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Chlorination of 1,5-Anhydro-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-D-*arabino*-hex-1-enitol; Highly Stereoselective Preparation of α-D-Glucopyranosyl Chloride and ω-Chloroalkyl β-D-Glucopyranosides

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Chlorination of 1,5-anhydro-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-D-*arabino*-hex-1-enitol in cyclic ethers such as tetrahydrofuran stereoselectively afforded the ω-chloroalkyl β-D-glycopyranoside derivatives, whereas in 1,4-dioxane α-D-glucopyranosyl chloride was obtained in high yield.

Extensive studies on chlorination of 3,4,6-tri-*O*-acetylglucal have been performed by Igarashi and his co-workers[1] as well as Boullanger and Descotes[2] and they found that the distribution of the stereoisomers of the adducts correlates with the polarity of the solvent. However, to our knowledge, there is no report of the formation of ω-chloroalkyl derivatives *via* the participation of ethers used as solvent in the halogenation of glycal derivatives, at least, as the major product.†

Here we report the chlorination of 1,5-anhydro-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-D-*arabino*-hex-1-enitol (**1**),[3] by which ω-chloroalkyl β-D-glucopyranoside derivatives and α-D-glucopyranosyl chloride were selectively obtained depending upon the ethers used as solvents.

Chlorination of (**1**) in carbon tetrachloride gave as expected the dichloro-derivative (**2**), m.p. 175—176 °C, $[\alpha]_D^{20}$ +151° (*c* 0.5, THF), $J_{1,2}$ 3.8, $J_{2,3}$ 10.5, and $J_{3,4}$ 9.8 Hz, in 80% isolated yield. However, to our surprise, similar chlorination in tetrahydrofuran provided the 4-chlorobutyl β-D-glucopyranoside (**4**), m.p. 88—89 °C, $[\alpha]_D^{20}$ −45.2° (*c* 0.5, CH_2Cl_2), $J_{1,2}$ 8.2, $J_{2,3}$ 10.5, and $J_{3,4}$ 9.7 Hz, in high yield. Compounds (**4**), (**2**), and the nitro-alkene (**5**), m.p. 119—120 °C, $[\alpha]_D^{20}$ −174° (*c* 0.5, acetone), δ 6.73 (2-H),‡ ν_{max} 1525 (C=C–NO_2) cm^{-1}, were isolated in 63, 5, and 30% yields, respectively, after flash column chromatography;[4] compound (**5**) arises mainly from (**4**) during column chromatography, since the ^1H n.m.r. spectrum of the crude product showed the presence of only a small amount of (**5**). Apparently the formation of (**4**) involves the oxonium intermediate (**3**) and subsequent ring opening by the attack of a chloride ion. Highly stereoselective formation of the β-anomer may be attributable to the reverse anomeric effect[5] in the oxonium intermediate.§

Similar chlorination of (**1**) in oxetane provided 3-chloropropyl β-D-glucopyranoside (**6**), m.p. 124—125 °C, $[\alpha]_D^{20}$ −37.1° (*c* 1, acetone), $J_{1,2}$ 8.2, $J_{2,3}$ 10.5, and $J_{3,4}$ 9.7 Hz, and the nitroalkene (**7**) as a syrup, $[\alpha]_D^{20}$ −131° (*c* 0.93, acetone), δ 6.74 (2-H),† ν_{max} 1535 (C=C–NO_2) cm^{-1}, in 67 and 11% yield, respectively, after flash column chromatography, from which an unidentified product was also obtained, but the dichloro-derivative (**2**) was not isolated. Similar chlorination

† *E.g.*, chlorination[1,2] and bromination[2] of triacetylglucal in diethyl ether and tetrahydrofuran (THF), respectively, gave only dihalogeno-derivatives.

‡ ^1H N.m.r. spectra recorded in $CDCl_3$ with tetramethylsilane as the internal standard.

§ It is noteworthy that 4-bromobutyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside was prepared in low yields in the reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with silver carbonate[6] or mercury bromide[7] in THF.

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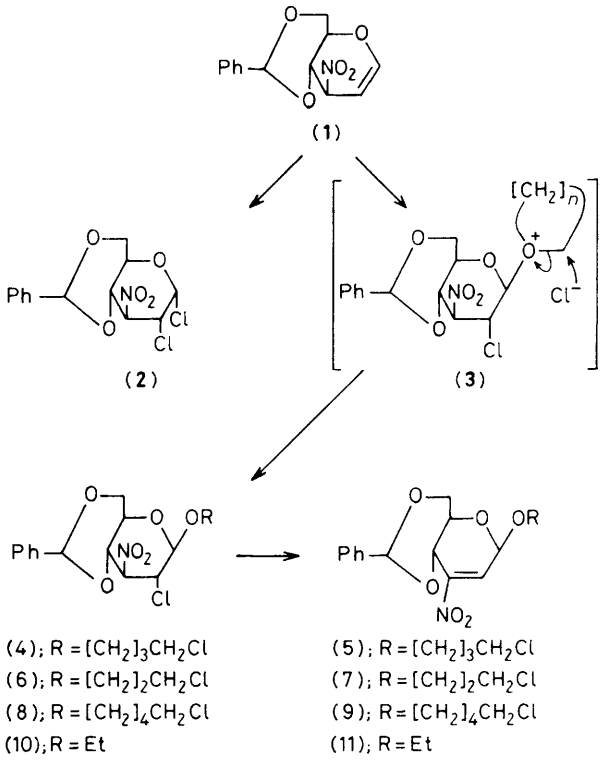

of (**1**) in tetrahydrodropyran yielded a mixture of 5-chloropentyl β-D-glucopyranoside (**8**) and (**2**) in the ratio of *ca.* 3 : 1 by ^{1}H n.m.r. spectroscopy, from which compound (**8**), m.p. 92—93 °C, $[\alpha]_D^{20}$ −23.6° (*c* 0.4, THF), $J_{1,2}$ 8.2, $J_{2,3}$ 10.5, and $J_{3,4}$ 9.7 Hz, the nitro-alkene (**9**), m.p. 68.5—71 °C, $[\alpha]_D^{20}$ −134° (*c* 1.1, acetone), δ 6.73 (2-H), ν_{max} 1535 (C=C–NO_2) cm^{-1}, and (**2**) were isolated in 45, 13, and 20% yields, respectively. A similar but not so significant effect of an acyclic ether was observed; chlorination in diethyl ether gave ethyl β-D-glucopyranoside (**10**), m.p. 123—124 °C, $[\alpha]_D^{20}$ −51.2° (*c* 1.2, acetone), $J_{1,2}$ 7.5, $J_{2,3} = J_{3,4} = 10$ Hz, in 13% yield, together with the nitro-alkene (**11**), m.p. 117.5—118.5 °C, $[\alpha]_D^{20}$ −169° (*c* 0.9, acetone), δ 6.76 (2-H),‡ ν_{max} 1525 (C=C–NO_2) cm^{-1}, in 3.3% yield and (**2**) in 45% yield. Chlorination in 1,4-dioxane, however, exclusively afforded the dichloro-derivative (**2**) in 92% yield. This is the best way to prepare (**2**), since crystalline (**2**), obtained just after evaporation of the solvent, was pure enough for further reactions.

Why chlorination of (**1**) afforded the ω-chloroalkyl derivative and dichloro-derivative in ethers such as THF and 1,4-dioxane, respectively, is not clear, but the product ratios of the ω-chloroalkyl derivative and (**2**) may be attributable to the stability of the intermediary oxonium ion and/or the basicity of the ether employed.

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