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THE SYNTHESIS OF SOME FLUORO DERIVATIVES OF SUCROSE*

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ABSTRACT

2,3,1′,3′4′,6′-Hexa-*O*-benzylsucrose was obtained by mild acid-catalysed hydrolysis of the 4,6-*O*-isopropylidene derivative and then converted into its 4,6-di-*O*-mesyl derivative. Selective displacement of this disulphonate with fluoride anion (from tetrabutylammonium fluoride) then afforded the 6-fluoro-4-mesylate. Removal of the protecting groups yielded 6-deoxy-6-fluorosucrose, which was characterised as its crystalline hepta-acetate. A derivative of 6-deoxy-6-fluoro-*galacto*-sucrose was formed when the above 6-fluoro-4-mesylate was subjected to nucleophilic displacement with benzoate anion.

INTRODUCTION

Previous communications have described our interests in the synthesis of deoxyfluoro sugars as possible inhibitors of glycosidases[1], including several fluorotrehaloses which showed inhibitory activity towards insect trehalase[2]. The possibility that fluoro derivatives of sucrose might function as inhibitors of dextransucrase elaborated by *Leuconostoc mesenteroides* and several other bacteria is of interest in preventing tooth decay[3]. Whilst Robyt and Zikopoulis[4], in a patent, have described the formation of a mixture of fluorinated sucroses from the reaction of 6,1′,6′-tri-*O*-tripsylsucrose penta-acetate with potassium fluoride followed by *O*-deacetylation, the products claimed, namely, the 1′-, 6-, and 6′-monofluorides, the 6,1′-, 1′,6′-, and 6,6′-difluorides, and the 6,1′,6′-trifluoride are unlikely. It is well known that nucleophilic substitution at C-1′ is difficult; indeed, Guthrie *et al.*[5] were unable to prepare 1′-deoxy-1′-fluorosucrose by this approach. In addition, Robyt and Zikopoulis[4] claimed the preparation of pure samples of 6-deoxy-6-fluorosucrose, 6,6′-dideoxy-6,6′-difluorosucrose, and 6,1′,6′-trideoxy-6,1′,6′-trifluorosucrose by reaction of the appropriately blocked perbenzoylated sucroses with di-

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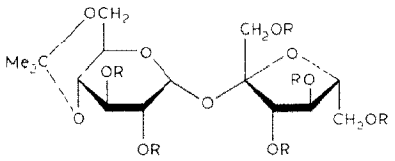
methylaminosulphur trifluoride, although they did not cite any physical data for these compounds.

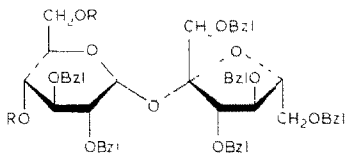
Furthermore, as a result of our discovery that certain chloro derivatives of sucrose are markedly sweeter than sucrose itself, it was of interest to prepare fluoro derivatives of sucrose for assessment of their sweetness[6].

RESULTS AND DISCUSSION

4,6-*O*-Isopropylidenesucrose (**1**) was prepared according to the procedure of Khan[7] and was best isolated as its highly crystalline hexabenzoate (**2**). Since acyl groups are unsuitable blocking-groups for fluoride displacement reactions[8], it was essential to replace them by benzyl groups, which are stable under these conditions but may be removed subsequently by catalytic hydrogenolysis. Accordingly, the hexabenzoate **2** was treated with sodium hydride and benzyl chloride in *N*,*N*-dimethylformamide to give the required hexabenzyl ether **3** in high yield. Acid hydrolysis of **3** with acetic acid removed the isopropylidene group and afforded the 4,6-diol **4** which, with mesyl chloride in pyridine, gave the required 4,6-dimesylate **5** in 95% yield. The ^{1}H-n.m.r. spectrum of **5** indicated the presence of two methanesulphonyloxy groups but, as with all of these compounds that contain several benzyl groups, the rest of the spectrum was beyond first-order interpretation because of very substantial overlap.



1 R = H
2 R = Bz
3 R = Bzl



4 R = H
5 R = Ms

Reaction of the dimesylate **5** with tetrabutylammonium fluoride[9] in boiling acetonitrile for 16 h afforded the 6-deoxy-6-fluoro-4-mesylate **6** in 80% yield as a syrup. The ^{19}F-n.m.r. spectrum of **6** displayed a single resonance as a triplet of doublets, consistent with the fluorine being present at a primary position[10]. Furthermore, the observed coupling constants ($J_{F,H-6}$ 47 and $J_{F,H-5}$ 21.9 Hz) were consistent with its being at C-6 of a glucopyranoside ring[11] in which the fluorine atom has an antiperiplanar relationship to H-5. Removal of the 4-mesylate group from the 6-fluoride **6** was achieved by treatment with boiling methanolic sodium hydroxide for 20 h, to give the 4-ol **7** in 78% yield. Difficulties were then experienced with the hydrogenolytic removal of the six benzyl ether groups. Hydrogenolysis of **7** in the usual way, with or without added acid, gave complex mixtures

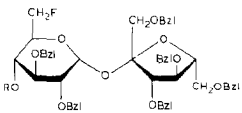
TABLE I

^{19}F-N.M.R. DATA[a]: CHEMICAL SHIFTS (P.P.M. TO HIGH FIELD OF EXTERNAL HEXAFLUOROBENZENE) AND COUPLING CONSTANTS (Hz) AT 56.4 MHz

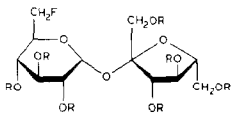
	6	**7**	**9**	**10**	**11**
F-6	72.12	70.3	67.12	63.68	63.03
$J_{F,H-6}$	47.0	46.4	47.6	42.6	47.6
$J_{F,H-5}$	21.9	27.6	22.6	16.3	12.5

[a]For solutions in $CDCl_3$.

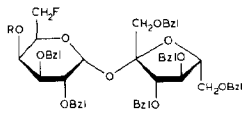
of products as indicated by t.l.c., probably because of the incomplete removal of the benzyl ether groups. However, catalytic transfer hydrogenation[12] with 20% palladium-on-charcoal in a mixture of boiling ethanol and cyclohexene for five days removed the benzyl groups, albeit slowly, to give a single product, 6-deoxy-6-fluorosucrose (**8**). The latter was isolated as a syrup which was characterised as its crystalline hepta-acetate **9** (71% yield from **7**). The ^{19}F-n.m.r. spectrum of **9** was in accord with this structure (Table I), and the mass spectrum of **9** showed ionic fragments at *m/z* 291 and 331 due to the 2,3,4-tri-*O*-acetyl-6-deoxy-6-fluoro-glucopyranosyl and 1,3,4,6-tetra-*O*-acetylfructofuranosyl moieties, respectively. The ion at *m/z* 291 underwent successive losses of acetic acid, ketene, and acetic acid, to give ions at *m/z* 231, 189, and 129, respectively, indicating that the fluorine was not located at any position other than C-6. In addition, the ^{1}H-n.m.r. spectrum was in complete accord with the proposed structure of the fluorosucrose (see Experimental).



6 R = Ms
7 R = H



8 R = H
9 R = Ac



10 R = Bz
11 R = H

Treatment of the 6-fluoro-4-mesylate **6** with sodium benzoate in hexamethylphosphoric triamide at 100° resulted in displacement of the mesyloxy group to give 81% of syrupy 4-*O*-benzoyl-6-fluoro-*galacto*-sucrose (**10**). The ^{19}F-n.m.r. spectrum of **10** was as expected for a 6-deoxy-6-fluorogalactopyranoside, inasmuch as the $J_{F,H-5}$ value (16.3 Hz) was markedly smaller than the corresponding value (22.6 Hz) for **9** and in the general range for galactopyranosides (12–18 Hz)[10,11].

Removal of the *O*-benzoyl group from **10** with sodium methoxide afforded the 4-ol **11** in 88% yield as a syrup. The ^{19}F-n.m.r. spectrum of **11** was in accord with the structure (Table I), although, as with similar compounds, the ^{1}H-n.m.r. spectrum of **11** was too complex, because of overlapping resonances, to be of help in structural elucidation.

EXPERIMENTAL

4,6-O-Isopropylidenesucrose hexabenzoate (**2**). — To a solution of sucrose (34.2 g, 0.1 mol) in dry *N,N*-dimethylformamide (400 mL) containing Type 3A molecular sieve as desiccant were added methyl isopropenyl ether (12.1 mL, 0.13 mol) and dry toluene-*p*-sulphonic acid (30 mg). The mixture was then heated at 70° for 40 min, when t.l.c. (chloroform–methanol, 2:1) indicated that the reaction was complete and that one major product had been formed. The mixture was cooled to room temperature and the acid neutralised by the addition of a little solid anhydrous sodium carbonate. The inorganic residue was then filtered off and the filtrate evaporated to dryness to give a syrup which was purified by elution from a column of silica gel with chloroform–methanol (10:1). Evaporation of the appropriate fractions afforded 4,6-*O*-isopropylidenesucrose (**1**; 25 g, 65%) as a white powder.

Conventional treatment of the foregoing product with benzoyl chloride–pyridine gave the hexabenzoate **2**, m.p. 167–168° (from ethanol), $[\alpha]_D$ +45.6° (*c* 1, chloroform); lit.[7] m.p. 168–170°, $[\alpha]_D$ +46°.

2,3-Di-O-benzyl-4,6-O-isopropylidene-α-D-glucopyranosyl 1,3,4,6-tetra-O-benzyl-β-D-fructofuranoside (**3**). — To a stirred solution of **2** (15 g) in dry *N,N*-dimethylformamide (300 mL) was added sodium hydride (20 g of a 60% dispersion in oil, ~0.5 mol) followed by benzyl chloride (100 mL, 0.87 mol). The mixture was stirred overnight at room temperature, and t.l.c. (light petroleum–ethyl acetate, 3:1) then showed a single component. Ethanol (100 mL) was added to decompose the excess of reagents, the resulting inorganic material was filtered off, and the filtrate was evaporated to dryness. The resulting syrup was purified by chromatography on silica gel with light petroleum–ethyl acetate (9:1), to give **3** (11 g, 93%) which failed to crystallise; $[\alpha]_D$ +41.2° (*c* 1.2, chloroform) (Found: C, 74.15; H, 6.42. $C_{57}H_{62}O_{11}$ calc.: C, 74.19; H, 6.72%).

2,3,1',3',4',6'-Hexa-O-benzylsucrose (**4**). — A mixture of **3** (10 g), acetic acid (100 mL), acetone (20 mL), and water (30 mL) was stirred at 85–90° for 30 min; t.l.c. then indicated that all of the starting material had disappeared to be replaced by a single slower-moving product. The solution was then evaporated to dryness and the last traces of acetic acid were removed by co-distillation with toluene. The resulting syrupy residue was purified by passage through a column of silica gel. A few minor impurities were first eluted with light petroleum–ether (2:1); the main product was then eluted with ether, and the appropriate fractions were evaporated to give **4** as a syrup (7.85 g, 83%), $[\alpha]_D$ +18.4° (*c* 1, chloroform) (Found: C, 73.73; H, 7.05. $C_{54}H_{58}O_{11}$ calc.: C, 73.47; H, 6.58%).

2,3-Di-O-benzyl-4,6-di-O-mesyl-α-D-glucopyranosyl 1,3,4,6-tetra-O-benzyl-β-D-fructofuranoside (**5**). — Mesyl chloride (1 mL) was added to an ice-cold solution of **4** (2.4 g) in anhydrous pyridine (20 mL). The solution was allowed to attain room temperature and to stand overnight with magnetic stirring, after which t.l.c. (light petroleum–ethyl acetate 2:1) revealed a single product. The mixture was then poured into ice–water and extracted with chloroform, in the usual way, to give

a syrupy product which was purified by passage through a short column of silica gel with light petroleum–ethyl acetate (9:1). The dimesylate **5** was obtained as a syrup which did not crystallise (2.7 g, 95%); $[\alpha]_D$ +94.9° (*c* 1.45, chloroform) (Found: C, 64.26; H, 6.21. $C_{56}H_{62}O_{15}S_2$ calc.: C, 64.74; H, 5.97%).

2,3-Di-O-benzyl-6-deoxy-6-fluoro-4-O-mesyl-α-D-glucopyranosyl 1,3,4,6-tetra-O-benzyl-β-D-fructofuranoside (**6**). — To a solution of **5** (1.4 g) in dry acetonitrile (20 mL) was added anhydrous tetrabutylammonium fluoride (2 g), and the solution was heated under reflux for 16 h with monitoring by t.l.c. (light petroleum–ethyl acetate 2:1) which revealed the formation of a faster-moving component. The solution was then evaporated to dryness and the residue was eluted from a column of silica gel with light petroleum–ethyl acetate (9:1). The 6-fluoride was isolated as a syrup which failed to crystallise (1 g, 80%); $[\alpha]_D$ +51.3° (*c* 1.05, chloroform) (Found: C, 68.27; H, 6.32. $C_{55}H_{59}FO_{12}S$ calc.: C, 68.60; H, 6.13%).

2,3-Di-O-benzyl-6-deoxy-6-fluoro-α-D-glucopyranosyl 1,3,4,6-tetra-O-benzyl-β-D-fructofuranoside (**7**). — Sodium hydroxide pellets (14 g) were added to a solution of **6** (7 g) in dry methanol (100 mL), and the mixture was boiled under reflux for 20 h; t.l.c. (light petroleum–ethyl acetate 2:1) then indicated that the hydrolysis of the sulphonic ester was complete. The cooled reaction mixture was diluted with water and extracted with chloroform. The chloroform extract was washed well with water, dried ($MgSO_4$), and concentrated to dryness, to give syrupy **7** (5 g, 78%), $[\alpha]_D$ +54.4° (*c* 1.4, chloroform) (Found: C, 72.74; H, 6.67. $C_{54}H_{57}FO_{10}$ calc.: C, 73.30; H, 6.45%).

6-Deoxy-6-fluorosucrose hepta-acetate (**9**). — A solution of **7** (0.2 g) in a mixture of ethanol (5 mL) and cyclohexene (5 mL) was heated under reflux for 5 days with 20% palladium hydroxide-on-charcoal (0.1 g). The reaction was monitored by t.l.c. which revealed a single product. The catalyst was then filtered off, the solvent was evaporated, and the resulting syrup was acetylated in the usual way with acetic anhydride–pyridine to give **9** (0.1 g, 71%), m.p. 101–102° (from methanol), $[\alpha]_D$ +68.3° (*c* 1, chloroform) (Found: C, 48.29; H, 5.47. $C_{26}H_{35}FO_{17}$ calc.: C, 48.90; H, 5.49%). Mass-spectral data: *m/z* 331 (6.4%), 291 (8.8), 231 (4), 189 (12.9), 171 (7.5), 129 (15.4), 109 (9.8), 101 (5.7), 81 (1.2), and 43 (100, Ac^+). 250-MHz ^1H-n.m.r. data ($CDCl_3$): δ 5.74 (d, $J_{1,2}$ 3.5 Hz, H-1), 5.47 (t, $J_{3,4}$ 10 Hz, H-3), 5.44 (d, $J_{3',4'}$ 6 Hz, H-3'), 5.38 (t, $J_{4',5'}$ 6 Hz, H-4'), 5.11 (t, $J_{4,5}$ 10 Hz, H-4), 4.85 (dd, $J_{2,3}$ 10 Hz, H-2), 4.51 (ddd, H-6a), 4.42 (ddd, H-6b), and 4.36 (m, H-5).

4-O-Benzoyl-2,3-di-O-benzyl-6-deoxy-6-fluoro-α-D-galactopyranosyl 1,3,4,6-tetra-O-benzyl-β-D-fructofuranoside (**10**). — A mixture of **6** (2.4 g), hexamethylphosphoric triamide (15 mL), and sodium benzoate (1.5 g) was stirred at 100° for 3 days. T.l.c. (light petroleum–ethyl acetate, 3:1) then indicated that the reaction was complete and that a faster-moving product had been formed. The mixture was diluted with ethyl acetate, washed several times with water, dried, and concentrated to dryness. Elution of the residue from a dry-packed column of silica gel with light petroleum–ethyl acetate (6:1) gave the 4-benzoate **10** (2 g, 81%) as a syrup, $[\alpha]_D$ +57.4° (*c* 1, chloroform) (Found: C, 74.54; H, 6.37. $C_{61}H_{61}FO_{11}$ calc.: C, 74.09; H, 6.18%).

2,3-Di-O-benzyl-6-deoxy-6-fluoro-α-D-galactopyranosyl 1,3,4,6-tetra-O-benzyl-β-D-fructofuranoside (**11**). — A solution of **10** (1.9 g) in dry methanol (20 mL) was treated with a catalytic amount of methanolic sodium methoxide, and the mixture kept at room temperature overnight. T.l.c. then revealed a single product. The solution was neutralised with Amberlite IR-120 (H^+) resin and then evaporated. The resulting syrup was eluted from a column of silica gel with light petroleum–ethyl acetate, to give **11** (1.5 g, 88%) as a syrup, $[\alpha]_D$ +40.1° (*c* 1, chloroform) (Found: C, 73.85; H, 7.04. $C_{54}H_{57}FO_{10}$ calc.: C, 73.30; H, 6.45%).

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