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Structure of a Modified β-Lactam Analogue

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Abstract. 4-[5-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-methoxy-1-(*p*-methoxyphenyl)-2-azetidinone, $C_{21}H_{29}NO_7$, $M_r = 378.23$, monoclinic, $P2_1$, $a = 14.024$ (1), $b = 10.288$ (1), $c = 15.912$ (2) Å, $\beta = 107.2$ (1)°, $V = 2192.8$ (3) Å^3, $Z = 4$, $D_m = 1.123$, $D_x = 1.115$ g cm^{-3}, λ(Mo $K\alpha$) = 0.71073 Å, $\mu = 0.831$ cm^{-1}, $F(000) = 872$, $T = 288$ K, final $R = 0.069$ for 1575 observed reflections. There are two molecules in the asymmetric unit. The β-lactam ring in both molecules is in a *cis* conformation and the N(1) atom in the β-lactam ring is 0.004 Å away from the mean plane containing C(4), C(2) and C(12) in molecule 1, and 0.088 Å away from the similar mean plane in molecule 2. Of the two dioxolane rings in each of the two molecules in the asymmetric unit, one is in an envelope conformation and the other in a twisted conformation.

Introduction. A large family of antibiotics is known whose single common structural feature is a β-lactam ring. Included are penicillin, ampicillin, cephalosporin and non-classical β-lactams. The antibiotics, in principle, inhibit bacterial cell-wall synthesis by inhibiting the enzyme D-alanyl-D-alanine transpeptidase which is responsible for the cross-linking reaction of bacterial cell-wall peptidoglycan.

Since the structure and conformation of β-lactams in general and the β-lactam ring in particular play a key role in the biological activity of β-lactam antibiotics, it is worthwhile studying their activity when modified by substituents or fused rings (Takasuka, Nishikawa & Tori, 1982).

As part of our investigation into stereochemical information on the lability of the β-lactam amide bonds and on the conformation of the antibiotic, especially in the region of the β-lactam ring, we report here the structure of the title compound.

The compound under investigation is a non-classical unfused β-lactam. It was synthesized from D-mannitol by a Bose reaction (Wagle, Garai, Chiang, Monteleone, Kurys, Strohmeyer, Hedge, Mannhas & Bose, 1988) in which two asymmetric centres in the β-lactam ring, C(3) and C(4), are created from two chiral moieties. The two molecules in the asymmetric unit are diastereoisomerically identical, but have a slight difference in conformation. The aim of this X-ray structure determination is to determine the relative configuration of two chiral centres, C(3) and C(4), in the molecule with respect to the absolute configuration of the chiral centres in D-mannitol (Jeffrey & Kim, 1970) and to identify the appropriate conformation of the β-lactam relative to its target (site of action).

Experimental. Needle-shaped crystals were grown from ethyl acetate–hexane by slow evaporation at room temperature. Preliminary oscillation and Weissenberg photographs indicated a monoclinic system with systematic absences only along $0k0$: k = odd, consistent with the space group $P2_1$. Good quality crystal of dimensions 0.30 × 0.30 × 0.20 mm selected for intensity data collection on a CAD-4 diffractometer, using graphite-monochromatized Mo $K\alpha$ radiation. Accurate cell parameters determined by least-squares refinement of the setting angles of 25 reflections. During data collection, three standard reflections were periodically observed with no significant intensity variation. Intensities of all reflections measured over the range $0 < 2\theta < 45°$ using ω-2θ step-scan mode at the rate of 2° min^{-1}. Range of hkl: −15 to 14, 0 to 10, 0 to 16 respectively. 3715 unique reflections measured, of which 1575 had $I > 3\sigma(I)$ and were used for structure determination and refinement. Corrections for Lorentz and polarization factors applied to the intensity values but no absorption correction (μ =

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0.83 cm^{-1}). Structure solved using *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). An *E* map generated from the best phase set of 100 reflections with the highest combined figure of merit located 21 atoms in two clusters as expected for two molecules in the asymmetric unit. The remaining 34 atoms were located by successive Fourier methods. All H atoms were located from difference Fourier maps. All 58 non-H atoms of the two asymmetric units were refined anisotropically in two blocks using *SHELX*76 (Sheldrick, 1976) including all H atoms which were refined isotropically. The function minimized was $\sum w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma^2|F_o|)$. Final $R = 0.069$, $wR = 0.068$, 696 refined parameters (348 in each cycle of refinement). A final difference Fourier synthesis showed peaks lying between 0.4 and -0.3 e $Å^{-3}$, $(\Delta/\sigma)_{max} = 0.37$. The number of reflections per refined variable was [(1575) × 2]/696 = 4.5. Geometrical parameters of the molecule were computed with *PARST* (Nardelli, 1983). All calculations were carried out on PC/AT(386) and MicroVAX II computers.

Discussion. The final atomic coordinates are given in Table 1.* A chemical diagram of the title compound is shown in Fig. 1 and a *PLUTO* (Motherwell & Clegg, 1978) diagram in Fig. 2. Bond lengths and angles are listed in Table 2. The torsion angles around the chiral centres which correspond to D-mannitol are given in Table 2. From the least-squares plane of β-lactam ring [N(1)—C(2)—C(3)—C(4)], it is observed (Fig. 2) that O(2) and O(3) atoms in both the molecules in the asymmetric unit are in the *cis* form and their deviations from the mean plane are 0.083 (14) Å for O(2) and 0.852 (10) Å for O(3) in molecule 1 and −0.057 (11) of O(2) and −0.974 (9) Å for O(3) in molecule 2, respectively. The amide N atoms in the β-lactam molecules are 0.004 (10) and 0.088 (10) Å above the plane containing C(4), C(2) and C(12) atoms in molecules 1 and 2, respectively. The sum of bond angles about N(1) is 360.0° in molecule 1 and 358.7° in molecule 2. The bond length N(1)—C(2) [1.347 (1) in molecule 1 and 1.371 (1) Å in molecule 2] is similar to those found in 1-phenoxy-9b-phenyl-1,4,5,9b-tetrahydro-2*H*-azeto-[1,2-*a*]isoquinolin-2-one (Pain, Biswas, Banerjee, De, Mathur, Bose & Iitaka, 1991), 1-oxa-β-lactam (Narisada, Yoshida, Onoue, Ohtani, Okada, Tsuji, Kikkawa, Haga, Satoh, Itani & Nagata, 1979) and L-1-benzyl-4-hydroxymethyl-2-azetidinone (Lee, Cho, Kim, Shin, Ruble & Craven, 1990).

Table 1. *Final atomic coordinates 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} (Å² × 10⁴)
O(4)	0.3213 (6)	0.7628 (9)	0.1651 (6)	533 (22)
O(5)	0.2578 (5)	0.6237 (10)	0.0493 (6)	506 (19)
O(6)	0.0150 (5)	0.7806 (9)	−0.0079 (6)	509 (20)
O(7)	−0.0396 (6)	0.6435 (10)	−0.1254 (5)	498 (20)
C(7)	0.1762 (8)	0.6924 (0)	0.0658 (8)	402 (21)
C(9)	0.1017 (9)	0.7220 (13)	−0.0233 (8)	467 (24)
C(8)	0.3408 (8)	0.6502 (14)	0.1217 (8)	498 (22)
C(6)	0.2221 (8)	0.8079 (12)	0.1184 (7)	379 (22)
C(8*A*)	0.3591 (12)	0.5439 (18)	0.1865 (11)	840 (25)
C(11)	0.0587 (9)	0.6042 (13)	−0.0801 (7)	501 (21)
C(16)	0.1308 (10)	0.4529 (17)	0.3521 (10)	712 (26)
N(1)	0.1813 (7)	0.7753 (12)	0.2655 (6)	489 (22)
C(12)	0.1339 (8)	0.6557 (13)	0.2740 (7)	408 (20)
C(15)	0.0379 (9)	0.4236 (14)	0.2922 (8)	472 (22)
C(14)	−0.0077 (8)	0.5155 (15)	0.2257 (8)	516 (22)
C(13)	0.0395 (9)	0.6299 (14)	0.2179 (8)	492 (24)
C(10*B*)	−0.1121 (9)	0.6310 (12)	−0.0046 (8)	463 (23)
O(2)	0.2834 (10)	0.8453 (14)	0.3995 (7)	1060 (21)
C(2)	0.2463 (10)	0.8552 (15)	0.3213 (8)	558 (23)
C(5)	0.3564 (13)	1.1155 (18)	0.2955 (12)	879 (24)
O(3)	0.3105 (7)	1.0228 (10)	0.2357 (7)	673 (22)
C(17)	0.1793 (9)	0.5668 (14)	0.3407 (8)	489 (22)
C(3)	0.2273 (10)	0.9579 (13)	0.2531 (9)	536 (22)
O(15)	−0.0142 (7)	0.3104 (11)	0.2953 (7)	722 (21)
C(18)	0.0420 (12)	0.2034 (17)	0.3378 (10)	762 (24)
C(10*A*)	−0.1477 (9)	0.8182 (13)	−0.1105 (9)	578 (24)
C(8*B*)	0.4320 (12)	0.6781 (18)	0.0885 (13)	946 (26)
C(4)	0.1727 (8)	0.8556 (12)	0.1873 (7)	390 (21)
C(10)	−0.0723 (8)	0.7166 (12)	−0.0631 (7)	368 (23)
C(15′)	−0.3711 (9)	0.6856 (16)	0.0049 (8)	528 (24)
O(15′)	−0.4301 (7)	0.6802 (12)	−0.0813 (6)	734 (22)
C(14′)	−0.3339 (10)	0.8101 (15)	0.0361 (9)	596 (24)
C(12′)	−0.2495 (9)	0.7174 (15)	0.1750 (8)	471 (24)
C(17′)	−0.2830 (9)	0.5935 (13)	0.1447 (7)	419 (24)
C(13′)	−0.2755 (11)	0.8264 (14)	0.1210 (8)	573 (24)
C(16′)	−0.3438 (8)	0.5771 (15)	0.0573 (9)	534 (24)
O(5′)	−0.4035 (7)	0.6381 (10)	0.3842 (7)	658 (22)
C(4′)	−0.1627 (9)	0.6584 (13)	0.3411 (8)	440 (25)
N(1′)	−0.1849 (7)	0.7360 (11)	0.2629 (6)	436 (22)
C(8′)	−0.3828 (8)	0.7736 (17)	0.3950 (8)	543 (24)
O(4′)	−0.2782 (6)	0.7842 (10)	0.3982 (6)	594 (22)
C(3′)	−0.0692 (8)	0.7522 (14)	0.3784 (8)	459 (24)
C(2′)	−0.1089 (11)	0.8240 (14)	0.2918 (8)	541 (24)
C(8*A*′)	−0.3913 (12)	0.8132 (20)	0.4824 (12)	1020 (27)
C(8*B*′)	−0.4420 (12)	0.8460 (18)	0.3184 (14)	905 (28)
O(3′)	−0.0614 (6)	0.8075 (11)	0.4584 (5)	591 (21)
C(7′)	−0.3304 (9)	0.5707 (12)	0.3549 (9)	437 (24)
C(6′)	−0.2385 (9)	0.6545 (13)	0.3950 (8)	414 (26)
O(6′)	−0.2527 (6)	0.3686 (10)	0.3471 (7)	616 (21)
O(7′)	−0.3864 (8)	0.2317 (14)	0.3232 (9)	1034 (26)
C(10*A*′)	−0.2280 (14)	0.1540 (18)	0.4020 (14)	1012 (28)
C(10′)	−0.2825 (10)	0.2375 (17)	0.3307 (10)	669 (26)
C(18′)	−0.4651 (12)	0.5553 (20)	−0.1155 (10)	922 (24)

According to the Cahn, Ingold and Prelog sequence rule, the configuration at C(3) and C(4) is *S* for both molecules. In molecule 1, the five-membered dioxolane ring [C(6)C(7)O(5)C(8)O(4)] is in an envelope (*E*) form with pseudorotation parameter $q = 0.2876$ and $\varphi = 36.04°$ (Cremer & Pople, 1975) and the second dioxolane ring [C(9)O(6)C(10)O(7)-C(11)] is in a major twisted form with the pseudorotation parameter $q = 0.2515$ and $\varphi = 13.15°$. In molecule 2, the above mentioned five-membered rings are in major envelope ($q = 0.2933$, $\varphi = 29.56°$) and major twisted ($q = 0.9557$ and $\varphi = -93.85°$) forms, respectively. The molecule is stabilized by the intramolecular short contacts between N(1)···O(4) (2.87 Å) and N(1)···O(3) (3.23 Å) for molecule 1 and N(1′)···O(4′) (2.87 Å) and N(1′)···O(3′) (3.16 Å) for

* Lists of structure factors, anisotropic thermal parameters, complete bond angles, least-squares planes and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54664 (18 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Bond lengths* (Å), *bond angles* (°) *and selected torsional angles* (°)

	Molecule 1	Molecule 2
O(4)—C(8)	1.4169 (17)	1.4565 (15)
O(4)—C(6)	1.4462 (13)	1.4531 (16)
O(5)—C(7)	1.4343 (14)	1.4252 (18)
O(5)—C(8)	1.4013 (13)	1.4243 (20)
O(6)—C(9)	1.4408 (16)	1.4483 (19)
O(6)—C(10)	1.4382 (12)	1.4134 (20)
O(7)—C(11)	1.4116 (14)	1.3316 (23)
O(7)—C(10)	1.4231 (15)	1.4275 (18)
C(7)—C(9)	1.5227 (15)	1.4529 (20)
C(7)—C(6)	1.4851 (13)	1.5238 (17)
C(9)—C(11)	1.5259 (18)	1.6013 (21)
C(8)—C(8*A*)	1.4722 (22)	1.4862 (24)
C(8)—C(8*B*)	1.5481 (24)	1.4594 (22)
C(6)—C(4)	1.5401 (18)	1.5509 (20)
C(16)—C(15)	1.4014 (17)	1.3780 (21)
C(16)—C(17)	1.3940 (22)	1.4103 (16)
N(1)—C(12)	1.4234 (17)	1.4358 (14)
N(1)—C(2)	1.3474 (16)	1.3707 (17)
N(1)—C(4)	1.4687 (16)	1.4338 (16)
C(12)—C(13)	1.3861 (15)	1.3944 (20)
C(12)—C(17)	1.4026 (17)	1.3940 (19)
C(15)—C(14)	1.4218 (18)	1.4155 (22)
C(15)—O(15)	1.3828 (18)	1.3779 (14)
C(14)—C(13)	1.3739 (20)	1.3662 (17)
C(10)—C(10*B*)	1.5043 (18)	1.5191 (17)
O(2)—C(2)	1.2033 (15)	1.1836 (19)
C(2)—C(3)	1.4807 (20)	1.5162 (18)
C(5)—O(3)	1.3667 (20)	1.4018 (18)
O(3)—C(3)	1.4407 (18)	1.3680 (16)
C(3)—C(4)	1.5218 (17)	1.5945 (17)
O(15)—C(18)	1.4059 (19)	1.4255 (23)
C(8)—O(4)—C(6)	107.84 (8)	108.82 (10)
C(7)—O(5)—C(8)	105.49 (6)	112.05 (9)
C(9)—O(6)—C(10)	108.22 (8)	109.51 (11)
C(11)—O(7)—C(10)	105.28 (2)	110.15 (13)
O(5)—C(7)—C(6)	105.13 (6)	100.88 (10)
O(6)—C(9)—C(11)	103.17 (10)	98.31 (11)
O(4)—C(8)—O(5)	109.07 (10)	104.12 (12)
C(8*A*)—C(8)—C(8*B*)	112.69 (13)	117.32 (13)
O(4)—C(6)—C(7)	102.95 (8)	104.41 (10)
C(7)—C(6)—C(4)	116.39 (9)	114.60 (10)
O(7)—C(11)—C(9)	103.28 (10)	107.90 (13)
C(15)—C(16)—C(17)	118.91 (13)	118.59 (13)
C(2)—N(1)—C(4)	94.88 (9)	97.37 (9)
C(12)—N(1)—C(2)	135.10 (10)	128.26 (10)
C(12)—N(1)—C(4)	130.02 (9)	133.14 (11)
C(13)—C(12)—C(17)	119.66 (12)	121.46 (12)
C(16)—C(15)—O(15)	123.50 (12)	115.86 (12)
C(16)—C(15)—C(14)	119.09 (13)	120.86 (12)
C(15)—C(14)—C(13)	120.93 (11)	120.55 (14)
C(12)—C(13)—C(14)	120.04 (12)	118.81 (13)
N(1)—C(2)—O(2)	129.14 (14)	134.53 (13)
N(1)—C(2)—C(3)	90.72 (10)	91.35 (11)
C(5)—O(3)—C(3)	115.53 (12)	112.56 (9)
C(16)—C(17)—C(12)	121.16 (12)	119.59 (12)
C(2)—C(3)—O(3)	119.38 (11)	123.35 (12)
C(2)—C(3)—C(4)	87.47 (10)	85.22 (9)
C(15)—O(15)—C(18)	116.68 (12)	117.03 (12)
N(1)—C(4)—C(3)	84.67 (9)	85.95 (9)
C(6)—C(4)—N(1)	118.79 (10)	119.04 (10)
C(10*B*)—C(10)—C(10*A*)	112.21 (9)	113.85 (15)
O(6)—C(10)—O(7)	106.01 (8)	107.13 (13)
C(9)—C(7)—C(6)—C(4)	95.62 (12)	91.10 (14)
C(6)—C(7)—C(9)—C(11)	176.51 (10)	179.68 (12)
C(7)—C(6)—C(4)—N(1)	69.58 (14)	76.12 (14)
C(12)—N(1)—C(4)—C(6)	−72.96 (16)	−77.67 (17)

molecule 2, respectively. Of these the first three are hydrogen bonds according to their geometry. A packing diagram is shown in Fig. 3. Possible hydrogen bonds are observed between the atoms O(3′) and C(18)($-x$, $y+\frac{1}{2}$, $-z+1$) (3.34 Å), C(3) and O(7)($-x$, $y+\frac{1}{2}$, $-z$) (3.39 Å, O3 and C(18′) ($-x$, $y+\frac{1}{2}$, $-z$) (3.30 Å) and C(8*B*) and C(15′)($x+1$, y, z) (3.40 Å) respectively.

From reports of structure–activity relationships and quantitative geometrical differences (Brufani & Cellai, 1984) for the active and inactive compound structures of the β-lactam series, it was concluded that compounds having the N(1) 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). According to this consideration, our compound is likely to be inactive, as indeed it is. Of course 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(1) atom in the β-lactam compound which changes with

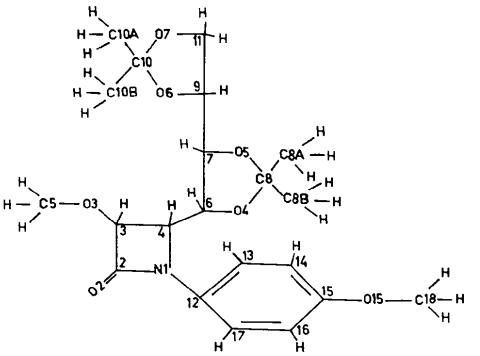


Fig. 1. Chemical diagram of the molecule with H atoms and labelled non-H atoms.

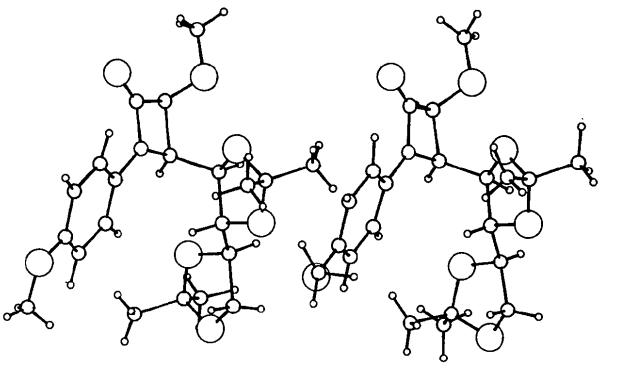


Fig. 2. *PLUTO* (Motherwell & Clegg, 1978) diagram of the two molecules in the asymmetric unit oriented for similar views.

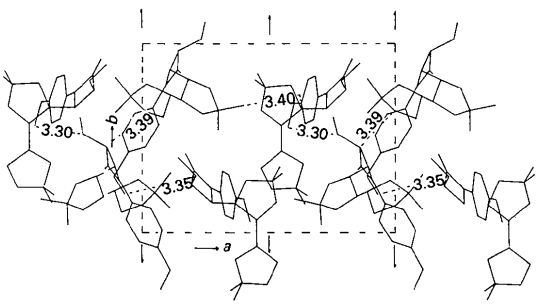
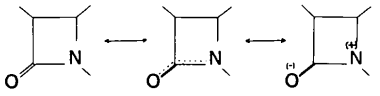


Fig. 3. Packing diagram of the molecule in *xy* projection. Distances are in Å.

the amount of delocalization of the lone pair as well as steric factors. In the present compound there is no restraint on delocalization of the lone pair on N(1) over C(2) and N(1) 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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Structure of RG-12561 Dichloromethane Solvate and a Diastereomer

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Abstract. (III): [4α,6β(*E*)]-(±)-6-{2-[2-(4-Fluoro-3-methylphenyl)-4,4,6,6-tetramethyl-1-cyclohexen-1-yl]ethenyl}-4-hydroxytetrahydropyran-2-one (RG-12561) dichloromethane solvate, $2C_{24}H_{31}FO_3.CH_2Cl_2$, M_r = 857.94, triclinic, $P\bar{1}$, a = 11.7413 (5), b = 13.0279 (5), c = 16.2332 (9) Å, α = 99.456 (4), β = 94.217 (4), γ = 101.893 (4)°, V = 2381.9 (4) Å^3, Z = 4 [four molecules of (III) + two molecules of solvent per unit cell], D_x = 1.195 g cm^{-3}, Cu $K\alpha$, λ = 1.54178 Å, μ = 16.69 cm^{-1}, $F(000)$ = 912, T = 293 K, final R = 0.053, wR = 0.060 for 4031 reflections with $I > 3\sigma(I)$. (IV): [4β,6α(*E*)]-(±)-6-{2-[2-(4-Fluoro-3-methylphenyl)-4,4,6,6-tetramethyl-1-cyclohexen-1-yl]ethenyl}-4-hydroxytetrahydropyran-2-one, $C_{24}H_{31}FO_3$, M_r = 386.51, triclinic, $P\bar{1}$, a = 6.054 (2), b = 12.931 (2), c = 14.838 (3) Å, α = 67.70 (2), β = 85.75 (2), γ = 82.85 (2)°, V = 1066.0 (8) Å^3, Z = 2, D_x = 1.203 g cm^{-3}, Cu $K\alpha$, λ = 1.54178 Å, μ = 6.86 cm^{-1}, $F(000)$ = 414, T = 293 K, final R = 0.073, wR = 0.081 for 1588 reflections with $I > 3\sigma(I)$. (III) is a potent HMG-CoA reductase inhibitor and has the potential to function as a superior hypocholesterolemic agent; (IV) lacks this activity. (III) and (IV) have different conformations and molecular-model calculations suggest that crystal-packing effects are primarily responsible for

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