α-Flupenthixol

By Michael L. Post, Olga Kennard* and George M. Sheldrick

University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, England

and Alan S. Horn

M.R.C. Neurochemical Pharmacology Unit, Medical School, Hills Road, Cambridge CB2 2QD, England

Abstract. α-Flupenthixol; *cis*-2-trifluoromethyl-9-{3-[4-(β-hydroxyethyl)-1-piperazinyl]propylidene}thioxanthene, $C_{23}H_{25}N_2OF_3S$, $M=434\cdot51$, orthorhombic, *Pbca*, $a=8\cdot827(3)$, $b=24\cdot048(9)$, $c=20\cdot251(7)$ Å, $D_x=1\cdot34$, $D_c=1\cdot34$ g cm^{-3}, $Z=8$. The side chain exhibits *cis* configuration at the exocyclic double bond and the angle between the two principal planes of the tricyclic moiety is $152°$.

Introduction. Crystals were supplied by Dr I. Moller Nielsen of H. Lundbeck & Co., Denmark, and space group and preliminary cell parameters were determined by photographic methods. Systematic absences were $0kl$, k odd; $h0l$, l odd; $hk0$, h odd, uniquely determining the space group *Pbca*. A crystal $0\cdot08 \times 0\cdot13 \times 0\cdot03$ mm was mounted with **a** parallel to the φ axis of a Picker, card-controlled four-circle diffractometer and data were collected up to $2\theta=120°$ with graphite-monochromated Cu $K\alpha$ radiation $(\lambda=1\cdot54178$ Å) and the $\theta-2\theta$ scan technique at $2°$ min^{-1} in 2θ. 3469 observations were recorded, but 1776 of these gave counts lower than a preset minimum and were excluded. Of the remainder, 597 yielded net intensities $<3\sigma(I)$ and were treated as unobserved. The remaining 1094 independent reflexions were scaled to four monitor reflexions, and Lorentz and polarization factors were applied. No correction was made for absorption.

The structure was solved by a multi-solution direct-methods technique for centrosymmetric space groups programmed by G.M.S. 282 E's $\geq 1\cdot1$ were used, and five of the 'best' E maps yielded essentially the same molecular fragment with three to five atoms poorly defined or absent. A difference synthesis was used to place the remaining atoms, and after full-matrix least-squares isotropic refinement including all non-hydrogen atoms, R was $0\cdot141$. Further refinement, allowing thermal anisotropy to all heavy atoms, reduced R to $0\cdot103$. A difference map indicated sites for 16 H atoms, including that on the hydroxyl group, with the C–H distances averaging $1\cdot07$ Å. In subsequent stages, contributions by the H atoms (originally in geometrically calculated positions with C–H=$1\cdot07$ Å) were included but their refinement was constrained so that the C–H vector retained its original magnitude and direction. Anisotropic refinement was continued,

with an overall isotropic thermal parameter for H, and a modified conjugate gradient method to solve the 'normal equations' of least squares; after 15 cycles R was $0\cdot067$. In the final stages the C–F distances were constrained to be within $0\cdot02$ Å of their mean to minimize the difficulties caused by their large thermal amplitudes, and refinement was concluded with four cycles of full-matrix least-squares calculations. Convergence was attained at an R of $0\cdot066$ for 1094 reflexions.† A weighting scheme based on counting statistics was used and the function minimized was $\sum w\{||F_o|-|F_c||\}^2$, where $w=\{\sigma(F_o)[2F_{min}+F_o+2F_o^2/F_{max}]\}^{-1}$. Final positional and thermal parameters are presented in Tables 1 and 2.

Discussion. Several thioxanthene derivatives in their α form (*i.e. cis* about the exocyclic double bond with respect to the tricyclic ring substituent) are efficacious

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† A table of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31100 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.
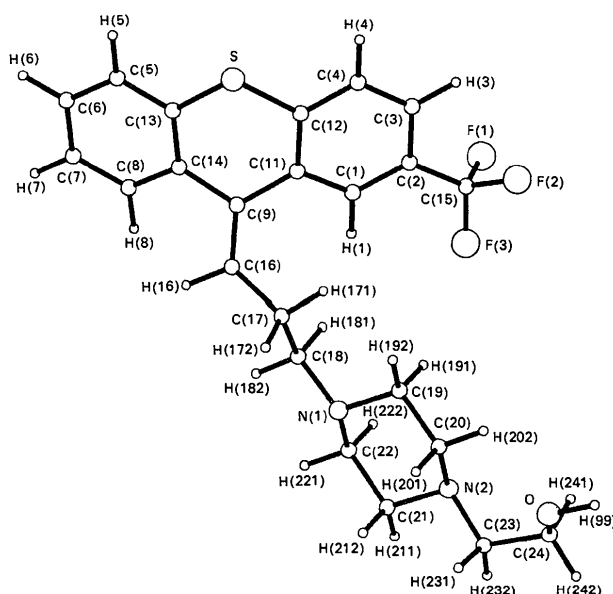
Fig. 1. Molecular diagram of α-flupenthixol.

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* External Staff, Medical Research Council.

Table 1. *Final positional* ($\times 10^4$) *and anisotropic thermal parameters* ($\text{Å}^2 \times 10^3$)
with estimated standard deviations in parentheses

$$T = \exp\left[-2\pi^2(U_{11}a^{*2}h^2 + U_{22}b^{*2}k^2 + U_{33}c^{*2}l^2 + 2U_{12}a^*b^*hk + 2U_{13}a^*c^*hl + 2U_{23}b^*c^*kl)\right]$$

	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S	540 (4)	4530 (1)	4030 (1)	71 (2)	71 (2)	49 (2)	12 (2)	−11 (2)	6 (2)
N(1)	520 (10)	5730 (3)	536 (3)	51 (5)	44 (5)	44 (5)	−1 (4)	−8 (5)	−9 (5)
N(2)	1219 (9)	6724 (3)	−198 (3)	46 (5)	40 (5)	42 (5)	−1 (4)	−3 (4)	2 (4)
O	4286 (9)	7391 (3)	−155 (3)	57 (5)	60 (5)	96 (5)	7 (4)	−23 (5)	−16 (5)
F(1)	−1644 (14)	7018 (4)	3097 (6)	238 (13)	120 (8)	243 (12)	81 (8)	137 (11)	95 (10)
F(2)	501 (16)	7176 (4)	3059 (6)	298 (16)	73 (6)	244 (12)	22 (7)	−144 (13)	−69 (9)
F(3)	−485 (15)	6841 (3)	2268 (4)	361 (15)	58 (5)	79 (5)	13 (4)	27 (8)	25 (8)
C(1)	−472 (12)	5781 (4)	2771 (4)	51 (7)	38 (5)	46 (6)	−4 (5)	12 (6)	0 (7)
C(2)	−126 (11)	6240 (4)	3144 (5)	49 (8)	48 (7)	59 (7)	−9 (6)	6 (6)	2 (6)
C(3)	403 (13)	6180 (4)	3796 (5)	61 (8)	50 (7)	68 (8)	−25 (6)	11 (7)	1 (7)
C(4)	592 (12)	5656 (4)	4045 (5)	38 (6)	66 (8)	58 (6)	−14 (7)	9 (6)	−2 (6)
C(5)	−1106 (14)	3618 (5)	3856 (6)	71 (9)	50 (7)	72 (8)	15 (7)	11 (7)	4 (7)
C(6)	−2016 (15)	3252 (5)	3516 (7)	89 (11)	54 (9)	112 (12)	31 (9)	25 (9)	6 (9)
C(7)	−2530 (14)	3387 (5)	2872 (6)	88 (10)	52 (8)	95 (10)	2 (7)	3 (8)	−10 (7)
C(8)	−2075 (13)	3877 (4)	2597 (5)	72 (9)	50 (6)	63 (7)	−2 (7)	−5 (6)	−1 (8)
C(9)	−494 (13)	4742 (3)	2595 (5)	63 (8)	35 (5)	49 (6)	0 (5)	−16 (6)	8 (7)
C(11)	−223 (10)	5238 (4)	3004 (5)	27 (6)	41 (5)	49 (6)	−7 (5)	−2 (5)	1 (5)
C(12)	286 (12)	5184 (4)	3668 (5)	57 (7)	55 (7)	41 (6)	4 (5)	7 (6)	5 (6)
C(13)	−664 (12)	4105 (4)	3567 (5)	65 (8)	36 (6)	50 (6)	−1 (5)	3 (6)	1 (7)
C(14)	−1076 (12)	4239 (4)	2923 (5)	52 (7)	43 (6)	50 (6)	4 (6)	4 (6)	−2 (6)
C(15)	−395 (18)	6791 (5)	2888 (6)	142 (14)	40 (8)	77 (10)	−13 (8)	23 (10)	12 (11)
C(16)	−113 (12)	4702 (4)	1960 (5)	74 (9)	59 (7)	34 (6)	17 (5)	5 (5)	−3 (6)
C(17)	718 (11)	5126 (4)	1539 (4)	58 (7)	46 (6)	42 (5)	−6 (5)	−15 (6)	4 (6)
C(18)	−355 (11)	5398 (4)	1022 (4)	45 (7)	54 (6)	50 (6)	13 (5)	−6 (6)	−3 (6)
C(19)	1262 (12)	6206 (4)	841 (4)	62 (8)	50 (6)	35 (6)	10 (5)	−14 (5)	−10 (6)
C(20)	2198 (11)	6525 (4)	340 (4)	53 (7)	57 (7)	36 (6)	8 (5)	−10 (5)	−5 (6)
C(21)	426 (12)	6250 (4)	−494 (4)	51 (7)	57 (7)	43 (6)	4 (5)	−20 (6)	−7 (6)
C(22)	−504 (12)	5935 (4)	17 (4)	47 (6)	52 (6)	41 (5)	11 (5)	−8 (6)	−17 (7)
C(23)	2128 (11)	7009 (4)	−716 (4)	64 (8)	44 (6)	43 (6)	−1 (5)	−11 (5)	5 (7)
C(24)	2940 (12)	7524 (4)	−494 (5)	71 (8)	45 (6)	64 (7)	5 (6)	−4 (7)	9 (7)

neuroleptic drugs (Moller Nielsen *et al.*, 1973; Kaiser, Warren & Zirkle, 1974). α-Flupenthixol is one of a group of such compounds which are presently under

Table 2. *Final hydrogen atom positional coordinates*
($\times 10^3$)

$U_{\text{iso}} = 0.076 \text{ Å}^2$ throughout.

	x/a	y/b	z/c
H(1)	−94	585	229
H(3)	66	654	409
H(4)	98	561	454
H(5)	−75	352	435
H(6)	−234	287	374
H(7)	−326	310	261
H(8)	−249	399	212
H(16)	1	461	145
H(171)	117	544	185
H(172)	163	492	129
H(181)	−114	566	127
H(182)	−96	508	77
H(191)	42	648	104
H(192)	199	606	123
H(201)	305	626	14
H(202)	272	687	58
H(211)	−31	640	−87
H(212)	124	597	−71
H(221)	−106	559	−21
H(222)	−133	621	23
H(231)	296	672	−89
H(232)	138	712	−111
H(241)	221	776	−17
H(242)	321	777	−92
H(99)	507	774	3

investigation by a combination of X-ray and pharmacological methods in an attempt to correlate drug activity with molecular spatial characteristics (Horn, Post & Kennard, 1975; and references therein).

The molecule is shown in Fig. 1 and bond lengths and angles are presented in Table 3. Some torsional angles involving the side chain are given in Table 4. The tricyclic rings are folded about the $S \cdots C(9)$ direction, with an angle of 152° between the aromatic ring mean planes, and with S and C(9) displaced from these planes by 0·04 and 0·13 Å respectively. S and

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

S——C(12)	1·75 (1)	C(11)–C(12)	1·42 (1)
S——C(13)	1·75 (1)	C(13)–C(14)	1·39 (1)
C(1)–C(2)	1·37 (1)	*C(15)–F(1)	1·30 (1)
C(1)–C(11)	1·41 (1)	*C(15)–F(2)	1·27 (1)
C(2)–C(3)	1·41 (1)	*C(15)–F(3)	1·26 (1)
C(2)–C(15)	1·44 (1)	C(16)–C(17)	1·52 (1)
C(3)–C(4)	1·37 (1)	C(17)–C(18)	1·56 (1)
C(4)–C(12)	1·40 (1)	C(18)–N(1)	1·48 (1)
C(5)–C(6)	1·38 (1)	N(1)—C(19)	1·46 (1)
C(5)–C(13)	1·37 (1)	N(1)—C(22)	1·47 (1)
C(6)–C(7)	1·42 (1)	C(19)–C(20)	1·52 (1)
C(7)–C(8)	1·37 (1)	C(20)–N(2)	1·47 (1)
C(8)–C(14)	1·40 (1)	N(2)—C(21)	1·47 (1)
C(9)–C(11)	1·47 (1)	N(2)—C(23)	1·49 (1)
C(9)–C(14)	1·47 (1)	C(21)–C(22)	1·52 (1)
C(9)–C(16)	1·33 (1)	C(23)–C(24)	1·50 (1)
		C(24)–O	1·41 (1)

Table 3 (cont.)

C(12)–S——C(13)	103 (1)	C(8)—C(14)–C(9)	121 (1)
C(2)—C(1)—C(11)	121 (1)	C(8)—C(14)–C(13)	118 (1)
C(1)—C(2)—C(3)	120 (1)	C(9)—C(14)–C(13)	121 (1)
C(1)—C(2)—C(15)	120 (1)	C(2)—C(15)–F(1)	114 (1)
C(3)—C(2)—C(15)	119 (1)	C(2)—C(15)–F(2)	118 (1)
C(2)·C(3)—C(4)	118 (1)	C(2)—C(15)–F(3)	117 (1)
C(3)—C(4)—C(12)	121 (1)	F(1)—C(15)–F(2)	98 (1)
C(6)—C(5)—C(13)	120 (1)	F(1)—C(15)–F(3)	103 (1)
C(5)—C(6)—C(7)	120 (1)	F(2)—C(15)–F(3)	104 (1)
C(6)—C(7)—C(8)	119 (1)	C(9)—C(16)–C(17)	128 (1)
C(7)—C(8)—C(14)	122 (1)	C(16)—C(17)–C(18)	112 (1)
C(11)—C(9)—C(14)	118 (1)	C(17)—C(18)–N(1)	111 (1)
C(11)—C(9)—C(16)	124 (1)	C(18)–N(1)—C(19)	112 (1)
C(14)—C(9)—C(16)	118 (1)	C(18)–N(1)—C(22)	110 (1)
C(1)—C(11)–C(9)	123 (1)	C(19)–N(1)—C(22)	108 (1)
C(1)—C(11)–C(12)	117 (1)	N(1)—C(19)–C(20)	111 (1)
C(9)—C(11)–C(12)	121 (1)	C(19)–C(20)–N(2)	110 (1)
S——C(12)–C(4)	119 (1)	N(2)—C(21)–C(22)	112 (1)
S——C(12)–C(11)	121 (1)	C(21)–C(22)–N(1)	109 (1)
C(4)—C(12)–C(11)	120 (1)	C(20)–N(2)—C(21)	109 (1)
S——C(13)–C(5)	117 (1)	C(20)–N(2)—C(23)	111 (1)
S——C(13)–C(14)	122 (1)	C(21)–N(2)—C(23)	109 (1)
C(5)—C(13)–C(14)	122 (1)	N(2)—C(23)–C(24)	115 (1)
		C(23)–C(24)–O	111 (1)

* These bond lengths were constrained during refinement.

C(9) lie 0·39 and 0·37 Å from the plane defined by C(11)→C(14) and there is no evidence of twisting in this moiety. In common with α-chlorprothixene (Post, Kennard & Horn, 1974) there is slight loss of planarity in the region of the exocyclic double bond, (e.g. $\tau\{C(11)–C(9)–C(16)–C(17)\} = 3°$) which is most probably due to intramolecular steric hindrance [$H(171)\cdots H(1) = 2·27$ Å]. This could also account for the large C(11)–C(9)–C(16) angle of 124° on the sp^2 C

atom. The piperazine ring has the expected chair configuration with N(1) and N(2) lying 0·70 and −0·67 Å from the plane defined by C(19)→C(22).

Table 4. Principal torsional angles for the side chain

C(11)–C(9)—C(16)–C(17)	3°
C(9)—C(16)–C(17)–C(18)	−109
C(16)–C(17)–C(18)–N(1)	−170
C(17)–C(18)–N(1)—C(19)	−65
C(20)-N(2)—C(23)-C(24)	−63
N(2)—C(23)-C(24)-O	80

There are intermolecular hydrogen bonds between hydroxyl O and piperazine N(2) [$O\cdots N(2) = 2·82$ Å, $O–H(99)\cdots N(2) = 173°$] which link pairs of molecules (at x, y, z and $\frac{1}{2}+x, 1\frac{1}{2}-y, -z$) related by the 2_1 screw axis parallel to **a**. There are no unusually close van der Waals intermolecular contacts.

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