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HYDROGENOLYSIS OF 3,5-O-BENZYLIDENE ACETALS WITH THE $LiAlH_4$-$AlCl_3$ REAGENT IN METHYL D-XYLOFURANOSIDES

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Abstract—The hydrogenolysis of methyl 3,5-O-benzylidene-α- and -β-D-xylofuranoside derivatives with the $LiAlH_4$–$AlCl_3$ reagent gave 5-benzyl ethers as main products. In some cases the attack of the reagent occured at the ring oxygen of the furanoside skeleton to yield 5-O-benzyl-1-O-methylxylitol derivatives. The structure of the synthesized compounds was proved by ^{13}C-NMR spectroscopy. Unambiguous assignment of lines in the ^{13}C-NMR spectra of numerous partially methylated methyl α-and β-D-xylofuranoside derivatives has been made.

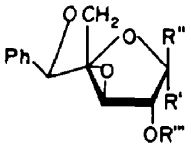
Benzylidene acetals of carbohydrates are useful starting materials for the synthesis of partially benzylated sugars. We have shown previously[1,2] that these important synthetic intermediates can be conveniently obtained by the use of the $LiAlH_4$–$AlCl_3$ reagent to cleave the acetal ring of the benzylidene acetals. In the case of 4,6-O-benzylilidene hexopyranosides[1] the direction of the ring opening reaction depends on the bulkyness of the C-3 substituent and by the steric exo- or endo-arrangement of the phenyl group in the used dioxolane-type benzylidene[2] derivatives. In all reactions investigated so far, the sugar derivatives were pyranosides: the dioxane rings were fused in 4,6-position, and the dioxolane rings were coupled in cis arrangement. In order to investigate the direction of the cleavage of dioxane-type benzylidene acetals in pentofuranosides methyl 3,5-O-benzylidene-α- (**1**) and -β-D-xylofuranoside (**2**), their 2-O-methyl (**3** and **4**) and 2-O-benzyl derivatives (**5** and **6**) were reacted with $LiAlH_4$–$AlCl_3$ reagent.

RESULTS AND DISCUSSION

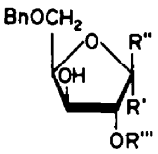
Compounds **1-4** were synthesized proviously;[3] conventional benzylation[4] of **1** and **2** gave **5** and **6**, respectively. The hydrogenolyses were carried out as reported earlier.[1] By monitoring the reactions by thin layer chromatography the following observations have been made. After 15–20 min the starting materials disappeared completely and in the case of compounds **3**, **4** and **6** the reaction mixtures contained one main product. The amount of minor products, detected by tlc and glc, was below 3–5% in all cases. That the main products (**9**, **10** and **12**) were 5-benzyl ethers with free OH group at the position 3, was proved by chemical and ^{13}C-NMR spectroscopic methods. To aid the analysis of ^{13}C-NMR spectra of the products, spectra of several methyl O-methyl-α- and -β-D-xylofuranosides[5–7] have been measured. Compared with the situation in the spectra of the methyl α-and β-D-xylofuranosides (Table), in the ^{13}C-NMR spectra of compounds **9**, **10** and **12** the C-2 and C-5 signals were shifted strongly downfield and the spectra were very similar to those of the respective methyl 2,5-di-O-methyl-α- and -β-D-xylofuranosides. The disappearence of the benzylidene groups was obvious from ^1H- and ^{13}C-NMR spectral data.

The hydrogeneolysis of compound **1** apparently resulted (tlc) again in one main product (**7**). Purification by column chromatography, to remove minor by-products, gave chromatographically homogeneous material that consumed 0.8 mole/mole of periodate calculated on the basis of **7**, without liberation of any formic acid. Examination of the oxidized reaction mixture by tlc showed that 10–15% of the starting material had not reacted. This quantity remained unchanged after prolonged reaction time (96 hr) and also in the presence of a large excess of $NaIO_4$ (4 molar proportion). Spectroscopic investigation of the tlc-homogeneous material showed that it contained about 10–15% of the 3-O-benzyl isomer (**15**). The mixture of **7** and **15** could not be separated by either tlc or glc. A comparison of the ^{13}C-NMR spectra of compound **7** and **15** showed characteristic differences: the signals for C-5 in compound **7** and **15** appeared at 69.3 and 61.9 ppm, respectively. In the case of **15** C-3 resonated at lowest field (83.9 ppm) and the spectrum showed characteristics similar to those found in the spectrum of methyl 3-O-methyl-α-D-xylofuranoside.

Compounds **2** and **5** reacted in an unexpected manner when treated with the $LiAlH_4$–$AlCl_3$ reagent. In both cases two products were formed in comparable quantities, they had different R_f-values (tlc) and produced different colours on charring with sulphuric acid. The compounds with the faster chromatographic mobility, giving black colour, proved to be the expected 5-O-benzyl derivatives (**8** and **11**). The ^1H- and ^{13}C-NMR spectra of compounds showing lower R_f-values and red colour did not contain anomeric proton and anomeric carbon signals. These findings and the very low $[\alpha]_D$ value of the substances suggested, that they were alditol

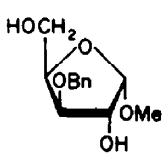


1: R′ = OMe, R″ = R‴ = H
2: R′ = R‴ = H, R″ = OMe
3: R″ = OMe, R‴ = H, R‴ = Me
4: R′ = H, R″ = OMe, R‴ = Me
5: R′ = OMe, R″ = H, R‴ = Bn
6: R′ = H, R″ = OMe, R‴ = Bn



7: R′ = OMe, R″ = R‴ = H
8: R′ = R‴ = H, R″ = OMe
9: R′ = OMe, R″ = H, R‴ = Me
10: R′ = H, R″ = OMe, R‴ = Me
11: R′ = OMe, R″ = H, R‴ = Bn
12: R′ = H, R″ = OMe, R‴ = Bn

Me = methyl Bn = benzyl



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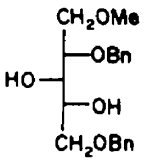

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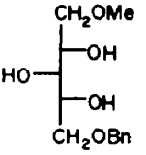

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derivatives, formed through the attack of the reagent on the furanoid ring oxygen atom. The assumed structures **13** and **14** were supported by the fact, that both compounds contained methyl groups (NMR), and that on periodic acid oxidation they consumed two molar proportions of the reagent, in the case of **14** with simultaneous liberation of formic acid. In the case of **13** the consumption of periodate was one mole per mole substrate, with no formic acid produced. It is noteworthy that we could not detect any 1,4-anhydro-xylitol derivatives in the reaction mixture, the formation of which would indicate the attack of the reagent on C-1 oxygen. Surprisingly, methyl 2,5-di-O-benzyl-α- or methyl 5-O-benzyl-β-D-xylofuranoside did not react with $LiAlH_4$–$AlCl_3$ reagent even on prolonged reaction time and elevated temperature. This observation suggests that the first step of the reaction leading to xylitol derivatives is the opening of the furanoid ring to give a 3,5-benzylidenexylitol derivatives, which subsequently react with the second mole of the reagent to give the end-products (**13** and **14**). Under the conditions applied the furanoid ring cleavage does not depend on the anomeric configuration. It is worth mentioning, in connection with this observation, that the hydrogenolysis of 2-alkoxy-tetrahydrofuran derivatives resulted in endo-ring cleaved products, whereas the 2-phenoxy-tetrahydrofuran derivatives gave exo-cleaved products.[8]

The analysis of ^{13}C-NMR spectra (Table) of the isolated products and of model compounds reveals important regularities. The formation of the dioxane ring (as in **1** and **2**) causes a very strong upfield shift of C-4, which is markedly stronger in the case of the β-anomer than in that of the α-anomer. Also, the formation of the acetal ring shifts the C-1 signal downfield by 2 ppm. As far as we know among the alkylated xylofuranoside derivatives only methyl 3-O-isopropyl-α and -β-D-xylofuranosides[9] were investigated by ^{13}C-NMR spectroscopy. This fact prompted us to record and analyze the ^{13}C-NMR spectra of methyl ethers of selected methyl α- and β-D-xylofuranosides. In accordance with Gorin's work[9] methylation results in a strong downfield shift (by 10–11 ppm) of the signal of the substituted ^{13}C nucleus (α-effect). The benzylation shifts amount to 6.6–8.3 ppm. In most cases, these alkylation shifts are accompanied by upfield shifts (by 1–2 ppm) of the signals of the adjacent carbon atoms (β-effects). The ^{13}C chemical shifts for the synthesized products and for the model compounds are summarised in Table.

EXPERIMENTAL

General. M.ps were determined on a Kofler hot-stage. TLC and column chromatography were performed on Kieselgel G; detection was effected by charring with sulphuric acid. Optical rotations were measured with a Perkin–Elmer 241 automatic polarimeter at room temperature. GLC was performed with a Hewlett–Packard 5830 A instrument and a column (s.s., 4 ft × 2.16 mm) packed with 10% of UCW 982 on Gas Chrom Q (80–100 mesh). The analyses were performed under the following conditions: injection port temperature, 275°; flame ionisation detector temperature, 300°; nitrogen flow-rate, 20 ml/min; for isothermal analyses the temperature is given in parentheses. ^{1}H-(for solutions in $CDCl_3$) and ^{13}C-NMR spectra (for solvents see Table) were obtained with JEOL MH-100 or Varian XL-100-15 F.T. instruments using Me_4Si as the internal standard.

The periodate oxidations were carried out at 4° in the dark. The periodate consumption was determined by Aspinall's method.[10] The formic acid production was measured by Smith's description.[11]

Methyl 2-O-benzyl-3,5-O-benzylidene-α-D-xylofuranoside (**5**)

Methyl 3,5-O-benzylidene-α-D-xylofuranoside **1** (2.52 g) was benzylated with benzyl chloride (10 ml) and powdered KOH (2 g). Crystallization of the product from ethanol (100 ml) gave **5** (3.35 g, 98%), m.p. 126–128°, $[\alpha]_D$ + 83.2° (c 0.63, chloroform), R_f 0.74 (dichloromethane–ethyl acetate, 9:1). ^{1}H-NMR data (δ, ppm): 7.40–7.20 (m, 10H, aromatic protons); 5.34 (s, 1H, Ph–C<u>H</u>); 5.20 (d, 1H, H-1; $J_{1,2}$ = 5 Hz); 4.64 (q, 2H, Ph–C<u>H</u>$_2$); 4.50–4.26 (m, 2H, H-2,3); 4.08 (m, 2H, H-5,5′); 4.10–3.90 (m, 1H, H-4); 3.46 (s, 3H, OMe-1). (Found: C, 70.69; H, 6.56. Calc. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48%).

Methyl 2-O-benzyl-3,5-O-benzylidene-β-D-xylofuranoside **6**

Methyl 3,5-O-benzylidene-β-D-xylofuranoside (**2**) (2.52 g) was benzylated as described for the preparation of **5**. Crystallization of the product from ethanol (22 ml) gave **6** (3.26 g; 95.3%), m.p. 80–81°, $[\alpha]_D$ − 29.7° (c 1.25, chloroform), R_f 0.87 (dichloromethane–acetone, 9:1). ^{1}H-NMR data (δ, ppm): 7.50–7.20 (m, 10H, aromatic protons); 5.36 (s, 1H, Ph–C<u>H</u>); 5.01 (s, 1H, H-1; $J_{1,2}$ = 1 Hz); 4.56 (s, 2H, Ph–C<u>H</u>$_2$); 4.46–3.94 (m, 5H, H-2,3,4,5,5′); 3.42 (s, 3H, OMe-1). (Found: C, 70.29; H, 6.59. Calc. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48%).

Methyl 5-O-benzyl-α-D-xylofuranoside (**7**)

Compound **1** (0.95 g; 3.76×10^{-3} mol) was hydrogenolyzed with $LiAlH_4$ (430 mg; 1.13×10^{-2} mol) and $AlCl_3$ (1.50 g; 1.13×10^{-2} mol) in 1:1 ether–dichloromethane (20 ml) for 15 min at room temperature. The reaction was terminated by addition of

Table 1. ^{13}C-NMR chemical shifts (δ) and coupling constants (Hz) of the model compounds and of the synthesized substances

Carbons	Methyl α-D-xylofuranosides													
		2-O-Me	3-O-Me	2,3-di-O-Me	2,5-di-O-Me	3,5-di-O-Me		1	7	15	9	11	13	14
C-1	102.8	100.5	102.9	100.3	100.8	102.2		104.2	102.0	101.8	100.8	100.9	72.7	74.2
$^1J_{CH}$	(174.4)	(170.7)										(169.5)		
C-2	77.5	87.7	77.1	86.7	87.7	76.8		76.2	77.2	77.5	87.9	85.3	79.1	71.6
C-3	75.8	75.2	86.0	84.3	74.8	85.9		81.4	76.9	83.9	75.5	75.3	70.4	71.2
C-4	79.0	77.2	78.0	77.0	76.6	77.1		71.8	78.4	77.9	76.4	76.2	71.4	71.6
C-5	61.2	61.8	61.5	62.1	72.0	71.5		67.3	69.3	61.9	69.5	69.5	71.9	71.8
OMe-1	56.3	55.1	55.4	55.0	55.1	55.5		56.5	55.5	55.5	55.2	55.1	59.2	59.1
OMe-2		58.3		58.6	58.3						58.3	72.5[+]	72.5[+]	
OMe-3			58.2	58.0		58.0				72.1[+]				
OMe-5					59.2	59.0		99.4[*]	73.6[+]		73.9[+]	73.7[+]	73.5[+]	73.6[+]
Carbons	Methyl β-D-xylofuranosides													
			3-O-Me	2,3-di-O-Me	2,5-di-O-Me		2,3,5-tri-O-Me	2	8		10	12		
C-1	109.6		109.8	107.8	109.9		107.9	111.2	108.9		107.0	107.2		
C-2	80.9		79.2	88.6	86.3		88.7	79.8	80.1		89.6	87.5		
C-3	76.0		87.0	84.9	78.7		84.4	80.2	76.7		74.9	75.7		
C-4	83.5		80.9	80.9	80.2		80.0	73.4	81.4		81.5	81.7		
C-5	62.1		62.2	62.0	72.3		72.2	67.4	69.8		69.6	69.6		
OMe-1	56.2		55.7	55.5	55.4		55.2	55.2	55.1		55.1	55.0		
OMe-2				57.6	58.4		57.5				57.5	72.0[+]		
OMe-3			58.5	58.3			58.1							
OMe-5					59.0		58.9	99.5[*]	73.5[+]		73.6[+]	73.6[+]		
Solvent	D_2O						$CDCl_3$							

*Chemical shifts of benzylidene carbons.
†δ-values of the CH_2 groups of C–O–CH_2–Ph moieties.

ethyl acetate (1 ml) and water (3 ml), the organic layer was decanted and washed with ether (2 × 20 ml). The combined solutions were washed with water (2 × 20 ml), dried (Na_2SO_4) and concentrated to give syrupy **7**. The crude product was chromatographed on a Kieselgel G (40 g) column using 9:1 dichloromethane–acetone as eluant, to give **7** (0.75 g, 78.9%), $[\alpha]_D$ +92.7° (c 1.33, chloroform), R_f 0.62 (dichloromethane–acetone, 85:15), R_T 4.12 min (225°). ^{13}C-NMR spectrum showed that **7** was contaminated with **15**.

Methyl 5-O-*benzyl*-β-D-*xylofuranoside* (**8**) *and* 5-O-*benzyl*-1-O-*methyl*-D-*xylitol* (**14**)

Compound **2** (1.89 g; 7.5×10^{-3} mol) was treated with $LiAlH_4$ (855 mg; 2.25×10^{-2} mol) and $AlCl_3$ (3.0 g; 2.25×10^{-2} mol) in 1:1 ether–dichloromethane (50 ml) for 10 min. TLC (85:15 dichloromethane–acetone) examination of the worked up syrup showed the presence of two major spots (R_f 0.48 and 0.36). Column chromatography of the crude product (1.65 g) on Kieselgel G (80 g) yielded two homogeneous components. The faster moving material proved to be **8** (795 mg, 42%), $[\alpha]_D$ −31.9° (c 0.37, chloroform), R_T 4.01 min (225°). The compound having lower R_f was **14** (630 mg, 33%), $[\alpha]_D$ −2.5° (c 0.92, chloroform), R_T 3.29 min (225°).

Methyl 5-O-*benzyl*-2-O-*methyl*-α-D-*xylofuranoside* (**9**)

Compound **3** (532 mg; 2×10^{-3} mol) was hydrogenolysed in the presence of $LiAlH_4$ (228 mg; 6×10^{-3} mol) and $AlCl_3$ (800 mg; 6×10^{-3} mol) in 1:1 ether–dichloromethane (20 ml). Conventional processing afforded, after purification by chromatography, **9** (430 mg; 80.2%), $[\alpha]_D$ +124.5° (c 1.3, chloroform), R_f 0.64 (dichloromethane–acetone, 9:1), R_T 3.95 min (225°). ^{1}H-NMR data (δ, ppm): 7.42–7.30 (m, 5H, aromatic protons); 4.96 (d, 1H, H-1; $J_{1,2}$ = 4.5 Hz); 4.56 (s, 2H, Ph–CH_2); 4.52–4.18 (m, 3H, H-2,3,4); 3.80–3.64 (m, 2H, H-5,5'); 3.46 (s, 3H, OMe-1); 3.40 (s, 3H, OMe-2); 3.23 (d, 1H, OH-3).

Methyl 5-O-*benzyl*-2-O-*methyl*-β-D-*xylofuranoside* (**10**)

Compound **4** (266 mg; 10^{-3} mol) was treated with $LiAlH_4$ (114 mg; 3×10^{-3} mol) and $AlCl_3$ (400 mg; 3×10^{-3} mol) in 1:1 ether–dichloromethane (10 ml). The yield of the produced **10** was 190 mg (70.8%), $[\alpha]_D$ −32.8° (c 1.54, chloroform), R_f 0.61 (dichloromethane–acetone, 9:1), R_T 3.69 min (225°). ^{1}H-NMR data (δ ppm): 7.45–7.30 (m, 5H, aromatic protons); 4.92 (s, 1H, H-1; $J_{1,2}$ = 1 Hz); 4.64 (q, 1H, H-2); 4.60 (s, 2H, Ph–CH_2); 4.40 (q, 1H, H-3); 4.21 (m, 1H, H-4); 3.72 (m, 2H, H-5,5'); 3.40 (s, 3H, OMe-1); 3.34 (s, 3H, OMe-2); 3.08 (d, 1H, OH-3).

Methyl 2,5-*di*-O-*benzyl*-α-D-*xylofuranoside* **11** *and* 2,5-*di*-O-*benzyl*-1-O-*methyl*-D-*xylitol* (**13**)

Compound **5** (1.71 g; 5×10^{-3} mol) was hydrogenolysed in 1:1 ether–dichloromethane (50 ml) with $LiAlH_4$ (570 mg: 1.5 × 10^{-2} mol) and $AlCl_3$ (2.0 g; 1.5×10^{-2} mol) at 40° for 15 min. TLC and GLC investigations showed the presence of two components, which were separated on a Kieselgel G column (150 g) using 9:1 dichloromethane–acetone as eluant. Eluted first was **11** (970 mg; 56.4%); m.p. 61° (from cyclohexane), $[\alpha]_D$ +89.3° (c 1.31, chloroform), R_f 0.51 (dichloromethane–acetone, 9:1), R_T 9.56 min (250°). ^{1}H-NMR data (δ, ppm): 7.38–7.26 (m, 10H, aromatic protons); 4.81 (d, 1H, H-1; $J_{1,2}$ = 4.7 Hz); 4.68 and 4.55 (2s, 4H, 2Ph–CH_2); 4.50 (q, 1H, H-2); 4.32 (m, 1H, H-4); 3.90 (q, 1H, H-3); 4.12 (m, 2H, H-5,5'); 3.36 (s, 3H, OMe-1); 3.08 (d, 1H, OH-3). (Found: C, 70.10; H, 6.98. Calc. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02%). Subsequently eluted was **13** (340 mg; 19.7%), syrup, $[\alpha]_D$ +25.4° (c 0.97, chloroform), R_f 0.30 (dichloromethane–acetone, 9:1), R_T 8.24 min (250°). ^{1}H-NMR data (δ, ppm): 7.40–7.20 (m, 10H, aromatic protons); 4.66 (q, 2H, Ph–CH_2–5); 4.48 (s, 2H, Ph–CH_2–2); 4.00–3.40 (m, 7H, skeleton protons); 3.32 (s, 3H, OMe-1); 3.04 (d, 2H, OH-3 and OH-4). (Found: C, 69.80; H, 7.68. Calc. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56%).

Methyl 2,5-*di*-O-*benzyl*-β-D-*xylofuranoside* (**12**)

Compound **6** (1.71 g) was allowed to react with the $LiAlH_4$–$AlCl_3$ reagent as described above for the preparation of **11**. TLC of the reaction mixture showed the presence of only one main product. Elution from a Kieselgel G column (120 g) with 9:1 dichloromethane–acetone furnished syrupy **12** (1.13 g; 65.7%), $[\alpha]_D$ −28.2° (c 1.41, chloroform), R_f 0.77 (dichloromethane–acetone, 9:1), R_T 9.35 min (250°).

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