Partial Esterification and Etherification of 1,5-Anhydro-4,6-*O*-benzylidene-D-glucitol

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Various publications^{1,2)} on partial esterification and etherification of methyl 4, 6-*O*-benzylidene-D-glucopyranosides have been reported. In connection with these studies, 1, 5-anhydro-4, 6-*O*-benzylidene-D-glucitol (**1**) seems to be a good model to investigate the influence of aglycon in esterification and etherification of the glycosides. Our previous publications reported reexaminations of partial tosylation³⁾ and benzoylation⁴⁾ of **1**. As an extension of the studies, this communication describes partial mesylation and methylation of **1**.

Reaction of **1** with one molar equivalent of mesyl chloride in pyridine at -40°C gave 1, 5-anhydro-4, 6-*O*-benzylidene-2-*O*-mesyl-D-glucitol (**3**) in 53% yield after column chromatography on silica gel. Tosylation of **3** gave 1, 5-anhydro-4, 6-*O*-benzylidene-2-*O*-mesyl-3-*O*-tosyl-D-glucitol (**5**), which was readily distinguishable from the corresponding 3-*O*-mesylate (**6**) prepared by mesylation of the known 1, 5-anhydro-

4, 6-*O*-benzylidene-2-*O*-tosyl-D-glucitol⁵⁾ by comparison of their physical properties. The structure of **3** was further confirmed by the PMR spectrum of its benzoate (1, 5-anhydro-3-*O*-benzoyl-4, 6-*O*-benzylidene-2-*O*-mesyl-D-glucitol (**7**)); the H-3 ring proton appeared as a triplet at a lower field (τ 4.38) than all others. The chromatographic separation also afforded three fractions; the 2, 3-di-*O*- (**2**) (8%), the 3-*O*- (**4**) (10%) mesylates, and the starting material (13%). Accordingly, the order of the relative reactivity of the secondary hydroxyl groups in **1** towards mesyl chloride is 2-OH→3-OH, which is in accordance with that^{3,5)} of **1** towards tosyl chloride (See Table I).

Reaction of **1** with one molar equivalent of methyl iodide in *N,N*-dimethylformamide in the presence of barium oxide and barium hydroxide octahydrate at room temperature gave a mixture which was fractionated by column chromatography to yield the 2, 3-di-*O*- (**8**) (19%), a mixture of the 2-*O*- (14%) and 3-*O*- (50%) methyl ethers, and the starting material (3%). The mixture was converted to tosyl derivatives which were separated to individual components. The faster moving component was assigned to 1, 5-anhydro-4, 6-*O*-benzylidene-3-*O*-methyl-2-*O*-tosyl-D-glucitol (**9**) which was identical with the product obtained by methylation of 1, 5-anhydro-4, 6-*O*-benzylidene-2-*O*-tosyl-D-glucitol.⁵⁾ Accordingly, the slower moving component was identified as the corresponding 3-*O*-tosylate (**10**) and the ratio of **9** and **10** was 7:2. This indicates that the order of the reactivity of **1** is 3-OH > 2-OH towards methyl iodide, in accordance with that of methyl 4, 6-*O*-benzylidene- β -D-glucopyranoside.²⁾

The results in sulfonylation of **1** are closely similar to those of methyl 4, 6-*O*-benzylidene- α -D-glucopyranoside.⁶⁾ This supports the finding³⁾ obtained previously

TABLE I. PRODUCTS FROM 1, 5-ANHYDRO-4, 6-*O*-BENZYLIDENE-D-GLUCITOL (**1**)
BY PARTIAL ESTERIFICATION AND ETHERIFICATION

Reaction-				Solvent	Major products	Yield (%)	R _f
No.	Reagent	Temp. (°C)	Hour				
1	PhCOCl	0	3	pyridine	2, 3-diester	10.9	4
					2-ester	27.5	
					3-ester	39.9	
2	PhCOCl	0	24	pyridine	2, 3-diester	16.6	4
					2-ester	27.6	
					3-ester	42.3	
3	CH ₃ C ₆ H ₄ SO ₂ Cl	5	48	pyridine	2, 3-diester	9.4	3
					2-ester	41.0	
					3-ester	6.8	
4	CH ₃ SO ₂ Cl	-40~0	48	pyridine	2, 3-diester	8.2	
					2-ester	53.2	
					3-ester	10.3	
5	CH ₃ I	r. t.	20	DMF	2, 3-diether	18.5	
					2-ether	14.2	
					3-ether	49.6

	R	R'
1	H	H
2	Ms	Ms
3	Ms	H
4	H	Ms
5	Ms	Ts
6	Ts	Ms
7	Ms	Bz
8	Me	Me
9	Ts	Me
10	Me	Ts

FIG. 1.

that under the absence of intramolecular hydrogen bonding, stereochemical factors (whether or not hydroxyl groups are adjacent to deoxy groups, $-\text{CH}_2-$) are important in sulfonylation of glycopyranosides with the *gluco*- and *xylo*- configurations. However, in benzoylation⁴⁾ of **1** with benzoyl chloride the reverse is true; the order is 3-OH—2-OH. The results in benzoylation and methylation of **1** and methyl 4, 6-*O*-benzylidene- β -D-glucopyranoside^{5,7)} suggest that if intramolecular hydrogen bonding is not present, electronic effects are more important in these reactions rather than steric factors.

EXPERIMENTAL

For general methods see ref. 4).

Partial mesylation of 1, 5-anhydro-4, 6-*O*-benzylidene-D-glucitol (**1**)

Mesyl chloride (0.37 ml, 1.2 molar eq) was added dropwise over a period of 15 min to a stirred solution of **1** (1 g) in pyridine (20 ml) at -40°C . The bath temperature was kept at -20°C for 3 hr and at 0°C for 48 hr. The resulting syrup obtained by the usual work-up was fractionated on a silica gel column. The first component in the eluate was 1, 5-anhydro-4, 6-*O*-benzylidene-2, 3-di-*O*-mesyl-D-glucitol (**2**, 132 mg, 8.2%), mp $192\sim 194^\circ\text{C}$, $[\alpha]_D^{25} -18.6^\circ$ ($c=1.0$, CHCl_3), PMR: τ 4.49 (1H, s, CHC_6H_5), 6.86 and 7.02 (6H, 2s, SO_2CH_3). Found: C, 44.28; H, 5.16. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_8\text{S}_2$: C, 44.10; H, 4.95%.

The second component eluted from the column was the corresponding 2-*O*-mesylate **3** (696 mg, 53.2%), mp $155\sim 157^\circ\text{C}$, $[\alpha]_D^{25} -10.6^\circ$ ($c=1.1$, CHCl_3). Found: C, 51.16; H, 5.74. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_7\text{S}$: C, 50.89; H, 5.50%.

The third component eluted was the 3-*O*-mesylate **4** (135 mg, 10.3%), mp $141\sim 143^\circ\text{C}$, $[\alpha]_D^{25} -23.2^\circ$ ($c=1.9$,

CHCl_3). Found: C, 50.72; H, 5.63. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_7\text{S}$: C, 50.89; H, 5.50%. Finally the starting material (133 mg, 13.3%) was eluted.

1, 5-Anhydro-4, 6-*O*-benzylidene-2-*O*-mesyl-3-*O*-tosyl-D-glucitol (**5**)

The 2-*O*-mesylate **3** (200 mg) was tosylated for 10 days at room temperature to give the tosylate **5** (252 mg, 85.7%), mp $205\sim 207^\circ\text{C}$, $[\alpha]_D^{25} -52.4^\circ$ ($c=0.9$, CHCl_3). Found: C, 51.90; H, 5.05. Calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_9\text{S}_2$: C, 51.94; H, 5.20%.

1, 5-Anhydro-4, 6-*O*-benzylidene-3-*O*-mesyl-2-*O*-tosyl-D-glucitol (**6**)

Mesyl chloride (0.06 ml) was added to a stirred solution of 1, 5-anhydro-4, 6-*O*-benzylidene-2-*O*-tosyl-D-glucitol¹⁵⁾ (60 mg) in pyridine (0.5 ml) at 0°C and the mixture was stirred at 5°C overnight. The usual work-up gave a syrup (69 mg, 88.5%) which was crystallized from ethanol to give **6**, mp $167\sim 169^\circ\text{C}$, $[\alpha]_D^{25} -30.9^\circ$ ($c=2.1$, CHCl_3). Found: C, 51.88; H, 5.10. Calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_9\text{S}_2$: C, 51.94, H, 5.20%.

1, 5-Anhydro-3-*O*-benzoyl-4, 6-*O*-benzylidene-2-*O*-mesyl-D-glucitol (**7**)

Treatment of **3** (240 mg) in pyridine (3 ml) with benzoyl chloride (0.5 ml) at 0°C overnight gave the benzoate **7** (305 mg, 96.8%), mp $146\sim 147^\circ\text{C}$, $[\alpha]_D^{24} -37.9^\circ$ ($c=1.3$, CHCl_3), PMR: τ 4.38 (1H, t, $J=9$ Hz, H-3), 4.53 (1H, s, CHC_6H_5), 5.08 (1H, o, H-2), 7.17 (3H, s, SO_2CH_3). Found: C, 58.33; H, 5.12. Calcd. for $\text{C}_{21}\text{H}_{22}\text{O}_9\text{S}$: C, 58.05; H, 5.11%.

Partial methylation of 1, 5-anhydro-4, 6-*O*-benzylidene-D-glucitol (**1**)

To a solution of **1** (1 g) in DMF (10 ml) were added methyl iodide (0.31 ml, 1.2 molar eq), barium oxide (1.25 g), and barium hydroxide octahydrate (0.5 g). The suspension was stirred for 20 hr at room temperature and the crystalline product isolated in the usual manner was chromatographed. The first component eluted from a silica gel column was 1, 5-anhydro-4, 6-*O*-benzylidene-2, 3-di-*O*-methyl-D-glucitol (**8**, 208 mg, 18.5%), mp $91\sim 92^\circ\text{C}$, $[\alpha]_D^{26} -7.8^\circ$ ($c=1.5$, CHCl_3), PMR: τ 4.50 (1H, s, CHC_6H_5), 6.35 and 6.50 (6H, 2s, OCH_3). Found: C, 64.05; H, 7.51. Calcd. for $\text{C}_{16}\text{H}_{20}\text{O}_6$: C, 64.26; H, 7.21%.

The 2-*O*- and 3-*O*- methyl derivatives were next eluted as a mixture (712 mg, 67.4%). Finally the starting material (25 mg, 2.5%) was eluted. The above mixture was tosylated for 3 days at room temperature. The usual work-up followed by column chromatographic separation gave two fractions. The first eluted fraction was identified as 1, 5-anhydro-4, 6-*O*-benzylidene-3-*O*-methyl-2-*O*-tosyl-D-glucitol (**9**, 827mg, 49.6%) by comparison of the physical properties with those of an authentic sample.

The second fraction was the corresponding 3-*O*-tosylate **10** (237 mg, 14.2%), mp 133~134°C, $[\alpha]_D^{25} -54.8^\circ$ ($c=1.5$, CHCl_3). Found: C, 59.77; H, 5.53. Calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_7\text{S}$: C, 59.98; H, 5.76%.

1, 5-Anhydro-4, 6-O-benzylidene-3-O-methyl-2-O-tosyl-D-glucitol (9)

1, 5-Anhydro-4, 6-O-benzylidene-2-O-tosyl-D-glucitol⁵⁾ (250 mg) was methylated with diazomethane and BF_3 etherate to give the 3-*O*-methyl derivative (220 mg, 78.3%), mp 165~166°C, $[\alpha]_D^{22} -31.4^\circ$ ($c=1.0$, CHCl_3). Found: C, 60.04; H, 5.76. Calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_7\text{S}$: C, 59.98; H, 5.76%.

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