# Alternative syntheses of methylated sugars. X.*
## Methyl pyranosides of 2-*O*-methyl-D-glucose

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Methyl 2-*O*-methyl-α-D-glucopyranoside and methyl 2-*O*-methyl-β-D--glucopyranoside have been obtained in crystalline condition by methylation of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α,β-D-glucopyranoside followed by chromatography and removal of the blocking groups in the isolated anomers. Debenzylidenation of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*--methyl-α-D-glucopyranoside, methylation and debenzylation afforded methyl 2,4,6-tri-*O*-methyl-α-D-glucopyranoside.

Identification of methyl 2(4?)-*O*-methyl-α-D-glucopyranoside, a possible by-product in the synthesis of 2,4-di-*O*-methyl-D-glucose [1], required authentic samples of the two mono-*O*-methyl-D-glucopyranosides. The needed methyl 2-*O*-methyl-α-D-glucopyranoside (*III*) could not be obtained simply by treatment of 2-*O*-methyl-D-glucose with methanolic hydrogen chloride as such treatment of any hexose with the $C_4$—OH free, results in the formation of four isomeric structures (two methyl pyranosides and two methyl furanosides). Since no dependable procedure for the synthesis of alkyl α-glycopyranosides, analogous to the well known Königs—Knorr synthesis of alkyl β-glycopyranosides. has been known as yet, the synthesis of *III* had to be carried out from a suitable precursor (properly substituted derivative of methyl α-D-glucopyranoside). We have decided to use for this purpose the recently reported sequence of *Hashimoto et al.* [2] which, contrary to other procedures [3, 4], takes advantage neither of migration of acyloxy groups during the methylation process [3] nor of partial methylation [4]. Here we wish to present evidence that the syrupy methyl 2-*O*-methyl-α-D-glucopyranoside of the Japanese workers [2] as well as the intermediates leading to it were anomeric mixtures and describe the preparation of anomerically pure, crystalline methyl 2-*O*-methyl--α-D-glucopyranoside (*III*) and methyl 2-*O*-methyl-β-D-glucopyranoside (*IV*). The synthesis of the hitherto unknown methyl 2,4,6-tri-*O*-methyl-α-D-glucopyranoside (*IX*) is also described.

## Experimental

Melting points were determined on a Kofler hot stage. Optical rotations were measured with JASCO ORD/UV-5 Spectrometer.

Thin-layer chromatography (TLC) on Silica gel G coated glass slides (4.5 × 12 cm) and preparative column chromatography on silica gel (0.05—0.1 mm) was carried out using: A. benzene—ethyl acetate 6 : 1, B. benzene—ethyl acetate 10 : 1, C. chloroform—methanol 6 : 1, D. hexane—ethyl acetate 4 : 1, and E. chloroform—acetone 9 : 2.

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*For Part IX see Ref. [1a].

The solvent ratios are based on volumes. The components were located by spraying with 5% sulfuric acid in ethanol and heating until permanent char spots were visible. Dry 1,2-dimethoxyethane [5] stored over sodium hydride was used throughout. Evaporations were done under diminished pressure on a rotary evaporator at $< 40°C$.

### -Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-methyl-α- and -β-D-glucopyranoside (I and II)

To an ice-cold solution of "methyl 3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside" (m.p. $172-174°C$ [2] (10 g)) in 1,2-dimethoxyethane (100 ml) sodium hydride (1.3 g) was added and the mixture was magnetically stirred, with the exclusion of atmospheric moisture and carbon dioxide for twenty minutes. With continued stirring methyl iodide (5 ml) was added and after 30 minutes TLC (system A) showed complete conversion of the starting material ($R_F$ 0.3) into two products ($R_F$ 0.5 and 0.7) of which the slower moving predominated. The reaction mixture was poured into ten volumes of water and the precipitated solid was filtered, dissolved in chloroform, the chloroform solution was washed with water, dried (anhydrous sodium sulfate), and concentrated. The crystalline residue was dissolved in a minimum of benzene and chromatographed on a column of silica gel (80 × 4.5 cm) using system B.

The faster moving component was methyl 3-O-benzyl-4,6-O-benzylidene-2-O-methyl--β-D-glucopyranoside II (1.1 g, 10.3%). Crystallization from ethanol gave material melting at $127.5-129°C$ and having $[\alpha]_D^{24}$ $-80°$ ($c = 1$, chloroform).

For $C_{22}H_{26}O_6$ (386.43) calculated: 68.37% C, 6.78% H, 16.06% $CH_3O$; found: 68.40% C, 6.74% H, 16.14% $CH_3O$.

The slower moving component was methyl 3-O-benzyl-4,6-O-benzylidene-2-O-methyl--α-D-glucopyranoside I (4.5 g, 37.5%). After recrystallization from ethanol I had m.p. $112-113°C$ and $[\alpha]_D^{24}$ $+31°$ ($c = 1.03$, chloroform) and $[\alpha]_D^{24}$ $+36.6°$ ($c = 1.16$, ethanol). Ref. [2] gives m.p. $103-104°C$ and $[\alpha]_D^{23}$ $+16.7°$ ($c = 1.5$, ethanol).

Found: 68.48% C, 6.86% H, 15.94% $CH_3O$.

An intermediate mixed fraction was also obtained.

### Methyl 2-O-methyl-α-D-glucopyranoside (III)

A solution of methyl 3-O-benzyl-4,6-O-benzylidene-2-O-methyl-α-D-glucopyranoside (3 g) in 1,2-dimethoxyethane (30 ml) was added with stirring into a mixture of liquid ammonia (200 ml) and 1,2-dimethoxyethane (10 ml). With continued stirring sodium (1.1 g) cut into small pieces was added and when an intense blue colour developed, indicating that the reaction was complete, the reaction mixture was worked up in the usual manner. The syrup containing a single charring component ($R_F$ 0.35, system C, cf. 0.95 for the starting material) spontaneously crystallized (1.6 g, ~100%). Recrystallization of the crude product from methyl ethyl ketone gave pure III melting at $147--148°C$ and having $[\alpha]_D^{24}$ $+162.2°$ ($c = 1.01$, water). Ref. [3] gives m.p. $147-148°C$ and $[\alpha]_D^{19}$ $+155°$ ($c = 0.7$, water).

### Methyl 2-O-methyl-β-D-glucopyranoside (IV)

Simultaneous debenzylation and debenzylidenation of II (2.2 g) under the above--described conditions afforded a syrup (1.1 g, 93.2%) containing a single charring component ($R_F$ 0.35, system C, cf. 0.95 for the starting material) which solidified on standing.

Crystallization from methyl acetate and recrystallization from methyl ethyl ketone gave pure *IV* of m.p. 96.5—97.5°C and $[\alpha]_D^{26}$ −36.4° (c = 5.0, water). Ref. [6] gives m.p. 97—98°C and $[\alpha]_D$ −37.5° (c = 5.04, water).

### Methyl 2-O-acetyl-3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (V)

"Methyl 3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside" (m.p. 172—174°C) [2] (3.7 g) was acetylated in pyridine (10 ml) with acetic anhydride (6 ml) in the usual manner. TLC of the reaction mixture in the solvent system D revealed the presence of two products ($R_F$ 0.2 and 0.3) of which the faster moving predominated. The product was isolated and since TLC showed that recrystallization did not give an anomerically pure product the crude material was chromatographed on a silica gel column (50 × 3 cm) which gave 1.7 g (41%) of the faster moving component. Crystallization from ethanol afforded pure *V*, m.p. 94.5—95.5°C and $[\alpha]_D^{24}$ +87.2° (c = 1.07, chloroform).

For $C_{23}H_{26}O_7$ (414.14) calculated: 66.65% C, 6.32% H, 7.48% $CH_3O$; found: 66.65% C, 6.23% H, 7.36% $CH_3O$.

### Methyl 3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (VI)

The acetate *V* (1 g) was deacetylated in dry methanol (50 ml) with a catalytic amount of sodium methoxide which, after usual work-up, gave pure *VI*, (0.85 g, 94%), m.p. 186.5—187.5°C (from ethanol), $[\alpha]_D^{24}$ +49.6° (c = 1.02, methanol), $[\alpha]_D^{24}$ +83.6° (c = 0.92, chloroform). Ref. [2] gives m.p. 172—174°C and $[\alpha]_D^{23}$ +30.4° (c = 1.1, methanol).

Methylation of *VI* gave a single product moving at the same rate and having physical constants identical with *I*.

### Methyl 3-O-benzyl-2-O-methyl-α-D-glucopyranoside (VII)

The fully substituted derivative *I* (2.5 g) was dissolved in acetic acid (12.5 ml) and heated in a boiling water bath for 15 min at which time the concentration of the acetic acid was adjusted to 60% by addition of water. After 45 minutes of continued heating TLC (system E) showed complete disappearance of the starting material ($R_F$ 0.8) and formation of one major product ($R_F$ 0.2). The solution was concentrated and the resulting syrup was eluted from a silica gel column (20 × 2 cm) with the solvent system E to give a chromatographically homogeneous syrup (1.65 g, 83%) having $[\alpha]_D^{24}$ +76.2° (c = 0.99, chloroform).

For $C_{15}H_{22}O_6$ (298.33) calculated: 60.39% C, 7.43% H, 20.81% $CH_3O$; found: 60.30% C, 7.52% H, 21.12% $CH_3O$.

### Methyl 3-O-benzyl-2,4,6-tri-O-methyl-α-D-glucopyranoside (VIII)

Compound *VII* (1.2 g) was dissolved in 1,2-dimethoxyethane (12 ml), cooled in an ice bath and sodium hydride (0.4 g) was added. The mixture was magnetically stirred, with atmospheric moisture and carbon dioxide excluded, for twenty minutes; then methyl iodide (1.56 ml) was added and the stirring was continued for additional thirty minutes. TLC (system E) then showed that the reaction was complete and one product was detected ($R_F$ 0.8, cf. 0.2 for the starting material). Ice water was added and the organic solvent with the excess of methyl iodide was evaporated. The separated oil was combined with the chloroform extract of the water layer and the chloroform solution was washed

with water, dried and concentrated to give a chromatographically pure syrup (1.3 g, 100%). Vacuum distillation (b.p. 134—136°C/0.02 torr) afforded pure *VIII* which could not be induced to crystallize. $[\alpha]_D^{24}$ +100.4° (c = 1.15, chloroform).

For $C_{17}H_{26}O_6$ (326.20) calculated: 62.54% C, 8.03% H, 38.04% CH₃O; found: 62.35% C, 7.99% H, 38.17% CH₃O.

### Methyl 2,4,6-tri-O-methyl-α-D-glucopyranoside (IX)

The methylated product *VIII* (1 g) was dissolved in methanol (50 ml) and hydrogenated in the presence of palladium on charcoal catalyst (0.1 g, Koch-Kight Laboratories, Ltd.) at room temperature. Hydrogenation was complete in about 30—40 min, as shown by TLC in solvent E, and the product ($R_F$ 0.4, cf. 0.8 for the starting material) was isolated by filtration through a Celite pad and concentration as a syrup (0.65 g, 95%). Vacuum distillation (b.p. 96—97°C/0.03 torr) gave pure *IX* having $[\alpha]_D^{24}$ +158.9° (c = 1.03, chloroform). The colourless oil could not be induced to crystallize.

For $C_{10}H_{20}O_6$ (236.16) calculated: 58.82% C, 8.53% H, 52.54% CH₃O; found: 59.0% C, 8.58% H, 52.54% CH₃O.

### Discussion

Methyl 2-O-methyl-α-D-glucopyranoside has been previously obtained by *Haworth et al.* [3] by deacetylation of the major product of methylation of methyl 2,3,4-tri-O--acetyl-α-D-glucopyranoside with methyl iodide and silver oxide. The triacetate of *III* was formed here as a result of the migration of the acetyl group from the $C_2$—OH to the $C_6$—OH position during the methylation process. As a possible source of *III* could serve also methyl 4,6-O-benzylidene-2-O-methyl-α-D-glucopyranoside which has been as the only crystalline product isolated from the products of partial methylation of methyl 4,6-O-benzylidene-α-D-glucopyranoside [4]. *Hashimoto et al.* [2] have reported on the preparation of methyl 3-O-benzyl-4,6-O-benzylidene-2-O-methyl-α-D-glucopyranoside (m.p. 103—104°C, $[\alpha]_D$ +16.7°) by the following sequence: 1,2 : 5,6-di-O-isopropylidene--3-O-benzyl-D-glucofuranose was first methanolyzed, the obtained syrupy mixture of methyl glycosides was benzylidenated and the isolated crystalline "methyl 3-O-benzyl--4,6-O-benzylidine-α-D-glucopyranoside" was methylated. Since in this procedure methylation was applied to a derivative having all hydroxyl groups, except the one at $C_2$, blocked with radicals known to be stable under usual conditions of methylation we have considered this procedure the most suitable for obtaining an authentic sample on methyl 2-O-methyl-α-D-glucopyranoside. Following this sequence we obtained a crystalline material whose physical constants agreed with the given values for methyl 3-O-benzyl--4,6-O-benzylidene-α-D-glucopyranoside of the Japanese workers [2]. Methylation of this product, as shown by TLC, gave, however, two products which we separated by silica gel chromatography. The faster moving component was methyl 3-O-benzyl-4,6-O--benzylidene-2-O-methyl-β-D-glucopyranoside *II* (m.p. 127.5—129°C, $[\alpha]_D^{24}$ −80°) and the slower moving component was methyl 3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside *I* (m.p. 112—113°C, $[\alpha]_D^{24}$ +36.6°). Removal of the blocking groups from the isolated anomers readily afforded crystalline methyl 2-O-methyl-α-D-glucopyranoside *III* and methyl 2-O-methyl-β-D-glucopyranoside *IV* whose physical constants compared very well with those reported earlier [3, 6]. It is evident from the presented results, that the compounds described by *Hashimoto et al.* [2] as methyl 3-O-benzyl-4,6-O-benzylidene--α-D-glucopyranoside and methyl 3-O-benzyl-4,6-O-benzylidene-2-O-methyl-α-D-gluco--

pyranoside as well as their syrupy methyl 2-$O$-methyl-$\alpha$-D-glucopyranoside were anomeric mixtures.

To find the correct physical constants of methyl 3-$O$-benzyl-4,6-$O$-benzylidene-$\alpha$-D--glucopyranoside attempts were made to obtain this compound in an anomerically pure state. Since recrystallization did not much change the situation (a product of which the melting point and the optical rotation would not change on further recrystallization and which on methylation would give a single product could not be obtained), the anomeric mixture (m.p. 172—174°C) was acetylated and methyl 2-$O$-acetyl-3-$O$-benzyl-4,6--$O$-benzylidene-$\beta$-D-glucopyranoside was from the produced acetates removed by silica gel chromatography. The isolated methyl 2-$O$-acetyl-3-$O$-benzyl-4,6-$O$-benzylidene-$\alpha$-D-

1. $(CH_3)_2CO$, $H^+$, $CuSO_4$
2. BzCl, KOH
3. MeOH, $H^+$
4. PhCHO, $ZnCl_2$

D-Glucose $\longrightarrow$

|  | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ |
|---|---|---|---|---|---|---|
| I | OMe | H | Me | Bz | —Be— | |
| II | H | OMe | Me | Bz | —Be— | |
| III | OMe | H | Me | H | H | H |
| IV | H | OMe | Me | H | H | H |
| V | OMe | H | Ac | Bz | —Be— | |
| VI | OMe | H | H | Bz | —Be— | |
| VII | OMe | H | Me | Bz | H | H |
| VIII | OMe | H | Me | Bz | Me | Me |
| IX | OMe | H | Me | H | Me | Me |
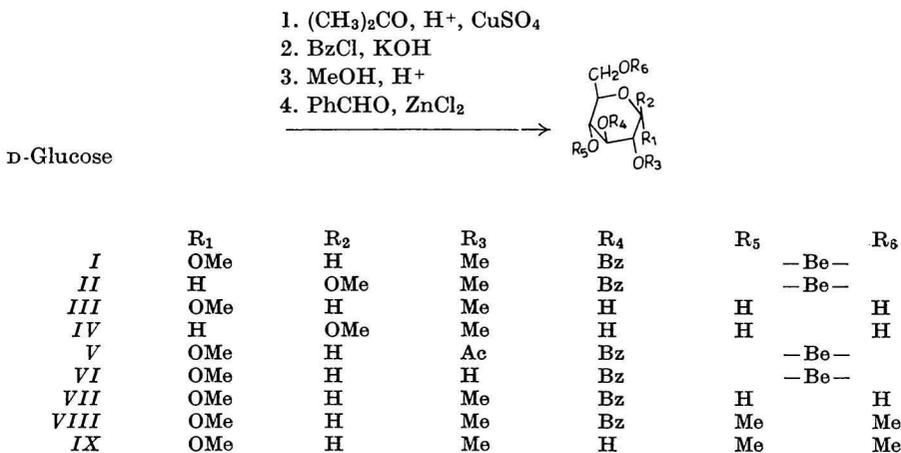
Ac — acetyl, Be — benzylidene, Bz — benzyl, Me — methyl, Ph — phenyl.

-glucopyranoside $V$ was deacetylated to give pure methyl 3-$O$-benzyl-4,6-$O$-benzylidene--$\alpha$-D-glucopyranoside $VI$. It is worth mentioning that while a mixture of methyl 3-$O$--benzyl-4,6-$O$-benzylidene-$\alpha$- and -$\beta$-D-glucopyranosides gives on TLC on silica gel one spot the 2-$O$-acetates and 2-$O$-methyl ethers of these compounds can be independently visible. Of the two 2-$O$-methyl derivatives the $\beta$-anomer is the faster moving component; the mobility of the two 2-$O$-acetates is reversed. Thus obtained methyl 3-$O$-benzyl-4,6--$O$-benzylidene-$\alpha$-D-glucopyranoside $VI$ has m.p. 186.5—187.5°C and $[\alpha]_D^{24}$ +49.6° and +83.6° taken in methanol and chloroform, respectively. Due to low solubility of $VI$ in alcohols we consider chloroform a better solvent for optical rotation measurements of this particular substance.

The physical constants of thus obtained $VI$ do not change on further recrystallization and its methylation gives one product undistinguishable from the slower moving component given rise to by methylation of "methyl 3-$O$-benzyl-4,6-$O$-benzylidene-$\alpha$-D-glucopyranoside" of the Japanese workers [2].

# References

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