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The Structure of the Methyl Ester of 5,5-Dimethyl-2-(2-phenoxyethyl-5-oxo-1,3-oxazolin-4-ylidene)-1,3-thiazolidine-4-carboxylic Acid

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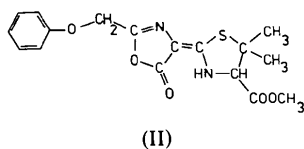
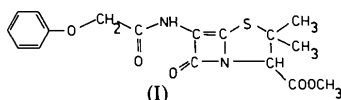
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Abstract

$C_{17}H_{18}N_2O_5S$ is monoclinic, space group $P2_1/c$, with $a = 10.60$ (3), $b = 15.53$ (3), $c = 12.63$ (3) Å, $\beta = 61.97$ (2)°, $Z = 4$, $V = 1835.25$ Å³, $\mu(Cu K\alpha) = 1.714$ mm⁻¹; $R = 0.097$ for 1738 observed reflexions. The crystallographic results confirm the structure reported by Bachi & Vaya [*Tetrahedron Lett.* (1977), pp. 2209–2212].

Introduction

$C_{17}H_{18}N_2O_5S$ was first reported by Brandt, Bassignani & Re (1976*a,b*) to have the configuration (I), i.e. that of a DL-5,6-didehydropenicillin, on the basis of spectroscopic data (IR, ¹H and ¹³C NMR, mass spectrometry). Bachi & Vaya (1977) suggested configuration (II) on the basis of a comparative study of UV and IR spectra.



X-ray structure analysis was carried out as a preliminary to investigation of the reported weak antibacterial activity of the unsaturated dehydropenicillin. The analysis has confirmed structure (II).

Experimental

The compound was obtained from Snamprogetti Società per Azioni. Single crystals were prepared by dissolving 30 mg in 2 ml ethyl acetate. To this solution, 1 ml cyclohexane was added slowly to prevent clouding. The solution was placed in a water bath warmed to not more than 313 K and protected from light and rapid evaporation. The compound crystallized as clear needle-shaped single crystals on slow cooling of the solution.

The cell dimensions were determined from zero-level equi-inclination Weissenberg photographs, the camera radius being determined from high-angle reflexions from an annealed gold wire. Systematic absences $h0l$, $l = 2n + 1$ and $0k0$, $k = 2n + 1$ indicated space group $P2_1/c$.

Intensities were recorded by the equi-inclination method on Stoe and Nonius Weissenberg cameras with Ni-filtered Cu $K\alpha$ radiation ($\lambda = 1.5418$ Å) and the multiple-film technique. The crystals were rotated about c^* with the long edge of the crystal parallel to the rotation axis. The X-ray films showed severe reduction in intensity of reflexions at high $\sin \theta$ after crystals had prolonged exposure to X-rays. Four crystals were used for collection of intensities which were measured by the Science Research Council microdensitometer at Daresbury. 1738 reflexions were of measurable intensity.

Structure determination and refinement

The major computations were performed on an ICL 1903A computer with *SHELX* (Sheldrick, 1976). The

structure was solved by direct methods (Germain, Main & Woolfson, 1970, 1971; Germain & Woolfson, 1968; Hauptman & Karle, 1956; Karle & Hauptman, 1956).

Unweighted full-matrix least-squares isotropic refinement including interlayer and overall scale factors produced $R = \sum |F_o| - |F_c| / \sum |F_o| = 0.175$. Anisotropic refinement initially resulted in $R = 0.106$ with H atoms included. H atoms were given the isotropic temperature factors of the carrier atoms, obtained at the isotropic refinement stage, the bond length being fixed at 1.08 Å.

An $F_o - F_c$ synthesis revealed a significant positive peak adjacent to O(19) which could not be removed during refinement. Further refinement was carried out with O(19) replaced by O[19(2)] in the position indicated by the $F_o - F_c$ peak. A further $F_o - F_c$ synthesis showed a positive peak at the previous position, O[19(1)]. The ratio of the peak heights in both syntheses (~2:1) was taken as an indication of alternative site occupation, in part confirmed by the departure from the expected benzene C—C length (1.39 Å) in the ring attached to O(19). Anisotropic refinement of the O[19(1)], O[19(2)] positions, performed with site-occupation factors of 0.7 and 0.3 respectively, finally resulted in $R = 0.097$.* The residual electron density in the final difference map was within -0.39 and 0.42 e Å⁻³. No further improvement could be made in F_o/F_c correlation probably due to the deterioration of the crystals during X-ray exposure.

Discussion

The final coordinates of the non-hydrogen atoms are given in Table 1, those of the H atoms in Table 2. Bond distances and angles are in Tables 3 and 4. Fig. 1 shows the labelling of the non-hydrogen atoms. Fig. 2 gives a view of the cell contents along *b* and Fig. 3 shows the cell contents viewed along *a*. The compound was claimed by Brandt, Bassignani & Re (1976*b*) to

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34691 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

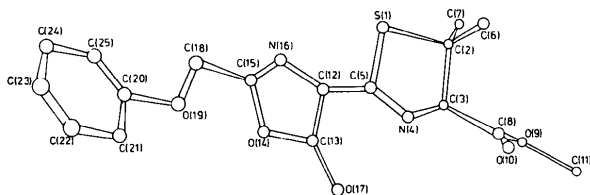


Fig. 1. Schematic labelling of the non-hydrogen atoms in the title compound.

Table 1. Final fractional coordinates ($\times 10^4$)

E.s.d.'s in parentheses are with respect to the last figures.

	x	y	z
S(1)	95 (3)	4164 (2)	1227 (3)
C(2)	1928 (13)	3912 (8)	990 (12)
C(3)	1831 (12)	3999 (7)	2277 (11)
N(4)	738 (9)	4650 (6)	2906 (7)
C(5)	-255 (11)	4733 (6)	2548 (9)
C(6)	2938 (17)	4553 (10)	83 (13)
C(7)	2297 (17)	3003 (9)	489 (14)
C(8)	3215 (13)	4248 (8)	2275 (11)
O(9)	4011 (10)	3558 (6)	2172 (9)
O(10)	3581 (10)	4975 (6)	2388 (10)
C(11)	5365 (13)	3650 (11)	2194 (14)
C(12)	-1502 (10)	5204 (6)	3204 (8)
C(13)	-1837 (10)	5604 (6)	4340 (9)
O(14)	-3196 (6)	5966 (4)	4710 (6)
C(15)	-3549 (9)	5775 (6)	3782 (8)
N(16)	-2609 (8)	5353 (5)	2881 (7)
O(17)	-1238 (8)	5685 (5)	4989 (7)
C(18)	-4939 (11)	6082 (7)	3904 (11)
O[19(1)]	-5397 (11)	6750 (6)	4755 (11)
O[19(2)]	-5858 (20)	6238 (14)	5007 (18)
C(20)	-6858 (11)	7007 (7)	5220 (9)
C(21)	-7166 (13)	7653 (8)	6090 (10)
C(22)	-8453 (14)	8077 (7)	6469 (11)
C(23)	-9336 (12)	7895 (7)	5991 (10)
C(24)	-9031 (10)	7251 (7)	5150 (11)
C(25)	-7744 (11)	6787 (6)	4716 (10)

Table 2. Coordinates of the H atoms ($\times 10^4$)

E.s.d.'s in parentheses are with respect to the last figures.

	x	y	z
H(C3)	1542 (12)	3378 (7)	2711 (11)
H(N4)	962 (9)	4869 (6)	3228 (7)
H(C6)(1)	2689 (17)	5197 (10)	442 (13)
H(C6)(2)	2823 (17)	4514 (10)	-722 (13)
H(C6)(3)	4024 (17)	4397 (10)	-128 (13)
H(C7)(1)	1566 (17)	2561 (9)	1155 (14)
H(C7)(2)	3380 (17)	2841 (9)	280 (14)
H(C7)(3)	2180 (17)	2959 (9)	-313 (14)
H(C11)(1)	5851 (13)	3024 (11)	2100 (14)
H(C11)(2)	5164 (13)	3930 (11)	3042 (14)
H(C11)(3)	6077 (13)	4063 (11)	1471 (14)
H(C18)(1)	-5673 (11)	5548 (7)	4137 (11)
H(C18)(2)	-4799 (11)	6369 (7)	3077 (11)
H(C21)	-6405 (13)	7797 (8)	6407 (10)
H(C22)	-8777 (14)	8553 (7)	7173 (11)
H(C23)	-292 (12)	8273 (7)	6248 (10)
H(C24)	-9806 (10)	7092 (7)	4853 (11)
H(C25)	-7436 (11)	6305 (6)	4022 (10)

show only weak antibacterial activity when tested against *Bacillus subtilis* and *Staphylococcus aureus* by the agar diffusion disc assay. It is therefore of interest to compare the conformation of the part of the molecule in common with that of penicillins, the thiazolidine ring. Boles & Girven (1976) compare the conformation of thiazolidine rings of known penicillin

Table 3. Bond lengths (Å) and their *e.s.d.*'s

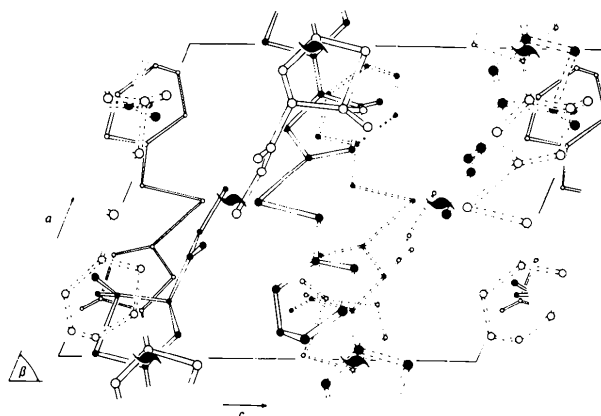
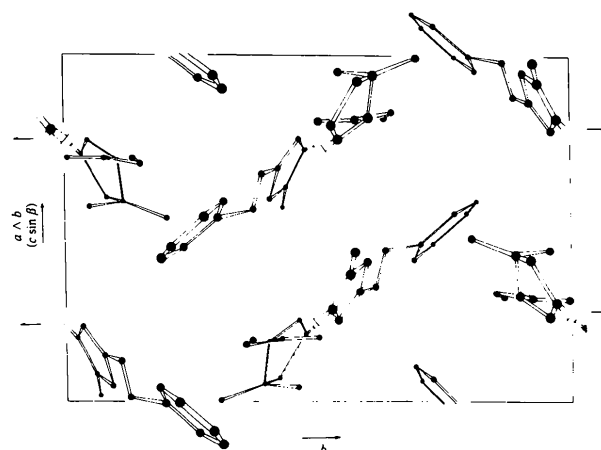
S(1)—C(2)	1.863 (15)	C(13)—O(14)	1.407 (12)
S(1)—C(5)	1.766 (11)	O(14)—C(15)	1.419 (15)
C(2)—C(3)	1.586 (22)	C(15)—N(16)	1.285 (11)
C(2)—C(6)	1.515 (18)	C(15)—C(18)	1.486 (17)
C(2)—C(7)	1.521 (19)	C(18)—O[19(1)]	1.407 (9)
C(3)—C(8)	1.516 (21)	C(18)—O[19(2)]	1.293 (20)
C(3)—N(4)	1.459 (13)	O[19(1)]—C(20)	1.431 (10)
N(4)—C(5)	1.333 (17)	O[19(2)]—C(20)	1.535 (19)
C(5)—C(12)	1.392 (13)	C(20)—C(21)	1.408 (16)
C(8)—O(9)	1.331 (17)	C(20)—C(25)	1.403 (19)
C(8)—O(10)	1.224 (17)	C(21)—C(22)	1.381 (19)
O(9)—C(11)	1.456 (20)	C(22)—C(23)	1.361 (23)
C(12)—C(13)	1.446 (15)	C(23)—C(24)	1.383 (16)
C(12)—N(16)	1.432 (16)	C(24)—C(25)	1.407 (14)
C(13)—O(17)	1.256 (17)		

Table 4. Bond angles (°) and their *e.s.d.*'s

C(5)—S(1)—C(2)	89.8 (0.6)	O(17)—C(13)—C(12)	136.6 (0.9)
C(3)—C(2)—S(1)	104.9 (0.7)	O(17)—C(13)—O(14)	119.7 (0.8)
C(6)—C(2)—S(1)	107.2 (1.1)	C(15)—O(14)—C(13)	105.6 (0.7)
C(6)—C(2)—C(3)	113.7 (1.3)	N(16)—C(15)—O(14)	116.2 (0.9)
C(7)—C(2)—S(1)	107.9 (1.1)	C(18)—C(15)—O(14)	118.7 (0.8)
C(7)—C(2)—C(3)	112.7 (1.2)	C(18)—C(15)—N(16)	125.0 (1.1)
C(7)—C(2)—C(6)	110.1 (1.0)	C(15)—N(16)—C(12)	103.2 (0.9)
N(4)—C(3)—C(2)	105.6 (1.1)	O[19(1)]—C(18)—C(15)	106.6 (0.4)
C(8)—C(3)—C(2)	115.1 (0.9)	O[19(2)]—C(18)—C(15)	112.3 (0.9)
C(8)—C(3)—N(4)	110.1 (1.0)	C(20)—O[19(1)]—C(18)	115.9 (0.7)
C(5)—N(4)—C(3)	115.7 (1.0)	C(20)—O[19(2)]—C(18)	116.3 (1.3)
N(4)—C(5)—S(1)	115.0 (0.7)	C(21)—C(20)—O[19(1)]	109.1 (0.4)
C(12)—C(5)—N(4)	121.9 (1.0)	C(21)—C(20)—O[19(2)]	125.4 (0.9)
C(12)—C(5)—S(1)	123.0 (1.1)	C(25)—C(20)—O[19(1)]	124.9 (0.4)
O(9)—C(8)—C(3)	111.3 (1.1)	C(25)—C(20)—O[19(2)]	106.6 (0.9)
O(10)—C(8)—C(3)	126.5 (1.2)	C(25)—C(20)—C(21)	124.7 (1.1)
O(10)—C(8)—O(9)	122.2 (1.4)	C(22)—C(21)—C(20)	116.0 (1.4)
C(11)—O(9)—C(8)	120.3 (1.1)	C(23)—C(22)—C(21)	121.3 (1.1)
C(13)—C(12)—C(5)	122.5 (1.2)	C(24)—C(23)—C(22)	122.0 (1.1)
N(16)—C(12)—C(5)	126.3 (1.0)	C(25)—C(24)—C(23)	120.3 (1.3)
N(16)—C(12)—C(13)	111.2 (0.8)	C(24)—C(25)—C(20)	115.6 (1.0)
O(14)—C(13)—C(12)	103.7 (1.0)		

structures. The ring exists with four of its five atoms nearly coplanar. The plane containing S(1), C(2) and C(5) is defined by $-0.2073x - 2.4491y + z = -0.8991$, where x , y and z are measured in fractions of cell edges. N(4) is 0.19 (1) Å out of this plane, and may be considered as in comparable structures to be the fourth atom in the plane. C(3) is 0.60 (1) Å out of the plane defined above. The configuration of the thiazolidine ring is therefore similar to that in phenoxymethylpenicillin, *p*-bromopenicillin and potassium benzylpenicillin, characterized by C(3) out of the common plane.

N(4)—C(5), 1.333 Å in the present compound, is significantly shorter than the equivalent bond in penicillin nuclei where the thiazolidine ring is constrained by the adjacent β -lactam, *e.g.* in amoxicillin trihydrate (Boles, Girven & Gane, 1978), ampicillin anhydrate (Boles & Girven, 1976) and ampicillin trihydrate (James, Hall & Hodgkin, 1968) the N(4)—C(5) lengths are 1.49, 1.45 and 1.47 Å respectively.

Fig. 2. The crystal structure viewed along *b*.Fig. 3. The crystal structure viewed along *a*.

O[19(1)] and O[19(2)] have positions almost symmetrical about the O(19)—C(20) bond, the angles O[19(1)]—C(20)—C(21) and O[19(2)]—C(20)—C(25) being 109.1 and 106.6°, and O[19(2)]—C(20)—C(21) and O[19(1)]—C(20)—C(25) being 125.4 and 124.9° respectively, compared with the expected values of 120°. This suggests that the coordinates of the atoms in the benzene ring attached to O(19) have refined to the values of the weighted mean of the alternative configurations.

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