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Structures of Tifluadom [5-(2-Fluorophenyl)-1-methyl-2-(3-thenoylaminomethyl)-2,3-dihydro-1*H*-1,4-benzodiazepine] Hydrochloride, $C_{22}H_{21}FN_3OS^+.Cl^-$, and of (+)-Tifluadom *p*-Toluenesulphonate, $C_{22}H_{21}FN_3OS^+.C_7H_7O_3S^-$, and the Absolute Configuration of the Latter

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Abstract. $C_{22}H_{21}FN_3OS^+.Cl^-$: $M_r = 429{\cdot}9$, orthorhombic, $P2_12_12_1$, $a = 21{\cdot}362$ (13), $b = 14{\cdot}919$ (3), $c = 6{\cdot}484$ (1) Å, $V = 2066$ Å^3, $Z = 4$, $D_x = 1{\cdot}38$ g cm^{-3}, Cu $K\alpha$ radiation, graphite monochromator, $\lambda = 1{\cdot}54178$ Å, $\mu = 28{\cdot}7$ cm^{-1}, $F(000) = 896$, room temperature, $R = 0{\cdot}051$, 2146 significant reflections, orange parallelepipeds from ethanol. (+)-$C_{22}H_{21}FN_3OS^+.C_7H_7O_3S^-$: $M_r = 565{\cdot}7$, orthorhombic, $P2_12_12_1$, $a = 10{\cdot}319$ (6), $b = 10{\cdot}824$ (5), $c = 24{\cdot}537$ (13) Å, $V = 2741$ Å^3, $Z = 4$, $D_x = 1{\cdot}37$ g cm^{-3}, Cu $K\alpha$ radiation as above, $\mu = 22{\cdot}5$ cm^{-1}, $F(000) = 1184$, room temperature, $R = 0{\cdot}041$, 2428 significant reflections, deep-yellow prisms from acetone. The absolute configuration is 2*S*, using standard chemical numbering. In both structures, the 2-substituent is axially placed on the diazepine ring. In (+)-tifluadom, this ring is in a twist-boat conformation with symmetry axis passing through C(5a), whereas in the hydrochloride the ring is a boat with a symmetry plane passing through C(3). The conformations are otherwise very similar in the two crystal structures, including the presence of two intermolecular hydrogen bonds from N(4) and the amide group of the 2-substituent to the anion. Bond distances and angles are normal.

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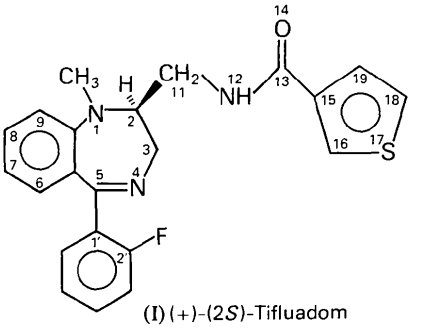
Introduction. Tifluadom [KC 5103, (I)] is a novel opioid drug, selective for opiate κ-receptors (Römer *et al.*, 1982*a*) and almost devoid of affinity for benzodiazepine binding sites (Römer *et al.*, 1982*b*).



(I) (+)-(2*S*)-Tifluadom

The crystal structure analysis of the racemic hydrochloride (which crystallizes in the noncentrosymmetric space group $P2_12_12_1$ so that individual crystals contain exclusively one or the other enantiomer) was undertaken to compare the conformation with those of classical opiates. After resolution of the racemate had shown that analgesic activity resides principally in the

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(+)-enantiomer, we determined the absolute configuration of this isomer in crystals of its *p*-toluenesulphonic acid salt.

Experimental. Data collected for both compounds on a CAD-4 diffractometer from crystals about 0·5 mm in each dimension using an ω–2θ scan in the range $1{\cdot}5 \le \theta \le 70°$ with Cu $K\alpha$ radiation. For the hydrochloride, the extent of the ω scan was $(1{\cdot}0 + 0{\cdot}14\tan\theta)°$, for the (+)-enantiomer $(0{\cdot}8 + 0{\cdot}14\tan\theta)°$. In both cases, the variable detector aperture was set at $(3{\cdot}0 + 0{\cdot}3\tan\theta)$ mm, and reflections were measured to a required precision $\sigma(I)/I$ of 2%, or for a maximum of 120 s. Intensity control reflections (2 and 1 respectively) were measured throughout the course of data collection and varied by 0·11 and 0·01%. Lattice parameters determined in each case by least squares from 12 automatically centred reflections in the range $10 \le \theta \le 15°$. Total reflections measured (including control reflections): hydrochloride 2358, (+)-enantiomer 2985; unique reflections: 2248, 2913; significant reflections 2146 $[I \ge 2{\cdot}5\sigma(I)]$, 2428 $[I \ge 3\sigma(I)]$; index ranges h 0/24, k 0/18, l 0/7 and 0/12, 0/13, 0/24, respectively. Data corrected for Lorentz and polarization effects and placed on an absolute scale by means of Wilson plots. Both structures solved by routine use of *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) and refined by block-diagonal least squares using anisotropic thermal parameters for the heavier atoms, together with a scale factor and an isotropic-extinction parameter. $w = 1/\sigma^2(F)$. Programs used were *MADIAL* or *LSD* (H.-P. Weber, unpublished, Sandoz Ltd). The quantity minimized was $\sum w(|F_o| - k|F_c|)^2$ with isotropic-extinction correction as described by Coppens & Hamilton (1970). G_{iso} corresponds to the quantity g'. $\bar{T}$ in that publication. In the hydrochloride, difference Fourier synthesis revealed excess positive density at the 6′-position, suggesting partial occupancy by F (180° rotational disorder of the *o*-fluorophenyl ring). The partial occupancies were refined to convergence with *SHELX*76 (Sheldrick, 1976) at 70:30 and then held fixed. In both structure analyses, H atoms were introduced in calculated positions with fixed isotropic temperature factors of 5·0 Å^2 after preliminary refinements with freely varying H atoms had shown that such refinement was not justifiable. The hydrochloride converged at $R(F) = 0{\cdot}051$ (272 parameters), $wR(F^2) = 0{\cdot}092$, $S = 2{\cdot}21$, $G_{iso} = 19$ (3). The structure of the (+)-enantiomer was refined to convergence without allowing for anomalous scattering: then f' and f'' were introduced and one cycle each of structure-factor calculation with the molecule in the 2*R* and in the 2*S*

Table 1. *Fractional atomic coordinates of tifluadom hydrochloride with estimated standard deviations and equivalent isotropic B's*

	x	y	z	B_{eq}(Å^2)‡
N(1)	0·8307 (1)	0·8557 (2)	0·4717 (4)	3·39
C(2)	0·7692 (1)	0·8710 (2)	0·5645 (4)	2·79
C(3)	0·7711 (1)	0·8585 (2)	0·7975 (4)	2·83
N(4)	0·7765 (1)	0·7643 (2)	0·8540 (4)	2·91
C(5)	0·8278 (1)	0·7198 (2)	0·8269 (4)	2·69
C(5a)	0·8831 (1)	0·7572 (2)	0·7307 (5)	3·02
C(6)	0·9408 (1)	0·7256 (2)	0·8069 (6)	3·95
C(7)	0·9970 (1)	0·7528 (2)	0·7304 (7)	4·26
C(8)	0·9964 (1)	0·8115 (2)	0·5641 (6)	4·38
C(9)	0·9422 (1)	0·8444 (2)	0·4869 (5)	3·96
C(9a)	0·8826 (1)	0·8215 (2)	0·5646 (4)	3·00
C(10)	0·8388 (2)	0·9108 (3)	0·2880 (6)	4·87
C(1′)	0·8287 (1)	0·6253 (2)	0·8991 (4)	2·83
C(2′)	0·8089 (1)	0·6009 (2)	1·0958 (5)	3·32
C(3′)	0·8098 (1)	0·5133 (2)	1·1621 (5)	3·76
C(4′)	0·8308 (1)	0·4469 (2)	1·0262 (6)	4·12
C(5′)	0·8498 (2)	0·4689 (2)	0·8317 (6)	4·31
C(6′)	0·8497 (1)	0·5581 (2)	0·7685 (5)	3·61
F(2′)*	0·7915 (1)	0·6623 (2)	1·2257 (5)	4·49
C(11)	0·7189 (1)	0·8138 (2)	0·4598 (5)	3·11
N(12)	0·6566 (1)	0·8394 (2)	0·5258 (4)	3·36
C(13)	0·6281 (1)	0·9119 (2)	0·4476 (5)	3·01
O(14)	0·6523 (1)	0·9573 (2)	0·3085 (4)	4·44
C(15)	0·5666 (1)	0·9370 (2)	0·5374 (5)	3·22
C(16)	0·5400 (1)	0·8979 (2)	0·7048 (7)	4·53
S(17)	0·47134 (4)	0·9483 (1)	0·7703 (2)	5·29
C(18)	0·4771 (1)	1·0239 (2)	0·5759 (6)	4·19
C(19)	0·5303 (1)	1·0099 (2)	0·4646 (6)	4·07
Cl	0·64217 (3)	0·7145 (1)	0·9369 (1)	3·54
F(6′)†	0·8593 (5)	0·5773 (5)	0·5903 (10)	5·54

* 70% occupancy.
† 30% occupancy.
‡ $B_{eq} = 4\det[\mathbf{BG}]^{1/3}$, where **B** is the matrix of the vibrational parameters and **G** is the metric matrix.

Table 2. *Fractional atomic coordinates of (+)-(2S)-tifluadom p-toluenesulphonate with estimated standard deviations and equivalent isotropic B's*

	x	y	z	B_{eq}*
N(1)	0·5512 (4)	0·2933 (4)	0·1284 (2)	4·43
C(2)	0·5647 (4)	0·4139 (4)	0·1543 (2)	3·72
C(3)	0·4379 (4)	0·4574 (4)	0·1788 (2)	3·43
N(4)	0·3529 (3)	0·5125 (3)	0·1384 (1)	3·32
C(5)	0·3219 (4)	0·4657 (4)	0·0916 (1)	3·11
C(5a)	0·3610 (4)	0·3461 (4)	0·0703 (2)	3·56
C(6)	0·2804 (6)	0·3038 (5)	0·0269 (2)	4·68
C(7)	0·2936 (8)	0·1913 (5)	0·0038 (2)	5·90
C(8)	0·3901 (7)	0·1131 (5)	0·0232 (3)	6·28
C(9)	0·4703 (6)	0·1479 (5)	0·0645 (2)	5·00
C(9a)	0·4623 (5)	0·2665 (4)	0·0894 (2)	3·64
C(10)	0·6340 (7)	0·1964 (6)	0·1518 (3)	6·60
C(11)	0·6311 (4)	0·5076 (5)	0·1156 (2)	4·07
N(12)	0·6749 (3)	0·6173 (3)	0·1432 (1)	3·87
C(13)	0·7966 (4)	0·6218 (4)	0·1647 (2)	3·49
O(14)	0·8675 (3)	0·5313 (3)	0·1639 (2)	5·18
C(15)	0·8409 (4)	0·7397 (4)	0·1882 (2)	3·66
C(16)	0·7665 (5)	0·8442 (5)	0·1949 (2)	4·96
S(17)	0·8525 (2)	0·9589 (2)	0·2249 (1)	6·45
C(18)	0·9903 (4)	0·8732 (5)	0·2301 (2)	4·63
C(19)	0·9683 (4)	0·7565 (5)	0·2084 (2)	4·53
C(1′)	0·2330 (4)	0·5464 (4)	0·0596 (2)	3·28
C(2′)	0·2644 (5)	0·5884 (5)	0·0079 (2)	4·61
F(2′)	0·3803 (3)	0·5544 (3)	−0·0131 (1)	6·58
C(3′)	0·1828 (6)	0·6606 (5)	−0·0233 (2)	5·21
C(4′)	0·0666 (6)	0·6975 (5)	−0·0017 (2)	5·26
C(5′)	0·0328 (5)	0·6612 (5)	0·0508 (2)	4·82
C(6′)	0·1146 (5)	0·5853 (4)	0·0813 (2)	3·94
C(1″)	0·2812 (4)	0·9505 (4)	0·1570 (2)	3·34
C(2″)	0·1948 (6)	0·9345 (5)	0·1150 (2)	5·07
C(3″)	0·1090 (6)	1·0295 (6)	0·1033 (3)	5·73
C(4″)	0·1090 (5)	1·1400 (5)	0·1318 (3)	5·16
C(4*m*″)	0·0148 (7)	1·2411 (7)	0·1186 (4)	7·91
C(5″)	0·1975 (5)	1·1540 (4)	0·1730 (2)	4·79
C(6″)	0·2836 (4)	1·0593 (4)	0·1863 (2)	3·91
S(7″)	0·3834 (1)	0·8262 (1)	0·17494 (4)	3·26
O(8″)	0·2962 (4)	0·7251 (3)	0·1895 (1)	5·19
O(9″)	0·4613 (3)	0·7938 (3)	0·1277 (1)	4·79
O(10″)	0·4607 (4)	0·8664 (4)	0·2202 (1)	5·67

* Defined in Table 1.

configuration yielded R's of 0·0494 and 0·0428 respectively. By Hamilton's (1965) R-factor-ratio test, based on the conventional R values, the configuration is 2S at a significance level $\gg$ 0·995. Further refinement of the 2S configuration (353 parameters) converged at $R(F) = 0{\cdot}041$, $wR(F^2) = 0{\cdot}086$, $S = 2{\cdot}14$, $G_{iso} = 4$ (1). In both refinements, $(\Delta/\sigma)_{max}$ in final cycles was <0·4. Atomic scattering factors and dispersion corrections from *International Tables for X-ray Crystallography* (1974). Final difference Fourier syntheses showed no features in excess of 0·9 e Å^{-3}, this in the neighbourhood of the Cl in the hydrochloride.

Discussion. Neither molecule exhibits any unusual bond lengths or angles. Atomic coordinates of the heavier atoms are given in Tables 1 and 2.* The conformations of the hydrochloride and of the (+)-enantiomer are shown in Figs. 1 and 2 and can be seen to be very similar. In the hydrochloride of (I), the seven-membered ring is in a boat conformation with the 2-substituent axial and a symmetry plane through C(3) and the centre of the C(5a)—C(9a) bond. This conformation is the same as that commonly seen in classical benzodiazepin-2-ones (Hamor & Martin, 1984, and references therein), and in medazepam (Gilli, Bertolasi & Sacerdoti, 1978) which is more closely analogous to tifluadom than the 2-ones. In (+)-(2S)-(I), this ring takes the form of a twist boat with symmetry axis through C(5a) and the centre of the C(2)—C(3) bond; the 2-substituent is in a flagpole orientation. Sufficient torsion angles to describe the molecular conformations are given in Table 3.

* Lists of structure factors, anisotropic thermal parameters, H-atom positions and bond lengths and angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42016 (38 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Selected torsion angles* (°)

	Tifluadom.HCl	(+)-Tifluadom *p*-toluenesulphonate
C(5)–C(5a)–C(9a)–N(1)	−1·0 (4)	−6·9 (7)
C(5a)–C(9a)–N(1)–C(2)	30·9 (4)	−5·7 (7)
C(9a)–N(1)–C(2)–C(3)	9·6 (3)	54·7 (5)
N(1)–C(2)–C(3)–N(4)	−72·9 (2)	−81·5 (4)
C(2)–C(3)–N(4)–C(5)	71·9 (2)	49·4 (5)
C(3)–N(4)–C(5)–C(5a)	−2·9 (4)	2·7 (6)
N(4)–C(5)–C(5a)–C(9a)	−34·8 (3)	−15·3 (6)
N(1)–C(2)–C(11)–N(12)	−170·2 (2)	−165·7 (3)
C(2)–C(11)–N(12)–C(13)	78·8 (3)	89·8 (4)
N(12)–C(13)–C(15)–C(16)	6·9 (4)	6·1 (6)
N(4)–C(5)–C(1′)–C(2′)	−49·3 (3)	122·4 (4)

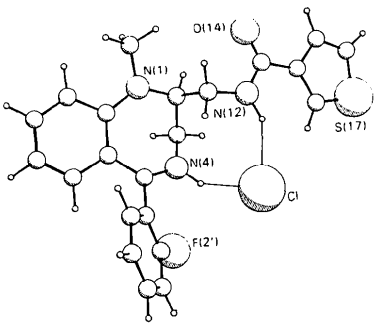

Fig. 1. Perspective drawing of tifluadom in crystals of the hydrochloride, projected on the plane of the unsubstituted phenyl ring (*PLUTO*, Motherwell 1977).

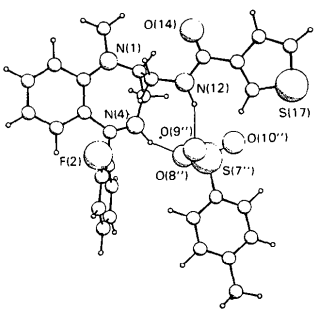

Fig. 2. Perspective drawing of (+)-(2S)-tifluadom in crystals of the *p*-toluenesulphonate projected similarly to Fig. 1.

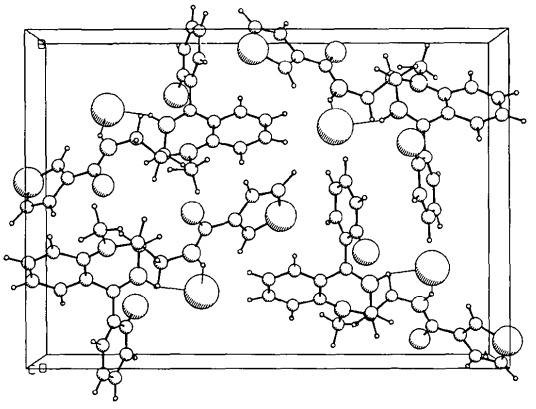

Fig. 3. Packing diagram of tifluadom hydrochloride projected along **c**.

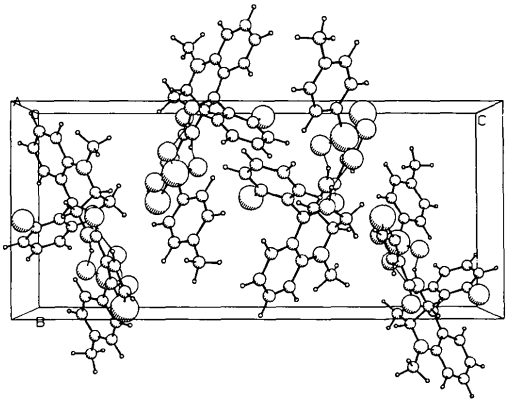

Fig. 4. Packing diagram of (+)-(2S)-tifluadom *p*-toluenesulphonate projected along **a**.

Table 4. *Hydrogen-bond geometry* (Å, degrees)

Tifluadom hydrochloride					
N(4)–Cl	3·013 (2)	H(4)–Cl	2·09	N(4)–H(4)–Cl	150
N(12)–Cl	3·267 (2)	H(12)–Cl	2·36	N(12)–H(12)–Cl	148
N(4)–F(2′)	2·868 (3)	H(4)–F(2′)	2·52	N(4)–H(4)–F(2′)	99
(+)-(2*S*)-Tifluadom *p*-toluenesulphonate					
N(4)–O(8″)	2·687 (4)	H(4)–O(8″)	1·74	N(4)–H(4)–O(8″)	153
N(12)–O(9″)	2·941 (4)	H(12)–O(9″)	1·99	N(12)–H(12)–O(9″)	155

Crystal packing arrangements are shown in Figs. 3 and 4. In both crystal structures, N(4) and N(12) form intermolecular hydrogen bonds to the anion. In the hydrochloride that from N(4) is bifurcated to Cl and intramolecularly to F(2′): details are given in Table 4.

The crystal structures were determined principally to give some insight into the conformation of this novel opioid. It is reasonable to assume, however, that the solid-state conformation of the side chain is largely determined by the above-mentioned *inter*molecular H bonds. NMR investigations suggest (Milkowski & Finner, 1981) that in organic solvents, the molecule folds so that there is π–π stacking of the thienyl and *o*-fluorophenyl rings. Such a conformation can readily be generated from the crystal structures by rotations of −120 and 180° about C(2)–C(11) and C(11)–N(12), respectively, and is certainly energetically not unfavourable. Further experimental and theoretical conformational studies are clearly necessary before these molecules can, with any degree of certainty, be compared with the known conformations of classical opiates.

We acknowledge the skilful experimental contribution of our coworker H. D. Reineke to the chemistry of these compounds.

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Acta Cryst. (1985). C**41**, 912–915

1,1-Dimethyl-3,3,4,4-tetraphenylgermacyclopentane, $C_{30}H_{30}Ge$

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Abstract. $M_r = 463{\cdot}2$, monoclinic, $P2_1/c$, $a = 12{\cdot}234$ (5), $b = 9{\cdot}942$ (4), $c = 19{\cdot}435$ (6) Å, $\beta = 97{\cdot}27$ (5)°, $V = 2345$ Å^3, $Z = 4$, $D_x = 1{\cdot}312$ Mg m^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 1{\cdot}4$ mm^{-1}, $F(000) = 968$, $T = 292$ (1) K, final $R = 0{\cdot}049$ for 2218 $[I > 2\sigma(I)]$ unique diffractometer data. The central part of the asymmetric monomeric molecule is a five-membered heterocycle consisting of one Ge and four C atoms. The coordination around Ge is a distorted tetrahedron. An extraordinarily long bond distance between two C atoms of the five-membered heterocycle [1·626 (7) Å] is probably caused by repulsion between the four phenyl groups bound to these C atoms and between the phenyl groups and C atoms of the heterocycle, which may be the reason for the surprising thermolability of the title compound. The initial step of the thermal decomposition is probably the cleavage of this highly strained and elongated C–C bond.

Introduction. Germacyclopentanes like 1,1-dimethyl-3,4-diphenylgermacyclopentane are normally stable up to at least 473 K (Köcher & Neumann, 1985). 1,1-Dimethyl-3,3,4,4-tetraphenylgermacyclopentane, however, gives a uniform fragmentation even at 353 K, and is a thermal source for dimethylgermylene, Me_2Ge, a member of (heavy) carbene analogues R_2M, M

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