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The Structure of (1,2-Benzisoxazol-3-yl)methanesulfonamide: A Novel Antiepileptic Drug

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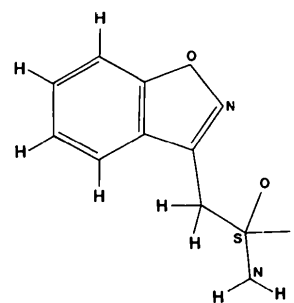
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Abstract. $C_8H_8N_2O_3S$, $M_r = 212.54$, monoclinic, $P2_1/a$, $a = 7.347(9)$, $b = 13.237(4)$, $c = 10.128(8)$ Å, $\beta = 108.916(6)^\circ$, $V = 931.9(1)$ Å³, $Z = 4$, $D_m = 1.52(4)$, $D_x = 1.514$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.54184$ Å, $\mu = 28.35$ cm⁻¹, $F(000) = 440$, room temperature, $R = 0.040$ for 1864 observed reflections. The sulfonamide N forms intermolecular hydrogen bonds with the benzisoxazole ring N and also with the O on the sulfonamide group. Centrosymmetrically related benzisoxazole ring pairs are π -bonded with a high degree of overlap.

Introduction. The title compound (zonisamide, I) is an experimental antiepileptic drug whose spectrum of activity in animals resembles that of phenytoin (one of the most extensively used drugs for the treatment of generalized seizures) but with a much higher ratio of

neurotoxic to effective anticonvulsant dose (Masuda, Utsui, Shiraishi, Karasawa, Yoshida & Shimizu, 1979). The structure analysis reported here was undertaken as part of a study of convulsant and anticonvulsant compounds.



(I)

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Experimental. Sample provided by Warner-Lambert/Parke-Davis Ltd. Colourless lozenge-shaped platelets prepared by slow evaporation from ethanol. Crystal $0.08 \times 0.24 \times 0.47$ mm used for data collection, preliminary Weissenberg photographs yielded approximate cell dimensions and showed monoclinic ($2/m$) Laue symmetry. Space group $P2_1/a$ from systematic absences ($h0l$, $h = 2n + 1$; $0k0$, $k = 2n + 1$); D_m by flotation (n -hexane/ CCl_4); Enraf-Nonius CAD-4 automated diffractometer, graphite monochromator, Cu $K\alpha$ radiation, 25 high-angle reflections ($25 \leq \theta \leq 30^\circ$) used to obtain accurate cell dimensions by least-squares fit. ω - 2θ scan, scan width $(0.85 + 0.15 \tan \theta)^\circ$, vertical aperture 4 mm. 2194 unique reflections measured ($0 \leq h \leq 8$, $0 \leq k \leq 16$, $-12 \leq l \leq 12$), 1951 with $I \geq 3\sigma(I)$, $3 \leq 2\theta \leq 69^\circ$; three intensity standards (044, 054 and 263) monitored at intervals of 100 reflections showed no significant variations during data collection; intensity data corrected for Lorentz-polarization factors; empirical absorption correction (North, Phillips & Mathews, 1968) applied to $|F|$ based on $\varphi = 0$ to $\varphi = 360^\circ$, normalized transmission factors 0.99 to 0.79. Structure solution by direct methods with *SHELX76* (Sheldrick, 1976). Atomic scattering factors from *SHELX76*; E map gave positions of S and attached non-hydrogen atoms. Refinement by full-matrix least squares with anisotropic thermal factors for all the non-hydrogen atoms, isotropic for H atoms [positions of H(1) and H(12), attached to N(1), initially from difference synthesis and subsequently by least squares; those of remaining six by calculation, C-H = 1.08 Å, riding on the C atoms]. The number of parameters refined was 141. Function minimized was $\sum w(|F_o| - |F_c|)^2$, $w = (\sigma^2 |F_o| + 0.0041 |F_o|^2)^{-1}$, $R = 0.040$, $wR = 0.050$, R (all data) = 0.054, max. (shift/ σ) = 0.17. Final difference electron density synthesis showed residual electron density -0.46 to $+0.23 \text{ e } \text{Å}^{-3}$. Geometrical calculations performed with *XANADU* (Roberts & Sheldrick, 1975) and molecular illustrations drawn with *PLUTO* (Motherwell & Clegg, 1978).

Discussion. The final atomic coordinates and equivalent isotropic thermal parameters for the non-hydrogen atoms, refined coordinates and isotropic thermal parameters for the amide hydrogens are given in Table 1.* Bond distances and angles are listed in Table 2. The molecular structure with the numbering scheme of the atoms is shown in Fig. 1, while Fig. 2 depicts the crystal packing.

The benzisoxazole moiety, comprising rings A and B (see Table 3), is planar. The equation of the least-

Table 1. Atomic positional parameters and equivalent isotropic temperature factors for non-hydrogen atoms with e.s.d.'s in parentheses

$$U_{\text{eq}} = (U_{11}U_{22}U_{33})^{1/3}$$

	x	y	z	$U_{\text{eq}}(\text{Å}^2)$
S(1)	0.36773 (8)	0.33484 (4)	0.39384 (5)	0.0406 (4)
O(2)	0.2426 (2)	0.3955 (1)	0.4449 (2)	0.0408 (9)
O(3)	0.2831 (3)	0.2651 (1)	0.2834 (2)	0.0536 (10)
O(1)	0.2526 (3)	0.6165 (1)	0.1090 (2)	0.0533 (10)
N(1)	0.5025 (3)	0.2727 (2)	0.5243 (2)	0.0501 (12)
N(2)	0.3619 (3)	0.5754 (1)	0.2392 (2)	0.0489 (11)
C(2)	0.5185 (3)	0.4190 (2)	0.3370 (2)	0.0401 (11)
C(3)	0.4020 (3)	0.4824 (1)	0.2184 (2)	0.0402 (11)
C(4)	0.3225 (3)	0.4557 (2)	0.0739 (2)	0.0419 (12)
C(5)	0.2310 (3)	0.5425 (2)	0.0112 (2)	0.0468 (12)
C(6)	0.1319 (4)	0.5503 (2)	-0.1308 (3)	0.0559 (14)
C(7)	0.1301 (4)	0.4660 (2)	-0.2077 (3)	0.0605 (17)
C(8)	0.2257 (5)	0.3762 (2)	-0.1469 (3)	0.0637 (18)
C(9)	0.3208 (4)	0.3688 (2)	-0.0063 (2)	0.0516 (16)
H(1)	0.575 (4)	0.312 (2)	0.599 (3)	0.057 (8)*
H(12)	0.561 (4)	0.229 (2)	0.497 (3)	0.053 (8)*

* U_{iso} .

Table 2. Bond lengths (Å) and bond angles ($^\circ$) with e.s.d.'s in parentheses

C(5)-C(6)	1.389 (3)	C(3)-C(2)	1.488 (3)
C(5)-C(4)	1.378 (3)	C(3)-N(2)	1.299 (3)
C(5)-O(1)	1.366 (3)	C(2)-S(1)	1.792 (2)
C(6)-C(7)	1.358 (4)	N(1)-S(1)	1.599 (2)
C(7)-C(8)	1.416 (4)	N(2)-O(1)	1.412 (2)
C(8)-C(9)	1.371 (4)	O(2)-S(1)	1.437 (2)
C(9)-C(4)	1.405 (3)	O(3)-S(1)	1.428 (2)
C(4)-C(3)	1.433 (3)		
C(6)-C(5)-C(4)	123.6 (2)	N(2)-C(3)-C(2)	120.3 (2)
C(6)-C(5)-O(1)	126.6 (2)	C(4)-C(3)-N(2)	111.1 (2)
C(4)-C(5)-O(1)	109.8 (2)	C(3)-C(2)-S(1)	110.8 (2)
C(7)-C(6)-C(5)	115.9 (2)	O(1)-N(2)-C(3)	107.7 (2)
C(8)-C(7)-C(6)	121.9 (2)	C(5)-O(1)-N(2)	107.4 (2)
C(8)-C(7)-C(5)	121.7 (3)	O(3)-S(1)-O(2)	118.4 (1)
C(8)-C(9)-C(4)	116.6 (2)	N(1)-S(1)-O(2)	106.7 (1)
C(5)-C(4)-C(3)	104.0 (2)	N(1)-S(1)-O(3)	108.1 (1)
C(9)-C(4)-C(5)	120.3 (2)	C(2)-S(1)-O(2)	107.6 (1)
C(9)-C(4)-C(3)	135.8 (2)	C(2)-S(1)-O(3)	107.9 (1)
C(4)-C(3)-C(2)	128.5 (2)	C(2)-S(1)-N(1)	107.7 (1)

Hydrogen-bond distances and angles

$D-H \cdots A$	Symmetry code	$D-H$ (Å)	$D-A$ (Å)	$H-A$ (Å)	$D-H \cdots A$ ($^\circ$)
N(1)-H(1) \cdots N(2)'	(i)	0.941 (32)	3.036 (3)	2.138	159.23
N(1)-H(12) \cdots O(2)'	(ii)	0.837 (33)	3.104 (2)	2.271	173.22

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

squares plane through atoms C(4), C(5), C(6), C(7), C(8), C(9) of the carbocyclic ring, A , is $0.839x' + 0.307y' - 0.450z' - 3.746 = 0$, where x', y', z' are the coordinates in Å with respect to the orthogonal cell (Rollet, 1965). The root mean square displacement of the six atoms from the plane is 0.005 Å. The average C-C bond length for the carbocyclic ring is 1.386 (5) Å; individual values range from 1.358 (4) to 1.416 (4) Å. Only one, C(5)-C(4)-C(9), of the internal angles of ring A is within two standard deviations of 120.0° ; the others show significant deviations from the mean value of $120.0(2)^\circ$. The fused five-membered ring, B , is

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51224 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

almost coplanar with ring *A* (dihedral angle 0.34°). The equation of the least-squares plane through its atoms [C(4), C(5), O(1), N(2), C(3)] is $0.842x' + 0.303y' - 0.447z' - 3.720 = 0$. The root mean square displacement of the six atoms from the plane is 0.001 \AA . The N(2)=C(3) [$1.299(3) \text{ \AA}$] bond displays typical double-bond character. The N(2)—O(1) [$1.412(2) \text{ \AA}$] bond lies within the normal limits expected for a single N—O bond and the C(5)—O(1) [$1.366(3) \text{ \AA}$] bond, although short, also lies within the anticipated range for a single C—O bond. Atom C(2), which links to the sulfonamide moiety, is nearly coplanar with ring *B*, deviating from it by 0.02 \AA . All these features indicate extensive electron delocalization within the benzisoxazole group. The arrangement of atoms around C(3) is unsymmetrical, bond angles being $120.3(2)$ and $128.5(2)^\circ$ respectively.

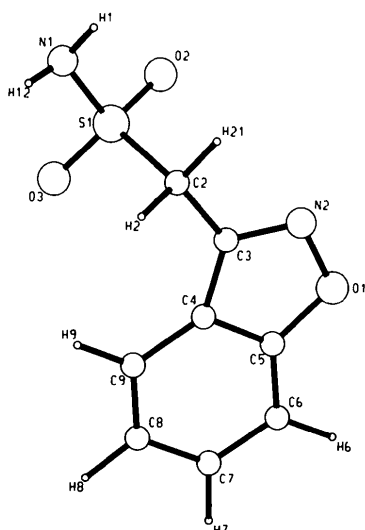


Fig. 1. View of the molecule showing atom numbering.

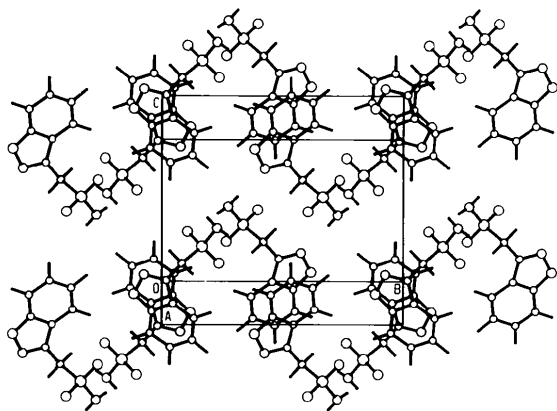


Fig. 2. The crystal structure viewed along *a*; *b* is horizontal and *c* vertical.

Table 3. Intermolecular close contacts and ring overlap distances

1	2	Symmetry code	Distance 1-2 (Å)
S(1)	N(2)	(i)	3.792 (2)
S(1)	N(1)	(ii)	3.664 (2)
O(3)	C(6)	(iii)	3.386 (4)
O(3)	C(3)	(ii)	3.273 (3)
O(2)	C(3)	(i)	3.387 (3)
C(6)	C(5)	(iv)	3.491 (3)
C_{AB}	C_{AB}	(iv)	3.413
C_A	C_B	(iv)	3.625

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

C_{AB} is the centroid of the ten-membered ring, and C_A and C_B the centroids of the six- and five-membered rings respectively.

The orientation of the sulfonamide moiety is characterized by the torsion angles N(2)—C(3)—C(2)—S(1), C(3)—C(2)—S(1)—N(1) and H(1)—N(1)—S(1)—C(2) which are $101.4(7)$, $-178.2(6)$, and $56.9(7)^\circ$ respectively. The arrangement of bonds around the S atom is distorted tetrahedral, a structural feature shared with acetazolamide (Mathew & Palenik, 1974) and sulthiame (Aupers, Carlisle & Lindley, 1974), two similar molecules which both exhibit anticonvulsant activity. Bond lengths S(1)—O(2) [$1.437(2) \text{ \AA}$] and S(1)—O(3) [$1.428(2) \text{ \AA}$] are both intermediate between a single and double S—O bond length, the double-bond character being more pronounced. These bond lengths for zonisamide are intermediate between the values quoted for acetazolamide (1.426 \AA) and sulthiame ($1.46, 1.47 \text{ \AA}$) respectively. It is also apparent that the O...O separation for zonisamide of 2.46 \AA is intermediate between the values given for acetazolamide and sulthiame (2.48 and 2.40 \AA respectively). These features are consistent with the O—S—O angle for zonisamide of $118.4(1)^\circ$ also being intermediate between those quoted for acetazolamide and sulthiame [$121.0(2)$ and $116.2(8)^\circ$ respectively] and suggest that reduction of the O—S—O angle increases the O...O repulsion in this group.

Intermolecular hydrogen bonds form between the sulfonamide N(1) and O(2) atoms and between N(1) and the ring nitrogen N(2) (Table 2). Other close intermolecular contacts (Table 3) indicate that centrosymmetrically related benzisoxazole ring pairs are π -bonded (Fig. 2) with a high degree of overlap.

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Structure of Thiomorpholin-3-one: Comments on the Geometry of Monocoordinated Metal Complexes

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Abstract. Perhydro-1,4-thiazin-3-one, C_4H_7NOS , $M_r = 117.2$, monoclinic, $P2_1/c$, $a = 10.642$ (2), $b = 6.089$ (1), $c = 9.133$ (1) Å, $\beta = 111.48$ (1)°, $V = 550.7$ (2) Å³, $Z = 4$, $D_x = 1.413$ g cm⁻³, $\lambda(Cu K\alpha) = 1.5418$ Å, $\mu = 41.6$ cm⁻¹, $F(000) = 248$, room temperature, $R = 0.038$, $wR = 0.054$ for 830 observed [$I > 3\sigma(I)$] reflections. The molecule adopts a half-chair conformation with the S atom 0.918 (2) Å from the best plane passing through the rest of the atoms in the molecule. The crystal structure is stabilized by a sequence of N–H...O hydrogen bonds resulting in a helical arrangement of molecules about an axis parallel to the b axis.

Introduction. Many of the p -block elements [p -block elements are defined as those whose p orbital is filling (Addison, 1961)] such as S, Se and halogens, have been shown to exhibit a characteristic pattern of secondary interactions (Rosenfield, Parthasarathy & Dunitz, 1977; Guru Row & Parthasarathy, 1981; Ramasubbu, Parthasarathy & Murray-Rust, 1986; Ramasubbu & Parthasarathy, 1987) which may be understood in terms of frontier molecular orbitals. Non-bonded interactions of S (and Se) with other atoms in a molecule have been analyzed in terms of electrophile–nucleophile interactions and have been categorized as Type I (involving electrophiles), Type II (involving nucleophiles), Type I–II pairing and Type III (interactions involving two atoms of one kind – for example S...S, Se...Se *etc.*) on the basis of spherical polar coordinates θ and ϕ , specifying the direction of the S(Se)... X vector, where X is the contacting atom,

with respect to the plane of the sulfide (selenide), Y–S(Se)–Z (Rosenfield *et al.*, 1977; Guru Row & Parthasarathy, 1981). The angle θ ($0 < \theta < 90^\circ$) is defined as the angle between the normal to the plane [Y–S(Se)–Z] and the vector S(Se)... X , and the angle ϕ ($0 < |\phi| < 180^\circ$) as the angle between the bisector of Y–S(Se)–Z and the direction of S(Se)... X projected onto the plane (Rosenfield *et al.*, 1977). To obtain more insight into the nature of such contacts we have undertaken crystallographic determinations of many S- and Se-containing compounds. In this paper we report the crystal structure of thiomorpholin-3-one which has a Type III contact.

Experimental. Crystals of the title compound were obtained from ethanol solutions by slow evaporation; crystal dimensions 0.3 × 0.3 × 0.1 mm; data collected on a CAD-4 diffractometer; Cu $K\alpha$ radiation; lattice parameters refined using 17 centered reflections ($16 < 2\theta < 32^\circ$); 1622 reflections measured of which 1162 were unique; $R_{\text{symm}} = 0.033$; reflections measured to the limit of Cu sphere using $\omega/2\theta$ scan; range of hkl : $h 0 \rightarrow 13$, $k 0 \rightarrow 7$ and $l -11 \rightarrow 11$; 830 reflections were significant with $I > 3\sigma(I)$; three reflections monitored every hour of X-ray exposure and showed no significant variation in intensity during the course of data collection; Lorentz and polarization, and anisotropy of absorption using ϕ -scan corrections applied; the average, maximum and minimum transmissions are 0.85, 0.99 and 0.64 respectively.

Structure was solved using *MULTAN80* (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980); structural parameters refined by full-matrix least-squares refinement; difference density maps cal-

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