

# Alternative Syntheses of Methylated Sugars. V.\* Methyl Furanosides of 6-*O*- and 2,6-Di-*O*-methyl-D-glucose

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Methyl furanosides of 6-*O*- and 2,6-di-*O*-methyl-D-glucose have been synthesized. The intermediates of the synthesis were methyl 3,5-di-*O*-benzyl-6-*O*-methyl- $\alpha,\beta$ -D-glucofuranoside and methyl 3,5-di-*O*-benzyl-2,6-di-*O*-methyl- $\alpha,\beta$ -D-glucofuranoside which were separated into individual anomers by column chromatography on silica gel. Subsequent debenylation of isolated compounds afforded the final products.

Constitutional studies on polysaccharides have broadly followed the pattern of methylation of the unsubstituted alcoholic groups in a carbohydrate, hydrolytic or methanolic disruption of the molecule and identification of the resulting fragments. In this way methyl ethers of sugars, despite the known shortcomings of the technique known as methylation analysis, have been invaluable in determination of the ring structure of the monosaccharides and of the constitution of complex polysaccharides.

The last step in methylation analysis *i.e.* the identification of the products of methanolysis is complicated by the fact that each sugar can yield up to four glycosides [1–3] (two pyranosides and two furanosides) which multiplies the number of components to be identified. This applies to both qualitative and quantitative evaluation of methylation analysis. We have previously described [4–6] the syntheses of methyl furanosides of *O*-methyl-D-xylose and showed their usefulness in identification [7] of the products of methanolysis of substances containing D-xylopyranose as a structural unit. Here we wish to present the synthesis of four methyl furanosides of partially methylated D-glucose which were hitherto unknown and which can accordingly be used for identification purposes in methylation analysis.

## Experimental

Melting points were determined on a Kofler hot stage. Optical rotation was determined using a Bendix–Ericsson automatic polarimeter. Thin-layer chromatography (TLC) was carried out on silica gel G coated glass slides (4 × 12 cm) irrigated with: A. benzene–ethyl acetate 4 : 1 and B. chloroform–acetone 9 : 4. The components were located by spraying with 5% sulfuric acid in ethanol and by heating until permanent char spots were visible. Column chromatography was carried out on silica gel (0.05–0.1 mm) with: C. hexane–ethyl acetate 4 : 1, D. benzene–ethyl acetate–acetone 40 : 5 : 1, E. chloroform–acetone 3 : 1 and F. chloroform–acetone 9 : 2. The solvent ratios are based on volume. Evaporations were done under diminished pressure on a rotary evaporator at <40°C. *p*-Nitrobenzoyl derivatives of the final products were prepared as described by *Ishikawa* and *Fletcher* [8].

\* For Part IV. see Ref. [6].

*Methyl 3,5-di-O-benzyl-6-O-methyl- $\alpha$ - and - $\beta$ -D-glucofuranoside*

3,5-Di-O-benzyl-1,2-O-isopropylidene-6-O-methyl-D-glucofuranose (39.8 g) obtained by benzylation [9] of 1,2-O-isopropylidene-6-O-methyl-D-glucofuranose [10] was treated, with exclusion of moisture, with boiling methanol containing 0.7% hydrogen chloride (500 ml) for 1 1/2 hour at which time TLC in solvent system A showed complete conversion of the starting material ( $R_F$  0.62) into two products ( $R_F$  0.37 and 0.18). The methanolate was neutralized with lead carbonate, filtered and concentrated to give 39 g (~100%) of methyl 3,5-di-O-benzyl-6-O-methyl- $\alpha,\beta$ -D-glucofuranoside of which 25 g was put on the top of a column (100  $\times$  3 cm) of silica gel and, using solvent system C, resolved into individual components. Vacuum distillation gave 8.3 g (33.2%) of chromatographically pure faster moving (b.p. 191–192°C/0.01 Torr) and 8.2 g (32.8%) of slower moving (b.p. 206–208°C/0.01 Torr) component.

The intermediate, mixed fraction was worked up as described below.

The faster moving component was found to be methyl 3,5-di-O-benzyl-6-O-methyl- $\alpha$ -D-glucofuranoside,  $[\alpha]_D^{24} + 37.4^\circ$  ( $c = 1.15$ , ethanol). The pale yellow syrup could not be induced to crystallize.

For  $C_{22}H_{28}O_6$  (388.45) calculated: 68.02% C, 7.26% H; found: 67.55% C, 7.27% H.

The slower moving component was syrupy methyl 3,5-di-O-benzyl-6-O-methyl- $\beta$ -D-glucofuranoside,  $[\alpha]_D^{24} - 10.08^\circ$  ( $c = 1.01$ , ethanol).

Found: 67.58% C, 7.23% H.

*Methyl 6-O-methyl- $\beta$ -D-glucofuranoside*

A solution of methyl 3,5-di-O-benzyl-6-O-methyl- $\alpha$ -D-glucofuranoside (8.3 g) in 1,2-dimethoxyethane (30 ml) was added with stirring to liquid ammonia (300 ml) followed by sodium (2.1 g) cut into small pieces. The last portion of sodium caused an intense blue colour to develop, which indicated that the reaction was complete. The reaction mixture was worked up in the usual manner [4] and the debenylation by-product bibenzyl (identified by its m.p. 51–52°C) and mass spectrometry ( $m/e$  182, 91, 39) was removed on a small silica gel column (30  $\times$  2 cm) irrigated with solvent system E. Fractions containing the charring component were collected ( $R_F$  0.16, system B, *cf.* 0.74 for the starting material), evaporated to dryness and vacuum distilled (b.p. 124–125°C/0.02 Torr). Yield 3.1 g (70%) of a chromatographically pure syrup.  $[\alpha]_D^{24} + 125^\circ$  ( $c = 1.52$ , ethanol).

For  $C_8H_{16}O_6$  (208.21) calculated: 46.14% C, 7.74% H, 29.81%  $CH_3O$ ; found: 45.78% C, 7.62% H, 29.96%  $CH_3O$ .

Methyl 6-O-methyl- $\alpha$ -D-glucofuranoside gave crystalline methyl 6-O-methyl-2,3,5-tris-*O*-*p*-nitrobenzoyl- $\alpha$ -D-glucofuranoside having m.p. 173–174°C and  $[\alpha]_D^{24} + 76.2^\circ$  ( $c = 1.16$ , chloroform).

For  $C_{25}H_{25}O_{15}N_3$  (655.52) calculated: 53.15% C, 3.84% H, 6.41% N, 9.47%  $CH_3O$ ; found: 53.0% C, 3.77% H, 6.30% N, 9.47%  $CH_3O$ .

*Methyl 6-O-methyl- $\beta$ -D-glucofuranoside*

Methyl 3,5-di-O-benzyl-6-O-methyl- $\beta$ -D-glucofuranoside (8 g) was debenzylated and the product isolated in the above described manner. Vacuum distillation (b.p. 146–147°C/0.03 Torr) gave 3.7 g (86%) of a chromatographically pure syrup ( $R_F$  0.11, solvent system B, *cf.* 0.73 for the starting material) of  $[\alpha]_D^{24} - 81.6^\circ$  ( $c = 1.37$ , ethanol).

Found: 45.73% C, 7.71% H, 29.94% CH<sub>3</sub>O.

Methyl 6-*O*-methyl- $\beta$ -D-glucufuranoside afforded crystalline methyl 6-*O*-methyl-2,3,5-tris-*O*-*p*-nitrobenzoyl- $\beta$ -D-glucufuranoside having m.p. 167.5–168.5°C and  $[\alpha]_D^{24} - 33.7^\circ$  ( $c = 1.33$ , chloroform).

Found: 53.16% C, 3.78% H, 6.44% N, 9.40% CH<sub>3</sub>O.

#### *Methyl 3,5-di-O-benzyl-2,6-di-O-methyl- $\alpha$ - and - $\beta$ -D-glucufuranoside*

Methyl 3,5-di-*O*-benzyl-6-*O*-methyl- $\alpha,\beta$ -D-glucufuranoside (20 g) was methylated at 50°C with methyl sulfate (10 ml) and sodium hydroxide (8 g) in tetrahydrofuran. After one hour, at which time TLC in solvent system A showed complete conversion of the starting material ( $R_F$  0.18 and 0.37) into two products ( $R_F$  0.45 and 0.62), the reaction mixture was worked up in the usual manner and methyl 3,5-di-*O*-benzyl-2,6-di-*O*-methyl- $\alpha,\beta$ -D-glucufuranoside (21 g, ~100%) was chromatographed, using solvent system D, on a silica gel column (130 × 3 cm). The isolated anomers were vacuum distilled whereupon 8.5 g (40.5%) of the faster moving (b.p. 174–176°C/0.05 Torr) methyl 3,5-di-*O*-benzyl-2,6-di-*O*-methyl- $\beta$ -D-glucufuranoside ( $[\alpha]_D^{24} - 92.4^\circ$ ;  $c = 1.04$ , ethanol) was obtained.

For C<sub>23</sub>H<sub>30</sub>O<sub>6</sub> (402.47) calculated: 68.63% C, 7.51% H; found: 68.62% C, 7.46% H. The slower moving component (b.p. 175–176°C/0.03 Torr) was methyl 3,5-di-*O*-benzyl-2,6-di-*O*-methyl- $\alpha$ -D-glucufuranoside. Yield 4.5 g (22%),  $[\alpha]_D^{24} + 54.4^\circ$  ( $c = 1.15$ , ethanol).

Found: 68.57% C, 7.48% H.

An intermediate, mixed fraction was also obtained.

#### *Methyl 2,6-di-O-methyl- $\beta$ -D-glucufuranoside*

Debenzylation of methyl 3,5-di-*O*-benzyl-2,6-di-*O*-methyl- $\beta$ -D-glucufuranoside (5.2 g) gave, after purification of the product on a silica gel column (30 × 2 cm) irrigated with solvent system F and vacuum distillation (b.p. 116–117°C/0.06 Torr), 2.1 g (72.5%) of a chromatographically pure syrup ( $R_F$  0.34, solvent system B,  $c_f$  0.9 for the starting material).  $[\alpha]_D^{24} - 73^\circ$  ( $c = 1.02$ , ethanol).

For C<sub>6</sub>H<sub>18</sub>O<sub>6</sub> (222.23) calculated: 48.63% C, 8.16% H, 41.89% CH<sub>3</sub>O; found: 48.32% C, 8.31% H, 41.30% CH<sub>3</sub>O.

Methyl 2,6-di-*O*-methyl- $\beta$ -D-glucufuranoside gave crystalline methyl 2,6-di-*O*-methyl-3,5-bis-*O*-*p*-nitrobenzoyl- $\beta$ -D-glucufuranoside having m.p. 128–130°C and  $[\alpha]_D^{24} - 236^\circ$  ( $c = 1.26$ , chloroform).

For C<sub>23</sub>H<sub>24</sub>O<sub>12</sub>N<sub>2</sub> (520.44) calculated: 53.07% C, 4.74% H, 5.38% N, 17.88% CH<sub>3</sub>O; found: 53.13% C, 4.70% H, 5.34% N, 17.91% CH<sub>3</sub>O.

#### *Methyl 2,6-di-O-methyl- $\alpha$ -D-glucufuranoside*

Debenzylation of methyl 3,5-di-*O*-benzyl-2,6-di-*O*-methyl- $\alpha$ -D-glucufuranoside (4.3 g) and isolation of the product in the above described manner afforded, after purification by chromatography in solvent system F and vacuum distillation (b.p. 119–120°C/0.07 Torr), 1.9 g (80%) of a chromatographically pure ( $R_F$  0.24, solvent system B,  $c_f$  0.9 for the starting material) syrup.  $[\alpha]_D^{24} + 135.9^\circ$  ( $c = 1.06$ , ethanol).

Found: 48.50% C, 8.18% H, 41.05% CH<sub>3</sub>O.

Methyl 2,6-di-*O*-methyl-3,5-bis-*O*-*p*-nitrobenzoyl- $\alpha$ -D-glucufuranoside could be obtained only in the form of a semisolid foam of  $[\alpha]_D^{24} - 76.1^\circ$  ( $c = 1.05$ , chloroform).

Found: 53.25% C, 4.70% H, 5.49% N, 17.99% CH<sub>3</sub>O.

## Discussion

Of the various synthetic routes for making 6-*O*-methyl-D-glucose [9–14] the most efficient is that of *Ohle* and *Varga* [10] based on nucleophilic opening of the anhydro-ring of 1,2-*O*-isopropylidene-5,6-anhydro-D-glucofuranose with sodium methoxide. *Varga* and *Ohle* originally believed that ring scission had resulted in the attachment of the methoxyl grouping to C-5 rather than C-6, but this erroneous interpretation of the reaction was disproved by *Levene* and *Raymond* [15] who undoubtedly showed that this reaction proceeds with the formation of 6-*O*-methyl derivative. 2,6-Di-*O*-methyl-D-glucose was synthesized *via* methyl 3,4-di-*N*-phenylcarbamyl- $\alpha$ -D-glycopyranoside and also through methyl  $\alpha$ -D-glycopyranoside 3,4-dinitrate [16, 17]. An alternative route was used by *Freundenberg* and *Hüll* [9] who benzylated the hydroxyl groups on C-3 and C-5 of 1,2-*O*-isopropylidene-6-*O*-methyl-D-glucofuranose, obtained through a considerably more roundabout way than by the authors [10, 15], and methanolized the fully substituted D-glucofuranose structure. Methylation of thus liberated hydroxyl at C-2 and subsequent debenylation gave a mixture of  $\alpha$ - and  $\beta$ -methyl furanosides of 2,6-di-*O*-methyl-D-glucose from which the free sugar was readily obtained by hydrolysis.

In the presented work two of the above-mentioned syntheses [9, 10] were utilized for preparation of the title methyl furanosides in the following way: 1,2-*O*-isopropylidene-6-*O*-methyl-D-glucofuranose, obtained according to *Ohle* and *Varga* [10] was benzylated and methanolized as described by *Freundenberg* and *Hüll* [9]. Methyl 3,5-di-*O*-benzyl-6-*O*-methyl- $\alpha,\beta$ -D-glucofuranoside thus obtained was resolved on a column of silica gel and the individual anomers were collected. The faster moving component was found to be methyl 3,5-di-*O*-benzyl-6-*O*-methyl- $\alpha$ -D-glucofuranoside and the slower moving component was methyl 3,5-di-*O*-benzyl-6-*O*-methyl- $\beta$ -D-glucofuranoside. Debenzylation of the isolated anomers with sodium in liquid ammonia then gave methyl 6-*O*-methyl- $\alpha$ - and - $\beta$ -D-glucofuranoside.

Methylation of methyl 3,5-di-*O*-benzyl-6-*O*-methyl- $\alpha,\beta$ -D-glucofuranoside followed by separation of the 2,6-di-*O*-methyl furanosides on a silica gel column gave individual anomers of methyl 3,5-di-*O*-benzyl-2,6-di-*O*-methyl-D-glucofuranoside. Here, like in the case of analogous methyl *O*-methyl-D-xylofuranosides [5, 6] where substitution of the hydroxyl group on C-2 with a methoxyl group reversed the mobility of the anomers, the faster moving component was methyl 3,5-di-*O*-benzyl-2,6-di-*O*-methyl- $\beta$ -D-glucofuranoside and the slower moving component was the  $\alpha$ -anomer. The isolated compounds were debenzylated whereupon methyl furanosides of 2,6-di-*O*-methyl-D-glucose were obtained.

It is known [18] that in the series of partially *O*-methylated methyl glycopyranosides the determining factor for the order of elution of a pair of anomers by gas-liquid chromatography is the state of the hydroxyl group at C-2. In all methyl *O*-methyl-glycopyranosides examined and on all liquid phases that anomer, in which the glycosidic methoxyl group is in *cis* relationship to the methoxyl group at C-2, has the higher retention time. When the C-2 hydroxyl group is unsubstituted, the order in which the anomers are eluted is reversed. In the series of methyl *O*-methyl-glycofuranosides, apparently because these compounds are only rarely obtained in purity sufficient for this kind of investigation, such a generalization could not be made yet. In our previous works [4–7] it could be concluded, that the generally accepted rule for the elution of a pair of anomers of methyl *O*-methyl-glycopyranosides is valid, with no exception, for both gas chromatography and chromatography on silica gel of methyl *O*-methyl-D-xylofuranosides. The presented work deals, from the point of view of the above-mentioned rule [18] with

two pairs of basically different methyl *O*-methyl-D-glucofuranosides, namely methyl 6-*O*-methyl-D-glucofuranosides with the free hydroxyl group at C-2 and methyl 2,6-di-*O*-methyl-D-glucofuranosides having the C-2 hydroxyl substituted with a methoxyl group. As showed above, on silica gel, the elution pattern of the title compounds as well as that of the intermediates throughout the presented synthesis is strictly in accordance with the rules for elution of methyl *O*-methyl-glycopyranosides. This, together with the findings in our previous works [4–7] indicates, that for chromatography of methyl *O*-methyl-glycopyranosides the same empirical rules can be applied as for methyl *O*-methyl-glycopyranosides.

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### References

1. Bishop C. T., Cooper F. P., *Can. J. Chem.* **40**, 224 (1962).
2. Bishop C. T., Cooper F. P., *Can. J. Chem.* **41**, 2743 (1963).
3. Smirnyagin V., Bishop C. T., *Can. J. Chem.* **46**, 3085 (1968).
4. Kováč P., Petříková M., *Carbohydr. Res.* **16**, 492 (1971).
5. Kováč P., Petříková M., *Carbohydr. Res.* **19**, 249 (1971).
6. Kováč P., *Chem. Zvesti* **25**, 460 (1971).
7. Anderle D., Petříková M., Kováč P., *J. Chromatogr.* **58**, 209 (1971).
8. Ishikawa T., Fletcher H. G., *J. Org. Chem.* **34**, 563 (1969).
9. Freundenberg K., Hüll G., *Ber.* **74**, 237 (1941).
10. Ohle H., Varga L., *Ber.* **62B**, 2435 (1929).
11. Helfrich B., Becker J., *Justus Liebigs Ann. Chem.* **440**, 1 (1924).
12. Helfrich B., Günther E., *Ber.* **64B**, 1276 (1931).
13. Ohle H., Tessmar K., *Ber.* **71B**, 1843 (1938).
14. Ball D. J., *J. Chem. Soc.* **1936**, 859.
15. Levene P. A., Raymond A. L., *J. Biol. Chem.* **97**, 751 (1932).
16. Ball D. J., Synge R. L. M., *J. Chem. Soc.* **1938**, 833.
17. Reeves R. E., *J. Amer. Chem. Soc.* **70**, 259 (1948).
18. Bishop C. T., *Advan. in Carbohydr. Chem.* **19**, 95 (1964).

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