

Synthesis of 4-*O*-Benzyl-D-Glucose

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A new method for the benzylation of hydroxyl groups in carbohydrates has been developed. The method, by which alkali-labile groups, such as acetate ester groups, are not removed, has been applied for the synthesis of 4-*O*-benzyl-D-glucose.

4-*O*-Benzyl-D-glucose, which has not been prepared before, was of interest in this Department, and we therefore looked for a convenient route to this substance. 4-*O*-Methyl-D-glucose has recently been prepared¹ by methylation of methyl 2,3,4-tri-*O*-acetyl- β -D-glucopyranoside with methyl iodide and silver oxide in dimethyl formamide, taking advantage of the facile migration of an acetyl group from the 4- to the 6-position and subsequent deacetylation and hydrolysis. An analogous route to the benzyl ether should be attractive. The benzylation of carbohydrates has recently been summarised by Mc Closkey²; it has always been done using strongly alkaline conditions, under which acyl groups should be split off. The benzylation of 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose with benzyl bromide and silver oxide in dimethyl formamide was investigated first; after hydrolysis of the product a good yield of 3-*O*-benzyl-D-glucose was obtained. Methyl 2,3,4-tri-*O*-acetyl- β -D-glucopyranoside was then benzylated in the same way and the product was deacetylated and hydrolysed. Paper electrophoresis in borate buffer revealed the presence of three substances, with the mobilities expected³ for glucose, and for 6-*O*- and 4-*O*-benzyl-D-glucose, of which the latter gave the strongest colour reaction. The first two substances were adsorbed on a column of Amberlite IR 400 in the borate state, a technique previously used by Richards and Lock⁴ for the fractionation of methylated glucoses. This gave the presumed 4-*O*-benzyl-D-glucose in a crystalline state in 23 % yield.

The product analysed as a monobenzylated glucose and had an electrophoretic mobility of 0.17, relative to glucose, as would be expected for the 2-*O*- or 4-*O*-benzyl ether. To distinguish between these possibilities the substance was treated with aqueous calcium hydroxide, in which the former should be stable and the latter degraded, chiefly to isosaccharinic acid⁵. The substance was degraded to acidic material at a slower rate than that at which 3-*O*-benzyl-D-glucose was degraded in a parallel experiment. 2-*O*-Methyl-D-glucose was quite stable under these conditions. This indicated that the substance was the 4-*O*-benzyl ether and in agreement with this it

consumed 2.92 moles of periodate with the formation of 1.91 moles of formic acid. The 4-*O*-benzyl-D-glucose melted at 178–179° and showed an optical rotation of 96° → 52° in water, indicating that the crystalline material was the α -form.

EXPERIMENTAL

Melting points are corrected. Paper chromatography was carried out on Whatman No. 1 filter paper with the solvent system ethyl acetate-acetic acid-water(3:1:3).

Paper electrophoresis was carried out on Whatman No. 3 MM filter paper in borate buffer at pH 10.

3-O-Benzyl-D-glucose. 1,2:5,6-Di-*O*-isopropylidene-D-glucopyranose (3 g) was dissolved in dimethyl formamide (60 ml) and benzyl bromide (12 ml) was added. Silver oxide (12 g) was added over 60 min with vigorous stirring and external cooling with tap water. Stirring was continued for 16 h. The solids were removed by centrifuging and washed, first with dimethyl formamide (50 ml) and then with chloroform (50 ml). Potassium cyanide (1 %, 500 ml) was added to the combined solutions, which were then extracted with chloroform (3 × 100 ml). The combined chloroform solutions were washed with water (3 × 500 ml) and concentrated to a syrup. This was dissolved in a mixture of sulphuric acid (1 %, 70 ml) and ethanol (30 ml) and heated on the steam bath for 1 h after which the ethanol was distilled off and heating was continued for a further 3 h. Neutralisation with barium carbonate, filtration and concentration yielded a slightly yellow syrup (3.2 g). The syrup was fractionated on a cellulose column (80 × 4 cm), using butan-1-ol, saturated with water as solvent. The main fraction (2.6 g) gave chromatographically and electrophoretically pure 3-*O*-benzyl-D-glucose, which could be crystallised from acetone. The yield of crystalline product, m. p. 137–138°, was 2.08 g. The R_{GLUC} -value was 5.5.

4-O-Benzyl-D-glucose. Methyl 2,3,4-tri-*O*-acetyl- β -D-glucopyranoside (3 g) was dissolved in dimethyl formamide (30 ml) and benzylated with benzyl bromide (12 ml) and silver oxide (12 g) as described above. The resulting syrup was deacetylated with catalytic amounts of sodium ethoxide in ethanol, hydrolysed with 8 % sulphuric acid at 100°C for 4 h, neutralised with barium carbonate and then concentrated. The mixture of free sugars gave three spots on paper electrophoresis, with M_G values 0.17, 0.66 (elongated spot) and 1.0. Filtration through a column (30 × 1.2 cm) of Amberlite IR 400 in the borate state removed the two components with the higher M_G values. The component which passed through the column (0.90 g) was chromatographically and electrophoretically pure and could be crystallised from butan-2-one. Three crystallisations yielded the pure substance (0.62 g), m. p. 178–179°, $[\alpha]_{\text{D}}^{20} +52^\circ$ ($c = 2.0$, in water). On periodate oxidation, using 0.04 N sodium metaperiodate at room temperature for 48 h, it consumed 2.92 moles of oxidant. In a parallel experiment, 1.91 moles of formic acid were formed. The R_{GLUC} value was 5.2. (Found: C 56.1; H 6.59. Calc. for $\text{C}_{13}\text{H}_{18}\text{O}_6$: C 57.6; H 6.68.)

2-*O*-Methyl-D-glucose, 3-*O*-benzyl-D-glucose and 4-*O*-benzyl-D-glucose were dissolved in saturated aqueous calcium hydroxide and kept at room temperature. The disappearance of sugar and the formation of acids was followed by paper electrophoresis in borate buffer (pH 10) and in acetate buffer (pH 4.5), using anisidine hydrogen chloride for the former and silver nitrate-sodium ethoxide for the latter as spraying reagents. The acids formed had the same electrophoretic mobilities as *meta*- and *isosaccharinic* acid, respectively, but were not further characterized. After 3 days most of the 3-*O*-benzyl ether and about half of the 4-*O*-benzyl ether were degraded into acids. After 5 days most of the latter was also degraded. The 2-*O*-methyl-D-glucose was quite stable.

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