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The Crystal and Molecular Structure of Sulfisoxazole

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Abstract ☐ Sulfisoxazole, $C_{11}H_{13}N_3O_3S$, crystallized in the orthorhombic system, space group Pbca, with a=14.492(1), b=11.563(1), c=14.900(2) Å and Z =8. Intensities for 1867(1360 observed) unique reflections were measured on a four-circle diffractometer with CuKα radiation(λ=1.5418Å). The structure was solved by heavy atom methods and refined by full-matrix least-squares procedures to a final R of 0.094. The benzene ring plane makes an angle of 68° with the plane of the isoxazole ring, which is planar. The conformational angle formed by the torsional angle C(4)-S-N(2)-C(7) is 54°. There are two intermolecular hydrogen bonds in the structure. One of them is of the type N-H···O with the length 2.970Å, and another is of the type N-H···N with the length 2.915Å. Thus two dimensional networks of hydrogen bonds form infinite molecular sheets parallel to the (001) plane. Adjacent sheets are bound together by van der Waals forces.

Keywords ☐ Sulfisoxazole, Heavy atom methods, Four-circle diffractometer, Full-matrix least-squares procedures

In spite of the increased use of antibiotics, the sulfanilamides remain of importance in the treatment of certain infections. The relationship between their chemical structures and pharmacological activities has been under investigation since their introduction into chemotherapy but has still not been completely elucidated.

Sulfisoxazole is one of the most potent sulfanilamides and is a typical example of this family of bacteriostatic drugs. The structural interest has centered on the conformational angle about the S-N bond and the angle between the benzene and isoxazole ring. This paper reports the results of a detailed study of the crystal and molecular structure of sulfisoxazole in which the complete stereochemistry of the molecule (in the crystal) has been revealed.

EXPERIMENTAL METHODS

Needle-like crystals of the compound were grown by slow evaporation from an acetone-ethanol solution at room temperature. Preliminary X-ray investigations using oscillation and Weissenberg photographic techniques showed that the crystal symmetry is orthorhombic with space group Pbca. The density of the crystal was measured by flotation in a mixture of carbonetetrachloride and chloroform. A crystal with approximate dimensions of 0.2×0.2×0.3 mm was used for the data collection. The lattice constants were refined by least-squares from the measured θ values for 25 well centered reflections, lying in the 2θ range of 25-65°. The crystal data are summarized in Table I. The intensities of 1867 independent reflections with $5° \leqq 2\theta \leqq 120°$ were measured using a Rigaku four-circle diffractometer with graphite-monochromatized Cu-Kα radiation in the ω-2θ scan mode, with a scan speed of $8°\text{min}^{-1}$ in 2θ and a scan width of $(1.2+0.5\tan\theta)°$ in ω. At

Table I: Crystal data of sulfisoxazole.

$C_{11}H_{13}N_3O_3S$	m.p.: 194°C
Orthorhombic	Space group: Pbca
M.W.: 267.30	Z: 8
a: 14.492(1)Å	V: 2496.8Å^3
b: 11.563(1)	F(000): 1120
c: 14.600(2)	D_c: 1.42gcm^{-3}
μ: 22.41mm^{-1}	D_m: 1.40gcm^{-3}
λ(Cu-Kα): 1.5418Å	

both ends of the scan range 10 sec background counts were taken for each reflection. Three standard reflections, measured after every 50 reflections during the data collection, showed only small deviations about their mean intensities. The intensity data were reduced to structure factors by the application of Lorentz and polarization factors, and no absorption corrections were applied.

STRUCTURE DETERMINATION AND REFINEMENT

The structure was determined by the heavy-atom methods. The position of the sulfur atom was deduced from a sharpened three-dimensional Patterson synthesis. The positions of the remaining seventeen non-hydrogen atoms were derived from a three dimensional, sulfur-phased, Fourier-synthesis. The trial structure was refined by full-matrix least-squares procedures using the program SHELX 76[1]. In the refinement of the structure, 1360 structure factors with $F_{obs} \geqq 5\sigma F_{obs}$, where σF_{obs} is the estimated standard deviation, were used. After refinement of the positional and anisotropic thermal parameters a difference Fourier map was computed and this gave all the hydrogen atom positions. In the subsequent refinements the hydrogen atoms were given the same thermal parameters. The final R value was 0.094. The final atomic

Table II: Positional and thermal parameters for sulfisoxazole.

(a) Positional parameters with e.s.d.'s.

	X/a	Y/b	Z/c
S	0.1658(2)	0.0703(3)	0.0920(2)
O(1)	0.1222(5)	−0.0376(8)	0.0696(6)
O(2)	0.1156(6)	0.1771(8)	0.0840(6)
O(3)	0.2246(6)	−0.1266(7)	0.2250(6)
N(1)	0.5068(9)	0.1101(12)	−0.1196(10)
N(2)	0.1928(7)	0.0671(8)	0.1996(7)
N(3)	0.2921(7)	−0.1975(8)	0.2678(7)
C(1)	0.4286(8)	0.0973(11)	−0.0690(8)
C(2)	0.4004(8)	0.1886(11)	−0.0138(9)
C(3)	0.3203(9)	0.1792(10)	0.0366(8)
C(4)	0.2670(7)	0.0806(10)	0.0313(7)
C(5)	0.2958(9)	−0.0100(13)	−0.0220(8)
C(6)	0.3749(9)	−0.0007(11)	−0.0714(9)
C(7)	0.2565(11)	−0.0157(10)	0.2317(8)
C(8)	0.3338(8)	−0.0088(9)	0.2759(8)
C(9)	0.3552(9)	−0.1255(10)	0.2974(8)
C(10)	0.4354(11)	−0.1713(16)	0.3496(12)
C(11)	0.3920(11)	0.0979(13)	0.2959(14)
N(1)H′	0.526(12)	0.049(13)	−0.127(12)
N(1)H″	0.545(8)	0.172(11)	−0.126(8)
C(2)H	0.429(8)	0.242(11)	−0.010(8)
C(3)H	0.292(8)	0.250(11)	0.082(8)
C(5)H	0.262(8)	−0.076(11)	−0.023(8)
C(6)H	0.406(8)	−0.053(11)	−0.108(8)
N(2)H	0.203(8)	0.139(11)	0.217(8)
C(10)H′	0.460(9)	−0.122(11)	0.407(9)
C(10)H″	0.452(8)	−0.269(10)	0.323(8)
C(10)H‴	0.481(9)	−0.141(13)	0.337(10)
C(11)H′	0.463(9)	0.094(11)	0.299(8)
C(11)H″	0.378(8)	0.133(11)	0.351(8)
C(11)H‴	0.376(8)	0.167(10)	0.238(8)

A list of structure factors is kept as a document at the office of the Pharmaceutical Society of Korea, College of Pharmacy, Seoul National University, Seoul 151, Korea.

(b) Thermal parameters $u_{ij}(\times 10^3)$ with e.s.d.'s of the nonhydrogen atoms.

The u_{ij} values given are defined by the temperature factor $\exp[-2\pi^2(u_{11}h^2a^{*2}+u_{22}k^2b^{*2}+u_{33}l^2c^{*2}+2u_{12}hka^*b^*+2u_{13}hla^*c^*+2u_{23}klb^*c^*)]$.

	u_{11}	u_{22}	u_{33}	u_{23}	u_{13}	u_{12}
S	26(1)	41(2)	50(2)	−1(2)	−3(1)	4(1)
O(1)	33(4)	56(6)	70(6)	−17(5)	2(4)	−14(4)
O(2)	46(5)	54(5)	72(6)	8(5)	−4(5)	20(4)
O(3)	46(5)	28(4)	62(6)	−2(4)	−11(4)	−10(4)
N(1)	53(8)	56(10)	67(8)	1(8)	19(6)	−18(7)
N(2)	32(6)	23(5)	51(7)	4(5)	6(5)	3(5)
N(3)	53(6)	29(6)	63(8)	−1(6)	−14(6)	−7(6)
C(1)	46(7)	44(8)	28(6)	15(6)	5(6)	−1(6)
C(2)	49(7)	28(7)	55(8)	13(7)	−4(6)	−19(6)
C(3)	42(8)	21(6)	40(7)	0(5)	0(6)	2(6)
C(4)	27(6)	35(6)	27(6)	3(5)	4(5)	1(5)
C(5)	47(8)	46(8)	44(8)	−4(7)	1(7)	−14(7)
C(6)	60(7)	32(7)	49(8)	−16(6)	34(7)	−3(6)
C(7)	42(10)	21(7)	33(8)	−7(6)	9(6)	−4(7)
C(8)	29(6)	13(6)	52(8)	−14(6)	6(6)	−10(5)
C(9)	45(8)	34(7)	32(7)	−4(6)	2(6)	1(6)
C(10)	58(10	53(11)	69(11)	−5(9)	−27(8)	−5(9)
C(11)	49(5)	38(9)	91(14)	−19(9)	−9(10)	−12(7)

parameters and thermal parameters are listed in Tables II(a) and (b).

STRUCTURE DESCRIPTION AND DISCUSSION

The bond lengths and angles with an atomic numbering scheme are given in Fig. 1. The bond lengths and angles are collected in Tables III(a) and (b).

The average value found for the C-C bond lengths in benzene ring is 1.381Å which is in agreement with the C-C bond length in crystalline benzene of 1.392Å[2]. The bond angles in benzene ring differ only slightly from the theoretical value of 120°. The C(1)-N(1) bond length of 1.368Å is in the usual range found in *p*-amino-substituted benzene (e.g. 1.368Å in sulfathiazole[3], 1.385Å in β-sulphanilamide[4]).

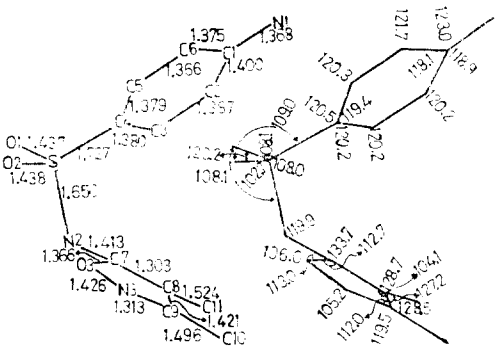

Fig. 1: Bond lengths (Å) and angles (°) in sulfisoxazole.

The atoms around the S atom are arranged in a distorted tetrahedral configuration. The O(1)-S-O(2) angle increases to 120.2° while the O(1)-S-N(2) angle narrows to 102.7°.

Table III: Bond lengths(Å) and angles(°) for sulfisoxazole.

(a) Bond lengths(Å) with e.s.d.'s.

S—C(4)	1.727(8)	C(9)—N(3)	1.313(12)
S—O(1)	1.437(7)	C(7)—O(3)	1.366(11)
S—O(2)	1.438(7)	N(3)—O(3)	1.426(10)
S—N(2)	1.650(9)	N(1)—N(1)H′	0.77(12)
C(1)—N(1)	1.368(14)	N(1)—N(1)H″	0.90(10)
C(1)—C(2)	1.400(14)	N(2)—N(2)H	0.88(10)
C(2)—C(3)	1.387(14)	C(2)—C(2)H	0.74(10)
C(3)—C(4)	1.380(13)	C(3)—C(3)H	1.14(10)
C(4)—C(5)	1.379(14)	C(5)—C(5)H	0.91(10)
C(5)—C(6)	1.366(14)	C(6)—C(6)H	0.93(10)
C(1)—C(6)	1.375(14)	C(10)—C(10)H′	1.09(10)
C(7)—N(2)	1.413(14)	C(10)—C(10)H″	1.22(10)
C(7)—C(8)	1.303(15)	C(10)—C(10)H‴	0.77(11)
C(8)—C(9)	1.421(13)	C(11)—C(11)H′	1.03(10)
C(8)—C(11)	1.524(14)	C(11(—C(11)H″	0.93(10)
C(9)—C(10)	1.496(15)	C(11)—C(11)H‴	1.20(10)

(b) Bond angles (°) with e.s.d. 's.

O(1)—S—O(2)	120.2(4)	C(9)—C(8)—C(11)	127.2(10)
O(1)—S—N(2)	108.1(4)	C(9)—N(3)—O(3)	105.2(7)
O(2)—S—N(2)	102.7(4)	N(2)—C(7)—O(3)	113.3(10)
S—C(4)—C(3)	120.2(7)	N(2)—C(7)—C(8)	133.7(9)
O(1)—S—C(4)	108.1(4)	N(3)—O(3)—C(7)	106.0(8)
O(2)—S—C(4)	109.0(4)	N(3)—C(9)—C(10)	119.5(10)
C(4)—S—N(2)	108.0(4)	C(1)—N(1)—N(1)H′	106(11)
S—C(4)—C(5)	120.5(7)	C(1)—N(1)—N(1)H″	130(6)
S—N(2)—C(7)	119.9(7)	C(1)H′—N(1)—H″	119(13)
N(1)—C(1)—C(2)	118.9(10)	C(1)—C(2)—C(2)H	120(8)
C(1)—C(1)—N(6)	123.0(10)	C(3)—C(2)—C(2)H	120(8)
C(1)—C(2)—C(3)	120.2(9)	C(2)—C(3)—C(3)H	125(5)
C(2)—C(3)—C(4)	120.2(9)	C(4)—C(3)—C(3)H	115(5)
C(3)—C(4)—C(5)	119.4(9)	C(4)—C(5)—C(5)H	119(6)
C(4)—C(5)—C(6)	120.3(10)	C(6)—C(5)—C(5)H	120(6)
C(5)—C(6)—C(1)	121.7(10)	C(5)—C(6)—C(6)H	132(6)
C(6)—C(1)—C(2)	118.1(9)	C(1)—C(6)—C(6)H	106(6)
C(7)—C(8)—C(9)	104.1(8)	C(7)—N(2)—N(2)H	115(6)
C(7)—C(8)—C(11)	128.7(10)	S—N(2)—N(2)H	107(6)
C(8)—C(9)—N(3)	112.0(9)	C(9)—C(10)—C(10)H′	118(6)
C(8)—C(9)—C(10)	128.5(10)	C(9)—C(10)—C(10)H″	108(5)
C(8)—C(7)—O(3)	112.7(10)	C(9)—C(10)—C(10)H‴	112(9)

C(10)H′—C(10)—C(10)H″	133(7)	C(8)—C(11)—C(11)H‴	107(5)
C(10)H′—C(10)—C(10)H‴	72(10)	C(11)H′—C(11)—C(11)H″	101(9)
C(10)H′—C(10—C(10)H‴	100(10)	C(11)H′—C(11)—C(11)H‴	104(8)
C(8)—C(11)—C(11)H′	122(6)	C(11)H″—C(11)—C(11)H‴	108(8)
C(8)—C(11)—C(11)H″	114(6)		

The average value of the angles around the S atom, 109.4°, is close to the ideal value. The two S-O bonds (1.437 and 1.438Å) have comparable and high π-bond character, ~60% according to Cruickshank[5]. The S-C(4) bond length of 1.727Å is slightly less than the theoretical S-C(sp^2) value 1.75Å calculated from the atomic radii and electronegativities given by Truter[6]. The S-N(2) bond length of 1.650 Å is in agreement with the 1.641Å in sulfametrole[7], the 1.641Å in tolasemide (II)[8] and the 1.644Å in chlorpropamide[9].

The bond lengths (C(7)-C(8) 1.303, C(7)-O(3) 1.366, C(8)-C(9) 1.421, C(9)-N(3) 1.313 and N(3)-O(3) 1.426Å) and angles in the isoxazole ring agree well with their equivalents in other isoxazole compounds[10~13].

The C-C single bond lengths out of the isoxazole ring are 1.496 and 1.524Å, as compared to the C-C bond lengths of 1.495 and 1.505Å in (RS)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) monohydrate[10].

Table IV shows the deviations of the atoms from the best planes through the benzene and isoxazole rings.

The benzene and isoxazole rings are planar within the experimental error. The N(1) and S atoms lie nearly in the benzene ring plane and methyl C atoms C(10) and C(11), attached to the isoxazole ring, lie nearly in this plane, but N(2) is displaced out of the plane of the isoxazole ring by 0.128Å. The benzene ring plane makes an angle of 68° with the isoxazole ring plane. The conformation angles about the

Table IV: Equations of the least-squares planes and deviations of the atoms from the planes in sulfisoxazole.

(a) LS plane through the atoms of benzeng ring.

$0.5206x-0.3872y+0.7610z=2.0202$

C(1)*	−0.005Å	S	−0.041Å
C(2)*	−0.001	N(1)	−0.046
C(3)*	0.009		
C(4)*	−0.012		
C(5)*	0.007		
C(6)*	0.002		

(b) LS plane through the atoms of isoxazole ring.

$-0.4975x+0.0963y+0.8621z=1.1203$

C(7)*	−0.011Å	C(10)	0.040Å
C(8)*	0.007	C(11)	−0.037
C(9)*	−0.001	N(2)	0.128
O(3)*	0.010		
N(3)*	−0.005		

* Atoms included in the calculations of the least-squares planes.

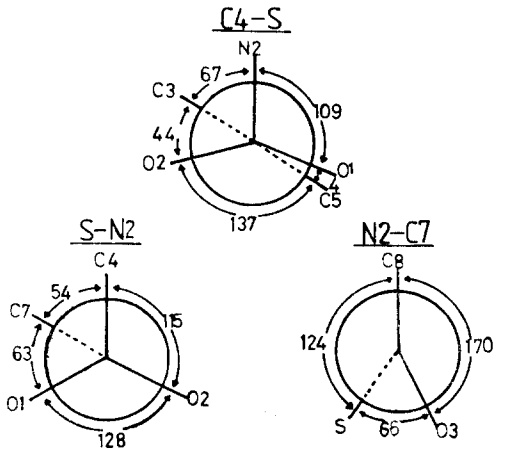

Fig. 2: Newman projection down the C(4)-S, S-N(2) and N(2)-C(7) bonds in sulfisoxazole showing the conformation angles in degrees.

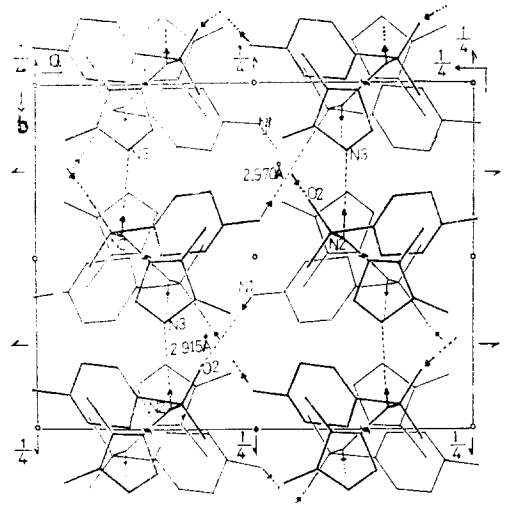

Fig. 3: The molecular packing diagram, excluding hydrogen atoms, viewed down the b-axis of sulfisoxazole.

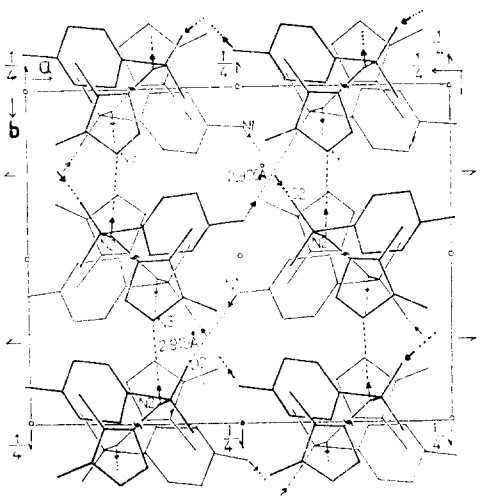

Fig. 4: The molecular packing diagram, excluding hydrogen atoms, viewed down the c-axis of sulfisoxazole.

C(4)-S, S-N(2) and N(2)-C(7) bonds are given in Fig. 2. Reference to Table V shows a comparison of the conformational angles about the S-N(2) bond obtained from the related compounds[14~17] containing sufonyl group. The overall conformation of these compounds is quite similar; these molecules have a gauche form about the S-N(2) bond and some differences of conformational angles among these compounds might be due to the crystal packing forces. The molecular packing is dipicted in Figs. 3 and 4 which represent projections of the crystal structure along the b and c axes respectively. Amino nitrogen atom, N(1), forms only one hydrogen bond of length 2.970Å with the atom O(2) which is related by the symmetry operation, $(1/2+x,\ 1/2-y,\ -z)$. The imino nitrogen atom, N(2), forms hydrogen bond of length 2.915Å with the isoxazole nitrogen, N(3), related by the symmetry operation, $(1/2-x,\ 1/2+y,\ z)$. Details of the hydrogen bonds and other intermolecular contact lengths are given in Table VI. As shown in Table VI, there are six intermolecular contacts less than 3.5Å. Thus the molecules are arranged in infinite strings along the a and b axial directions by means of intermolecular hydrogen bonds and the inter-layer force appears to be van der Waals in character.

Table V: A comparison of conformation angles about the S-N(2) bond in sulfisoxazole and related compounds.

	A	B	C	D	E
C(4)-S-N(2)-C(7)	54°	61°	73°	76°	77°
C(4)-S-N(2)-O(2)	115	118	115	114	115
O(1)-S-N(2)-O(2)	128	125	128	127	126
C(7)-S-N(2)-O(1)	63	56	47	42	42

A: sulfisoxazole, B: sulfadimethoxine[14], C: sodium sulfisoxazole hexahydrate[15], D: sulfaguanidine monohydrate[16], E: sulfadiazine[17]

Table VI: Details of the hydrogen bonds and other intermolecular atomic contacts(Å) in sulfisoxazole.

(a) Hydrogen bonds.

D-H···A	D-H(Å)	H···A(Å)	D···A(Å)	<D-H···A(°)
N(1)-N(1)H''···O(2)(a)	0.90	2.21	2.970	156
N(2)-N(2)H···N(3)(b)	0.88	2.05	2.915	170

(b) Intermolecular atomic contacts less than the sum of the van der Waals radii.

C(2)···O(1)(b)	3.417Å
C(3)···O(1)(b)	3.415
C(10)···O(1)(c)	3.341
N(3)···O(2)(b)	3.377
N(1)···C(9)(d)	3.324
N(1)···C(8)(d)	3.484

symmetry code

	x,	y,	z
a	$\frac{1}{2}+x$,	$\frac{1}{2}-y$,	z
b	$\frac{1}{2}-x$,	$\frac{1}{2}+y$,	z
c	$\frac{1}{2}+x$,	y,	$\frac{1}{2}-z$
d	$1-x$,	$-y$,	$-z$

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