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Acta Cryst. (1975). B31, 2724

 β -Flupenthixol

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(Received 5 June 1975; accepted 12 June 1975)

Abstract. β -Flupenthixol; *trans* form of 2 trifluoromethyl-9-[3-[4-(β -hydroxyethyl)-1-piperazinyl]propylidene]thioxanthene, C₂₃H₂₅N₂OF₃S, *M* = 434.51, monoclinic, *P*2₁/*c*, *a* = 9.011 (2), *b* = 15.218 (3), *c* = 18.493 (4) Å, β = 120.37 (1)°, *D*_x = 1.32, *D*_c = 1.31 g cm⁻³, *Z* = 4. The dihedral angle of the thioxanthene moiety is 143.1° and an intramolecular hydrogen bond is formed between the hydroxyl group and a piperazinyl N atom. There is evidence of thermal disorder toward the side-chain extremity.

Introduction. Space group and preliminary cell parameters were determined from precession and Weissenberg photographs. Systematic absences were *h*0*l*, *l* odd; 0*k*0, *k* odd; space group *P*2₁/*c*. A crystal 0.70 × 0.75 × 0.70 mm was mounted, with **b** parallel to the φ axis of a Picker card-controlled four-circle diffractometer. Data were collected throughout the range 4° ≤ 2 θ ≤ 120° with graphite-monochromated Cu *K* α radiation (λ = 1.54178 Å) with a θ -2 θ scan operating at 2° min⁻¹ in 2 θ , and of 3472 independent observations, 2308 had *I* ≥ 4 σ (*I*) and were used in subsequent stages. Scaling, with respect to monitor reflexion values, and Lorentz and polarization corrections were applied. No correction was made for absorption (μ = 15.7 cm⁻¹).

The structure was solved by multi-solution direct methods (Sheldrick, 1975) with 567 *E* values ≥ 1.4. The 'best' *E* map revealed sites for all but three of the non-hydrogen atoms, and those remaining were located on a subsequent difference map. Six cycles of full-

matrix least-squares isotropic refinement yielded an *R* of 0.18 and indicated two regions of high thermal motion, one involving the -CF₃ group and the other, between the piperazine ring and hydroxyl O atom, at C(23) and C(24). The behaviour of F atoms during refinement was markedly improved by allocating an occupancy of 0.85 to the major F positions, and of 0.15 to secondary positions, F(*nn*) in Table 1, which were found in a difference map. A difference synthesis, calculated with C(23) and C(24) omitted showed, in that region, an elongated ellipsoid of electron density extending for *ca* 2.5 Å in which two very diffuse maxima were embedded. No chemically reasonable model could be chosen to describe the effect and these two atoms were, therefore, allowed unrestricted refinement, but with resultant unreliability in associated bond parameters. All atoms {except F(*nn*) which remained isotropic} were then refined with anisotropic thermal parameters, and following six cycles *R* was 0.081. A difference synthesis then showed H atoms at all the expected sites, apart from C(23) and C(24), and refinement was continued with H atoms included. Positional and isotropic thermal parameters for the H atoms were refined in all but four cases, these requiring to be constrained so that respective C-H vectors retained their original magnitude and direction. Convergence was attained after eight cycles at an *R* of 0.063 for 2308 reflexions.‡ The function minimized was $\sum w\{|F_o| - |F_c|\}^2$ where $w = 1/\sigma^2(F)$ and the final $R_w = \sum w^{1/2}\{|F_o| - |F_c|\} / \sum w^{1/2}|F_o| = 0.063$. Final atomic parameters are presented in Tables 1 and 2.

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‡ A table of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31198 (15 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

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

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

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₂₃	<i>U</i> ₁₃	<i>U</i> ₁₂
S	5489 (1)	1145 (1)	4899 (1)	48 (1)	59 (1)	82 (1)	2 (1)	29 (1)	-12 (1)
N(1)	8729 (4)	1855 (2)	2389 (2)	50 (2)	73 (2)	36 (1)	10 (1)	23 (1)	8 (1)
N(2)	10845 (5)	1403 (3)	1685 (2)	75 (3)	136 (3)	71 (2)	29 (2)	52 (2)	45 (2)
O	11256 (6)	1371 (3)	285 (3)	130 (3)	134 (3)	117 (3)	25 (2)	95 (3)	42 (3)
F(1)	13560 (5)	-293 (3)	674 (4)	78 (2)	86 (3)	229 (6)	28 (4)	26 (3)	26 (2)
F(2)	13823 (5)	890 (5)	7326 (3)	65 (2)	295 (7)	82 (3)	-100 (4)	6 (2)	-8 (3)
F(3)	13867 (4)	830 (5)	6217 (3)	62 (2)	279 (6)	142 (4)	113 (4)	62 (2)	41 (3)
*F(11)	13685 (18)	143 (11)	7291 (10)	51 (3)					
*F(22)	13873 (18)	1312 (9)	6799 (11)	57 (3)					
*F(33)	13692 (18)	95 (12)	6271 (9)	54 (3)					
C(1)	10455 (4)	1331 (2)	5541 (2)	47 (2)	49 (2)	37 (2)	2 (1)	23 (2)	-4 (1)
C(2)	11206 (4)	670 (2)	6133 (2)	50 (2)	52 (2)	36 (2)	-1 (1)	18 (1)	-1 (2)
C(3)	10193 (5)	136 (2)	6315 (2)	61 (2)	56 (2)	46 (2)	10 (2)	22 (2)	-5 (2)
C(4)	8447 (5)	296 (2)	5933 (2)	65 (2)	53 (2)	53 (2)	8 (2)	29 (2)	-12 (2)
C(5)	4015 (5)	2739 (3)	4655 (2)	52 (2)	79 (3)	60 (2)	-1 (2)	30 (2)	2 (2)
C(6)	3842 (6)	3623 (3)	4469 (2)	64 (3)	93 (3)	57 (2)	1 (2)	35 (2)	24 (2)
C(7)	5000 (6)	4046 (3)	4309 (2)	84 (3)	65 (2)	62 (2)	7 (2)	43 (2)	21 (2)
C(8)	6335 (5)	3578 (2)	4316 (2)	75 (3)	53 (2)	50 (2)	8 (2)	39 (2)	13 (2)
C(9)	7877 (4)	2155 (2)	4455 (2)	52 (2)	46 (2)	36 (2)	3 (1)	24 (1)	3 (1)
C(11)	8702 (4)	1482 (2)	5127 (2)	46 (2)	43 (2)	32 (1)	0 (1)	20 (1)	-3 (1)
C(12)	7709 (4)	972 (2)	5352 (2)	49 (2)	47 (2)	42 (2)	-3 (1)	22 (2)	-9 (1)
C(13)	5336 (4)	2270 (2)	4650 (2)	46 (2)	58 (2)	41 (2)	-5 (1)	19 (2)	-3 (2)
C(14)	6494 (4)	2669 (2)	4463 (2)	52 (2)	51 (2)	32 (2)	1 (1)	21 (1)	4 (1)
C(15)	13095 (5)	550 (3)	6601 (2)	57 (2)	68 (2)	47 (2)	6 (2)	19 (2)	5 (2)
C(16)	8379 (5)	2229 (2)	3889 (2)	64 (2)	58 (2)	43 (2)	11 (2)	32 (2)	16 (2)
C(17)	7667 (7)	2816 (3)	3130 (2)	101 (3)	85 (3)	55 (2)	29 (2)	54 (2)	44 (3)
C(18)	7263 (6)	2307 (4)	2354 (2)	68 (3)	111 (4)	47 (2)	29 (2)	35 (2)	37 (3)
C(19)	9959 (6)	2462 (3)	2384 (3)	73 (3)	81 (3)	67 (3)	1 (2)	40 (2)	-7 (2)
C(20)	11439 (6)	1979 (4)	2408 (3)	59 (3)	156 (5)	77 (3)	20 (3)	37 (3)	4 (3)
C(21)	9640 (8)	797 (4)	1697 (3)	116 (4)	94 (3)	65 (3)	6 (3)	54 (3)	32 (3)
C(22)	8138 (6)	1261 (3)	1675 (2)	69 (3)	91 (3)	42 (2)	-1 (2)	29 (2)	2 (2)
C(23)	12295 (9)	946 (6)	1685 (4)	121 (5)	260 (10)	138 (6)	81 (6)	93 (5)	123 (6)
C(24)	12273 (12)	898 (7)	1010 (5)	203 (8)	315 (11)	161 (7)	112 (8)	151 (7)	187 (9)

* Isotropic refinement only.

Table 2. Final H atom positional ($\times 10^3$) and isotropic thermal parameters ($\text{\AA}^2 \times 10^2$) with estimated standard deviations in parentheses

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso}
H(1)	1113 (4)	169 (2)	543 (2)	5 (1)
*H(3)	1090	-37	682	13 (2)
H(4)	723 (5)	-13 (2)	607 (2)	6 (1)
H(5)	329 (8)	241 (4)	480 (4)	9 (2)
H(6)	295 (7)	396 (3)	445 (3)	11 (2)
H(7)	467 (5)	470 (3)	408 (3)	8 (1)
H(8)	729 (4)	390 (2)	424 (2)	5 (1)
H(16)	923 (5)	185 (3)	391 (2)	6 (1)
H(171)	863 (7)	332 (3)	326 (3)	10 (2)
*H(172)	646	311	302	14 (2)
H(181)	640 (6)	180 (3)	224 (3)	9 (1)
H(182)	678 (6)	264 (3)	191 (3)	8 (1)
H(191)	928 (8)	281 (4)	184 (4)	14 (2)
H(192)	1013 (9)	279 (5)	277 (4)	14 (3)
H(201)	1210 (7)	170 (4)	300 (4)	12 (2)
*H(202)	1232	241	233	18 (4)
H(211)	926 (7)	48 (3)	128 (3)	10 (2)
H(212)	1031 (14)	24 (7)	234 (6)	22 (4)
H(221)	755 (6)	162 (3)	114 (3)	7 (1)
*H(222)	725	79	170	15 (2)
H(99)	1066 (9)	161 (4)	50 (4)	14 (2)

* The positions of these atoms were constrained during refinement.

Discussion. β -Flupenthixol is the pharmacologically almost inactive geometric isomer of the potent neuroleptic α -flupenthixol, for which structural details have been previously reported (Post, Kennard, Sheldrick & Horn, 1975). The present analysis has been undertaken as part of a programme to investigate which spatial parameters of tricyclic drugs are of most significance with respect to pharmacological activity (Horn, Post & Kennard, 1975).

The molecule (Fig. 1) exists in *trans* form, with respect to the $-\text{CF}_3$ substituent, about the exocyclic double bond C(9)–C(16). Bond lengths and angles for the non-hydrogen atoms are listed in Table 3. The thermal disorder in the C(23)–C(24) region is possibly due to the combination of a relatively low m. p. for the crystalline material (87–91°) and the relative freedom of the side-chain extremity from steric and bonding restrictions. The latter effect is probably more important and results from the overall lattice packing for this part of the molecule being 'loose', with no close van der Waals contacts. The hydroxyl O atom, however, has smaller thermal motion and is well defined owing to extra rigidity imposed by the formation of an intramolecular hydrogen bond to N(2), $\{\text{O} \cdots \text{N}(2) = 2.80$

Table 3. Bond distances (Å) and angles (°) involving the non-hydrogen atoms

Estimated standard deviations <0.002 Å and <0.2°.			
S—C(12)	1.755	C(15)—F(1)	1.334
S—C(13)	1.761	C(15)—F(2)	1.267
C(1)—C(2)	1.386	C(15)—F(3)	1.290
C(1)—C(11)	1.382	C(15)—F(11)	1.269
C(2)—C(3)	1.385	C(15)—F(22)	1.308
C(2)—C(15)	1.480	C(15)—F(33)	1.214
C(3)—C(4)	1.382	C(16)—C(17)	1.504
C(4)—C(12)	1.390	C(17)—C(18)	1.504
C(5)—C(6)	1.378	C(18)—N(1)	1.462
C(5)—C(13)	1.392	N(1)—C(19)	1.446
C(6)—C(7)	1.379	N(1)—C(22)	1.460
C(7)—C(8)	1.392	C(19)—C(20)	1.504
C(8)—C(14)	1.403	C(20)—N(2)	1.455
C(9)—C(11)	1.487	N(2)—C(21)	1.433
C(9)—C(14)	1.479	N(2)—C(23)	1.480
C(9)—C(16)	1.340	C(21)—C(22)	1.510
C(11)—C(12)	1.397	C(23)—C(24)	1.240
C(13)—C(14)	1.392	C(24)—O	1.383
C(12)—S—C(13)	101.0	C(9)—C(14)—C(13)	120.8
C(2)—C(1)—C(11)	121.5	C(2)—C(15)—F(1)	112.8
C(1)—C(2)—C(3)	120.0	C(2)—C(15)—F(2)	113.2
C(1)—C(2)—C(15)	120.6	C(2)—C(15)—F(3)	114.8
C(3)—C(2)—C(15)	119.3	C(2)—C(15)—F(11)	114.9
C(2)—C(3)—C(4)	119.5	C(2)—C(15)—F(22)	110.4
C(3)—C(4)—C(12)	120.1	C(2)—C(15)—F(33)	116.6
C(6)—C(5)—C(13)	119.2	F(1)—C(15)—F(2)	103.9
C(5)—C(6)—C(7)	120.4	F(1)—C(15)—F(3)	102.9
C(6)—C(7)—C(8)	120.2	F(2)—C(15)—F(3)	108.2
C(7)—C(8)—C(14)	120.5	C(9)—C(16)—C(17)	128.7
C(11)—C(9)—C(14)	115.1	C(16)—C(17)—C(18)	111.6
C(11)—C(9)—C(16)	119.2	C(17)—C(18)—N(1)	115.0
C(14)—C(9)—C(16)	125.7	C(18)—N(1)—C(22)	112.2
C(1)—C(11)—C(9)	121.7	C(18)—N(1)—C(22)	110.1
C(1)—C(11)—C(12)	117.9	C(19)—N(1)—C(22)	108.7
C(9)—C(11)—C(12)	120.4	N(1)—C(19)—C(20)	111.0
S—C(12)—C(4)	117.6	C(19)—C(20)—N(2)	111.0
S—C(12)—C(11)	121.5	N(2)—C(21)—C(22)	112.0
C(4)—C(12)—C(11)	120.9	C(21)—C(22)—N(1)	110.7
S—C(13)—C(5)	116.8	C(20)—N(2)—C(21)	107.6
S—C(13)—C(14)	121.3	C(20)—N(2)—C(23)	111.6
C(5)—C(13)—C(14)	121.9	C(21)—N(2)—C(23)	111.9
C(8)—C(14)—C(9)	121.6	N(2)—C(23)—C(24)	117.5
C(8)—C(14)—C(13)	117.6	C(23)—C(24)—O	127.7

Å}. The angle O—H(99)···N(2) is 131.1° and the orientation of H(99) with the N(2) lone pair is favourable. No other H-bonding possibility exists for the O atom.

The thioxanthene tricyclic nucleus exhibits the usual fold about the S···C(9) direction with an angle of 143.1° between the aromatic ring mean planes. The

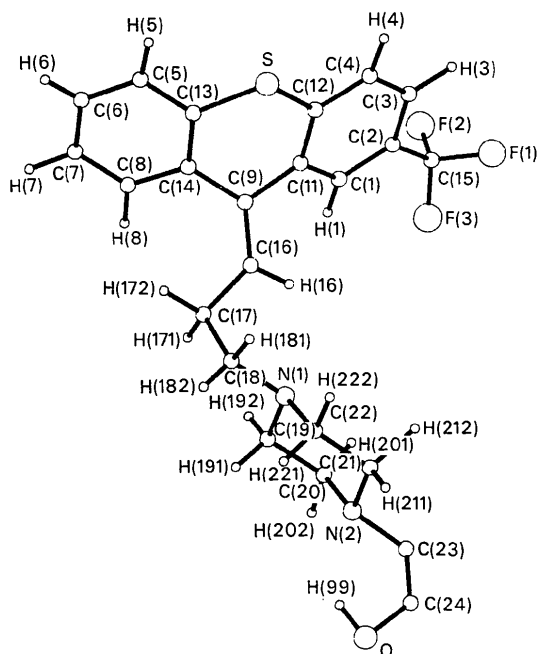


Fig. 1. General view of the molecular structure of β -flupenthixol.

bond geometry at C(9) is very similar to that found in the α -isomer (Post *et al.*, 1975), and yields well balanced intramolecular H···H approaches between side chain and aromatic ring H atoms on each side of the molecule.

We thank Dr I. Moller Nielsen for the crystals, Miss S. A. Stephenson for assistance with manuscript preparation, the Medical Research Council for financial support and the Science Research Council for provision of the diffractometer.

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