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2-(Biphenyl-2-yl)-5-(1-methylhydrazino)-1,3,4-thiadiazole: a thiadiazole–hydrazine derivative with anticonvulsant properties

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In the title compound, $C_{15}H_{14}N_4S$, the outer phenyl ring makes an angle of 101.4 (2)° with the plane through the inner benzene ring, and the planes of the thiadiazole ring and the attached benzene ring intersect at an angle of 146.7 (2)°. In addition to weak N—H···N hydrogen bonds, creating a two-dimensional network parallel to the *bc* plane of the crystal structure, there is also one non-standard hydrogen-bond interaction of the type C—H···N. Stereochemical comparison with the closely related compound 1-[5-(biphenyl-2-yl)-1,3,4-thiadiazol-2-yl]methanaminium chloride shows that the two compounds utilize the same mechanism for anticonvulsant activity.

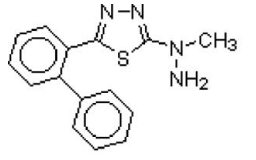
Key indicators

Single-crystal X-ray study
T = 294 K
Mean σ(C–C) = 0.009 Å
R factor = 0.071
wR factor = 0.136
Data-to-parameter ratio = 11.7

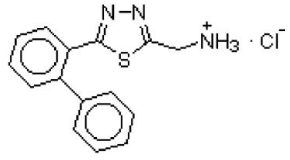
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Comment

Promising anticonvulsant activity has been reported in some members of a series of synthetic substituted thiadiazole hydrazines (Chapleo *et al.*, 1986). Subsequently, aminoalkyl analogues were prepared in order to avoid the presence of a potentially troublesome free hydrazine group (Stillings *et al.*, 1986), and a number of those derivatives were equally potent anticonvulsants. We determined the structure of the most potent of the aminoalkyl thiadiazole hydrazine derivatives, 1-[5-(biphenyl-2-yl)-1,3,4-thiadiazol-2-yl]methanaminium chloride, (II), and despite its chemical dissimilarity to conventional antiepileptic drugs such as phenytoin, we were able to identify stereochemical features in common which may be responsible for their similar anticonvulsant properties (Camerman *et al.*, 2005). We now report the structure of the most potent of the original hydrazine series, 2-biphenyl-2-yl-5-(1-methylhydrazino)-1,3,4-thiadiazole, (I), and show that it too contains the stereochemical properties correlated with anticonvulsant activity.



(I)



(II)

The structure of (I) is presented in Fig. 1. Bond distances and angles are within normal ranges, even with higher than usual values for the anisotropic displacement parameters, especially for the atoms of the outer phenyl ring. The sum of the angles at the amino atom N7 is 327°, indicating sp^3 hybridization. The torsion angles N3—C2—N6—N7 and N3—C2—N6—C8 are 173.6 (5) and 15.9 (7)°, respectively. The

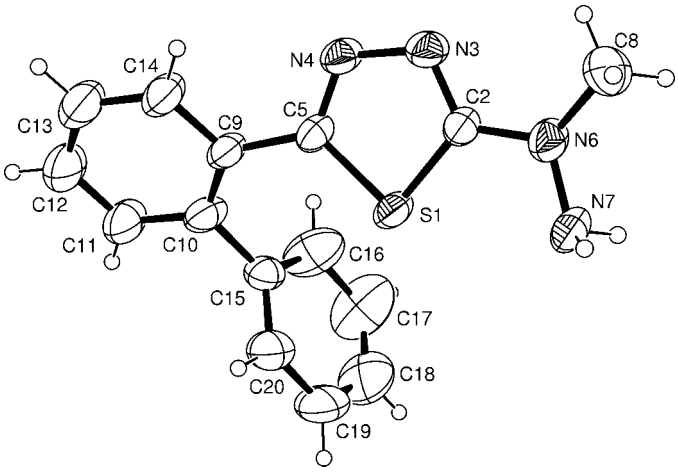


Figure 1
The molecular structure of (I), showing 35% probability displacement ellipsoids. H atoms are drawn as small circles of arbitrary radii.

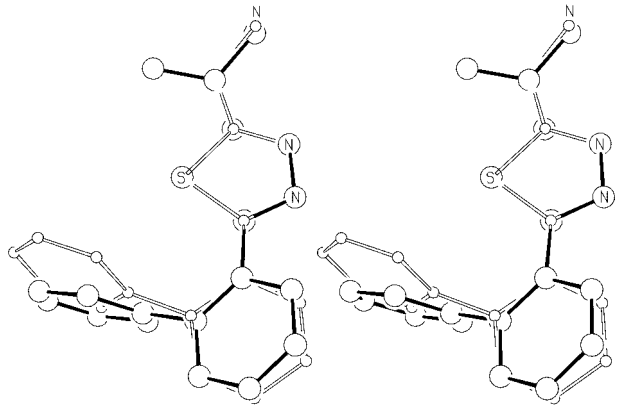


Figure 3
A stereodiagram of the superimposition of (I) and 1-[5-(biphenyl-2-yl)-1,3,4-thiadiazol-2-yl]methanaminium chloride (light bonds and large circles). Thiadiazole ring atoms in each molecule were fitted in the superimposition.

thiadiazole ring is planar. The plane of the outer phenyl ring makes an angle of 101.4 (2)° with that of the inner benzene ring, which in turn intersects the plane of the thiadiazole ring at an angle of 146.7 (2)°. For comparison, the same parameters in (II) are 98.3 (2) and 165.5 (4)°, respectively.

Weak N—H···N hydrogen bonds (Table 1) produce a two-dimensional network of molecules parallel to the *bc* plane (Fig. 2), and create distinct hydrophobic (benzene rings) and hydrophilic (thiadiazole ring) parallel regions. A non-standard C—H···N interaction and van der Waals contacts also contribute to the crystal packing. The weak intermolecular interactions between the molecules and the existence of an empty 40.2 Å^3 volume in the hydrophobic environment of the benzene rings contribute substantially to the loose crystal packing and the high thermal displacement parameters of the benzene rings.

We have superimposed the structures of (I) and the aminoalkyl derivative, (II); the results are shown in Fig. 3. The overall stereochemistry and the spatial arrangement of the electronegative atoms is very similar in the two active compounds. It is extremely likely, therefore, that the two compounds exert their anticonvulsant properties through the same mechanism.

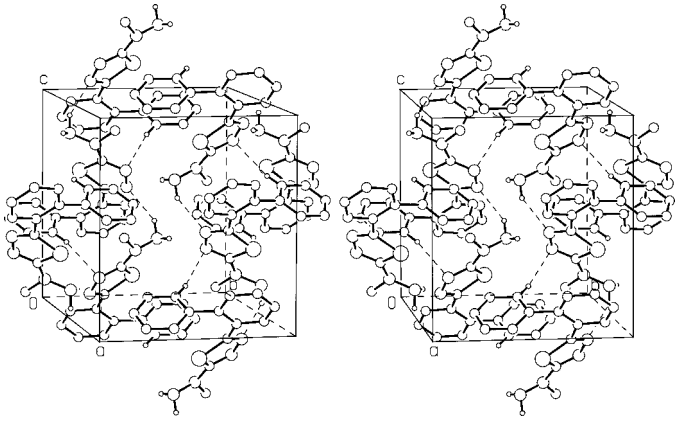


Figure 2
A stereoscopic view of the molecular packing and hydrogen-bond scheme (shown as dashed lines between atoms). Atoms are drawn as circles of arbitrary radii. For clarity, only H atoms involved in the hydrogen bonding are shown.

Experimental

The title compound was obtained from Reckitt & Colman plc, UK. Extensive crystallization experiments to find proper crystallization conditions produced only crystals of low quality. The crystal used was obtained by slow evaporation of a 1:1 petroleum ether–ethyl acetate solution at 294 K. Efforts to obtain better crystals were unsuccessful.

Crystal data

$C_{15}H_{14}N_4S$
M_r = 282.36
Monoclinic, $P2_1/c$
a = 13.886 (3) Å
b = 9.898 (2) Å
c = 10.896 (2) Å
β = 91.46 (2)°
V = 1497.1 (5) Å^3
Z = 4
D_x = 1.253 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 32 reflections
θ = 19–38°
μ = 1.88 mm^{-1}
T = 294 (2) K
Needle, colourless
0.25 × 0.07 × 0.04 mm

Data collection

Picker FACS-1 four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.851, T_{max} = 0.926
2259 measured reflections
2259 independent reflections
1111 reflections with $I > 2\sigma(I)$
θ_{max} = 62.5°
$h = 0 \rightarrow 15$
$k = 0 \rightarrow 11$
$l = -9 \rightarrow 12$
3 standard reflections
every 100 reflections
intensity decay: 2.3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.071
$wR(F^2)$ = 0.136
S = 0.89
2259 reflections
193 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0477P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.17 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.0014 (3)

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N7—H71···N4^{i}	0.99 (6)	2.21 (7)	3.118 (7)	151 (5)
N7—H72···N3^{ii}	0.91 (6)	2.20 (7)	3.100 (7)	169 (5)
C16—H16···N3^{iii}	0.93	2.62	3.534 (8)	168

Symmetry codes: (i) $x, -y+\frac{1}{2}, z+\frac{1}{2}$; (ii) $-x+1, y-\frac{1}{2}, -z+\frac{3}{2}$; (iii) $x, -y+\frac{1}{2}, z-\frac{1}{2}$.

All H atoms were visible in a difference map. However, due to the paucity of intensity data, the H atoms were refined using a riding-model approximation, except for the two H atoms from the amino group, which were taken from the difference map and refined freely. One overall displacement parameter was refined for H atoms in the methyl group [U_{iso}(H) = 0.143 (15) Å^2] and another for the remaining benzene-ring H atoms [0.123 (7) Å^2]. The range of C—H distances is 0.93–0.96 Å and the range of N—H distances is 0.91–0.99 (6) Å

Data collection: *Picker Operating Manual* (Picker, 1967); cell refinement: *Picker Operating Manual*; data reduction: *DATRDN* in *The XRAY System* (Stewart, 1976); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

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