Table 1. *Fractional atomic coordinates and equivalent isotropic thermal parameters* (Å^2)

$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
S1	0.0606 (1)	0.9747 (1)	0.1036 (1)	0.0446 (5)
O1	0.2625 (3)	1.0043 (4)	0.1195 (1)	0.059 (2)
O2	−0.3423 (4)	0.9542 (3)	0.1068 (1)	0.047 (1)
O3	−0.0605 (4)	0.8572 (4)	0.2325 (1)	0.052 (2)
C1	0.0638 (5)	0.7695 (4)	0.0723 (1)	0.040 (2)
C2	0.1624 (5)	0.6231 (5)	0.0890 (1)	0.046 (2)
C3	0.1690 (5)	0.4697 (6)	0.0631 (1)	0.047 (2)
C4	0.0792 (5)	0.4613 (6)	0.0202 (1)	0.046 (2)
C5	−0.0170 (6)	0.6087 (7)	0.0053 (1)	0.053 (2)
C6	−0.0255 (6)	0.7626 (6)	0.0303 (1)	0.050 (2)
C7	0.0943 (9)	0.2954 (8)	−0.0089 (2)	0.069 (3)
C8	−0.0694 (5)	0.9065 (4)	0.1538 (1)	0.037 (2)
C9	−0.2866 (5)	0.8912 (5)	0.1505 (1)	0.036 (2)
C10	−0.3618 (5)	0.7053 (4)	0.1597 (1)	0.034 (2)
C11	−0.4812 (5)	0.6749 (5)	0.1967 (1)	0.040 (2)
C12	−0.5620 (6)	0.5106 (5)	0.2042 (1)	0.052 (2)
C13	−0.5226 (6)	0.3713 (6)	0.1745 (2)	0.057 (3)
C14	−0.4025 (6)	0.4003 (6)	0.1374 (1)	0.053 (2)
C15	−0.3238 (5)	0.5653 (5)	0.1303 (1)	0.045 (2)
C16	0.0287 (5)	0.8948 (5)	0.1925 (1)	0.044 (2)
C17	0.0577 (9)	0.8626 (8)	0.2727 (2)	0.063 (3)

Table 2. *Geometric parameters* (Å, °)

S1—O1	1.506 (2)	C16—O3	1.351 (4)
S1—C1	1.794 (4)	O3—C17	1.434 (7)
S1—C8	1.797 (3)	C8—C9	1.530 (5)
C1—C2	1.389 (5)	C9—O2	1.412 (4)
C2—C3	1.380 (5)	C9—C10	1.520 (5)
C3—C4	1.398 (4)	C10—C11	1.383 (5)
C4—C5	1.371 (6)	C11—C12	1.378 (5)
C5—C6	1.370 (6)	C12—C13	1.387 (6)
C6—C1	1.374 (5)	C13—C14	1.386 (6)
C4—C7	1.513 (7)	C14—C15	1.375 (6)
C8—C16	1.322 (4)	C15—C10	1.382 (5)
O1—S1—C1	105.8 (2)	C9—C8—C16	124.5 (3)
S1—C1—C6	118.6 (3)	C8—C16—O3	120.4 (3)
S1—C1—C2	120.8 (2)	C16—O3—C17	115.4 (3)
C1—C2—C3	119.3 (3)	C8—C9—O2	107.8 (3)
C2—C3—C4	120.7 (4)	O2—C9—C10	111.8 (3)
C4—C5—C6	122.6 (3)	C8—C9—C10	113.8 (3)
C5—C6—C1	119.0 (4)	C9—C10—C15	121.8 (3)
C6—C1—C2	120.5 (3)	C9—C10—C11	120.0 (3)
C3—C4—C7	120.5 (4)	C10—C11—C12	121.4 (3)
C7—C4—C5	121.7 (3)	C11—C12—C13	119.9 (3)
C5—C4—C3	117.9 (4)	C12—C13—C14	119.1 (4)
O1—S1—C8	105.0 (2)	C13—C14—C15	120.1 (4)
S1—C8—C16	116.6 (3)	C14—C15—C10	121.4 (3)
S1—C8—C9	118.4 (2)		

A colorless parallelepipedic crystal, obtained by slow evaporation at room temperature of a pentane/ether solution, was isolated. Its quality was tested with Laue photographs.

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Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55782 (13 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: PA1027]

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Structure of 5-Amino-1,3,4-thiadiazole-2-sulfonamide, an Inhibitor of the Enzyme Carbonic Anhydrase

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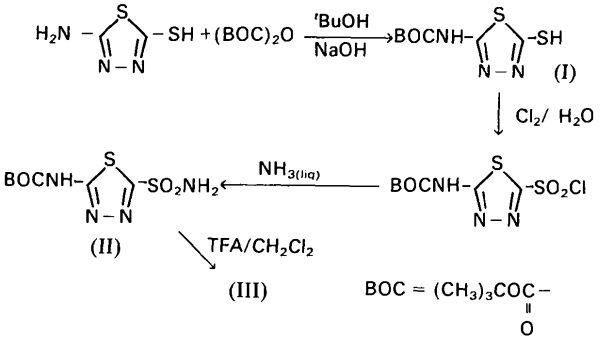
Abstract

Bond lengths and angles indicate a strong interaction between the NH_2 group and the thiadiazole ring. The sulfonamido moiety adopts a distorted arrangement around the S atom. Structural features of the compound are compared with those of acetazolamide, *N*-[5-sulfamoyl-1,3,4-thiadiazol-2(3*H*)-ylidene]-acetamide (H_2acm), methazolamide, *N*-[3-methyl-5-sulfamoyl-1,3,4-thiadiazol-2(3*H*)-ylidene]acetamide (Hmacm), and 5-amino-1,3,4-thiadiazole-2-thiol (Hatm).

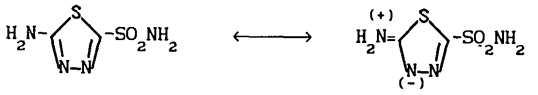
Comment

The success of *N*-[5-sulfamoyl-1,3,4-thiadiazole-2(3*H*)-ylidene]acetamide (H_2acm) as a therapeutically effective inhibitor of the enzyme carbonic anhydrase has encouraged further synthesis of structural variants so that the effects of these changes on inhibitory activity and pharmacological properties may be studied. This work has been undertaken as part of our program of systematic studies of unsubstituted sulfonamides and their metal complexes (Alzuet, Ferrer & Borrás, 1991*a*). The effect of the substituent on the molecular geometry may give an insight into the biological activity and coordination properties of these compounds.

The synthesis of 5-amino-1,3,4-thiadiazole-2-sulfonamide (Hats) was originally described by Roblin & Clapp (1950). We have obtained Hats by a different method, following that published by Young, Wood, Eichler, Vaughan & Anderson (1956) for other 1,3,4-thiadiazolesulfonamides.



The heterocyclic ring is planar within experimental error and the endocyclic bond length C(2)—N(2), 1.283 (2) Å, clearly indicates a double bond. N(3) is displaced by 0.071 (2) Å out of the plane of the ring, but the distances C(1)—N(1) and C(1)—N(3), 1.317 (2) and 1.333 (2) Å, respectively, indicate delocalization of electron density over these three atomic centers (Allen, Kennard, Watson, Brammer, Orpen & Taylor, 1987) consistent with two possible tautomeric forms in the molecule:



The large deviation of the bond angles in the ring from the 120° usually found in trigonal planar arrangements is common in five-membered rings (Downie, Harrison & Raper, 1972).

S(2) lies in the ring plane, with a displacement of −0.002 (1) Å, and has a distorted tetrahedral environment. The significant widening of the O—S—O angle from its ideal tetrahedral value is the result of non-bonding interactions between the short S—O bonds (Cotton & Stokley, 1970). Bond lengths S(2)—O(1) and S(2)—O(2) are comparable to the values quoted for H_2acm (Mathew & Palenick, 1974) and Hmacm (Alzuet, Ferrer & Borrás, 1991*b*). The S(2)—O(1) distance is slightly longer than that for S(2)—O(2), which may be a consequence of the stronger hydrogen bond involving the O(1) atom. The S—N bond length of 1.569 (2) Å (N being pyramidal and the disposition of the nitrogen lone pair being roughly in the C—S—N plane) suggests an interaction of the nitrogen lone pair with the 3*d*

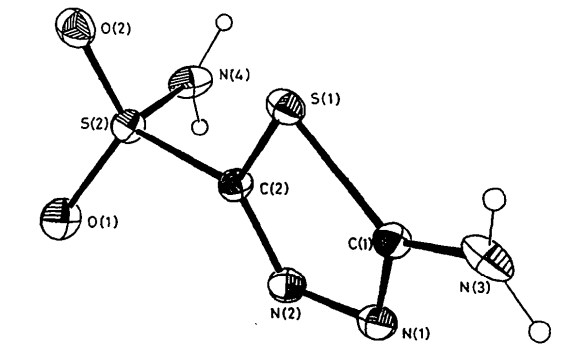


Fig. 1. *ORTEP* (Johnson, 1965) diagram showing a view of the compound and the atomic numbering scheme.

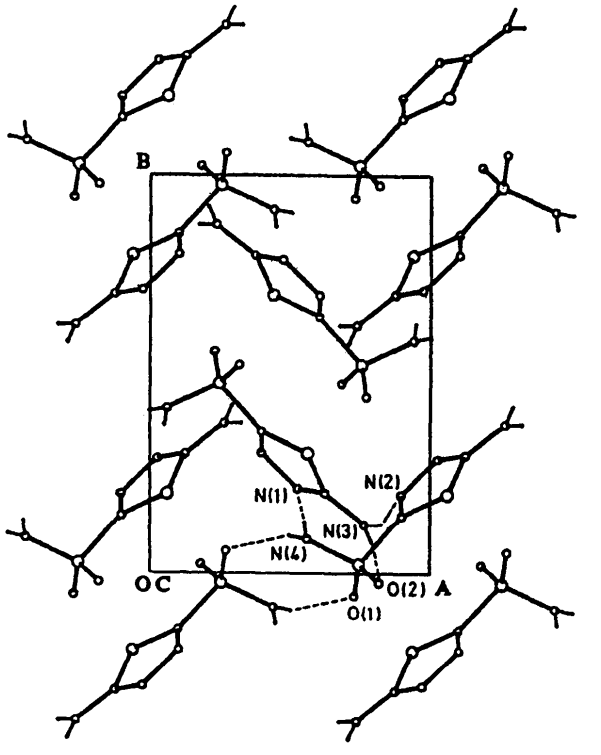


Fig. 2. *PLUTO* (Motherwell & Clegg, 1978) diagram showing the crystallographic packing along the *z* axis.

orbitals of sulfur [$(d$–$p)$–π overlap] (Bindal, Golab & Katzenellenbogen, 1990).

Table 3 contains a selected comparison of dimensions of the thiadiazole ring found in this study with relevant values from other investigations. The agreement generally in bond distances and angles is better for the sulfonamides than with Hatm. If an interaction between the thiadiazole ring and the acetamido groups in H_2acm and Hmacm similar to that between the NH_2 and the heterocycle in Hatm is assumed, the difference of Hatm with respect to the 1,3,4-thiadiazolesulfonamide derivatives can be explained by the π delocalization between the SH group and the ring, something which is not possible in the SO_2NH_2 group because of its tetrahedral geometry.

Probable hydrogen bonds (Fig. 2) are indicated by broken lines. The crystal structure is stabilized by an intricate network of intermolecular hydrogen bonds. The H atoms attached to N(4) form hydrogen bonds N(4)—H(41)···N(1) and N(4)—H(42)···O(1) with distances of 2.842 (2) and 2.949 (2) Å, respectively. The H atoms attached to N(3) form hydrogen bonds N(3)—H(31)···O(2) and N(3)—H(32)···N(2) with distances of 3.167 (2) and 3.028 (2) Å, respectively (Table 3).

Experimental

Crystal data

$C_2H_4N_4O_2S_2$
M_r = 180.19
Monoclinic
$P2_1/n$
a = 7.5160 (2) Å
b = 10.536 (2) Å
c = 8.342 (2) Å
β = 95.69 (1)°
V = 657.4 (2) Å^3
Z = 4
D_x = 1.81 Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 20–24°
μ = 72.0 mm^{-1}
T = 293 K
Prismatic
0.42 × 0.2 × 0.2 mm
Colorless

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: empirical
T_{min} = 0.63, T_{max} = 1.20
4064 measured reflections
1911 independent reflections
1580 observed reflections [$I>3\sigma(I)$]
R_{int} = 0.018
θ_{max} = 25°
h = −10 → 10
k = −14 → 14
l = 0 → 11
3 standard reflections
frequency: 60 min
intensity variation: 0.99–1.02%

Refinement

Refinement on F
Final R = 0.032
wR = 0.035
S = 9.04
1580 reflections
107 parameters
Only H-atom coordinates refined
$w = 1/[\sigma^2(F_o)+0.00010F_o^2]$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.032 e Å^{-3}
$\Delta\rho_{min}$ = −0.60 e Å^{-3}
'Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic thermal parameters* (Å^2)

$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
S(1)	0.06106 (6)	0.19884 (4)	0.79510 (4)	3.66 (1)
S(2)	−0.25372 (5)	0.02382 (4)	0.69229 (5)	3.64 (1)
O(1)	−0.2712 (2)	−0.0567 (1)	0.5541 (2)	5.24 (5)
O(2)	−0.1820 (2)	−0.0236 (1)	0.8461 (2)	5.04 (4)
N(1)	0.0268 (2)	0.2881 (1)	0.5069 (2)	4.00 (4)
N(2)	−0.1032 (2)	0.1968 (1)	0.5115 (2)	3.85 (4)
N(3)	0.2646 (3)	0.3775 (2)	0.6696 (2)	5.21 (6)
N(4)	−0.4406 (2)	0.0858 (2)	0.7101 (2)	4.84 (5)
C(1)	0.1251 (2)	0.2992 (2)	0.6459 (2)	3.46 (4)
C(2)	−0.1014 (2)	0.1443 (2)	0.6504 (2)	3.27 (4)

Table 2. *Geometric parameters* (Å, °)

S(1)—C(1)	1.737 (2)	S(1)—C(2)	1.728 (1)
S(2)—O(1)	1.427 (1)	S(2)—O(2)	1.432 (1)
S(2)—N(4)	1.569 (2)	S(2)—C(2)	1.767 (2)
N(1)—N(2)	1.375 (2)	N(1)—C(1)	1.317 (2)
N(2)—C(2)	1.283 (2)	N(3)—C(1)	1.333 (2)
C(2)—S(1)—C(1)	85.9 (1)	O(2)—S(2)—O(1)	120.9 (1)
N(4)—S(2)—O(1)	108.2 (1)	N(4)—S(2)—O(2)	108.7 (1)
C(2)—S(2)—O(1)	106.1 (1)	C(2)—S(2)—O(2)	103.6 (1)
C(2)—S(2)—N(4)	108.8 (1)	C(1)—N(1)—N(2)	112.1 (1)
C(2)—N(2)—N(1)	112.5 (1)	N(1)—C(1)—S(1)	114.0 (1)
N(3)—C(1)—S(1)	122.7 (1)	N(3)—C(1)—N(1)	123.3 (2)
S(2)—C(2)—S(1)	121.8 (1)	N(2)—C(2)—S(1)	115.5 (1)
N(2)—C(2)—S(2)	122.6 (1)		

Table 3. *Hydrogen-bond geometry* (Å, °)

D—H···A	D—H	D···A	H···A	D—H···A
N(3)—H(31)···O(2^{i})	0.84 (2)	3.167 (2)	2.34 (2)	168 (2)
N(3)—H(32)···N(2^{ii})	0.81 (2)	3.028 (2)	2.29 (2)	153 (2)
N(4)—H(41)···N(1^{iii})	0.86 (2)	2.842 (2)	1.98 (2)	176 (2)
N(4)—H(42)···O(1^{iv})	0.81 (2)	2.949 (2)	2.19 (2)	157 (2)

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

Table 4. *Bond distances* (Å) *and angles* (°) *of the thiadiazole ring found in this study and in other relevant compounds*

	S(1)—C(2)	C(2)—N(2)	N(2)—N(1)	N(1)—C(1)	C(1)—S(1)
Hats	1.728	1.288	1.375	1.317	1.737
H_2acm	1.724	1.294	1.372	1.311	1.730
Hmacm	1.726	1.283	1.373	1.347	1.741
Hatm*	1.738	1.334	1.382	1.305	1.746
	∠S(1)	∠C(2)	∠N(2)	∠N(1)	∠C(1)
Hats	85.9	115.5	112.5	112.5	114.0
H_2acm	85.0	116.4	111.3	112.1	112.1
Hmacm	87.5	117.3	108.7	117.0	109.3
Hatm*	89.6	108.4	117.8	110.2	113.3

* Downie *et al.* (1952).

tert-BuOH/H_2O (1:1, 30 ml) and NaOH (0.6 g, 15 mmol) were added in an ice bath to 1.86 g of 5-amino-1,3,4-thiadiazole-2-thiol. To this solution, $(BOC)_2O$ (3.275 g, 15 mmol) was added at room temperature with stirring. The resulting mixture was stirred for 14 h and the excess $(BOC)_2O$ was extracted with ethyl

acetate (25 ml). The aqueous layer was treated with aqueous $KHSO_4$ (2.5 g in 20 ml H_2O) and extracted with ethyl acetate (2 × 30 ml). After the usual workup and recrystallization, 2.44 g (75%) of (I) was isolated. 2.3 g of (I) in 200 ml of glacial acetic acid was chlorinated for 0.5 h at 278 K. Without purification, the sulfonyl chloride obtained was added in portions, under inert atmosphere, to about 50 ml of freshly condensed liquid ammonia. Excess ammonia was removed under reduced pressure to give 2.1 g [75% referred to (I)] of crude *N*-BOC derivative (II). Trifluoroacetic acid (TFA) (35 mol) in CH_2Cl_2 (10 ml) was added to a solution of (II) (2.1 g, 7.5 mol) in CH_2Cl_2 (10 ml) at room temperature. After the solution was stirred for 2 h, the solvent evaporated and aqueous 3 *M* NaOH (30 ml) and CH_2Cl_2 (30 ml) were added. The organic layer was worked up to give 1.2 g (89%) of (III) after recrystallization from water.

Profile analysis was performed on all reflections (Lehmann & Larsen, 1974; Grant & Gabe, 1978); a semi-empirical absorption correction was applied, using ψ scans (North, Phillips & Mathews, 1968). The structure was solved by direct methods using *SHELXS*86 (Sheldrick, 1985) and Fourier synthesis. Isotropic least-squares refinement was carried out using *SHELX*76 (Sheldrick, 1976). Empirical absorption correction was applied using *DIFABS* (Walker & Stuart, 1983). Geometrical calculations were made with *PARST* (Nardelli, 1983). All calculations were performed on a MicroVAX 3400 at the Scientific Computer Center of the University of Oviedo, Spain.

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Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55610 (18 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: LI1011]

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Structures of Pyrazole Derivatives. I. A Potential Bioisoster of Thromboxane Synthetase Inhibitors

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Abstract

In (*E*)-5-(1-phenyl-4-pyrazolylium)-2-pentenoate, the N···O distances lie in the range 8.557 (5)–8.812 (5) Å. The phenyl and pyrazole rings are planar making a dihedral angle of 14.1 (5)°. The molecular packing involves C—H···O contacts.

Comment

Thromboxane A_2 synthetase inhibitors (TXSi) have therapeutic utility in several conditions where platelets are believed to play a role in the pathogenesis of the disease process, *e.g.* ischemia, arrhythmias, pulmonary hypertension and thromboembolic disorders [for a recent review see Collington & Finch (1989)]. Among the great variety of heterocyclic substances