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Note

On the product of the Koenigs-Knorr reaction between methyl 4,6-*O*-benzylidene-α-D-glucopyranoside and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide

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The original chemical synthesis of sophorose (2-*O*-β-D-glucopyranosyl-D-glucopyranose) (**1**) involved the Koenigs-Knorr condensation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**2**) with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**3**), in the presence of silver carbonate, to give methyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**4**), followed by removal of the protecting groups[1,2]. A simplified, two-step method based on the same reaction, and giving an improved yield, has been devised by Coxon and Fletcher[3]. Simultaneous formation of the derivative of laminarabiose (3-*O*-β-D-glucopyranosyl-D-glucopyranose) **5** in the reaction, performed accordingly to the method of Coxon and Fletcher[3], was observed by Yamaoka *et al.*[4], who isolated **5** in 5.6% yield (based on **2**) from the mother liquor of **4**, by sequential acetolysis, column chromatographic purification of the acetolyzate, *O*-deacetylation, and fractionation of the free sugars on a carbon–Celite column; the isolation of any intermediary compounds was not described.

In connection with our studies on the partial etherification[5] and esterification[6–8] of oligosaccharides, **1** was prepared by the condensation of **2** with **3** under the exact conditions described earlier[3]. Examination of the reaction product by t.l.c. indicated the presence, in a substantial amount, of minor disaccharide derivatives, besides **4** and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**6**) arising from the hydrolysis of **3**. By careful isolation of the disaccharide derivatives formed, we were able to determine the relative reactivity of the hydroxyl groups in **2** towards **3** in the Koenigs–Knorr reaction under the conditions described by Coxon and Fletcher[3].

From the reaction mixture, **4** crystallized in the previously described[3] yield (41%). The mother liquor of **4** became slightly acidic on storage for 2 days at room temperature, which caused considerable debenzylidenation of the products (t.l.c.), probably due to the hydrogen bromide liberated from the residual **3** in trace amount. The residue from the mother liquor was converted by successive treatment with aqueous acetic acid and acetic anhydride–pyridine into a mixture of the per-*O*-acetyl-

ated derivatives. T.l.c. examination showed the mixture to comprise four components, all of which were isolated by column chromatography.

The fastest-moving component was a monosaccharide derivative having physical constants in good agreement with those of 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose[9] (**7**).

The component (5%) next eluted from the column was identified as methyl α-sophoroside heptaacetate (**8**) by comparison with an authentic specimen.

The third component (15%) proved to be methyl α-laminarabioside heptaacetate (**9**) by comparison with an authentic sample synthesized by the orthoester method[10]. It is noteworthy that the laminarabiose derivative **9** was obtained in a yield much higher than that of the derivative **5** isolated previously[4].

The component (4%) of lowest mobility had physical properties identical with those of β,β-trehalose octaacetate[11] (**10**). It is assumed to be produced by the condensation of **3** with **6**.

On the basis of the yields of the reaction products, the ratio of 2- to 3-*O*-substitution in **2** was found to be 3:1. In contrast, a similar condensation of *p*-nitrophenyl 4,6-*O*-benzylidene-β-D-glucopyranoside with 1.3 molar equivalents of **3**, followed by removal of the protecting groups, gave an equimolar mixture of *p*-nitrophenyl β-sophoroside and *p*-nitrophenyl-β-laminarabioside[12], and the reaction of benzyl 4,6-*O*-benzylidene-β-D-glucopyranoside with 2 molar equivalents of **3**, in the presence of silver oxide, followed by deblocking reactions, led to approximately equivalent amounts of **1** and **5**, in addition to the trisaccharide 3,6-di-*O*-(β-D-glucopyranosyl-D-glucopyranose[13].

EXPERIMENTAL

The general experimental specifications were the same as those described previously[8]. The average yields (calculated on the basis of **2**) of three experiments were recorded.

Condensation of methyl 4,6-O-benzylidene-α-D-glucopyranoside (**2**) *with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide* (**3**). — Compound **2** (11.5 g) was treated with **3** (20.9 g, 1.25 molar equiv.) under the conditions described in ref. 3. The reaction mixture was filtered through a Celite pad, and the filtrate was washed successively with 5% $Na_2S_2O_2$ (to remove free iodine) and water, dried (Na_2SO_4), and evaporated. The residue was crystallized from 2-ethoxyethanol to give methyl 4, 6-*O*-benzylidene-2-O-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**4**) (10.1 g, 41%), m.p. 226–227°, $[\alpha]_D^{24}$ +43.8° (*c* 2.0, chloroform); lit.[3] m.p. 227–228° (from 2-ethoxyethanol), $[\alpha]_D^{20}$ +42.4° (chloroform).

The mother liquor of **4** was concentrated to a syrup which was dissolved in 60% acetic acid (80 ml), and the solution was heated for 20 min at 100°. Removal of the solvents by repeated codistillation with toluene gave a syrup that was dissolved in 1:1 acetic anhydride–pyridine (100 ml). The solution was kept overnight at room temperature, poured into ice–water, and the resulting viscous solid was washed

extensively with water, and dissolved in chloroform. The solution was dried (Na_2SO_4) and evaporated. T.l.c. with 3:2 (v/v) ethyl acetate–benzene showed the product to be composed of two major components having R_F values of 0.75 (**7**) and 0.44 (**9**), and two minor components having R_F values of 0.54 (**8**) and 0.31 (**10**). The mixture was fractionated on a column of silica gel (500 g) with 1:1 (v/v) ethyl acetate–benzene.

The fractions containing the first major component were evaporated to give a syrup that was crystallized from 95% methanol to give 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose (**7**) (6.9 g), m.p. and mixed m.p. 112–113°, $[\alpha]_D^{23}$ +101.0° (*c* 1.4, chloroform); lit.[9] m.p. 112–113° (from 95% ethanol), $[\alpha]_D^{20}$ +102° (chloroform).

The second fraction was crystallized from 80% methanol to give methyl 3,4,6-tri-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**8**) (1.4 g, 5%), m.p. and mixed m.p. 131–132°, $[\alpha]_D^{24}$ +51.5° (*c* 1.5, chloroform); lit.[2] m.p. 132° (from aqueous methanol), $[\alpha]_D^{20}$ +50.2° (chloroform).

The third fraction, which contained the major component, was crystallized from ethanol to give methyl 2,4,6-tri-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**9**) (4.1 g, 15%), m.p. and mixed m.p. 193–194°, $[\alpha]_D^{23}$ +38.0° (*c* 2.5, chloroform); lit.[10] m.p. 189–192° (ether–petroleum ether), $[\alpha]_D$ +39° (*c* 2.18, chloroform).

The fourth fraction was crystallized from chloroform–ether–petroleum ether to give 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**10**) (1.1 g, 4%), m.p. 183–184°, $[\alpha]_D^{24}$ −18.5° (*c* 1.5, chloroform); lit.[11] m.p. 181.5–182.5° (from chloroform–ether–petroleum ether), $[\alpha]_D$ −17° (chloroform).

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