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Acta Cryst. (1995). C**51**, 1921–1923

3,4-Di-*O*-acetyl-2,5-anhydro-1,6-di-*O*-(*p*-tolylsulfonyl)-D-mannitol

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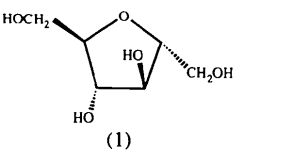
(*Received* 6 *May* 1994; *accepted* 8 *March* 1995)

Abstract

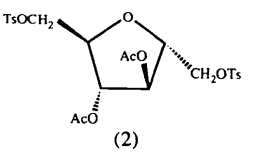
The title compound, 2,5-bis(4-methylphenylsulfonyloxymethyl)oxolane-3,4-diyl diacetate, $C_{24}H_{28}O_{11}S_2$, lies on a crystallographic twofold axis. It adopts a perfect twist ^3_4T conformation in the solid state. The puckering parameters of the tetrahydrofuran ring are $q = 0.32\,(8)$ Å and $\varphi = 92.3\,(5)°$. The acetyl groups are planar, with the non-H atoms deviating less than 0.002 (3) Å from their mean plane. They have an (*S*)-*cis* conformation with the C—O and C═O bonds eclipsed, and each acetyl group is orientated with the C═O group syndiaxial to the C—H bond at the ring C atom to which the group is attached.

Comment

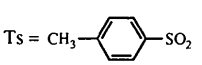
We have utilized structurally locked fructofuranose analogs to establish the anomeric specificity of the active and regulatory sites of phosphofructokinase and certain other enzymes (Younathan, Voll & Koerner, 1981). We have also reported that 2,5-anhydro-D-mannitol, (1), lowers blood sugar in both normal and experimentally diabetic rats (Hanson, Ho, Wiseberg, Simpson, Younathan & Blair, 1984). As part of our study on the biological effects of analogs of 2,5-anhydro-D-mannitol, we have synthesized a variety of 2,5-anhydro-D-mannitol derivatives. Interestingly, we have discovered that some of these derivatives may adopt different conformations in the solid state from those adopted in solution (Shalaby, Fronczek, Lee & Younathan, 1995).

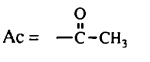


(1)



(2)





The title compound, 3,4-di-*O*-acetyl-2,5-anhydro-1,6-di-*O*-(*p*-tolylsulfonyl)-D-mannitol, (2), was found to adopt similar conformations both in the solid state and in solution. The ^{13}C NMR spectrum of (2) in solution shows resonances consistent with C_2 symmetry. The ^1H NMR spectrum also shows a high degree of symmetry in solution. Similarly, the X-ray data reveal that the molecule lies on a twofold axis of symmetry; its furanose ring adopts a perfect twist ^3_4T conformation (Cremer & Pople, 1975), with a phase angle (P) of 180° and a pseudorotation amplitude (τ_m) of −28.41° (Altona & Sundaralingam, 1972). The corresponding puckering parameters (Cremer & Pople, 1975) are $q = 0.32\,(8)$ Å and $\varphi = 92.3\,(5)°$.

The C—C bond lengths in the furanose ring, 1.518 (3) and 1.523 (3) Å, are normal, while the ring C—O distance is 1.421 (3) Å. These are in good agreement with the values reported for other carbohydrates (Allen, Kennard, Watson, Brammer, Orpen & Taylor, 1987). Also, the O-atom ring valence angle [111.6 (2)°] is normal and similar to that of 109.7 (2)° found in 2,5-anhydro-D-mannitol (Watkins, Abboud, Voll, Koerner & Younathan, 1983).

The C11—O5 bond length of 1.348 (3) Å agrees well with those found in several peracetylated pentofuranoses (Luger & Paulsen, 1978). The C═O bond length of 1.199 (3) Å is within the range of expected values for the carbonyl group. The acetyl groups have an (*S*)-*cis* conformation with the C—O and C═O bonds eclipsed. This is the conformation most commonly observed in simple esters (Leung & Marchessault, 1974; Shalaby, Fronczek & Younathan, 1994). The acetyl groups are planar, with the non-H atoms deviating by less than 0.002 Å from their mean plane. The acetyl group is oriented with the C═O group syndiaxial to the C—H bond at the ring C atom to which the group is attached (John & Radom, 1977; Oliver & Strickland, 1984). Comparison of the data for the tosyl grouping shows no notable differences from those values observed in the unsymmetrical ditosylated compound, methyl 3,4-anhydro-1,6-di-1,6-*O*-(*p*-tolylsulfonyl)-β-D-tagatofuranoside (Guthrie, Jenkins, Yamasaki, Skelton & White, 1981).

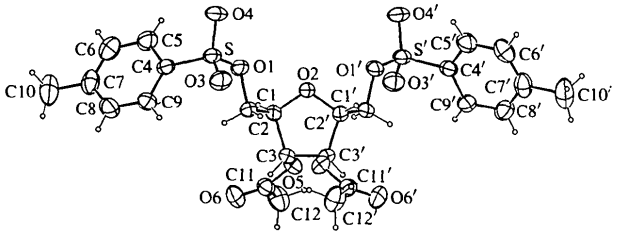


Fig. 1. *ORTEP* (Johnson, 1965) drawing of the title compound, with displacement ellipsoids drawn at the 30% probability level. H atoms are represented as spheres of arbitrary radii.

Experimental

Crystals of 3,4-di-*O*-acetyl-2,5-anhydro-1,6-di-*O*-(*p*-tolylsulfonyl)-D-mannitol were recrystallized from ethanol.

Crystal data

$C_{24}H_{28}O_{11}S_2$
$M_r = 556.6$
Monoclinic
$C2$
$a = 15.885\ (2)$ Å
$b = 5.6895\ (4)$ Å
$c = 14.889\ (2)$ Å
$\beta = 93.359\ (9)°$
$V = 1343.4\ (5)$ Å^3
$Z = 2$
$D_x = 1.376$ Mg m^{-3}
Cu $K\alpha$ radiation
$\lambda = 1.54184$ Å
Cell parameters from 25 reflections
$\theta = 11–25°$
$\mu = 2.3$ mm^{-1}
$T = 299$ K
Needle
0.75 × 0.10 × 0.08 mm
Colorless

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: ψ scans (North, Phillips & Mathews, 1968)
$T_{min} = 0.932$, $T_{max} = 0.997$
1566 measured reflections
1524 independent reflections
1449 observed reflections $[I > 3\sigma(I)]$
$R_{int} = 0.025$
$\theta_{max} = 75°$
$h = 0 \rightarrow 18$
$k = 0 \rightarrow 7$
$l = -18 \rightarrow 18$
3 standard reflections
frequency: 166.6 min
intensity decay: <1%

Refinement

Refinement on F
$R = 0.030$
$wR = 0.041$
$S = 2.295$
1449 reflections
200 parameters
$w = 4F_o^2/[\sigma^2(I) + (0.02F_o^2)^2]$
$(\Delta/\sigma)_{max} = 0.07$
$\Delta\rho_{max} = 0.17$ e Å^{-3}
$\Delta\rho_{min} = -0.24$ e Å^{-3}
Extinction correction: $(I + gI_c)^{-1}$ applied to F_c
Extinction coefficient: $g = 6.8\ (6) \times 10^{-6}$
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

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

	x	y	z	U_{eq}
S	0.55514 (5)	0.0000	0.27223 (4)	0.0605 (1)
O1	0.5593 (1)	0.0677 (3)	0.1704 (1)	0.0644 (4)
O2	1/2	0.1971 (5)	0	0.0762 (6)
O3	0.4952 (1)	0.1447 (4)	0.3128 (1)	0.0766 (5)
O4	0.5446 (1)	−0.2483 (4)	0.2708 (1)	0.0831 (6)
O5	0.5932 (1)	0.6432 (3)	−0.0599 (1)	0.0628 (4)
O6	0.6917 (1)	0.8272 (5)	0.0274 (1)	0.0817 (6)
C1	0.5521 (1)	0.3168 (4)	0.1473 (1)	0.0592 (5)
C2	0.5614 (1)	0.3376 (4)	0.0481 (1)	0.0560 (5)
C3	0.5460 (1)	0.5899 (4)	0.0170 (1)	0.0542 (5)
C4	0.6561 (1)	0.0665 (4)	0.3190 (1)	0.0572 (5)
C5	0.7217 (2)	−0.0874 (6)	0.3067 (2)	0.0800 (8)
C6	0.8005 (2)	−0.0391 (7)	0.3462 (2)	0.091 (1)
C7	0.8153 (2)	0.1595 (8)	0.3968 (2)	0.0858 (9)
C8	0.7493 (2)	0.3111 (7)	0.4071 (2)	0.0860 (9)
C9	0.6699 (2)	0.2699 (5)	0.3684 (2)	0.0727 (7)
C10	0.9013 (2)	0.208 (1)	0.4425 (2)	0.127 (1)
C11	0.6636 (1)	0.7738 (5)	−0.0462 (2)	0.0624 (6)
C12	0.6986 (2)	0.8390 (8)	−0.1326 (2)	0.099 (1)

Table 2. *Selected geometric parameters* (Å, °)

S—O1	1.570 (2)	C2—C3	1.523 (3)
S—O3	1.420 (2)	C3—C3′	1.518 (3)
S—O4	1.423 (2)	C4—C5	1.382 (4)
S—C4	1.751 (2)	C4—C9	1.382 (4)
O1—C1	1.461 (3)	C5—C6	1.379 (4)
O2—C2	1.421 (3)	C6—C7	1.371 (5)
O5—C3	1.437 (3)	C7—C8	1.373 (5)
O5—C11	1.348 (3)	C7—C10	1.515 (4)
O6—C11	1.199 (3)	C8—C9	1.376 (4)
C1—C2	1.497 (3)	C11—C12	1.478 (4)
O1—S—O3	109.6 (1)	C2—C3—C3′	103.6 (2)
O1—S—O4	104.0 (1)	S—C4—C5	119.4 (2)
O1—S—C4	103.96 (9)	S—C4—C9	120.4 (2)
O3—S—O4	120.0 (1)	C5—C4—C9	120.2 (2)
O3—S—C4	109.1 (1)	C4—C5—C6	119.4 (3)
O4—S—C4	109.0 (1)	C5—C6—C7	121.4 (3)
S—O1—C1	117.3 (1)	C6—C7—C8	118.2 (3)
C2—O2—C2′	111.6 (2)	C6—C7—C10	121.2 (3)
C3—O5—C11	117.6 (2)	C8—C7—C10	120.6 (4)
O1—C1—C2	107.4 (2)	C7—C8—C9	122.2 (3)
O2—C2—C1	110.4 (2)	C4—C9—C8	118.6 (3)
O2—C2—C3	106.5 (2)	O5—C11—O6	122.6 (2)
C1—C2—C3	110.5 (2)	O5—C11—C12	111.0 (2)
O5—C3—C2	111.1 (2)	O6—C11—C12	126.3 (2)
O5—C3—C3′	105.7 (2)		

The structure was solved using *DIRDIF* (Beurskens, 1984) beginning with the S-atom position deduced from the Patterson function. H atoms were refined isotropically, except for those of methyl groups which were placed in calculated positions, using difference maps as a guide, with a C—H distance of 0.95 Å and $B_{iso} = 1.3B_{eq}$ of the bonded C atom. The inversion-related structure was refined under identical conditions to $R = 0.032$, $wR = 0.045$ and $S = 2.503$. The absolute configuration thus determined is that expected from the starting materials. Programs used include *MolEN* (Fair, 1990) and *ORTEP* (Johnson, 1965).

The financial support of the National Institutes of Health (grant No. DK 40401 to ESY) is gratefully acknowledged.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: SZ1011). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1995). C**51**, 1923–1925

Prolyl Endopeptidase Inhibitors. I. A Peptidyl α-Keto Ester Derivative

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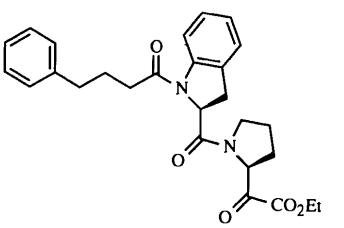
(*Received* 18 *April* 1994; *accepted* 16 *March* 1995)

Abstract

In the crystal structure of the synthetic prolyl endopeptidase (PEP) inhibitor ethyl α-oxo-1-{1-(4-phenylbutanoyl)-2(*S*)-indolinoyl}-2(*S*)-pyrrolidineacetate, $C_{27}H_{30}N_2O_5$, the N-terminal amide bond is *cis*. The proline amide bond is *trans*. The dipeptide has a polyproline II conformation. The O atoms of both the ketone and the ester carbonyl groups point in the same direction.

Comment

Prolyl endopeptidase (PEP) (E.C. 3.4.21.26) (Welches, Brosnihan & Ferrario, 1993) is a serine protease that cleaves proline-containing peptides such as substance P, vasopressin and bradykinin. It is thought that PEP inhibitors may improve learning and memory by prolonging the half-life of neuropeptides (Angelucci *et al.*, 1993). A series of α-keto esters have been successfully incorporated into peptidyl protease inhibitors (Angelastro, Mehdi, Burkhart, Peet & Bey, 1990). In order to investigate the inhibition mechanism, it is important to determine the molecular structure of the α-keto ester inhibitor, (I), which is the subject of this study.



(I)

The title dipeptide, with φ_1 and ψ_1, and φ_2 and ψ_2 of $-59(1)$ and $154(9)$, and $-70(1)$ and $159(9)°$, respectively (IUPAC–IUB Commission on Biochemical Nomenclature, 1971), has a polyproline II conformation. The N-terminal amide bond is *cis* [C19—C18—N1—C4 $-8(1)°$]. The C-terminal proline amide bond is *trans*

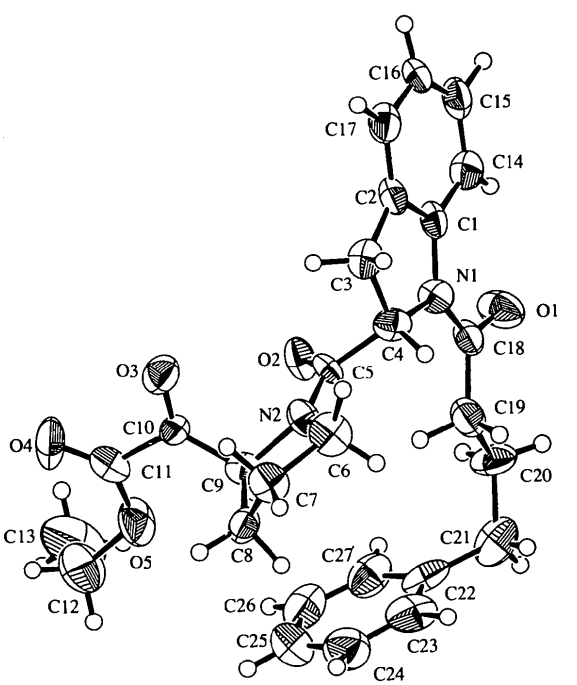


Fig. 1. The molecular structure of title compound with the crystallographic numbering scheme (*ORTEP*II; Johnson, 1976). Displacement ellipsoids are shown at the 50% probability level and H atoms are drawn as spheres of arbitrary size.