groupes carbonyles sont très fortement polarisés. Les courbes de potentiel électrostatique moléculaire calculées suivant des méthodes semi-quantiques, par le programme *VSEM* (Escale, Girard, Rossi, Teulade & Grassy, 1983) sont représentées sur la Fig. 1. Le potentiel crée par les groupes carbonyles est très intense et s'étend largement au delà de l'enveloppe de van der Waals. Les atomes d'oxygène O(18) et O(25) sont donc susceptibles d'interagir fortement (liaisons hydrogène) avec un éventuel récepteur. Les charges atomiques du cycle pyridinique et de la chaîne aminoalkyle sont également importantes par suite de la présence des atomes d'azote N(1) et N(50), dont la distance est égale à 4,36 (1) Å. Les charges atomiques du fragment plan de la molécule créent un moment dipolaire élevé: $\mu = 8{,}15$ debye ($27{,}19 \times 10^{-3}$ C m). Le groupement volumineux $N(C_2H_5)_2$, grâce à sa charge globale négative non négligeable, peut induire des interactions électrostatiques et jouer un rôle important au niveau d'un site récepteur.

Dans le cristal, les molécules s'arrangent en dimères et s'enroulent autour de l'axe hélicoïdal (Fig. 2). Un dimère est formé de deux molécules dont les cycles pyridiniques, distants de 3,33 (1) Å se recouvrent partiellement. Cette distance interplanaire très courte est à comparer aux valeurs de 3,35 et 3,37 Å trouvées respectivement pour le graphite (Kitaigorodskii, 1973) et le benzopérylène (Trotter, 1959). Il est probable que l'énergie d'interaction électrostatique entre ces molécules fortement polarisées induise ou renforce la formation de tels dimères. Il n'existe aucune liaison hydrogène et la cohésion moléculaire n'est assurée que par de faible forces de van der Waals.

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Structure of Tifluadom Hydrate*

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(*Received* 25 *July* 1986; *accepted* 2 *March* 1987)

Abstract. $C_{22}H_{20}FN_3OS.H_2O$, $M_r = 411{\cdot}50$, monoclinic, $P2_1$, $a = 12{\cdot}008\,(2)$, $b = 6{\cdot}6467\,(6)$, $c = 13{\cdot}763\,(3)$ Å, $\beta = 113{\cdot}368\,(9)°$, $V = 1008{\cdot}4\,(3)$ Å^3, $Z = 2$, $F(000) = 432$, $D_x = 1{\cdot}355$, D_m (by flotation) = $1{\cdot}324$ g cm^{-3}, Cu $K\alpha$ ($\lambda = 1{\cdot}54178$ Å, Ni filter), $\mu = 16{\cdot}3$ cm^{-1}, $T = 173\,(5)$ K, $R = 0{\cdot}063$, $wR = 0{\cdot}078$, 1754 reflections. The 3-thenoylaminomethyl side chain is in an extended conformation placing the thiophene ring approximately parallel to the benzo portion of the benzodiazepine moiety. The orientation of the side chain, relative to the diazepine ring, is stabilized by intermolecular hydrogen bonds to the water molecule of

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* Tifluadom is *N*-{[5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1*H*-1,4-benzodiazepin-2-yl]methyl}-3-thiophenecarboximide (*Chemical Abstracts* name).

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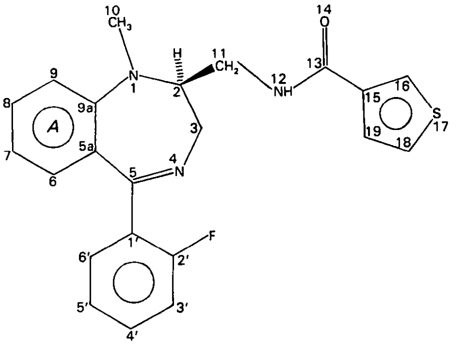
crystallization. One of these hydrogen bonds is similar to that found in the benzomorphan κ agonists. Also, three portions of tifluadom are arranged similarly to the preferred geometry of benzomorphans. In contrast, tifluadom is larger in key dimensions than any benzodiazepine receptor ligand. These similarities and differences may account for the unique pharmacological profile of tifluadom.

Introduction. Tifluadom (1), although similar in chemical structure to the anxiolytic 1,4-benzodiazepines, has no affinity for the receptor for benzodiazepines that mediates anxiety and sedation. Instead, this unique compound has been identified (Römer *et al.*, 1982) as an opiate agonist with specific affinity for the κ opiate receptor. The crystal structures of a number of κ agonists of the benzomorphan family have been determined (Verlinde, Blaton, De Ranter & Peeters, 1984; and references cited therein); these compounds were found to have similar three-dimensional shapes. The conformation and absolute configuration of (+)-tifluadom *p*-toluenesulfonate and the conformation of the HCl salt of tifluadom have been determined (Petcher, Widmer, Maetzel & Zeugner, 1985) and, as in the benzomorphan case, the conformations were similar. The crystal structure of the free base of tifluadom has been determined to ascertain the effects of both the protonation of the drug and the ionic crystalline environment on the conformation of the molecule. In general, studies of the structure of tifluadom may help to explain the affinity of this compound for the opiate receptor and not for the benzodiazepine receptor.



(1)

Experimental. Yellow plates from an ethanol/water mixture; $0{\cdot}10 \times 0{\cdot}20 \times 0{\cdot}20$ mm; Enraf–Nonius CAD-4F; $\theta_{\max} = 65°$; range for 25 reflections that define orientation matrix and cell: $\theta = 27{\cdot}9$–$44{\cdot}5°$; empirical absorption correction applied after convergence of the isotropic refinement, $A_{\min} = 0{\cdot}86$, $A_{\max} = 1{\cdot}28$ (Walker & Stuart, 1983); *hkl* range: $\pm h$, $+k$, $+l$; standards 901, 041, $\bar{2}$,0,11, variation < 2%. 2029 measured, 1875 unique, 1549 had $I \geq 2{\cdot}5\sigma(I)$; *MULTAN*78 (Germain, Main & Woolfson, 1971); $\sum w(|F_o| - |F_c|)^2$ minimized; weights defined as $w^{-1} = [\sigma^2(F_o) + 0{\cdot}005(F_o)^2]$; $R = 0{\cdot}063$, $wR = 0{\cdot}078$, $S = 0{\cdot}87$; max. shift/e.s.d. = 0·02; max./min. difference Fourier map peaks were $\pm$ 0·6 e Å^{-3} and were associated with the disordered thiophene ring; programs: *XRAY*76 (Stewart, 1976), *DIFABS* (Walker & Stuart, 1983); scattering factors from Cromer & Mann (1968) and for H atoms from Stewart, Davidson & Simpson (1965).

The configuration of tifluadom was determined by reference to the absolute configuration determined by Petcher *et al.* (1985) to be 2*S* and consistent with the anomalous scattering of the sulfur atom. The position of the water molecule of crystallization was identified in a difference Fourier synthesis. The thiophene ring is disordered and has two positions differing, approximately, by 180° rotation about the bond connecting the ring to the carboxamide side chain. The ring was modeled by two superimposed thiophene rings based on β-thiophenic acid (Hudson & Robertson, 1964). All of the atoms of the ring, including C(15), the connecting atom, were assigned population parameters of 0·75/0·25 based on the peak heights in the Fourier synthesis; isotropic thermal parameters were assigned and not refined whereas the coordinates were refined in alternate cycles. H atoms in the ordered structure and on the water molecule were located in difference Fourier syntheses. These atoms were included in the model with isotropic thermal parameters assigned at 1·2 × the thermal parameter of the atom to which they were bonded and the H-atom parameters were not refined. The final cycles of full-matrix least squares refined the coordinates of all non-hydrogen atoms (disordered model in alternate cycles) and the anisotropic thermal parameters of the ordered non-hydrogen atoms. The 1754 reflections included in the refinement were the observed reflections and those unobserved reflections that were calculated to be greater than the unobserved reflection threshold, *i.e.* those reflections with $F_c > 5{\cdot}0\sigma(F_o)$ were included in the refinement.

Discussion. Atomic coordinates of the non-hydrogen atoms are given in Table 1* and the molecular conformation is shown in Fig. 1. As is evident from the torsion angles given in Table 2, the diazepine ring is in a boat conformation and the 3-thenoylaminomethyl side chain is anticlinal allowing the aromatic thiophene ring to be approximately parallel to the benzo portion of the benzodiazepine. The angle between the planes of these two aromatic systems is 28·7 (3)°.

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* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, and bond lengths and angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43835 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester, CH1 2HU, England.

As shown in Fig. 1, the water molecule of crystallization is hydrogen bonded to N(4) of the seven-membered ring and to N(12) of the 3-thenoylaminomethyl side chain, thus linking the side chain to the diazepine ring. In addition, the water molecule acts as a hydrogen donor to the carbonyl oxygen atom, O(14), of a neighboring molecule at $x,\ y+1,\ z$. The parameters of the hydrogen bonds are given in Table 3.

Table 1. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters* ($\times 10$) *for the non-hydrogen atoms of tifluadom*

Isotropic B values ($\times 10$) are given for the atoms of the disordered thiophene ring. The y coordinate for C(10) was fixed to define the origin.

$$B_{\rm eq} = \tfrac{8}{3}\pi^2 \textstyle\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$B_{\rm eq}$(Å^2)
C(10)	−12014 (7)	−6318	−6776 (6)	36 (4)
N(1)	−11816 (5)	−4415 (12)	−7214 (4)	23 (2)
C(2)	−10653 (6)	−3486 (13)	−6522 (5)	19 (3)
C(3)	−10711 (5)	−1207 (13)	−6558 (5)	19 (2)
N(4)	−10683 (4)	−411 (12)	−7534 (4)	18 (2)
C(5)	−11661 (5)	−639 (14)	−8370 (4)	20 (2)
C(6)	−13870 (5)	−599 (14)	−9016 (5)	24 (3)
C(7)	−14995 (5)	−1255 (15)	−9105 (5)	28 (3)
C(8)	−15055 (6)	−2987 (16)	−8573 (5)	32 (3)
C(9)	−14005 (6)	−4002 (15)	−7949 (5)	33 (3)
C(5a)	−12800 (5)	−1544 (14)	−8388 (4)	19 (2)
C(9a)	−12851 (5)	−3309 (13)	−7826 (5)	21 (3)
C(11)	−9662 (6)	−4305 (14)	−6816 (5)	23 (3)
N(12)	−8441 (5)	−3669 (12)	−6109 (4)	21 (2)
C(13)	−7704 (6)	−4828 (13)	−5331 (5)	20 (3)
O(14)	−7999 (4)	−6562 (12)	−5173 (3)	26 (2)
C(151)	−6501 (9)	−3965 (20)	−4633 (8)	33
C(161)	−5967 (8)	−2266 (20)	−4826 (8)	33
S(171)	−4601 (2)	−1839 (9)	−3871 (2)	33
C(181)	−4626 (8)	−3949 (25)	−3110 (7)	33
C(191)	−5774 (9)	−4862 (20)	−3667 (7)	33
C(152)	−6512 (26)	−3978 (54)	−4640 (23)	33
C(162)	−5828 (26)	−5052 (52)	−3667 (23)	33
S(172)	−4616 (6)	−3706 (14)	−3026 (6)	33
C(182)	−4634 (26)	−1174 (51)	−3691 (23)	33
C(192)	−5960 (25)	−2285 (51)	−4853 (23)	33
C(1′)	−11662 (5)	206 (14)	−9372 (5)	21 (3)
C(2′)	−11993 (6)	−883 (14)	−10293 (5)	22 (3)
C(3′)	−12000 (6)	−170 (18)	−11222 (5)	36 (4)
C(4′)	−11626 (6)	1786 (18)	−11247 (6)	39 (4)
C(5′)	−11259 (6)	2955 (16)	−10349 (6)	41 (4)
C(6′)	−11262 (6)	2182 (15)	−9406 (6)	32 (3)
F(2′)	−12366 (4)	−2813 (11)	−10281 (4)	46 (2)
O(1)	−8178 (4)	500 (11)	−6758 (4)	27 (2)

Table 2. *Selected torsion angles* (°)

	Free base*	Tifluadom.HCl†
C(5)—C(5a)—C(9a)—N(1)	1·8 (11)	−1·0 (4)
C(5a)—C(9a)—N(1)—C(2)	41·0 (10)	30·9 (4)
C(9a)—N(1)—C(2)—C(3)	−0·2 (8)	9·6 (3)
N(1)—C(2)—C(3)—N(4)	−75·3 (7)	−72·9 (2)
C(2)—C(3)—N(4)—C(5)	73·4 (8)	71·9 (2)
C(3)—N(4)—C(5)—C(5a)	3·2 (13)	−2·9 (4)
N(4)—C(5)—C(5a)—C(9a)	−43·9 (13)	−34·8 (3)
N(1)—C(2)—C(11)—N(12)	−173·6 (6)	−170·2 (2)
C(2)—C(11)—N(12)—C(13)	98·7 (9)	78·8 (3)
N(12)—C(13)—C(151)—C(161)	−14·0 (20)	6·9 (4)
N(12)—C(13)—C(152)—C(162)	−16·0 (40)	
N(4)—C(5)—C(1′)—C(2′)	128·7 (8)	−49·3 (3)

* This work.
† Petcher *et al.* (1985).

The two hydrogen bonds that link N(4) of the diazepine ring to N(12) of the thenoylaminomethyl side chain are observed in all three crystalline forms of tifluadom. These hydrogen bonds stabilize a single global conformation for the tifluadom molecule even though the molecule is observed in three different packing environments. In this single conformation, the thiophene ring is projected away from the benzodiazepine framework and is nearly perpendicular to the C(5)-phenyl group in contrast to the NMR prediction that π–π interaction occurs between the thiophene ring and the C(5)-phenyl group (Petcher *et al.*, 1985).

The finding that three different observations of tifluadom have the same molecular conformation provides evidence that this extended conformation is a low-energy form of the molecule. Also the consistent observation of two strong intermolecular hydrogen bonds formed by N(4) and N(12) provides a model for the interaction of this molecule with a receptor site. Together these findings suggest that the crystallographic conformation is the binding conformation for this molecule. A comparison of the tifluadom structure with two κ-agonist benzomorphan structures [bremazocine (Verlinde *et al.*, 1984) and ketazocine (Verlinde & De Ranter, 1983)] shows that the arrangement of the N—H···X hydrogen bond to the aromatic ring (A in the benzomorphans and tifluadom) is conserved. In the benzomorphans, the separation between the center of the A ring and the hydrogen-bond acceptor atom is, on average, 7·2 Å and, in both cases, the N—H group and the acceptor atom are on the same side of the plane of the A ring. In tifluadom, the separation between the center of the A ring and the O atom of the acceptor water molecule is 6·60 (1) Å and, as in the benzomorphans, both N(12) and O(1) are on the same side of the plane of the aromatic A ring. The shorter distance in

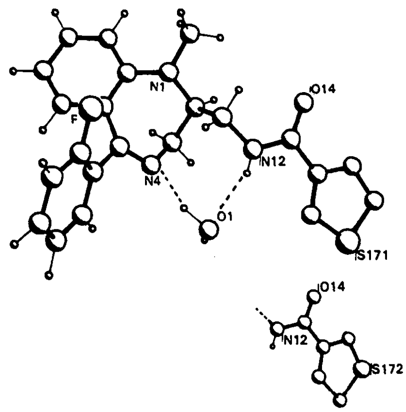

Fig. 1. The molecular conformation of tifluadom free base. The inset shows the alternative orientation of the thiophene ring (25% of total population). Hydrogen bonds are shown as dashed lines (*PLUTO*, Motherwell, 1977).

Table 3. *Hydrogen-bond geometry* (Y—H···X)

	H···X(Å)	Y···X(Å)	Y—H···X(°)
O(1W)–H(1W)···N(4)	1·76	2·822 (8)	168
N(12)–H(12)···O(1W)	2·16	2·967 (10)	160
O(1W)–H(2W)···O(14)*	1·82	2·871 (9)	173

* At ($x, y+1, z$).

tifluadom is due, in part, to the shorter N···O distance of 2·97 (1) Å compared with the N···Cl distance of 3·145 (3) in ketazocine and 3·157 (4) Å in bremazocine and, in part, to the second hydrogen bond from N(4) to the water molecule. It is clear that these κ agonists could all bind to the same aromatic pocket and form a hydrogen bond to a common acceptor site ~7 Å distant from the center of the pocket.

A second similarity in these κ-agonist compounds is that, in all three molecules mentioned above, an O atom is positioned on the opposite side of the molecule from the N—H···X hydrogen bond and could provide a third interaction site with the receptor.

A comparison of tifluadom to benzodiazepine receptor ligands indicates that although the overall shape of the molecule is similar to both the 1,4-benzodiazepine agonists and the antagonist, R015-1788 (Codding & Muir, 1985), the dimensions of the structure are quite different. In benzodiazepine receptor ligands, the separation between the center of the *A* ring and a hydrogen-bond acceptor (usually a carbonyl oxygen) atom is different for ligands with different biological effects. Agonist ligands have an average separation of 4·95 Å, for antagonists the distance is *ca* 6·1 Å, and for inverse agonists the separation is 6·45 Å (Muir, 1985). Tifluadom, by contrast, is much larger: the separation between O(14) and the center of the *A* ring is 7·31 (1) Å, apparently too long to fit in the benzodiazepine receptor binding site.

The differences between the protonated forms (Petcher *et al.*, 1985) and the unprotonated form of tifluadom are mainly in the conformation of the diazepine ring and in the bond angle subtended by the protonated nitrogen atom N(4). One protonated form of tifluadom, the *p*-toluenesulfonate, exhibits a twist-boat conformation for the diazepine ring. Although both the protonated hydrochloride and the free base structures exhibit a boat conformation with a symmetry plane through C(3), the seven-membered ring in the free base assumes a more symmetric conformation than in the hydrochloride: the ΔC_s parameter (Duax, Weeks & Rohrer, 1976) is 2·6° for the free base and 4·5° for the hydrochloride (a perfectly symmetrical boat conformation would have a ΔC_s of 0·0°).

The effect of protonation on N(4) is to open the ring bond angle by *ca* 10°. The angle C(3)—N(4)—C(5) is 115·7 (6)° in the free base structure and is typical of the values for this angle that are observed in 1,4-benzodiazepines (Butcher, Hamor & Martin, 1983; Gilli, Bertolasi, Sacerdoti & Borea, 1978). In the two protonated structures reported by Petcher *et al.* (1985) the angles subtended by N(4) are 125·8 (2)° for the hydrochloride salt and 126·4 (4)° for the *p*-toluenesulfonate salt. The bond distances involving N(4) are nearly the same whether or not the atom is protonated.

The dimensions of the hydrogen bonds may play a role in the distortions observed in the seven-membered rings. In both protonated forms, large anions had to be accommodated in the space between N(4) and N(12); the distortions in the boat conformations and the ring opening at N(4) may result from steric interactions with these anions. By contrast, the water molecule found in the free base structure is smaller and could be accommodated with less strain on the ring system.

In summary, the unique pharmacological effect of tifluadom may be due to the combined presence of an aromatic ring and a hydrogen-bond donor (N—H) group that are separated by *ca* 7 Å, a separation like that found in other κ-agonist ligands. Furthermore, the tifluadom structure is too large to fit in the benzodiazepine receptor recognition site.

We acknowledge the technical assistance of T. A. Lee and J. Jakana and the financial support of the Medical Research Council of Canada (Grant MA-8087 to PWC).

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