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Stereochemical basis for activity in thiadiazole anticonvulsants: 1-[5-(biphenyl-2-yl)-1,3,4-thiadiazol-2-yl]-methanaminium chloride and two inactive analogues, 2-(biphenyl-4-yl)-5-[2-(1-methylethylidene)hydrazino]-1,3,4-thiadiazole and the methanol solvate of its hydrochloride salt

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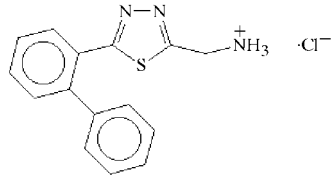
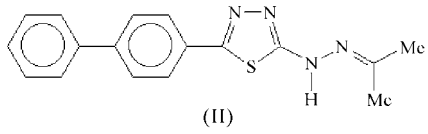
In 1-[5-(biphenyl-2-yl)-1,3,4-thiadiazol-2-yl]methanaminium chloride, $C_{15}H_{14}N_3S^+\cdot Cl^-$, the protonation occurs at the amine N atom. The outer phenyl ring makes an angle of 88.0 (2)° with the plane through the inner benzene ring, and the planes of the thiadiazole ring and the attached benzene ring intersect at an angle of 165.5 (4)°. In addition to classical N—H···N and N—H···Cl^- hydrogen bonds producing chains parallel to the *c* axis, there are weak C—H···N and C—H···Cl^- hydrogen bonds. The hydrogen bonds and packing interactions result in hydrophilic and hydrophobic planar areas in the crystal, perpendicular to the *a* axis. Stereochemical comparison with phenytoin shows that the two compounds may utilize similar mechanisms of action. 2-(Biphenyl-4-yl)-5-[2-(1-methylethylidene)hydrazino]-1,3,4-thiadiazole, $C_{17}H_{16}N_4S$, where $Z' = 2$, and the methanol solvate of its hydrochloride salt, 5-(biphenyl-4-yl)-2-[2-(1-methylethylidene)hydrazino]-1,3,4-thiadiazol-3-ium chloride methanol solvate, $C_{17}H_{17}N_4S^+\cdot Cl^-\cdot CH_3OH$, adopt linear almost planar molecular conformations. The *para* position of the outer phenyl ring in these compounds precludes adoption of the phenytoin anticonvulsant stereochemistry.

Comment

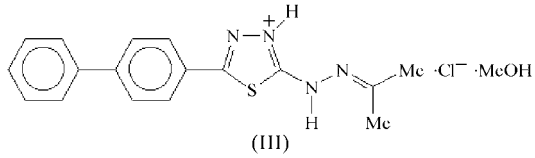
Pharmacological testing of a number of substituted 2-aryl-5-hydrazino-1,3,4-thiadiazoles, designed and synthesized as antihypertensives, showed them to possess anticonvulsant activity as well (Chapleo *et al.*, 1986). Subsequently, a series of aminoalkyl derivatives were synthesized in order to negate possible side effects of a free hydrazine group, and these



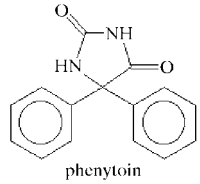
(I)



(II)



(III)



phenytoin
(IV)

derivatives were evaluated for anticonvulsant properties. The most promising of the series was 1-[5-(biphenyl-2-yl)-1,3,4-thiadiazol-2-yl]methanaminium chloride, (I), chemically dissimilar from well known anticonvulsants, such as carbamazepine, phenobarbital and phenytoin, but with a similar anticonvulsant profile (Stillings *et al.*, 1986). We have elucidated the three-dimensional structure of this compound in an effort to identify structural determinants of its anticonvulsant activity and possible stereochemical correlations with other anticonvulsants. In addition, we have determined the structure of an inactive analogue in the series of 2-biphenyl-4-ylhydrazinothiadiazoles, in order to identify further conformational and stereochemical parameters responsible for activity and lack thereof. We obtained two crystalline forms of 2-(biphenyl-4-yl)-5-[2-(1-methylethylidene)hydrazino]-1,3,4-thiadiazole from solutions of the hydrochloride salt, one

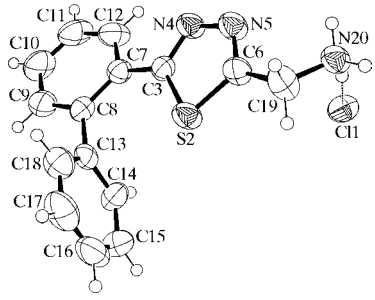


Figure 1
The molecular structure of (I), showing 50% probability displacement ellipsoids. H atoms are drawn as small circles of arbitrary radii.

‡ Deceased.

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unprotonated with two molecules in the asymmetric unit, (II), and the second, (III), as a hydrochloride containing a methanol solvent molecule.

In the active anticonvulsant, (I) (Fig. 1), the bond distances and angles are within normal ranges. Protonation of the molecule occurs at atom N20 and the sum of the angles at this atom is 328°. The thiadiazole ring is planar. The plane of the outer phenyl ring is almost perpendicular [88.0 (2)° angle] to that of the inner benzene ring, which, in turn, intersects the plane of the thiadiazole ring at an angle of 165.5 (4)°. N—H···Cl^- and N—H···N hydrogen bonds (Table 1) produce chains parallel to [001], and weak C—H···N and C—H···Cl^- hydrogen bonds along with van der Waals interactions contribute to the crystal packing. The molecules are packed in head-to-head and tail-to-tail fashion, creating distinct hydrophilic and hydrophobic regions running perpendicular to the unit-cell *a* axis (Fig. 2).

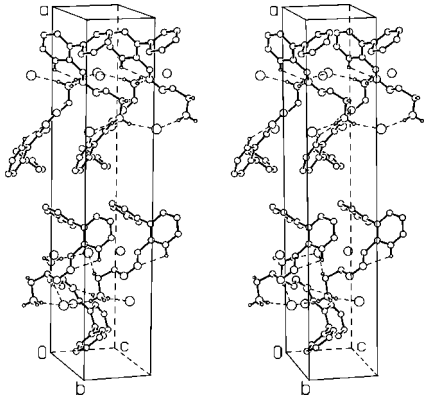

Figure 2
A stereodiagram of the molecular packing and hydrogen-bond scheme for (I). Atoms are drawn as circles of arbitrary radii and hydrogen bonds are shown as dashed lines. H atoms not involved in hydrogen bonding have been omitted.

The dissimilarity of the chemical structure of this molecule from those of any of the familiar anticonvulsant drugs has led to speculation about a different mode of action (Stillings *et al.*, 1986). However, the fact that (I) has a comparable potency to phenytoin has led us to investigate stereochemical similarities in the two drugs. Accordingly, we have compared the two structures by a molecular superposition, which initially optimized the fit of the two carbonyl O atoms in phenytoin with atoms N4 and N20 in the title compound, and atom C5, the phenyl-substituted hydantoin C atom in phenytoin, with the thiadiazole ring S atom. Subsequently, two allowable benzene group rotations were performed in the title compound, *viz.* 65° about the C7—C3 bond, followed by 80° about C8—C13. The resulting fit (Fig. 3) demonstrates that the two O and two N atoms in the molecules superpose closely, and the outer phenyl ring of the title compound is positioned very similarly to a phenytoin phenyl group. Since these features are the determinants of anticonvulsant activity in phenytoin (Camerman & Camerman, 1980), this is persuasive evidence that, notwithstanding their different chemical structures, these similar stereochemical features may enable the thiadiazoles to exert their anticonvulsant activities, at least in part, through mechanisms similar to those of phenytoin.

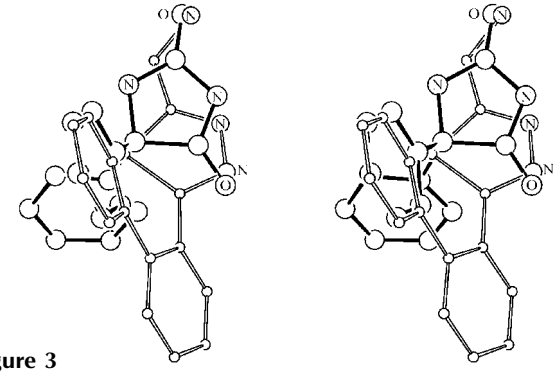

Figure 3
A stereodiagram showing superposition of the title compound, after bond rotations, and phenytoin (large circles, solid bonds).

In both (II) (Fig. 4) and (III) (Fig. 5), the bond distances and angles are within normal ranges. The two independent molecules in (II) are both roughly planar in overall conformation; the angles between the planes of the two benzene rings, the thiadiazole ring and the five-membered hydrazine group are, respectively, 152.1 (2), 156.3 (2) and 170.0 (3)° for molecule *A*, and 143.9 (2), 178.5 (2) and 179.9 (2)° for molecule *B*. N—H···N hydrogen bonds (Table 2) connect the molecules, producing distinct dimers, and a weak C—H···N hydrogen bond along with van der Waals contacts contribute to the crystal packing of (II) (Fig. 6). In the crystal structure of (III), protonation occurs at the thiadiazole ring atom N4. The

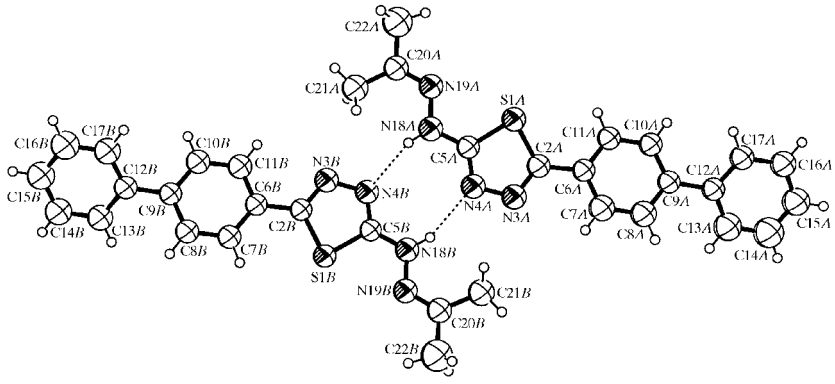

Figure 4
The molecular structure of (II), showing 50% probability displacement ellipsoids. H atoms are drawn as small circles of arbitrary radii and hydrogen bonds are shown as dashed lines.

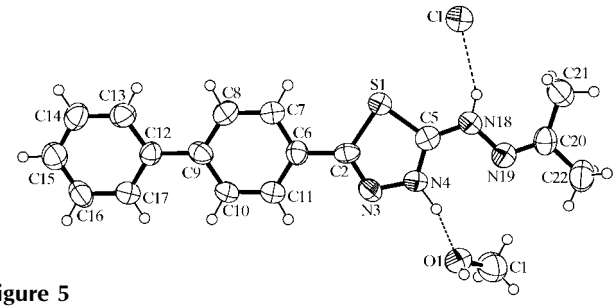

Figure 5
The molecular structure of (III), showing 50% probability displacement ellipsoids. H atoms are drawn as small circles of arbitrary radii.

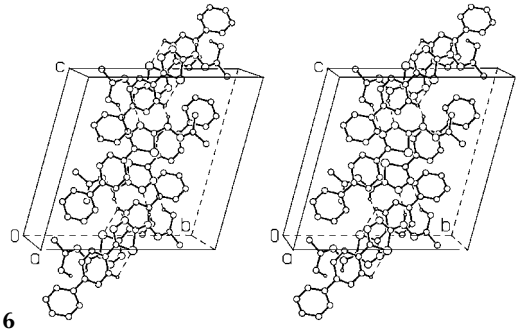

Figure 6
A stereodiagram of the molecular packing and hydrogen-bond scheme of (II). Atoms are drawn as circles of arbitrary radii and hydrogen bonds are shown as dashed lines. H atoms not involved in hydrogen bonding have been omitted.

molecule is very nearly planar, with angles between the planes through the rings and the hydrazine group, beginning from the outer phenyl ring, of 170.6 (3), 178.7 (2) and 178.3 (2)°. The largest deviation from a plane taken through all the non-H atoms is 0.14 (1) Å for the outer phenyl ring atom C17. In addition to the hydrochloride molecule, the asymmetric unit also contains a methanol molecule, which donates a hydrogen bond to the Cl^- ion and accepts one from the protonated atom N4 (Table 3). All intermolecular hydrogen bonding is through the Cl^- ion and the methanol molecule, resulting in infinite chains running parallel to the *c* axis. Because of the *para* relationship of the phenyl and thiadiazole substituents, molecular manipulations with these molecules could not give a conformation containing the stereochemical properties of the active anticonvulsants.

The structural results presented here, in addition to identifying conformational and stereochemical features in (I) that are likely to be responsible for its anticonvulsant activity, also explain other structure–activity observations in the series of thiadiazoles tested (Chapleo *et al.*, 1986; Stillings *et al.*, 1986). Activity is abolished (i) when the outer phenyl ring is in the *para* position or (ii) as the alkylamine chain length is increased; our results show that (i) superposition with the phenytoin phenyl ring is then not possible and (ii) the correspondence of the N atoms with phenytoin O atoms becomes problematic.

Experimental

After extensive experiments to find proper crystallization conditions, crystals of (I) were produced by slow evaporation from a 6:3:1 ethyl acetate–methanol–ethanol mixture at 278 K. The crystals were small colorless needles. Crystallization experiments with 2-(biphenyl-4-yl)-5-[2-(1-methylethylidene)hydrazino]-1,3,4-thiadiazole hydrochloride resulted in two different products. A triclinic compound, (II), was obtained by slow evaporation from a 1:1 methanol–dimethylformamide mixture, and a monoclinic compound, (III), by slow evaporation from a 1:1 methanol–ethyl acetate mixture, both at room temperature. However, the quality of the crystals was poor for both (II) and (III), and tweaking the crystallization conditions proved unsuccessful.

Compound (I)

Crystal data

$C_{15}H_{14}N_3S^+\cdot Cl^-$
M_r = 303.80
Orthorhombic, $P2_12_12_1$
a = 28.882 (6) Å
b = 9.198 (2) Å
c = 5.605 (1) Å
V = 1489.0 (5) Å^3
Z = 4
D_x = 1.355 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 32 reflections
θ = 21–47°
μ = 3.52 mm^{-1}
T = 294 (2) K
Needle, colorless
0.39 × 0.12 × 0.08 mm

Data collection

Picker FACS-1 four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.630, T_{max} = 0.753
1515 measured reflections
1515 independent reflections
1138 reflections with $I > 2\sigma(I)$
θ_{max} = 65.0°
$h = 0 \rightarrow 33$
$k = 0 \rightarrow 10$
$l = 0 \rightarrow 6$
3 standard reflections
every 100 reflections
intensity decay: 2.7%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.057
$wR(F^2)$ = 0.124
S = 1.04
1515 reflections
185 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + 1.4774P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.26 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0016 (4)
Absolute structure: Flack (1983)
Flack parameter: 0.02 (5)

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

D—H···A	D—H	H···A	D···A	D—H···A
N20—H20A···Cl1	0.89	2.25	3.134 (6)	170
N20—H20B···Cl1^{i}	0.89	2.22	3.070 (6)	160
N20—H20C···N4^{ii}	0.89	2.03	2.906 (7)	167
C19—H19B···Cl1^{iii}	0.97	2.57	3.492 (7)	159

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

Compound (II)

Crystal data

$C_{17}H_{16}N_4S$
M_r = 308.40
Triclinic, $P\overline{1}$
a = 7.988 (2) Å
b = 14.150 (3) Å
c = 14.545 (3) Å
α = 74.77 (3)°
β = 89.60 (2)°
γ = 80.79 (2)°
V = 1564.8 (7) Å^3
Z = 4
D_x = 1.309 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 32 reflections
θ = 27–53°
μ = 1.84 mm^{-1}
T = 294 (2) K
Needle, colorless
0.33 × 0.04 × 0.02 mm

Data collection

Picker FACS-1 four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.913, T_{max} = 0.961
5739 measured reflections
5322 independent reflections
3511 reflections with $I > 2\sigma(I)$

R_{int} = 0.073
θ_{max} = 65.0°
$h = -9 \rightarrow 0$
$k = -16 \rightarrow 16$
$l = -17 \rightarrow 17$
3 standard reflections
every 100 reflections
intensity decay: 3.1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.073
$wR(F^2)$ = 0.177
S = 1.03
5322 reflections
406 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0632P)^2 + 1.0582P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.31 e Å^{-3}
$\Delta\rho_{min}$ = −0.28 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0033 (3)

Table 2
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N18*A*—H18*A*···N4*B*	0.86	2.26	3.022 (5)	147
N18*B*—H18*B*···N4*A*	0.86	2.18	2.990 (5)	157
C21*B*—H21*F*···N3*A*	0.96	2.63	3.312 (6)	129

Compound (III)

Crystal data

$C_{17}H_{17}N_4S^+\cdot Cl^-\cdot CH_4O$
M_r = 376.90
Monoclinic, $P2_1/c$
a = 7.472 (3) Å
b = 16.437 (4) Å
c = 15.532 (2) Å
β = 101.41 (2)°
V = 1869.9 (9) Å^3
Z = 4

D_x = 1.339 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 32 reflections
θ = 18–41°
μ = 2.96 mm^{-1}
T = 294 (2) K
Needle, colorless
0.21 × 0.05 × 0.03 mm

Data collection

Picker FACS-1 four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.835, T_{max} = 0.912
3167 measured reflections
3167 independent reflections

1725 reflections with $I > 2\sigma(I)$
θ_{max} = 65.1°
$h = 0 \rightarrow 8$
$k = -19 \rightarrow 0$
$l = -18 \rightarrow 17$
3 standard reflections
every 100 reflections
intensity decay: 1.8%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.092
$wR(F^2)$ = 0.264
S = 0.89
3167 reflections
237 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.1328P)^2 + 4.9564P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···Cl^{iv}	0.75 (13)	2.32 (13)	3.064 (8)	169 (13)
N4—H4···O1	1.02 (8)	1.67 (8)	2.664 (9)	163 (7)
N18—H18···Cl	0.86	2.26	3.061 (7)	155

Symmetry code: (iv) $x, -y+\frac{3}{2}, +z+\frac{1}{2}$.

Although all H atoms could be located from difference maps for compounds (I), (II) and (III), H atoms were allowed for as riding atoms, except for two H atoms in (III). For (I), the difference map indicated clearly that protonation occurred at atom N20. One overall isotropic displacement parameter was refined for the H atoms on N20 [U_{iso}(H) = 0.13 (2) Å^2] and another for the remaining H atoms [0.082 (8) Å^2]. The range of C—H distances is 0.93–0.97 Å. For (II), one overall isotropic displacement parameter was refined for the outer phenyl ring H atoms [U_{iso}(H) = 0.084 (5) Å^2], one for the inner benzene ring atoms [0.063 (4) Å^2], one for the methyl groups [0.130 (6) Å^2], and another for the H atom at atom N18 [0.128 (16) Å^2]. The range of C—H distances was 0.93–0.96 Å. In the case of (III), one overall isotropic displacement parameter was refined for methyl group H atoms [U_{iso}(H) = 0.141 (14) Å^2] and another for the remainder [0.081 (8) Å^2]. The range of C—H distances was 0.93–0.96 Å. Atoms H1 in the water molecule and H4 at the protonated N4 atom were refined from the difference-map locations. The N4—H4 distance is 1.02 (8) and the O1—H1 distance is 0.75 (11) Å.

For all compounds, data collection: *Picker Operating Manual* (Picker, 1967); cell refinement: *Picker Operating Manual*; data reduction: *DATRDN: The X-ray System* (Stewart, 1976); structure solution: *SHELXS97* (Sheldrick, 1990); structure refinement: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1394). Services for accessing these data are described at the back of the journal.

References

Camerman, A. & Camerman, N. (1980). *Antiepileptic Drugs: Mechanism of Action*, edited by G. H. Glaser, J. K. Henry & D. M. Woodbury, pp. 223–231. New York: Raven Press.
Chapleo, B. C., Myers, M., Myers, P. L., Saville, J. F., Smith, A. C. B., Stillings, M. R., Tulloch, I. F., Walter, D. S. & Welbourn, A. P. (1986). *J. Med. Chem.* **29**, 2273–2280.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.
Picker (1967). *Picker Operating Manual.* Picker, Cleveland, Ohio, USA.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
Stewart, J. M. (1976). *DATRDN: The X-ray System*. Technical Report TR-446 of the Computer Science Center, University of Maryland, College Park, Maryland, USA.
Stillings, M. R., Welbourn, A. P. & Walter, D. S. (1986). *J. Med. Chem.* **29**, 2280–2284.