Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

2-(Acetylamino)-*N*-benzyl-2-(ethylsulfinyl)-acetamide: structural basis for lack of anticonvulsant activity

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Key indicators

Single-crystal X-ray study
T = 294 K
Mean σ(C–C) = 0.014 Å
R factor = 0.077
wR factor = 0.188
Data-to-parameter ratio = 8.7

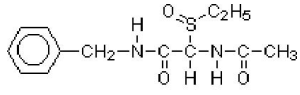
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 2 June 2005
Accepted 9 June 2005
Online 17 June 2005

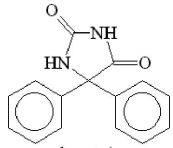
In the crystal structure of the title compound, $C_{13}H_{18}N_2O_3S$, there are two independent molecules in the asymmetric unit. Both molecules have linearly extended conformations, with interplanar angles between the two amide groups of 150.4 (3) and 148.8 (3)°. In addition to the standard N—H···O hydrogen bonds, which form infinite molecular chains parallel to the *a* axis, a host of weak non-standard C—H···O bonds and van der Waals contacts contribute to the crystal packing. Although the molecule contains stereochemical features consonant with anticonvulsant properties, steric interference by the ethylsulfinyl group may prevent interactions with receptors.

Comment

2-(Acetylamino)-*N*-benzyl-2-(ethylsulfinyl)acetamide belongs to a series of functionalized α-heteroatom-substituted synthetic amino acids which have been tested for anti-convulsant activity (Kohn *et al.*, 1991). We have determined the crystal structures of the two most potent compounds of the series and identified stereochemical features likely to be responsible for their anticonvulsant properties (Camerman *et al.*, 2005). Although the title compound, (I), potentially contains similar stereochemical features, it demonstrated poor anticonvulsant activity. We have therefore determined its structure in order to investigate the structural basis for this observation.



(I)



phenytoin

The molecular structure of (I) is presented in Fig. 1. The asymmetric unit contains two independent molecules, *A* and *B*. Both molecules have extended conformations, with an interplanar angle between the two amide-group planes (atoms C7/N8/C9/C10/O14 and C10/N11/C12/C13/O19) of 150.4 (3) and 148.8 (3)° for molecules *A* and *B*, respectively. The large anisotropic displacement parameters observed for the C atoms of the phenyl rings in both molecules are responsible for the shorter than usual average C—C phenyl ring distances

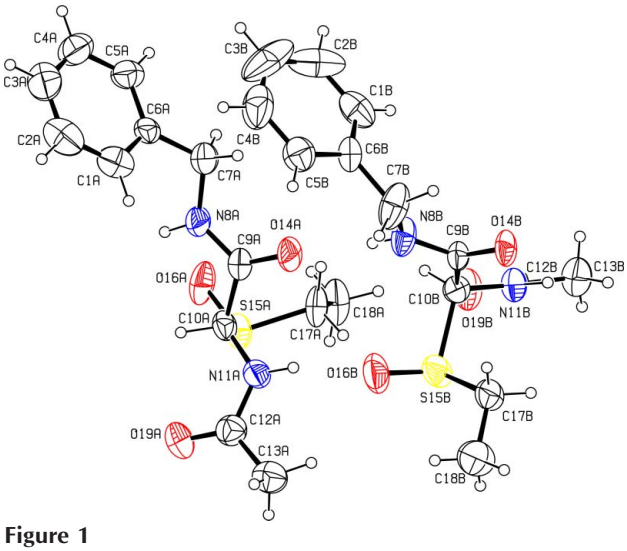


Figure 1
The structure of the asymmetric unit of (I), showing 30% probability displacement ellipsoids. H atoms are drawn as small circles of arbitrary radii.

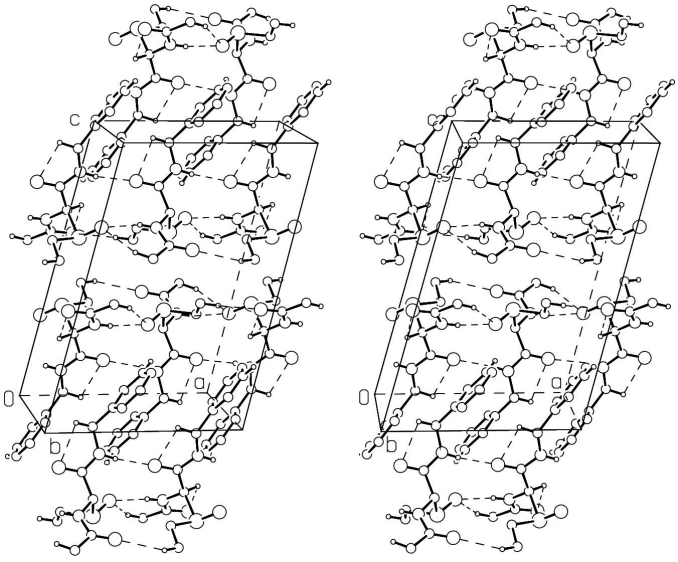


Figure 2
A stereoscopic view of the molecular packing and hydrogen-bond scheme (shown as dashed lines between atoms). Atoms are drawn as circles of arbitrary radii. For clarity, only H atoms involved in hydrogen bonds are shown.

of 1.36 and 1.35 Å in molecules *A* and *B*, respectively. Similar observations of large displacement parameters (disorder) in outer phenyl ring C atoms have been observed previously in the crystal structure of a closely related compound, 2-(acetylamino)-*N*-benzyl-2-(2-furyl)acetamide (Kohn *et al.*, 1990).

Relatively weak classical hydrogen bonds (Table 1) and loose crystal packing in the vicinity of the phenyl rings allow for high atomic displacement parameters, especially for the outer phenyl ring C atoms. Hydrogen-bonded molecules form infinite ribbons running parallel to the *a* axis. Weak C—H···O interactions, along with van der Waals contacts, also contribute to the crystal packing (Fig. 2).

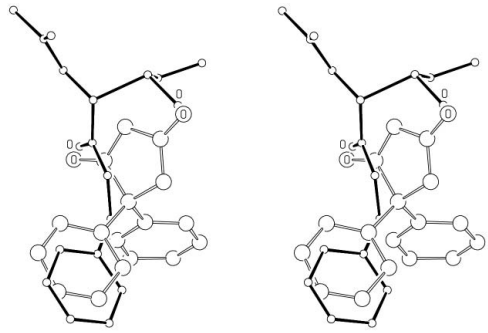


Figure 3
Superposition of phenytoin and molecule *A* of (I). The atoms fitted are O14, O16 and C5 of (I) with the carbonyl O atoms and a phenyl ring C atom of phenytoin.

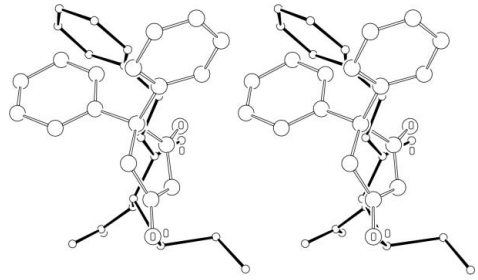


Figure 4
Superposition of phenytoin and molecule *B* of (I). The atoms fitted are O14, O16 and C5 of (I) with the carbonyl O atoms and a phenyl ring C atom of phenytoin.

Although the molecule of (I) contains in its chemical structure features which may potentially confer anticonvulsant properties (two appropriately spaced carbonyl/sulfonyl O atoms and a hydrophobic phenyl ring), superposition with similar features in the well known anticonvulsant drug phenytoin (Figs. 3 and 4) is revealing. In both enantiomers, the ethylsulfinyl group is responsible for interfering sterically with the electronegative O atoms approaching a putative receptor, thus preventing pharmacological action. In the two active molecules from the series of compounds tested, no such steric hindrance was observed in the structures (Camerman *et al.*, 2005).

Experimental

The title compound was obtained from Dr H. Kohn (Kohn *et al.*, 1991). Extensive crystallization experiments failed to produce good quality crystals of the title compound. Best results were obtained by very slow evaporation of a 1:1:1 benzene–chloroform–toluene solution. The crystals were small colorless prisms.

Crystal data

$C_{13}H_{18}N_2O_3S$
M_r = 282.35
Triclinic, $P\overline{1}$
a = 10.114 (2) Å
b = 10.260 (2) Å
c = 15.126 (3) Å
α = 78.70 (3)°
β = 73.88 (3)°
γ = 87.45 (3)°
V = 1478.6 (6) Å^3
Z = 4
D_x = 1.268 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 32 reflections
θ = 16–38°
μ = 2.00 mm^{-1}
T = 294 (2) K
Prism, colorless
0.31 × 0.11 × 0.09 mm

Data collection

Picker FACS-1 four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.765, T_{max} = 0.833
3030 measured reflections
3030 independent reflections
2057 reflections with $I > 2\sigma(I)$
θ_{max} = 50.0°
$h = -10 \rightarrow 0$
$k = -10 \rightarrow 10$
$l = -15 \rightarrow 14$
3 standard reflections
every 100 reflections
intensity decay: 3.4%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.077
$wR(F^2)$ = 0.188
S = 1.03
3030 reflections
350 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.063P)^2 + 2.4793P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.34 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N8A—H8A···O14B^{i}	0.86	2.14	2.988 (7)	169
N8B—H8B···O14A^{ii}	0.86	2.10	2.952 (7)	173
N11A—H11A···O16B^{ii}	0.86	1.96	2.808 (7)	167
N11B—H11B···O16A^{iii}	0.86	1.97	2.818 (7)	167
C4A—H4A···O16A^{iv}	0.93	2.57	3.442 (12)	156
C4B—H4B···O16B^{v}	0.93	2.60	3.453 (14)	153
C10A—H10A···O19A^{ii}	0.98	2.37	2.723 (8)	100
C13A—H13C···O16B^{ii}	0.96	2.42	3.252 (10)	145
C13B—H13E···O16A^{iii}	0.96	2.51	3.351 (8)	147
C18A—H18B···O19B^{ii}	0.96	2.53	3.289 (9)	136
C18B—H18E···O19A^{iii}	0.96	2.45	3.235 (10)	139
C7B—H7B1···O14B^{ii}	0.97	2.46	2.819 (9)	102
C7A—H7A2···O14A^{ii}	0.97	2.45	2.821 (9)	102

Symmetry codes: (i) $x+1, y, z$; (ii) x, y, z; (iii) $x-1, y, z$; (iv) $-x+2, -y, -z+2$; (v) $-x+1, -y+1, -z+2$.

All H atoms were placed in calculated positions and allowed for in the riding-model approximation. The range of C—H distances is 0.93–0.98 Å and N—H distances are 0.86 Å. One overall isotropic displacement parameter was refined for methyl H atoms [final value 0.15 (1) Å^2], another for phenyl and amide H atoms [final value 0.122 (8) Å^2] and a third for the remaining H atoms [final value 0.082 (7) Å^2].

Data collection: *Picker Manual* (Picker, 1967); cell refinement: *Picker Manual*; data reduction: *DATRDN* (Stewart, 1976); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP3 for Windows* (Farrugia, 1997) and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

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