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Monomolar Etherification of Methyl 4, 6-*O*-Benzylidene-α- and β-D-Glucopyranosides

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Selective esterification[1~3] and etherification[4,5] provide a facile synthetic route for the preparation of important intermediates[1~6] of carbohydrates. It is well known[1,7] that the order of the relative reactivity of the hydroxyl groups of carbohydrates in these reactions is closely correlated to their stereochemistry, and close examination of such observations could lead to important information on electronic and configurational relationships. This communication describes monomolar methylation and benzylation of methyl 4,6-*O*-benzylidene-α- and β-D-glucopyranosides with special reference to the order of the relative reactivity of the secondary hydroxyl groups in both anomers.

A solution of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**I**) in *N*,*N*-dimethylformamide (DMF) in the presence of barium oxide and barium hydroxide was treated with 1 molar eq of methyl iodide for 20 hr at room temperature. Chromatographic separation of the reaction products on silicic acid by stepwise elution with mixtures of benzene and ethyl acetate gave four fractions: methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside (21%), the 3-*O*-methyl ether (29%), the 2-*O*-methyl ether (30%) and the starting material **I** (4%). Similar treatment of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**II**) with 1 molar eq of methyl iodide followed by column chromatographic fractionation gave four fractions: methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-β-D-glucopyranoside (11%), the 2-*O*-methyl ether (13%), the 3-*O*-methyl ether (46%) and the starting material **II** (1%). Thus, it follows that the order of the reactivity of the secondary hydroxyl groups in **I** towards methyl iodide is 2-OH≧3-OH, conforming to the result[8] of monomethylation of **I** with methyl iodide in tetrahydrofuran in the presence of silver oxide. On the other hand, the order of the reactivity in **II** was found to be 3-OH>2-OH. This observation contrasts with the result[8] that the hydroxyl group at C-2 is the most reactive to monomethylation of **II** with methyl iodide in tetrahydrofuran containing silver oxide.

Partial benzylation of **I** was effected with 1 molar eq of benzyl bromide in DMF containing barium oxide and barium hydroxide. After stirring for 20 hr at room temperature, the reaction mixture was chromatographed on silicic acid to yield four fractions: methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (11%), the 2-*O*-benzyl ether (11%), the 3-*O*-benzyl ether (3%) and the starting material **I** (30%). Similar treatment of **II** with 1 molar eq of benzyl bromide gave four products after chromatographic separation, methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (5%), the 2-*O*-benzyl ether (8%), the 3-*O*-benzyl ether (20%) and the starting material **II** (14%). Accordingly, the order of the reactivity of the secondary hydroxyl groups in **I** towards benzyl bromide is 2-OH>3-OH, which is in accordance with that of methylation of **I** under the same conditions. Above results indicate that the 2-OH group in the α-D-anomer is more selective towards benzylation than methylation. It is of interest to note that methylation of the α-D-anomer is less selective than that of β-D-anomer, since it is generally indicated[3,9] that the reaction of α-D-glycosides with acid chloride is more selective than that of β-D-glycosides. This suggests that in this reaction intramolecular hydrogen bonding has little effect on the reactivity of the 2-OH group in **I**. On the other hand, the order of the reactivity in **II** towards benzyl bromide is 3-OH>2-OH, the order conforming to that of methylation with methyl iodide in DMF.

EXPERIMENTAL

Melting points were determined on a Yanagimoto hot stage microscope and are uncorrected. Column chromatography was carried out on silicic acid (Mallinkrodt, 100 mesh). PMR spectra were measured at 90 MHz on a Hitachi-Perkin-Elmer R-22 spectrometer using tetramethylsilane as an internal reference.

Monomolar methylation of methyl 4, 6-O-benzylidene-α-D-glucopyranoside (**I**)

To a solution of **I** (2 g) in DMF (20 ml), containing barium oxide (2.5 g) and barium hydroxide octahydrate (1 g), was added methyl iodide (0.6 ml, 1.2 molar eq). The mixture was stirred for 20 hr and then diluted with chloroform. The inorganic component was filtered on a Celite bed, the filtrate was evaporated to dryness, and the residue was extracted with chloroform. The extract was washed successively with 10% sodium bisulfite solution and water, dried over anhydrous sodium sulfate, and evaporated to dryness. The resulting residue was chromatographed on silicic acid (300 g) and eluted with benzene-ethyl acetate (9:1, v/v) to give methyl 4, 6-*O*-benzylidene-2, 3-di-*O*-methyl-α-D-glucopyranoside (461 mg, 21.0%), mp 125~127°C $[\alpha]_D^{14}$ +110.3° (c=1.1, $CHCl_3$); lit.,[10] mp 122~123°C, $[\alpha]_D^{18}$ +98° (acetone). Elution with benzene-ethyl acetate (4:1, v/v) gave methyl 4, 6-*O*-benzylidene-3-*O*-

methyl-α-D-glucopyranoside (606 mg, 29.0%), mp 153 ~154°C, $[\alpha]_D^{29}$ +114.4°C (c=1, $CHCl_3$); lit.,[11] mp 150 ~151°C, $[\alpha]_D^{14}$ +119.5° (c=1.61, tetrachloroethane). Elution with benzene-ethyl acetate (2: 1, v/v) gave methyl 4, 6-*O*-benzylidene-2-*O*-methyl-α-D-glucopyranoside (628 mg, 30.0%), mp 166°C, $[\alpha]_D^{14}$ +96.4° (c=1.1, $CHCl_3$); lit.,[12] mp 165~166°C, $[\alpha]_D$ +95.4° (c=0.6, $CHCl_3$). Finally the starting material **I** (76 mg, 3.8%) was eluted with pure methanol.

Monomolar methylation of methyl 4, 6-O-benzylidene-β-D-glucopyranoside (**II**)

Compound **II** (2 g) was methylated as described for the α-D-anomer, using 1.2 molar eq of methyl iodide. The crystalline product isolated in the usual manner was fractionated on a silicic acid column. Methyl 4, 6-*O*-benzylidene-2, 3-di-*O*-methyl-β-D-glucopyranoside (235 mg, 10,7%) was first eluted with benzene-ethyl acetate (9: 1, v/v), mp136~137°C, $[\alpha]_D^{14}$ −59.8° (c=1, $CHCl_3$); lit.,[10] mp 133~134°C, $[\alpha]_D^{23}$ −61° (ethanol). Elution with benzene-ethyl acetate (4: 1, v/v) gave methyl 4,6-*O*-benzylidene-2-*O*-methyl-β-D-glucopyranoside (275 mg, 13.2%), mp 175~176°C, $[\alpha]_D^{14}$ −67.3° (c=1.6, $CHCl_3$), the PMR data (in DMSO-d_6): τ 4.40 (1H, singlet, benzylic H), 4.86 (1H, doublet, J=4.5 Hz, OH), 5.64 (1H, doublet, $J_{1,2}$=8.0 Hz, H-1), 6.53 (3H, singlet, OCH_3), 6.56 (3H, singlet, OCH_3). *Anal.* Found: C, 60.75; H, 6.79. Calcd. for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Elution with benzene-ethyl acetate (2: 1, v/v) gave methyl, 4, 6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside (962 mg, 46.0%), mp 172~273°C, $[\alpha]_D^{14}$ −40.0° (c=0.3, $CHCl_3$); lit.,[10] mp 164°C, $[\alpha]_D^{18}$ −39.1° (tetrachloroethane). Finally the starting material **II** (22 mg, 1.1%) was eluted with pure methanol.

Monomolar benzylation of methyl 4, 6-O-benzylidene-α-D-glucopyranoside (**I**)

To a solution of **I** (2 g) in DMF (20 ml) were added benzyl bromide (1 ml, 1.2 molar eq), barium oxide (2.5g) and barium hydroxide octahydrate (1 g). The suspension was stirred for 20 hr at room temperature and then the reaction mixture was worked-up and purified as described earlier. The resultant residue was chromatographed on silicic acid and eluted with benzene-ethyl acetate (9: 1, v/v) giving methyl 2, 3-di-*O*-benzyl-4, 6-*O*-benzylidene-α-D-glucopyranoside (347 mg, 10.6%), mp 96~99°C, $[\alpha]_D^{21}$ −32.0° (c=1.2, $CHCl_3$); lit.,[13] mp 93°C, $[\alpha]_D^{20}$ −31.2° (c=5, $CHCl_3$). Further elution with benzene-ethyl acetate (4: 1, v/v) gave methyl 2-*O*-benzyl-4, 6-*O*-benzylidene-α-D-glucopyranoside (301 mg, 11.4 %), mp 129~130°C, $[\alpha]_D^{10}$ −26.0° (c=0.4, $CHCl_3$), the PMR data (in DMSO-d_6): τ 4.44 (1H, singlet, benzylic H), 4.66 (1H, doublet, J=5.0 Hz, OH), 5.24 (1H, doublet, $J_{1,2}$=3.7 Hz, H-1), 5.37 (2H, singlet, benzyl methylene), 6.72 (3H, singlet, OCH_3). *Anal.* Found: C, 67.53; H. 6.59. Calcd. for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Elution with benzene-ethyl acetate (2: 1, v/v) gave methyl 3-*O*-benzyl-4, 6-*O*-benzylidene-α-D-glucopyranoside (87 mg, 3.3%), mp 183~185°C, $[\alpha]_D^{14}$ +36.2° (c=0.48, $CHCl_3$); lit.,[14] mp 178~180°C, $[\alpha]_D^{20}$ +47° ($CHCl_3$). Elution with methanol gave the starting material **I** (589 mg, 29.5%).

Monomolar benzylation of methyl 4, 6-O-benzylidene-β-D-glucopyranoside (**II**)

Compound **II** was benzylated under the same conditions described for the α-D-anomer, using 1.2 molar eq of benzyl bromide. The resultant residue was subjected to column chromatographic fractionation. Elution with benzene-ethyl acetate (9: 1, v/v) gave methyl 2, 3-di-*O*-benzyl-4, 6-*O*-benzylidene-β-D-glucopyranoside (169 mg, 5.2%), mp 120~122°C, $[\alpha]_D^{14}$ −34.2° (c=0.72, $CHCl_3$); lit.,[15] mp 119~120°C, $[\alpha]_D^{20}$ −35.8° (c=3.02, $CHCl_3$). Elution with benzene-ethyl acetate (4: 1, v/v) gave methyl 2-*O*-benzyl-4, 6-*O*-benzylidene-β-D-glucopyranoside (214 mg, 8.1%), mp 125~126°C, $[\alpha]_D^{14}$ −26.0° (c=0.68, $CHCl_3$), the PMR data (in DMSO-d_6): τ 4.40 (1H, singlet, benzylic H), 4.54 (1H, doublet, J= 5.2 Hz, OH), 5.29 (2H, singlet, benzyl methylene), 5.58 (1H, doublet, $J_{1,2}$=7.6 Hz H-1), 6.59 (3H, singlet, OCH_3). *Anal.* Found: C, 67.80; H, 6.52. Calcd. for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Elution with benzene-ethyl acetate (2: 1, v/v) gave methyl 3-*O*-benzyl-4, 6-*O*-benzylidene-β-D-glucopyranoside (529 mg, 20.0%), mp 190°C, $[\alpha]_D^{21}$ −45.5° (c=0.88, $CHCl_3$); lit.,[16] mp 180°C, $[\alpha]_D^{20}$ −47° (c=1, $CHCl_3$). Elution with methanol gave the starting material **II** (228 mg, 14.4%).

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