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3-Isopropylamino-7-nitro-1,4,2-benzodithiazine 1,1-dioxide

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.005 Å
R factor = 0.052
wR factor = 0.156
Data-to-parameter ratio = 13.0

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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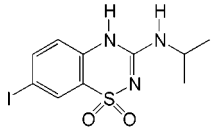
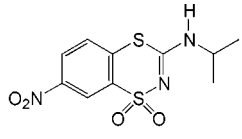
The crystal structure of the title compound, $C_{10}H_{11}N_3O_4S_2$, an inactive dithiazine analogue of 3-alkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxides that are known to be pancreatic B-cell selective K_{ATP} channel openers, reveals that the exocyclic NH group and the alkyl chain are oriented in the same spatial direction as in the active thiadiazine derivatives. The lack of activity is probably the result of the replacement of the NH group in the 4-position by an S atom. The crystal packing involves one N—H···O hydrogen bond.

Comment

3-Alkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxides such as 3-isopropylamino-7-iodo-4*H*-1,2,4-benzothiadiazine 1,1-dioxide, (I) (Dupont *et al.*, 1999), are known to be ATP-sensitive potassium channel openers. According to the position of the double bond in the thiadiazine ring and the spatial orientation adopted by the alkyl chain, these compounds may exist in multiple tautomeric forms. Such a structural parameter is important for biological activity, since the conformation required for activity is found to be the tautomeric form for which the two NH groups (the ring NH group in the 4-position and the exocyclic NH group in the 3-position) are oriented in the same direction. This conformation forces the alkyl chain to adopt its particular position in space [as shown in (I)]. Previous crystallographic studies also showed that the double bond in the thiadiazine ring is always located between positions 2 and 3 (4*H*-tautomer), rather than between positions 3 and 4 (2*H*-tautomer).



(I)



(II)

In order to study the impact of the replacement of the NH group in the 4-position by a sulfur bridge on the geometry and the biological activity of the molecule, 3-isopropylamino-7-nitro-1,4,2-benzodithiazine 1,1-dioxide (II) was synthesized. The C3—N2 and C3—N11 distances [1.315 (3) and 1.318 (4) Å, respectively] (Fig. 1), the geometry of the N11—H11···O2^{i} [symmetry code: (i) 1 + *x*, *y*, *z*; Table 2] hydrogen bond, and the lack of involvement of N2 in any close intermolecular contact, confirm the predominance, in the crystalline state, of tautomeric form (II). It must be emphasized that the H11, attached to N11, was located by Fourier difference synthesis, and included in the refinement without constraints.

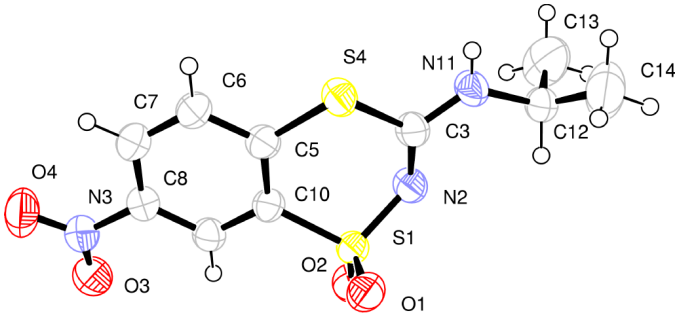


Figure 1
The molecular structure of (II), with the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are drawn as small circles of arbitrary radius.

The crystallographic study demonstrates that the conformation adopted by 3-alkylamino-1,4,2-benzodithiazine 1,1-dioxides [such as (II)] is comparable to that previously described for 3-alkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxides [such as (I)]. However, (II) is inactive as a potassium channel opener. Such a result indicates that, even if the alkyl chain of the new drug adopts the correct position, the presence of an NH group in the 4-position is also required for activity.

Experimental

The title compound was obtained in one step from 2-chloro-5-nitrobenzenesulfonamide, by reacting the latter with isothiocyanate in acetone, in the presence of a base (detailed synthetic procedure, to be published elsewhere). A single crystal was obtained by slow evaporation of a methanol solution.

Crystal data

$C_{10}H_{11}N_3O_4S_2$
M_r = 301.34
Monoclinic, $P2_1/n$
a = 7.4143 (7) Å
b = 21.461 (4) Å
c = 8.3958 (11) Å
β = 101.840 (12)°
V = 1307.5 (3) Å^3
Z = 4
D_x = 1.531 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 31 reflections
θ = 34.1–41.5°
μ = 3.85 mm^{-1}
T = 293 (2) K
Prism, colourless
0.68 × 0.53 × 0.34 mm

Data collection

Stoe–Siemens AED four-circle diffractometer
ω scans
Absorption correction: ψ scan (*EMPIR*; Stoe & Cie, 1987)
T_{min} = 0.137, T_{max} = 0.270
2498 measured reflections
2317 independent reflections
1955 reflections with $I > 2\sigma(I)$
R_{int} = 0.044
θ_{max} = 67.9°
$h = -8 \rightarrow 0$
$k = 0 \rightarrow 25$
$l = -9 \rightarrow 10$
2 standard reflections
frequency: 60 min
intensity decay: 10%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.052
$wR(F^2)$ = 0.156
S = 1.08
2317 reflections
178 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.1169P)^2 + 0.1969P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.44 e Å^{-3}
$\Delta\rho_{min}$ = −0.57 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0102 (13)

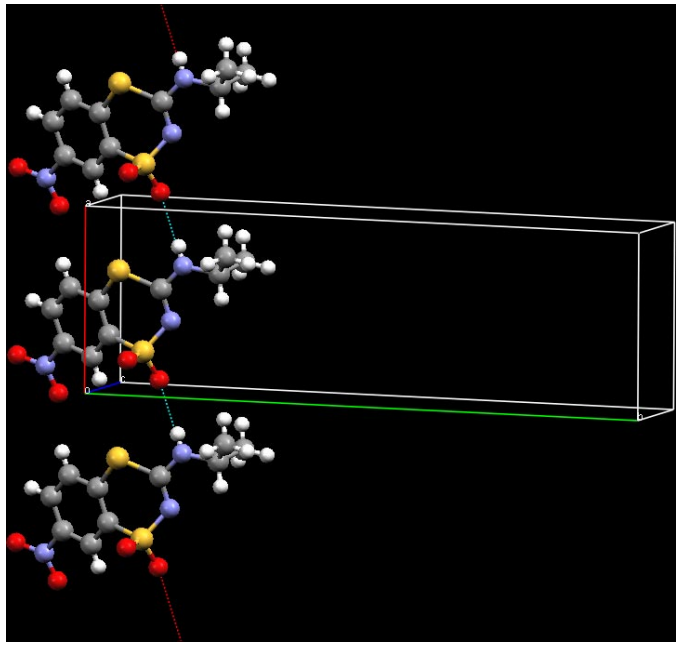


Figure 2
MERCURY (Bruno *et al.*, 2002) view of the packing of (II), showing the hydrogen-bonding scheme.

Table 1
Selected geometric parameters (Å, °).

S1—N2	1.595 (2)	C8—N3	1.462 (4)
S1—C10	1.765 (3)	N11—C12	1.475 (4)
N2—C3	1.315 (3)	N11—H11	0.77 (4)
C3—N11	1.318 (4)	N3—O3	1.217 (4)
C3—S4	1.774 (3)	N3—O4	1.226 (4)
S4—C5	1.757 (3)		
N2—S1—C10	106.26 (12)	N11—C3—S4	111.6 (2)
C3—N2—S1	121.10 (19)	C5—S4—C3	102.69 (13)
N2—C3—N11	121.7 (3)	C3—N11—C12	125.3 (3)
N2—C3—S4	126.7 (2)		
C10—S1—N2—C3	47.4 (3)	N11—C3—S4—C5	163.1 (2)
S1—N2—C3—N11	159.7 (2)	N2—C3—N11—C12	−7.5 (5)
S1—N2—C3—S4	−20.5 (4)	C3—N11—C12—C14	−134.7 (4)
N2—C3—S4—C5	−16.7 (3)	C3—N11—C12—C13	101.2 (4)

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

D—H···A	D—H	H···A	D···A	D—H···A
N11—H11···O2^{i}	0.77 (4)	2.19 (4)	2.957 (3)	175 (4)

Symmetry code: (i) $1 + x, y, z$.

H atoms were constrained (included as riding atoms), except for the H atom on N11, which was freely refined, with isotropic displacement parameters fixed at $1.2U_{eq}$ of the parent atom ($1.5U_{eq}$ for methyl H atoms).

Data collection: *DIF*4 (Stoe & Cie, 1987); cell refinement: *DIF*4; data reduction: *REDU*4 (Stoe & Cie, 1987); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Burnett & Johnson, 1996); software used to prepare material for publication: *SHELXL*97.

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