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Note

Synthesis of 1,5-anhydro-3,4-di-*O*-*p*-tolylsulfonyl-D-mannitol*

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The sulfonic esters of sugars are very useful intermediates in synthesis, as sulfonyloxy groups can be replaced by a variety of nucleophiles, giving amino, halogeno, thio, and anhydro sugars.

Examples of reactions leading to anhydro rings, through internal, nucleophilic displacement of tosyloxy groups, are the syntheses of the dialkyl dithioacetals of 2,5-anhydro-D-ribose, and -D-xylose, accomplished[2] by the action of one molar equivalent of a sulfonyl chloride on the corresponding aldose dialkyl dithioacetal in pyridine solution at 0–5°. Other closely related reactions leading to the synthesis of derivatives of anhydroalditols, through intramolecular displacement of sulfonyloxy groups under basic, neutral, or acidic conditions, have been reported[3].

From the reaction of 3,4-di-*O*-tosyl-D-mannitol with one molar equivalent of *p*-toluenesulfonyl chloride in anhydrous pyridine at 0°, 1,5-anhydro-3,4-di-*O*-*p*-tolylsulfonyl-D-mannitol (**1**) was isolated by column chromatography on silica gel. In this case, the closure reaction is produced by an internal, nucleophilic displacement, of the tosyloxy group introduced on C-1, by the hydroxyl group located on C-5.

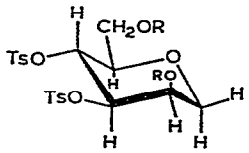
The structure of **1** was determined by ^{1}H-n.m.r. spectroscopy, and it agrees well with other experimental data. The 100-MHz spectrum of **1** showed a triplet and a pair of doublets at low field, which were assigned to H-3 and H-4, as they are bonded to carbon atoms bearing electronegative substituents. These protons are spin-coupled, and the value of $J_{3,4}$ (9.5 Hz) indicates a *trans*-diaxial relationship.

The areas for methyl and aromatic protons of the tosyl groups indicate that there are two *p*-tolylsulfonyl groups per molecule. The remaining signals are too crowded together to allow any further analysis. The 220-MHz spectrum improved the separation of some of the signals (H-2 and H-6), although it was not possible to apply first-order analysis to most of them.

The 100-MHz spectrum of the 2,6-diacetate **2** did allow a first-order analysis for most of the signals, with the exception of H-5 and H-6,6′; this analysis was corroborated by the 220-MHz spectrum.

*The Sulfonyl Derivatives of Alditols, Part II. For Part I, see ref. 1.

For the diacetate **2**, the pattern for H-3 and H-4 is the same as that given by **1**, whereas the H-2 and H-6 signals are shifted downfield, due to the effect of the acetyl groups attached to O-2 and O-6. The geminal coupling of H-1*a* and H-1*e* (13.2 Hz)



Ts = *p*-tolylsulfonyl
1 R = H
2 R = Ac

is in very good agreement with the value reported by Coxon[4] for the 5-methylene protons of a pentopyranose derivative having an axial OR-4 substituent ($J_{5a,5e}$ 13.3 ±0.3 Hz), which bears the same structural relationship to the 5-methylene group as the methylene group involving C-1 does to the OR group on C-2 in compounds **1** and **2**.

Another interesting feature of the ^{1}H-n.m.r. spectra of **1** and **2** is that H-2 appears as a broad singlet. The coupling constant between H-1*a* and H-2 is small, due to the orientation effect[5] of the electronegative substituent attached to C-2, and, for the same reason, $J_{2,3}$ is small, too. Besides, H-2 bears a *trans* relationship to the ring oxygen-atom[6], and therefore $J_{2,1e}$ is also small.

In Table I, assignments of ^{13}C-n.m.r. chemical shifts are shown. The values obtained agree with the structures found for compounds **1** and **2**.

An increase in shielding relative to the primary carbon atom (C-6) of ~26 p.p.m. is found for C-1, which is in good agreement with the value reported for 1,5-anhydro-D-mannitol (25 p.p.m.) in relation to α,β-D-mannopyranose[7]. The esterification shift due to *p*-toluenesulfonylation is quite remarkable for the α-carbon atom. No data are available in the literature for the effect of *p*-toluenesulfonylation on ^{13}C chemical shifts, but these values ($\Delta\delta$ = 6.5–7.5 p.p.m.) are in accordance with those found for some tosyl derivatives of D-mannitol[8]. The effect on β-carbon atoms is relatively small.

Acetylation at O-2 and O-6 in compound **1** produces downfield shifts of the

TABLE I

ASSIGNMENTS OF SIGNALS IN THE ^{13}C-N.M.R. SPECTRA OF **1**, **2**, AND 1,5-ANHYDRO-D-MANNITOL

Compounds	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	Ph-CH_3	$OCOCH_3$
1	68.55	70.50	81.94	75.11	80.56	61.62	21.29	
2	67.20	73.80	78.00	70.20	76.90	63.00	21.00	20.51
1,5-Anhydro-D-mannitol[a]	70.9	70.1	74.6	68.3	81.6	62.6		

[a]Solvent, D_2O.

C-6 (1.38 p.p.m.) and C-2 (3.30 p.p.m.) resonances. Carbon atoms in the β position suffer upfield shifts (1.35–3.90 p.p.m.).

The high shielding of C-4 (4.91 p.p.m.) upon acetylation can be explained as due to a steric compression shift caused by the acylation of the axial hydroxyl group on C-2.

EXPERIMENTAL

General methods. — Melting points are uncorrected, and they were measured with an Electrothermal melting-point apparatus. Optical rotations were measured with a Hilger–Watts polarimeter. Proton n.m.r. spectra (100 and 220 MHz) were recorded at 30°, and integrated, with Varian HA-100 and Varian HR-220 spectrometers. Tetramethylsilane was used as the internal reference, and the concentration of the samples was 6–8%. Coupling constants were measured on 250- and 500-Hz sweep-width spectra. ^{13}C-N.m.r. spectra were recorded with a CFT-20 spectrometer, operating in the deuterio-lock mode, for solutions (10–15%) of the compounds in pyridine-d_5. Chemical shifts are given on the δ scale, relative to that of internal Me_4Si. The spectra were recorded both with complete proton-decoupling and with off-resonance decoupling; the resonances of methylene carbon atoms were assigned by the latter technique. Evaporations were conducted *in vacuo*, below 40°.

1,5-Anhydro-3,4-di-O-p-*tolylsulfonyl*-D-*mannitol* (**1**). — To a stirred, ice-water-cooled solution of 3,4-di-*O*-*p*-tolylsulfonyl-D-mannitol (4.9 g, 10 mmol) in anhydrous pyridine (10 mL) was added a solution of *p*-toluenesulfonyl chloride (2.0 g, 11 mmol) in anhydrous pyridine (6 mL), dropwise, during 30 min. The mixture was stirred for 30 h at room temperature. Then, the pyridine was evaporated off, and the residual syrup was chromatographed on a column (37 × 3.3 cm) of Merck 60 silica gel. Benzene–ethyl acetate (2:1) was used as the eluant, and 10-mL fractions were collected.

Fractions 56–170 yielded, after evaporation, compound **1** (22%). A sample recrystallized from benzene had m.p. 162–163°, $[\alpha]_D^{20}$ −33.0° (*c* 0.5, pyridine); ^{1}H-n.m.r. (220 MHz; pyridine-d_5): δ 2.25 (*s*, 6 H, CH_3, tosyl), 3.84 (*d*, 1 H, H-1*a*, spacing 12 Hz), 3.87 (*m*, 1 H, H-5), 3.98 (*dd*, 1 H, H-1*e*, spacings 12.0 and 6.0 Hz), 4.21 (*m*, 2 H, H-6,6′), 4.64 (*broad s*, 1 H, H-2), 5.28 (*dd*, 1 H, H-3, $J_{3,4}$ 9.5 Hz, $J_{3,2}$ 3.0 Hz), 5.82 (*t*, 1 H, H-4, $J_{4,3} = J_{4,5} = 9.5$ Hz), 7.3 (aromatic, superimposed upon C_5D_4HN signals), and 8.1 (*m*, 4 H, aromatic).

Anal. Calc. for $C_{20}H_{24}O_9S_2$: C, 50.87; H, 5.11; S, 13.57. Found: C, 50.87; H, 5.15; S, 13.40.

2,6-Di-O-*acetyl-1,5-anhydro-3,4-di*-O-p-*tolylsulfonyl*-D-*mannitol* (**2**). — Compound **1** (150 mg) was acetylated with acetic anhydride and pyridine, affording **2** as needles, m.p. 158–160°. A sample recrystallized from 95% ethanol had m.p. 159–160°, $[\alpha]_D^{20}$ −56.1° (*c* 1.25, chloroform); ^{1}H-n.m.r. (220 MHz; chloroform-*d*): δ 2.04 (*s*, 3 H, -CH_2-CO_2CH_3), 2.11 (*s*, 3 H, >CH-OCOCH_3), 2.46 (*s*, 6 H, CH_3 of tosyl), 3.50 (*d*, 1 H, H-1*a*, $J_{1a,1e}$ 13.2 Hz), 3.57 (m, 1 H, H-5, spacing 2.5 Hz), 4.03 (*dd*, 1H,

H-1*e*, $J_{1e,1a}$ 13.2 Hz, $J_{1e,2}$ 2.4 Hz), 4.24 (*AB type q*, 1 H, H-6, $J_{6,6'}$ 12.5 Hz), 4.26 (*AB type q*, H-6', $J_{6,6'}$ 12.5 Hz), 4.67 (*dd*, 1 H, H-3, $J_{3,4}$ 9.5 Hz, $J_{3,2}$ 3.5 Hz), 5.0 (*t*, 1 H, H-4, $J_{4,3}$ 9.5 Hz, $J_{4,5}$ 9.5 Hz), 5.16 (*broad s*, 1 H, H-2), 7.35 (*AB system*, 4 H, aromatic), and 7.82 (*AB system*, 4 H, aromatic).

Anal. Calc. for $C_{24}H_{28}O_{11}S_2$: C, 51.78; H, 5.07; S, 11.52. Found: C, 51.83; H, 5.22; S. 11.97.

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