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The Structure of Haloperidol Hydrobromide {4-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone HBr}

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Abstract. $C_{21}H_{24}ClFNO_2^+.Br^-$, M_r = 456·8, monoclinic, $P2_1/c$, a = 17·162 (9), b = 10·064 (5), c = 13·884 (8) Å, β = 118·40 (4)°, Z = 4, D_c = 1·44 Mg m^{-3}, V = 2109·4 Å^3. The final full-matrix least-squares refinement gave R = 0·078. Though the unit cells differ, the observed conformation is very similar to that of the analogous substance R1616, but differs from those observed in the free bases.

Introduction. Haloperidol hydrobromide (R2420) is a very potent (average dose 3 mg a day) neuroleptic drug (Janssen, 1967). The structure of haloperidol base (R1625), $C_{21}H_{23}ClFNO_2$, was determined by Reed & Schaefer (1973) and those of the closely related 4′-fluoro-4-[4-(4-fluorophenyl)-4-hydroxypiperidino]-butyrophenone, $C_{21}H_{23}F_2NO_2$ (R1616 base), and its hydrochloride, $C_{21}H_{24}F_2NO_2^+.Cl^-$ (R1616), were analysed by Koch & Germain (1972). The crystal structure of haloperidol hydrobromide was determined to investigate the analogies and differences among the three-dimensional structures of these butyrophenone, psychotropic drugs, primarily to gain additional observed data on the flexibility of the conformational degrees of freedom of these substances.

Crystals of haloperidol hydrobromide were provided by Paul Janssen. The thin, colourless, plate crystals were recrystallized from a methanol 5% water mixture. Laue symmetry and preliminary cell parameters were determined from oscillation and precession photographs. The refined cell parameters and their e.s.d.'s were obtained by a least-squares refinement of the angular parameters of 12 diffraction maxima measured with a peak-finding technique on a computer-controlled four-circle Stoe diffractometer (Busing, Ellison, Levy, King & Rosebury, 1968).

Three-dimensional X-ray diffraction data were collected on the diffractometer using Mo $K\alpha$ radiation (graphite monochromator), a coupled θ–2θ step-scan with $\Delta 2\theta$ = 0·04°, a counting time of 8 s per step and a peak width of 1·6°. A standard reflection was measured every 25 measurements. In the range 2θ = 5–45°, 3244 maxima (being one quadrant of reciprocal space) were measured, of which 2031 observed, unique maxima [$I \geq 3\sigma(I)$] were used to determine and refine the structure. The data were corrected for Lorentz and polarization effects, but not for absorption or extinction.

The position of the Br ion was determined from a Patterson synthesis. An observed Fourier synthesis phased on the Br ion produced a satisfactory partial, trial structure. A second Fourier synthesis phased on this trial structure revealed all non-hydrogen atoms. Successive cycles of full-matrix least-squares refinement of positional and isotropic thermal parameters for the non-hydrogen atoms gave R = 0·125 and further cycles of anisotropic, full-matrix refinement of all non-hydrogen atoms converged to an R value of 0·083. At this stage the 24 H atom positions were included in positions calculated using accepted geometrical parameters. H atoms were included in further refinements (but

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† Deceased 17 June 1976.

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Table 1. *Final positional parameters* (×10⁴), *with estimated standard deviations in parentheses*

	x	y	z
Br(1)	1760 (1)	780 (2)	577 (1)
Cl(1)	5896 (3)	−334 (5)	7570 (4)
C(1)	3085 (10)	599 (14)	5020 (11)
C(2)	3588 (13)	−359 (20)	4851 (16)
C(3)	4441 (12)	−646 (20)	5643 (16)
C(4)	4807 (12)	21 (16)	6590 (13)
C(5)	4332 (12)	966 (19)	6805 (13)
C(6)	3484 (11)	1243 (17)	6009 (14)
N(1)	734 (8)	1569 (11)	1919 (9)
C(7)	1202 (10)	2664 (14)	2742 (11)
C(8)	2154 (9)	2240 (14)	3543 (11)
C(9)	2151 (9)	954 (14)	4178 (10)
C(10)	1683 (10)	−135 (14)	3297 (11)
C(11)	731 (10)	276 (14)	2516 (11)
O(1)	1612 (7)	1119 (9)	4681 (8)
C(12)	−220 (9)	1919 (15)	1149 (11)
C(13)	−275 (10)	2892 (16)	207 (12)
C(14)	−1253 (10)	3015 (15)	−622 (12)
C(15)	−1452 (11)	3513 (17)	−1669 (13)
O(2)	−835 (9)	3855 (16)	−1822 (10)
C(16)	−2358 (10)	3595 (15)	−2603 (12)
C(17)	−2478 (12)	4032 (18)	−3613 (14)
C(18)	−3326 (14)	4099 (21)	−4510 (17)
C(19)	−4019 (13)	3721 (19)	−4351 (16)
C(20)	−3942 (14)	3311 (20)	−3342 (17)
C(21)	−3090 (11)	3237 (17)	−2468 (14)
F(1)	−4847 (7)	3735 (12)	−5227 (9)

were not themselves refined), with an isotropic thermal parameter for all H atoms of 0·051 Å². Two cycles of anisotropic refinement of non-hydrogen atoms converged to $R = 0{\cdot}078$ and all non-hydrogen parameter shifts were $\leq 0{\cdot}1\sigma$. The function minimized was $\sum w(|F_o| - |F_c|)^2$ with $w = 1$ for all maxima. The final positional parameters for non-hydrogen atoms are listed in Table 1.*

Discussion. 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 Table 2. The two phenyl rings are planar within experimental error and observed bond distances and angles are in good agreement with those found in the related structures. The piperidine ring is in the chair conformation with the chlorophenyl group and the alkyl chain in equatorial positions, the hydroxyl group being in the axial position. The mean plane of the piperidine ring makes an angle of 53·8° with that of the chlorophenyl ring and 61·7° with the mean plane of the fluorophenyl ring. The variable torsion angles of haloperidol HBr, haloperidol base (Reed & Schaefer, 1973), R1616 base and R1616 (Koch & Germain, 1972) are compared in Table 3 which gives the values of the five important torsional parameters around the C(1)–C(9), N(1)–C(12), C(12)–C(13), C(13)–C(14) and C(14)–C(15) bonds found in the four structures. Although the cell parameters and packing of the four substances are different, Table 3 shows that the observed conformations of the two salts and those of the two bases are very similar, but that those of the salts are quite different from those of the bases. In all four substances the carbonyl group C(15)O(2)C(14) is in the plane of the fluorophenyl ring F(1)C(16)–C(21), which with a barely significant shortening of C(15)–C(16) (mean 1·48 Å) indicates the partial double-bond character of

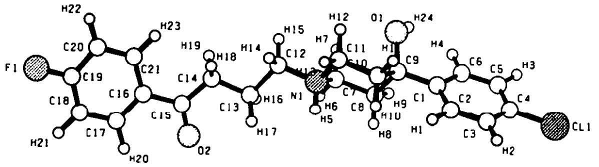

Fig. 1. View of the haloperidol cation as observed in crystals of the hydrobromide with the atomic numbering used.

Table 2. *Interatomic distances* (Å) *and angles* (°) *for non-hydrogen atoms with estimated standard deviations in parentheses in terms of the least significant figure given*

Br(1)–N(1)	3·21 (1)	O(1)–C(9)	1·41 (1)
C(2)–C(1)	1·39 (2)	C(12)–N(1)	1·51 (1)
C(3)–C(2)	1·38 (2)	C(13)–C(12)	1·60 (2)
C(4)–C(3)	1·34 (2)	C(14)–C(13)	1·52 (2)
C(4)–Cl(1)	1·75 (2)	C(15)–C(14)	1·42 (2)
C(5)–C(4)	1·38 (2)	O(2)–C(15)	1·22 (2)
C(6)–C(1)	1·37 (2)	C(16)–C(15)	1·48 (2)
C(6)–C(5)	1·37 (2)	C(17)–C(16)	1·39 (2)
C(7)–N(1)	1·51 (2)	C(18)–C(17)	1·40 (2)
C(8)–C(7)	1·54 (2)	C(19)–C(18)	1·36 (2)
C(9)–C(1)	1·51 (2)	C(20)–C(19)	1·41 (2)
C(9)–C(8)	1·57 (2)	C(21)–C(16)	1·40 (2)
C(10)–C(9)	1·55 (2)	C(21)–C(20)	1·39 (2)
C(11)–N(1)	1·54 (2)	F(1)–C(19)	1·36 (2)
C(11)–C(10)	1·53 (2)		
C(3)–C(2)–C(1)	121·4 (17)	O(1)–C(9)–C(10)	105·0 (10)
C(3)–C(4)–Cl(1)	119·4 (15)	C(12)–N(1)–C(7)	111·8 (11)
C(4)–C(3)–C(2)	120·2 (17)	C(12)–N(1)–C(11)	107·3 (11)
C(5)–C(4)–C(3)	120·7 (16)	C(13)–C(12)–N(1)	110·1 (12)
C(5)–C(4)–Cl(1)	119·8 (15)	C(14)–C(13)–C(12)	106·4 (12)
C(5)–C(6)–C(1)	122·9 (16)	C(15)–C(14)–C(13)	116·4 (14)
C(6)–C(1)–C(2)	116·3 (15)	O(2)–C(15)–C(14)	118·1 (15)
C(6)–C(5)–C(4)	118·5 (16)	C(16)–C(15)–C(14)	124·0 (14)
C(8)–C(7)–N(1)	110·1 (12)	C(16)–C(15)–O(2)	117·9 (14)
C(8)–C(9)–C(1)	110·2 (11)	C(17)–C(16)–C(15)	119·5 (15)
C(9)–C(1)–C(2)	123·4 (14)	C(18)–C(17)–C(16)	120·5 (17)
C(9)–C(1)–C(6)	120·3 (13)	C(19)–C(18)–C(17)	117·5 (18)
C(9)–C(8)–C(7)	110·5 (11)	C(20)–C(19)–C(18)	124·6 (18)
C(10)–C(9)–C(1)	113·8 (12)	C(20)–C(21)–C(16)	120·5 (16)
C(10)–C(9)–C(8)	106·2 (11)	C(21)–C(16)–C(15)	120·2 (14)
C(10)–C(11)–N(1)	109·5 (12)	C(21)–C(16)–C(17)	120·3 (15)
C(11)–N(1)–C(7)	110·1 (11)	C(21)–C(20)–C(19)	116·6 (17)
C(11)–C(10)–C(9)	110·3 (12)	F(1)–C(19)–C(18)	118·2 (16)
O(1)–C(9)–C(1)	110·5 (11)	F(1)–C(19)–C(20)	117·2 (16)
O(1)–C(9)–C(8)	111·1 (11)		

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* Lists of structure factors, anisotropic thermal parameters and H atom positional parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34287 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

this bond. Our interest is in the observed molecular structure, not in the packing, and we shall not discuss the latter further. The major difference in the observed conformations of the two salts is a rotation of the chlorophenyl ring C(1)–C(6) about the C(1)–C(9) bond of approximately 36°.

The molecular packing is shown in Fig. 2 viewed down the *b* axis. There are no unusually short intermolecular distances and no evidence of hydrogen bonds between the N atom and O atoms, but the N–H(5)··· Br distances indicate an electrostatic hydrogen bond. The shortest F–F intermolecular atomic distance is 2·72 Å. An analysis of other butyrophenone-type neuroleptics has been carried out by Koch (1974).

The calculations were performed on the University of London CDC 6600, the University College London IBM 360/651, and our Dec GT-44. Figs. 1 and 2 were drawn using a modified (Jones & Pauling, unpublished) version of the program *PLUTO* (Sam Motherwell).

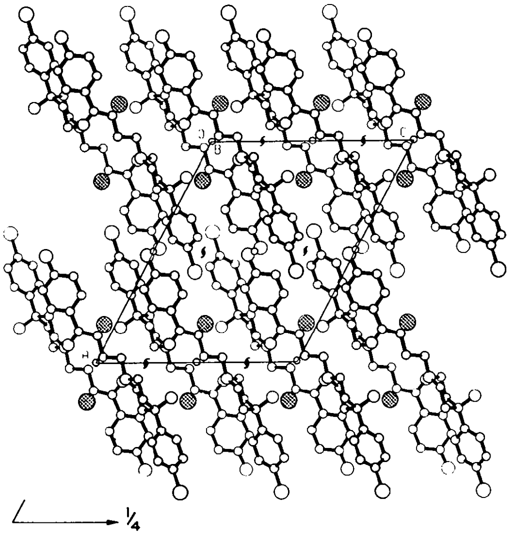

Fig. 2. Molecular packing of haloperidol hydrobromide viewed along the *b* axis.

Table 3. *Comparison of selected torsion angles* (°) *for non-hydrogen atoms in terms of the atomic numbering of Fig.* 1

The e.s.d.'s are ≃1·5°.

	Haloperidol HBr	R1616*	Haloperidol*	R1616 base*
C(13)–C(12)–N(1)–C(7)	80	76	−56	−61
C(13)–C(12)–N(1)–C(11)	−159	−162	−178	−179
C(14)–C(13)–C(12)–N(1)	171	174	−170	−166
C(15)–C(14)–C(13)–C(12)	−163	−162	−69	−68
O(2)–C(15)–C(14)–C(13)	−3	−5	2	1
C(16)–C(15)–C(14)–C(13)	175	174	−178	−177
C(17)–C(16)–C(15)–C(14)	−177	−173	−178	179
C(17)–C(16)–C(15)–O(2)	1	5	2	1
C(21)–C(16)–C(15)–C(14)	4	5	1	−2
C(21)–C(16)–C(15)–O(2)	−179	−177	−179	180
C(8)–C(9)–C(1)–C(2)	−99	−64	−88	−89
C(8)–C(9)–C(1)–C(6)	80	115	95	91
C(10)–C(9)–C(1)–C(2)	20	56	149	151
C(10)–C(9)–C(1)–C(6)	−160	−124	−28	−28
O(1)–C(9)–C(1)–C(2)	138	174	23	28
O(1)–C(9)–C(1)–C(6)	−43	−6	−155	−152
C(15)–C(16) distance (Å)	1·48	1·48	1·47	1·50

* Recalculated from the data published by Koch & Germain (1972) and Reed & Schaefer (1973).

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