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1,3,4,6-TETRA-*O*-BENZYL-D-FRUCTOFURANOSE AND SOME OF ITS DERIVATIVES*

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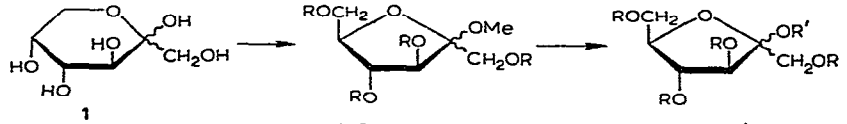
ABSTRACT

Crystalline 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**4**) has been obtained in 60% overall yield from D-fructose through the following steps: D-fructose→methyl D-fructofuranoside→methyl tetra-*O*-benzyl-D-fructofuranoside→**4**. The new D-fructofuranose derivative has been further characterized through the preparation of a *p*-nitrobenzoate, a *p*-phenylazobenzoate and a benzoate — all crystalline derivatives. To confirm the structure of **4**, it was also made through the hydrolysis of octa-*O*-benzylsucrose and by the partial oxidation of 1,3,4,6-tetra-*O*-benzyl-D-mannitol (**11**); the preparation of **11** and of two crystalline derivatives therefrom is described.

DISCUSSION

During a general study of the chemistry of the ketoses, 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**4**) was required. Initial attempts to prepare **4** from D-fructose (**1**) were patterned after the route used earlier for the conversion of D-arabinose into 2,3,5-tri-*O*-benzyl-D-arabinose[1-3]. A crude mixture of syrupy methyl D-fructofuranosides (**2**), obtained directly from D-fructose (**1**), was benzylated and the product (**3**) was hydrolyzed under relatively mild conditions (aqueous acetic acid at *ca.* 92°) to yield a crude, amorphous tetra-*O*-benzylhexulose from which crystalline *p*-nitro-



1

2, R = H
3, R = CH_2Ph

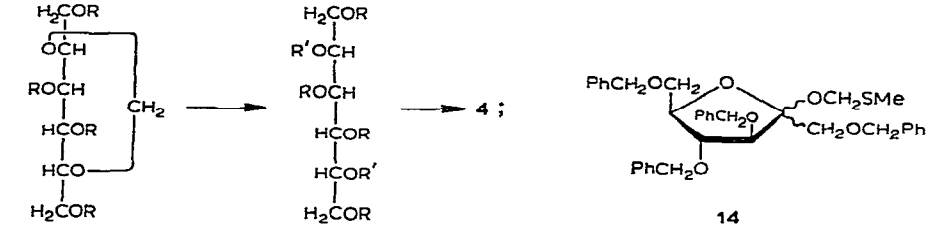
4, R = CH_2Ph ; R' = H
5, R = CH_2Ph ; R' = $C(=O)-C_6H_4-NO_2$ (*p*)
6, R = CH_2Ph ; R' = $C(=O)-C_6H_4N_2Ph$ (*p*)
7, R = CH_2Ph ; R' = Bz
8, R = CH_2Ph ; R' = Ac

benzoyl (**5**) and *p*-phenylazobenzoyl (**6**) esters were prepared. To provide unequivocal proof that the syrupy product was indeed 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**4**),

*Dedicated to the memory of Professor M. L. Wolfrom.

two further and wholly independent syntheses of this substance were undertaken. The readily accessible cyclic acetal 2,5-*O*-methylene-D-mannitol[4] (**9**) was converted into its crystalline tetrabenzyl ether (**10**) and the acetal bridge was cleaved by acidic hydrolysis in the presence of phloroglucinol. The 1,3,4,6-tetra-*O*-benzyl-D-mannitol (**11**) thus prepared proved to be a readily crystallizable substance; it was further characterized through its dibenzoate (**12**) and *p*-phenylazobenzoate (**13**).

The end-to-end symmetry of mannitol makes the hydroxyl groups in 1,3,4,6-tetra-*O*-benzyl-D-mannitol (**11**) equivalent. It was expected that oxidation of one of these hydroxyl groups would be followed very rapidly by hemiacetal formation, effectively protecting the second hydroxyl group from further oxidation and yielding 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose. Actually, the oxidation of **11** with methyl sulfoxide–acetic anhydride[5] proved to be a somewhat complex reaction, although its progress could readily be monitored by polarimetry and by t.l.c. Preparative chromatography of the crude product allowed isolation (in 14% yield) of a product which proved to be identical with that obtained earlier from D-fructose. In addition, two other amorphous products were separated. One of these had the properties expected of a 2-*O*-acetyl-1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**8**); the other had the elemental composition of a (methylthio)methyl 1,3,4,6-tetra-*O*-benzyl-D-fructofuranoside (**14**).



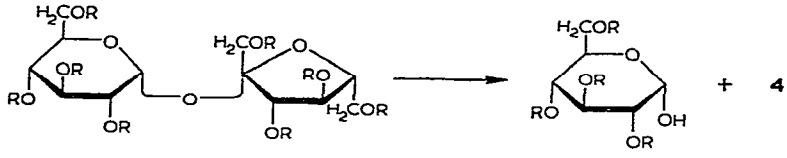
14

9, R = H
10, R = CH_2Ph

11, R = CH_2Ph ; R' = H
12, R = CH_2Ph ; R' = Bz
13, R = CH_2Ph ; R' = $\overset{O}{\overset{\|}{C}}-C_6H_4N_2Ph$ (*p*)

Another approach to the synthesis of 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**4**) was to use the D-fructofuranoside, sucrose (**15**). Because this disaccharide is markedly labile toward alkali, it cannot be benzylated with benzyl chloride and potassium hydroxide. However, the Kuhn-type of alkylation, with benzyl bromide, barium oxide, and silver oxide in *N*,*N*-dimethylformamide, was successfully applied to sucrose (**15**) by Tate and Bishop[6] and this procedure was repeated in the present work. The octa-*O*-benzylsucrose (**16**) was obtained, after chromatography, as a syrup having the appropriate elemental composition. Hydrolysis of **16** was effected in a mixture of water, acetic acid, and sulfuric acid at 65°, the highly insoluble 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose[7] (**17**) crystallizing directly from the reaction mixture in quantitative yield. Chromatography of a sample of the material remaining in the mother liquor led to the crystallization, for the first time, of 1,3,4,6-tetra-*O*-

benzyl-D-fructofuranose (**4**). With seed crystals available, the syrupy products obtained from D-fructose (**1**) and from 1,3,4,6-tetra-*O*-benzyl-D-mannitol (**11**) readily crystallized, and it was then found possible to obtain crystalline **4** from D-fructose in 60% overall yield. A crystalline benzoate (**7**) and an amorphous acetate (**8**) were



15, R = H
16, R = CH_2Ph

17, R = CH_2Ph

prepared from crystalline **4**; the optical rotation of the latter derivative ($[\alpha]_D^{20}$ +13.0°, chloroform) was reasonably close to that of the amorphous acetate ($[\alpha]_D^{20}$ +9.7°, chloroform) obtained as a byproduct in the methyl sulfoxide–acetic anhydride oxidation of 1,3,4,6-tetra-*O*-benzyl-D-mannitol (**11**).

The preparation of 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**4**) from 1,3,4,6-tetra-*O*-benzyl-D-mannitol (**11**) and from sucrose (**15**) constitutes unequivocal proof of its structure. Crystalline **4** shows a very slight dextromutarotation when dissolved in chloroform or in aqueous *p*-dioxane, but convincing evidence for the anomeric configuration of this substance as well as of the various esters of **4** reported here (**5**–**8**) is not presently available. Some chemical properties of **4** will be reported in a future communication.

EXPERIMENTAL

General methods. — Melting points are equivalent to corrected values. Qualitative t.l.c. was carried out 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 Silica Gel GF-254 (2 mm, E. Merck AG, Darmstadt). Column chromatography was carried out with Silica Gel No. 7734 (0.05–0.20 mm) of E. Merck.

1,3,4,6-Tetra-O-benzyl-D-fructofuranose (**4**) *from* D-*fructose* (**1**). — D-Fructose (45.0 g) was added to anhydrous methanol (900 ml) and the mixture was stirred at room temperature until the sugar was largely dissolved. Concentrated sulfuric acid (3.4 ml) was added cautiously and stirring was continued for 25 min, by which time the solution gave but a very faintly positive Fehling test. Amberlite IR-45 (CO_3^{2-}) (60 g) was added and the suspension was stirred for 5 min before being poured onto a column (4 × 44 cm) of Amberlite IR-45 (CO_3^{2-}). When the solution had passed through the column, the resin was washed with methanol (1 liter), the washings being added to the main solution. The solution was then evaporated *in vacuo* at 35° (bath) to a syrup to which was added benzyl chloride (125 ml) and powdered potassium hydroxide (50 g). The mixture was stirred and heated to 115–120°; while stirring

and heating were continued, more potassium hydroxide (175 g) was added over the course of 20 min. Inasmuch as the reaction is exothermic, the source of heat was removed from time to time in order to maintain the temperature at 115–116°. When addition of the potassium hydroxide was complete, the heating and stirring were continued for 5.5 h; the mixture was then cooled slightly and subjected to steam distillation for *ca.* 3 h in order to remove benzyl chloride and benzyl alcohol. The mixture (*ca.* 1 liter) was then cooled and the two phases were separated. The aqueous layer was extracted with four 100-ml portions of dichloromethane and the combined extracts were added to the organic layer which was then washed with water (1 liter) containing *ca.* 35 ml of acetic acid. (Omission of the acetic acid leads to the formation of intractable emulsions). The aqueous extract was washed with four 100-ml portions of dichloromethane, these extracts being added to the main organic solution. Moisture was removed from this solution with magnesium sulfate and the solution was filtered through a layer of decolorizing carbon. Evaporation of the solution *in vacuo*, eventually at *ca.* 1 mmHg and 140° (bath), gave a syrup (124 g) which was dissolved in acetic acid (500 ml). Water (120 ml) was added and the cloudy suspension was heated on a steam bath, becoming a clear solution as it warmed. After 2 h at 92° (steam bath), the solution was examined by t.l.c. (1:4 ether–benzene) and hydrolysis of the benzylated glycoside (**3**) was found to be complete. Cooled to room temperature, the mixture was diluted with water (1 liter) and the crude product was extracted with four 150-ml portions of dichloromethane. The combined extracts were shaken gently with water (1 liter) containing sodium hydrogen carbonate (80 g) until the evolution of carbon dioxide had ceased*. The organic layer was separated and washed with water (1 liter). Moisture was removed with magnesium sulfate and the solution was evaporated *in vacuo* (35° bath) to a thick syrup (125 g) which was dissolved, without heating, in isopropyl ether (437 ml, 3.5 ml/g). The solution was cooled to −5° and seeded with crystals of 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**4**), obtained as described later in this paper. The solution was kept at −5° and stirred from time to time over the course of several days as crystallization progressed. When crystallization appeared to have ceased, a chilled mixture of pentane (25 ml) and isopropyl ether (50 ml) was stirred into the mass and the solid was removed by filtration, the crystals being washed at −5° with a chilled mixture of pentane (50 ml) and isopropyl ether (100 ml) and then dried thoroughly *in vacuo* at room temperature: yield, 81.1 g (60%), m.p. 39–41°. For recrystallization, the 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose was dissolved in isopropyl ether (324 ml) without heating. The solution was filtered through a layer of decolorizing carbon (Darco X, 3 g) and the carbon was washed with 81 ml of isopropyl ether (to make a total of 5 ml/g); the solution was then cooled to −5° and seeded. The mixture was stirred from time to time over the course of 2 days as crystallization progressed. A chilled mixture of pentane (50 ml) and isopropyl ether (100 ml) was stirred into the crystalline mass and the pure product

*Owing to the serious foaming which can take place at this stage, it is advisable to conduct the operation in a capacious vessel; the authors used a 6-l flask.

was removed by filtration and dried *in vacuo* at room temperature; yield 70 g, m.p. 42–43°, $[\alpha]_D^{20}$ +6.5→+8.7° (25 h, *c* 1.43, chloroform); $[\alpha]_D^{20}$ −3.3→+5.7° (equilibrium, 28 h, *c* 1.07, 1:9 water–*p*-dioxane.)

Anal. Calc. for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found: C, 75.63; H, 6.90.

1,3,4,6-Tetra-O-*benzyl-2*-O-p-*nitrobenzoyl*-D-*fructofuranose* (**5**). — *p*-Nitrobenzoyl chloride (0.34 g) was added to pyridine (2.5 ml) and the mixture, cooled to −5°, was stirred while 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (0.5 g) was added. Stirring of the reaction mixture was continued at −5° overnight; t.l.c. (1:4 ether–benzene) then showed the acylation to be incomplete. The mixture was brought to room temperature and stirred for a day; t.l.c. then showed the reaction to be complete, two products having been formed in approximately equal quantities. The reaction mixture was worked up in conventional fashion to give a syrup (0.55 g) which was dissolved in a mixture of acetone (2.5 ml) and methanol (7 ml). At +5° crystallization progressed rapidly to give 0.28 g (45%) of **5**. Recrystallized from acetone–methanol, the product had m.p. 66–67° and $[\alpha]_D^{20}$ +35.7° (*c* 1.77, chloroform).

Anal. Calc. for $C_{41}H_{39}NO_9$: C, 71.40; H, 5.70; N, 2.03. Found: C, 71.24; H, 5.69; N, 1.98.

Prior to the crystallization of 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**4**), the *p*-nitrobenzoate (**5**) was obtained through *p*-nitrobenzoylation of crude, syrupy **4**, the yield of **5** being 29%, based on D-fructose.

1,3,4,6-Tetra-O-*benzyl-2*-O-p-*phenylazobenzoyl*-D-*fructofuranose* (**6**). — A mixture of 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**4**, 2.0 g), *p*-phenylazobenzoyl chloride (2.0 g), and pyridine (10 ml) was stirred for 2 days at room temperature. T.l.c. (1:4 ether–benzene) then showed the presence of two major colored products as well as of a trace of a third colored product; starting material was absent. A few drops of water were added and the reaction mixture was left at room temperature for 15 min to decompose the excess of *p*-phenylazobenzoyl chloride. Dichloromethane (20 ml) was added and the solution was washed with 1.5M sulfuric acid, the *p*-phenylazobenzoic acid thus precipitated then being removed by filtration. After being washed successively with aqueous sodium hydrogen carbonate solution and with water, the solution was dried with magnesium sulfate and evaporated *in vacuo* to a syrup (2.6 g) which was dissolved in acetone. On standing at −5° overnight, the solution deposited 1.5 g (54%) of fine needles, m.p. 123–124°. Recrystallization from acetone failed to change this m.p.: the pure substance (**6**) had $[\alpha]_D^{20}$ +34.6° (*c* 1.0, chloroform).

Anal. Calc. for $C_{47}H_{44}N_2O_7$: C, 75.38; H, 5.92; N, 3.74. Found: C, 75.29; H, 5.95; N, 4.04.

Compound **6** may be prepared directly from crude, syrupy **4**, the yield of **6** from D-fructose then being 26%.

2-O-*Benzoyl-1,3,4,6-tetra*-O-*benzyl*-D-*fructofuranose* (**7**). — Crystalline **4** (5.0 g) was added to a chilled mixture of benzoyl chloride (1.7 ml) and pyridine (6 ml) and the resulting mixture was kept for 26 h at room temperature; t.l.c. (11:1 benzene–ether) then showed that **4** was no longer present. The mixture was worked up in conventional fashion to yield, from absolute alcohol solution, 1.75 g (29%) of

crystalline product. After recrystallization from isopropyl alcohol, the material had m.p. 52–54° and $[\alpha]_D^{20}$ +37.0° (*c* 2.5, chloroform).

Anal. Calc. for $C_{41}H_{40}O_7$: C, 76.37; H, 6.25. Found: C, 76.23; H, 6.09.

2-O-Acetyl-1,3,4,6-tetra-O-benzyl-D-fructofuranose (**8**). — A solution of **4** (2.00 g) in a mixture of acetic anhydride (2.5 ml) and dry pyridine (10 ml) was heated for 3 h at 100°; examination by t.l.c. (5:1 benzene–ether) then showed the presence of only a small amount of **4**. The reaction mixture was worked up in conventional fashion to yield a crude product which was subjected to preparative t.l.c. (5:1 benzene–ether) to yield a major component (0.83 g, 38%) which was rechromatographed and finally obtained as a clear syrup which was dried for 8 h at 0.1 mm and 100°: $[\alpha]_D^{20}$ +13° (*c* 2.4, chloroform).

Anal. Calc. for $C_{36}H_{38}O_7$: C, 74.20; H, 6.57. Found: C, 73.95; H, 6.59.

1,3,4,6-Tetra-O-benzyl-2,5-O-methylene-D-mannitol (**10**). — A well-stirred mixture of 2,5-*O*-methylene-D-mannitol[4] (**9**, 15 g), benzyl chloride (150 ml) and powdered potassium hydroxide (75 g) was slowly heated at 115–125° and kept for 4.5 h in this temperature range (stirring being continued). The mixture was cooled, water (500 ml) was added, and the whole was subjected to steam distillation for 3.5 h. Again the mixture was cooled and now the organic (lower) layer was removed in a separatory funnel. The aqueous layer was washed with five 100-ml portions of ether, the extracts being added to the organic layer. The latter was extracted with three 100-ml portions of water, a few ml of acetic acid being added to break the emulsion which formed. Moisture was removed with magnesium sulfate and the solution was evaporated *in vacuo* to a syrup (39.2 g) that was dissolved in methanol (70 ml). Crystallization was allowed to progress, first at room temperature and then at −5°, to give 31 g (72%) of product, m.p. 54–56°, which appeared homogeneous by t.l.c. (1:25 ether–dichloromethane). The material was dissolved in isopropyl ether (2 ml/g) and the solution was treated with decolorizing carbon; crystallization was allowed to proceed at −5° and the crystals were washed with chilled 1:2 pentane–isopropyl ether to give 30 g of pure 1,3,4,6-tetra-*O*-benzyl-2,5-*O*-methylene-D-mannitol (**10**), m.p. 55–56°. Further recrystallization failed to change this m.p. and yielded material having $[\alpha]_D^{20}$ −6.6° (*c* 1.02, chloroform).

Anal. Calc. for $C_{35}H_{38}O_6$: C, 75.78; H, 6.91. Found: C, 75.52; H, 6.98.

1,3,4,6-Tetra-O-benzyl-D-mannitol (**11**). — The hydrolytic cleavage of the methylene acetal (**10**) was patterned after a procedure described by Wolfrom, Lew, and Goepp[8]. Tetra-*O*-benzyl-2,5-*O*-methylene-D-mannitol (**10**, 20 g) and phloroglucinol (38 g) were dissolved in *p*-dioxane (1100 ml) and the solution was diluted with 0.6M hydrochloric acid (770 ml). The reaction mixture was boiled gently under reflux, the progress of the hydrolysis being monitored by t.l.c. with 1:4 ether–dichloromethane. After 21 h, concentrated hydrochloric acid (81 ml) was added and the heating was continued for a further 10 h. The cooled mixture was then evaporated *in vacuo* at 35° (bath) to a dry, crystalline mass which was shaken with dichloromethane (200 ml) at room temperature. Unchanged phloroglucinol was removed by filtration and washed with more (100 ml) dichloromethane; the combined filtrate

and washings were washed with aqueous sodium hydrogen carbonate solution and then with water. Moisture was removed with magnesium sulfate and the solution was filtered through a small amount of decolorizing carbon and evaporated *in vacuo* to a syrup (17.3 g), which was dissolved in a mixture of ether (100 ml) and pentane (130 ml). Crystallization progressed at −5° to give 15.1 g (77%) of product in two crops; recrystallized from ether–pentane and then from isopropyl ether, the pure 1,3,4,6-tetra-*O*-benzyl-D-mannitol (**11**) had m.p. 55–56° and $[\alpha]_D^{20}$ +31.2° (*c* 0.87, chloroform).

Anal. Calc. for $C_{34}H_{38}O_6$: C, 75.25; H, 7.06. Found: C, 75.20; H, 6.96.

2,5-Di-O-benzoyl-1,3,4,6-tetra-O-benzyl-D-mannitol (**12**). — A mixture of 1,3,4,6-tetra-*O*-benzyl-D-mannitol (**11**, 100 mg), benzoyl chloride (0.1 ml), and pyridine (0.5 ml) was heated for 2 h at 45° and the cooled reaction mixture was then diluted with water. Rubbed with fresh water, the precipitated syrup crystallized: yield, 78 mg (57%). Recrystallized twice from alcohol, the product had m.p. 68–69° and $[\alpha]_D^{20}$ +15.4° (*c* 1.0, chloroform).

Anal. Calc. for $C_{48}H_{46}O_8$: C, 76.78; H, 6.18. Found: C, 76.78; H, 5.93.

1,3,4,6-Tetra-O-benzyl-2,5-di-O-p-phenylazobenzoyl-D-mannitol (**13**). — A mixture of 1,3,4,6-tetra-*O*-benzyl-D-mannitol (**11**, 200 mg), *p*-phenylazobenzoyl chloride (360 mg) and pyridine (1 ml) was heated for 1.3 h at 45° and then cooled. Water was added and the product was extracted with dichloromethane; after washing the extract with cold 1.5M sulfuric acid it was filtered (to remove *p*-phenylazobenzoic acid) and washed with sodium hydrogen carbonate solution. Moisture was removed with magnesium sulfate and the solution was evaporated *in vacuo* to a syrup to which ethanol (15 ml) was added. On standing at room temperature, the mixture afforded fine needles: yield, 240 mg (68%). The crude product thus obtained was stirred with isopropyl ether (6 ml) and the insoluble solid (30 mg) was removed by filtration. The filtrate was concentrated *in vacuo* to dryness and the residue was dissolved in dichloromethane (1 ml); absolute ethanol (10 ml) was added, and crystallization was allowed to progress; yield 190 mg, m.p. 62–63°, $[\alpha]_D^{20}$ −15.0° (*c* 1.15, chloroform).

Anal. Calc. for $C_{60}H_{54}N_2O_8$: C, 75.14; H, 5.68; N, 5.84. Found: C, 75.25; H, 5.90; N, 5.95.

The oxidation of 1,3,4,6-tetra-O-benzyl-D-mannitol (**11**) *with methyl sulfoxide–acetic anhydride.* — In a preliminary experiment, a solution of **11** (2.05 g) in methyl sulfoxide (90 ml) was diluted with acetic anhydride (60 ml) and the optical rotation of the resulting reaction mixture was observed in a 1-dm tube at 20°; the rotation is plotted in Fig. 1 as a function of time. At 125 min (A), 198 min (B), 231 min (C), 389 min (D), and 50 h (E) a small portion of the reaction mixture was removed and treated with 40 times its volume of water. The aqueous layer was separated from the syrup and extracted with dichloromethane; both the syrup and the dichloromethane extract together were examined by t.l.c. (1:1 ether–carbon tetrachloride). At time A, 1,3,4,6-tetra-*O*-benzyl-D-mannitol (**11**) preponderated, the 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**4**) representing less than *ca.* 5% of the mixture; at time B, the same two components were detected, the **4** then representing *ca.* 20%

of the mixture. At time C, **11** and **4** were present in approximately equal quantities and were accompanied by traces of an acetate of **4** (see below). By time D, no **11**

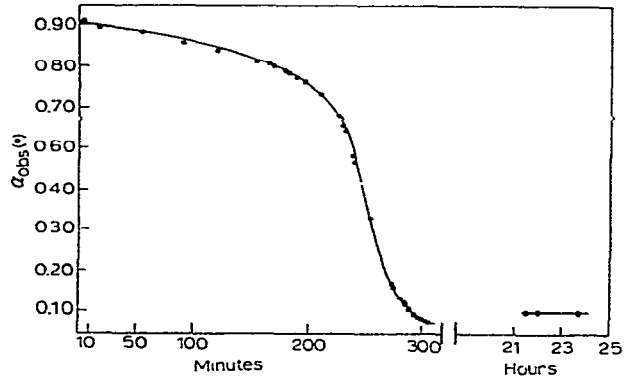


Fig. 1. Optical rotation of 1,3,4,6-tetra-*O*-benzyl-D-mannitol (**11**) in methyl sulfoxide–acetic anhydride.

could be detected; the mixture was approximately 50% **4**, 30% of an acetate of **4**, and 20% of a compound which was assumed to be a (methylthio)methyl 1,3,4,6-tetra-*O*-benzyl-D-fructofuranoside (**14**, see below). By time E, the **4** had disappeared, leaving **14** and the acetate of **4** in a ratio of approximately 3:7.

Acetic anhydride (57 ml) was added to a solution of **11** (1.92 g) in methyl sulfoxide (85 ml). When the optical rotation of the resulting mixture was close to the minimum (4.3 h), the solution was poured into ice–water (800 ml). The mixture was extracted with dichloromethane and the extract was washed thoroughly with aqueous sodium hydrogen carbonate solution. Moisture was removed with magnesium sulfate and the solution was evaporated *in vacuo* to a syrup which was dissolved in methanol. Methanolic barium methoxide was added to cleave the acetate of **4** (t.l.c.); the methanolic solution was evaporated *in vacuo* to give a semi-crystalline mass which was subjected to preparative t.l.c. (1:6 ether–benzene). The band having the migration rate of **4** was eluted with ether and the eluate was evaporated to give crystalline material which was recrystallized from isopropyl ether to yield 268 mg (14%) of **4**, m.p. 41–42°; a mixture m.p. with **4**, derived from D-fructose as described earlier, was undepressed.

A reaction, similar to that described above, was carried out with 199.1 mg of **11** and halted after 4.75 h. The syrupy product was subjected to preparative t.l.c. (1:1 ether–carbon tetrachloride) and separated into three bands. The slowest-moving component (56.6 mg) was **4**; the middle band afforded a component (48.3 mg) which had $[\alpha]_D^{20}$ +9.7° (*c* 1.3, chloroform) and strong absorption at 1700 cm^{-1} (neat). After treatment of this material with barium methoxide in methanol solution, it was examined by t.l.c. (1:1 ether–carbon tetrachloride) and then found to be chromatographically identical with **4**. The fastest-moving band yielded a syrupy material (51.4 mg) which had $[\alpha]_D^{20}$ +6° (*c* 2.4, chloroform) and an i.r. spectrum devoid of carbonyl and hydroxyl absorption. Its elemental composition is consistent with the

conclusion that it is a (methylthio)methyl 1,3,4,6-tetra-*O*-benzyl-D-fructofuranoside (**14**).

Anal. Calc. for $C_{36}H_{40}O_6S$: C, 71.97; H, 6.71; S, 5.34. Found: C, 72.12; H, 7.01; S, 5.33.

Octa-O-benzylsucrose (**16**). — Sucrose (**15**) was benzylated in *N,N*-dimethylformamide solution with benzyl bromide, barium oxide, and silver oxide as described by Tate and Bishop[6], the temperature of the stirred mixture being kept for 3 h at 50–55°. After removal of the excess of the reactants, the crude product was chromatographed on a column of silica gel, benzyl ether and benzyl alcohol being eluted with 1:5 isopropyl ether–cyclohexane. The octa-*O*-benzylsucrose (**16**) was eluted with 1:1 isopropyl ether–cyclohexane and obtained as a syrup which showed $[\alpha]_D^{20}$ +38.6° (*c* 1.31, chloroform); lit.[6] $[\alpha]_D^{20}$ +31.6° (*c* 1.65, chloroform), $[\alpha]_D^{20}$ +38.6° (*c* 1.62, chloroform)[9].

Anal. Calc. for $C_{68}H_{71}O_{11}$: C, 76.81; H, 6.64. Found: C, 76.74; H, 6.17.

Hydrogenolysis of a small sample of **16** over a palladium catalyst readily led to the isolation of crystalline sucrose.

The hydrolysis of octa-O-benzylsucrose (**16**). — Octa-*O*-benzylsucrose (**16**, 5.4 g) was dissolved in glacial acetic acid (50 ml) and the solution was heated at 65° (water bath) and stirred while 2M sulfuric acid was added in 4-ml portions, care being taken to avoid the precipitation of a syrup. After 10 min, 12 ml of the dilute sulfuric acid had been added and the precipitation of crystalline 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**17**) began. Crystallization was allowed to proceed in the stirred mixture over the course of 6 h at 65°, 2M sulfuric acid being added cautiously from time to time (to a total of 26 ml) without precipitating syrup. Finally, the reaction mixture was stirred overnight at room temperature and the 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**17**) was removed by filtration: 2.8 g (102%). Recrystallized from hot propyl alcohol, the **17** (2.1 g, 76%) had m.p. and mixture m.p. 153–154° and $[\alpha]_D^{20}$ +19.1° (*c* 1.57, chloroform); lit.[7] $[\alpha]_D^{20}$ +21.2 ±0.6° (*c* 3.5, chloroform).

The filtrate remaining after the removal of the 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose was diluted with water and extracted with dichloromethane. The extract was washed successively with aqueous sodium hydrogen carbonate solution and with water. Moisture was removed with magnesium sulfate and the solution was evaporated *in vacuo* (35° bath) to a syrup (1.8 g) which was dissolved in isopropyl ether and seeded* to give 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**4**); yield, 0.48 g (17%). After recrystallization from isopropyl ether at −5°, the product (0.25 g) had m.p. 42–43°; a mixture m.p. with a sample of **4**, prepared from D-fructose as described earlier, was undepressed.

*A sample of the material from a similar preparation was chromatographed on a column of silica gel with 1:1 ether–carbon tetrachloride. Saturated solutions of the chromatographically homogeneous product in pentane and in hexane gave the first crystals of **4** when they were kept for several days at +5°.

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REFERENCES

1 R. BARKER AND H. G. FLETCHER, JR., *J. Org. Chem.*, 26 (1961) 4605.
2 S. TEJIMA AND H. G. FLETCHER, JR., *J. Org. Chem.*, 28 (1963) 2999.
3 C. P. J. GLAUDEMANS AND H. G. FLETCHER, JR., in W. W. ZORBACH AND R. S. TIPSON (Eds.), *Synthetic Procedures in Nucleic Acid Chemistry*, Vol. 1, Interscience, New York, 1968, p. 126.
4 A. T. NESS, R. M. HANN, AND C. S. HUDSON, *J. Amer. Chem. Soc.*, 65 (1943) 2215.
5 J. D. ALBRIGHT AND L. GOLDMAN, *J. Amer. Chem. Soc.*, 87 (1965) 4214; *ibid.*, 89 (1967) 2416.
6 M. E. TATE AND C. T. BISHOP, *Can. J. Chem.*, 41 (1963) 1801.
7 O. TH. SCHMIDT, T. AUER, AND H. SCHMADEL, *Chem. Ber.*, 93 (1960) 556.
8 M. L. WOLFROM, B. W. LEW, AND R. M. GOEPP, *J. Amer. Chem. Soc.*, 68 (1946) 1443.
9 T. IWASHIGE AND H. SAEKI, *Chem. Pharm. Bull.* (Tokyo), 15 (1967) 1803.