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Note

Synthesis of 6-thiosucrose, and an improved route to 6-deoxysucrose*

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Over the past decade, various specific modifications of the primary hydroxyl groups of sucrose have been accomplished, including the synthesis of disubstituted sucroses in which substituents to C-6 and C-6′ have been modified[1–6] and various monosubstitutions made[7,8]. The synthesis of cyclic acetals by Khan *et al.*[9] has made it possible to select just one of the primary hydroxyl groups[8] in later modifications. We now report the synthesis of 6-thiosucrose (**7**) and 6-deoxysucrose (**9**) *via* the 4,6-isopropylidene acetal of sucrose.

Selective iodination of 2,3,1′,3′,4′,6′-hexa-*O*-benzoylsucrose[9] (**3**) with triphenylphosphine, iodine, and imidazole[10] gave 2,3,1′,3′,4′,6′-hexa-*O*-benzoyl-6-deoxy-6-iodosucrose (**4**) in 75% yield. Nucleophilic displacement of the iodine by potassium thioacetate[11] gave 6-*S*-acetyl-2,3,1′,3′4′,6′-hexa-*O*-benzoyl-6-thiosucrose (**5**), which was de-esterified with sodium methoxide in methanol[12], and treated with 1,4-dithiothreitol[13], to yield crystalline 6-thiosucrose (**7**) in 48% yield from the iodo derivative.

The synthesis of 6-deoxysucrose (**9**) was accomplished by direct hydrogenation of **4** in tetrahydrofuran, in the presence of Pd–C catalyst[14], to give **8** in a yield of 85%. De-esterification of **8** with sodium methoxide in methanol gave 6-deoxysucrose (**9**) in 80% yield.

In none of the steps of the syntheses were chromatographic methods used, as had previously been done in the synthesis of many modified sucroses[1–4,6,8]. Instead, we employed selective crystallizations, which greatly increased the amounts of material that we could obtain.

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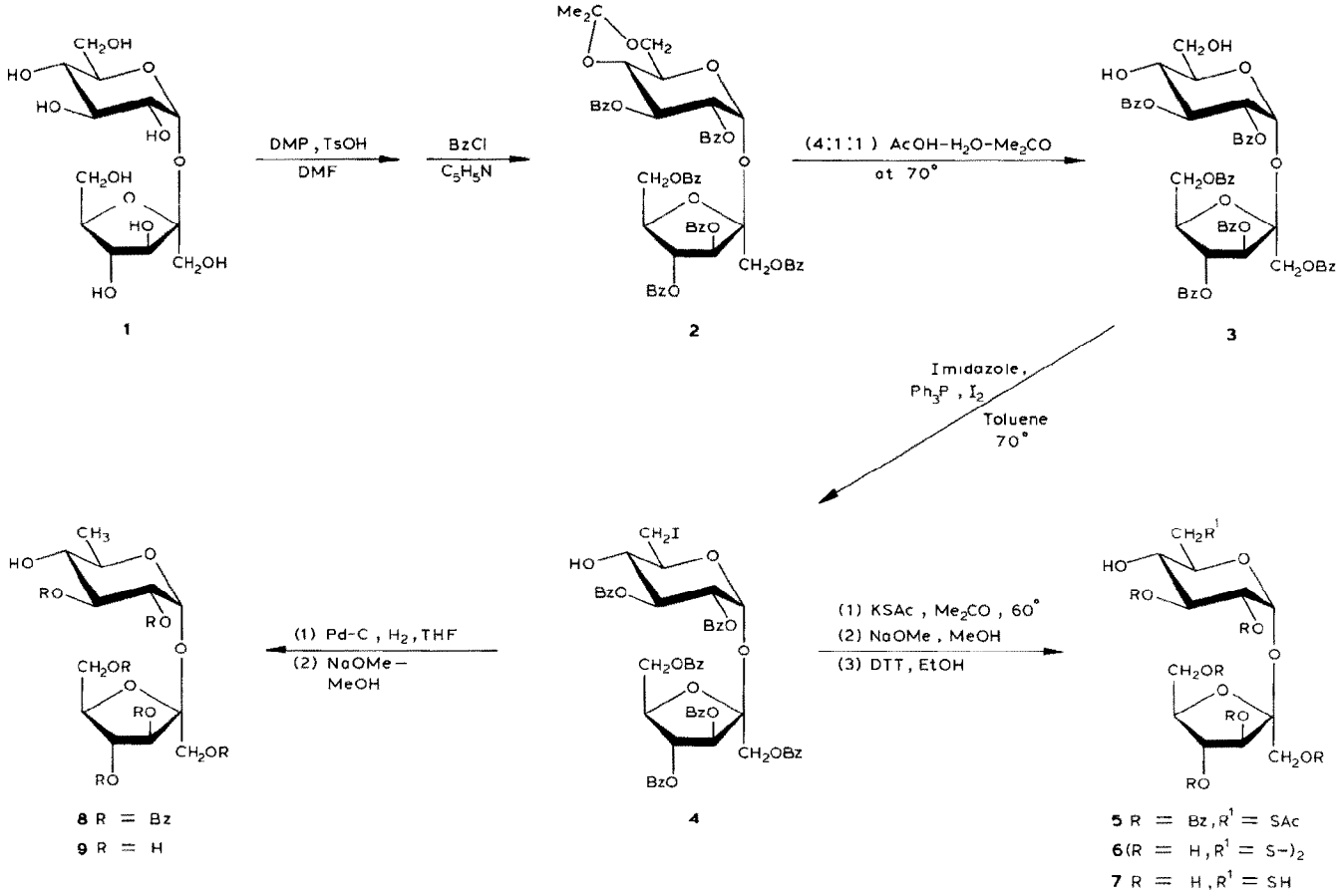

DMP = 2,2-dimethoxypropane , DTT = 1,4-dithiothreitol , TsOH = *p*-toluenesulfonic acid

EXPERIMENTAL

General methods. — Thin-layer chromatography (t.l.c.) was conducted on Analtech HETLC-GHLF t.l.c. plates in 2:1 (v/v) ether–hexane, compounds being detected by fluorescence quenching. Melting and decomposition points were determined by using a Mel-Temp melting-point apparatus. Optical rotations were recorded with a Rudolph polarimeter and a sodium light-source. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. ^{13}C-Nuclear magnetic resonance (n.m.r.) spectra were recorded with a JEOL FX-90Q Fourier-transform spectrometer.

4,6-O-Isopropylidenesucrose hexabenzoate (**2**). — Compound **2** was prepared by the following modification of the procedure of Khan *et al.*[9]. Sucrose (30 g) was acetalated with 2,2-dimethoxypropane (140 mL) and *p*-toluenesulfonic acid (500 mg) in *N,N*-dimethylformamide (300 mL), with stirring, for 1 h at 20°. The acid was neutralized by stirring for 15 min with Amberlite IR-45 (OH^-) resin, the suspension filtered, and the filtrate evaporated to a syrup under diminished pressure at 35° with a condenser cooled with Dry Ice–acetone. The resulting syrup was treated with benzoyl chloride (72 mL) and pyridine (500 mL) for 1 h at 0°, kept for 12 h at 20°, and the solution poured slowly, with rapid stirring, into ice–water slush (3 L) containing sodium hydrogencarbonate (90 g); the resulting white foam was filtered off, washed several times with water, and dissolved in dichloromethane (200 mL). The solution was poured into hot ethanol, and kept for 12 h at −20°. The ethanol was decanted, leaving a heavy syrup which was shown by t.l.c. to contain three major components. Compound **2** was selectively crystallized by dissolving the syrup in dichloromethane (100 mL), adding warm ether at 32° (400 mL), and then slowly adding hexane (800 mL), with stirring. As the solution cooled, **2** usually crystallized, but, in some preparations, addition of seed crystals was necessary. One recrystallization yielded pure **2** (30 g, 34%); m.p. 167–170°, $[\alpha]_D$ +52.5° (*c* 6.6, dichloromethane); lit.[9] m.p. 168–170°, $[\alpha]_D$ +46° (chloroform); the ^{1}H-n.m.r. data were similar to those previously reported[9].

2,3,1',3',4',6'-Hexa-O-benzoylsucrose (**3**). — Compound **3** was prepared by the following modification of the procedure previously reported[9]. To a solution of compound **2** (20 g) in acetone (100 mL) was added glacial acetic acid (400 mL), the solution was heated to 70°, and water (100 mL) was slowly added with stirring. The solution was kept for 20 min at 70°; t.l.c. then showed that none of the starting material remained. The solution was concentrated under vacuum to 300 mL, and the concentrate poured into dichloromethane (200 mL). The organic phase was washed three times with water (800 mL), and evaporated *in vacuo* to a syrup. Ether (250 mL) was added, with stirring, and then hexane (250 mL) was slowly added, with stirring. Compound **3** crystallized during the next 2 h; yield, 16.5 g (86%); m.p. 122–126°, $[\alpha]_D$ +71.0° (*c* 1.97, dichloromethane); lit.[9] m.p. 124–125°, $[\alpha]_D$ +59° (chloroform); the ^{1}H-n.m.r. data were similar to those previously reported[9].

2,3,1',3',4',6'-Hexa-O-benzoyl-6-deoxy-6-iodosucrose (**4**). — A solution of

compound **3** (12 g) in toluene (360 mL) was warmed to 50°, and iodine (4.26 g) was added, followed by slow addition, with stirring, of a mixture of triphenylphosphine (4.7 g) and imidazole (2.5 g). The resulting solution was kept for 1 h at 70°, when t.l.c. showed none of the starting material remaining. A saturated solution of sodium thiosulfate in water (200 mL) was added; the organic phase was separated, washed twice with water, and evaporated to a syrup that was dissolved in hot ethanol (300 mL), stirred for 1 h at 20°, cooled to 0° with stirring, and kept overnight at −20°. The product crystallized continuously throughout this procedure. Recrystallization from 1:1 (v/v) ether–hexane gave **4** (12 g, 75%); m.p. 137–140°, $[\alpha]_D$ +50.2° (*c* 2.1, dichloromethane); ^{13}C-n.m.r. data (p.p.m. from tetramethylsilane): δ 78.5, 77.1, and 75.6; ($CDCl_3$, internal standard): 104.6 (C-2′), 91.2 (C-1), 79.0, 77.5, 76.5, 73.3 (2 signals superimposed), 70.8 and 70.3 (C-2,3,4,5,3′4′5′; not specifically assigned), 64.7 and 64.3 (C-1′ and 6′; not specifically assigned), and 7.8 (C-6).

6-Thiosucrose (**7**). — To a solution of compound **4** (5 g) in acetone (20 mL) in a small flask was added powdered potassium thioacetate (1.1 g). The flask was sealed, and the suspension was stirred for 1 h at 60°, when t.l.c. showed that no starting material remained. The mixture was then poured into a saturated solution of sodium thiosulfate in water (50 mL), and extracted with dichloromethane (50 mL). The extract was washed twice with water (100 mL), dried (calcium sulfate), decolorized with charcoal, and evaporated under reduced pressure, to give 6-*S*-acetyl-2,3,1′,3′,4′,6′-hexa-*O*-benzoyl-6-thiosucrose (**5**) as a foam (4 g). The foam was dissolved in dry methanol (100 mL), to which was added sodium methoxide (300 mg). This solution was stirred for 24 h at 20°, the base neutralized with Amberlite IRC-50 (H^+) cation-exchange resin, the suspension filtered, and the filtrate concentrated to 5 mL. Water (2 mL) and iodine (0.25 g) were added, to convert **7**

TABLE I

^{13}C-N.M.R CHEMICAL SHIFTS[a]

Carbon atom	*Sucrose*[b]	*6-Thiosucrose*	*6-Deoxysucrose*
1	93.0	93.1	92.1
2	71.9	72.1 (2 signals)	69.4 72.3,
3	73.4	72.8, 73.4	73.4, 76.1
4	70.0	(resonances not	(resonances not
5	73.2	assigned)	assigned)
6	60.9	26.0	17.7
1′	62.1	62.7	62.6
2′	104.5	104.6	104.6
3′	77.2	77.7	77.7
4′	74.8	75.1	75.1
5′	82.1	82.4	82.4
6′	63.2	63.5	63.3

[a]In p.p.m. from tetramethylsilane. Solvent was D_2O; internal standard was methanol (49.9 p.p.m.). [b]Data from Morris and Hall[15].

into the disulfide, 6,6-dithiodisucrose (**6**). Addition of acetonitrile (40 mL) precipitated compound **6**, which was washed with acetonitrile, and dissolved in water (2 mL) containing 1,4-dithiothreitol (1 g). This solution was stirred for 1 h; then, ethanol (25 mL) and acetonitrile (50 mL) were added, and the solution was kept overnight at 5°, to give crystalline **7** (0.8 g, 48%; yield from sucrose, 10.5%); m.p. 182–190° (dec.), $[\alpha]_D$ +56.4° (*c* 1.02, water); see Table I for ^{13}C-n.m.r. data.

Anal. Calc. for $C_{12}H_{22}O_{10}S$: C, 40.20; H, 6.19; S, 8.95. Found: C, 40.45; H, 6.17; S, 9.13.

2,3,1′3′,4′,6′-Hexa-O-benzoyl-6-deoxysucrose (**8**). — To a solution of **4** (1 g) in tetrahydrofuran (25 mL) were added diethylamine (2 mL) and 10% palladium-on-charcoal (0.1 g). Hydrogen was slowly bubbled through the stirred mixture for 9 h, at which time, t.l.c. showed that the reaction was complete. The suspension was filtered, and the filtrate evaporated under reduced pressure, to a foam that was dissolved in dichloromethane (10 mL), and the solution washed twice with a saturated solution of sodium thiosulfate in water (20 mL) and once with water (20 mL), concentrated to 1 mL, and ether (5 mL) added. The solution was warmed to 30°, and hexane (5 mL) was slowly added, with stirring. The solution was kept, with slow stirring for 24 h at 20°, during which time, **8** crystallized (0.75 g, 85%); m.p. 111–115°, $[\alpha]_D$ +63.1° (*c* 2.59, dichloromethane); ^{13}C-n.m.r. data (p.p.m. from tetramethylsilane): δ 129.1, 128.0, and 126.9, (benzene-d_6, internal standard): 104.0 (C-2′), 91.3 (C-1), 79.6, 77.9, 77.3, 75.2, 74.4, 72.0, 69.3 (C-2,3,4,5,3′,4′,5′; not specifically assigned), 65.1 (C-1′,6′, superimposed), and 17.7 (C-6).

6-Deoxysucrose (**9**). — A solution of compound **8** (0.75 g) in dry methanol (30 mL) to which sodium methoxide (0.05 g) had been added was stirred for 48 h at 20°, and then treated with Amberlite IRC-50 (H^+) cation-exchange resin, the suspension filtered, and the filtrate evaporated to a syrup that was dissolved in ethanol (10 mL), and ether (20 mL) added to precipitate **9** (0.20 g, 80%; yield from sucrose, 14.9%). Compound **9** crystallized from hot ethanol; m.p. 172–180° (dec.), $[\alpha]_D$ +54.8° (*c* 1.03 water); see Table I for ^{13}C-n.m.r. data.

Anal. Calc. for $C_{12}H_{23}O_{10}$: C, 44.03; H, 7.08. Found: C, 44.28; H, 6.94.

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