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Dorzolamide hydrochloride: an anti-glaucoma agent

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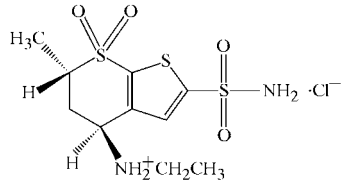
Dorzolamide hydrochloride [systematic name: (4*S*)-*trans*-4-ethylammonio-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide chloride], $C_{10}H_{17}N_2O_4S_2^+\cdot Cl^-$, belongs to a class of drugs called carbonic anhydrase inhibitors. The ethylammonio side chain is in an extended conformation and is protonated at the N atom, which is hydrogen bonded to the Cl^- anion. The dihedral angle between the planes of the thiophene ring and the sulfonamide group is 80.7 (1)°. A comparison is made with the dorzolamide bound in human carbonic anhydrase in the solid state. Hydrogen bonding is mediated by Cl^- anions, resulting in indirect connectivity between the molecules.

Comment

Dorzolamide hydrochloride is one of a number of topical medications used to treat glaucoma (Baldwin *et al.*, 1989). Glaucoma is a potentially devastating eye disease, caused by the build-up of abnormally high pressure in the eye. Dorzolamide belongs to a class of drugs called carbonic anhydrase inhibitors and has become commercially available since 1995 for topical ophthalmic use (Seong *et al.*, 2001). It is thought to reduce the raised intraocular pressure by the same mechanism as that of carbonic anhydrase-II in the ciliary body. It is an effective second line agent for patients of open angle glaucoma and ocular hypertension who are unable to tolerate ophthalmic β-blockers (Balfour & Wilde, 1997). The United States Food and Drug Administration has granted marketing clearance to Merck & Co. Inc. in the brand names Trusopt (contains only dorzolamide) and Cosopt, the first eye drop that combines a topical carbonic anhydrase inhibitor (dorzolamide) and a topical β-blocking agent (timolol maleate). In a continuation of our ongoing programmes for the structural elucidation of drug molecules and structure–activity relationships, the crystal structure of dorzolamide hydrochloride, (I), has been determined.

The molecular framework (Fig. 1) consists of a central thienothiopyran bicyclic ring system with a sulfonamide and an ethylamino substituent. The bond distances and angles (Table 1) are in normal ranges (Allen *et al.*, 1987) and are comparable to those of similar structures. Owing to the high basicity of ethylamine, the protonation, as anticipated, occurs at atom N1 preferentially over sulfonamide atom N2.



(I)

The arrangement of bonds around atom S3 is distorted tetrahedral, a structural feature commonly found in sulfonamide compounds (Liu *et al.*, 1994; Pedregosa *et al.*, 1993; Lisgarten & Palmer, 1988). The largest deviation is in the O3—S3—O4 angle [119.8 (1)°], while the other angles are in the range 105.3 (1)–110.7 (1)°. The S3—N2 bond length (Table 1) is intermediate between the values found in actazolamide [1.594 (3) Å; Mathew & Palenik, 1974] and methazolamide [1.575 (2) Å; Alzuet *et al.*, 1991]. The crystal structures of the complexes dorzolamide–human carbonic anhydrase (HCAII) [dHCA; Smith *et al.*, 1994; Protein Data Bank (Berman *et al.*, 2000) entry 1cil] and brinzolamide–HCAII (bHCA; Stams *et al.*, 1998; Protein Data Bank entry 1a42) are available and the extracted ligand structures are used here for comparison.

The sulfonamide group plays an anchoring role at the active site through coordination of its N atom with the Zn atom of HCAII (Greer *et al.*, 1994). In (I), its orientation with respect to the thiophene ring, defined by the torsion angle N2—S3—C1—S2, is 81.0 (2)°. The corresponding angle observed in the dHCA complex is 144°, while it is 152° in bHCA. It is interesting that the *ab initio* molecular orbital calculations at the 3–21G* level (Greer *et al.*, 1994) suggest that the preferred torsion angle is 72°, which is close to that found here. Recently, Zou *et al.* (2005) reported the crystal structure of a key

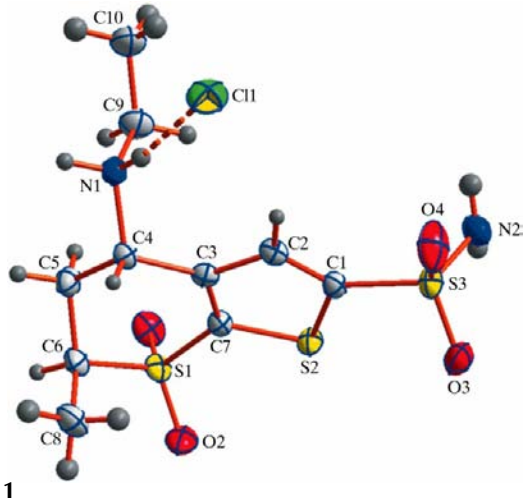


Figure 1
A view of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. The dashed line indicates a hydrogen bond.

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intermediate of the carbonic anhydrase inhibitor similar to the title compound (having an acetamide instead of an ethylammonio side chain), where this angle is −74.9 (1)°. Given the potential importance of a C3 substituent in triggering the conformational change of His64 (a key residue in the enzymatic active site of HCAII), the orientation of the ethylammonio chain is considered to be significant (Smith *et al.*, 1994). In (I), it is in an extended conformation, with C9—N1 bound *cis* with respect to C4—C3 [C9—N1—C4—C3 = 56.4 (2)°], whereas in both dHCA and bHCA, it is found to be *trans* (168 and 165°, respectively; see Fig. 2). It is noteworthy

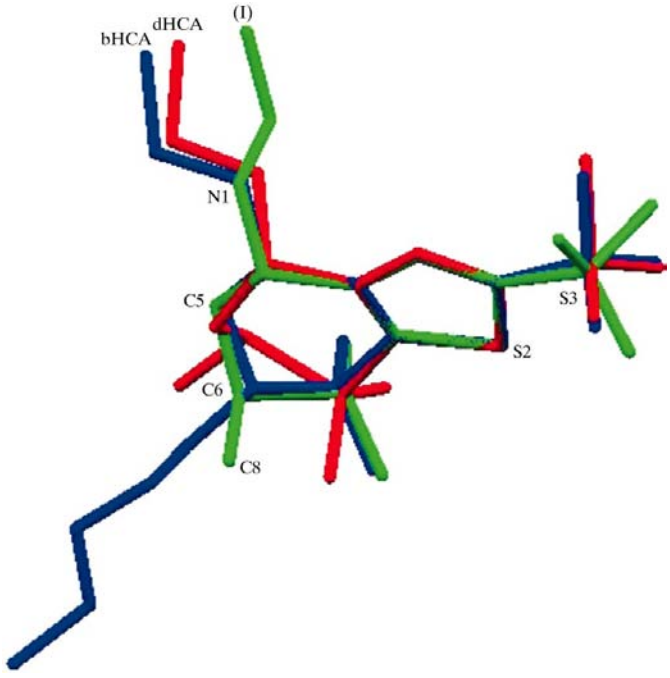

Figure 2
An overlay of (I) with dHCA (r.m.s deviation = 0.026 Å) and bHCA (r.m.s deviation = 0.018 Å), superimposing the thiophene ring, revealing the differences of the orientations of the substituents. H atoms have been omitted for clarity.

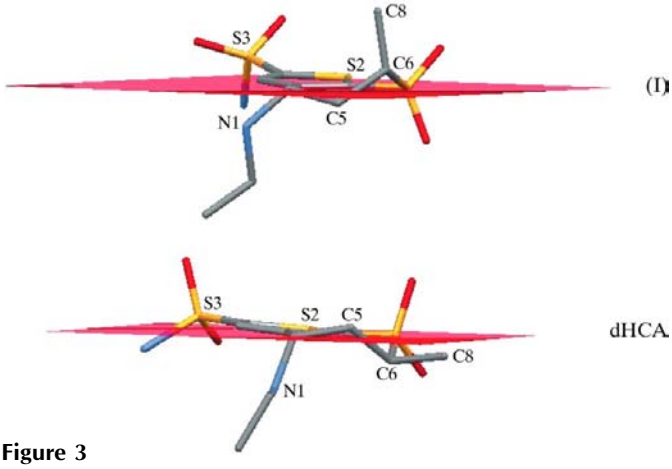

Figure 3
A least-squares plane projection, fitted through atoms C4, C3, C7 and S1 of the thiopyran ring, depicting the C6-atom 'flip' and the pseudo-axial/pseudo-equatorial orientation of the methyl/ethylammonio substituents (see *Comment*). H atoms have been omitted for clarity.

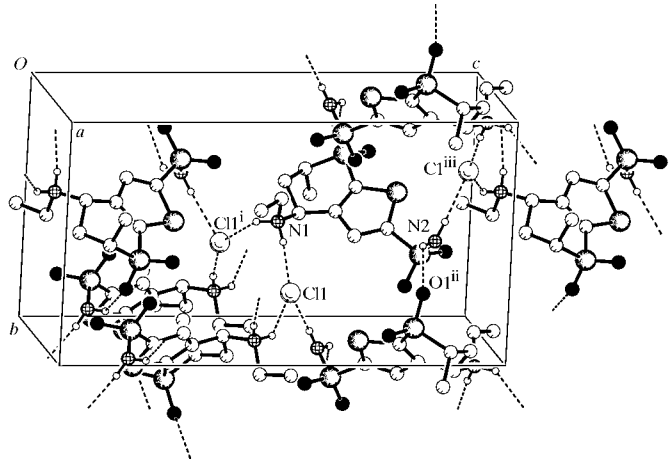

Figure 4
Part of the crystal structure of (I), viewed down the *a* axis, showing the network of hydrogen bonds (dashed lines). Only atoms involved in hydrogen bonding are labelled. [Symmetry codes: (i) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+1$; (ii) $-x+1, y+\frac{1}{2}, -z+\frac{3}{2}$; (iii) $-x+1, y-\frac{1}{2}, -z+\frac{3}{2}$.]

that methyl group C8, introduced into the thienothiopyran ring system, stabilizes the alkylamino substituent in what would otherwise be a less favourable pseudo-axial conformation (Davis *et al.*, 2003). Considering the torsion angles N1—C4—C3—C7 and C8—C6—S1—C7 (Table 1), the ethylammonio group and the methyl group prefer pseudo-equatorial and pseudo-axial conformations, respectively. In contrast, the corresponding torsion angles are −103 and −171° in dHCA, and −131 and −163° in bHCA.

The six-membered thiopyran ring adopts a half-chair conformation in both (I) and the dHCA complex. However, atom C6 in the ring is 'flipped' up and down in both (Fig. 3), which may allow the methyl group and the ethylammonio group to adopt their preferred orientations. This flip in (I) may be attributed to the involvement of the protonated N1 atom of the ethylammonio group in hydrogen bonding with Cl atoms (Table 2). The structure–activity distance between the centre of the thiophene ring and the two N atoms (the interaction sites) is 3.625 Å for N1 and 3.894 Å for N2, and to the methyl atom occupying the lipophillic groove the distance is 4.145 Å. The corresponding distances in dHCA are 3.460, 3.878 and 5.212 Å, and those in bHCA are 3.592, 3.777 and 4.913 Å, respectively.

The crystal structure is stabilized by a network of hydrogen bonds, largely mediated by the Cl atoms. Each Cl1 atom bridges three molecules *via* N—H···Cl hydrogen bonds. An intermolecular hydrogen bond is found between sulfonamide atom N2 and atom O1 of the sulfoxide group (Fig. 4); weaker C—H···Cl and C—H···O interactions are also present (Table 2).

Experimental

To obtain crystals suitable for X-ray studies, dorzolamide hydrochloride (Pharmacology Department, IICT, Hyderabad) was dissolved in a methanol–water solution (80:20 *v*/*v*) and the solvents were allowed to evaporate slowly.

Crystal data

$C_{10}H_{17}N_2O_4S_3^+\cdot Cl^-$
M_r = 360.89
Orthorhombic, $P2_12_12_1$
a = 8.1272 (6) Å
b = 10.0646 (8) Å
c = 18.2504 (14) Å
V = 1492.8 (2) Å^3
Z = 4
D_x = 1.606 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.69 mm^{-1}
T = 293 (2) K
Block, colourless
0.19 × 0.14 × 0.11 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
ω scans
10633 measured reflections
2630 independent reflections
2586 reflections with $I > 2\sigma(I)$
R_{int} = 0.025
θ_{max} = 25.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.024
$wR(F^2)$ = 0.065
S = 1.06
2630 reflections
199 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0416P)^2 + 0.2442P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.17 e Å^{-3}
Absolute structure: Flack & Bernardinelli (2000), 1098 Friedel pairs
Flack parameter: −0.01 (6)

Table 1
Selected geometric parameters (Å, °).

S1—O1	1.4333 (16)	S3—O4	1.4193 (17)
S1—O2	1.4345 (16)	S3—O3	1.4312 (16)
S1—C7	1.7440 (19)	S3—N2	1.584 (2)
S1—C6	1.782 (2)	S3—C1	1.7538 (18)
S2—C1	1.7135 (19)		
C7—S1—C6	100.63 (9)	C3—C4—N1	112.42 (15)
C7—S2—C1	89.80 (9)	C8—C6—C5	114.96 (18)
C9—N1—C4	116.06 (16)		
C7—C3—C4—N1	−137.54 (18)	C7—S1—C6—C8	−78.85 (15)

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N1···Cl1^{i}	0.88 (3)	2.48 (2)	3.2088 (17)	139 (2)
N1—H2N1···Cl1	0.87 (3)	2.24 (3)	3.1016 (19)	170 (2)
N2—H1N2···O1^{ii}	0.83 (3)	2.57 (3)	3.197 (3)	133 (3)
N2—H2N2···Cl1^{iii}	0.87 (3)	2.37 (3)	3.215 (3)	165 (3)
C2—H2···Cl1	0.93	2.82	3.672 (2)	152
C9—H9*A*···O4^{iii}	0.97	2.52	3.358 (3)	144

Symmetry codes: (i) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+1$; (ii) $-x+1, y+\frac{1}{2}, -z+\frac{3}{2}$; (iii) $-x+1, y-\frac{1}{2}, -z+\frac{3}{2}$.

H atoms attached to N atoms were located in a difference density map and refined isotropically. All other H atoms were positioned geometrically and treated as riding on their parent C atoms, with C—H distances of 0.93–0.98 Å, and with U_{iso}(H) values of1.5U_{eq}(C) for methyl H atoms and 1.2U_{eq}(C) for the other H atoms. The absolute configuration of the procured material was known in advance and was confirmed by unambiguous refinement of the absolute structure parameter (Flack & Bernardinelli, 2000).

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL/PC* (Sheldrick, 1990), *DIAMOND* (Brandenburg & Putz, 2005) and *MERCURY* (Macrae *et al.*, 2006); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA3036). Services for accessing these data are described at the back of the journal.

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