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The Crystal and Molecular Structure of the Neuroleptic Pimozide Hydrochloride, 1-{1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidyl}-2-benzimidazolinone HCl

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Abstract

Crystals of pimozide, $C_{28}H_{29}F_2N_3O \cdot HCl$, are monoclinic, space group $P2_1/c$ with unit-cell dimensions $a = 10.007$ (3), $b = 25.880$ (9), $c = 10.014$ (4) Å, $\beta = 99.15$ (7)°, $Z = 4$. The crystal structure was analysed by the heavy-atom method and refined by full-matrix least-squares calculations to a final R of 0.046.
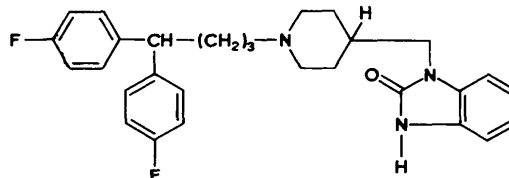
Introduction

Pimozide, $C_{28}H_{29}F_2N_3O \cdot HCl$ (*R*24970; pimozide base: *R*6238; pimozide HBr: *R*24969) is a neuroleptic

(major tranquillizer) drug with anticholinergic activity. As part of a systematic study of substances affecting the peripheral and central nervous systems, the crystal structure of pimozide HCl was analyzed.

Experimental

Crystals of pimozide hydrochloride (*R*24970) obtained from Janssen Laboratories, grown from a saturated solution of methanol and water (4:1) at 313

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K are colourless plates elongated along the c axis and show the forms {100} and {010}. Space group and preliminary cell parameters were determined from oscillation and precession photographs. Refined cell parameters and standard deviations were determined by use of the cell-refinement program written by Busing, Ellison, Levy, King & Rosebury (1968).

Crystal data

Pimozide HCl, $C_{28}H_{29}F_2N_3O$. HCl, $M_r = 498 \cdot 029$, $a = 10 \cdot 007$ (3), $b = 25 \cdot 880$ (9), $c = 10 \cdot 014$ (4) Å, $\beta = 99 \cdot 15$ (7)°, $V = 2560 \cdot 5$ Å^3, $D_m = 1 \cdot 295$ Mg m^{-3}, $Z = 4$, $D_x = 1 \cdot 292$ Mg m^{-3}. Systematic absences: $h0l$ for $l = 2n + 1$, $0k0$ for $k = 2n + 1$. Space group $P2_1/c$.

Data collection and processing

Three-dimensional X-ray intensity data from a single crystal were collected on a computer-controlled Stoe four-circle diffractometer using Mo $K\alpha$ radiation with graphite monochromator (002). A coupled θ–2θ step scan with $\Delta 2\theta = 0 \cdot 04$°, a counting time of 2 s per step and a peak width of $1 \cdot 6$° were used. The standard reflexion ($\bar{3}11$) was measured at an interval of 25 reflexions. In the range $2\theta = 5$–45°, 3811 reflexions covering one quadrant of reciprocal space ($\pm h,k,l$) were collected of which 2529 had $I \geq 3\sigma(I)$. These 2529 symmetry-independent observed data were used for the determination of the structure. The data were corrected for Lorentz and polarization effects. No corrections for absorption or extinction were made.

Structure determination and refinement

The position of the chloride ion was determined from a sharpened Patterson synthesis. A Fourier synthesis using observed data phased on the chloride ion produced a satisfactory trial structure. A subsequent Fourier map phased on the trial structure revealed all non-hydrogen atoms. Several cycles of full-matrix isotropic refinement converged to an R of $0 \cdot 13$ and a further two cycles of anisotropic full-matrix refinement of all non-hydrogen atoms converged to an R of $0 \cdot 081$. A difference Fourier map phased with these refined atoms showed all the hydrogen atom positions. The hydrogen atoms were assigned isotropic thermal parameters of $0 \cdot 063$ Å^2 (U_{iso}). The final anisotropic refinement of all the non-hydrogen atoms and positional-parameter refinement of all the hydrogen atoms were continued until all parameter shifts were $\leq 0 \cdot 1\sigma$. The function minimized was $\sum w(|F_o| - |F_c|)^2$ with $w = 1$ for all reflexions. The final R was $0 \cdot 046$. Atomic scattering factors for neutral carbon, nitrogen, oxygen, fluorine and for the chloride ion were taken from the

published values of Cromer & Waber (1965) and for hydrogen from *International Tables for X-ray Crystallography* (1962). The final positional parameters for non-hydrogen atoms are listed in Table 1 and hydrogen atom positions in Table 2.*

Table 1. *Fractional coordinates* ($\times 10^4$) *from least-squares refinement with estimated standard deviations in parentheses*

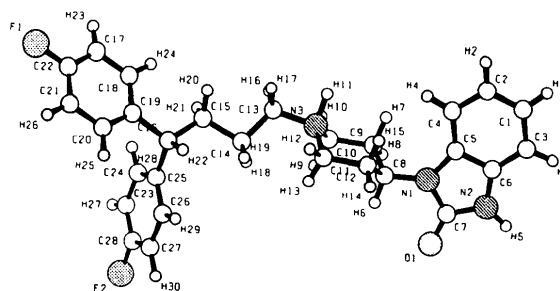|	x	y	z
Cl(1)	221 (1)	754 (0)	1380 (1)
C(1)	5287 (5)	1759 (2)	162 (5)
C(2)	4007 (5)	1565 (2)	244 (5)
C(3)	6444 (5)	1501 (2)	751 (5)
C(4)	3837 (4)	1105 (2)	910 (4)
C(5)	4994 (4)	849 (1)	1510 (4)
C(6)	6279 (4)	1044 (1)	1417 (4)
N(1)	5204 (3)	389 (1)	2256 (3)
C(7)	6585 (4)	293 (2)	2598 (4)
N(2)	7224 (3)	706 (1)	2098 (3)
O(1)	7101 (3)	−79 (1)	3223 (3)
C(8)	4195 (4)	21 (1)	2610 (4)
C(9)	3404 (4)	−222 (2)	1339 (4)
C(10)	2304 (4)	−583 (1)	1687 (4)
N(3)	1386 (3)	−281 (1)	2434 (3)
C(11)	2140 (4)	−93 (2)	3748 (4)
C(12)	3263 (4)	276 (2)	3484 (4)
C(13)	67 (4)	−576 (2)	2570 (5)
C(14)	155 (4)	−964 (2)	3708 (5)
C(15)	−1248 (4)	−1224 (2)	3545 (5)
C(16)	−1568 (4)	−1474 (1)	4824 (4)
C(17)	−5341 (5)	−1722 (2)	3568 (6)
C(18)	−3987 (4)	−1607 (2)	3573 (5)
C(19)	−3069 (4)	−1601 (1)	4756 (5)
C(20)	−3545 (4)	−1705 (2)	5954 (5)
C(21)	−4902 (5)	−1813 (2)	5978 (5)
C(22)	−5759 (4)	−1816 (2)	4770 (6)
F(1)	−7092 (3)	−1930 (1)	4775 (4)
C(23)	−215 (5)	−2861 (2)	4959 (5)
C(24)	−948 (4)	−2418 (2)	4533 (5)
C(25)	−717 (4)	−1958 (1)	5251 (4)
C(26)	267 (4)	−1946 (2)	6369 (5)
C(27)	1014 (4)	−2387 (2)	6822 (5)
C(28)	744 (4)	−2829 (2)	6068 (5)
F(2)	1467 (3)	−3263 (1)	6503 (3)

Fig. 1. View of the pimozide molecule as observed in crystals of the hydrochloride and atomic numbering.

Description and discussion of the structure

Fig. 1 shows the atom-numbering scheme on a drawing of the molecule with depth cues. Bond distances and angles for a unique molecule are listed in Tables 3 and 4. Table 5 gives the mean-plane equations for certain groups of atoms in the molecule. It shows that each of the aromatic benzene rings is planar within experimental error. The fused six-membered aromatic ring [C(1)–C(6)] and five-membered ring [C(5)–C(7)] and O(1) are nearly coplanar. The conformation of the molecule is described in terms of selected torsion angles in Table 6. Intermolecular distances <3·6 Å for non-hydrogen atoms are shown in Table 7.

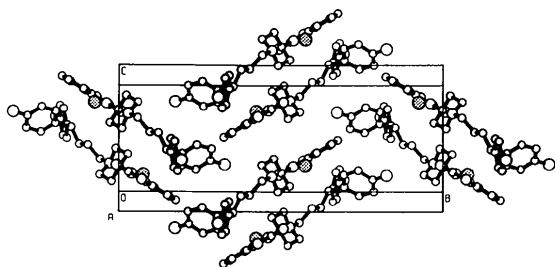Fig. 2. Molecular packing of pimozide hydrochloride viewed along the −a* axis.

Fig. 2 shows the molecular packing viewed down the −a* axis. The figure was produced using a modified version of the program *PLUTO* written by Motherwell, Jones & Pauling (unpublished). All computational work was carried out on the University College London IBM 360, University of London CDC 6600 and our GT 44. The programs for the GT 44 were written by Douglas Richardson.

Table 2. *Fractional coordinates for hydrogen atoms* (×10³) *with estimated standard deviations in parentheses*

	x	y	z
H(1)	535 (5)	207 (2)	−37 (5)
H(2)	321 (5)	175 (2)	−22 (5)
H(3)	733 (5)	163 (2)	61 (5)
H(4)	290 (5)	97 (2)	89 (5)
H(5)	820 (5)	71 (2)	210 (5)
H(6)	475 (5)	−26 (2)	320 (5)
H(7)	294 (5)	6 (2)	66 (5)
H(8)	401 (5)	−42 (2)	85 (5)
H(9)	270 (5)	−89 (2)	230 (5)
H(10)	172 (5)	−73 (2)	79 (5)
H(11)	77 (5)	2 (2)	176 (5)
H(12)	143 (5)	8 (2)	436 (5)
H(13)	246 (5)	−37 (2)	437 (5)
H(14)	374 (5)	38 (2)	439 (5)
H(15)	281 (5)	58 (2)	304 (5)
H(16)	−36 (5)	−72 (2)	171 (5)
H(17)	−73 (5)	−25 (2)	273 (5)
H(18)	91 (5)	−120 (2)	366 (5)
H(19)	42 (5)	−77 (2)	467 (5)
H(20)	−196 (5)	−94 (2)	317 (5)
H(21)	−141 (5)	−149 (2)	269 (5)
H(22)	−120 (5)	−115 (2)	548 (5)
H(23)	−599 (5)	−174 (2)	277 (5)
H(24)	−367 (5)	−154 (2)	262 (5)
H(25)	−290 (5)	−172 (2)	685 (5)
H(26)	−523 (5)	−192 (2)	684 (5)
H(27)	−34 (5)	−320 (2)	453 (5)
H(28)	−167 (5)	−243 (2)	383 (5)
H(29)	47 (5)	−161 (2)	698 (5)
H(30)	180 (5)	−238 (2)	768 (5)

Table 3. *Interatomic distances* (Å) *and angles* (°) *for non-hydrogen atoms with estimated standard deviations in parentheses*

(a) Bond distances

C(1)–C(2)	1·390 (6)	C(13)–C(14)	1·511 (5)
C(1)–C(3)	1·384 (6)	C(14)–C(15)	1·542 (5)
C(2)–C(4)	1·388 (6)	C(15)–C(16)	1·514 (5)
C(4)–C(5)	1·385 (5)	C(17)–C(18)	1·386 (6)
C(3)–C(6)	1·380 (6)	C(16)–C(19)	1·528 (5)
C(5)–C(6)	1·398 (5)	C(18)–C(19)	1·379 (6)
C(5)–N(1)	1·403 (5)	C(19)–C(20)	1·386 (6)
N(1)–C(7)	1·391 (5)	C(20)–C(21)	1·390 (6)
C(6)–N(2)	1·385 (4)	C(17)–C(22)	1·358 (7)
C(7)–N(2)	1·380 (4)	C(21)–C(22)	1·367 (7)
C(7)–O(1)	1·218 (5)	C(22)–F(1)	1·367 (7)
N(1)–C(8)	1·472 (4)	C(23)–C(24)	1·392 (6)
C(8)–C(9)	1·523 (5)	C(16)–C(25)	1·535 (5)
C(9)–C(10)	1·527 (5)	C(24)–C(25)	1·392 (5)
C(10)–N(3)	1·494 (5)	C(25)–C(26)	1·369 (5)
N(3)–C(11)	1·490 (5)	C(26)–C(27)	1·400 (6)
C(8)–C(12)	1·527 (5)	C(23)–C(28)	1·349 (6)
C(11)–C(12)	1·530 (5)	C(27)–C(28)	1·372 (6)
N(3)–C(13)	1·549 (5)	C(28)–F(2)	1·370 (5)
		N(3)–Cl(1)	3·044 (3)

(b) Angles

C(2)–C(1)–C(3)	121·1 (5)	N(3)–C(13)–C(14)	116·4 (4)
C(1)–C(2)–C(4)	121·5 (5)	C(13)–C(14)–C(15)	105·5 (4)
C(1)–C(3)–C(6)	117·6 (5)	C(14)–C(15)–C(16)	114·1 (4)
C(2)–C(4)–C(5)	117·4 (4)	C(15)–C(16)–C(19)	113·2 (4)
C(4)–C(5)–C(6)	120·8 (4)	C(15)–C(16)–C(25)	113·7 (4)
C(4)–C(5)–N(1)	132·9 (4)	C(19)–C(16)–C(25)	109·6 (4)
C(6)–C(5)–N(1)	106·3 (3)	C(18)–C(17)–C(22)	118·3 (5)
C(3)–C(6)–C(5)	121·5 (4)	C(17)–C(18)–C(19)	121·5 (5)
C(3)–C(6)–N(2)	130·9 (2)	C(16)–C(19)–C(18)	123·8 (4)
C(5)–C(6)–N(2)	107·6 (2)	C(16)–C(19)–C(20)	118·3 (4)
C(5)–N(1)–C(7)	110·0 (3)	C(18)–C(19)–C(20)	117·9 (4)
C(5)–N(1)–C(8)	128·8 (3)	C(19)–C(20)–C(21)	121·7 (5)
C(7)–N(1)–C(8)	121·2 (3)	C(20)–C(21)–C(22)	117·6 (5)
N(1)–C(7)–N(2)	105·8 (2)	C(17)–C(22)–C(21)	123·1 (5)
N(1)–C(7)–O(1)	126·3 (4)	C(17)–C(22)–F(1)	118·7 (5)
N(2)–C(7)–O(1)	127·9 (6)	C(21)–C(22)–F(1)	118·2 (5)
C(6)–N(2)–C(7)	110·4 (9)	C(24)–C(23)–C(28)	118·1 (5)
N(1)–C(8)–C(9)	110·5 (4)	C(23)–C(24)–C(25)	120·8 (4)
N(1)–C(8)–C(12)	111·3 (3)	C(16)–C(25)–C(24)	121·0 (4)
C(9)–C(8)–C(12)	112·0 (4)	C(16)–C(25)–C(26)	120·4 (4)
C(8)–C(9)–C(10)	111·0 (4)	C(24)–C(25)–C(26)	118·7 (4)
C(9)–C(10)–N(3)	108·5 (4)	C(25)–C(26)–C(27)	121·7 (5)
C(10)–N(3)–C(11)	110·4 (3)	C(26)–C(27)–C(28)	116·8 (5)
C(10)–N(3)–C(13)	112·8 (4)	C(23)–C(28)–C(27)	123·9 (5)
C(11)–N(3)–C(13)	113·7 (4)	C(23)–C(28)–F(2)	118·7 (4)
N(3)–C(11)–C(12)	109·5 (4)	C(27)–C(28)–F(2)	117·4 (4)
C(8)–C(12)–C(11)	111·2 (4)		

Table 4. *Interatomic distances* (Å) *involving hydrogen with estimated standard deviations in parentheses*

H(1)—C(1)	0.98 (4)	H(16)—C(13)	0.97 (6)
H(2)—C(2)	0.98 (4)	H(17)—C(13)	1.19 (6)
H(3)—C(3)	0.98 (4)	H(18)—C(14)	0.98 (5)
H(4)—C(4)	1.00 (4)	H(19)—C(14)	1.08 (5)
H(5)—N(2)	0.97 (6)	H(20)—C(15)	1.05 (5)
H(6)—C(8)	1.03 (4)	H(21)—C(15)	1.10 (5)
H(7)—C(9)	1.04 (4)	H(22)—C(16)	1.09 (4)
H(8)—C(9)	0.98 (5)	H(23)—C(17)	0.94 (4)
H(9)—C(10)	1.05 (4)	H(24)—C(18)	1.07 (4)
H(10)—C(10)	1.06 (5)	H(25)—C(20)	1.02 (5)
H(11)—N(3)	1.15 (7)	H(26)—C(21)	1.00 (4)
H(12)—C(11)	1.10 (5)	H(27)—C(23)	0.98 (4)
H(13)—C(11)	0.97 (5)	H(28)—C(24)	0.93 (4)
H(14)—C(12)	0.99 (4)	H(29)—C(26)	1.07 (4)
H(15)—C(12)	0.98 (4)	H(30)—C(27)	1.07 (4)

Table 5. *Equations of mean planes with displacements* (Å) *of relevant atoms in square brackets*

Equations are based on orthonormalized coordinates; X is parallel to the crystallographic a axis, Y is perpendicular to X in the plane ab, and Z is perpendicular to the plane ab and completes a right-handed set of axes X, Y, Z.

Plane (1) C(1), C(2), C(3), C(4), C(5), C(6)
$$-0.145X + 0.509Y + 0.848Z = 6.097$$
[C(1) 0.001, C(2) 0.002, C(3) 0.000, C(4) −0.005, C(5) 0.006, C(6) −0.004]

Plane (2) C(1), C(2), C(3), C(4), C(5), C(6), N(1), N(2), C(7), O(1)
$$-0.142X + 0.506Y + 0.851Z = 6.134$$
[C(1) −0.006, C(2) −0.007, C(3) 0.001, C(4) −0.009, C(5) 0.010, C(6) 0.002, N(1) 0.023, C(7) −0.004, N(2) 0.014, O(1) −0.024]

Plane (3) C(17), C(18), C(19), C(20), C(21), C(22)
$$-0.202X + 0.974Y + 0.106Z = 8.295$$
[C(17) −0.010, C(18) 0.008, C(19) −0.001, C(20) −0.004, C(21) 0.002, C(22) 0.005]

Plane (4) C(23), C(24), C(25), C(26), C(27), C(28)
$$0.783X + 0.254Y − 0.568Z = 8.411$$
[C(23) −0.005, C(24) 0.004, C(25) −0.005, C(26) 0.007, C(27) −0.008, C(28) 0.008]

Table 6. *Selected torsion angles* (°) *for non-hydrogen atoms*

C(8)—C(12)—C(11)—N(3)	−55	C(14)—C(13)—N(3)—C(11)	−44
C(9)—C(8)—N(1)—C(5)	63	C(14)—C(13)—N(3)—C(10)	82
C(9)—C(8)—N(1)—C(7)	−113	C(15)—C(14)—C(13)—N(3)	−176
C(10)—C(9)—C(8)—N(1)	−177	C(16)—C(15)—C(14)—C(13)	−158
N(3)—C(10)—C(9)—C(8)	58	C(18)—C(19)—C(16)—C(15)	15
C(11)—C(12)—C(8)—N(1)	175	C(19)—C(16)—C(15)—C(14)	165
C(12)—C(11)—N(3)—C(13)	−169	C(20)—C(19)—C(16)—C(15)	−164
C(12)—C(8)—N(1)—C(5)	−62	C(24)—C(25)—C(16)—C(15)	−72
C(12)—C(8)—N(1)—C(7)	122	C(25)—C(16)—C(15)—C(14)	−69
C(13)—N(3)—C(10)—C(9)	168	C(26)—C(25)—C(16)—C(15)	109

$$\sigma(\tau) = 0.5°.$$

Table 7. *Intermolecular distances* (Å) <3.6 Å *for non-hydrogen atoms*

Cl(1)···N(2^i)	3.20	C(27^v)···F(1^{iii})	3.23
C(13)···O(1^i)	3.40	C(28^v)···F(1^{iii})	3.56
C(15)···O(1^i)	3.37	C(10^{iv})···F(2^v)	3.11
C(11)···O(1^{ii})	3.04	C(13^{iv})···F(2^v)	3.55
C(12)···O(1^{ii})	3.42	C(14^v)···F(2^{vi})	3.41
C(5)···C(21^{vi})	3.55	C(17^{iv})···F(2^{vii})	3.52
C(3)···F(2^v)	3.37	F(1^{iii})···F(2^{vi})	3.41
C(4)···C(20^{vi})	3.56		
C(9)···C(6^{viii})	3.54		
C(26^v)···F(1^{iii})	3.30		

Roman numerals as superscripts denote the following symmetry transformations:

(i)	$x-1, y, z$	(v)	$-x, \frac{1}{2}+y, \frac{1}{2}-z$
(ii)	$1-x, -y, 1-z$	(vi)	$-x, -y, 1-z$
(iii)	$-x-1, \frac{1}{2}+y, \frac{1}{2}-z$	(vii)	$1-x, \frac{1}{2}+y, \frac{1}{2}-z$
(iv)	$-x, -y, -z$	(viii)	$1-x, -y, -z.$

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