Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

4-Benzoyloxy-2-methyl-*N*-(2-pyridyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide

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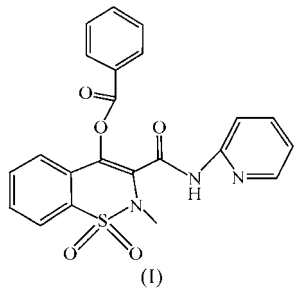
Received 3 April 2006
Accepted 31 May 2006
Online 23 June 2006

The crystal structure of the title compound, $C_{22}H_{17}N_3O_5S$, contains dimers linked by N—H···O hydrogen bonds about inversion centers. The dimers are packed in a herring-bone framework without classical hydrogen bonds between the structure-forming units.

Comment

Piroxicam, 4-hydroxy-2-methyl-*N*-(2-pyridyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide, is a non-steroidal anti-inflammatory and analgesic drug belonging to a new class of compounds called oxicams (Hirai *et al.*, 1997, Khalil *et al.*, 2000). Besides great therapeutic potential, oxicams are very interesting polyfunctional chemical compounds by virtue of their dynamic structural features, which include tautomeric switches and their possible polymorphism (Banerjee & Sarkar, 2002). Piroxicam benzoate, (I), was synthesized by an acylation reaction from piroxicam and benzoyl chloride (Boneschans *et al.*, 2003). This acyl piroxicam derivative proved to be useful in therapy as a non-steroidal anti-inflammatory agent (Lombardino, 1982). Compound (I) has been characterized by elemental analysis, IR spectroscopy, high-performance liquid chromatography (HPLC) and thermal analysis (melting point) (Boneschans *et al.*, 2003; Lombardino, 1982), but its crystal structure has not been solved until now. The structure of a compound of similar composition, namely 4-ethoxy-2-methyl-*N*-(2-pyridyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide, (II), which contains an ethoxy group instead of the benzoyloxy group, was solved by Hammen *et al.* (1989).

We have synthesized piroxicam benzoate according to a modified procedure and have studied the crystalline structure. Single crystals of (I), grown from ethyl acetate, are monoclinic (space group $P2_1/n$, $Z = 4$), with one molecule in the asymmetric unit (Fig. 1). Selected geometric parameters of the molecule are listed in Table 1. The geometric parameters of the piroxicam group in (I) are similar to those in β-piroxicam. The C2—O4 bond length in (I) is the longest among those of



(I)

polymorphs of piroxicam [1.339 (15)–1.350 (9) Å; Kojić-Prodić & Ruzic-Toros, 1982; Reck *et al.*, 1988] or the monohydrate of piroxicam [1.268 (5)–1.279 (5) Å; Bordner *et al.*, 1984; Reck *et al.*, 1988], but is close to that in (II) [1.377 (7) Å; Hammen *et al.*, 1989]. Conversely, the C10—O3 bond length is somewhat shorter than those in other piroxicam-based structures [1.223 (7)–1.262 (10) Å]. Despite the fact that only one O atom of the SO_2 group is involved in hydrogen bonding, the S1—O1 and S1—O2 bond lengths are identical within the limits of experimental error, as is the case for β-piroxicam (Kojić-Prodić & Ruzic-Toros, 1982). In piroxicam monohydrate and (II), these lengths differ from one another, and the greatest difference is found in α-piroxicam [1.465 (14) and 1.406 (10) Å; Reck *et al.*, 1988]. There are remarkable differences in the C2—C1—C10—O3 torsion angle (Table 1). This angle is about −177° in piroxicam monohydrate and (II), but 6.0 (5) and 1 (2)° in β- and α-piroxicam, respectively. In piroxicam benzoate, atom O3 is on the same side of the molecule as atom O4, but the N2—H2 group is on the opposite side. This fact is very important, because atom N2 is involved in hydrogen bonding. The angle between the planes of the C3–C8 and C17–C22 rings in (I) is 53.3 (1)°.

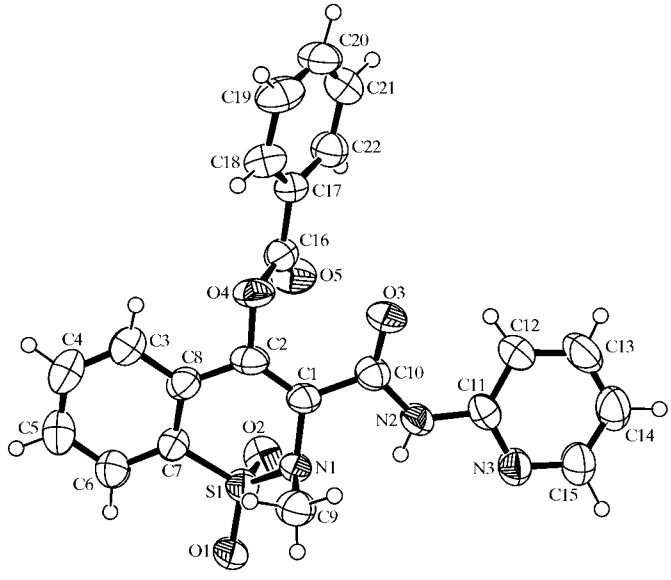


Figure 1
A view of piroxicam benzoate, showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

 DOI: 10.1107/S0108270106020567

The molecules of (I) are linked together by paired N—H···O hydrogen bonds (Table 2), forming a centrosymmetric $R_2^2(14)$ dimer (Fig. 2). Similar dimers are observed in β-piroxicam. The structure of α-piroxicam is formed by uncoupled molecules. There is an infinite three-dimensional framework of N—H···O and C—H···O hydrogen bonds in piroxicam monohydrate, with water molecules playing an important role in bonding. In turn, in (II), there are no conventional hydrogen bonds, only intramolecular N—H···O ones.

The molecules in (I) are linked into a three-dimensional framework by C—H···O bonds, in which atom O5 accepts bonds from the C5—H5 group of the benzyl ring and the C13—H13 group of the pyridine ring in two neighboring molecules (Fig. 3 and Table 2). The molecules are packed in a herring-bone structure, with O5 as the site of junction.

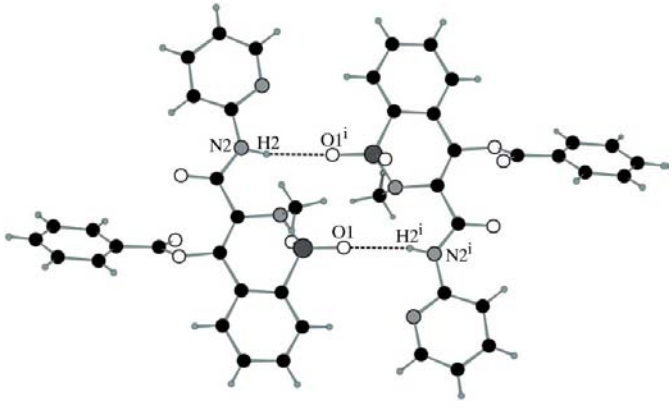


Figure 2
The dimer of piroxicam benzoate, with dashed lines indicating hydrogen bonds. [Symmetry code: (i) $-x+1, -y+1, -z$.]

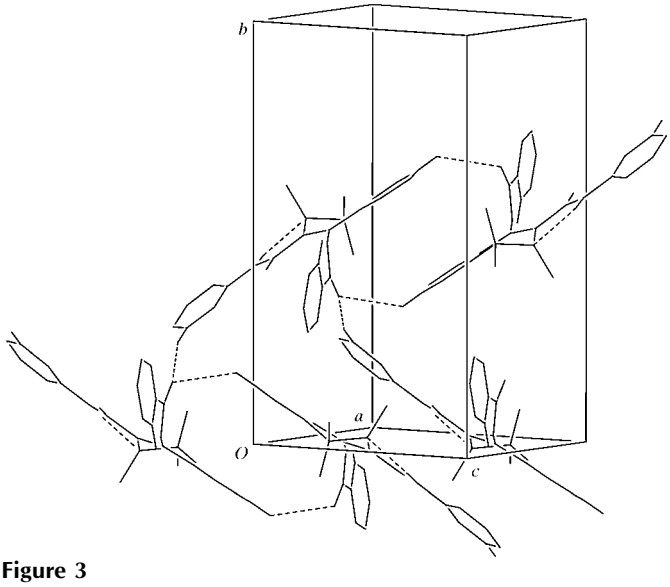


Figure 3
Part of the crystal structure of piroxicam benzoate. The molecules are packed in a herring-bone structure, with atom O5 as the site of junction. [Symmetry codes: (ii) $-x+1, -y+1, -z+1$; (iii) $x-\frac{1}{2}, -y+\frac{1}{2}, z-\frac{1}{2}$.]

Among the remaining short distances between atoms belonging to different molecules, the C—H···N contacts involving atom N3 of the pyridine ring are very interesting. This atom appears to be the site of a junction between three molecules. The C21—H21 group in the molecule at $(\frac{1}{2}+x, \frac{1}{2}-y, -\frac{1}{2}+z)$ [symmetry code (iv)] is at a C21^{iv}···N3 distance of 3.439 (5) Å (H21^{iv}···N3 = 2.68 Å and C21^{iv}—H21^{iv}···N3 = 139°), and the C18—H18 group in the molecule at $(-x, 1-y, -z)$ [symmetry code (v)] is at a C18^{v}···N3 distance of 3.434 (4) Å (H18^{v}···N3 = 2.69 Å and C18^{v}—H18^{v}···N3 = 138°). The parameters of the C—H···N contacts are identical within the limits of experimental errors, but they are not related to one another *via* symmetry. The C—H···N contacts form an infinite two-dimensional-framework.

Experimental

A solution of benzoyl chloride (0.4 ml, 3.0 mmol) in CCl_4 (5.0 ml) and a solution of triethylamine (0.6 ml, 4.5 mmol) in CCl_4 (5.0 ml) were simultaneously added dropwise to a suspension of piroxicam (0.99 g, 3.0 mmol) in dry CCl_4 (9.0 ml) under a nitrogen atmosphere while cooling in an ice bath. The mixture was then stirred at room temperature under a nitrogen atmosphere for 5 h. The solvent was evaporated *in vacuo* and the residue was treated according to a standard procedure to obtain the crude product (1.27 g, 86% purity, HPLC). The product was recrystallized from ethyl acetate to give pure (I) [m.p. 421–423 K; literature 418–421 K (Boneschans *et al.*, 2003)].

Crystal data

$C_{22}H_{17}N_3O_5S$
M_r = 435.46
Monoclinic, $P2_1/n$
a = 11.106 (3) Å
b = 16.5606 (16) Å
c = 12.0351 (18) Å
β = 111.463 (12)°
V = 2060.0 (7) Å^3
Z = 4
D_x = 1.404 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.20 mm^{-1}
T = 295 (3) K
Block, colorless
0.42 × 0.34 × 0.23 mm

Data collection

Stoe Stadi-4 four-circle diffractometer
ω scans
Absorption correction: ψ scan (*X-RED*; Stoe & Cie, 1997)
T_{min} = 0.900, T_{max} = 0.956
9810 measured reflections
4717 independent reflections
2544 reflections with $I > 2\sigma(I)$
R_{int} = 0.055
θ_{max} = 27.5°
3 standard reflections
frequency: 180 min
intensity decay: 3.8%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.062
$wR(F^2)$ = 0.135
S = 1.09
4717 reflections
331 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0353P)^2 + 0.7359P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}

All H atoms were located in a difference Fourier synthesis and then treated as riding atoms, with C—H distances of 0.93 (aromatic) and 0.96 Å (CH_3), an N—H distance of 0.86 Å, and U_{iso}(H) values of $1.2U_{eq}$(C,N) or $1.5U_{eq}$(methyl C).

Table 1
Selected geometric parameters (Å, °).

C2—O4	1.388 (3)	N1—S1	1.639 (2)
C10—O3	1.216 (3)	O1—S1	1.425 (2)
C16—O5	1.196 (3)	O2—S1	1.424 (2)
C16—O4	1.366 (3)		
C16—O4—C2	118.9 (2)	N1—S1—C7	101.29 (13)
O2—S1—O1	120.03 (14)		
C2—C1—C10—O3	12.9 (5)	C1—C2—O4—C16	71.3 (4)
C1—C10—N2—C11	177.9 (3)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2···O1^{i}	0.86	2.47	3.275 (3)	157
C5—H5···O5^{ii}	0.93	2.54	3.244 (5)	132
C13—H13···O5^{iii}	0.93	2.34	3.240 (4)	163

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

Data collection: *STADI4* (Stoe & Cie, 1997); cell refinement: *STADI4*; data reduction: *X-RED* (Stoe & Cie, 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997), *PowderCell* (Kraus & Nolze, 1999) and *MERCURY* (Macrae *et al.*, 2006); software used to prepare material for publication: *WinGX* (Farrugia, 1999), *SHELXL97* and *X-RED*.

This study was supported by two grants from BRHE (Nos. NO-008-X1 and Y3-C-08-01) and grant No. 2.2.2.3.2007 from the Russian Ministry of Education and Science.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: AV3014). Services for accessing these data are described at the back of the journal.

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