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Structure of Dopexamine Hydrochloride

By Stephen C. Eyley and Francis Ince

*Fisons plc, Pharmaceuticals Division, Bakewell Road, Loughborough, Leicestershire LE*11 0*RH, England*

and Andrew A. Freer*

*Department of Chemistry, University of Glasgow, Glasgow G*12 8*QQ, Scotland*

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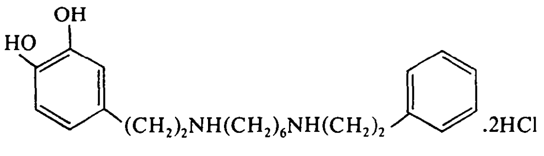
Abstract. 4-{2-[6-(*N*-2-Phenylethylamino)hexylamino]ethyl}-1,2-benzenediol dihydrochloride, $C_{22}H_{34}N_2O_2^{2+}.2Cl^-$, $M_r = 429{\cdot}4$, monoclinic, $C2/c$, $a = 16{\cdot}279\,(4)$, $b = 9{\cdot}902\,(2)$, $c = 14{\cdot}239\,(3)$ Å, $\beta = 99{\cdot}34\,(2)°$, $V = 2264{\cdot}6$ Å^3, $Z = 4$, $D_x = 1{\cdot}26$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 3{\cdot}09$ cm^{-1}, $F(000) = 920$, $T = 291$ K, final $R = 0{\cdot}066$ for 1651 unique reflections. There is a disordered arrangement of dopexamine hydrochloride molecules about the crystallographic twofold axes. The long chain connecting the two aromatic rings has a central torsion angle C(10)—C(11)—C(11′)—C(10′) of −73·6 (5)° but is otherwise fully extended and orthogonal to the plane of the catechol ring.

Introduction. Crystals of dopexamine hydrochloride (I) were prepared at Fisons plc, Pharmaceutical Division, Loughborough. Dopexamine hydrochloride is a novel long-chain dopamine analogue developed for the treatment of acute heart failure (Brown, Farmer, Hall, Kasprzak, O'Connor & Smith, 1984; Brown, Farmer, Hall, Humphries, O'Connor & Smith, 1984). Since its overall pharmacological profile differs considerably from that of dopamine hydrochloride the analysis was undertaken to compare the stereochemistry of dopexamine hydrochloride with other dopaminergic substances.



(I)

Experimental. Colourless plate-shaped crystals grown in a concentrated HCl medium, crystal *ca* 0·6 × 0·4 × 0·2 mm used in data collection, CAD-4 diffractometer. Preliminary Weissenberg photographs indicated crystals to be monoclinic, $C2/c$ or Cc. D_m not measured. 1986 independent intensities, θ limit 25°, ω–2θ scan. 2 standard reflections gave <3% variation in intensity. Least-squares technique based on 25 reflections, $\theta > 12°$, used to refine lattice parameters. No absorption correction, h 0 to 19, k 0 to 11, l −16 to 16. Structure solution by direct methods in the space group $C2/c$ using *MITHRIL* (Gilmore, 1984) with negative quartet invariants in convergence procedure and figures of merit. Full-matrix refinement of F of coordinates and anisotropic thermal parameters for all nonhydrogen atoms, H-atom positions and isotropic thermal parameters converged to R and wR of 0·066 and 0·063, unit weights. 1651 unique reflections, $I \geq 2{\cdot}5\sigma_I$ used. $\Delta_{\max}/\sigma = 0{\cdot}25$; max. and min. heights in final difference Fourier synthesis = 0·72 and −0·33 e Å^{-3}. Scattering factors from *International Tables for X-ray Crystallography* (1974). All calculations on a Gould SEL 32/27 computer using *Glasgow GX* package (Mallinson & Muir, 1985).

Discussion. Final positional and equivalent isotropic thermal parameters are given in Table 1.† Bond lengths and angles with their standard deviations are given in Table 2. An *ORTEP* (Johnson, 1976) diagram, Fig. 1, illustrates the numbering scheme for the molecule, while Fig. 2 shows a stereoview of the packing arrangement of the molecule looking down the short b axis. The numbering scheme is that adopted by Carlström & Bergin (1967).

The molecules are disordered about the twofold axes with random alternation of the catechol and phenyl rings. The possibility that the space group could be noncentrosymmetric Cc, with one complete molecule in the asymmetric unit, was investigated. Although the R value was slightly lower, 0·061, correlations approaching unity were found for related atoms, and distortion of

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* To whom correspondence should be addressed.

† Lists of structure factors, anisotropic temperature factors and hydrogen-atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42887 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Final positional parameters and equivalent isotropic thermal parameters* (Å^2)

$$U_{\text{eq}} = \tfrac{1}{3}\textstyle\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
Cl	0·44496 (7)	0·18120 (13)	0·08429 (8)	0·063
O(1)	1·4561 (5)	0·4580 (10)	1·4438 (5)	0·088
O(2)	1·3191 (7)	0·6100 (10)	1·4717 (5)	0·186
N(1)	1·1096 (2)	0·5963 (4)	1·0113 (2)	0·046
C(1)	1·3132 (3)	0·4033 (5)	1·2274 (3)	0·064
C(2)	1·3827 (3)	0·3929 (6)	1·2926 (4)	0·082
C(3)	1·3882 (3)	0·4604 (6)	1·3741 (4)	0·074
C(4)	1·3248 (4)	0·5420 (6)	1·3950 (3)	0·081
C(5)	1·2489 (3)	0·5524 (5)	1·3246 (3)	0·067
C(6)	1·2457 (3)	0·4796 (4)	1·2405 (3)	0·048
C(7)	1·1712 (3)	0·4878 (7)	1·1633 (4)	0·071
C(8)	1·1847 (3)	0·5885 (5)	1·0872 (3)	0·049
C(9)	1·1172 (3)	0·6960 (5)	0·9343 (3)	0·048
C(10)	1·0394 (3)	0·6947 (5)	0·8602 (3)	0·052
C(11)	1·0389 (3)	0·8068 (5)	0·7883 (3)	0·054

Table 2. *Bond lengths* (Å) *and angles* (°)

O(1)—C(3)	1·360 (10)	O(2)—C(4)	1·298 (10)
N(1)—C(8)	1·497 (6)	N(1)—C(9)	1·496 (6)
C(1)—C(2)	1·347 (8)	C(1)—C(6)	1·371 (7)
C(2)—C(3)	1·329 (9)	C(3)—C(4)	1·382 (9)
C(4)—C(5)	1·462 (8)	C(5)—C(6)	1·391 (7)
C(6)—C(7)	1·501 (7)	C(7)—C(8)	1·515 (8)
C(9)—C(10)	1·510 (7)	C(10)—C(11)	1·510 (7)
C(11)—C(11′)	1·532 (7)	N(1)—H(1N)	1·053 (4)
Cl$\cdots$O(1^{i})	3·237 (10)	N(1)—H(2N)	0·943 (5)
Cl$\cdots$O(2^{ii})	3·159 (10)	Cl$\cdots$H(1N^{iii})	2·090 (4)
Cl$\cdots$N(1^{iii})	3·143 (4)	Cl$\cdots$H(2N^{iii})	2·201 (4)

Symmetry code: (i) $2{\cdot}0 - x,\ y,\ 1{\cdot}5 - z$; (ii) $-1{\cdot}0 + x,\ 1{\cdot}0 - y,\ -1{\cdot}5 + z$; (iii) $-0{\cdot}5 + x,\ -0{\cdot}5 + y,\ -1{\cdot}0 + z$.

C(8)—N(1)—C(9)	114·1 (4)	C(2)—C(1)—C(6)	123·4 (5)
C(1)—C(2)—C(3)	119·5 (6)	O(1)—C(3)—C(2)	124·0 (7)
O(1)—C(3)—C(4)	113·6 (6)	C(2)—C(3)—C(4)	122·4 (6)
O(2)—C(4)—C(3)	129·9 (7)	O(2)—C(4)—C(5)	111·8 (7)
C(3)—C(4)—C(5)	118·1 (5)	C(4)—C(5)—C(6)	117·6 (5)
C(1)—C(6)—C(5)	119·0 (5)	C(1)—C(6)—C(7)	120·0 (5)
C(5)—C(6)—C(7)	121·0 (5)	C(6)—C(7)—C(8)	111·4 (5)
N(1)—C(8)—C(7)	110·7 (4)	N(1)—C(9)—C(10)	110·3 (4)
C(9)—C(10)—C(11)	112·3 (4)	C(10)—C(11)—C(11′)	113·3 (4)
Cl$\cdots$H(1N)—N(1)	169 (3)		
Cl$\cdots$H(2N)—N(1)	177 (4)		

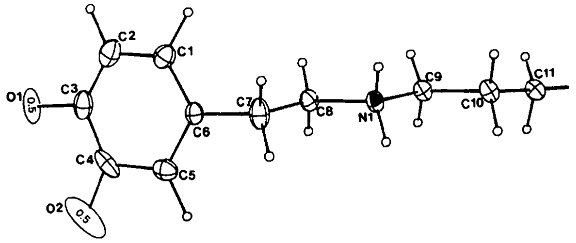

Fig. 1. A view of half the molecule showing the numbering scheme and vibrational ellipsoids (50% probability level).

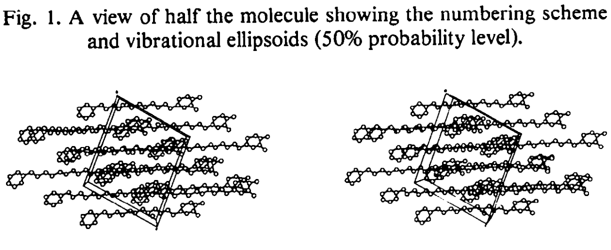

Fig. 2. A stereoview of the unit-cell contents looking down the b axis.

the catechol ring with subsequent high thermal parameters lead to the conclusion that the more probable space group is indeed $C2/c$. Despite the disorder-induced distortion of the catechol ring, in particular the C(4)—C(5) and O(2)—C(4) bonds, 1·462 (8) and 1·298 (10) Å, respectively, the benzene ring deviates only slightly from planarity with a maximum displacement of −0·006 (6) Å for C(1), with the two O atoms being −0·008 (9) and 0·044 (10) Å, respectively, out of this plane.

The long side chain is almost fully extended, forming a plane that is nearly orthogonal to the plane of the catechol ring, a situation that appears to favour biological activity. The values of the torsion angles C(1)—C(6)—C(7)—C(8) and C(6)—C(7)—C(8)—N(1) of −80·7 (6) and 179·5 (6)° are similar to those found in dopamine hydrochloride (Giesecke, 1980) and epinine hydrobromide (Giesecke, 1976). The slightly greater bond angle of 123·4 (7)° for C(2)—C(3)—O(1) and the height of the N atom over the ring plane, 1·460 (4) Å, are also close to the values observed for other dopamine derivatives.

The stereo diagram, Fig. 2, shows the packing arrangement of the molecules. They extend in rows at an approximate angle of 45° to the ac plane with the midpoint of the C(11)—C(11′) bond at $0y\frac{1}{4}$ and $0\bar{y}\frac{3}{4}$ thereby introducing the symmetry within the disordered molecule. The H atoms (with 50% occupancy because of the disorder) attached to O(1) and O(2) could not be located unambiguously from the final difference Fourier synthesis. As in dopamine hydrochloride, the chloride ion is central to the hydrogen-bonding network stabilizing the structure by forming covalent bonds with both O atoms, 3·237 (10) and 3·159 (10) Å, in the catechol ring and to each of the H atoms attached to the N in the extended side chain. Thus the distances Cl$\cdots$H(1N) and Cl$\cdots$H(2N), 2·090 (4) and 2·201 (4) Å, and their respective Cl$\cdots$H(N)—N bond angles of 169 (3) and 177 (4)° indicate reasonably strong intermolecular hydrogen bonds.

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