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Note

Synthesis of isomaltose and other α-D-glucopyranosides

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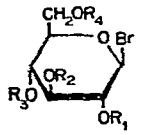
The chemical synthesis of disaccharides wherein the glycosidic bond has the *cis* orientation to the bond to the hydroxyl group on C-2 presents greater difficulty than that of the analogous 1,2-*trans* compounds. Hence, the synthesis of disaccharides having, for example, the α-D-glucopyranoside and β-D-mannopyranoside structures still constitutes a challenge. Synthesis of the former compounds generally involves the use at O-2 of a nonparticipating group; this is often a benzyl ether, although other approaches have been used[1]. This Note briefly reports some observations on the synthesis of isomaltose and related compounds.

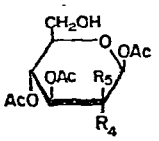
Preparation of 1,2-*cis*-D-glucosides by a Koenigs–Knorr reaction would be facilitated were the β-D-bromide readily available and the reaction to proceed by a normal SN2 inversion; consequently, we were attracted by the work of Ishikawa and Fletcher[2], who studied the solvolysis of substituted β-D-glucopyranosyl bromides with alcohols of low molecular weight. At the time our work was started, solvolysis of these bromides had not been extended to the synthesis of disaccharides, but Flowers[3] has now reported the use of this approach.

Ishikawa and Fletcher[2] investigated the rate of hydrolysis of β-D-glucopyranosyl bromides as a function of the number of benzyl ether and *p*-nitrobenzoyl groups in the monosaccharide derivative. The rate was found to increase with increase in the number of benzyl groups, and it was thus of interest to compare the merits of the 2-*O*-benzyl and 2,3-di-*O*-benzyl derivatives as reagents in the synthesis of disaccharides. First, the preparation of isomaltose (**9**) by use of 2-*O*-benzyl-3,4,6-tri-*O*-(*p*-nitrobenzoyl)-β-D-glucopyranosyl bromide (**1**) and 2,3-di-*O*-benzyl-4,6-di-*O*-(*p*-nitrobenzoyl)-β-D-glucopyranosyl bromide (**2**) was compared. Compound **1** was also employed to prepare 6-*O*-α-D-glucopyranosyl-D-mannose (**11**) (previously obtained[4] in low yield by use of a trichloroacetyl group as the nonparticipating substituent) and 4-*O*-α-D-glucopyranosyl-L-rhamnose (already reported[5]). Compound **2** served, in addition, for the preparation of 6-*O*-α-D-glucopyranosyl-D-galactose (**12**), since described by Flowers[3].

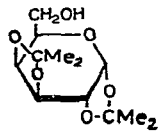
Reaction of **1** with 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (**3**) in absolute nitromethane at room temperature, with mercuric cyanide as the acid acceptor,



	R_1	R_2	R_3	R_4
1	CH_2Ph	$COC_6H_4NO_2$-*p*	$COC_6H_4NO_2$-*p*	$COC_6H_4NO_2$-*p*
2	CH_2Ph	CH_2Ph	$COC_6H_4NO_2$-*p*	$COC_6H_4NO_2$-*p*



	R_4	R_5
3	OAc	H
4	H	OAc



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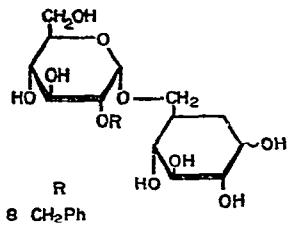
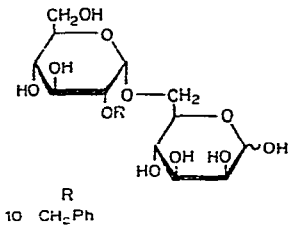
proceeded very slowly and, after two days, most of the **3** remained unchanged. The use of acetonitrile as the solvent gave no improvement, but, with nitromethane as the solvent, when the temperature was raised to 40–50°, an appreciable reaction occurred, although, even after three days, some **3** remained unreacted. Deacylation, and hydrogenolysis of the product (**8**), gave (in 48% yield based on **3**) isomaltose (**9**), characterized as the octaacetate. The p.m.r. spectrum of the crude isomaltose did not show the presence of any gentiobiose, although a trace amount of this compound was detectable by chromatography on paper. It should be noted that, in this preparation and related syntheses, small amounts of β-D-linked disaccharides could not usually be detected by t.l.c. of the intermediates, and their presence was revealed only by heavily loaded paper chromatograms conducted with the free sugars.

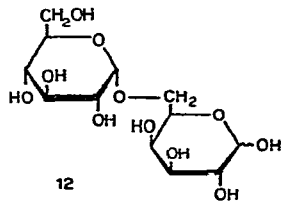
Similarly, reaction of **1** with 1,2,3,4-tetra-*O*-acetyl-β-D-mannopyranose (**4**) gave (*via* **10**), in 44% yield based on **4**, syrupy 6-*O*-α-D-glucopyranosyl-D-mannose (**11**) containing only a trace of the β anomer. 4-*O*-α-D-Glucopyranosyl-L-rhamnose has been obtained[5] in 40% yield by an analogous procedure.

Compared to bromide **1**, bromide **2** was more reactive, as indicated by its anomerization and decomposition during purification, and the higher rate at which it condensed with substrates. Thus, the reaction of **2** with **3** in nitromethane at room temperature was complete in five hours (based on **2**; some **3** remained unchanged due to side reactions of **2**). Removal of the protecting groups gave a 35% yield of disaccharides, at least 95% of which was isomaltose (**9**), the rest being gentiobiose. Similarly, reaction of **2** with 1,2:3,4-di-*O*-isopropylidene-α-D-galactose (**5**) was complete in six hours and gave, in 26% yield, 6-*O*-D-glucopyranosyl-D-galactose, of which more than 90% was the α-D-linked disaccharide (**12**).

In a parallel experiment, 2,3-di-*O*-benzyl-4,6-di-*O*-(*p*-nitrobenzoyl)-α-D-glucopyranosyl bromide (**2a**, obtained by fortuitous anomerization of **2**) was treated with **5**,







to give, after processing, 70% of the α- and 30% of the β-D-linked 6-*O*-D-glucopyranosyl-D-galactose, thus indicating the greater stereospecifity of the β-D-bromide **2**. This result contrasts with that of Takiura and co-workers[6], who obtained isomaltose in only 18% yield by reaction for five days of the α anomer of **1**, namely, 2-*O*-benzyl-3,4,6-tri-*O*-(*p*-nitrobenzoyl)-α-D-glucopyranosyl bromide, and who found the ratio of isomaltose to gentiobiose to be 16:3. As an illustration of the ease of anomerization of these β-bromides, it should be noted that Takiura and co-workers failed to prepare **1**, and obtained only the α-D anomer, probably because they modified the published procedure[2] by instituting a water-wash of the crude bromide, instead of using the nonaqueous purification prescribed.

These results clearly indicate that the principles enunciated by Ishikawa and Fletcher[2] are extendible to the synthesis of α-D-glucopyranosyl disaccharides. Despite the fact that the 2,3-di-*O*-benzyl bromide **2** is somewhat more readily prepared than **1**, its greater reactivity is a disadvantage that leads to various side-reactions and contributes to low yields of the desired product. The 2-*O*-benzyl-D-glucose (**7**) needed for the preparation of **1** may be obtained in 70% yield *via* 3,4,6-tri-*O*-acetyl-1-deoxy-1-piperidino-β-D-glucopyranose[7], provided that the benzylation[5] thereof is effected with an excess of only 0.2 molar proportions of benzyl bromide and is performed with freshly prepared silver oxide and in the presence of a desiccant (Drierite). Under these conditions, etherification to the 2-benzyl ether (**6**) is achieved in 2–4 hours, instead of four days[8].

EXPERIMENTAL

General methods. — Thin-layer chromatography (t.l.c.) was conducted with solvent systems *A*, *B*, and *C* on silica gel G; solvent *A*, 2:1 ethyl ether–toluene; solvent *B*, 4:1 benzene–ethyl ether; solvent *C*, butanone–water azeotrope. Paper-chromatographic separations were conducted on Whatman No. 1 paper with solvent system *D*, 4:1:1 ethyl acetate–pyridine–water, and reducing sugars were detected with a spray of *p*-anisidine trichloroacetate. Optical rotations were recorded at 22 ±2°.

2-O-Benzyl-3,4,6-tri-O-(p-nitrobenzoyl)-β-D-glucopyranosyl bromide (**1**). — 3,4,6-Tri-*O*-acetyl-1-deoxy-1-piperidino-β-D-glucopyranose[7] (35 g), freshly prepared, powdered, dry silver oxide (40 g), and ground Drierite (30 g) were stirred in dry benzene (250 ml) for 30 min in the dark at room temperature with exclusion of moisture. The

mixture was then cooled to ~15°, benzyl bromide (13 ml) was added, and stirring was continued for 3.5 h at room temperature, when t.l.c. (solvent *A*) indicated that the reaction was complete. The mixture was filtered, the salts were washed with benzene, and the filtrate and washings were combined and evaporated, affording a product that crystallized. Recrystallization from hot methanol (3 ml/g) gave pure 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-1-deoxy-1-piperidino-β-D-glucopyranose (**6**), 38.7 g (89%), m.p. 99–100°, $[\alpha]_D$ +42° (*c* 2.2, methanol); lit.[8] m.p. 100°, $[\alpha]_D$ +41.5° (*c* 0.9, methanol).

Compound **6** (35 g) was treated with 2% sodium methoxide in anhydrous methanol (300 ml) at room temperature. T.l.c. (solvent *A*) showed that the reaction was complete within 30 min. Sulfuric acid (2M, ~100 ml) was added until the pH of the solution was 3, and the mixture was boiled under reflux[9] for 1 h. After neutralization of the acid (barium carbonate) and evaporation of the filtrate, the resulting crystals of compound **7** were recrystallized from hot methanol (10 ml/g); yield 16 g, m.p. 176–177°, $[\alpha]_D$ +47° (*c* 2, methanol); lit.[8,9] m.p. 176–177°, $[\alpha]_D$ +47° (*c* 1.0, methanol).

Compound **7** (10 g) was converted in 95% yield into the tetrakis-*p*-nitrobenzoate, 15 g of which was dissolved in a saturated solution of hydrogen bromide in absolute dichloromethane (700 ml) and the solution kept under anhydrous conditions for 6 h at room temperature. The mixture was filtered, the filtrate was evaporated at 35°, and the residue dried (vacuum pump) for 30 min, during which time crystallization occurred. The product was recrystallized from dry dichloromethane–anhydrous ether; yield, 4.2 g, m.p. 142–143°, $[\alpha]_D$ +3° (*c* 2.0, dichloromethane); lit.[2] m.p. 143–144°, $[\alpha]_D$ +2.4° (*c* 2.1, dichloromethane). On some occasions, **1** co-crystallized with an impurity (probably the α anomer) that was difficult to remove by recrystallization; however, this impurity did not interfere with the condensation step. The bromide was stored over phosphorus pentaoxide at room temperature in a vacuum desiccator, or at 0° in a stoppered flask.

6-O-(2-O-Benzyl-α-D-glucopyranosyl)-D-glucopyranose (**8**). — To a solution of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose[10] (**3**) (1 g, 2.87 mmoles) and mercuric cyanide (1.3 g, 5.1 mmoles) in absolute nitromethane (50 ml, distilled from calcium hydride) was added an excess of bromide **1** (4 g, 5.1 mmoles), and the mixture was stirred under anhydrous conditions for 3 days at 40–45°. Examination of the mixture by t.l.c. (solvent *B*) then showed zones having the following R_F values: tetraacetate **3**, 0.03; bromide **1**, 0.16; product, 0.19 (that is, small amounts of tetraacetate **3** and bromide **1** remained unreacted). The solution was evaporated, the resulting syrup was diluted with chloroform (100 ml), and the solution was washed successively with water (2 × 100 ml), saturated sodium hydrogen carbonate (3 × 100 ml), and water (2 × 100 ml), dried (sodium sulfate), filtered, and the filtrate evaporated. The mixture was dissolved in dichloromethane (25 ml), 0.2M sodium methoxide in anhydrous methanol (50 ml) was added, and, after 30 min, the base was neutralized with Amberlite IR-120 (H^+) resin; evaporation gave a syrup that, by t.l.c. (solvent *C*), contained product **8** (R_F 0.06), 2-*O*-benzylglucose (R_F 0.34), and glucose (R_F 0.0). Methyl *p*-nitrobenzoate was removed by dissolving the syrup in water (30 ml) and washing

the solution with chloroform (4 × 20 ml); the aqueous layer (containing the disaccharide) was evaporated under diminished pressure. The resulting mixture was chromatographed[11] on a short column (4 × 25 cm) of silica gel G (160 g) with solvent *C*, 20-ml fractions being collected every 4 to 5 min. Fractions 21–60 were heterogeneous, and 61–180 contained the disaccharide intermediate **8** (600 mg; 48% from **3**). The heptaacetate obtained by acetylation (Ac_2O–NaOAc) of **8** had $[\alpha]_D$ +66° (*c* 1.5, chloroform) and R_F 0.35 (t.l.c., solvent *A*).

6-O-α-D-Glucopyranosyl-D-glucopyranose (*isomaltose*, **9**). — Compound **8** (475 mg) in absolute ethanol (15 ml) was hydrogenolyzed with hydrogen at 50 lb.in.$^{-2}$, with 5% palladium-on-carbon (1 g) as the catalyst. The mixture was shaken overnight at room temperature, filtered, and the filtrate evaporated, to give **9** as a syrup (390 mg). Paper-chromatographic analysis showed mainly isomaltose (R_{Glc} 0.14, solvent *D*), and a faint spot (<5%, that could not be detected by p.m.r. spectroscopy) corresponding to 6-*O*-β-D-glucopyranosyl-D-glucose (gentiobiose). After being dried at 65°/1 torr over phosphorus pentaoxide, the syrup had $[\alpha]_D$ +95° (*c* 1.2, water); lit.[12,13] $[\alpha]_D$ +120° (*c* 1.2, water). The p.m.r. spectrum (D_2O, external Me_4Si) of **9** showed: τ 4.74 (doublet, $J_{1,2}$ 3.5 Hz, H-1 of α-D-glucose residue), 5.29 (doublet, $J_{1,2}$ 7.2 Hz, H-1 of β-D-glucose residue) (the ratio of β:α was ~2:1), and 5.02 (1-proton doublet, $J_{1,2}$ 3.5 Hz, H-1 of α-D-glucopyranosyl group). Isomaltose octaacetate was obtained by acetylation with acetic anhydride–sodium acetate; it crystallized from ethanol on nucleation, and was recrystallized from the same solvent; m.p. and mixed m.p. 145–146°, $[\alpha]_D$ +95° (*c* 1.3, chloroform); lit.[14] m.p. 144–145°, $[\alpha]_D$ +95° (*c* 1.0, chloroform).

6-O-(2-O-Benzyl-α-D-glucopyranosyl)-D-mannopyranose (**10**). — 1,2,3,4-Tetra-*O*-acetyl-β-D-mannopyranose[15] (**4**) (1 g, 2.87 mmoles), mercuric cyanide (1.3 g, 5.1 mmoles), and bromide **1** (4.0 g, 5.1 mmoles) in absolute nitromethane were stirred under anhydrous conditions for 2 days at 40°. The product was deacylated and the resulting syrup was chromatographed on silica (170 g) with 3:1 chloroform–methanol as the eluant, 20-ml fractions being collected every 5 min. Fractions 81–140 contained pure **10** (550 mg; 44% based on **4**), the heptaacetate of which was obtained as a syrup having $[\alpha]_D$ +69° (*c* 2.3, chloroform).

6-O-α-D-Glucopyranosyl-D-mannopyranose (**11**). — Compound **10** (197 mg) in absolute ethanol (10 ml) was hydrogenolyzed at 50 lb.in.$^{-2}$ for 2 days at room temperature, with 5% Pd–C as the catalyst (10% Pd–C caused some reduction to the glucosylmannitol). The disaccharide **11** was obtained as a syrup (154 mg) having $[\alpha]_D$ +74° (*c* 0.5, water); R_{Glc} 0.21 (solvent *D*); p.m.r. data (D_2O, external Me_4Si): τ 4.83 (doublet, $J_{1,2}$ 1.7 Hz, H-1 of α-D-mannopyranose residue), 5.11 (doublet, $J_{1,2}$ 1.0 Hz, H-1 of β-D-mannopyranose residue), 5.05 (1-proton doublet, $J_{1,2}$ 3.2 Hz, H-1 of α-D-glucopyranosyl group).

The phenylosazone had m.p. 158° (lit.[16] 160°); the octaacetate was a syrup having $[\alpha]_D$ +74° (*c* 3.1, chloroform).

4-O-α-D-Glucopyranosyl-L-rhamnopyranose. — This disaccharide was obtained in 40% yield in an analogous way[5].

2,3-Di-O-benzyl-4,6-di-O-(p-nitrobenzoyl)-β(and α)-D-glucopyranosyl bromide (**2** *and* **2a**). — 2,3-Di-*O*-benzyl-D-glucose (4 g, prepared by acetolysis of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside) was converted into the tris-*p*-nitrobenzoate (6.5 g); 2 g of this was dissolved in a saturated solution of hydrogen bromide in dichloromethane (150 ml), and the solution was kept for 2.5 h at room temperature. The *p*-nitrobenzoic acid was filtered off, and the filtrate evaporated below 35°, the contents of the flask being protected from ingress of moisture from the rotary evaporator by a tube containing Drierite. The last traces of volatile material were removed (oil pump, 0.5 torr), giving **2** as amorphous material. Two different batches had $[\alpha]_D$ +17°, +26° (*c* 1.0, 0.7; dichloromethane) {lit.[2] $[\alpha]_D$ +10.2° (*c* 2.24, dichloromethane)}.

In one experiment a syrup having $[\alpha]_D$ +76° (*c* 1.6 dichloromethane) was obtained, indicating anomerization to the α-bromide **2a**.

6-O-α-D-Glucopyranosyl-D-glucopyranose (*isomaltose*, **9**). — A mixture of tetraacetate **3** (100 mg, 0.29 mmole) and mercuric cyanide (125 mg 0.49 mmole) in absolute nitromethane (5 ml) was stirred at room temperature with the exclusion of moisture. An excess of bromide **2** (crude ~500 mg, ~0.5 mmole) was added in three portions, and the mixture was stirred for 5 h. Deacylation, purification of the product by t.l.c. (R_F 0.26, solvent *C*), and hydrogenolysis overnight at 50 lb.in.$^{-2}$ in ethanol in the presence of 10% Pd–C (100 mg) gave a syrup (40 mg) that, by paper chromatography, was estimated to contain >95% of isomaltose. Its octaacetate had m.p. and mixed m.p. (with authentic octaacetate) 143–145°, $[\alpha]_D$ +94° (*c* 0.8, chloroform).

6-O-α-D-Glucopyranosyl-D-galactopyranose (**12**). — Reaction of **5** (100 mg, 0.38 mmole) with an excess of bromide **2** in nitromethane (8 ml) in the presence of mercuric cyanide (200 mg, 0.8 mmole) for 5 h at room temperature gave, after removal of the protecting groups, compound **12** (32 mg), $[\alpha]_D$ +112° (*c* 0.3, water); lit.[3] $[\alpha]_D$ +123° (*c* 1.0, water).

When bromide **2a** was used, the reaction needed 3 days, and the initial product was resolvable, by t.l.c. with 4:1 benzene–ether, into two fractions. The faster (R_F 0.49) was shown by p.m.r. spectroscopy to be 6-*O*-[2,3-di-*O*-benzyl-4,6-di-*O*-(*p*-nitrobenzoyl)-α-D-glucopyranosyl]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, $[\alpha]_D$ +27° (*c* 1.9, chloroform), and the slower (R_F 0.40) was the β anomer, $[\alpha]_D$ −3° (*c* 1.3, chloroform). The ratio of α:β was 7:3, and the combined yield of substituted disaccharide was 43%.

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