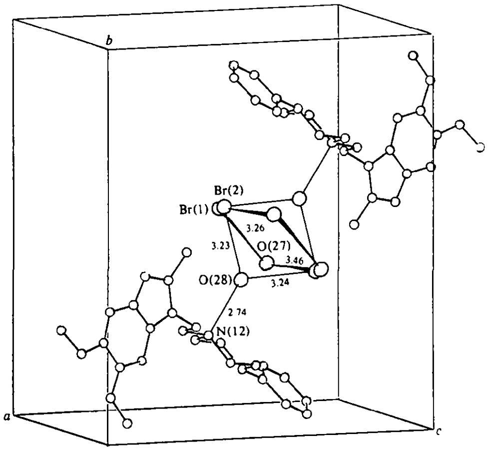

Fig. 1. Diagram depicting the hydrogen-bonding scheme and disorder associated with the molecule (viewed down the a axis with counterclockwise rotations of 15 and 20° about the b and c axes respectively). The molecules are related by a center of inversion at $(0,\frac{1}{2},\frac{1}{2})$.

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33681 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Equations of molecular planes and perpendicular out-of-plane distances* (Å)

x, y, and z are fractional coordinates in the crystal system.

(*A*) Indole nucleus

$$9\cdot274x - 1\cdot337y - 6\cdot258z = 3\cdot848$$

N(1)	0·00	C(10)*	−0·05
C(2)	−0·01	N(12)*	1·32
C(3)	0·01	C(25)*	−0·08
C(4)	0·00	C(26)*	0·13
C(5)	−0·01	O(5)*	−0·03
C(6)	−0·01	O(6)*	−0·02
C(7)	0·02	C(24)*	−0·07
C(8)	−0·01	N(15)*	1·82
C(9)	0·01		

r.m.s.(Δ) = 0·01 Å.

(*B*) Ethylamine chain

$$1\cdot985x + 15\cdot532y - 4\cdot385z = 5\cdot268$$

C(3)	0·11	C(11)	−0·12
C(10)	−0·11	N(12)	0·11

r.m.s.(Δ) = 0·13 Å.

(*C*) Benzene ring

$$-4\cdot322x + 12\cdot241y + 8\cdot107z = 5\cdot159$$

C(18)	0·01	N(12)*	0·66
C(19)	0·00	N(15)*	−0·01
C(20)	−0·01		
C(21)	0·01		
C(22)	−0·01		
C(23)	0·00		

r.m.s.(Δ) = 0·01 Å.

(*D*) Piperazine ring

$$-2\cdot263x + 15\cdot759y + 3\cdot996z = 4\cdot767$$

C(13)	0·00	N(12)*	0·69
C(14)	0·00	N(15)*	−0·65
C(16)	0·00		
C(17)	0·00		

r.m.s.(Δ) = 0·01 Å.

Angles between planes

$BA = 89\cdot9°$ $CD = 23\cdot0°$ $BD = 24\cdot9°$

* Atoms not defining the plane.

The bond distances and angles shown in Fig. 2 are characteristic of other indolealkylamines (Carlström, Bergin & Falkenberg, 1973). The bond lengths about N(12) are gathered about a mean value of 1·50 Å and the bond angles associated with N(12) are tetrahedral, as expected for a protonated tertiary amine. The bond distances and angles about N(15) show some sp^2 character due to the phenyl group attached to N(15).

The torsion angle τ_1 [C(2)–C(3)→C(10)–C(11)] is 102°, indicating the position of C(11) in the ethylamine chain relative to the ring system. The torsion angle τ_2 [C(3)–C(10)→C(11)–N(12)] is 163°, indicating that the ethylamine chain is almost maximally extended. The piperazine ring is in the standard chair conformation.

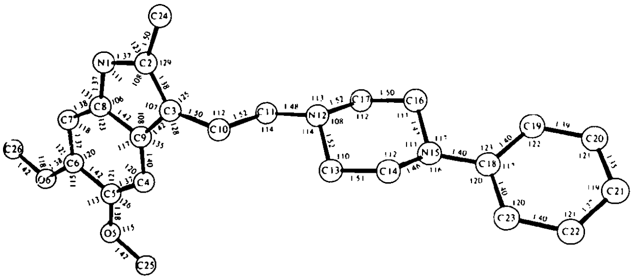

Fig. 2. Diagram (*ORTEP*, Johnson, 1965) depicting the conformation of oxypertine, including the bond distances (Å) and angles (°). The estimated standard deviations for the bond lengths and angles are 0·01 Å and 1·0° respectively. The atoms are represented as spheres of arbitrary size.

Carlström *et al.* (1973) in their review on the structures of biogenic monoamines found that indoleamines can be placed into two well-defined groups with regard to their τ_2 angles and that hallucinogenic substances belong to the group having a fully extended ethylamine side chain (τ_2 approximately 180°). Thus, oxypertine falls into the same class as the hallucinogenic indoleamines; however, there have been no reports of hallucinogenic activity associated with the use of the drug.

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