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596. 2,4,6-*Tri*-O-*acetyl*-3-O-*benzyl*-α-D-*glucopyranosyl Bromide: A New Intermediate for the Koenigs–Knorr Synthesis of Glycosides.*

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2,4,6-Tri-*O*-acetyl-3-*O*-benzyl-α-D-glucopyranosyl bromide has been prepared; reactions are described which illustrate its potential as a substituted glucosyl bromide.

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The synthesis of glycosides (oligosaccharide synthesis being a special case of glycoside synthesis) from poly-*O*-substituted glycosyl bromides by the Koenigs–Knorr reaction [1] has found extensive application.[2] The glycosyl bromides used have had substituents of two main types, (1) *O*-acetyl and *O*-benzoyl (on rare occasions other *O*-acyl or *O*-aroyl groups have been used, *e.g.*, *O*-triacetylgalloyl [3]), and (2) *O*-methanesulphonyl and and *O*-toluene-*p*-sulphonyl. Frequently glycosyl bromides have been used which contain substituents of both types in the one molecule. However, there have been few reports of the preparation or use of a poly-*O*-substituted glycosyl bromide in which one of the hydroxyl groups has been protected by a group which can be preferentially removed after formation of the glycosidic linkage. Such a compound would open up a new approach to the synthesis of substituted glycosides by the Koenigs–Knorr reaction (it would for instance obviate the use of a disaccharide glycosyl bromide in a trisaccharide synthesis).

Reynolds and Kenyon [4] have used bis-(2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl bromide) 6,6-carbonate in a synthesis of gentiobiose but the carbonate ester group, while being suitable as a protecting group, has the disadvantage that preferential removal is seldom practicable. We are examining the use of poly-*O*-acetylglycosyl bromides having one *O*-benzyl group as intermediates for the synthesis of substituted glycosides, and now report the preparation of crystalline 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-α-D-glucopyranosyl bromide. The only *O*-benzylglycosyl bromides previously reported were amorphous 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide,[5] 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-mannopyranosyl bromide,[6] 2,3,5-tri-*O*-benzyl-D-ribofuranosyl bromide and 2,3,5-tri-*O*-benzyl-L-arabinofuranosyl bromide.[7] The last three compounds were obtained as syrups.

1,2:5,6-Di-*O*-isopropylidene-D-glucofuranose was benzylated by Zemplen's [5] method. Removal of the ketal groups gave 3-*O*-benzyl-D-glucose which was converted by Freudenberg and Plankenhorn's method [8] into 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranose (I). Treatment with hydrogen bromide at 5—10° for 3 hours followed by chromatographic purification [9] gave a good yield of 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-α-D-glucopyranosyl bromide (II), which was also obtained by treating 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranose with titanium tetrabromide under conditions similar to those employed by Zemplen and Gerecs [10] in the conversion of tetra-*O*-acetyl-L-rhamnopyranose into 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl bromide. The α-configuration was assigned to (II) on the basis of its high positive rotation, $[\alpha]_D$ +145°. Treatment of the triacetylpyranosyl bromide (II) with silver acetate gave 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranose (I). The glycosyl bromide (II) was treated with methanol as for

[1] Koenigs and Knorr, *Ber.*, 1901, **34**, 957.
[2] For reviews see Evans, Reynolds, and Talley, *Adv. Carbohydrate Chem.*, 1951, **6**, 27; Haynes and Newth, *ibid.*, 1955, **10**, 207; Conchie, Levvy, and Marsh, *ibid.*, 1957, **12**, 157.
[3] Schmidt, Berg, and Baer, *Annalen*, 1951, **571**, 19.
[4] Reynolds and Kenyon, *J. Amer. Chem. Soc.*, 1942, **64**, 1110.
[5] Zemplen, Csuros, and Angyal, *Ber.*, 1937, **70**, 1848.
[6] Gorin and Perlin, *Canad. J. Chem.*, 1961, **39**, 2474.
[7] Barker and Fletcher, *J. Org. Chem.*, 1961, **26**, 4605.
[8] Freudenberg and Plankenhorn, *Annalen*, 1938, **536**, 257.
[9] Finan and Warren, *J.*, 1962, 2823.
[10] Zemplen and Gerecs, *Ber.*, 1934, **67**, 2049.

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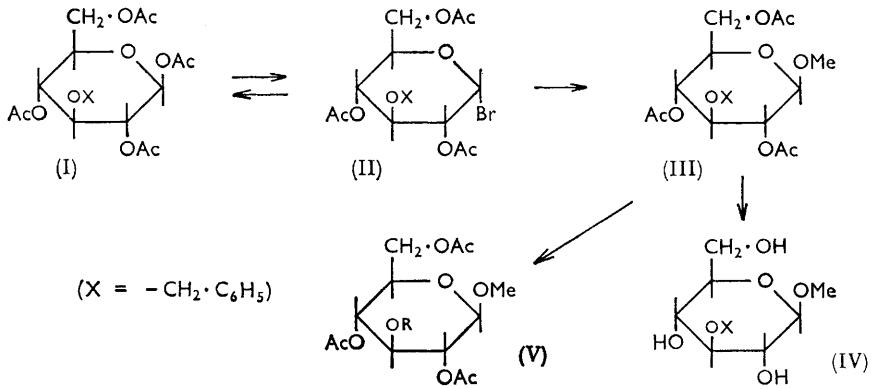
the Koenigs–Knorr reaction; crystalline methyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranoside (III) was obtained in excellent yield. Deacetylation gave methyl 3-*O*-benzyl-β-D-glucopyranoside (IV), acid hydrolysis of which gave 3-*O*-benzyl-D-glucose, thus proving that the *O*-benzyl group remained undisturbed in the transformations (I) ⟶ (II) ⟶ (III). Hydrogenation of methyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranoside gave crystalline methyl 2,4,6-tri-*O*-acetyl-β-D-glucopyranoside (V; R = H) in high yield. The latter on treatment with toluene-*p*-sulphonyl chloride in pyridine gave the known [11] methyl 2,4,6-tri-*O*-acetyl-3-*O*-toluene-*p*-sulphonyl-β-D-glucopyranoside (V; R = toluene-*p*-sulphonyl) thus showing that the hydrogenation of (III) was not accompanied by acyl migration. The conversion of methyl 2,4,6-tri-*O*-acetyl-β-D-glucopyranoside (V; R = H) into methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (V; R = Ac) establishes as correct the assignation of the β-configuration to the glucosides (III), (IV), and (V).



Experimental

M. p.s are uncorrected. Specific rotations were measured at 22—24°.

3-O-*Benzyl*-D-*glucose*.—1,2:5,6-Di-*O*-isopropylidene-D-glucose (50 g.), flaked sodium hydroxide (60 g.), and benzyl chloride (250 ml.) were heated (steam-bath) with vigorous stirring. During the first hour more sodium hydroxide (60 g.) was added. After 6 hr. the mixture was cooled, diluted with water (300 ml.), and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure, excess of benzyl chloride distilling at 85°/15 mm. 3-*O*-Benzyl-1,2 : 5,6-di-*O*-isopropylidene-D-glucose (54 g.) was obtained as a pale yellow oil, b. p. 145—149°/0·5 mm. (previously reported [12] b. p. 165—169°/0·5 mm.). Without further purification this was dissolved in methanol (400 ml.), 2N-sulphuric acid (50 ml.) was added, and the resulting homogeneous solution was heated (steam-bath) for 5 hr. The methanol was removed by evaporation under reduced pressure and the residual solution was diluted with 50 ml. of water and heated (steam-bath) for 1 hr. After cooling and neutralisation (barium carbonate) the solution was concentrated under reduced pressure. The syrup was taken up in warm ethyl acetate and on cooling 3-*O*-benzyl-D-glucose (27·5 g., 53% based on 1,2:5,6-di-*O*-isopropylidene-D-glucose) was obtained as prisms, m. p. 128—130°. Further recrystallisation raised the m. p. to 137—138° (Sowden and Kuenne [13] report m. p. 136—138°).

3-*O*-Benzyl-D-glucose was acetylated [8] (acetic anhydride and pyridine); 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranose was obtained as needles, m. p. 107° (previously reported [8] m. p. 107°).

2,4,6-*Tri*-O-*acetyl*-3-O-*benzyl*-α-D-*glucopyranosyl Bromide* (II).—(*a*) To 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranose (20 g.) in acetic acid (40 ml.) at 10°, a solution of hydrogen bromide in acetic acid (50% w/v; 20 ml.) was added slowly. The mixture was stirred at 5—10° for 3 hr., diluted with alcohol-free chloroform (300 ml.), washed (with ice–water, aqueous

[11] Ohle and Spenker, *Ber.*, 1926, **59**, 1836.
[12] Freudenberg, von Hochstetter, and Engles, *Ber.*, 1925, **58**, 666.
[13] Sowden and Kuenne, *J. Amer. Chem. Soc.*, 1952, **74**, 686.

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sodium hydrogen carbonate, and water), and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a syrup which was taken up in ether and adsorbed on silica gel (350 g.). Elution with light petroleum (b. p. 60—80°; 400 ml.) gave benzyl bromide (3 g.). Further elution with ether (300 ml.) gave a syrup which crystallised on cooling. Recrystallisation from ether gave 2,4,6-*tri*-O-*acetyl*-3-O-*benzyl*-α-D-*glucopyranosyl bromide* (15 g., 75% yield) as needles, m. p. 78—79°, $[\alpha]_D$ +145° (*c*, 1 in chloroform) (Found: C, 49·8; H, 5·1; Br, 17·4. $C_{19}H_{23}BrO_8$ requires C, 49·7; H, 5·0; Br, 17·4%); $\nu_{max.}$ 1745 (C=O of acetate), 1490 (aromatic skeletal vibration), 755, 735, and 700 cm.$^{-1}$ (monosubstituted benzene).

(*b*) A mixture of 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranose (8·5 g.) and titanium tetrabromide (8·5 g.) in alcohol-free chloroform (250 ml.) was stirred at 5° for 6 hr. Acetic acid (3 ml.) was added and the dark red solution was washed with water and dried ($MgSO_4$). Removal of solvent under reduced pressure left a syrup which was adsorbed on silica gel. Elution with light petroleum (b. p. 40—60°; 150 ml.) gave benzyl bromide (0·3 g.). Elution with ether (250 ml.) gave 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-α-D-glucopyranosyl bromide (6·9 g., 82% yield), m. p. 78—79°, identical with the material prepared by method (*a*).

Treatment of 2,4,6-*Tri*-O-*acetyl*-3-O-*benzyl*-α-D-*glucopyranosyl Bromide with Silver Acetate*.—A mixture of the bromo-compound (0·5 g.) and freshly prepared silver acetate (0·5 g.) in alcohol-free chloroform (40 ml.) was stirred in darkness at room temperature for 12 hr. The mixture was filtered and the filtrate was evaporated to a syrup which crystallised on trituration with ether–light petroleum (b. p. 60—80°). Recrystallisation from aqueous ethanol gave 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranose, m. p. and mixed m. p. 107°.

Methyl 2,4,6-*Tri*-O-*acetyl*-3-O-*benzyl*-β-D-*glucopyranoside* (III).—A mixture of 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-α-D-glucopyranosyl bromide (13 g.), silver carbonate (13 g.), and methanol (200 ml.) was stirred in darkness at room temperature for 12 hr. The precipitate was well washed with methanol and the combined filtrate and washings were concentrated to a syrup which slowly crystallised. Recrystallisation from ethanol gave *methyl* 2,4,6-*tri*-O-*acetyl*-3-O-*benzyl*-β-D-*glucopyranoside* (10 g., 86% yield) as needles, m. p. 90°, $[\alpha]_D$ −25° (*c*, 1 in chloroform) (Found: C, 58·3; H, 6·1; OMe, 8·0. $C_{20}H_{26}O_9$ requires C, 58·5; H, 6·3; OMe, 7·6%); $\nu_{max.}$ 1745 and 1725 (C=O of acetates), 1490 (aromatic skeleton), 895 (β-glucopyranoside), 755, 740, and 700 cm.$^{-1}$.

Methyl 3-O-*Benzyl*-β-D-*glucopyranoside* (IV).—Methyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranoside (3 g.) was treated with sodium methoxide (from 0·1 g. of sodium) in methanol (50 ml.) at room temperature for 12 hr. The solution was passed through a column of "Biodeminrolit" mixed-bed resin (B.D.H.; 5 g.) and was then concentrated under reduced pressure. The residue was recrystallised from ethyl acetate giving *methyl* 3-O-*benzyl*-β-D-*glucopyranoside* (2·1 g., 98% yield) as needles, m. p. 99—100°, $[\alpha]_D$ −10° (*c*, 1 in water), (Found: C, 59·0; H, 7·0; OMe, 10·6. $C_{14}H_{20}O_6$ requires C, 58·7; H, 7·1; OMe, 11·0%); $\nu_{max.}$ 3400—3200 (broad; bonded −OH), 1495 (aromatic skeleton), 890 (β-glucopyranoside), 745 (vw), 740 and 700 cm.$^{-1}$ (monosubstituted benzene).

The benzyl glucoside (0·1 g.) in 0·1N-sulphuric acid was heated at 80° for 12 hr. After neutralisation with barium carbonate the solution was evaporated to dryness under reduced pressure. The residue was extracted thoroughly with ethyl acetate affording 3-*O*-benzyl-D-glucose, m. p. and mixed m. p. 136—138°.

Methyl 2,4,6-*Tri*-O-*acetyl*-β-D-*glucopyranoside* (V; R = H).—Methyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranoside (3 g.) in ethyl acetate (100 ml.) was hydrogenated at atmospheric presure by using 10% palladium on charcoal catalyst. One mole of hydrogen (180 ml. at 23°/755 mm.) was rapidly taken up. The catalyst was filtered off and the filtrate evaporated, giving *methyl* 2,4,6-*tri*-O-*acetyl*-β-D-*glucopyranoside* (2·2 g., 88% yield) as needles, m. p. 94—95°, $[\alpha]_D$ −44° (*c*, 1 in chloroform) (Found: C, 48·9; H, 6·1; OMe, 9·8. $C_{13}H_{20}O_9$ requires C, 48·8; H, 6·25; OMe, 9·7%); $\nu_{max.}$ 3380 (sharp, OH), 1735 and 1725 (C=O of acetates), 884 cm.$^{-1}$ (β-glucopyranoside).

Characterisation of Methyl 2,4,6-*Tri*-O-*acetyl*-β-D-*glucopyranoside*.—(*a*) A mixture of the glucoside (0·21 g.), pyridine (20 ml.), and acetic anhydride (10 ml.) was left at room temperature for 24 hr. The mixture was poured into water and extracted with chloroform. Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (0·23 g., 96%) was obtained, having m. p. 103—104° undepressed on admixture with an authentic specimen.

(*b*) A mixture of the glucoside (0·5 g.), pyridine (25 ml.), and toluene-*p*-sulphonyl chloride (0·8 g.) was kept at room temperature for 36 hr. Water (3 ml.) was added dropwise and after

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1 hr. the mixture was poured into an excess of ice–water (200 ml.) and extracted with chloroform. Removal of solvent left a syrup which slowly crystallised; recrystallisation from aqueous methanol gave methyl 2,4,6-tri-*O*-acetyl-3-*O*-toluene-*p*-sulphonyl-β-D-glucopyranoside (V; R = *O*-toluene-*p*-sulphonyl) (0·36 g.) as needles, m. p. 132°, $[\alpha]_D$ −18° (*c*, 1 in chloroform) (previously found [11] m. p. 131—132°, $[\alpha]_D$ −18°).

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