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A novel heterocyclic sulfonamide: *N*-benzyl-5-[*N*-benzyl-*N*-(*tert*-butyl oxycarbonyl)amino]-*N*-(*tert*-butyl oxycarbonyl)-1,3,4-thiadiazole-2-sulfonamide

Gerardo Camí,[a] Juan Server-Carrió,[b]* Santos Fustero[c] and José Pedregosa[a]

[a]Departamento de Química, Facultad de Química, Bioquímica y Farmacia, Universidad Nacional de San Luis (PIP-CONICET 4929/96), Chacabuco y Pedernera, 5700 San Luis, Argentina, [b]Departamento de Química Inorgánica, Facultad de Farmacia, Universitat de Valencia, Avd. Vicent Andrés Estellés s/n, 46100 Burjassot, Valencia, Spain, and [c]Departamento de Química Orgánica, Facultad de Farmacia, Universitat de Valencia, Avd. Vicent Andrés Estellés s/n, 46100 Burjassot, Valencia, Spain
Correspondence e-mail: juan.server@uv.es

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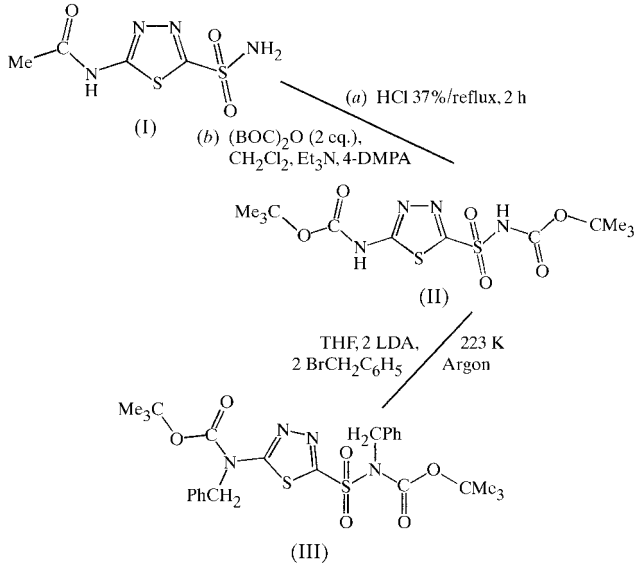
The title compound, $C_{26}H_{32}N_4O_6S_2$, is a heterocyclic sulfonamide which is a 1,3,4-thiadiazole derivative. Structural data for this compound are compared with those of related compounds.

Comment

Since Davenport (1945) reported that thiophene-2-sulfonamide is a carbonic anhydrase (CA) inhibitor 40 times more active than other sulfonamides, many heterocyclic sulfonamides have been prepared. We have obtained and determined the crystal structures of several 1,3,4-thiadiazolesulfonamides following the method proposed by Young *et al.* (1956) with minor modifications (Alzuet *et al.*, 1991*a*; Pedregosa *et al.*, 1993). The results obtained by our group with these sulfonamides have rendered data which indicate a notable increase in CA inhibitory properties (Chufán *et al.*, 2000). In addition, Krebs' (1948) investigations on compounds presenting the modified sulfonamido group has led to the conclusion that substitution within the sulfonamido group drastically affects inhibitory activity and increases lipoaffinity (Duffel *et al.*, 1986). Based on these investigations, it was interesting to prepare compounds with the substituted sulfonamido group and to determine their crystal structures. Furthermore, following our programme for systematic studies on unsubstituted and substituted heterocyclic sulfonamides and their metal complexes (Alzuet *et al.*, 1991*b*; Pedregosa *et al.*, 1995), we will study the role of these bulky groups with regard to CA inhibition and lipoaffinity.

In this work, we obtained the crystal structure of the title compound, (III), and compared it with related compounds, such as acetazolamide (5-acetylamino-1,3,4-thiadiazole-2-sulfonamide; Mathew & Palenik, 1974), 5-amino-1,3,4-thiadiazole-2-sulfonamide (Pedregosa *et al.*, 1993), 5-*tert*-butyloxycarbonylamino-1,3,4-thiadiazole-2-sulfonamide (Pedregosa *et al.*, 1995), 5-amino-1,3,4-thiadiazole-2-thiol (Downie *et al.*, 1972) and 5-*tert*-butyloxycarbonylamino-1,3,4-thiadiazole-2-sulfonyl chloride (Pedregosa *et al.*, 1996). The main features of the new structure, *i.e.* planarity of the 1,3,4-thiadiazole ring, distorted tetrahedral geometry in the sulfonamide group and a coplanar arrangement of the disubstituted 5-amino group and the 1,3,4-thiadiazole ring, are in agreement with the compared compounds.



Experimental

The synthesis of (III) was performed in three steps. In the first step, the acid hydrolysis of acetazolamide (I) to give 5-amino-1,3,4-thiadiazole-2-sulfonamide was performed following the literature procedure of Supuran *et al.* (1990). In the second step (group protection), the product (0.5 g, 2.77 mmol) of the previous reaction, triethylamine (Et_3N, Aldrich, 1 ml, 7.2 mmol), 4-dimethyl-aminopyridine (4-DMAP, Aldrich, 100 mg, 4.6 mmol) and di-*tert*-butyldicarbonate [$(BOC)_2O$, Aldrich, 1.2 g, 5.54 mmol] were added in order and with permanent stirring at room temperature to CH_2Cl_2 (50 ml, Merck) under an inert argon atmosphere. The reaction was followed by thin-layer chromatography (TLC). After 18 h, the solvent was removed by vacuum extraction. The obtained solid (II) was purified by treatment with 1 *N* HCl, filtered and washed with distilled water (3–4 times) and hexane (3–4 times). Recrystallization from ethanol/dichloromethane (1:1) rendered crystals that were washed with ethanol/hexane (1:20) giving 0.9 g (86%) of (II) (m.p. 436–438 K). Finally, the third step consisted of deprotonation of (II). Lithium diisopropylamide (LDA) was prepared by addition of diisopropylamine (2 ml, 14.28 mmol) and *n*-butyllithium (1.32 ml, 14.23 mmol) to tetrahydrofuran (50 ml, Supelco) on an acetone/solid CO_2 cold bath (213 K) under an inert argon atmosphere. The mixture was stabilized at 213 K for 30 min. Subsequently, (II) (0.5 g,

1.32 mmol) was added. After 30 min of stabilization at the same temperature, benzylbromide (0.4 ml, 3.29 mmol) was added. The reaction was followed by TLC. After 24 h, when the bath reached room temperature, the solvent was removed by vacuum extraction. The obtained solid (III), was purified with 1 *N* HCl and washed with distilled water and hexane. Recrystallization was performed as described in step two and 0.55 g (75% yield) of (III) were isolated (m.p. 389–391 K).

Crystal data

$C_{26}H_{32}N_4O_6S_2$	D_x = 1.277 Mg m^{-3}
M_r = 560.68	Mo $K\alpha$ radiation
Monoclinic, $P2_1/n$	Cell parameters from 25 reflections
a = 15.408 (1) Å	θ = 9.5–13.6°
b = 10.256 (1) Å	μ = 0.227 mm^{-1}
c = 19.402 (1) Å	T = 293 (2) K
β = 107.91 (1)°	Prismatic, colourless
V = 2917.4 (4) Å^3	0.30 × 0.25 × 0.20 mm
Z = 4	

Data collection

Enraf–Nonius CAD-4 diffractometer	θ_{max} = 24.99°
$\omega/2\theta$ scans	$h = 0 \rightarrow 18$
5807 measured reflections	$k = 0 \rightarrow 12$
5114 independent reflections	$l = -23 \rightarrow 21$
3022 reflections with $I > 2\sigma(I)$	3 standard reflections
R_{int} = 0.0074	frequency: 90 min
	intensity decay: none

Refinement

Refinement on F^2	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)]$ = 0.049	$w = 1/[\sigma^2(F_o^2) + (0.0755P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2)$ = 0.156	$(\Delta/\sigma)_{max}$ = 0.001
S = 1.057	$\Delta\rho_{max}$ = 0.23 e Å^{-3}
5114 reflections	$\Delta\rho_{min}$ = −0.27 e Å^{-3}
360 parameters	

The H atoms were placed geometrically and treated with a riding model in which the C—H distance, common to all H atoms bonded to the same C, was free to refine.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *XRAY*80 (Stewart, 1980); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997).

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