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(2,6-Dimethoxyphenyl)penicillin Methyl Ester (Methicillin Methyl Ester)

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Abstract. $C_{18}H_{22}N_2O_6S$, monoclinic, $P2_1$, a = 14·728 (5), b = 9·733 (5), c = 6·901 (5) Å, β = 102·85 (5)°, $Z = 2$, $D_c = 1{\cdot}36$, $D_m = 1{\cdot}38$ g cm^{-3}. The structure was solved by direct methods and refined to R = 0·029 for 1673 observed intensities. Bond distances and angles agree with those of other penicillin derivatives.

Introduction. Crystals suitable for X-ray analysis were obtained by slow evaporation of an isopropanol solu-

Table 1. *Fractional atomic coordinates* (×10⁴, *for* H ×10³) *and thermal parameters* (×10⁴)

The form of the anisotropic thermal factor is exp[$-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + hk\beta_{12} + hl\beta_{13} + kl\beta_{23})$]. Estimated standard deviations are in parentheses.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
S(1)	7187·6 (5)	6367 (0)	3337 (1)	48·6 (3)	114·2 (2)	199 (1)	29 (1)	−7 (1)	−75 (2)
C(2)	8466 (2)	6333 (4)	4157 (4)	46 (1)	109 (3)	200 (5)	21 (4)	38 (4)	−26 (9)
C(3)	8642 (2)	6916 (3)	6305 (4)	40 (1)	79 (3)	195 (5)	−1 (3)	31 (4)	1 (7)
N(4)	7855 (1)	6528 (3)	7126 (3)	32 (1)	88 (2)	186 (4)	5 (3)	14 (3)	5 (6)
C(5)	7094 (2)	5775 (3)	5763 (4)	37 (1)	72 (3)	261 (7)	8 (3)	1 (5)	−12 (8)
C(6)	6399 (2)	6547 (3)	6766 (4)	34 (1)	87 (3)	220 (6)	14 (3)	14 (4)	40 (7)
C(7)	7237 (2)	7473 (3)	7622 (4)	38 (1)	102 (3)	165 (5)	12 (3)	6 (4)	−8 (7)
O(8)	7367 (2)	8583 (3)	8378 (3)	54 (1)	122 (3)	289 (5)	9 (3)	11 (4)	−136 (6)
C(9)	8892 (2)	7284 (5)	2814 (5)	70 (2)	173 (5)	249 (7)	32 (5)	107 (5)	54 (11)
C(10)	8834 (2)	4869 (4)	4108 (5)	59 (1)	120 (4)	320 (8)	36 (4)	48 (6)	−120 (10)
C(11)	9589 (2)	6485 (3)	7536 (4)	35 (1)	100 (3)	228 (5)	−13 (4)	27 (4)	−27 (8)
O(12)	10298 (1)	7007 (3)	7341 (4)	41 (1)	203 (4)	499 (8)	−43 (3)	39 (5)	197 (10)
O(13)	9546 (1)	5491 (2)	8795 (3)	37 (1)	125 (2)	229 (4)	9 (3)	7 (3)	55 (6)
N(14)	5573 (1)	7138 (2)	5561 (3)	33 (1)	68 (2)	233 (5)	11 (2)	4 (4)	10 (6)
C(15)	4915 (2)	6273 (3)	4634 (4)	37 (1)	71 (2)	230 (6)	2 (3)	32 (4)	−4 (8)
O(16)	5037 (2)	5021 (2)	4751 (4)	52 (1)	66 (2)	382 (6)	3 (3)	13 (4)	3 (7)
C(17)	4029 (2)	6884 (3)	3452 (4)	37 (1)	74 (3)	208 (6)	−3 (3)	−2 (4)	−22 (7)
C(18)	4016 (2)	7628 (3)	1726 (4)	49 (1)	100 (3)	216 (6)	1 (4)	15 (5)	−33 (8)
C(19)	3176 (2)	8130 (4)	606 (5)	63 (2)	128 (4)	231 (8)	14 (5)	−31 (6)	13 (10)
C(20)	2376 (2)	7878 (4)	1232 (5)	50 (1)	138 (5)	322 (9)	20 (5)	−58 (6)	−42 (11)
C(21)	2364 (2)	7154 (4)	2951 (5)	36 (1)	120 (4)	368 (9)	−8 (4)	5 (5)	−75 (10)
C(22)	3203 (2)	6663 (3)	4079 (5)	40 (1)	87 (3)	282 (7)	−12 (3)	13 (5)	−35 (8)
O(23)	3298 (1)	5983 (3)	5825 (4)	51 (1)	170 (3)	374 (6)	−11 (3)	87 (4)	143 (8)
C(24)	2493 (3)	5655 (5)	6530 (6)	72 (2)	191 (5)	465 (11)	−83 (6)	157 (6)	−27 (15)
O(25)	4856 (1)	7779 (3)	1253 (3)	60 (1)	166 (3)	259 (5)	19 (3)	76 (4)	80 (7)
C(26)	4936 (3)	8728 (6)	−292 (6)	105 (2)	198 (6)	375 (8)	46 (7)	220 (6)	139 (13)
C(27)	10420 (2)	5038 (4)	10046 (5)	44 (1)	175 (5)	309 (9)	48 (5)	−19 (6)	38 (12)

	x	y	z	B (Å²)		x	y	z	B (Å²)
H(3)	866 (2)	794 (3)	630 (4)	4·0 (6)	H(20)	182 (2)	830 (4)	46 (5)	6·5 (9)
H(5)	715 (2)	472 (4)	594 (4)	4·6 (7)	H(21)	182 (2)	695 (4)	343 (5)	7·5 (8)
H(6)	620 (2)	589 (4)	780 (4)	4·3 (7)	H(241)	202 (2)	514 (5)	567 (5)	10·7 (11)
H(91)	859 (2)	827 (4)	265 (5)	6·4 (8)	H(242)	286 (2)	510 (5)	782 (6)	14·4 (11)
H(92)	961 (2)	732 (4)	332 (5)	5·3 (8)	H(243)	218 (2)	667 (2)	698 (5)	11·6 (10)
H(93)	876 (2)	679 (4)	138 (5)	7·7 (8)	H(261)	457 (2)	849 (4)	861 (5)	10·4 (9)
H(101)	867 (2)	455 (4)	285 (5)	5·4 (9)	H(262)	475 (2)	960 (5)	5 (6)	7·9 (9)
H(102)	952 (2)	488 (4)	437 (5)	6·0 (9)	H(263)	562 (2)	883 (5)	−21 (5)	6·3 (9)
H(103)	852 (2)	434 (4)	500 (5)	7·6 (9)	H(271)	92 (2)	521 (4)	951 (5)	9·4 (9)
H(14)	550 (2)	802 (4)	547 (4)	5·0 (7)	H(272)	1052 (2)	552 (4)	1123 (5)	10·5 (9)
H(19)	316 (2)	862 (4)	−49 (5)	5·9 (8)	H(273)	1042 (2)	415 (4)	997 (5)	11·1 (9)

tion. Intensities were collected by the $\omega/2\theta$ scan method on a four-circle Nonius CAD-4 diffractometer with graphite-monochromated Cu $K\alpha$ radiation and a crystal 0·1 × 0·2 × 0·2 mm. Among the 2070 independent reflexions with $\theta \leq 72°$, 1673 had $I \geq 3\sigma(I)$ and were used for the subsequent analysis. The data were corrected for Lorentz and polarization effects, but not for absorption. The structure was solved by direct methods (Germain, Main & Woolfson, 1971). The best figure of merit gave an E map in which 13 of the 27 non-hydrogen atoms were recognized; the others were located by Fourier syntheses. Refinement was by full-matrix least squares to $R = 0{\cdot}054$. A difference map revealed all H atoms, which were then included in the last cycle with anisotropic temperature factors for non-hydrogen atoms, isotropic for H. The final R was 0·029 for the observed reflexions.* The atomic coordinates and temperature factors are given in Table 1. All calculations were done with the *SDP* system of programs written for use on a PDP-11 computer (Okaya & Frenz, 1975).

Discussion. This study was undertaken in order to examine the structural features of β-lactamase inhibitors (Blanpain & Durant, 1976*a*,*b*). Methicillin, like other semi-synthetic penicillins which have a sterically hindered side chain, has been reported to competitively inhibit the hydrolysis of susceptible penicillins by β-lactamases (Hou & Poole, 1971).

The interatomic distances and angles for non-hydrogen atoms are shown in Fig. 1 and bond lengths and angles involving H atoms in Table 2. The stereochemistry of the molecule can be seen from Fig. 2 and from the least-squares-planes calculations (Table 3).

The bond distances and angles of the nucleus, β-lactam and thiazolidine rings agree with those of other penicillin derivatives (Sweet, 1972). The thiazolidine ring adopts the conformation: α-CH_3 axial, β-CH_3 equatorial and α-CO_2CH_3 equatorial. N(4) in the β-lactam ring lies 0·44 Å from the plane of C(3), C(5) and C(7). The conformation of the side chain is stabilized by two opposing effects: one is a result of the steric effects of the two bulky groups in the O,O′ positions and the other is the tendency of the

Table 2. *Bond lengths* (Å) *to hydrogen atoms*

C(3)–H(3)	1·00 (2)	C(20)–H(20)	0·96 (2)
C(5)–H(5)	1·03 (2)	C(21)–H(21)	0·96 (2)
C(6)–H(6)	1·05 (2)	C(24)–H(241)	0·95 (3)
C(9)–H(91)	1·06 (3)	C(24)–H(242)	1·07 (3)
C(9)–H(92)	1·03 (2)	C(24)–H(243)	1·16 (3)
C(9)–H(93)	1·08 (2)	C(26)–H(261)	0·86 (2)
C(10)–H(101)	0·91 (3)	C(26)–H(262)	0·94 (3)
C(10)–H(102)	0·92 (2)	C(26)–H(263)	1·00 (3)
C(10)–H(103)	0·99 (3)	C(27)–H(271)	0·92 (2)
N(14)–H(14)	0·87 (3)	C(27)–H(272)	0·93 (3)
C(19)–H(19)	0·89 (3)	C(27)–H(273)	0·87 (3)

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32171 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

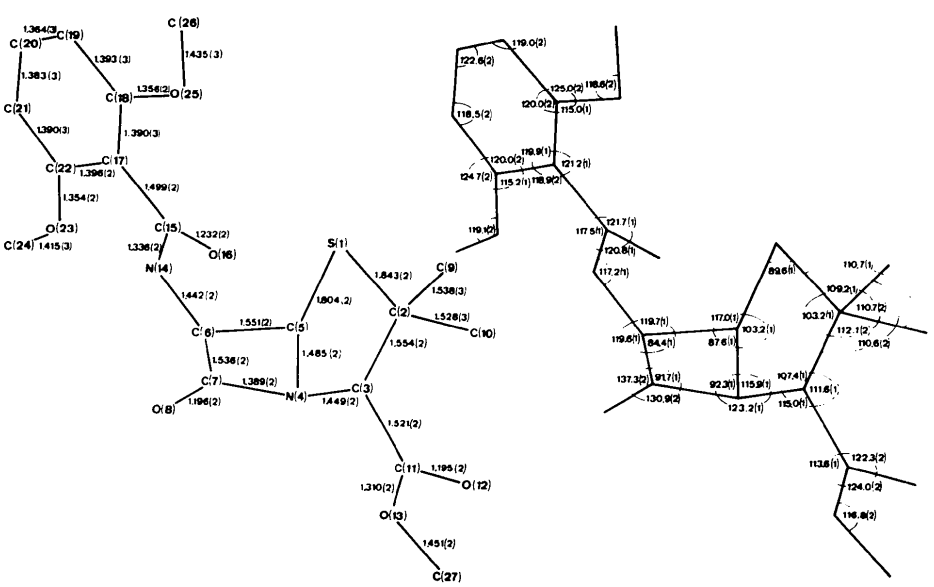


Fig. 1. Bond lengths (Å) and angles (°). The estimated standard deviations are in parentheses.

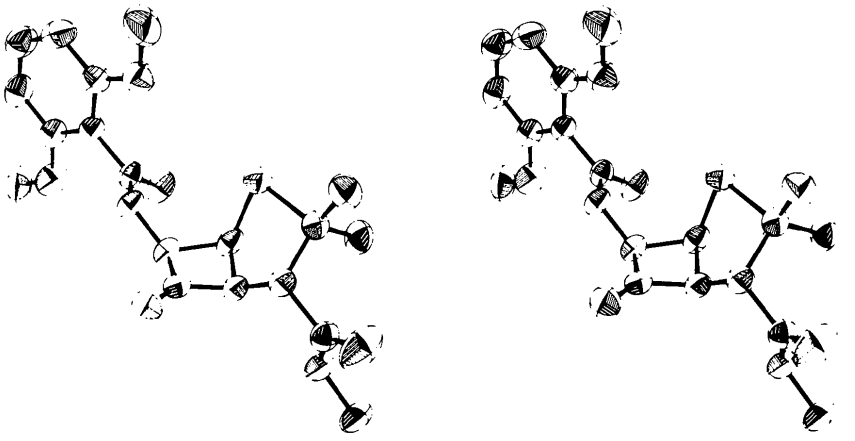


Fig. 2. Stereoscopic view of the molecule with 50% probability thermal ellipsoids (*ORTEP*: Johnson, 1965).

Table 3. *Least-squares planes*

Deviations (Å) of the atoms from some least-squares planes in the molecule are given. (The asterisk indicates an atom excluded from the calculation of the plane.)

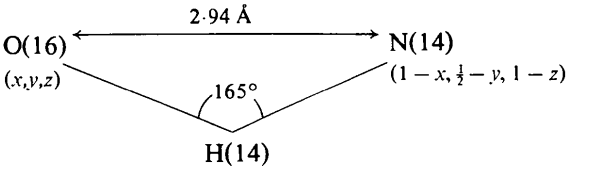
Plane 1		Plane 2	
C(3)	0·000	N(4)	−0·104
N(4)	0·444*	C(5)	0·093
C(5)	0·000	C(6)	−0·090
C(7)	0·000	C(7)	0·101
Plane 3		**Plane 4**	
C(6)	−0·027	C(17)	0·008
N(14)	0·025	C(18)	−0·002
C(15)	0·005	C(19)	−0·004
O(16)	0·005	C(20)	0·005
C(17)	−0·015	C(21)	0·002
		C(22)	−0·008

Dihedral angles

∠ (Plane 2) (Plane 3)	45·5°
∠ (Plane 3) (Plane 4)	67·3

aromatic ring and the exocyclic amide group to be coplanar.

Only one hydrogen bond is observed between exocyclic amide groups of successive molecules.



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