## 815. *Glycosides. Part II.* The Preparation of Methyl* 3,4,6-*Tri*-O-*acetyl*-2-O-*methyl*-β-D-*glucopyranoside.*

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Methylation of methyl 2,4,6-tri-*O*-acetyl-β-D-glucopyranoside with methyl iodide and silver oxide gave a high yield of methyl 3,4,6-tri-*O*-acetyl-2-*O*-methyl-β-D-glucopyranoside, the structure of which was proved by an alternative synthesis.

In Part I * of this series we described the preparation of methyl 2,4,6-tri-*O*-acetyl-β-D-glucopyranoside (I) by hydrogenation of its 3-benzyl ether. Structure (I) was based on the assumption that acyl migration did not occur during hydrogenation and the observation that the compound readily afforded the well-characterised 3-toluene-*p*-sulphonate [1] under mild conditions. We now report that compound (I) with methyl iodide in the presence of silver oxide gave a high yield of its 2-methyl ether (II) which on deacetylation gave methyl 2-*O*-methyl-β-D-glucopyranoside (III).

Brigl and Schinle [2] have prepared compound (II) by methylation of 3,4,6-tri-*O*-acetyl-D-glucose, while compound (III) has been obtained by Oldham [3] using a Koenigs–Knorr reaction on 3,4,6-tri-*O*-benzoyl-2-*O*-methyl-α-D-glucopyranosyl bromide. While the properties of our products (II) and (III) agreed with those reported by Brigl and Schinle,[2] and Oldham,[3] respectively, the syntheses carried out by these workers do not provide structural proof owing to the possibility of acyl migration during methylation. Accordingly we have carried out an unambiguous synthesis of the ether (III). Our results establish the correctness of formulæ (II) and (III); and since the latter has been converted [2,5] into 2-*O*-methyl-D-glucose by hydrolysis, our work furnishes further synthetic proof for the position of the methyl ether group in the latter: a reliable synthetic proof [6] for this had been lacking until Weygand and Trauth [7] methylated the syrupy mixture of anomeric methyl 3,5,6-tri-*O*-benzyl-D-glucofuranosides and obtained, after hydrolysis, 2-*O*-methyl-D-glucose identical with the product obtained previously by a variety of ambiguous methods. The proof provided by our results has the advantage that all the intermediates were crystalline.

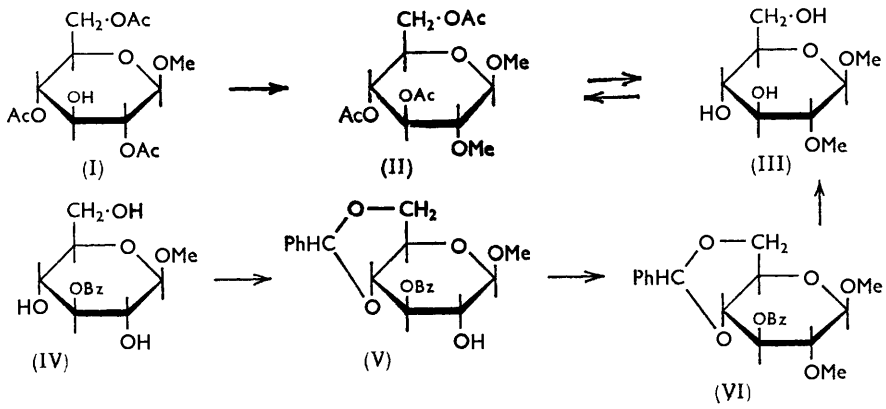
Methyl 3-*O*-benzyl-β-D-glucopyranoside (IV) was condensed with benzaldehyde to give methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (V). The position of the benzylidene grouping was established by benzylation to give methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside, identical with the compound obtained by benzylation [8] of the well-characterised methyl 4,6-*O*-benzylidene-β-D-glucopyranoside. Compound (V) with methyl sulphate and alkali gave the 2-methyl ether (VI) which on hydrogenation gave crystalline methyl 2-*O*-methyl-β-D-glucopyranoside (III). The latter afforded the triacetate (II).

The production of methyl 3,4,6-tri-*O*-acetyl-2-*O*-methyl-β-D-glucopyranoside (II) from the triacetate (I) must involve acetyl migration during methylation. A similar migration of benzoyl has been reported by Bourne *et al.*[9] who obtained methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside by treatment of the 2-*O*-benzoyl isomer with mild alkali. Presumably the migration of acetyl during the transformation (I) ⟶ (II) proceeds

* The paper by Finan and Warren, *J.*, 1962, 3089, is considered to be Part I.

[1] Ohle and Spenker, *Ber.*, 1926, **59**, 1836.
[2] Brigl and Schinle, *Ber.*, 1929, **62**, 1716.
[3] Oldham, *J. Amer. Chem. Soc.*, 1934, **56**, 1360.
[4] Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 1086.
[5] Finan and Warren, unpublished work.
[6] For a discussion see Bourne and Peat, *Adv. Carbohydrate Chem.*, 1950, **5**, 145.
[7] Weygand and Trauth, *Ber.*, 1952, **85**, 57.
[8] Dennison and McGilvray, *J.*, 1951, 1616.
[9] Bourne, Huggard, and Tatlow, *J.*, 1953, 735.

through a cyclic orthoacetate.[10] Further work is in progress towards gaining a better understanding of the steric requirements of migrations of this type.




## Experimental

Specific rotations were measured at 22—24°. The alumina used was kept under ethyl acetate for 24 hr., washed with methanol, then with water, and dried at 150° for 4 hr.

*Methylation of Methyl* 2,4,6-*Tri*-O-*acetyl*-β-D-*glucopyranoside*.—Methyl 2,4,6-tri-*O*-acetyl-β-D-glucopyranoside (0·5 g.), methyl iodide (100 ml.), and silver oxide (1 g.) were stirred at 40° for 3 days. The methyl iodide was removed by distillation and the residue extracted with chloroform. The extract was dried ($Na_2SO_4$) and evaporated to a syrup which was chromatographed on alumina. Elution with benzene gave methyl 3,4,6-tri-*O*-acetyl-2-*O*-methyl-β-D-glucopyranoside (0·34 g., 66%), needles (from ethanol), m. p. 75°, $[\alpha]_D$ +4° (*c* 0·05 in $CHCl_3$) (lit.,[2] m. p. 75°, $[\alpha]_D$ 6°). A mixed m. p. with a specimen prepared as described below showed no depression.

Treatment of this product (0·05 g.) with 1% sodium methoxide in methanol gave methyl 2-*O*-methyl-β-D-glucopyranoside (0·03 g.), prisms (from methanol), m. p. 93—95°, undepressed on admixture with a specimen prepared as described below.

*Methyl* 3-O-*Benzyl*-4,6-O-*benzylidene*-β-D-*glucopyranoside* (V).—Methyl 3-*O*-benzyl-β-D-glucopyranoside (5 g.), benzaldehyde (20 g.), and anhydrous zinc chloride (5 g.) were stirred at room temperature for 3 hr. Water was added, followed by light petroleum (b. p. 60—80°). A solid separated. This was filtered off and recrystallised from ethanol, giving *methyl* 3-O-*benzyl*-4,6-O-*benzylidene*-β-D-*glucopyranoside* (4·5 g., 69%) as needles, m. p. 180°, $[\alpha]_D$ −47° (*c* 1 in $CHCl_3$) (Found: C, 67·9; H, 6·5; OMe, 8·4. $C_{21}H_{24}O_6$ requires C, 67·9; H, 6·5; OMe, 8·3%).

To the benzylidene compound (0·1 g.) in acetone (5 ml.) N-hydrochloric acid (50 ml.) was added and the mixture was kept at room temperature for 16 hr. After neutralisation by solid sodium hydrogen carbonate and filtration the solution was evaporated to dryness. Extraction with ethyl acetate afforded methyl 3-*O*-benzyl-β-D-glucopyranoside (0·05 g., 75%), m. p. and mixed m. p. 99—100°.

The benzylidene compound (0·3 g.) in ethyl acetate (15 ml.) was hydrogenated over 10% palladised charcoal at atmospheric pressure; 3 mol. (60 ml.) of hydrogen were rapidly taken up. The catalyst and solvent were removed, giving a quantitative yield of methyl β-D-glucopyranoside, m. p. and mixed m. p. 105°.

*Methyl* 2,3-*Di*-O-*benzyl*-4,6-O-*benzylidene*-β-D-*glucopyranoside*.—Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (0·5 g.), powdered sodium hydroxide (0·5 g.), and benzyl chloride (20 ml.) were heated on the steam-bath with stirring. After 2 hr. more sodium hydroxide (0·5 g.) was added, followed by another portion (0·5 g.) after a further 2 hr. After 12 hr. the mixture was cooled, diluted with water, and extracted with ether. The extract was washed with water, dried ($Na_2SO_4$), and evaporated at 110°/17 mm. Addition of light

[10] For a review, see Pacsu, *Adv. Carbohydrate Chem.*, 1945, **1**, 77; for a summarising paper, see Bonner, *J. Org. Chem.*, 1959, **24**, 1388.

petroleum (b. p. 60—80°) to the residue gave a solid which recrystallised from ethanol, giving methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (0·47 g., 75%) as needles, m. p. 117—118°, $[\alpha]_D$ −35° (*c* 1 in $CHCl_3$). The m. p. was undepressed on admixture with the product of benzylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside.[8]

*Methyl* 3-O-*Benzyl*-4,6-O-*benzylidene*-2-O-*methyl*-β-D-*glucopyranoside* (VI).—To a mixture of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (1 g.) and powdered sodium hydroxide (0·4 g.) in acetone (20 ml.), methyl sulphate (0·5 ml.) was added dropwise with stirring at 45°. The mixture was warmed to 60° during 1 hr. and was stirred at this temperature for 3 hr. After cooling, water was added and the mixture extracted with chloroform. The extract was dried ($Na_2SO_4$) and evaporated to a syrup which was chromatographed on alumina. Elution with benzene gave *methyl* 3-O-*benzyl*-4,6-O-*benzylidene*-2-O-*methyl*-β-D-*glucopyranoside* (0·72 g., 70%) as needles (from ethanol), m. p. 125°, $[\alpha]_D$ −75° (*c* 1 in $CHCl_3$) (Found: C, 68·5; H, 6·55. OMe, 15·8. $C_{22}H_{26}O_6$ requires C, 68·4; H, 6·7; OMe, 16·1%).

*Methyl* 2-O-*Methyl*-β-D-*glucopyranoside* (III).—Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-methyl-β-D-glucopyranoside (0·5 g.) in ethyl acetate (10 ml.) was hydrogenated over 10% palladium–charcoal at atmospheric pressure. When hydrogen uptake (90 ml., 3 mol.) had ceased the mixture was filtered. Evaporation gave methyl 2-*O*-methyl-β-D-glucopyranoside (0·27 g., 90%), prisms, m. p. 95°, $[\alpha]_D$ −26° (*c* 1 in EtOH) (lit.,[3] m. p. 95—97°, $[\alpha]_D$ −24°).

The latter glycoside (0·36 g.) in a mixture of pyridine (10 ml.) and acetic anhydride (5 ml.) was kept at room temperature for 24 hr. The mixture was poured into water and extracted with chloroform. The extract was dried ($Na_2SO_4$) and evaporated, to give methyl 3,4,6-tri-*O*-acetyl-2-*O*-methyl-β-D-glucopyranoside (0·34 g.), needles (from ethanol), m. p. 75°, $[\alpha]_D$ +4° (*c* 1 in $CHCl_3$).

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