HYDROGENOLYTIC CLEAVAGE OF METHYL 4,6-O-(4-METHOXYBENZYLIDENE)-α-D-GLUCOPYRANOSIDE WITH $LiAlH_4$–$AlCl_3$

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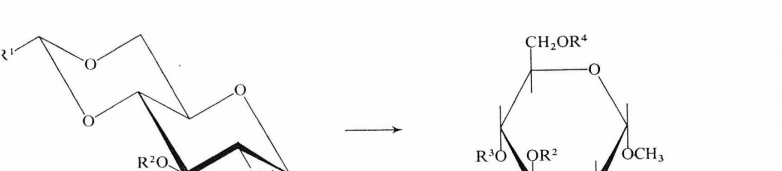
The title reaction leads to 4-O-(4-methoxybenzylidene) derivative and its 6-O isomer in a 3 : 2 ratio. Hydrogenolysis of 4,6-O-(4-methoxybenzylidene)-2,3-di-O-methyl-α-D-glucopyranoside (*IX*) was found to be regiospecific. Stability of the prepared 4-O- and 6-O-(4-methoxybenzyl) ethers towards acid catalyzed hydrolysis was examined.

The reductive cleavage of 1,3-dioxane derivatives with $LiAlH_4$–$AlCl_3$ was applied for preparation of some ethers of saccharides from the corresponding acetals[1-3]. This paper deals with a hydrogenolytic cleavage of acetals for preparation of 4-O- and 6-O-(4-methoxybenzyl) and also 4-O- and 6-O-benzyl ethers of methyl-α-D--glucopyranoside as model substances for an α-ether type of lignin–polysaccharide linkages in wood.

Methyl 4,6-O-benzylidene-α-D-glucopyranoside (*I*) gave, upon reaction with $LiAlH_4$—$AlCl_3$ and subsequent separation by column chromatography over silica gel, 4-O- and 6-O-benzyl derivatives in the respective 27 and 18% yields. The predicted structure was completely confirmed by periodate oxidation and by ^{1}H-NMR spectral evidence for crystalline 4-O- (*II*) and syrupy 6-O-benzyl-α-D-glucopyranoside (*III*). The above-mentioned reaction was already applied[1] to cleave *I*, nevertheless the corresponding ethers *II* and *III* have not been isolated. The reductive cleavage of methyl 4,6-O-(4-methoxybenzylidene)-α-D-glucopyranoside (*IV*) with $LiAlH_4$–$AlCl_3$ followed by fractional crystallization of products furnished crystalline 4-O-(*V*) and syrupy 6-O-(4-methoxybenzyl) derivative (*VI*) in 48 and 32% yields, respectively. The structure of both derivatives was verified after their methylation on the basis of chemical shifts of methyl groups in ^{1}H-NMR spectra[2] of the corresponding 4-O-(4-methoxybenzyl)-2,3,6-tri-O-methyl (*VII*) and 6-O-(4-methoxybenzyl)-2,3,4-tri--O-methyl (*VIII*) derivatives of methyl α-D-glucopyranoside. Acetylation of *V* and *VI* with acetic anhydride in pyridine afforded the proper triacetates *XI* and *XII*. The greater reactivity of *IV* with $LiAlH_4$—$AlCl_3$, when compared with *I*, could be rationalized by the electron-donating effect of the 4-methoxyphenyl group bound at $C_{(2)}$ of the 1,3-dioxane ring. The results are in accordance with those obtained

from the study of relation of the substituent effect on the rate of cleavage of substituted 1,3-dioxolanes[3]. A similarity between results of reductive cleavage and rates of acid catalyzed hydrolysis of acetals *I* and *IV* was observed[4].



I, $R^1 = C_6H_5$ $R^2 = R^3 = H$
IV, $R^1 = 4\text{-}CH_3OC_6H_4$ $R^2 = R^3 = H$
IX, $R^1 = 4\text{-}CH_3OC_6H_4$ $R^2 = R^3 = CH_3$

II, $R^1 = R^2 = R^4 = H$ $R^3 = C_6H_5CH_2$
III, $R^1 = R^2 = R^3 = H$ $R^4 = C_6H_5CH_2$
V, $R^1 = R^2 = R^4 = H$ $R^3 = 4\text{-}CH_3OC_6H_4CH_2$
VI, $R^1 = R^2 = R^3 = H$ $R^4 = 4\text{-}CH_3OC_6H_4CH_2$
VII, $R^1 = R^2 = R^4 = CH_3$ $R^3 = 4\text{-}CH_3OC_6H_4CH_2$
VIII, $R^1 = R^2 = R^3 = CH_3$ $R^4 = 4\text{-}CH_3OC_6H_4CH_2$
X, $R^1 = R^2 = CH^3$, $R^4 = H$ $R^3 = 4\text{-}CH_3OC_6H_4CH_2$
XI, $R^1 = R^2 = R^4 = CH_3CO$ $R^3 = 4\text{-}CH_3OC_6H_4CH_2$
XII, $R^1 = R^2 = R^3 = CH_3CO$ $R^4 = 4\text{-}CH_3OC_6H_4CH_2$

The preferred formation of 4-O-over the 6-O derivative in a 3 : 2 ratio under conditions of hydrolytic cleavage of both acetals *I* and *IV* is likely due to an easier accessibility of the attacking reagent to the lone electron pair at oxygen O-6 than to that of O-4. The ratio of the formed 4-O and 6-O-(4-methoxybenzyl) ethers was substantially changed when *IV* was replaced by 4,6-O-(4-methoxybenzylidene)-2,3-di-O-methyl-α-D-glucopyranoside (*IX*). Thus, methyl 4-O-(4-methoxybenzyl)-2,3-di-O-methyl-α-D-glucopyranoside (*X*) was isolated in a 92% yield, whereas the corresponding 6-O-ether was not found to be present. Evidently, the fragmentation pathway of 4,6-O-(4-methoxybenzylidene) ring is influenced by the presence of a methoxyl group at $C_{(3)}$ of the pyran ring, which hinders the access of the reagent to the electron pair at O-4. A similar regiospecificity of the ring cleavage was reported[5] for some 3-O-benzyl and 2,3-di-O-benzyl-4,6-O-benzylidenehexopyranoside derivatives.

As generally known, benzyl ethers of saccharides are considerably resistant towards acid catalyzed hydrolysis. The influence of *para*-methoxyl group on the rate of hydrolysis of benzyl ethers has so far not been studied. It was, therefore, interesting to investigate the stability of the synthesized 4-methoxybenzyl ethers towards acid catalyzed hydrolysis. Results from kinetic study of hydrolysis of *V* and *VI* showed both

ethers to be hydrolyzed under a relatively mild conditions (0·1M-HCl, 60°C) at like rates ($k_{(VI)} = (2{\cdot}8 \pm 0{\cdot}5) \cdot 10^{-3}$ min^{-1}, $k_{(IV)} = (2{\cdot}5 \pm 0{\cdot}5) \cdot 10^{-3}$ min^{-1}). The observed relatively low stability of 4-methoxybenzyl ethers towards acid catalyzed hydrolysis under conditions at which the glycosidic group does not undergo hydrolysis is associated with a polar effect of the methoxyl group in *para*-position to the benzyl ether bond.

EXPERIMENTAL

Melting points determined on a Kofler micro hot-stage are uncorrected. Optical rotations of chloroform solutions were measured with a Perkin-Elmer polarimeter, model 141, at c 1. The ^{1}H-NMR spectra recorded on a Tesla BS-487 instrument at 80 MHz in deuteriochloroform (unless stated otherwise) are given in ppm on the δ scale. Thin layer chromatography refers to silica gel Merck PF_{254} and column chromatography to silica gel Merck (0·063—0·1 mm) in a solvent system A chloroform–2-propanone 3 : 1 and B chloroform–2-propanone 5 : 1.

Kinetic hydrolyses of ethers were monitored with an automatic polarimeter Perkin–Elmer, model 141, in a tempered quartz cell at 60° (±0·1) using the substrate (1%) dissolved in 0·1M-HCl in ethanol–water (1 : 1). The product of hydrolysis (methyl α-D-glucopyranoside) was stable during experiments. The rate constants were calculated from the first order equation

$$k_{obs} = \frac{2{\cdot}3}{t} \cdot \log \frac{(\alpha_0 - \alpha_\infty)}{(\alpha_t - \alpha_\infty)},$$

where α_t, α_0, α_∞ are the optical rotations of solution at time t at the beginning and at the end of the experiment. The relationship $\ln (\alpha_t - \alpha_\infty) = f(t)$ was linear.

Reaction of Methyl 4,6-O-Benzylidene-α-D-glucopyranoside (*I*) with $LiAlH_4$—$AlCl_3$

Substance *I* (ref.[6]) was reacted with $LiAlH_4$ according to[1]. The crude reaction product was separated on a silica gel column (solvemt system A) to give fractions identified as methyl 4-O-benzyl-α-D-glucopyranoside (*II*, 27%) and methyl 6-O-benzyl-α-D-glucopyranoside (*III*, 18%).

II: m.p. 124—125°C, $[\alpha]_D^{20}$ +156, ^{1}H-NMR (hexadeuterio–2-propanone): 7·05—7·50 (ss, 5 H, aromatic protons), 4·50—4·70 (m, 2 H, benzyl), 4·50—4·00 (m, H-2,3,4,5,6,6'), 3·35 (s, CH_3O-1), 2·90 (s, H, OH). For $C_{14}H_{20}O_6$ (284·3) calculated: 59·14% C, 7·09% H; found: 59·05% C, 7·00% H.

III: Syrup, $[\alpha]_D^{20}$ +96. ^{1}H-NMR (deuteriochloroform–hexadeuteriodimethyl sulphoxide): 7·15—7·50 (ss, 5 H, aromatic protons), 4·40—4·92 (m, H-1, benzyl), 3·30—4·00 (m, H-2,3,4,5,6,6'), 3·38 (s, CH_3O-1), 2·55 (s, OH). For $C_{14}H_{20}O_6$ (284·3) calculated: 59·14% C. 7·09% H; found: 59·18% C, 7·12% H.

Methyl 4-O-(4-Methoxybenzyl)-α-D-glucopyranoside (*V*) and Methyl 6-O-(4-Methoxybenzyl)-α-D-glucopyranoside (*VI*)

Compound *IV* (ref.[7]) was hydrogenolyzed by procedure described for *I*. The reaction compound contained constituents of R_F 0·14 and 0·16 (B). The crude reaction product crystallizing from a mixture 2-propanone–chloroform (1 : 3, 200 ml) afforded substance *V* in a 48% yield; m.p.

125—126°C, $[\alpha]_D^{20}$ +138. ^{1}H-NMR (hexadeuterio-2-propanone): 6·75—7·40 (ss, 4 H, aromatic protons), 4·49 (s, 2 H, benzyl), 4·65 (d, H-1), 3·30—4·00 (m, H-2,3,4,5,6,6′), 3·75 (s, CH_3O), 3·38 (s, CH_3O-1). For $C_{15}H_{22}O_7$ (314·4) calculated: 57·31% C, 7·05% H; found: 57·14% C, 6·95% H.

Mother liquor was thickened and the syrupy residue was separated on a silica gel column in the solvent system B. Collection and work-up of the appropriate fractions gave syrup *VI* (32%), $[\alpha]_D^{20}$ +71. ^{1}H-NMR (deuteriochloroform–hexadeuteriodimethyl sulphoxide): 6·75 to 7·41 (sss, 4 H, aromatic protons), 4·45—5·00 (m, H-1, benzyl), 3·30—4·00 (m, H-2,3,4,5,6,6′), 3·75 (s, CH_3O), 3·35 (s, CH_3O-1), 2·55 (s, OH). For $C_{15}H_{22}O_7$ (314·4) calculated: 57·31% C, 7·05% H; found: 57·61% C, 6·98% H.

Methyl 4-O-(4-Methoxybenzyl)-2,3,6-tri-O-methyl-α-D-glucopyranoside (*VII*)

Treatment of *V* with methyl iodide and silver oxide in N,N-dimethylformamide furnished the syrupy *VII* in a 82% yield. $[\alpha]_D^{20}$ +68. ^{1}H-NMR: 6·75—7·40 (ss, 4 H, aromatic protons), 4·49 (s, 2 H, 4-methoxybenzyl), 4·65 (d, H-1), 3·30—4·00 (m, H-2,3,4,5,6,6′), 3·75 (s, CH_3O), 3·64 (s, CH_3O-3), 3·50 (s, CH_3O-2), 3·35 (s, CH_3O-1), 3·33 (s, CH_3O-6). For $C_{18}H_{28}O_7$ (356·5) calculated: 60·65% C, 7·91% H; found: 60·59% C, 7·87% H.

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

The syrupy *VIII* was obtained from *VI* in a 78% yield by procedure described for *VII*. $[\alpha]_D^{20}$ +112. ^{1}H-NMR: 6·75—7·41 (ss, 4 H, aromatic protons), 4·45—5·00 (m, H-1, 4-methoxybenzyl), 3·30—4·00 (m, H-2,3,4,5,6,6′), 3·75 (s, CH_3O), 3·64 (s, CH_3O-3), 3·50 (s, CH_3O-2), 3·35 (s, CH_3O-1), 3·57 (s, CH_3O-4). For $C_{18}H_{28}O_7$ (356·5) calculated: 60·65% C, 7·91% H; found: 60·70% C, 7·85% H.

Methyl 4-O-(4-Methoxybenzyl-(2,3-4-di-O-methyl-α-D-glucopyranoside (*X*)

Compound *IX* (ref.[7]) was hydrogenolyzed by procedure given for *II*. The syrupy product solidified on prolonged time and melted at 37—38°C, $[\alpha]_D^{20}$ +68. ^{1}H-NMR: 6·75—7·40 (ss, 4 H, aromatic protons), 4·49 (s, 2 H, 4-methoxybenzyl), 4·65 (d, H-1), 3·30—4·00 (m, H-2,3,4,5,6,6′), 3·40 (s, CH_3O-1), 3·50 (s, CH_3O-2), 3·64 (s, CH_3O-3), 3·78 (s, CH_3O). For $C_{17}H_{26}O_7$ (342·5) calculated: 59·63% C, 7·65% H; 59·50% C, 7·70% H.

Methyl 2,3,6-Tri-O-acetyl-4-O-(4-methoxybenzyl)-α-D-glucopyranoside (*XI*)

Esterification of *V* with acetic anhydride–pyridine gave the syrupy *XI* in a 98% yield. $[\alpha]_D^{20}$ +99. ^{1}H-NMR: 6·75—7·40 (ss, 4 H, aromatic protons), 4·20—4·60 (m, 2 H, 4-methoxybenzyl), 4·75 to 5·20 (m, H-1,2), 5·45 (t, H-3), 3·28—4·00 (m, H-3,4,5,6,6′), 3·78 (s, CH_3O), 3·38 (s, CH_3O-1), 2·07, 2·06, 1·90 (ss, CH_3COO-2, CH_3COO-3, CH_3COO-6). For $C_{21}H_{28}O_{10}$ (440·5) calculated: 57·26% C, 6·40% H; found: 57·40% C, 6·38% H.

Methyl 2,3,4-Tri-O-acetyl-6-O-(4-methoxybenzyl)-α-D-glucopyranoside (*XII*)

Acetylation of *VI* by the procedure described with *XI* gave the syrupy *XII* in a 95% yield. $[\alpha]_D^{20}$ +97. ^{1}H-NMR: 6·75—7·40 (ss, 4 H, aromatic protons), 4·20—4·60 (m, 2 H, 4-methoxybenzyl), 4·70—5·00 (m, H-1,2), 5·55 (t, H-3), 3·30—4·00 (m, H-4,5,6,6′), 3·78 (s, CH_3O), 3·38 (s, CH_3O-1),

2·00; 2·02; 2·05; 3 s, CH_3COO-2, CH_3COO-3, CH_3COO-4). For $C_{21}H_{28}O_{10}$ (440·5) calculated: 57·26% C, 6·40% H; found: 57·22% C, 6·33% H.

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