

The Crystal and Molecular Structure of Piflutixol, a Tricyclic Neuroleptic Drug

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(Received 29 April 1977; accepted 27 May 1977)

The tricyclic neuroleptic drug piflutixol, $C_{24}H_{25}F_4NOS$, is monoclinic, space group $C2/c$, with $a = 29.360$ (5), $b = 11.594$ (4), $c = 17.388$ (4) Å, $\beta = 131.88$ (3)°, $Z = 8$. The structure was refined to an R of 0.039 for 2554 counter reflexions. The side chain is *cis* to the trifluoromethyl group at the exocyclic double bond.

Introduction

The neuroleptics are drugs used in the treatment of schizophrenia (Klein & Davis, 1969) and their clinical effects are thought to be due to their ability to block dopamine receptors in the brain (Horn & Snyder, 1971; Horn, Post & Kennard, 1975). One of the more interesting subdivisions of neuroleptics is the thioxanthene class which, because of an exocyclic double bond, can exist in the *cis* form (otherwise known as the α or Z form, with the ring 2-substituent and side chain on the same side of the double bond) or the *trans* (β or E) form. These isomers display a high degree of stereoselective pharmacological activity; nearly all the neuroleptic activity is confined to the *cis* isomers (Møller Nielsen *et al.*, 1973; Miller, Horn & Iversen, 1974). In our continuing studies of possible relations between the conformation of these drugs and their mode of action (Horn *et al.*, 1975 and references therein; Rodgers, Horn & Kennard, 1976; Post, Kennard, Sheldrick & Horn, 1975; Post, Kennard & Horn, 1975) we have determined the structure of one of the newest and most potent neuroleptics, piflutixol (I) (Møller Nielsen *et al.*, 1977). It differs from α -flupenthixol (Post, Kennard &

Horn, 1975) in having a piperidine rather than a piperazine ring, and an F atom at the 6 position.

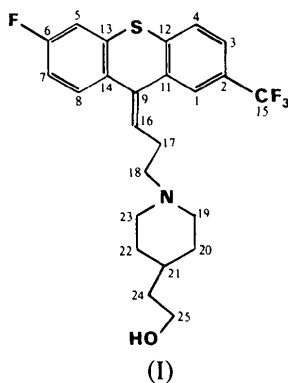
Experimental

Crystal data

Piflutixol; 2-trifluoromethyl-6-fluoro-9-[4'-(2''-hydroxyethyl)piperidino-1-propylid-3(*Z*)-ene]thioxanthene (I), $C_{24}H_{25}F_4NOS$, $M_r = 451.53$. Monoclinic, $C2/c$, $a = 29.360$ (5), $b = 11.594$ (4), $c = 17.388$ (4) Å, $\beta = 131.88$ (3)°, $U = 4407$ Å³, $Z = 8$, D_m (density column) = 1.36, $D_x = 1.361$ g cm⁻³, $\mu = 16.3$ cm⁻¹ (Cu $K\alpha$).

Crystallographic measurements

Solutions of 5–10% piflutixol in isopropyl ether were made by adding the ether to dichloromethane solutions of the compound, and then distilling off the dichloromethane. The hot solutions were seeded and left to crystallize at room temperature. Preliminary photographic investigations showed a non-standard *I*-centred monoclinic cell with $a = 17.4$, $b = 11.6$, $c = 21.9$ Å and $\beta = 96^\circ$. A lattice-geometry program written by Dr J. E. Davies established the alternative standard *C*-centred cell. Systematic absences hkl , $h + k$ odd and $h0l$, l odd indicated space group Cc or $C2/c$. Intensities were measured on an automated Syntex $P2_1$ four-circle diffractometer with Cu $K\alpha$ radiation, a graphite monochromator, and a crystal $0.35 \times 0.35 \times 0.2$ mm. Cell dimensions were obtained by least squares from 15 strong reflexions. The crystal, initially colourless, turned yellow on exposure to X-rays, but a repeatedly monitored check reflexion did not significantly alter in intensity. 3128 reflexions were measured in the range $0 < 2\theta < 116^\circ$; averaging equivalent reflexions (Lp but no absorption corrections being applied) gave 2556 reflexions with $F > 4\sigma(F)$.



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Structure analysis

The structure was solved in space group $C2/c$ by multiresolution Σ_2 sign expansion with 568 E values $>$

Table 1. *Atom coordinates ($\times 10^4$) and isotropic temperature factors ($\text{\AA}^2 \times 10^3$)*

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i>
S(1)	133 (1)	1703 (1)	6283 (1)	
O(1)	2826 (1)	11663 (1)	8324 (1)	
N(1)	1900 (1)	7275 (1)	7934 (1)	
F(1)	1321 (1)	-657 (1)	9542 (1)	
F(2)	-134 (1)	7401 (2)	6389 (3)	
F(3)	-967 (2)	6832 (3)	5848 (3)	
F(4)	-851 (2)	7059 (3)	4816 (3)	
F(2')	-205 (3)	7392 (4)	5778 (7)	
F(3')	-583 (5)	7094 (5)	6428 (6)	
F(4')	-1079 (2)	6965 (4)	4894 (4)	
C(1)	211 (1)	5131 (2)	6735 (2)	
C(2)	-380 (1)	5467 (2)	5886 (2)	
C(3)	-804 (1)	4655 (2)	5174 (2)	
C(4)	-642 (1)	3517 (2)	5314 (2)	
C(5)	785 (1)	513 (2)	8074 (2)	
C(6)	1243 (1)	391 (2)	9123 (2)	
C(7)	1615 (1)	1278 (2)	9754 (2)	
C(8)	1532 (1)	2342 (2)	9313 (2)	
C(9)	1032 (1)	3610 (2)	7763 (2)	
C(11)	393 (1)	3994 (2)	6871 (2)	
C(12)	-44 (1)	3170 (2)	6159 (2)	
C(13)	708 (1)	1579 (2)	7637 (2)	
C(14)	1089 (1)	2509 (2)	8245 (2)	
C(15)	-569 (1)	6699 (2)	5738 (2)	
C(16)	1532 (1)	4174 (2)	8085 (2)	
C(17)	1573 (1)	5214 (2)	7630 (2)	
C(18)	1882 (1)	6225 (2)	8385 (2)	
C(19)	2362 (1)	8084 (2)	8754 (2)	
C(20)	2400 (1)	9168 (2)	8316 (2)	
C(21)	1787 (1)	9786 (2)	7574 (2)	
C(22)	1304 (1)	8920 (2)	6772 (2)	
C(23)	1297 (1)	7843 (2)	7253 (2)	
C(24)	1790 (1)	10848 (2)	7067 (2)	
C(25)	2199 (1)	11825 (2)	7787 (2)	
H(1)	2869 (10)	11843 (18)	7946 (17)	60 (2)
H(11)	483 (9)	5624 (19)	7212 (16)	57 (2)
H(31)	-1208 (10)	4855 (20)	4614 (16)	57 (2)
H(41)	-964 (10)	2939 (19)	4791 (16)	57 (2)
H(51)	531 (10)	-97 (19)	7660 (16)	57 (2)
H(71)	1921 (9)	1237 (20)	10518 (16)	57 (2)
H(81)	1763 (10)	2986 (18)	9709 (17)	57 (2)
H(161)	1904 (10)	3826 (19)	8687 (17)	57 (2)
H(171)	1818 (10)	4978 (21)	7432 (17)	60 (2)
H(172)	1171 (10)	5452 (19)	6951 (17)	60 (2)
H(181)	2293 (10)	5991 (20)	8921 (17)	60 (2)
H(182)	1647 (10)	6389 (20)	8637 (17)	60 (2)
H(191)	2283 (10)	8305 (19)	9203 (17)	60 (2)
H(192)	2775 (10)	7662 (20)	9195 (17)	60 (2)
H(201)	2732 (10)	9646 (19)	8904 (17)	60 (2)
H(202)	2537 (9)	8958 (20)	7949 (17)	60 (2)
H(211)	1661 (10)	9984 (21)	7976 (16)	60 (2)
H(221)	1400 (10)	8730 (20)	6331 (17)	60 (2)
H(222)	910 (10)	9222 (19)	6358 (17)	60 (2)
H(231)	1005 (10)	7288 (20)	6723 (16)	60 (2)
H(232)	1204 (10)	8021 (19)	7690 (17)	60 (2)
H(241)	1374 (10)	11194 (20)	6569 (17)	60 (2)
H(242)	1919 (10)	10580 (19)	6681 (16)	60 (2)
H(251)	2191 (10)	11874 (19)	8372 (16)	60 (2)
H(252)	2073 (10)	12566 (20)	7414 (17)	60 (2)

1-2. The best E map gave sites for all non-H atoms; however, extra peaks in the CF_3 region suggested the possibility of disorder in this group. Anisotropic least-squares refinement followed by a difference synthesis showed all H atoms, except the hydroxyl H; three substantial difference peaks were associated with the CF_3 group, suggesting twofold disorder. Three further F atoms, F(2'), F(3') and F(4'), were introduced at the positions of these peaks; the sum of the site occupation factors of the alternative CF_3 groups was constrained to 1. H atoms were introduced at the sites indicated,

Table 2. *Bond lengths (\AA) for non-hydrogen atoms*

S(1)-C(13)	1.762 (4)	S(1)-C(12)	1.749 (4)
O(1)-C(25)	1.413 (4)	N(1)-C(18)	1.467 (4)
N(1)-C(19)	1.474 (3)	N(1)-C(23)	1.474 (4)
F(1)-C(6)	1.356 (4)	F(2)-C(15)	1.283 (4)
F(3)-C(15)	1.313 (9)	F(4)-C(15)	1.287 (7)
F(2')-C(15)	1.301 (11)	F(3')-C(15)	1.310 (16)
F(4')-C(15)	1.247 (6)	C(13)-C(5)	1.386 (4)
C(13)-C(14)	1.397 (4)	C(5)-C(6)	1.371 (4)
C(6)-C(7)	1.362 (4)	C(7)-C(8)	1.386 (5)
C(8)-C(14)	1.398 (4)	C(14)-C(9)	1.474 (4)
C(9)-C(11)	1.494 (3)	C(9)-C(16)	1.341 (4)
C(11)-C(1)	1.383 (4)	C(11)-C(12)	1.405 (4)
C(1)-C(2)	1.386 (4)	C(2)-C(3)	1.383 (4)
C(2)-C(15)	1.491 (5)	C(3)-C(4)	1.368 (5)
C(4)-C(12)	1.400 (4)	C(16)-C(17)	1.491 (5)
C(17)-C(18)	1.527 (5)	C(19)-C(20)	1.512 (6)
C(20)-C(21)	1.521 (5)	C(21)-C(22)	1.525 (5)
C(21)-C(24)	1.519 (6)	C(22)-C(23)	1.511 (6)
C(24)-C(25)	1.512 (5)		

Table 3. *Bond angles ($^\circ$) for non-hydrogen atoms*

C(13)-S(1)-C(12)	100.7 (2)	C(18)-N(1)-C(19)	110.4 (3)
C(18)-N(1)-C(23)	110.4 (3)	C(19)-N(1)-C(23)	109.2 (3)
S(1)-C(13)-C(5)	117.7 (3)	S(1)-C(13)-C(14)	121.1 (3)
C(5)-C(13)-C(14)	121.2 (3)	C(13)-C(5)-C(6)	118.5 (3)
F(1)-C(6)-C(5)	118.2 (3)	F(1)-C(6)-C(7)	119.1 (3)
C(5)-C(6)-C(7)	122.7 (3)	C(6)-C(7)-C(8)	118.4 (3)
C(7)-C(8)-C(14)	121.5 (3)	C(13)-C(14)-C(8)	117.6 (3)
C(13)-C(14)-C(9)	120.6 (3)	C(8)-C(14)-C(9)	121.8 (3)
C(14)-C(9)-C(11)	115.9 (3)	C(14)-C(9)-C(16)	120.4 (3)
C(11)-C(9)-C(16)	123.6 (3)	C(9)-C(11)-C(1)	122.4 (3)
C(9)-C(11)-C(12)	119.2 (3)	C(1)-C(11)-C(12)	118.4 (3)
C(11)-C(1)-C(2)	121.1 (3)	C(1)-C(2)-C(3)	120.1 (3)
C(1)-C(2)-C(15)	120.7 (3)	C(3)-C(2)-C(15)	119.2 (3)
C(2)-C(3)-C(4)	120.0 (3)	C(3)-C(4)-C(12)	120.5 (3)
S(1)-C(12)-C(11)	122.1 (2)	S(1)-C(12)-C(4)	118.0 (3)
C(11)-C(12)-C(4)	119.9 (3)	C(9)-C(16)-C(17)	128.8 (3)
C(16)-C(17)-C(18)	112.1 (3)	N(1)-C(18)-C(17)	113.0 (3)
N(1)-C(19)-C(20)	111.8 (3)	C(19)-C(20)-C(21)	112.1 (3)
C(20)-C(21)-C(22)	108.4 (3)	C(20)-C(21)-C(24)	114.4 (3)
C(22)-C(21)-C(24)	111.4 (3)	C(21)-C(22)-C(23)	112.7 (3)
N(1)-C(23)-C(22)	111.2 (3)	C(21)-C(24)-C(25)	115.8 (3)
O(1)-C(25)-C(24)	114.3 (3)	F(2)-C(15)-F(3)	104.8 (5)
F(2)-C(15)-F(4)	109.1 (5)	F(3)-C(15)-F(4)	104.4 (5)
F(2')-C(15)-F(3')	105.1 (8)	F(2')-C(15)-F(4')	102.0 (6)
F(3')-C(15)-F(4')	104.2 (7)	F(2)-C(15)-C(2)	114.7 (3)
F(3)-C(15)-C(2)	110.6 (4)	F(4)-C(15)-C(2)	112.4 (5)
F(2')-C(15)-C(2)	112.6 (5)	F(3')-C(15)-C(2)	114.3 (5)
F(4')-C(15)-C(2)	117.1 (4)		

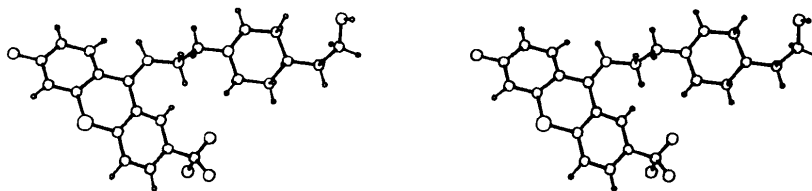


Fig. 1. Stereo pair of a piflutixol molecule.

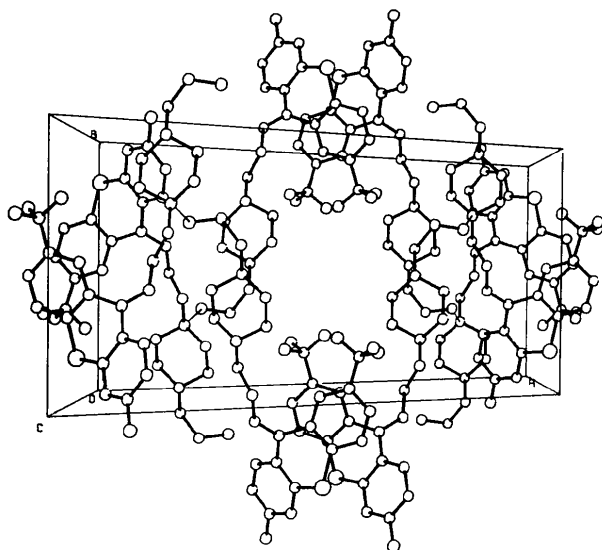


Fig. 2. Packing diagram of the unit-cell contents (perspective view).

with C—H distances constrained to 1.08 Å and H—C—H angles to 109.5°. After further refinement the only significant difference peak remaining was the peak associated with the hydroxyl H atom. In the final cycles of refinement all H atoms were allowed to refine freely, separate overall isotropic temperature factors being employed for (I) H atoms bonded to sp^2 C atoms and (II) all other H: two reflexions (804 and 514) were omitted, being considerably in error. Final site-occupation factors were 0.611 (3) [F(2) to F(4)] and 0.389 (3) [F(2') to F(4')]. The final $R' = \Sigma w^{1/2} \Delta / \Sigma w^{1/2} |F_o|$ was 0.0448, with a corresponding R of 0.0389; the weighting scheme was $w = 1/[\sigma^2(F) + 0.001F^2]$, which gave mean values of $w\Delta^2$ virtually independent of $\sin \theta$ or $|F_o|$. A final difference map had no peaks greater than 0.15 e Å⁻³. Complex neutral-atom scattering factors were employed. Final atomic parameters are given in Table 1,* bond lengths and angles in Tables 2 and 3. C—H distances (not shown) ranged from 0.87 to 1.05 Å. The H atoms [except the

hydroxyl H(1)] are numbered such that H(mn) is the n th H atom on C(m). Diagrams of the structure are given in Figs. 1 and 2. (Only one position of the disordered CF₃ group is shown.)

Discussion

The molecule exists in the expected *cis* (*Z*) form (I), as do the other efficacious thioxanthene neuroleptics α -flupenthixol (Post, Kennard, Sheldrick & Horn, 1975) and α -chlorprothixene (Post, Kennard & Horn, 1974). In our earlier structure-activity analysis of α -flupenthixol (Horn *et al.*, 1975) we suggested that one of the N atoms of the piperazine ring was more important than the other for neuroleptic activity. This hypothesis is supported by the fact that piflutixol has only one N atom and yet is more potent than α -flupenthixol (Møller Nielsen *et al.*, 1977). The distances from the N atom to the centroids of the two benzene rings are 5.80 and 7.49 Å; these distances are very similar to those involving one N atom in α -flupenthixol (and in other related drugs). The shorter of these two distances resembles reasonably closely the corresponding distance in dopamine (5.14 Å) and this is thought to be a factor enabling blocking of dopamine receptors. A difference of about 1.5 Å in the two N—benzene distances also seems necessary for physiological activity (Horn *et al.*, 1975).

The presence of the F atom in the molecule prolongs its pharmacological effects and this may be related to reduced metabolic degradation (Møller Nielsen *et al.*, 1977). It also apparently enhances the affinity of the molecule for the dopamine receptor, since the F-substituted species is more active *in vitro* in blocking the dopamine-sensitive adenylate cyclase enzyme system.

The tricyclic rings are folded about the line S...C(9) with an angle of 145° between the aromatic ring planes (*cf.* 152° in α -flupenthixol and 142° in α -chlorprothixene). The central ring has the boat conformation; the piperidine ring is in the expected chair form. In common with α -chlorprothixene and α -flupenthixol, there is loss of planarity about the exocyclic double bond [a typical torsion angle is C(14)—C(9)—C(16)—H(161) = -6.7°]; this is probably due to steric hindrance [H(161)—H(81) = 2.29, H(172)—H(11) = 2.35 Å]. There are intermolecular

* Lists of structure factors, anisotropic thermal parameters and bond lengths and angles involving H atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32808 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

hydrogen bonds between the hydroxyl O (at $\frac{1}{2} - x$, $-\frac{1}{2} + y$, $1\frac{1}{2} - z$) and piperidine N (at x, y, z) with N(1)—O(1), 2.88 and N(1)—H(1), 2.11 Å. There are no other unusually short interatomic contacts.

We thank Dr I. Møller Nielsen of H. Lundbeck & Co., Denmark for supplying the crystals, the Medical Research Council for financial support and the Science Research Council for provision of the diffractometer. The structure was solved with the *SHELX* series of programs written by Dr G. M. Sheldrick and the figures drawn with the program *PLUTO* written by Dr W. D. S. Motherwell.

References

- HORN, A. S., POST, M. L. & KENNARD, O. (1975). *J. Pharm. Pharmacol.* **27**, 553–563.
- HORN, A. S. & SNYDER, S. H. (1971). *Proc. Natl. Acad. Sci. US*, **68**, 2325–2328.
- KLEIN, D. F. & DAVIS, J. M. (1969). In *Diagnosis and Drug Treatment of Psychiatric Disorders*. Baltimore: Williams & Wilkins.
- MILLER, R. J., HORN, A. S. & IVERSEN, L. L. (1974). *Mol. Pharmacol.* **10**, 759–766.
- MØLLER NIELSEN, I., BOECK, V., CHRISTENSEN, A. V., DANNESKIOLD-SAMSOE, P., HYTELL, J., LANGELAND, J., PEDERSEN, V. & SVENDSEN, O. (1977). *Acta Pharmacol. Toxicol.* In the press.
- MØLLER NIELSEN, I., PEDERSEN, V., NYMARK, M., FRANCK, K. F., BOECK, V., FJALLAN, B. & CHRISTENSEN, A. V. (1973). *Acta Pharmacol. Toxicol.* **33**, 353–362.
- POST, M. L., KENNARD, O. & HORN, A. S. (1974). *Acta Cryst.* **B30**, 1644–1646.
- POST, M. L., KENNARD, O. & HORN, A. S. (1975). *Acta Cryst.* **B31**, 2724–2726.
- POST, M. L., KENNARD, O., SHELDRIK, G. M. & HORN, A. S. (1975). *Acta Cryst.* **B31**, 2366–2368.
- RODGERS, J. R., HORN, A. S. & KENNARD, O. (1976). *J. Pharm. Pharmacol.* **28**, 246–247.

Acta Cryst. (1977). **B33**, 3747–3751

Un Exemple de Délocalisation Electronique Totale dans l'Anneau Cyclobutadiénique: Structure Cristalline et Moléculaire de $\{[(C_2H_5)_4C_4]NiBr_2\}_2$

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(Reçu le 9 mai 1977, accepté le 1 juin 1977)

The crystal structure of $\{[(C_2H_5)_4C_4]NiBr_2\}_2$ has been determined from three-dimensional single-crystal X-ray data. Two dimer molecules occupy a monoclinic unit cell of space group $P2_1/c$ and dimensions $a = 8.36$, $b = 14.79$, $c = 12.84$ Å and $\beta = 113.78^\circ$. The Ni atoms are bound to three Br atoms forming the trigonal base of a kind of tetrahedron, the apex of which is occupied by the centre of gravity (*G*) of the cyclobutadiene ring. In the carbon ring the C—C distances are equivalent, which implies total electron delocalization. The $NiBr_3G$ units share a Br—Br edge in order to form the dimer.

La cyclotrimérisation et la polymérisation d'alcynes substitués par l'intermédiaire des métaux de transition a fait l'objet d'un certain nombre d'études. Ainsi, à basse température et sous atmosphère inerte, en présence du bromure de nickel et du bromure de phényl ou mésitylmagnésium, l'hexyne-3 est transformé en hexaéthylbenzène et en polyhexyne-3 linéaire (Mauret, Pellegrina

& Guersch, 1975; Mauret, Guersch & Ollagnier, 1977). Lorsque la réaction est terminée par chauffage au reflux et hydrolyse acide, on isole également un complexe organique du nickel.

Ce complexe est facilement recristallisé de solutions acétoniques sous forme de cristaux violet foncé. Il est soluble dans un grand nombre de solvants organiques: