1-[4-(3-Chlorophenyl)-1-(4-fluorophenyl-4-oxobutyl)-4-piperidinylcarbonyl]-pyrrolidine (Haloperidide)

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Abstract. Monoclinic, $P2_1/c$; $a = 13 \cdot 395$, $b = 8 \cdot 923$, $c = 19 \cdot 687$ Å, $\beta = 99 \cdot 75°$; 25°C; $C_{26}H_{30}N_2O_2FCl$, M.W. $456 \cdot 99$; $Z = 4$, $D_c = 1 \cdot 309$, $D_m = 1 \cdot 304$ g cm^{-3}.

Introduction. Haloperidide is a very potent neuroleptic which belongs to the class of butyrophenones. The crystals were obtained by evaporation of a solution in ethanol. The space group was determined from Weissenberg photographs. The cell dimensions and intensities were measured with a Nonius CAD-4 automatic four-circle diffractometer. The experimental conditions are given in Table 1. Lorentz and polariza-tion factors were applied but no corrections were made for absorption. The structure was solved by direct methods with *MULTAN* (Germain, Main & Woolfson, 1971) and refined by full-matrix least squares with the X-RAY program system (Stewart, Kruger, Ammon,

Table 1. *Experimental data*

Source Cu $K\alpha$; $\lambda = 1 \cdot 5418$ Å; $\theta_{min} = 2°$, $\theta_{max} = 70°$
Graphite monochromator; $\theta - 2\theta$ scan; $(\Delta 2\theta)° = 1 \cdot 10 + 0 \cdot 4$ tg θ
Confidence level: $2 \cdot 5\sigma$
Total number of independent reflexions: 4678
Total observed: 3220

Table 2. *Final positional and thermal parameters* ($\times 10^4$) (*with standard deviations in parentheses*)

The expressions used for the temperature factors are:

$$\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)] \text{ and } \exp[-2\pi^2 U(2 \sin \theta/\lambda)^2].$$

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(1)	239 (1)	2288 (1)	5024 (1)	734	703	954	−294	288	85
C(2)	1278 (3)	2310 (6)	4586 (2)	539	415	573	−141	32	91
C(3)	1618 (4)	997 (5)	4335 (3)	689	295	687	−110	−67	95
C(4)	2426 (4)	1061 (5)	3999 (3)	733	269	701	10	−6	−39
C(5)	2905 (3)	2415 (5)	3908 (2)	604	302	617	25	91	−25
C(6)	2556 (3)	3742 (5)	4160 (2)	475	243	464	7	37	29
C(7)	1730 (3)	3677 (5)	4496 (2)	532	304	563	−56	137	16
C(8)	3050 (3)	5281 (4)	4090 (2)	410	246	434	3	114	−12
C(9)	2182 (3)	6399 (4)	3847 (2)	423	254	494	−9	116	33
C(10)	1948 (2)	7340 (3)	4249 (1)	574	355	673	123	96	−126
C(11)	1660 (3)	6308 (4)	3210 (2)	508	401	484	84	15	27
C(12)	793 (4)	7327 (6)	3017 (3)	545	628	765	141	−41	73
C(13)	253 (5)	6693 (12)	2346 (4)	901	2249	808	744	−212	−348
C(14)	802 (5)	5453 (8)	2128 (4)	753	762	979	−79	−245	−74
C(15)	1720 (4)	5186 (7)	2670 (2)	755	773	560	93	−11	−113
C(16)	3607 (3)	5755 (4)	4812 (2)	486	372	405	−27	108	23
C(17)	4202 (3)	7207 (5)	4807 (2)	507	403	420	−36	126	−38
C(18)	4916 (2)	7185 (4)	4319 (2)	467	346	432	−44	110	1
C(19)	4372 (3)	6810 (5)	3628 (2)	504	429	410	−28	142	−4
C(20)	3868 (3)	5281 (5)	3621 (2)	452	392	496	4	136	−49
C(21)	5425 (3)	8646 (5)	4333 (2)	515	395	527	−72	141	1
C(22)	6326 (3)	8628 (5)	3952 (2)	580	466	693	−77	227	−25
C(23)	6858 (3)	10155 (5)	3978 (2)	509	502	555	−83	155	−2
C(24)	6302 (3)	11319 (5)	3502 (2)	559	551	445	−166	110	−38
C(25)	5472 (3)	11078 (4)	3156 (2)	769	865	698	−386	−160	208
C(26)	6796 (3)	12819 (5)	3441 (2)	495	473	441	−84	181	−77
C(27)	6288 (4)	13864 (6)	2975 (2)	604	552	458	5	119	−55
C(28)	6725 (4)	15234 (6)	2881 (3)	696	548	604	27	181	26
C(29)	7671 (4)	15520 (5)	3262 (3)	796	429	839	−107	427	−78
C(30)	8197 (4)	14552 (6)	3732 (3)	522	578	676	−118	167	−82
C(31)	7745 (3)	13169 (5)	3821 (2)	486	539	515	−59	107	−41
F(32)	8107 (2)	16881 (3)	3171 (2)	1042	507	1286	−217	452	42

Table 2 (cont.)

	x	y	z	U
H(3)	1239	155	4348	597
H(4)	2677	214	3734	584
H(5)	3479	2403	3604	493
H(7)	1507	4595	4679	480
H(151)	2424	5457	2482	665
H(152)	1726	4122	2898	665
H(141)	833	5577	1454	886
H(142)	311	4685	2201	886
H(131)	92	7522	1841	1237
H(132)	9513	6357	2483	1237
H(121)	1104	8268	2974	655
H(122)	437	7212	3471	655
H(161)	3113	5530	5123	388
H(162)	4066	4932	5014	388
H(171)	3745	7979	4731	429
H(172)	4623	7423	5292	429
H(191)	4889	6755	3275	436
H(92)	3792	7560	3391	436
H(201)	4412	4621	3788	425
H(202)	3571	4951	3089	425
H(211)	4959	9454	4168	449
H(212)	5672	8944	4879	449
H(221)	6816	7754	4229	564
H(222)	6053	8342	3401	564
H(231)	6955	10630	4467	513
H(232)	7589	10095	3903	513
H(27)	5519	13644	2668	524
H(28)	6267	16009	2488	612
H(30)	8938	14845	3976	557
H(31)	8147	12391	4173	489

Dickinson & Hall, 1972). The positions of the H atoms were calculated and refined with isotropic thermal parameters. The final $R = \sum ||F_o| - |F_c||/\sum |F_o| = 0.06$ for all observed reflexions. The scattering factors are those of Cromer & Mann (1968) except for H for which those of Stewart, Davidson & Simpson (1965) were used. The final parameters are given in Table 2.*

Discussion. The numbering scheme and the bond distances and angles are shown in Fig. 1, and the conformation of the molecule is shown in Fig. 2. The distances and angles involving H atoms are in Table 3.

The conformation of the molecule is defined by the torsion angles in Table 4. The conformation of the butyrophenone chain corresponds to one of the ex-
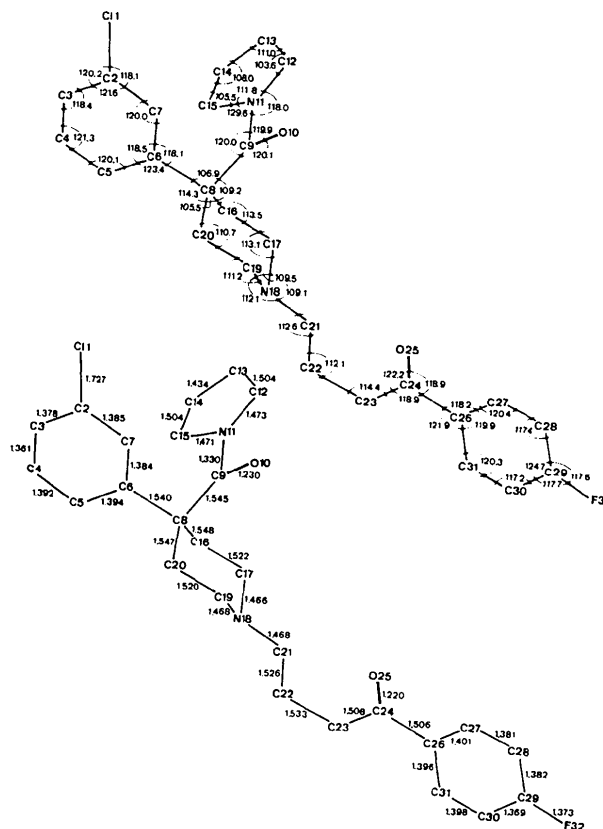

Fig. 1. Atomic numbering, bond distances (Å) and angles (°) for haloperidide. The e.s.d.'s are 0·005 Å for the distances and 0·3° for the angles.
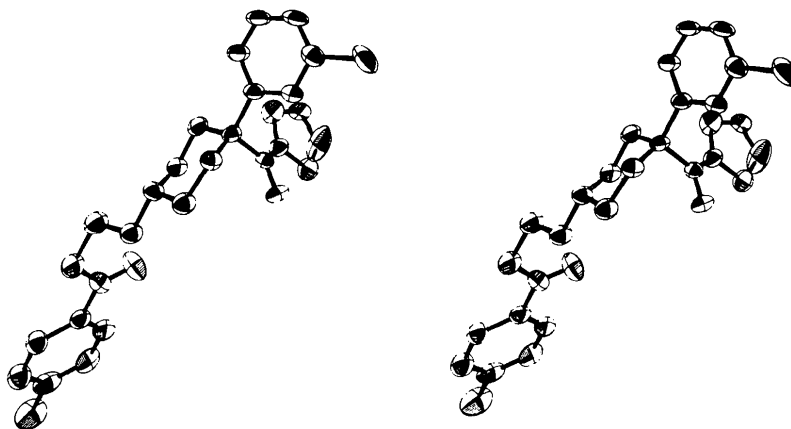

Fig. 2. Stereoscopic view of haloperidide with 50% probability ellipsoids.

Table 3. *Distances and angles involving hydrogen atoms*

The e.s.d.'s are 0·05 Å for the distances and 3° for the angles.

H(3)——C(3)	0·91 Å	C(2)—C(3)—H(3)	118°
H(4)——C(4)	1·01	C(3)—C(4)—H(4)	125
H(5)——C(5)	1·05	C(4)—C(5)—H(5)	117
H(7)——C(7)	0·96	C(2)—C(7)—H(7)	122
H(151)-C(15)	1·10	C(14)-C(15)-H(151)	111
H(152)-C(15)	1·05	C(14)-C(15)-H(152)	113
H(141)-C(14)	1·34	C(13)-C(14)-H(141)	109
H(142)-C(14)	0·98	C(13)-C(14)-H(142)	96
H(131)-C(13)	1·23	C(12)-C(13)-H(131)	118
H(132)-C(13)	1·11	C(12)-C(13)-H(132)	101
H(121)-C(12)	0·95	N(11)-C(12)-H(121)	103
H(122)-C(12)	1·09	N(11)-C(12)-H(122)	99
H(161)-C(16)	0·98	C(8)—C(16)-H(161)	108
H(162)-C(16)	0·99	C(8)—C(16)-H(162)	109
H(171)-C(17)	0·92	C(16)-C(17)-H(171)	107
H(172)-C(17)	1·04	C(16)-C(17)-H(172)	110
H(191)-C(19)	1·06	N(18)-C(19)-H(191)	110
H(192)-C(19)	1·07	N(18)-C(19)-H(192)	118
H(201)-C(20)	0·95	C(19)-C(20)-H(201)	103
H(202)-C(20)	1·10	C(19)-C(20)-H(202)	109
H(211)-C(21)	0·97	N(18)-C(21)-H(211)	112
H(212)-C(21)	1·10	N(18)-C(21)-H(212)	107
H(221)-C(22)	1·10	C(21)-C(22)-H(221)	102
H(222)-C(22)	1·11	C(21)-C(22)-H(222)	109
H(231)-C(23)	1·04	C(22)-C(23)-H(231)	112
H(232)-C(23)	1·02	C(22)-C(23)-H(232)	113
H(27)—C(27)	1·12	C(26)-C(27)-H(27)	122
H(28)—C(28)	1·14	C(27)-C(28)-H(28)	115
H(30)—C(30)	1·06	C(29)-C(30)-H(30)	119
H(31)—C(31)	1·06	C(30)-C(31)-H(31)	118

Table 4. *Torsion angles*

$\psi 1$	O(10)-C(9)—C(8)—C(6)	107°
$\psi 2$	C(5)—C(6)—C(8)—C(9)	134
$\psi 3$	O(10)-C(9)—N(11)-C(12)	-2
$\psi 4$	C(6)—C(8)—C(20)-C(19)	-175
$\psi 5$	C(6)—C(8)—C(16)-C(17)	175
$\psi 6$	C(8)—C(20)-C(19)-N(18)	63
$\psi 7$	C(8)—C(16)-C(17)-N(18)	-54
$\psi 8$	C(21)-N(18)-C(17)-C(16)	178
$\psi 9$	C(21)-N(18)-C(19)-C(20)	179
$\psi 10$	C(17)-N(18)-C(21)-C(22)	169
$\psi 11$	N(18)-C(21)-C(22)-C(23)	-179
$\psi 12$	C(21)-C(22)-C(23)-C(24)	-76
$\psi 13$	C(22)-C(23)-C(24)-C(26)	-175
$\psi 14$	O(25)-C(24)-C(26)-C(27)	1

to (120, 140), (−120, −140), (120, −40) and (−120, 40°) are allowed, in agreement with the experimental values. Hence the angle between the mean planes of the piperidine ring and the phenyl group is always close to 45°, at variance with the situation found in other neuroleptics.

References

CROMER, D. T. & MANN, J. B. (1968). *Acta Cryst.* A24, 321–324.

DINER, S., MALRIEU, J. P., JORDAN, F. & GILBERT, M. (1969). *Theoret. Chim. Acta,* 15, 100–110.

GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* A27, 368–376.

KOCH, M. H. J. (1974). *Mol. Pharmacol.* 10, 425–437.

STEWART, J. M., KRUGER, G. J., AMMON, H. L., DICKINSON, C. H. & HALL, S. R. (1972). The X-RAY system – version of June 1972. Tech. Rep. TR-192, Computer Science Center, Univ. of Maryland, College Park, Maryland.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* 42, 3175–3187.

pected energy minima (Koch, 1974). Energy calculations using the PCILO method [Perturbative Configuration Interaction using Localized Orbitals (Diner, Malrieu, Jordan & Gilbert, 1969)] show that for the set of torsion angles $(\psi 1, \psi 2)$ only combinations close

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5-Methoxy-5-phenyl-10,11-dihydro-5*H*-dibenzo[*b*, *f*]silepin

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Abstract. $C_{21}H_{20}OSi$, $M = 316·48$; monoclinic, $P2_1/c$; $a = 10·833$ (2), $b = 8·330$ (3), $c = 20·665$ (7) Å, $\beta = 110·58$ (3)°; $Z = 4$, $D_m = 1·18$ (2), $D_c = 1·20$ g cm^{-3}; $U = 1745·8$ Å^3. 5-Methoxy-5-phenyl-10,11-dihydro-5*H*-dibenzo-[*b*,*f*]silepin adopts a folded boat conformation with a dihedral angle between benzo-group planes of 138·3°. The phenyl substituent occupies the pseudo-axial position.

Introduction. Crystals were prepared by J. Corey (Corey, Dueber & Bichlmeir, 1971). A crystal 0·22 × 0·24 × 0·30 mm was mounted on a Syntex $P2_1$ diffrac-

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