Note

Synthesis of sucrose and of α-D-glucopyranosyl α-D-fructofuranoside through the use of 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose

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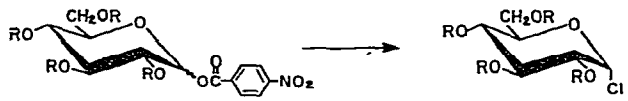
In a recent paper[1], we described the preparation of 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**4**) in crystalline form. The accessibility of this compound, together with the well-recognized tendency of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (**2**) and bromide to yield α-D-glucopyranose derivatives on nucleophilic attack[2–4], suggested that interaction of **2** with **4** might lead to the formation of octa-*O*-benzylsucrose (**5**), although it must be conceded that the anomeric configuration of the crystalline form of **4** is as yet undetermined. We now report two experiments in which the use of 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**4**) has led to the formation of mixtures from which α-D-glucopyranosyl D-fructofuranosides could be isolated.

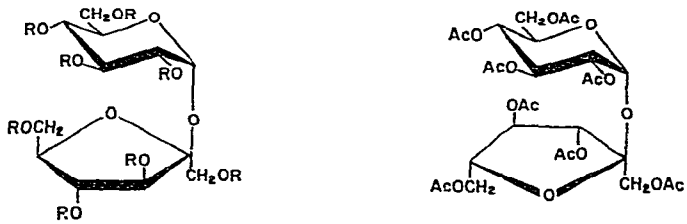
Chittenden[3] has recently reported that the condensation of **2** with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**3**) in the presence of silver carbonate, Drierite, and silver perchlorate affords (after debenzylation) α-D-glucopyranosyl α-D-glucopyranoside (α,α-trehalose) and α-D-glucopyranosyl β-D-glucopyranoside (α,β-trehalose). A similar condensation in which **3** was replaced by 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**4**) was found in the course of the present research to give, after repeated chromatography, a crude syrup (in 36% yield) which showed an optical rotation not far from that[1,5,6] of octa-*O*-benzylsucrose (**5**). As **5** has not as yet been obtained in crystalline form, the crude material was debenzylated and then benzoylated. The known solvate of octa-*O*-benzoylsucrose (**6**) with carbon tetrachloride[7] was isolated in crystalline form in an overall yield of 4.5%, based on the crystalline 2,3,4,6-tetra-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-D-glucopyranose (**1**) that had been used for the preparation of **2**. The yield of **6** closely approximates that of octa-*O*-acetylsucrose (5.5%) that Lemieux and Huber[8] obtained subsequent to the condensation of 3,4,6-tri-*O*-acetyl-1,2-anhydro-α-D-glucopyranose with 1,3,4,6-tetra-*O*-acetyl-D-fructofuranose; it is, however, significantly less than the yield of octa-*O*-methylsucrose (6–8%) that Klemer and Dietzel[9] attained through the condensation of 2,3,4,6-tetra-*O*-methyl-D-glucopyranose with 1,3,4,6-tetra-*O*-methyl-D-fructofuranose in the presence of anhydrous zinc chloride. However, the parameters affecting such condensations are numerous and, in the example reported here, no attempt was made to maximize the yield. The reader will have noted that the yield of crude product obtained from the

condensation of **2** with **4** was substantially greater than that of the octa-*O*-benzoylsucrose isolated. In a separate experiment, a sample of the crude product was catalytically debenzylated, and two major products were then separated chromatographically. One of these was sucrose, constituting ~35% of the mixture, and the other (~45%) showed a specific rotation close to that reported[10] for α-D-glucopyranosyl α-D-fructofuranoside; the properties of a crystalline acetate (**7**), prepared from the material, confirmed this identification.



1, R = PhCH$_2$ **2**, R = PhCH$_2$

3, R = PhCH$_2$ **4**, R = PhCH$_2$



5, R = PhCH$_2$
6, R = PhCO

7

Klemer and Kutz[11] have shown that 2,3,4,6-tetra-*O*-methyl-D-glucopyranose undergoes self-condensation when treated in toluene solution with Drierite and perchloric acid. We have carried out a similar reaction with an equimolar mixture of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**3**) and 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**4**). Chromatography showed that the mixture produced was complex. It was found possible, however, to separate from it those components that were formed when either **3** or **4**, alone, was subjected to the condensation conditions. Catalytic debenzylation of the remaining mixture, followed by acetylation and further chroma-

tography, led to the isolation of the octaacetate of α-D-glucopyranosyl α-D-fructofuranoside (**7**) in 6% yield. Although other D-glucopyranosyl D-fructofuranosides had quite probably been formed, the quantities involved were too small for isolation under the conditions employed.

EXPERIMENTAL

General methods. — Melting points are equivalent to corrected values. Qualitative t.l.c. was conducted on Silica Gel GF (250 μm, Analtech, Inc., Wilmington, Del.) with the solvent systems specified. Components were detected with a Gelman–Camag "universal" u.v. lamp, Model 51402, and also by spraying with 10% sulfuric acid and heating. Preparative t.l.c. was performed on plates (20 × 20 × 0.2 cm) of Silica Gel No. 3370 (E. Merck, Darmstadt). Column chromatography was carried out with Silica Gel No. 7734 (0.05–0.20 mm; E. Merck). The composition of solvent mixtures used in chromatography is indicated in terms of volume, except for the aqueous phenol which was measured by weight.

Condensation of 1,3,4,6-tetra-O-benzyl-D-fructofuranose (**4**) *with 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl chloride* (**2**). — A suspension of molecular sieve (type 4A, 4 g) and silver carbonate (2 g, 7.3 mmoles) in a solution of 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**4**, 2.00 g, 3.7 mmoles) in dry benzene (4 ml) was stirred in the dark for several minutes. Dry benzene was evaporated from silver perchlorate (0.2 g, 1 mmole), and the salt was added to the mixture, stirring being continued. A solution of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (**2**) was prepared in the following way: a mixture of the anomers of 2,3,4,6-tetra-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-D-glucopyranose[2,5] (**1**, 2.00 g, 2.9 mmoles) in dry dichloromethane (20 ml) was saturated at room temperature with hydrogen chloride and, when precipitation was complete, the *p*-nitrobenzoic acid was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. Dichloromethane and benzene were successively added to and distilled from the residual syrup, which was then dissolved in dry benzene (20 ml); the solution was added during 10 min to the stirred solution of **4**, already described. After 4 h, t.l.c. (11:1 benzene–ether) revealed the presence of a new product; 4 h later, t.l.c. showed no further change. After 48 h, the reaction mixture was placed on a column of Silica Gel (425 g), prepacked in dichloromethane and then treated (immediately prior to use) with benzene (25 ml). The column was eluted with benzene (50 ml) and then with 60:1 dichloromethane–methanol (3.3 liters), 23.5-ml fractions of eluate being collected. Fractions 141–152 contained the condensation product (2.53 g); each fraction (~0.25 g) was subjected to preparative t.l.c., first with 80:1 dichloromethane–methanol and then, after drying of the plates, with a 60:1 mixture of these solvents. The major component, which migrated at a rate slightly greater than that of **4**, was eluted with ether; like fractions thus obtained were pooled, and dried *in vacuo* to give 1.12 g (36%, based on **1**) of syrupy product that gave a positive color test for a fructose derivative when t.l.c. spots were sprayed with an orcinol–hydrochloric acid reagent. In chloroform (*c* 1.62), the material showed

$[\alpha]_D^{20}$ +45.0°; values of +38.6° (refs. 1 and 6) and +31.6° (ref. 5) have been recorded for the specific rotation of octa-*O*-benzylsucrose (5) in this solvent.

A portion (502 mg) of the syrupy material was dissolved in warm methanol (10 ml), and well-washed palladium catalyst (freshly made by the reduction of 1.0 g of palladium chloride in methanolic suspension) was added. The suspension was shaken with hydrogen for 24 h, and then examined by t.l.c. with 3:1:1 propyl alcohol–ethyl acetate–water; no material visible under u.v. light was detected. The catalyst was removed from the reaction mixture, and successively washed thoroughly with methanol and water. Concentration of the combined filtrate and washings afforded a syrup, wt. 167 mg (103%). T.l.c. with 3:1:1 propyl alcohol–ethyl acetate–water and with 5:1:4 butyl alcohol–ethanol–water revealed the presence of two major and two minor components; one of the major components was chromatographically indistinguishable from sucrose. The whole material (167 mg) was treated overnight with a mixture of benzoyl chloride (0.5 ml) and pyridine (2 ml). After the usual processing, the crude, syrupy product (453 mg) was subjected to preparative t.l.c with 80:1 dichloromethane–methanol. After the solvent front had advanced, the plate was dried and further developed with 60:1 dichloromethane–methanol. Three clearly separated bands were discernible; the intermediate band was extracted with ether to give a syrup (158 mg) which, from its solution in carbon tetrachloride–pentane, gave 88 mg (69 mg on a solvent-free basis, 4.5% of the theoretical from 1) of crystalline material, m.p. 61–64°, undepressed on admixture with an authentic sample of the carbon tetrachloride solvate of octa-*O*-benzoylsucrose[7]. Dried at 57°/0.15 torr, the product lost 21.7% of its weight, leaving a residue that showed $[\alpha]_D^{20}$ +40.0° (*c* 2.09, chloroform). Solvent-free octa-*O*-benzoylsucrose, prepared through its crystalline solvate with carbon tetrachloride, has been reported[7] to have $[\alpha]_D^{20}$ +40.6° (*c* 1.55, chloroform).

Another sample (499 mg) of the once-chromatographed product from the condensation was catalytically debenzylated as described earlier, to give 179 mg of a syrup. G.l.c. of the per(trimethylsilyl) derivative of this material on 1% SE-30 (on Gas-Chrom P) at 211° failed to effect a resolution. Parallel experiments with authentic specimens of sucrose and isosucrose (β-D-glucopyranosyl α-D-fructofuranoside) showed that their trimethylsilyl derivatives were not separable under these conditions, suggesting that this chromatographic technique is of doubtful value for the investigation of isomers of sucrose. The remainder of the syrupy material (177 mg) was chromatographed on a column of silica gel (100 g) with 16:3:1 ethyl acetate–methanol–water and collection of 8-ml fractions of eluate. One major component appeared in fractions 69–93 (79.9 mg, 45%) and the other major component was found in fractions 124–174 (61.2 mg, 35%). The material in the second group of fractions was chromatographically homogeneous, and indistinguishable from sucrose on t.l.c. in 16:3:1 ethyl acetate–methanol–water and in 4:1 phenol–water. On hydrolysis with 0.05 M sulfuric acid at 60°, both major components afforded glucose and fructose, as shown by t.l.c. with 4:1 phenol–water. The faster-moving major component (fractions 69–93, 79.9 mg) was slightly contaminated with sucrose,

as shown by t.l.c. in phenol–water. In water (after clarification of the solution with decolorizing carbon and Filter-Cel), the material showed $[\alpha]_D^{20}$ +109.5° (*c* 3.22); Klemer, Gaupp, and Buhe[10] reported $[\alpha]_D^{20}$ +118.3° (*c* 0.8, water) for α-D-glucopyranosyl α-D-fructofuranoside. Acetylation of the sample (64.5 mg) used for the determination of the optical rotation gave a crystalline acetate: 26.3 mg (3.7%, based on **1**), m.p. 111–112°, $[\alpha]_D^{20}$ +83.0°, $[\alpha]_{546}^{20}$ +97.4°, $[\alpha]_{436}^{20}$ +162°, $[\alpha]_{365}^{20}$ +252° (all *c* 0.8, chloroform); lit.[10] for α-D-glucopyranosyl α-D-fructofuranoside octaacetate (**7**), m.p. 110–112°, $[\alpha]_D^{20}$ +83.5° (*c* 1, chloroform).

*The condensation of 2,3,4,6-tetra-*O*-benzyl-α-*D*-glucopyranose* (**3**) *with 1,3,4,6-tetra-*O*-benzyl-*D*-fructofuranose* (**4**) *in the presence of perchloric acid.* — A mixture of **3** (999 mg, 1.85 mmoles) and **4** (998 mg, 1.85 mmoles) was added to dry benzene (40 ml), and the suspension was warmed slightly to effect dissolution. The solution was stirred while molecular sieve (type 4A, 1 g) and 70% perchloric acid (54 μl, 0.6 mmole) were added; stirring was continued and, after 67 h, the mixture was concentrated *in vacuo* and then placed on a column of silica gel (270 g) prepacked in benzene. The column was successively eluted with benzene (15 ml) and 11:1 benzene–ether (1.5 liters), 10-ml fractions of eluate being collected. Fractions 81–95 were examined by t.l.c. (11:1 benzene–ether) and were found to contain three or four components that did not appear to be present in the products from parallel experiments involving **3** or **4** alone. Of these components, that which moved most slowly in t.l.c. greatly preponderated; it was isolated from these fractions by preparative t.l.c. with 11:1 benzene–ether. The syrupy product (587 mg, 30%) contained a small amount of a slightly faster-moving component; a sample (360 mg) in methanol solution was catalytically debenzylated with hydrogen in the presence of well-washed palladium black (freshly prepared by the reduction of 1.0 g of palladium chloride). After removal of the catalyst, and concentration of the solution, the product was precipitated by the addition of ether—a procedure which was found (t.l.c., 4:1 phenol–water) to remove a faster-moving impurity. The precipitate was acetylated at room temperature with acetic anhydride–pyridine to yield a two-component mixture (t.l.c., ether) which was preparatively chromatographed (t.l.c., ether). The slower-moving component crystallized from its solution in ethanol–pentane, and proved to be chromatographically indistinguishable from the octaacetate of α-D-glucopyranosyl α-D-fructofuranoside (**7**): 47 mg (6%, based on **3**), m.p. 111–112°, $[\alpha]_D^{20}$ +82.0° (*c* 1.58, chloroform).

The faster-moving band of acetylated material was obtained as a mixture of two crystalline forms from its solution in ethanol–ether. Analytical data and the p.m.r. spectrum of this material showed it to be a mixture of the anomeric D-glucopyranose pentaacetates.

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