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Piroxicam* Monohydrate: a Zwitterionic Form, $C_{15}H_{13}N_3O_4S.H_2O$

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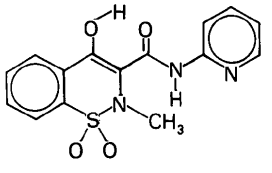
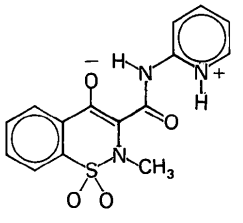
Abstract. $M_r = 349{\cdot}4$, $P\bar{1}$, $a = 12{\cdot}721$ (4), $b = 12{\cdot}909$ (4), $c = 10{\cdot}481$ (3) Å, $\alpha = 99{\cdot}31$ (2), $\beta = 108{\cdot}88$ (2), $\gamma = 102{\cdot}64$ (2)°, $V = 1537{\cdot}9$ (7) Å^3, $Z = 4$, $D_m = 1{\cdot}52$ (aqueous KI), $D_x = 1{\cdot}509$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å, $\mu = 21{\cdot}3$ cm^{-1}, $F(000) = 728$, room temperature, $R = 0{\cdot}057$ (3110 non-zero reflections). Two intramolecular hydrogen bonds are formed by internal rotation of the neutral structure. The side chain and the atoms in the thiazine ring are planar.

Introduction. Piroxicam (Wiseman, Chang & Lombardino, 1976) is a non-steroidal antiinflammatory agent and analgesic which has emerged as an important new agent (Feldene®) in the relief of arthritic symptoms (Brogden, Heel, Spright & Avery, 1981). Its chemical structure (I) was the subject of a recent crystallographic study (Kojić-Prodić & Ružić-Toroš, 1982). Piroxicam also crystallizes, in the presence of water, as a yellow monohydrate whose zwitterionic structure (II) is described in this paper.



(I)



(II)

Experimental. Prismatic crystals (0·47 × 0·45 × 0·55 mm), Syntex $P\bar{1}$, cell dimensions from 15 reflections with $2\theta > 50°$, no absorption corrections, max. $\sin\theta/\lambda = 0{\cdot}5$ Å^{-1}, 3 standard reflections with variation within counter statistics, 3184 reflections collected, 3110 non-zero [$I > 1{\cdot}0\,\sigma(I)$], phase determination by direct methods (*MULTAN*; Germain, Main & Woolfson, 1971), full-matrix least squares minimizing $\sum w(F_o^2-F_c^2)^2$, hydrogens located by difference Fourier techniques except on aromatic carbons (calculated), hydrogen parameters not refined, all non-hydrogen atoms refined anisotropically in single matrix; $R = 0{\cdot}057$, GOF $= [\sum w(F_o^2-F_c^2)^2/(m-s)]^{1/2} = 4{\cdot}13$, $w = 1/\sigma^2(F_o^2)$ based on $\sigma^2(I) = S + \alpha^2(B1 + B2) + (dS)^2$, S is the scan count, $B1$ and $B2$ are the background counts, d is an empirical constant set at 0·02, and α is the scan time to total background time ratio; refinement terminated when calculated shifts $< 0{\cdot}1\sigma$; final difference map had max. $\Delta\rho$ excursions of about 0·7 e Å^{-3}; secondary extinction (Larson, 1967) where $F^2 = (F_c)^2/[1 + g\beta(F_c)^2]$, $g = 6{\cdot}2\ (5) \times 10^{-6}$, atomic scattering factors taken from *International Tables for X-ray Crystallography* (1962), except that for hydrogen which was taken from Stewart, Davidson & Simpson (1965), all calculations facilitated by the *CRYM* system (Duchamp, 1964).†

Discussion. The results of this analysis unambiguously establish that piroxicam monohydrate, unlike the previously reported piroxicam structure, exists in a zwitterionic form, the enolic hydrogen on O(4*B*) having been transferred to pyridine N(13). Internal rotations of the neutral structure occur which result in intramolecular hydrogen bonding between enolate O(4*B*) and the hydrogen on N(11), and between carbonyl O(10) and the hydrogen on pyridine N(13). The two molecules in the asymmetric unit are hydrogen bonded to water molecule one [O(1*W*)] through O(4*B*) of one molecule and O(10) of the other. The second water molecule seems to be in a position to interact with water molecule one, but the distances are rather long for the normal hydrogen bond. Pertinent hydrogen-bond distances are summarized in Table 1. Another notable structural feature of the molecules is the planar nature of the side chain and the atoms in the heterocyclic ring. This planarity is demonstrated in

* Piroxicam is 4-hydroxy-2-methyl-*N*-2-pyridyl-2*H*-1λ^6,2-benzothiazine-3-carboxamide 1,1-dioxide.

† Lists of structure factors, anisotropic thermal parameters, bond distances and angles and H-atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39090 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 2. Coordinates for the non-hydrogen atoms in this structure are presented in Table 3. A stereoscopic view of the molecule and a packing diagram are presented in Figs. 1 and 2 (Johnson, 1965).

Table 1. *Hydrogen-bond distances*

Proton donor	Proton acceptor	Distance (Å) between electronegative atoms
N(11)–H	O(4*B*)	2·589 (4)
N(11′)–H	O(4*B*′)	2·524 (4)
N(13)–H	O(10)	2·651 (4)
N(13′)–H	O(10′)	2·671 (4)
O(1*W*)–H*a*	O(4*B*)	2·773 (4)
O(1*W*)–H*b*	O(10′)^{i}	2·856 (4)
O(2*W*)–H*a*	O(1*W*)^{i}	2·940 (5)
O(2*W*)–H*b*	O(1*W*)^{ii}	2·890 (5)

Symmetry code: (i) $-x+2\cdot0, -y+2\cdot0, -z+2\cdot0$; (ii) $x, y, z+1\cdot0$

Table 2. *Planar portion of the molecules*

Atom	Deviation (Å) from least-squares plane	Atom	Deviation (Å) from least-squares plane
N(2)	−0·096 (3)	N(2′)	0·111 (3)
C(3)	−0·030 (4)	C(3′)	−0·032 (4)
C(4)	−0·042 (4)	C(4′)	−0·055 (4)
O(4*B*)	0·060 (4)	O(4*B*′)	−0·028 (3)
C(9)	0·055 (4)	C(9′)	−0·018 (4)
O(10)	0·079 (4)	O(10′)	0·062 (3)
N(11)	0·110 (3)	N(11′)	−0·072 (3)
C(12)	0·005 (4)	C(12′)	−0·017 (4)
N(13)	−0·052 (3)	N(13′)	−0·139 (4)
C(17)	−0·088 (4)	C(17′)	0·187 (5)

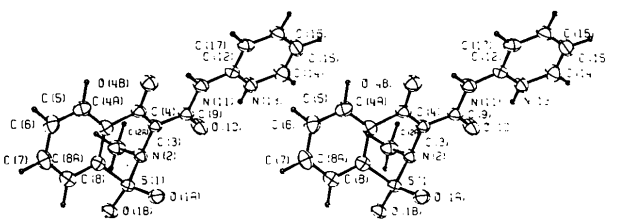

Fig. 1. An *ORTEP* (Johnson, 1965) drawing of the molecule.

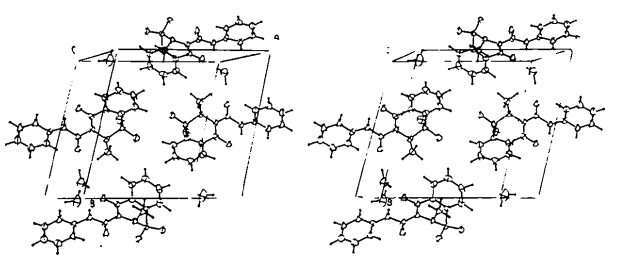

Fig. 2. Packing diagram for the molecule.

Table 3. *Coordinates* ($\times10^4$), *thermal parameters* (Å^2 $\times10^4$) *and their e.s.d.'s*

$U_{eq} = \frac{1}{3}$ trace U.

	x	y	z	U_{eq}
S(1)	4923 (1)	8144 (1)	7797 (1)	322 (6)
O(1*A*)	4949 (2)	7299 (2)	6763 (3)	405 (18)
O(1*B*)	3978 (2)	7942 (2)	8276 (3)	492 (19)
N(2)	6135 (3)	8500 (3)	9136 (3)	328 (20)
C(2*A*)	6150 (4)	9175 (4)	10422 (4)	444 (28)
C(3)	7143 (3)	8861 (3)	8790 (4)	318 (24)
C(4)	7169 (3)	9605 (3)	7963 (4)	337 (25)
C(4*A*)	6112 (4)	9974 (3)	7382 (4)	348 (26)
O(4*B*)	8044 (2)	9991 (2)	7653 (3)	486 (19)
C(5)	6197 (4)	10938 (3)	6940 (4)	419 (28)
C(6)	5228 (4)	11274 (4)	6385 (5)	489 (31)
C(7)	4140 (4)	10646 (4)	6238 (5)	507 (31)
C(8)	4028 (4)	9683 (4)	6658 (4)	400 (28)
C(8*A*)	5002 (3)	9352 (3)	7225 (4)	341 (26)
C(9)	8067 (3)	8408 (3)	9362 (4)	351 (26)
O(10)	8043 (2)	7756 (2)	10108 (3)	534 (20)
N(11)	9033 (3)	8746 (3)	9027 (4)	396 (22)
C(12)	9962 (3)	8333 (3)	9261 (4)	317 (25)
N(13)	10047 (3)	7572 (3)	9992 (3)	404 (22)
C(14)	10928 (4)	7109 (4)	10233 (5)	488 (30)
C(15)	11759 (4)	7404 (4)	9709 (5)	505 (31)
C(16)	11688 (4)	8190 (4)	8931 (5)	459 (30)
C(17)	10806 (4)	8656 (3)	8717 (4)	402 (27)
S(1′)	12192 (1)	5217 (1)	12526 (1)	399 (7)
O(1*A*′)	13364 (3)	5882 (3)	12935 (3)	583 (21)
O(1*B*′)	11539 (3)	4719 (2)	11084 (3)	526 (21)
N(2′)	11480 (3)	5953 (3)	13123 (3)	349 (21)
C(2*A*′)	12143 (4)	6795 (4)	14454 (5)	435 (28)
C(3′)	10339 (3)	5315 (3)	12993 (4)	324 (26)
C(4′)	10214 (4)	4340 (3)	13434 (4)	346 (26)
C(4*A*′)	11202 (4)	3859 (3)	13804 (4)	356 (26)
O(4*B*′)	9268 (2)	3802 (2)	13495 (3)	435 (19)
C(5′)	11148 (4)	3005 (3)	14465 (4)	440 (28)
C(6′)	12021 (4)	2520 (4)	14769 (5)	536 (32)
C(7′)	12984 (4)	2868 (4)	14427 (5)	609 (34)
C(8′)	13060 (4)	3709 (4)	13766 (5)	568 (32)
C(8*A*′)	12171 (4)	4186 (3)	13460 (4)	409 (27)
C(9′)	9431 (3)	5798 (3)	12528 (4)	328 (26)
O(10′)	9531 (2)	6689 (2)	12188 (3)	406 (18)
N(11′)	8372 (3)	5198 (3)	12500 (4)	400 (22)
C(12′)	7370 (3)	5480 (3)	12161 (4)	366 (27)
N(13′)	7249 (3)	6306 (3)	11568 (4)	491 (24)
C(14′)	6271 (4)	6625 (4)	11227 (6)	655 (35)
C(15′)	5367 (4)	6112 (4)	11532 (6)	697 (37)
C(16′)	5446 (4)	5234 (4)	12125 (6)	650 (35)
C(17′)	6431 (4)	4913 (4)	12443 (5)	512 (31)
O(1*W*)	9361 (3)	11060 (3)	6343 (4)	738 (25)
O(2*W*)	8642 (3)	9775 (3)	13517 (4)	879 (29)

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