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Note

Methyl 4,6-anhydro-4-deoxy-2,3-di-*O*-methyl-4-methylamino-α-D-galactopyranoside and related compounds

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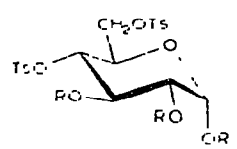
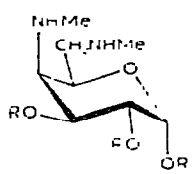
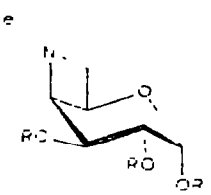
During the course of experiments designed to afford derivatives of 4,6-diamino-4,6-dideoxy-α-D-glucopyranose and -galactopyranose (that were required for the preparation of 1,3,2-diazaphosphorinane derivatives analogous to 1,3,2-oxazaphosphorinane derivatives described previously[1]), it was observed that treatment of methyl 2,3-*O*-methyl-4,6-di-*O*-tosyl-α-D-glucopyranoside (**1**) with ethanolic methylamine at 120° afforded not only the required bis(methylamino) sugar **3** in 30% yield but also methyl 4,6-anhydro-4-deoxy-2,3-di-*O*-methyl-4-methylamino-α-D-galactopyranoside (**5**) in 30% yield. The azetidine derivative **5** was tentatively identified on the basis of i.r., n.m.r. (see Table I), and microanalytical data. Presumably, the mechanism of reaction involves initial formation of the 6-methylamino-4-tosyl derivative[1] **7** and then intramolecular attack at C-4 by the 6-methylamino group, to displace the tosyloxy group with inversion of configuration. As expected, when a



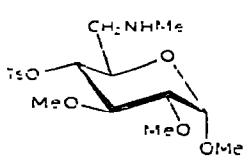
1 R = Me
2 R = Bzl



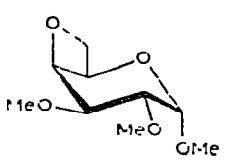
3 R = Me
4 R = Bzl



5 R = Me
6 R = Bzl



7



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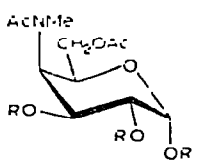

9 R = Me
10 R = Bzl

TABLE 1

CHEMICAL SHIFTS[a] AND COUPLING CONSTANTS[b] FOR 5, 6, AND 8

		H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
5	($CDCl_3$)	4.87	3.76	—	—	4.19	3.31	2.78	2.9	9.5	4.7	4.7	<1	4.7	7.8
	(C_6D_6)	4.80	3.97	3.58	3.00	3.94	—	2.43							
6	($CDCl_3$)	4.93	—	—	3.28	—	3.29	2.71	2.7	9.3	4.7	4.3	<1	4.7	8.0
	(C_6D_6)	4.98	4.32	4.01	3.00	3.98	3.31	2.42							
8	($CDCl_3$)	4.93	3.77	—	5.24	4.47	4.16	4.78	2.5	9.5	4.5	4.1	1.4	4.1	7.0
	(C_6D_6)	4.77	3.82	3.53	4.83	—	—	4.37							

[a]P.p.m. [b]Hz.

solution of **7** in ethanol was heated in a sealed tube at 120° for 4 h, a good yield of the azetidine **5** was obtained.

The intramolecular reaction is favoured to a greater extent in the tri-*O*-benzyl derivative **2** which, on treatment with methylamine, afforded the azetidine **6** in 63% yield and the bis(methylamino) sugar **4** in only 4% yield.

Although intramolecular displacements of sulphonyloxy groups by amine groups are not uncommon in carbohydrate chemistry, the formation of an azetidine ring at C-4 and C-6 of a galactopyranoside does not appear to have been described hitherto. Further, only passing reference appears to have been made to a corresponding oxetane, methyl 4,6-anhydro-2,3-di-*O*-benzyl-α-D-galactopyranoside[2]. Consequently, the oxetane **8** was prepared for comparison purposes, and some chemical characterisation of the azetidines **5** and **6** was attempted.

The oxetane **8** was prepared in 84% yield by boiling a solution of methyl 2,3-di-*O*-methyl-6-*O*-tosyl-α-D-galactopyranoside in aqueous, alcoholic sodium hydroxide for 1 h. The n.m.r. data for **8** and the azetidines **5** and **6**, given in Table I, are consistent with a slightly flattened chair conformation of the pyranoid ring, and the values for $J_{5,6}$, $J_{5,6'}$, and $J_{6,6'}$ are consistent with those expected for azetidines and oxetanes.

Azetidines are readily cleaved by acetic anhydride[3]. Accordingly, a solution of **5** in acetic anhydride was stored at 100° for 1.5 h; no **5** remained, and the only product isolated was **9** (80% yield). Similarly, **6** afforded **10**. For purposes of identification, **9** was also prepared from methyl 2,3-di-*O*-methyl-α-D-glucopyranoside by sequential selective benzoylation, tosylation, treatment with methylamine, and acetylation.

Both **5** and **6** were unaffected by prolonged treatment with ethanolic methylamine at 130°; with 2M hydrogen chloride in ethanol, the azetidine hydrochlorides were produced. With conc. hydrochloric acid, **5** and **6** each gave complex mixtures of products. The oxetane **8** was unaffected by treatment with boiling 6M NaOH in aqueous ethanol and was only moderately affected by treatment with boiling 6M hydrochloric acid.

EXPERIMENTAL

General methods. — ^{1}H-N.m.r. spectra were recorded with a JEOL JNM-4-H-100 spectrometer at 100 MHz, with deuteriochloroform as solvent and tetramethylsilane as internal standard. Optical rotations were measured for solutions in chloroform. Although only selected n.m.r. and i.r. data are reported, all compounds had spectra consistent with the assigned structures. Column chromatography was performed with Merck silica gel of particle size 0.05–0.2 mm and the same solvent as used for t.l.c. Solvents were dried over anhydrous magnesium sulphate.

Methyl 4,6-anhydro-4-deoxy-2,3-di-O-methyl-4-methylamino-α-D-galactopyranoside (**5**). — A solution of methyl 2,3-di-*O*-methyl-4,6-di-*O*-tosyl-α-D-glucopyranoside (**1**, 4 g) in a 33% solution of methylamine in ethanol (15 ml) was heated in a sealed tube at 120° for 4 h. The solvent was removed under reduced pressure.

Chromatography of the resulting orange oil gave **5** (0.5 g, 30%) as a clear oil, R_F 0.4 (ether), $[\alpha]_D$ +205° (*c* 2) (Found: C, 55.0; H, 8.7; N, 6.6. $C_{10}H_{19}NO_4$ calc.: C, 55.3; H, 8.8; N, 6.5%), and methyl 4,6-dideoxy-2,3-di-*O*-methyl-4,6-bis(methylamino)-α-D-galactopyranoside (**3**, 0.56 g, 30%).

Treatment of **5** with excess of methyl iodide in benzene gave the expected salt (80%), m.p. 190–192° (dec.) (from ethanol–ether), $[\alpha]_D$ +111° (*c* 3); n.m.r. data (CD_3OD): δ 3.27 and 2.39 (2 s, NMe_2) (Found: C, 36.6; H, 6.1; N, 3.9. $C_{11}H_{22}INO_4$ calc.: C, 36.7; H, 6.1; N, 3.9%).

Benzyl 4,6-anhydro-4-deoxy-2,3-di-O-methyl-4-methylamino-α-D-galactopyranoside (**6**). — When treated as described above for **1**, benzyl 2,3-di-*O*-benzyl-4,6-di-*O*-tosyl-α-D-glucopyranoside (**2**, 2.4 g) gave **6** (0.88 g, 63%) as a clear oil, R_F 0.5 (ether), $[\alpha]_D$ +96° (*c* 2) (Found: C, 75.2; H, 7.0; N, 3.0. $C_{28}H_{31}NO_4$ calc.: C, 75.5; H, 7.0; N, 3.1%); and benzyl 2,3-di-*O*-benzyl-4,6-dideoxy-4,6-bis(methylamino)-α-D-galactopyranoside (**4**; 0.06 g, 4%).

Treatment of **6** with methyl iodide gave the expected salt (70%) as a light-yellow, oily solid, $[\alpha]_D$ +96° (*c* 4). N.m.r. data (C_6D_6): δ 3.36 and 3.42 (2 s, NMe_2).

Methyl 4,6-anhydro-2,3-di-O-methyl-α-D-galactopyranoside (**8**). — A solution of methyl 2,3-di-*O*-methyl-6-*O*-tosyl-α-D-galactopyranoside[1] (4 g) in sodium hydroxide (6M) in water–ethanol (3:1) was boiled under reflux for 1 h. The mixture was then poured into water and extracted with dichloromethane. The solvent was removed from the extract under reduced pressure to give a clear oil which, after chromatography, gave **8** (0.95 g, 84%), b.p. 95°(bath)/0.1 mmHg, R_F 0.4 (benzene–acetone–methanol, 8:1:1), $[\alpha]_D$ +244° (*c* 1.7) (Found: C, 53.3; H, 8.0. $C_9H_{16}O_5$ calc.: C, 52.9; H, 7.9%).

Treatment of **5** *and* **6** *with acetic anhydride.* — A solution of each azetidine in acetic anhydride was stored at 100° for 1.5 h, and t.l.c. then showed that no starting material remained. The mixture was poured into excess of aqueous sodium carbonate and extracted with dichloromethane. Removal of the solvent under reduced pressure and chromatography of the resulting brown oil gave (from **5**) methyl 6-*O*-acetyl-4-deoxy-2,3-di-*O*-methyl-4-(*N*-methylacetamido)-α-D-galactopyranoside (**9**, 80%) as a clear oil, R_F 0.5 (benzene–acetone–methanol, 8:1:1), $[\alpha]_D$ +112° (*c* 1), ν_{max}^{liquid} 1655 and 1755 cm^{-1}; n.m.r. data: δ 2.03 and 2.09 (2 s, 2 Ac) 3.11 (s, NMe), 4.90 (d, $J_{1,2}$ 3.6 Hz), 5.35 (dd, $J_{3,4}$ 5.3, $J_{4,5}$ 2.7 Hz) (Found: C, 52.7; H, 7.8; N, 4.4. $C_{14}H_{25}NO_7$ calc.: C, 52.7; H, 7.9; N, 4.4%). From **6**, benzyl 6-*O*-acetyl-2,3-di-*O*-benzyl-4-deoxy-4-(*N*-methylacetamido)-α-D-galactopyranoside (**10**, 81%) was obtained as a clear oil, R_F 0.8 (benzene–acetone–methanol, 8:1:1), $[\alpha]_D$ +100° (*c* 0.8), ν_{max}^{liquid} 1655 and 1755 cm^{-1}; n.m.r. data (C_6D_6): δ 1.27 and 1.34 (2 s, 2 Ac), 2.74 (s, NMe), 4.88 (d, $J_{1,2}$ 4 Hz), 5.48 (dd, $J_{3,4}$ 6, $J_{4,5}$ 3 Hz) (Found: C, 70.2; H, 6.8; N, 2.8. $C_{32}H_{37}NO_7$ calc.: C, 70.2; H, 6.8; N, 2.6%).

Conversion of methyl 2,3-di-O-methyl-α-D-glucopyranoside into **9**. — Benzoyl chloride (1.6 ml) was slowly added to a cooled solution of the glucopyranoside (3 g) in pyridine (10 ml). The solution was allowed to attain room temperature, then stirred for 2 h, poured into excess of water, and extracted with dichloromethane.

Removal of the solvent from the extract under reduced pressure and chromatography of the resulting oil gave methyl 4,6-di-*O*-benzoyl-2,3-di-*O*-methyl-α-D-glucopyranoside (0.5 g, 9%), m.p. 119° (from di-isopropyl ether), $[\alpha]_D$ +113° (*c* 0.6), R_F 0.7 (ether) (Found: C, 64.2; H, 6.1. $C_{23}H_{26}O_8$ calc.: C, 64.2; H, 6.1%); and methyl 6-*O*-benzoyl-2,3-di-*O*-methyl-α-D-glucopyranoside (3.9 g, 88%), m.p. 71–73° (from di-isopropyl ether), $[\alpha]_D$ +85° (*c* 0.7), R_F 0.4 (ether), ν_{max}^{KBr} 1720 and 3330 cm^{-1} (Found: C, 58.7; H, 6.7. $C_{16}H_{22}O_7$ calc.: C, 58.9; H, 6.8%).

A solution of the monobenzoate (3.8 g) and excess of tosyl chloride in pyridine was stirred at room temperature for 2 days and then poured into water. The solution was extracted with dichloromethane. Removal of the solvent at reduced pressure and chromatography of the resulting oil gave methyl 6-*O*-benzoyl-2,3-di-*O*-methyl-4-*O*-tosyl-α-D-glucopyranoside (3.3 g, 59%) as a clear oil, R_F 0.75 (benzene–acetone–methanol, 8:1:1), $[\alpha]_D$ +87° (*c* 0.3); ν_{max}^{liquid} 1100, 1175, 1280, 1360, and 1735 cm^{-1}.

A solution of the monotosylate (3 g) in 33% methylamine in ethanol (50 ml) was heated in a sealed tube at 120° for 8 h. It was then poured into 5% aqueous hydrochloric acid and extracted with chloroform. The aqueous phase was basified with sodium carbonate, and then repeatedly extracted with chloroform. The organic portion was concentrated to dryness and the resulting yellow oil was chromatographed to give methyl 4-deoxy-2,3-di-*O*-methyl-4-methylamino-α-D-galactopyranoside (0.8 g, 41%) as a clear oil, R_F 0.1 (benzene–acetone–methanol, 8:1:1), $[\alpha]_D$ +163° (*c* 0.1); ν_{max}^{liquid} 3400 (broad), 1450, 1125, 1095, and 1055 cm^{-1}. N.m.r. data: δ 2.55 (s, NMe), 2.85 (s, NH and OH).

A solution of the amino sugar (0.8 g) in acetic anhydride was warmed to 65° for 30 min and then poured into excess of aqueous sodium carbonate. The mixture was extracted with dichloromethane, and the organic phase was concentrated to dryness under reduced pressure. Pyridine was removed from the residue by distillation of toluene therefrom. Chromatography of the resulting oil gave **9** (0.88 g, 81%).

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