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Structure of a Modified β-Lactam Antibiotic

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Abstract. 1-Phenoxy-9b-phenyl-1,4,5,9b-tetrahydro-2*H*-azeto[1,2-*a*]isoquinolin-2-one, $C_{23}H_{19}NO_2$, is a carbocyclic analogue of cephalosporin. The crystals are monoclinic, $M_r = 341$, $C2/c$, $a = 23{\cdot}054$ (1), $b = 7{\cdot}315$ (2), $c = 23{\cdot}713$ (4) Å, $\beta = 115{\cdot}08$ (6)°, $V = 3621{\cdot}9$ Å^3, $Z = 8$, $D_m = 1{\cdot}24$, $D_x = 1{\cdot}25$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 5{\cdot}96$ cm^{-1}, $F(000) = 1440$, $T = 288$ K, final $R = 0{\cdot}071$ for 2450 observed reflections. The β-lactam N atom, N(7), is 0·229 Å away from mean plane containing C(11), C(5) and C(25). From the plane N(7)–C(5)–C(11)–C(3), atoms O(2) and O(1) are in the *trans* position whereas O(1) and C(8) are in the *cis* position. The crystal structure is stabilized by base–base interactions about the center of inversion.

Introduction. A large family of antibiotics is known whose single common structural feature is a β-lactam ring. As a class, they consist of penicillins, the cephalosporins and non-classical β-lactam antibiotics. The penicillins and cephalosporins show bactericidal reactions by interfering with bacterial cell-wall synthesis and inhibiting the enzymes that catalyse the cross-linking reaction of D-alanyl peptides on peptidoglycan strands of the growing cell wall (Blumberg & Strominger, 1974). Several penicillins and cephalosporin antibiotics inhibit the synthesis of bacterial cell walls.

Since the β-lactam ring plays a key role in the biological activity of β-lactam antibiotics, its activity can be influenced by substituents or fused rings (Takasuka, Nishikawa & Tori, 1982).

The compound reported here is a carbocyclic analogue of cephalosporin (Sharma, Mehra & Gupta, 1978; Bose, Amin, Kapur & Manhas, 1976) the structure of which was sought as a part of an investigation into the geometrical features which provide significant stereochemical information on the lability of the β-lactam amide bonds and on the conformation of the antibiotic in the region of the

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Table 1. *Final atomic coordinates and* U_{eq} *values of non-*H *atoms*

$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j$.

	x	y	z	U_{eq}(Å^2)
O(1)	0·2789 (2)	0·1646 (6)	0·6520 (2)	0·0477
O(2)	0·2126 (2)	0·5049 (5)	0·6820 (2)	0·0597
C(3)	0·2239 (2)	0·1659 (7)	0·6652 (2)	0·0375
C(4)	0·1255 (3)	−0·1262 (8)	0·6709 (3)	0·0422
C(5)	0·1579 (2)	0·1109 (7)	0·6099 (2)	0·0348
C(6)	0·1574 (3)	−0·1641 (9)	0·5447 (3)	0·0503
N(7)	0·1439 (2)	0·3073 (6)	0·6040 (2)	0·0465
C(8)	0·1634 (2)	0·0240 (8)	0·5536 (2)	0·0393
C(9)	0·0786 (3)	−0·2036 (10)	0·6854 (3)	0·0604
C(10)	0·3771 (3)	0·0452 (11)	0·6647 (3)	0·0630
C(11)	0·1971 (3)	0·3588 (8)	0·6551 (3)	0·0461
C(12)	0·3191 (2)	0·0152 (8)	0·6693 (2)	0·0411
C(13)	0·0013 (3)	0·0027 (11)	0·6157 (4)	0·0651
C(14)	0·1101 (2)	0·0177 (7)	0·6283 (2)	0·0374
C(15)	0·1757 (3)	0·1319 (11)	0·5118 (3)	0·0647
C(16)	0·1840 (3)	0·0433 (13)	0·4619 (3)	0·0678
C(17)	0·0174 (3)	−0·1393 (11)	0·6583 (4)	0·0714
C(18)	0·4218 (3)	−0·0978 (12)	0·6827 (3)	0·0730
C(19)	0·0472 (3)	0·0789 (8)	0·6000 (3)	0·0490
C(20)	0·3070 (3)	−0·1465 (9)	0·6900 (3)	0·0498
C(21)	0·1784 (3)	−0·1355 (15)	0·4541 (3)	0·0736
C(22)	0·3524 (3)	−0·2833 (11)	0·7080 (3)	0·0647
C(23)	0·0311 (3)	0·2325 (10)	0·5525 (3)	0·0642
C(24)	0·1649 (4)	−0·2442 (12)	0·4951 (4)	0·0673
C(25)	0·0792 (3)	0·3895 (10)	0·5754 (4)	0·0661
C(26)	0·4105 (3)	−0·2585 (12)	0·7048 (3)	0·0704

Table 2. *Bond lengths* (Å) *and angles* (°) *of non-*H *atoms*

O(1)—C(3)	1·429 (7)	O(1)—C(12)	1·378 (7)
O(2)—C(11)	1·218 (7)	C(3)—C(5)	1·583 (5)
C(3)—C(11)	1·518 (8)	C(4)—C(9)	1·387 (11)
C(4)—C(14)	1·397 (8)	C(5)—N(7)	1·466 (7)
C(5)—C(8)	1·532 (7)	C(5)—C(14)	1·509 (7)
C(6)—C(8)	1·390 (9)	C(6)—C(24)	1·389 (13)
N(7)—C(11)	1·362 (6)	N(7)—C(25)	1·479 (7)
C(8)—C(15)	1·387 (9)	C(9)—C(17)	1·362 (9)
C(10)—C(12)	1·404 (9)	C(10)—C(18)	1·402 (10)
C(12)—C(20)	1·354 (9)	C(13)—C(17)	1·385 (12)
C(13)—C(19)	1·379 (11)	C(14)—C(19)	1·388 (7)
C(15)—C(16)	1·431 (11)	C(16)—C(21)	1·319 (14)
C(18)—C(26)	1·356 (12)	C(19)—C(23)	1·521 (9)
C(20)—C(22)	1·378 (9)	C(21)—C(24)	1·389 (13)
C(22)—C(26)	1·385 (10)	C(23)—C(25)	1·527 (9)

C(3)—O(1)—C(12)	119·2 (4)	O(1)—C(3)—C(11)	108·1 (4)
O(1)—C(3)—C(5)	116·6 (4)	C(5)—C(3)—C(11)	85·5 (4)
C(9)—C(4)—C(14)	120·1 (6)	C(3)—C(5)—C(14)	116·0 (3)
C(3)—C(5)—C(8)	114·9 (4)	C(3)—C(5)—N(7)	85·7 (3)
C(8)—C(5)—C(14)	113·9 (4)	N(7)—C(5)—C(14)	108·2 (4)
C(8)—C(6)—C(24)	120·4 (6)	C(5)—C(7)—C(25)	125·5 (5)
C(5)—N(7)—C(11)	96·1 (4)	C(5)—C(8)—C(6)	120·2 (4)
C(6)—C(8)—C(15)	119·5 (5)	C(4)—C(9)—C(17)	120·2 (7)
C(12)—C(10)—C(18)	117·4 (6)	C(3)—C(11)—N(7)	92·1 (4)
O(2)—C(11)—N(7)	131·5 (6)	O(2)—C(11)—C(3)	136·3 (6)
C(10)—C(12)—C(20)	120·9 (6)	C(17)—C(13)—C(19)	120·0 (7)
C(4)—C(14)—C(5)	123·8 (5)	C(5)—C(14)—C(19)	117·1 (4)
C(4)—C(14)—C(19)	119·1 (5)	C(8)—C(15)—C(16)	118·2 (7)
C(15)—C(16)—C(21)	121·7 (7)	C(9)—C(17)—C(13)	120·4 (7)
C(10)—C(18)—C(26)	121·8 (7)	C(13)—C(19)—C(14)	120·2 (6)
C(14)—C(19)—C(23)	118·2 (6)	C(12)—C(20)—C(22)	120·0 (6)
C(16)—C(21)—C(24)	120·4 (8)	C(20)—C(22)—C(26)	120·8 (7)
C(19)—C(23)—C(25)	112·3 (6)	C(6)—C(24)—C(21)	119·7 (8)
N(7)—C(25)—C(23)	107·2 (6)	C(18)—C(26)—C(22)	118·9 (7)

β-lactam ring. The lability to base hydrolysis of the lactam amide bond in these antibiotics correlates with biological activity. The compound under investigation was synthesized with the aim of examining the structural and conformational aspects of the β-lactam ring and making a database of structure activity/inactivity relationships of antibiotics.

Experimental. The title compound was synthesized (Bose *et al.*, 1976; imines prepared according to Whaley & Govindachavi, 1951) and was crystallized by slow evaporation from hexanol/ether in the form of needles at room temperature, dimensions 0·30 × 0·25 × 0·15 mm. Lattice parameters were obtained from 15 intermediate-angle axial reflections in the range $17 < 2\theta < 38°$. Three standard reflections were monitored periodically with no significant intensity variation. 2833 [2450 with $I > 3\sigma(I)$] unique reflections were collected on a Philips four-circle diffractometer with Ni-filtered Cu $K\alpha$ radiation in θ–2θ step-scan mode up to $2\theta < 110°$. Ranges of h, k and l were −28 to 25, 0 to 8 and 0 to 27 respectively. The reflections observed were for hkl: $h + k = 2n$; $h0l$: $l = 2n$ ($h = 2n$); $0k0$: ($k = 2n$) which confirmed the space group $C2/c$. Data were corrected for Lorentz–polarization factors but not for absorption (μ = 5·96 cm^{-1}).

The structure was solved by *SHELXS*86 (Sheldrick, 1986) using 350 E values ($E > 1·5$) and refined by least-squares methods on F with *SHELX*76 (Sheldrick, 1976). All 29 H atoms were located from a difference Fourier map. Anisotropic refinement of 26 non-H atoms, keeping 19 H atoms fixed as isotropic, led to $R = 0·071$ and $wR = 0·071$, where $w = 1/\sigma^2(F_o)$. $\Delta\rho$ peaks were 0·4 to −0·3 e Å^{-3}, $(\Delta/\sigma)_{max} = 0·78$. All calculations were carried out on PC/AT (386) and MicroVAXII computers with scattering factors from *SHELX*.

Discussion. The final atomic coordinates are given in Table 1.* The chemical diagram of the title compound is given in Fig. 1, and the *PLUTO* diagram is shown in Fig. 2. Bond lengths and angles are listed in Table 2.

From the least-squares plane of the β-lactam ring [N(7)–C(5)–C(11)–C(3)], it is found (Fig. 2) that O(2) and O(1) are in the *trans* position whereas O(1) and C(8) are in the *cis* position. It is found that the amide N atom, N(7) of the β-lactam compound, is 0·229 Å below the plane containing C(11), C(5) and C(25). The sum of bond angles about N(7) is 359·4° (Table 2). The bond length N(7)—C(11), 1·362 (6) Å, is

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53219 (18 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

similar to those found in 1-oxa-β-lactam (Narisada *et al.*, 1979) and 1-oxacephen (Shiro, Hiroshi, Fumihiko & Kikkawa, 1982).

The packing diagram is shown in Fig. 3 and shows the association of the β-lactam molecules along the *a* axis with gaps along the *c* axis of the crystal. The crystal structure is probably stabilized by base–base interactions about the center of inversion. There is no unusual hydrogen bonding in the molecular assembly pattern in the crystal.

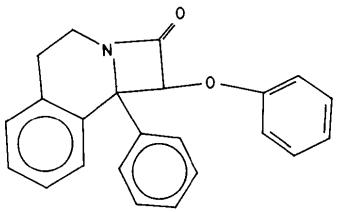


Fig. 1. Chemical diagram of the title compound.

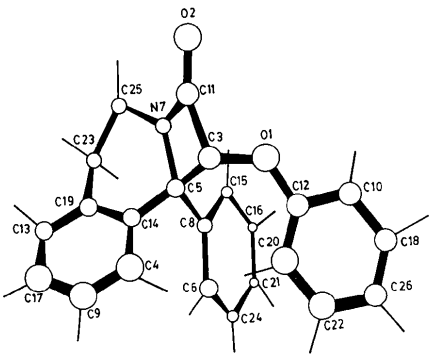


Fig. 2. *PLUTO* diagram of the molecule with atomic numbering scheme.

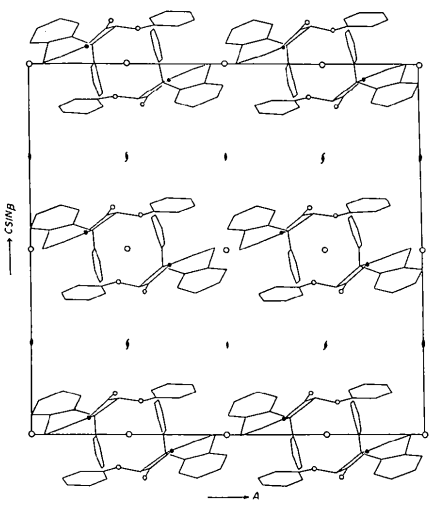
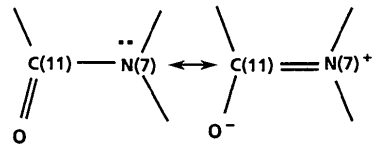


Fig. 3. Packing diagram of the molecule in *xz* projection.

From reports of structure–activity relationships and quantitative geometrical differences (Brufani & Cellai, 1984) for the active and inactive compound structures in the β-lactam series, it was concluded that compounds having the N(7) atom at a distance 0·4–0·5 Å from the plane containing the other atoms of the β-lactam ring have antibiotic activity (Brufani & Cellai, 1984). Accordingly, our compound is likely to be inactive, and this is what is found. Other factors such as the ring and side-chain conformations of these compounds may also be involved. The activity of these compounds may also depend on the lability of the lone pair of the N(7) atom in the β-lactam compound which changes with the amount of delocalization of the lone pair as well as with steric factors. In our compound there is no restraint or delocalization of the lone pair at N(7) over C(11) and N(7) atoms, which are conjugated with the C=O bond (Sweet, 1972).



This can be expected to make enzymatic attack at the C—N bond less likely.

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