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Crystal and Molecular Structure of *p*-Methoxybenzyl 2α-Methyl-2β-[(*R*)-acetoxy(methoxy)methyl]-6β-phenoxyacetamidopenam-3α-carboxylate

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Abstract

The title compound, $C_{27}H_{30}N_2O_9S$, crystallizes in the orthorhombic space group $P2_12_12_1$ with a = 20·526 (5), b = 12·756 (2), c = 10·298 (3) Å, Z = 4. The structure has been solved by direct methods and refined by a least-squares procedure to a conventional R value of 0·033 (absolute configuration) for 2562 observed independent reflections. A comparison of several known structures of penicillin derivatives is made. Only small differences are observed for the characteristic moiety of this class of compounds. In the title compound the thiazolidine ring exhibits slight puckering, the C(3) atom is 0·39 Å out of the plane through the remaining four atoms. The N atom of the β-lactam ring is 0·37 Å out of the plane of its ligand C atoms. The phenoxymethyl moiety is compared with that of other penicillin and cephalosporin derivatives. Packing results from normal van der Waals contacts.

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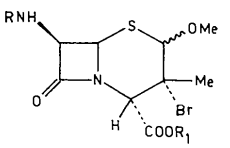
Introduction

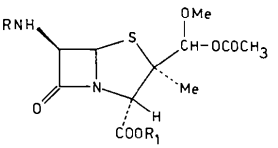
In recent years the study of interconversion reactions of penicillins and cephalosporins has received considerable attention (Cooper & Spry, 1972; Cooper, Hatfield & Spry, 1973; Kukolja, Lammert, Gleissner & Ellis, 1975; Tanida, Tsuji, Tsushima, Ishitobi, Irie, Yano, Matsumura & Tori, 1975). This interconversion is usually supposed to occur through a mechanism implying the formation and the rearrangement of thiiranium ion intermediates (Cooper & Spry, 1972; Cooper, Hatfield & Spry, 1973; Kukolja *et al.*, 1975; Barton, Comer, Greig, Lucente, Sammes & Underwood, 1970).

As a continuation of our studies of the chemistry of the dihydrothiazine ring moiety of cephalosporins (Balsamo, Crotti, Domiano, Macchia, Macchia, Nannini & Rosai, 1978; Domiano, Nardelli, Balsamo, Macchia, Macchia & Meinardi, 1978), we started an

investigation (Balsamo, Damiani, Domiano, Macchia, Macchia, Meinardi, Nannini & Rosai, 1978) with the objective of verifying the importance of a cepham system compared with a penam system. During this research the title compound (2) was isolated in good yield as a crystalline solid from the reaction of a mixture of *p*-methoxybenzyl 2α- and 2β-methoxy-3α-bromo-3β-methyl-7β-phenoxyacetamidocepham-4α-carboxylate (1) (Balsamo, Crotti, Macchia, Macchia, Nannini, Dradi & Forgione, 1976) with silver acetate in acetic acid.



(1)



(2)

R = $C_6H_5OCH_2CO$; R_1 = *p*-$MeOC_6H_4CH_2$

On the basis of spectroscopic data alone it was not possible to assign unambiguously the cepham or penam structure, or the stereochemistry of this product, so the crystal structure analysis was carried out. The results show that the presence of an electron-donor substituent, such as the methoxy group, at C(2) is effective in directing the transformation of (1) towards penam derivatives.

X-ray data, structure determination and refinement

Crystals of the title compound were obtained by slow evaporation of a dichloromethane–chloroform–diisopropyl ether solution as well formed colourless prisms. Preliminary investigation by rotation and Weissenberg photographs showed the crystal system to be orthorhombic, the space group being $P2_12_12_1$. Least-squares cell dimensions were determined from the 2θ values of 17 reflections accurately measured on a Siemens AED computer-controlled diffractometer. The relevant experimental data are summarized in Table 1.

The collection of 2893 reflections with $2\theta \leq 140°$ was carried out at room temperature using Ni-filtered Cu $K\alpha$ radiation; 331 reflections whose intensities were less than twice the standard error based on counting statistics were considered unobserved. The structure was solved by direct methods with the program

Table 1. *X-ray crystal data*

Molecular formula $C_{27}H_{30}N_2O_9S$	M_r	558·6
a = 20·526 (5) Å	Crystal size	0·10 × 0·14 × 0·52 mm
b = 12·756 (2)	2θ range	3–140°
c = 10·298 (3)	Number of intensity data	2562
V = 2696·2 (1·1) Å^3	Radiation	Cu $K\bar{\alpha}$, λ = 1·5418 Å
Space group $P2_12_12_1$	Measurement mode	θ–2θ scan
Z = 4	Check reflection	One in every twenty
ρ_c = 1·38 Mg m^{-3}	Corrections	Lorentz, polarization
μ = 1·45 mm^{-1}		
F(000) = 1176		

Table 2. *Atomic fractional coordinates* (× 10^4)

	x	y	z
S	2446 (0)	4377 (1)	1724 (1)
C(2)	2486 (1)	2938 (2)	1637 (3)
C(3)	2599 (1)	2558 (2)	3082 (3)
N(4)	2914 (1)	3411 (2)	3777 (2)
C(5)	2757 (1)	4480 (2)	3369 (3)
C(6)	3493 (2)	4773 (2)	3606 (3)
C(7)	3577 (1)	3601 (2)	3910 (3)
O(8)	4025 (1)	3030 (2)	4176 (2)
C(9)	1859 (2)	2531 (3)	1022 (3)
C(10)	3076 (2)	2590 (2)	821 (3)
O(11)	2968 (1)	2983 (2)	−488 (2)
C(12)	3097 (2)	2331 (2)	−1497 (3)
O(13)	3335 (2)	1489 (2)	−1376 (3)
C(14)	2901 (3)	2818 (4)	−2750 (4)
O(15)	3640 (1)	3024 (2)	1317 (2)
C(16)	4226 (2)	2455 (4)	1066 (5)
C(17)	1968 (1)	2289 (2)	3781 (3)
O(18)	1681 (1)	2875 (2)	4481 (2)
O(19)	1781 (1)	1306 (2)	3505 (2)
C(20)	1189 (1)	930 (2)	4137 (3)
C(21)	1293 (1)	707 (2)	5545 (3)
C(22)	1910 (1)	454 (2)	6006 (3)
C(23)	2014 (1)	223 (2)	7305 (3)
C(24)	1497 (2)	250 (2)	8173 (3)
C(25)	885 (2)	484 (3)	7741 (3)
C(26)	783 (1)	723 (3)	6425 (4)
O(27)	1660 (1)	17 (2)	9436 (2)
C(28)	1153 (2)	−163 (5)	10336 (4)
N(29)	3856 (1)	5141 (2)	2532 (2)
C(30)	4181 (1)	6062 (2)	2529 (3)
O(31)	4227 (1)	6639 (2)	3461 (2)
C(32)	4497 (2)	6347 (3)	1252 (3)
O(33)	4453 (1)	5485 (2)	382 (2)
C(34)	4560 (1)	5659 (3)	−916 (3)
C(35)	4366 (2)	4858 (4)	−1735 (4)
C(36)	4476 (2)	4949 (5)	−3062 (4)
C(37)	4757 (2)	5829 (5)	−3573 (4)
C(38)	4943 (2)	6631 (4)	−2740 (4)
C(39)	4854 (2)	6554 (3)	−1409 (3)
H(3)	2863 (13)	1953 (22)	3094 (27)
H(5)	2389 (19)	4756 (32)	3907 (41)
H(6)	3560 (19)	5223 (32)	4308 (41)
H(91)	1455 (22)	2742 (37)	1600 (50)
H(92)	1771 (19)	2879 (30)	162 (41)
H(93)	1896 (22)	1672 (37)	929 (47)
H(10)	3066 (17)	1884 (30)	733 (36)
H(141)	3037 (22)	2400 (30)	−3537 (30)
H(142)	2407 (6)	2789 (37)	−2719 (46)
H(143)	3107 (17)	3541 (18)	−2821 (41)
H(161)	4570 (31)	2729 (44)	1435 (61)
H(162)	4201 (30)	1667 (53)	1354 (66)
H(163)	4351 (30)	2633 (52)	193 (68)
H(201)	810 (15)	1463 (27)	3823 (44)
H(202)	1086 (18)	368 (32)	3709 (38)
H(22)	2274 (18)	358 (31)	5411 (39)
H(23)	2491 (22)	0 (38)	7593 (39)
H(25)	560 (15)	469 (24)	8404 (32)
H(26)	341 (17)	957 (26)	6134 (36)
H(281)	1389 (19)	−359 (33)	11271 (45)
H(282)	896 (22)	485 (36)	10302 (45)
H(283)	825 (28)	−655 (43)	9958 (56)
H(29)	3732 (20)	4721 (34)	1729 (48)
H(321)	4238 (20)	7029 (35)	819 (45)
H(322)	4949 (18)	6571 (29)	1398 (36)
H(35)	4162 (23)	4356 (36)	−1382 (49)
H(36)	4319 (25)	4462 (42)	−3529 (59)
H(37)	4833 (26)	5899 (49)	−4607 (67)
H(38)	5082 (25)	7214 (45)	−2946 (57)
H(39)	5005 (16)	7023 (28)	−756 (38)

MULTAN (Germain, Main & Woolfson, 1971) employing the 300 E values larger than 1·50; the solution came from the set having the highest combined figure of merit. The positions of 32 of the 39 independent non-hydrogen atoms were revealed from the E map, the remaining atoms were located from a Fourier map. After the first cycle of anisotropic least-squares refinement, 29 of the 30 H atoms were found in the ΔF map; the refinement was completed with anisotropic temperature factors for non-hydrogen atoms and isotropic for H's; the missing H(39) atom was placed at its calculated position. The final conventional residual error indices were: $R = 0{\cdot}033$ and $R_w = 0{\cdot}037$ for the observed reflections, $R = 0{\cdot}041$ and $R_w = 0{\cdot}040$ for all reflections ($w = 1/\sigma^2$). The atomic scattering factors used in all the calculations take into account the anomalous-scattering effects (*International Tables for X-ray Crystallography*, 1974). The atomic coordinates given in Table 2* correspond to those which gave the best refinement. An alternative refinement based on the mirror image of the molecule led to $R = 0{\cdot}046$, so the assumed structure corresponds to the absolute configuration. Both refinements were carried out by the full-matrix least-squares method.

Discussion

The structure of the molecule is represented in Fig. 1, the corresponding bond distances and angles and relevant torsion angles are given in Tables 3, 4 and 5. Correction for rigid-body motion (Schomaker & Trueblood, 1968) did not change the bond distances significantly (maximum deviation 0·002 Å).

It is interesting to compare the results of the present analysis with those found for other penicillin deriva-

* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34231 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

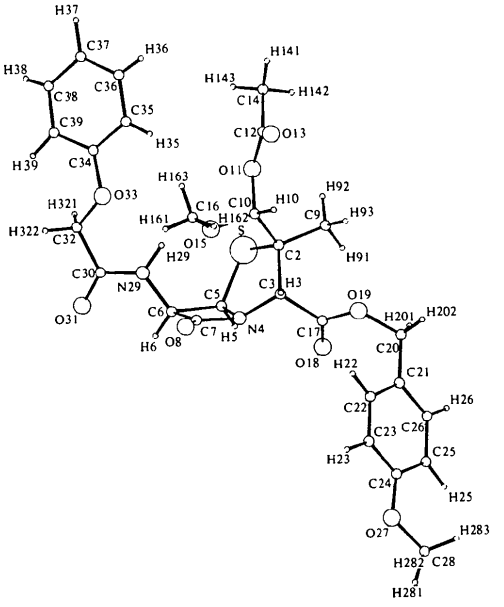


Fig. 1. Projection of a molecule of the title compound.

Table 3. *Interatomic distances* (Å) *with their e.s.d.'s in parentheses*

S–C(2)	1·840 (3)	O(19)–C(20)	1·460 (4)
S–C(5)	1·816 (4)	C(20)–C(21)	1·493 (5)
C(2)–C(3)	1·583 (5)	C(21)–C(22)	1·391 (4)
C(2)–C(9)	1·526 (5)	C(21)–C(26)	1·385 (5)
C(2)–C(10)	1·540 (5)	C(22)–C(23)	1·387 (5)
C(3)–N(4)	1·455 (4)	C(23)–C(24)	1·388 (5)
C(3)–C(17)	1·521 (4)	C(24)–C(25)	1·366 (6)
N(4)–C(5)	1·463 (4)	C(24)–O(27)	1·376 (4)
N(4)–C(7)	1·390 (3)	C(25)–C(26)	1·405 (6)
C(5)–C(6)	1·576 (5)	O(27)–C(28)	1·412 (5)
C(6)–C(7)	1·538 (4)	N(29)–C(30)	1·351 (4)
C(6)–N(29)	1·414 (4)	C(30)–O(31)	1·214 (4)
C(7)–O(8)	1·205 (4)	C(30)–C(32)	1·511 (5)
C(10)–O(11)	1·456 (4)	C(32)–O(33)	1·422 (5)
C(10)–O(15)	1·382 (5)	O(33)–C(34)	1·373 (4)
O(11)–C(12)	1·357 (4)	C(34)–C(35)	1·384 (6)
C(12)–O(13)	1·187 (5)	C(34)–C(39)	1·388 (6)
C(12)–C(14)	1·488 (6)	C(35)–C(36)	1·390 (6)
O(15)–C(16)	1·429 (5)	C(36)–C(37)	1·368 (9)
C(17)–O(18)	1·194 (4)	C(37)–C(38)	1·389 (8)
C(17)–O(19)	1·342 (4)	C(38)–C(39)	1·387 (6)

Table 4. *Bond angles* (°) *with their e.s.d.'s in parentheses*

C(2)–S–C(5)	95·9 (1)	C(3)–C(17)–O(19)	110·7 (2)
S–C(2)–C(10)	110·5 (2)	C(3)–C(17)–O(18)	124·4 (3)
S–C(2)–C(9)	108·8 (2)	O(18)–C(17)–O(19)	124·9 (3)
S–C(2)–C(3)	105·5 (2)	C(17)–O(19)–C(20)	116·8 (3)
C(9)–C(2)–C(10)	109·8 (3)	O(19)–C(20)–C(21)	112·1 (2)
C(3)–C(2)–C(10)	108·0 (2)	C(20)–C(21)–C(26)	121·7 (4)
C(3)–C(2)–C(9)	114·2 (3)	C(20)–C(21)–C(22)	120·4 (3)
C(2)–C(3)–C(17)	112·9 (3)	C(22)–C(21)–C(26)	117·9 (3)
C(2)–C(3)–N(4)	107·4 (2)	C(21)–C(22)–C(23)	121·3 (3)
N(4)–C(3)–C(17)	108·3 (2)	C(22)–C(23)–C(24)	119·9 (4)
C(3)–N(4)–C(7)	127·9 (3)	C(23)–C(24)–O(27)	114·7 (4)
C(3)–N(4)–C(5)	117·3 (3)	C(23)–C(24)–C(25)	119·9 (4)
C(5)–N(4)–C(7)	94·7 (2)	C(25)–C(24)–O(27)	125·4 (4)
S–C(5)–N(4)	106·2 (2)	C(24)–C(25)–C(26)	119·9 (4)
N(4)–C(5)–C(6)	88·0 (2)	C(21)–C(26)–C(25)	121·0 (4)
S–C(5)–C(6)	119·9 (3)	C(24)–O(27)–C(28)	118·4 (4)
C(5)–C(6)–N(29)	117·6 (3)	C(6)–N(29)–C(30)	123·4 (3)
C(5)–C(6)–C(7)	84·7 (2)	N(29)–C(30)–C(32)	115·0 (3)
C(7)–C(6)–N(29)	115·0 (3)	N(29)–C(30)–O(31)	124·4 (3)
N(4)–C(7)–C(6)	92·3 (3)	O(31)–C(30)–C(32)	120·6 (3)
C(6)–C(7)–O(8)	136·1 (4)	C(30)–C(32)–O(33)	109·6 (3)
N(4)–C(7)–O(8)	131·7 (4)	C(32)–O(33)–C(34)	118·6 (3)
C(2)–C(10)–O(15)	110·0 (3)	O(33)–C(34)–C(39)	124·0 (4)
C(2)–C(10)–O(11)	106·7 (3)	O(33)–C(34)–C(35)	115·4 (3)
O(11)–C(10)–O(15)	109·4 (3)	C(35)–C(34)–C(39)	120·7 (4)
C(10)–O(11)–C(12)	117·9 (3)	C(34)–C(35)–C(36)	119·4 (5)
O(11)–C(12)–C(14)	110·8 (3)	C(35)–C(36)–C(37)	121·0 (5)
O(11)–C(12)–O(13)	123·7 (4)	C(36)–C(37)–C(38)	118·9 (6)
O(13)–C(12)–C(14)	125·5 (4)	C(37)–C(38)–C(39)	121·5 (5)
C(10)–O(15)–C(16)	115·8 (4)	C(34)–C(39)–C(38)	118·5 (4)

Table 5. *Relevant torsion angles* (°) *with their e.s.d.'s in parentheses*

A torsion angle α–β–γ–δ is positive if, when viewed down the β–γ bond the α–β bond will eclipse the γ–δ bond when rotated less than 180° in a clockwise direction.

C(2)–S–C(5)–C(6)	100·1 (2)	C(5)–C(6)–C(7)–N(4)	−4·0 (2)	C(20)–C(21)–C(22)–C(23)	−178·6 (2)
C(2)–S–C(5)–N(4)	2·9 (2)	C(7)–C(6)–N(29)–C(30)	−137·5 (3)	C(22)–C(23)–C(24)–O(27)	−179·4 (3)
C(5)–S–C(2)–C(3)	13·0 (2)	N(29)–C(6)–C(7)–O(8)	58·5 (5)	C(23)–C(24)–O(27)–C(28)	−168·6 (3)
S–C(2)–C(3)–N(4)	−25·5 (3)	C(2)–C(10)–O(15)–C(16)	153·8 (3)	C(25)–C(24)–O(27)–C(28)	10·7 (5)
S–C(2)–C(3)–C(17)	93·9 (2)	C(2)–C(10)–O(11)–C(12)	−136·5 (3)	O(27)–C(24)–C(25)–C(26)	179·1 (3)
C(2)–C(3)–C(17)–O(18)	−96·3 (3)	O(11)–C(10)–O(15)–C(16)	−89·4 (4)	C(6)–N(29)–C(30)–O(31)	4·3 (5)
C(2)–C(3)–C(17)–O(19)	83·8 (3)	C(10)–O(11)–C(12)–O(13)	−5·5 (5)	C(6)–N(29)–C(30)–C(32)	−175·7 (3)
C(2)–C(3)–N(4)–C(5)	31·3 (3)	C(10)–O(11)–C(12)–C(14)	174·6 (3)	N(29)–C(30)–C(32)–O(33)	−8·3 (4)
C(2)–C(3)–N(4)–C(7)	−89·9 (3)	C(3)–C(17)–O(19)–C(20)	178·5 (2)	O(31)–C(30)–C(32)–O(33)	171·7 (3)
C(3)–N(4)–C(5)–S	−20·9 (3)	O(18)–C(17)–O(19)–C(20)	−1·4 (4)	C(30)–C(32)–O(33)–C(34)	163·9 (3)
C(3)–N(4)–C(7)–O(8)	−45·9 (5)	C(17)–O(19)–C(20)–C(21)	−73·3 (3)	C(32)–O(33)–C(34)–C(35)	−165·8 (3)
C(5)–N(4)–C(7)–C(6)	4·3 (2)	O(19)–C(20)–C(21)–C(22)	−25·6 (4)	C(32)–O(33)–C(34)–C(39)	15·7 (5)
C(7)–N(4)–C(5)–C(6)	−4·2 (2)	O(19)–C(20)–C(21)–C(26)	155·7 (3)	O(33)–C(34)–C(39)–C(38)	179·1 (4)
N(4)–C(5)–C(6)–C(7)	3·8 (2)	C(20)–C(21)–C(26)–C(25)	178·3 (3)	O(33)–C(34)–C(35)–C(36)	−177·8 (4)
S–C(5)–C(6)–N(29)	11·8 (4)				

tives. To do this all the relevant structural parameters were recalculated from the atomic coordinates quoted in the original papers, using the same program as for our compound, so only the structures whose atomic coordinates are available from the literature were considered. Comparison of course is possible for the common central part of the molecule consisting of a thiazolidine ring fused with a β-lactam ring carrying an exocyclic amide group. In all these compounds the thiazolidine ring [SC(2)C(3)N(4)C(5)] is not planar, but only one atom is significantly out of the plane running through the other four atoms.* Depending on the nature of this atom the compounds can be divided in three groups which will be indicated hereafter as C(3)-type, S-type and C(5)-type, as shown in Tables 6, 7 and 8 where the relevant features of the central moiety of these compounds are compared. While the puckering of the C(5)-type compounds may be interpreted as a consequence of the sp^2 character of the C(2) and C(3) atoms, there is no obvious explanation for the difference between the C(3)-type and the S-type compounds where all the C atoms of the ring are sp^3. Probably the difference is required to minimize intramolecular non-bonding interactions as there are no significant differences between corresponding bond distances. Alternatively, the puckering of the thiazolidine ring is described by the q_2 and φ_2 parameters, calculated by the method of Cremer & Pople (1975)† and is illustrated by the stereographic projections of Fig. 2, where the vectors connecting the geometrical centre of the ring with the atoms are projected on the mean plane through the ring. From these projections and the parameters of Tables 6, 7 and 8, puckering is largest for the S-type compounds (q_2 = ~0·5 Å) and smallest for the C(5)-type compounds (q_2 ≃ 0·2 Å), the conformation being near to 'envelope' for all three types of compounds. In all cases the N(4) atom is out of the plane defined by C(3)C(5)C(7) and the value of the out-of-plane distance does not seem to be related to the type of puckering of the thiazolidine moiety, nor does there seem to be a correlation between this distance and the puckering of the β-lactam ring. This puckering is not so large as that of thiazolidine, but is quite remarkable as indicated by the dihedral angle N(4)C(5)C(6)–N(4)C(6)C(7) and by the q parameters given in Tables 6, 7 and 8. There is some degree of correlation between this puckering and the distance of O(8) from the mean plane through the β-lactam ring, as a consequence of the trigonal character of C(7). The dihedral angle formed by the mean planes through the β-lactam and the thiazolidine rings is larger for the C(3)-type compounds (59–65°) than for the other two types (45–58°).

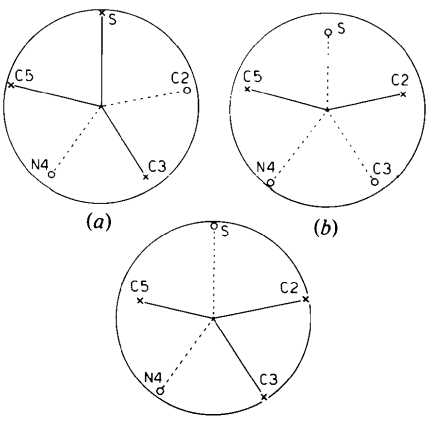
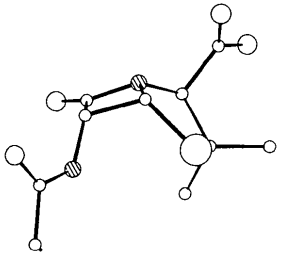


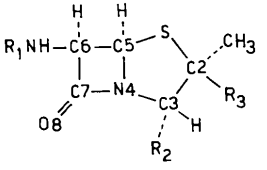
Fig. 2. Conformation of the thiazolidine ring in different types of penicillin derivatives: (*a*) C(3)-type, (*b*) S-type, (*c*) C(5)-type.

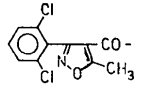
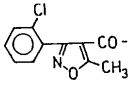
* These atoms are not perfectly coplanar, but the displacements do not exceed 0·075 Å.

† The total degree of pucker is described by one radial parameter q in the case of a four-membered ring, and by one radial q and one angular φ parameter in the case of a five-membered ring.

Table 6. *Comparison of relevant data for the central moiety of the* C(3)*-type penicillin derivatives*



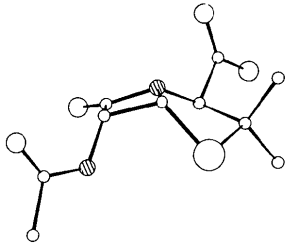


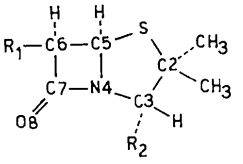
		Distances (Å)			Puckering parameters†			Dihedral angles (°)			
	R %	C(3) from SC(2)N(4)C(5)	N(4) from C(3)C(5)C(7)	O(8) from N(4)C(5)C(6)C(7)	β-lactam q_1 (Å)	thiazolidine q_2 (Å)	thiazolidine φ_2 (°)	N(4)C(5)C(6) N(4)C(6)C(7)	β-lactam thiazolidine	β-lactam exocyclic amide	References
p-Methoxybenzyl 2α-methyl-2β-[(*R*)-acetoxymethoxymethyl]-6β-phenoxyacetamidopenam-3α-carboxylate R_1 = Ph–O–CH_2–CO– R_2 = –$COOCH_2PhOCH_3$ R_3 = –$CH(OCH_3)$–O–$COCH_3$	3·3	0·39	0·37	0·09	−0·05	0·27	285	6	59	89	(*a*)
Potassium penicillin G R_1 = Ph–CH_2–CO– R_2 = –COO^- R_3 = –CH_3	7·2	0·43	0·38	0·22	−0·07	0·28	291	8	61	72	(*b*)
Dicloxacillin methyl ester R_1 =  R_2 = –$COOCH_3$ R_3 = –CH_3	6·4	0·44 0·47	0·41 0·41	0·48 0·36	−0·18 −0·16	0·31 0·33	277 277	19 18	64 65	89 89	(*c*)
Cloxacillin methyl ester R_1 =  R_2 = –$COOCH_3$ R_3 = –CH_3	5·1	0·48	0·39	0·26	−0·14	0·33	283	15	62	83	(*d*)
Benzylpenicillin 1′-diethylcarbonate ester R_1 = Ph–CH_2–CO– R_2 = –COO–$CH(CH_3)$–O–$COOC_2H_5$ R_3 = –CH_3	4·0	0·51	0·38	0·23	−0·11	0·35	287	12	63	84	(*e*)
Phenoxymethylpenicillin (penicillin V)* R_1 = Ph–O–CH_2–CO– R_2 = –COOH R_3 = –CH_3	12·6	0·51	0·40	0·16	−0·08	0·35	302	9	60	67	(*f*)

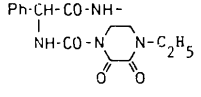
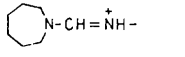
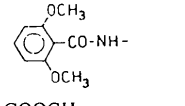
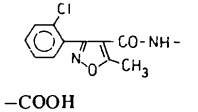
*,† See Table 8.

References: (*a*) Present work. (*b*) Dexter & Van der Veen (1978). (*c*) Blanpain & Durant (1977). (*d*) Blanpain & Durant (1976*a*). (*e*) Csöregh & Palm (1977). (*f*) Abrahamsson, Crowfoot Hodgkin & Maslen (1963).

Table 7. *Comparison of relevant data for the central moiety of the* S*-type penicillin derivatives*





		Distances (Å)						Dihedral angles (°)			
		S	N(4)	O(8)	Puckering parameters†				β-lactam	β-lactam	
	R	from	from	from	β-lactam thiazolidine			N(4)C(5)C(6)	thiazoli-	exocyclic	
	%	C(2)C(3)N(4)C(5)	C(3)C(5)C(7)	N(4)C(5)C(6)C(7)	q_1 (Å)	q_2 (Å)	φ_2 (°)	N(4)C(6)C(7)	dine	amide	References
Aqueous procaine penicillin G* R_1 = Ph–CH_2–CO–NH R_2 = $-COO^-$	7·3	0·73	0·40	0·39	−0·18	0·43	187	20	58	74	(*b*)
Piperacillin hydrate R_1 = 	5·0	0·80	0·44	0·25	−0·14	0·47	173	15	55	79	(*g*)
R_2 = –COOH											
Bacmecillinam hydrochloride R_1 = 	5·2	0·82	0·42	0·22	−0·11	0·50	168	12	49	72‡	(*h*)
R_2 = $-COO-CH(CH_3)-O-COOC_2H_5$											
Ampicillin anhydrate R_1 = Ph–$CH(NH_3^+)$–CO–NH– R_2 = $-COO^-$	10·6	0·84	0·39	0·13	−0·06	0·50	169	7	45	85	(*i*)
(2,6-Dimethoxyphenyl)penicillin methyl ester (methicillin methyl ester) R_1 = 	2·9	0·87	0·44	0·40	−0·20	0·52	176	21	54	46	(*j*)
R_2 = $-COOCH_3$											
Cloxacillin sulphoxide R_1 = 	4·7	0·89	0·41	0·30	−0·17	0·53	177	19	55	53	(*k*)
R_2 = –COOH											

*,† See Table 8.

‡ In this compound the angle refers to the β-lactam and amidino groups.

References: (*b*) Dexter & Van der Veen (1978). (*g*) Lovell & Perkinson (1978). (*h*) Palm & Csöregh (1978). (*i*) Boles & Girven (1976). (*j*) Blanpain, Melebeck & Durant (1977). (*k*) Blanpain & Durant (1976*b*).

Table 8. *Comparison of relevant data for the central moiety of the* C(5)*-type penicillin derivatives*

	R %	Distances (Å) C(5) from SC(2)C(3)N(4)	Distances (Å) N(4) from C(3)C(5)C(7)	Distances (Å) O(8) from N(4)C(5)C(6)C(7)	Puckering parameters† β-lactam thiazolidine q_1 (Å)	q_2 (Å)	φ_2 (°)	Dihedral angles (°) N(4)C(5)C(6) thiazolidine	N(4)C(6)C(7) β-lactam exocyclic amide	References
Phenoxymethylanhydropenicillin* $R = H$	5·4	0·23	0·42	0·17	−0·08	0·14	225	8	54	90	(*l*)
6-Methoxy(phenoxymethyl)anhydropenicillin $R = CH_3O$	6·2	0·33	0·38	0·20	−0·10	0·21	212	11	53	40	(*m*)

* The atomic coordinates published for the starred structures do not correspond to the correct absolute configuration. The corresponding centrosymmetrical coordinates were assumed in all calculations.

† q = amplitude of puckering; φ = phase angle of maximum amplitude:

$$q_m \cos\varphi_m = (2/N)^{1/2} \sum_{j=1}^{N} z_j \cos\left(2\pi m \frac{j-1}{N}\right); \quad q_m \sin\varphi_m = -(2/N)^{1/2} \sum_{j=1}^{N} z_j \sin\left(2\pi m \frac{j-1}{N}\right) \text{(Cremer \& Pople, 1975).}$$

References: (*l*) Simon, Morin & Dahl (1972). (*m*) Chaney & Jones (1973).

Table 8 (*cont.*)

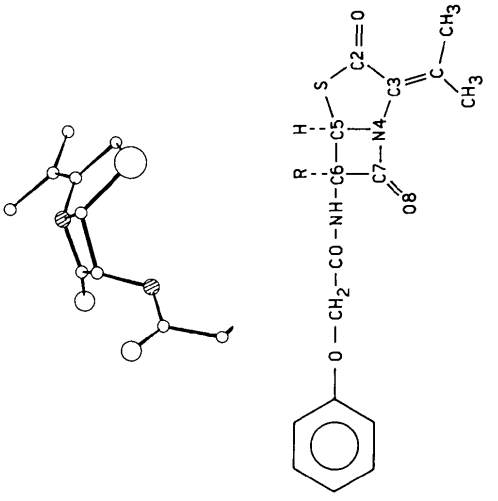


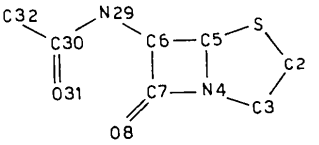
Table 9 gives the averaged bond distances and angles. The averaging formulae used are:

$$x_m = \sum_{i=1}^{N} w_i x_i \Big/ \sum_{i=1}^{N} w_i \qquad w_i = 1/\sigma_i^2,$$

$$\sigma_m = \left\{ \left[\sum_{i=1}^{N} w_i x_i^2 - x_m^2 \sum_{i=1}^{N} w_i + N - 1 \right] \Big/ \left[(N-1) \sum_{i=1}^{N} w_i \right] \right\}^{1/2},$$

where σ_i is the e.s.d. of x_i. For the data related to the thiazolidine ring the averages are taken for compounds of the same type. From these data it appears that significant differences are observed in the thiazolidine parameters for the three types of compounds, particularly for the C(5)-type with respect to the others, when C(2) and C(3) are involved, as expected. However, bond distances for the C(3)-type and S-type compounds do not appear to be influenced by the type of ring puckering and only angles involving S show significant differences. In the case of C(3)-type and S-type compounds the S—C(2) distance is significantly longer than the S—C(5) distance and also significantly longer than the 1·81 Å usually assumed for a C(sp^3)—S single bond. The angle at the S atom is influenced by the ring puckering; in particular its value, α_S, can be correlated with the distance, d_S, of the S atom from the mean plane through the other atoms of the ring. As expected, the larger this distance, the narrower the angle, the relation being linear: $\alpha_S = 96{\cdot}7 - 7{\cdot}9 d_S$ ($n = 15$, $r^2 = 0{\cdot}900$). The C(3)-type compounds exhibit the largest values for this angle, the S-type the smallest. The structural differences observed in the thiazolidine moiety of the penam system of the penicillin derivatives compared in this paper allowed us to make interesting correlations between the chemical and biological properties of β-lactam antibiotics, which will be published elsewhere.

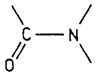
Table 9. *Averaged bond distances* (Å) *and angles* (°) *for the central moiety of penicillin derivatives*



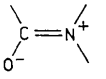
	C(3)-type I	Δ/σ I–II	S-type II	Δ/σ II–III	C(5)-type III	Δ/σ I–III
S–C(5)	1·818 (4)	2·2	1·804 (5)	1·0	1·796 (6)	3·1
S–C(2)	1·848 (5)	0·9	1·842 (4)	3·5	1·801 (11)	3·9
C(2)–C(3)	1·572 (6)	1·4	1·560 (6)	8·2	1·490 (6)	9·7
C(3)–N(4)	1·457 (3)	0·2	1·456 (5)	3·7	1·430 (5)	4·6
N(4)–C(5)	1·467 (5)	1·7	1·479 (5)	2·0	1·457 (10)	0·9
C(5)–S–C(2)	95·7 (2)	10·2	90·2 (5)	3·1	92·9 (7)	3·8
S–C(2)–C(3)	105·2 (3)	2·4	103·8 (5)	11·7	110·6 (3)	12·7
C(2)–C(3)–N(4)	106·6 (4)	0·8	107·0 (3)	4·1	109·4 (5)	4·4
C(3)–N(4)–C(5)	116·8 (3)	0·6	116·5 (4)	0·6	116·8 (3)	0·0
N(4)–C(5)–S	105·5 (3)	3·8	103·6 (4)	6·0	107·0 (4)	3·0

N(4)–C(7)	1·392 (4)	C(6)–N(29)	1·429 (3)	C(5)–N(4)–C(7)	94·2 (3)	C(5)–C(6)–N(29)	118·3 (4)
C(7)–O(8)	1·194 (4)	N(29)–C(30)	1·343 (3)	N(4)–C(7)–O(8)	131·8 (3)	C(7)–C(6)–N(29)	115·9 (5)
C(7)–C(6)	1·541 (4)	C(30)–O(31)	1·219 (4)	O(8)–C(7)–C(6)	136·6 (3)	C(6)–N(29)–C(30)	121·4 (6)
C(6)–C(5)	1·560 (4)	C(30)–C(32)	1·505 (6)	N(4)–C(7)–C(6)	91·4 (3)	N(29)–C(30)–O(31)	123·1 (4)
				C(7)–C(6)–C(5)	84·8 (2)	N(29)–C(30)–C(32)	116·1 (3)
				C(6)–C(5)–N(4)	88·1 (2)	O(31)–C(30)–C(32)	120·9 (3)

Bond distances and angles in the N(4)C(7)O(8) endocyclic amide system are not influenced by the type of thiazolidine puckering and their values in all the compounds are in agreement with a reduced delocalization of the unshared electron pair of the N atom which is also indicated by the non-planarity of this atom, as already observed by Simon, Morin & Dahl (1972). It is interesting to compare these averaged data with the corresponding values for the exocyclic amide system quoted in Table 9. In terms of Pauling's resonance theory the contributions of the two canonical forms



(I)



(II)

for the two amide systems are

(I) 77%, (II) 23%, for N(4)C(7)O(8),

(I) 60%, (II) 40%, for N(29)C(30)O(31),

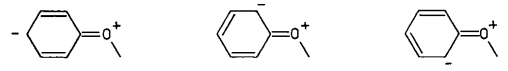
in accordance with a more pronounced delocalization in the exocyclic system. The orientation of the plane of this last system can be defined by the dihedral angle it forms with the mean plane through the β-lactam ring (Tables 6, 7 and 8), the values this angle assumes being in the range 40–90°.

In the title compound the carboxyl group at C(3) is esterified as the *p*-methoxybenzyl ester. The configuration of C(3) is *S* and the group is axial, making a dihedral angle of 66·9° with the C(2)C(3)N(4) plane, the contact responsible for this torsion being O(18)···N(4) = 2·720 (3) Å. The conformation of this substituent is defined by the torsion angles C(17)O(19)-C(20)C(21) = −73·2 (3), O(19)C(20)C(21)C(26) = 155·7 (3) and C(23)C(24)O(27)C(28) = −168·6 (3)°.

The other chiral centres in the molecule are those at C(5) and C(6), characteristic of this class of compounds, and those at C(2) and C(10); for all these centres the configuration is *R*. The methyl group C(9) is equatorial and the acetoxymethoxymethyl chain is axial with a *gauche* conformation along C(10)–C(2).

In Fig. 3 relevant data for the phenoxyacetamido side chain in penicillin derivatives are compared. From the comparison it appears that the geometry and conformation of this moiety do not change significantly from one derivative to another; in particular the conformation about C(30)–C(32) is such that O(33) is *trans* with respect to O(31) and nearly in the amide plane allowing the formation of an internal non-linear hydrogen bond N(29)–H···O(33) = 2·61 (2) Å (average) [for the title compound H(29)···O(33) = 2·25 (5) Å, N(29)–H(29)···O(33) = 96 (3)°] which has been considered responsible for the stability of the molecule (Abrahamsson, Crowfoot Hodgkin & Maslen, 1963). The orientation of the phenyl group, which is defined by the torsion angles about C(34)–O(33), is essentially determined by non-bonding intramolecular and packing interactions, particularly by the C(32)···C(39) = 2·83 (1) Å (av.) contact. The phenyl ring shows a tendency to be coplanar with the amide system, causing enlargement of the angle O(33)–C(34)–C(39) = 124·2 (3)° (av.) and narrowing of the angle O(33)–C(34)–C(35) = 115·4 (3)° (av.). This

tendency could be justified by some degree of conjugation between O and the phenyl ring, giving rise to some shortening of the C(ar)–O bond [1·376 (3) Å, av.].



The same kind of distortion is present in the anisole moiety C(21)C(22)C(23)C(24)C(25)C(26)O(27)C(28) of the title compound and in anisoles (Di Rienzo, Domenicano, Portalone & Vaciago, 1976).

There are two ester and three ether groups in the title compound. The C–O distances and the C–O–C angles in them are significantly different depending on the nature of the bond; in particular in each C–O–C bridge one of the two C–O distances is always significantly shorter than the other (Δ/σ ranging from 5·6 to 20·9).* With the exception of C(10)–O(15)–C(16), for which the difference is not directly explainable, in all the other cases the differences are justified by the different hybridization states of the two C atoms and by conjugative effects, as was pointed out in the case of the esters by Merlino (1971), so, when C is sp^2, the distance is related to the arylic or carboxylic character of C, as indicated by the following averaged values:

C(sp^3)–O(ether)	= 1·421 (6) Å	C(sp^3)–O–C(sp^3)	= 115·8 (4)°
C(sp^3)–O(ester)	= 1·458 (3)	C(sp^3)–O–C(sp^2)(ether)	= 118·5 (3)
C(sp^2)–O(ester)	= 1·350 (8)	C(sp^3)–O–C(sp^2)(ester)	= 117·4 (6).
C(sp^2ar.)–O(ether)	= 1·375 (3)		

The C=O distances in the ester groups are not significantly different and their average value, 1·191 (5) Å, is a little longer than the value (1·17 Å) usually assumed for a C–O double bond.

The two phenyl groups show no significant differences in the C–C bond distances, the average value being 1·387 (3) Å. However, the differences in bond angles are systematic and some of them significant; they can be interpreted as resulting from the effects of substituents, as pointed out by Domenicano, Vaciago & Coulson (1975). From the data quoted in Fig. 3 it appears that the same distortions are present in the phenyl rings of other phenoxymethylpenicillin and phenoxymethylcephalosporin derivatives. Assuming a local $2m$ (C_{2v}) symmetry with the mirror through C(34) and C(37), the averaged values (considering also the phenyl ring of the *p*-methoxybenzyl group of the title compound) are as shown in Table 10 where they are compared with those calculated by Domenicano, Vaciago & Coulson (1975) for hexaphenoxycyclotri(phosphazene) (Marsh & Trotter, 1971). The differences are noticeable and can be explained on the basis of the different extent of conjugation between the O atom and the ring (Domenicano & Vaciago, 1976), but the trend is the same and it does not seem to be coincidental that the differences between the angles α–δ and γ–β are nearly the same (~2°) for the two sets of data. The O atom of the phenoxy group is out of the phenyl plane by nearly the same displacement (0·030–0·037 Å) in all the penicillin derivatives.

* $\Delta/\sigma = |x_1 - x_2|/(\sigma_1^2 + \sigma_2^2)^{1/2}$.

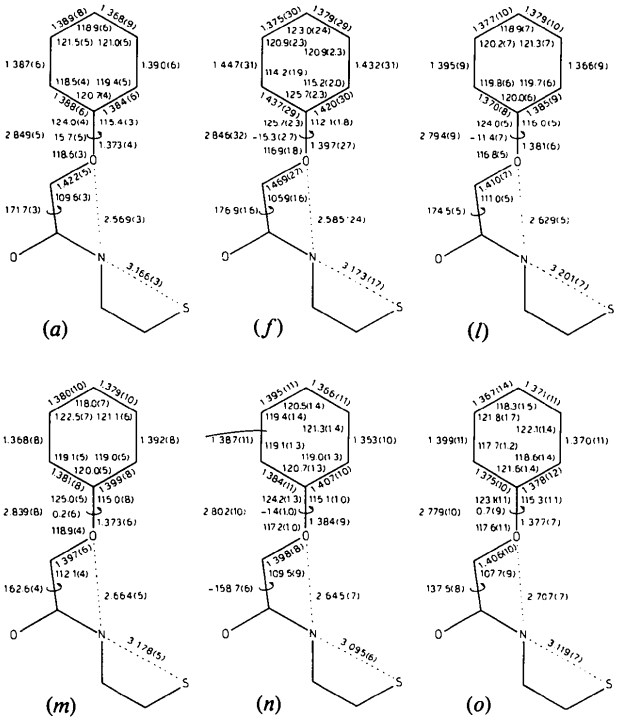
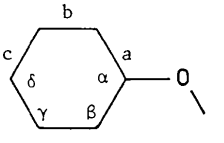


Fig. 3. Relevant data for the phenoxyacetamido side chain in penicillin and cephalosporin derivatives. (*a*)–(*f*) See references in Table 6. (*l*)–(*m*) See references in Table 8. (*n*) 3-Methyl-4-acetyl-7β-phenoxy-Δ^3-cephem (Domiano, Nardelli, Balsamo, Macchia, Macchia & Meinardi, 1978). (*o*) Phenoxymethyl-Δ^2-deacetoxycephalosporin (Sweet & Dahl, 1970).

Table 10. *Comparison of averaged bond distances* (Å) *and angles* (°) *in the phenyl ring of phenoxy groups*



	(*p*)	(*q*)	Δ/σ
a	1·384 (4)	1·368 (3)	3·2
b	1·387 (4)	1·388 (5)	0·2
c	1·383 (4)	1·364 (4)	3·4
α	120·3 (3)	122·5 (3)	5·2
β	119·3 (3)	118·1 (2)	3·3
γ	121·2 (2)	120·3 (2)	3·2
δ	118·3 (4)	120·6 (5)	3·6
α–δ	2·0	1·9	
γ–β	1·9	2·2	

References: (*p*) Averaged values of the data quoted in Fig. 3. (*q*) Averaged values calculated by Domenicano, Vaciago & Coulson (1975) for hexaphenoxycyclotri(phosphazene) (Marsh & Trotter, 1971).

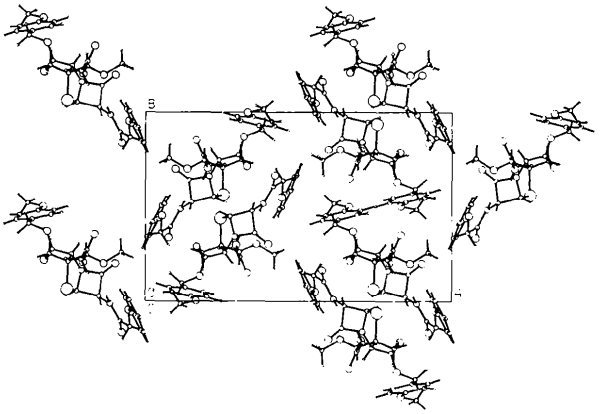


Fig. 4. Projection of the structure along the *c* axis.

The bond distances and corresponding e.s.d.'s involving the H atoms in the title compound are in the ranges 0·82–1·11 Å and 0·01–0·07 Å respectively.

Packing of the molecules in the crystal is determined by normal van der Waals interactions as shown in Fig. 4.

All calculations were carried out on the Cyber 76 computer of the Centro di Calcolo Elettronico Interuniversitario dell'Italia Nord-Orientale, Casalecchio, Bologna, using the *SHELX* 76 system of computer programs (Sheldrick, 1976). The figures have been drawn with the program *PLUTO* (Motherwell, 1976); bond distances, angles, planarities, puckering coordinates and other structural parameters were calculated using programs written at the Centro per la Strutturistica Diffrattometrica del CNR, Parma.

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