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Note

The Koenigs–Knorr condensation of methyl 4,6-*O*-benzylidene-β-D-galactopyranoside with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide

ANDRZEJ TEMERIUSZ, JAN RADOMSKI, JANUSZ STĘPIŃSKI, AND BOGUSŁAWA PIEKARSKA
Department of Chemistry, University of Warsaw, Warsaw (Poland)
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Takeo *et al.*[1] have reported that the Koenigs–Knorr condensation of benzyl 4,6-*O*-benzylidene-β-D-galactopyranoside with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**1**) gave benzyl 4,6-*O*-benzylidene-2-*O*- (20%) and -3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-galactopyranoside (28%). Gorin[2] reported that a similar condensation of methyl 4,6-*O*-benzylidene-β-D-galactopyranoside (**2**) with **1** gave the β-(1→2)- and β-(1→3)-linked disaccharide derivatives in the ratio 2:3.

We have described[3,4] the condensation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**3**) or **1** and now report the condensation of **2** and **3**, in the presence of silver carbonate, Drierite, and 1,2-dichloromethane, under Koenigs–Knorr conditions. Crystalline methyl 4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-galactopyranoside (**4**, 29.9%) was isolated after reaction for 22 h together with 44.5% of **2**. When the molar proportion of **3** was increased (from 1:1 to 1:2) and the reaction time was extended to 44 h (see Experimental), the yield of **4** was increased to 39%. The non-crystalline products were debenzylidenated and deacetylated, and then fractionated on Dowex 1 (HO^-) resin. Eight fractions were obtained which were subjected to ^{13}C-n.m.r. and methylation analysis (modified Hakomori method[5]). More of the β-(1→3)-linked disaccharide derivative was isolated, namely, methyl 3-*O*-β-D-glucopyranosyl-β-D-galactopyranoside (**12**, the combined yield of **4** and **12** was 66.3%).

Two other main products were shown to be methyl 2-*O*-β-D-glucopyranosyl-β-D-galactopyranoside (**16**, 24.2%) and methyl 2,3-di-*O*-β-D-glucopyranosyl-β-D-galactopyranoside (**20**, 4.7%). Smaller yields of four other products were obtained, namely, methyl 2-*O*- (**5**, 1.3%) and 3-*O*-α-D-glucopyranosyl-β-D-galactopyranoside (**9**, 0.5%), methyl 6-*O*-β-D-glucopyranosyl-β-D-galactopyranoside (**7**, 0.6%), and methyl 2,3-di-*O*-α,β-D-glucopyranosyl-β-D-galactopyranoside (**11**, 0.8%). The presence of a β-(1→6)-linked disaccharide derivative has been observed and discussed[3]; Takeo *et al.*[1] did not obtain such a product. In the *galacto* series, the

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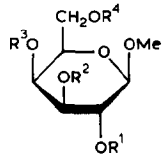

5 $R^2 = R^3 = R^4 = H, R^1 = \alpha$-D-Glc*p*
6 $R^2 = R^3 = R^4 =$ Ac, $R^1 =$ 2,3,4,6-tetra-*O*-acetyl-α-D-Glc*p*
7 $R^1 = R^2 = R^3 = H, R^4 = \beta$-D-Glc*p*
8 $R^1 = R^2 = R^3 =$ Ac, $R^4 =$ 2,3,4,6-tetra-*O*-acetyl-β-D-Glc*p*
9 $R^1 = R^3 = R^4 = H, R^2 = \alpha$-D-Glc*p*
10 $R^1 = R^3 = R^4 =$ Ac, $R^2 =$ 2,3,4,6-tetra-*O*-acetyl-α-D-Glc*p*
11 $R^3 = R^4 = H, R^1 = R^2 = \alpha,\beta$-D-Glc*p*
12 $R^1 = R^3 = R^4 = H, R^2 = \beta$-D-Glc*p*
13 $R^1 = R^3 = R^4 =$ Ac, $R^2 =$ 2,3,4,6-tetra-*O*-acetyl-β-D-Glc*p*
16 $R^2 = R^3 = R^4 = H, R^1 = \beta$-D-Glc*p*
17 $R^2 = R^3 = R^4 =$ Ac, $R^1 =$ 2,3,4,6-tetra-*O*-acetyl-β-D-Glc*p*
20 $R^3 = R^4 = H, R^1 = R^2 = \beta$-D-Glc*p*
21 $R^3 = R^4 =$ Ac, $R^1 = R^2 =$ 2,3,4,6-tetra-*O*-acetyl-β-D-Glc*p*

migration of the benzylidene group is unlikely and our result points to scission of the acetal group.

Comparison with the results of Gorin[2] indicates that the procedure described above enhanced the yields of the two main disaccharide derivatives (90.5% combined yield of **4, 12,** and **16**). The ratio of β-(1→3)- and β-(1→2)-linked derivatives was 3:1.

The yield (5.5%) of trisaccharide derivatives depends on the molar proportion of glucosyl bromide **3** used. In the reactions of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside and **3**[3] or **1**[4], the overall yields of the trisaccharide derivatives were 8% and 11% when ~3 mol of glycosyl bromide was used.

EXPERIMENTAL

General. — Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter for solutions in chloroform at 25°, unless otherwise noted. I.r. spectra were recorded with a UR-20 Zeiss spectrophotometer. N.m.r. spectra (internal Me_4Si) were recorded with Tesla BS 407 (^1H, 80 MHz) and Jeol FX 90 Q (^{13}C, 25 MHz) spectrometers. Mass spectra (70 eV) were recorded with a LKB 2091 instrument and ion-source temperature of 250°. T.l.c. was performed on silica gel DC-Alurole Kieselgel F 254, using *A*, chloroform–acetone mixtures (1:4); and *B*, 1-propanol–ethyl acetate–water (3:2:1); and detection by charring with sulfuric acid. G.l.c. was performed on a Pye Unicam 104 apparatus, using a flame-ionisation detector and a column of 15% of XE-60 on Gas-Chrom Q (100–120 mesh) at 210° with N_2 as the carrier gas. Chromatography on Dowex 1-X8 (HO^-) resin (200–400 mesh) involved columns measuring 2.5 × 65 cm. Commercial

TABLE I

^{13}C-NMR DATA

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-1'* *C-1''*	*C-2'* *C-2''*	*C-3'* *C-3''*	*C-4'* *C-4''*	*C-5'* *C-5''*	*C-6'* *C-6''*	*OMe*	*CH_3COO*	*CH_3COO*
5[a]	104.07	76.11	71.82[c]	68.22	74.85	60.64[d]	97.91	72.08	73.29	70.04	71.65[c]	60.25[d]	56.27		
11[a]	104.07	76.50	80.57	67.18	74.55	60.68	103.42	73.64	76.50	69.70	76.50	60.42	55.78		
							96.57	72.17	72.86	69.70	71.56	60.42			
12[a]	104.20	69.65[c]	83.18	67.22	74.73	60.82	103.59	73.77	76.59[d]	69.35[c]	76.11[d]	60.82	55.61		
16[a]	103.77	79.36	73 12	67.70	74.90	60.25[c]	102.33	74.29	76.85[d]	69.85	76.29[d]	60.90[c]	55.57		
20[a]	103.51	76.59	81.70	67.44	74.68	60.37	102.68	73.60	76 58	69.74	76.58	60.85	55.22		
							102.29	73.95	76.58	70.70	76.58	60.85			
6[b]	104 14	73.50	72.00	67.24	69.95	61.28	95.73	68.59	70.54	67.62	70.71	61.77	57 05	169.42, 169.75, 170.34, 170.56	20.64
8[b]	102.13	68.97	72.38	67.73[c]	71.19	67.18[c]	100.50	71.08	72.00	68.38	72.82	61.87	56.94	169.10, 169.42 170.01, 170.50	20.53
10[b]	102.34	69.73	73.20	68.00	70.87	61.44[c]	93.03	68.75	69.46	65.07	69.35	61.82[c]	56.67	169.31, 169.63 169.85	20.53 26.04
13[b]	101.75	70.56	76 29	68.92	71.14	61.17[c]	100.67	71 14	71.84	68.38	72.55	62.04[c]	56.56	169.04, 169.20 169.85, 170.57	20.37, 20.53 20.69, 20.86
17[b]	102.99	76.01	72.00	67.40	70.49	61 28[c]	100.61	71.80	72.00	68.54	72.43	62.20[c]	57.16	169.04, 169.85 170.01, 170.56	20.59
21[b]	101.80	73.47	76.20	68.70	70.76	61.71	100.83	71.08	71.90	68.32	72.82	61.44	56 84	169.20, 169.26	20.42, 20.59
							99.04	71.24	71.90	68.32	72 55	61.44		169.30, 170.18 170 26, 170.66	20.75

[a]In $(CD_3)_2SO$. [b]In $CDCl_3$. [c,d]Assignments may be reversed.

resin was washed repeatedly with water, 5% hydrochloric acid, water, aqueous 5% potassium hydroxide, and water. Percentage yields for chromatography are related to **2**.

Condensation of methyl 4,6-O-benzylidene-β-D-galactopyranoside (**2**) *with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide* (**3**). — A mixture of dichloromethane (200 mL), silver carbonate (26.0 g), and Drierite (49 g) was stirred for 2 h in the dark with exclusion of moisture. Iodine (3 g) and **2** (14.1 g, 50 mmol) were added, and stirring was continued for 1 h. A solution of **3** (23.4 g, 57 mmol) in dichloromethane (100 mL) was then added and stirring was continued for 19 h. More silver carbonate (23.1 g), Drierite (31 g), and iodine (3 g) were added followed, after stirring for 1 h, by **3** (17.7 g, 43 mmol). Stirring was continued for 24 h at room temperature, the mixture was then filtered through a pad of Celite, and the insoluble material was washed with dichloromethane. The combined filtrate and washings were concentrated *in vacuo* at 50°, and the residue was crystallised from methanol to give methyl 4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-galactopyranoside[6] (**4**; 11.9 g, 38.9%), which, after recrystallisation from methanol, had 186–187°, $[\alpha]_D$ +10° (*c* 2).

The mother liquor was concentrated to give a syrup which was treated with aqueous 60% acetic acid at 100° for 0.5 h. The solvent was evaporated and the residue was deacetylated conventionally with methanolic sodium methoxide. The sodium ions were removed using Dowex 50 (H^+) resin, the solvent was evaporated *in vacuo*, part (10 g) of the syrupy residue was eluted from a column of Dowex 1-X8 (HO^-) resin (250 g) with aqueous 5% 1,4-dioxane, and the fractions were analysed by t.l.c. (solvent *B*).

The first fraction contained traces of methyl β-D-galactopyranoside.

The second fraction gave methyl 2-*O*-α-D-glucopyranosyl-β-D-galactopyranoside (**5**; 92 mg, 1.3%), m.p. 188–189° (from ethanol), $[\alpha]_D$ +91° (*c* 1, water). Acid hydrolysis of **5** gave D-glucose and D-galactose in the ratio 1:1. Methylation analysis gave acetylated 2,3,4,6-tetra- and 3,4,6-tri-*O*-methylalditols. The hepta-acetate (**6**) of **5** had m.p. 169–170°, $[\alpha]_D$ +87° (*c* 1).

Anal. Calc. for $C_{27}H_{38}O_{18}$: C, 49.84; H, 5.90. Found: C, 49.68; H, 5.80.

The third fraction gave methyl 6-*O*-β-D-glucopyranosyl-β-D-galactopyranoside (**7**; 50 mg, 0.7%), m.p. 130°, $[\alpha]_D$ +6° (*c* 0.5, water). Hydrolysis of **7** gave D-glucose and D-galactose in the ratio 1:1. Methylation analysis gave acetylated 2,3,4,6-tetra- and 2,3,4-tri-*O*-methylalditols. The hepta-acetate (**8**) of **7** had m.p. 120–122°, $[\alpha]_D$ −18° (*c* 1).

Anal. Calc. for $C_{27}H_{38}O_{18}$: C, 49.84; H, 5.90. Found: C, 49.72; H, 5.81.

The fourth fraction gave methyl 3-*O*-α-D-glucopyranosyl-β-D-galactopyranoside (**9**; 35 mg, 0.5%), m.p. 224–225°, $[\alpha]_D$ +104° (*c* 0.5, water). Hydrolysis of **9** gave D-glucose and D-galactose in the ratio 1:1. Methylation analysis gave acetylated 2,3,4,6-tetra- and 2,4,6-tri-*O*-methylalditols. The hepta-acetate (**10**) of **9** had $[\alpha]_D$ +8° (*c* 1.1).

Anal. Calc. for $C_{27}H_{38}O_{18}$: C, 49.84; H, 5.90. Found: C, 49.76; H, 5.82.

The fifth fraction gave methyl 2,3-di-*O*-α,β-D-glucopyranosyl-β-D-galactopyranoside (**11**; 95 mg, 0.8%), m.p. 251–253°, $[\alpha]_D$ +57° (*c* 1, water). Hydrolysis of **11** gave D-glucose and D-galactose in the ratio 2:1. Methylation analysis gave acetylated 2,3,4,6-tetra- and 4,6-di-*O*-methylalditols.

Anal. Calc. for $C_{19}H_{34}O_{16}$: C, 44.01; H, 6.61. Found: C, 43.82; H, 6.70.

The sixth fraction gave methyl 3-*O*-β-D-glucopyranosyl-β-D-galactopyranoside (**12**; 1.95 g, 27.4%), m.p. 185–187°, $[\alpha]_D$ +2° (*c* 1, water); lit.[7] $[\alpha]_D^{25}$ +8.3° (methanol). Hydrolysis of **12** gave D-glucose and D-galactose in the ratio 1:1. Methylation analysis gave acetylated 2,3,4,6-tetra- and 2,4,6-tri-*O*-methylalditols. Acetylation of **12** gave hepta-acetate **13**, m.p. 140–141°, $[\alpha]_D$ +41.5° (*c* 1).

Anal. Calc. for $C_{27}H_{38}O_{18}$: C, 49.84; H, 5.90. Found: C, 49.85; H, 6.00.

Acetolysis[8] of **12** with acetic anhydride and sulfuric acid in the cold, with column chromatography (chloroform–acetone, 4:1) of the product, gave 1,2,4,6-tetra-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranoside (**14**), m.p. 175–176°, $[\alpha]_D$ +67° (*c* 1). ^{1}H-N.m.r. data ($CDCl_3$): δ 6.26 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4.65 (d, 1 H, $J_{1',2'}$ 7 Hz, H-1'), 2.17–1.97 (m, 24 H, 8 OAc).

Anal. Calc. for $C_{28}H_{38}O_{18}$: C, 49.56; H, 5.64. Found: C, 49.64; H, 5.70.

Deacetylation of **14** with methanolic sodium methoxide gave 3-*O*-β-D-glucopyranosyl-D-galactose (**15**), m.p. 177–179°, $[\alpha]_D$ +40→ +24° (*c* 1, water); lit.[9–11] m.p. 203–205°, $[\alpha]_D^{22}$ +40° (*c* 0.8, water); m.p. 200°, $[\alpha]_D$ +40.7° (water); $[\alpha]_D^{23}$ +35° (*c* 0.2, water).

The seventh fraction gave methyl 2-*O*-β-D-glucopyranosyl-β-D-galactopyranoside (**16**; 1.72 g, 24.2%), m.p. 112–115°, $[\alpha]_D$ −13° (*c* 1, water). The hepta-acetate (**17**) of **16** was amorphous and had $[\alpha]_D$ −12° (*c* 1). Hydrolysis of **16** gave D-glucose and D-galactose in the ratio 1:1. Methylation analysis gave acetylated 2,3,4,6-tetra- and 3,4,6-tri-*O*-methylalditols.

Acetolysis[8] of **16**, as for **12**, gave 1,3,4,6-tetra-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranoside (**18**), $[\alpha]_D$ +39° (*c* 1). ^{1}H-N.m.r. data ($CDCl_3$): δ 6.42 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4.42 (d, 1 H, $J_{1',2'}$ 7 Hz, H-1'), 2.20–1.92 (m, 24 H, 8 OAc).

Anal. Calc. for $C_{28}H_{38}O_{19}$: C, 49.56; H, 5.64. Found: C, 49.60; H, 5.64.

Deacetylation of **18** with methanolic sodium methoxide gave 2-*O*-β-D-glucopyranosyl-D-galactose (**19**), m.p. 163–164°, $[\alpha]_D$ +52°→ +33° (*c* 0.5, water); lit.[12,13] m.p. 171–172°, $[\alpha]_D$ +42.6° (water); m.p. 164–170°, $[\alpha]_D$ +42.0→ +40.6° (water).

The eight fraction gave methyl 2,3-di-*O*-β-D-glucopyranosyl-β-D-galactopyranoside (**20**; 490 mg, 4.7%), m.p. 220–226°, $[\alpha]_D$ −7° (*c* 1.5, water). Hydrolysis of **20** gave D-glucose and D-galactose in the ratio 2:1. Methylation analysis gave acetylated 2,3,4,6-tetra- and 4,6-di-*O*-methylalditols. The deca-acetate (**21**) of **20** had $[\alpha]_D$ −11° (*c* 0.2).

Anal. Calc. for $C_{39}H_{54}O_{26}$: C, 49.89; H, 5.80. Found: C, 50.06; H, 5.75.

REFERENCES

1 K. TAKEO, M. KITAJIMA, AND T. FUKATSU, *Carbohydr. Res.*, 112 (1983) 158–164.
2 P. A. J. GORIN, *Carbohydr. Res.*, 101 (1982) 13–20.
3 A. TEMERIUSZ, B. PIEKARSKA, J. RADOMSKI, AND J. STĘPIŃSKI, *Pol. J. Chem.*, 56 (1982) 141–147.
4 A. TEMERIUSZ, B. PIEKARSKA, J. RADOMSKI, AND J. STĘPIŃSKI, *Carbohydr. Res.*, 108 (1982) 298–301.
5 J. KARKKAINEN, *Carbohydr. Res.*, 14 (1970) 27–33.
6 A. TEMERIUSZ, B. PIEKARSKA, J. RADOMSKI, AND J. STĘPIŃSKI, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, 28 (1982) 587–591.
7 A. STOFFYN AND P. STOFFYN, *J. Org. Chem.*, 32 (1967) 4001–4006.
8 A. TEMERIUSZ, B. PIEKARSKA, J. RADOMSKI, AND J. STĘPIŃSKI, *Pol. J. Chem.*, 55 (1981) 783–791.
9 H. M. FLOWERS, *Carbohydr. Res.*, 4 (1967) 312–317.
10 R. KUHN, I. LOW, AND H. TRISCHMANN, *Chem. Ber.*, 88 (1955) 1492–1507.
11 L. H. BRIGGS, R. C. CAMBIE, AND J. L. HOARE, *J. Chem. Soc.*, (1963) 2848–2853.
12 M. A. GAKHOKIDZE AND N. D. KUTIDZE, *Zh. Obshch. Khim.*, 22 (1952) 139–147
13 T. KAWASAKI AND T. YAMAUCHI, *Chem. Pharm. Bull.*, 11 (1963) 1221–1224.