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7-Iodo-3-isopropylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxide

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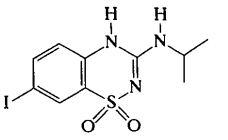
Abstract

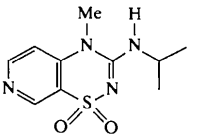
The title compound, $C_{10}H_{12}IN_3O_2S$, belongs to a new family of heterocyclic drugs developed as putative pancreatic B-cell ATP-sensitive potassium-channel openers. The crystal structure is compared with that of 3-isopropylamino-4-methyl-4*H*-pyrido[4,3-*e*][1,2,4]thiadiazine 1,1-dioxide and 3-isopropylamino-4*H*-pyrido-[4,3-*e*][1,2,4]thiadiazine 1,1-dioxide. The title compound adopts the 4*H*-tautomeric form, as in the corresponding pyridinic class of compounds.

Comment

7-Iodo-3-isopropylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxide, (I), is an example of a new family of heterocyclic drugs, the 3-alkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxides, structurally related to 3-alkylamino-4*H*-pyrido[4,3-*e*][1,2,4]thiadiazine 1,1-dioxides. The latter have been reported as powerful pancreatic B-cell ATP-sensitive potassium-channel (K_{ATP} channel) openers (Pirotte *et al.*, 1993, 1994; de Tullio *et al.*, 1996; Lebrun *et al.*, 1996). They are of great therapeutic interest as substitutes of diazoxide (7-chloro-3-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide) in the treatment of some pancreatic disorders characterized by an excess of insulin secretion. The 7-iodo-substituted compound was prepared in order to have a potential pharmacological tool for studying the K_{ATP} channels. Further work will investigate the possibility of labelling the 7-position of the heterocycle with a radioactive I atom.



(I)



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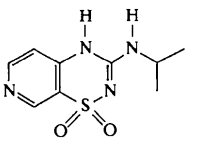

(III)

The crystallographic study of (I) should help the structural comparison of 3-alkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxides with their isosteric pyridines, for instance, with the structures of 3-isopropylamino-4-methyl-4*H*-pyrido[4,3-*e*][1,2,4]thiadiazine 1,1-dioxide [(II); Dupont *et al.*, 1996] and 3-isopropylamino-4*H*-pyrido[4,3-*e*][1,2,4]thiadiazine 1,1-dioxide [(III); de Tullio *et al.*, 1996]. In (II), a typical 4*H*-tautomeric form results from the presence of the methyl substituent at the 4-position of the thiadiazine 1,1-dioxide ring. The C3—N4 [1.381 (4) Å] and C3—N2 [1.326 (4) Å] distances in (II) are useful references with respect to C—N double- and single-bond length in such a ring system. The corresponding distances in (I) [1.367 (8) and 1.334 (9) Å] and (III) [1.366 (4) and 1.315 (4) Å] lead to the conclusion that the 4*H*-tautomeric form is also favoured in the crystalline state for that example of a benzothiadiazine 1,1-dioxide. It agrees with previous results observed in diazoxide (Bandoli & Nicolini, 1977). This is confirmed by the hydrogen-bonding scheme, which includes N4—H4 in (I) and (III). Moreover, there is no close intermolecular contact including N2 in the three crystal structures. The distance between H(C12) and a hypothetical H(N2) atom [2.12 and 2.14 Å in (I) and (III), respectively]

would have values of about double the H-atom van der Waals radius. In (I), as in the two other structures, N11—H11 participates in an intermolecular hydrogen bond.

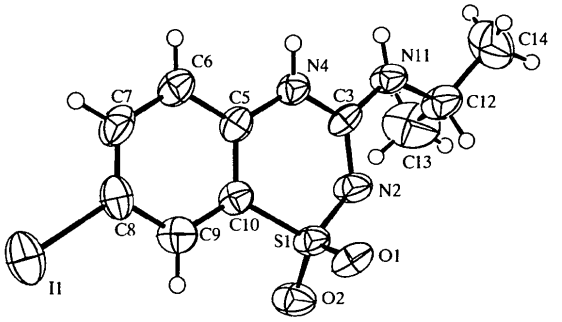

Fig. 1. The molecular structure of (I) with the atom-labelling scheme. Displacement ellipsoids are shown at 50% probability levels and H atoms are drawn as small circles of an arbitrary radius.

Experimental

The title compound was synthesized at the Laboratory of Medicinal Chemistry of Liège. Crystals were obtained by slow evaporation of a methanol solution at room temperature.

Crystal data

$C_{10}H_{12}IN_3O_2S$
M_r = 365.19
Monoclinic
$P2_1/n$
a = 6.6557 (8) Å
b = 20.988 (3) Å
c = 9.5188 (15) Å
β = 95.473 (14)°
V = 1323.6 (3) Å^3
Z = 4
D_x = 1.833 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54180 Å
Cell parameters from 38 reflections
θ = 20.28–26.29°
μ = 20.460 mm^{-1}
T = 293 (2) K
Prismatic
0.46 × 0.34 × 0.30 mm
Colourless

Data collection

Stoe–Siemens AED four-circle diffractometer
ω scans
Absorption correction: semi-empirical *via* ψ scans (*EMPIR*; Stoe & Cie, 1988*a*)
T_{min} = 0.038, T_{max} = 0.064
2534 measured reflections
2326 independent reflections

1402 reflections with $I > 2\sigma(I)$
R_{int} = 0.061
θ_{max} = 67.97°
$h = -7 \rightarrow 0$
$k = 0 \rightarrow 25$
$l = -11 \rightarrow 11$
2 standard reflections
frequency: 60 min
intensity decay: 5.0%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.051
$wR(F^2)$ = 0.141
S = 0.926
2326 reflections
163 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.093P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$

$\Delta\rho_{max}$ = 1.095 e Å^{-3} (0.96 Å from I1)
$\Delta\rho_{min}$ = −0.968 e Å^{-3} (0.79 Å from I1)
Extinction correction: *SHELXL*97 (Sheldrick, 1997*a*)
Extinction coefficient: 0.0017 (2)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

I1—C8	2.094 (7)	C3—N4	1.367 (8)
S1—N2	1.573 (6)	N4—H4	0.88 (2)
N2—C3	1.334 (9)	N11—H11	0.86 (2)
C3—N11	1.324 (10)		
C3—N2—S1	121.8 (5)	C3—N4—H4	121 (5)
N11—C3—N2	119.1 (6)	C5—N4—H4	115 (5)
N11—C3—N4	117.3 (6)	C3—N11—C12	124.1 (6)
N2—C3—N4	123.7 (7)	C3—N11—H11	121 (6)
C3—N4—C5	124.2 (6)	C12—N11—H11	114 (6)
C10—S1—N2—C3	24.6 (7)	N2—C3—N4—C5	−11.2 (11)
S1—N2—C3—N11	169.0 (6)	N2—C3—N11—C12	3.8 (12)
S1—N2—C3—N4	−11.1 (10)		

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N4—H4···O1^{i}	0.88 (2)	2.27 (5)	3.025 (8)	144 (7)
N4—H4···O1^{ii}	0.88 (2)	2.62 (6)	3.276 (8)	133 (6)
N11—H11···O1^{ii}	0.86 (2)	2.08 (3)	2.909 (8)	161 (8)

Symmetry codes: (i) $1-x, 2-y, -z$; (ii) $1+x, y, z$.

H atoms were allowed to ride on their parent atoms, with isotropic displacement parameters fixed at $1.2U_{eq}$ of the parent atom ($1.5U_{eq}$ for the methyl-H atoms), except for the H4 and H11 atoms, the positions of which were refined with N—H distances restrained to 0.87 (2) Å.

Data collection: *DIF*4 (Stoe & Cie, 1988*b*). Cell refinement: *DIF*4. Data reduction: *REDU*4 (Stoe & Cie, 1988*c*). Program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997*b*). Program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997*a*). Molecular graphics: *ORTEP*III (Burnett & Johnson, 1996). Software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GS1034). Services for accessing these data are described at the back of the journal.

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(*Z*)-*N*-Benzyl-2,3-dihydro-2-(2-methoxybenzylidene)-4*H*-1,4-benzoxazine

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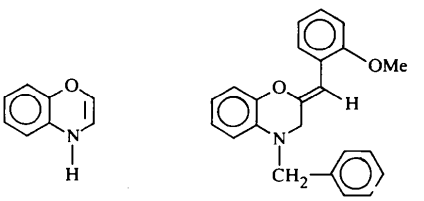
Abstract

In the title compound, $C_{23}H_{21}NO_2$, the molecule contains three essentially planar benzo rings (*A*, *B* and *C*) and displays the *Z*-configuration. The six-membered oxazine ring adopts a half-boat conformation and is fused to phenyl ring *A*. The dihedral angle between the planar part of the oxazine moiety and ring *A* is 4.70 (6)°. A strong conjugation effect is reflected in the C—O [1.377 (3)–1.385 (3) Å] and C—N [1.396 (2) Å] bond lengths.

Comment

Benzoxazine, (1), a heterocyclic ring system, is present in many natural products (Sainsbury, 1984). Substituted benzoxazines have attracted considerable attention for their therapeutic, antioxidant and stabilizing activities (Abood *et al.*, 1997; Mylari *et al.*, 1990; Palmer *et al.*, 1988). As part of our on-going study of heterocyclic systems of biological importance (Chaudhuri *et al.*, 1998; Khan *et al.*, 1998), we have synthesized the title compound, (2), *via* a palladium-catalysed reaction between 2-methoxyiodobenzene and 2-(*N*-benzyl-*N*-prop-2-ynyl)aminophenyl tosylate. The present X-ray structural study of (2) was undertaken in order to establish the regio- and stereoselectivities of the reaction.



(1) (2)

The structure of (2) contains discrete molecules separated by normal van der Waals distances. The molecular dimensions (Table 1) are comparable with those in related structures (Chamontin *et al.*, 1998; Lubini & Wouters, 1996; Millini *et al.*, 1993).

The *Z*-configuration of the molecule, with a methoxyphenyl group on the Csp^2 atom of the oxazine ring, is established by the C7—C8—C9—O1 torsion angle of −1.8 (3)°. The three aromatic rings *A* (C11–C16), *B* (C2–C7) and *C* (C18–C23) exhibit the expected planar geometries, with a maximum deviation of 0.007 (3) Å for an in-plane atom (C22) from the corresponding least-squares plane through the endocyclic atoms. The dihedral angles *A*/*B*, *A*/*C* and *B*/*C* are 23.95 (6), 84.82 (6) and 102.54 (6)°, respectively. The six-membered heterocyclic ring (C9, C10, N, C16, C11 and O1) adopts an approximately half-boat conformation and is fused to the phenyl ring *A*. Atoms C10 and C11 lie on the same side of the best plane through C9, O1, C16 and N, with displacements of 0.606 (2) and 0.082 (2) Å, respectively.

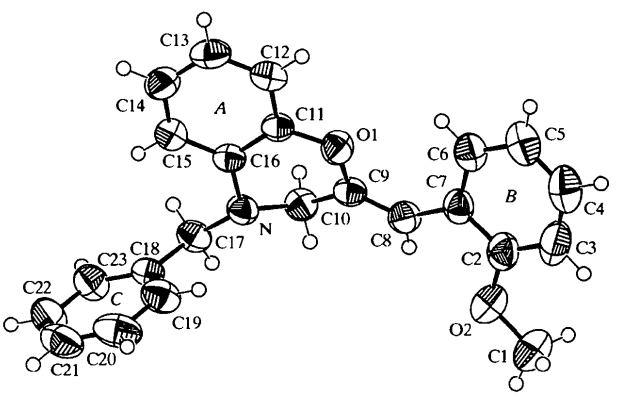


Fig. 1. *ORTEP*II (Johnson, 1976) view of molecule (2). Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of an arbitrary radius.