Carbohydrate Research, 29 (1973) 291–296

SUCROCHEMISTRY

PART X[1]. 1′,4,6′-TRI-*O*-MESYLSUCROSE PENTA-ACETATE: A COMPARISON OF THE REACTIVITY AT THE 4 AND 1′ POSITIONS

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(Received November 15th, 1972; accepted for publication, December 18th, 1972)

ABSTRACT

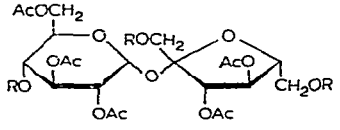
The 1′,4,6′-trisulphonate **2**, obtained by mesylation of sucrose 2,3,3′,4′,6-penta-acetate (**1**), undergoes nucleophilic substitution with sodium benzoate in hexamethylphosphoric triamide at positions 1′,4, and 6′ to give 1,6-di-*O*-benzoyl-β-D-fructofuranosyl 4-*O*-benzoyl-α-D-galactopyranoside penta-acetate (**3**), and selectively at positions 4 and 6′ to give 6-*O*-benzoyl-1-*O*-mesyl-β-D-fructofuranosyl 4-*O*-benzoyl-α-D-galactopyranoside penta-acetate (**4**). The products **3** and **4** were identified from their ^{1}H-n.m.r. spectra and by *O*-deacylation to give β-D-fructofuranosyl α-D-galactopyranoside (**5**) and its 1-methanesulphonate **6**, respectively. Treatment of the trisulphonate **2** with sodium azide gave analogous products, namely, 1,6-diazido-1,6-dideoxy-β-D-fructofuranosyl 4-azido-4-deoxy-α-D-galactopyranoside penta-acetate (**8**) and 6-azido-6-deoxy-1-*O*-mesyl-β-D-fructofuranosyl 4-azido-4-deoxy-α-D-galactopyranoside penta-acetate (**7**).

INTRODUCTION

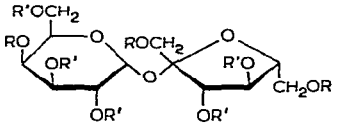
A study of the nucleophilic substitution reactions of sucrose octamethanesulphonate with bromide and azide ions has revealed[1,2] that reaction proceeds most readily at the primary positions C-6 and C-6′, followed by a selective reaction at the secondary C-4 in preference to the primary C-1′. Thus, it was possible to prepare, under the appropriate conditions, 6,6′-disubstituted derivatives of sucrose and 4,6,6′-tri- and 1′,4,6,6′-tetra-substituted derivatives of β-D-fructofuranosyl α-D-galactopyranoside[1]. We have extended these studies by the preparation of 1′,4,6′-tri-*O*-mesylsucrose penta-acetate (**2**) and a study of its substitution reactions with nucleophilic reagents in hexamethylphosphoric triamide.

RESULTS AND DISCUSSION

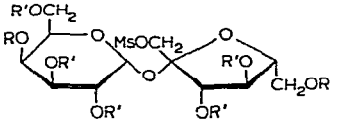
2,3,3′,4′,6-Penta-*O*-acetylsucrose[3] (**1**) was converted by mesyl chloride in pyridine into crystalline 1′,4,6′-tri-*O*-mesylsucrose penta-acetate (**2**). The 1′,4,6′-tri-*O*-tosyl derivative has been described by Lemieux and Barrette[4]. Reaction of the trisulphonate **2** with sodium benzoate in hexamethylphosphoric triamide gave two products which were separated on silica gel and subsequently characterised as the dibenzoate **4** and 1,6-di-*O*-benzoyl-β-D-fructofuranosyl 4-*O*-benzoyl-α-D-galacto-pyranoside penta-acetate (**3**). Compound **3** was identified from the 100-MHz ^{1}H-n.m.r. spectrum, in which the parameters $J_{3,4}$ 3.5 Hz and $J_{4,5}$ 1.5 Hz clearly showed that inversion of configuration has occurred at C-4 in the reaction **2** → **3** to give a galacto-pyranoside. The structural assignment was confirmed by *O*-deacylation with methanolic sodium methoxide to give the known[5] β-D-fructofuranosyl α-D-galactopyranoside (**5**). The ^{1}H-n.m.r. spectrum of the dibenzoate **4** also showed low values for $J_{3,4}$ and $J_{4,5}$ (3.0 and 1.0 Hz, respectively), consistent with a galactopyranoside structure and indicating that selective nucleophilic substitution of **2** had occurred at C-6′ and C-4. Careful *O*-deacylation of the benzoate **4** gave the 1-methanesulphonate **6** which, on hydrolysis with 50% formic acid, gave two products (paper chromatography), one of which was coincident with galactose and the other faster moving than fructose, as expected for 1-*O*-mesylfructose. It follows that the disubstituted product is 6-*O*-benzoyl-1-*O*-mesyl-β-D-fructofuranosyl 4-*O*-benzoyl-α-D-galactopyranoside (**4**).



1 R=H
2 R=Ms



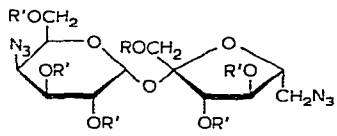
3 R=Bz, R'=Ac
5 R=R'=H



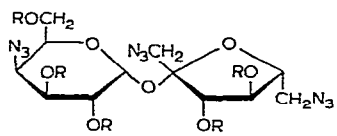
4 R=Bz, R'=Ac
6 R=R'=H

The reaction of 1′,4,6′-tri-*O*-mesylsucrose penta-acetate (**2**) with sodium azide in hexamethylphosphoric triamide was also incomplete after 20 h, and t.l.c. then revealed some *O*-deacetylation. After re-acetylation of the reaction products and separation on silica gel, a triazide and a diazide were obtained and subsequently characterised as **8** and **7**, respectively. The ^{1}H-n.m.r. spectrum of the latter product was consistent with the expected structure, namely 3,4-di-*O*-acetyl-6-azido-6-deoxy-1-*O*-mesyl-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-azido-4-deoxy-α-D-galactopyranoside (**7**). Additional evidence was obtained by replacement of the 1-mesyloxy group in **7** by reaction with sodium benzoate in hexamethylphosphoric triamide to give the 1-benzoate **10**. De-esterification of **10** with methanolic sodium methoxide gave **11** which on acid hydrolysis did not give (paper chromatography) galactose or fructose. Hence, the azido groups must have been introduced into both the pyranoid and furanoid rings of the sucrose trisulphonate **2**, thus confirming the structural assignment of **7**. The triazido derivative was assigned the structure 3,4-di-*O*-acetyl-1,6-diazido-

1,6-dideoxy-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-azido-4-deoxy-α-D-galactopyranoside (**8**), by analogy with the previous benzoate displacements and from its H^1-n.m.r. spectrum. It had physical properties identical with those of the product erroneously[2] described by Umezawa *et al.*[6] as the 1',6,6'-triazide. *O*-Deacetylation of the triazide **8** with methanolic ammonia, followed by mesylation, gave a crystalline pentamethanesulphonate (**9**) which differed in physical properties from the 1',6,6'-triazido pentamethanesulphonate prepared[7] *via* 1',6,6'-tri-*O*-tosylsucrose[8], and also differed from the 4,6,6'-triazido pentamethanesulphonate prepared by Hough and Mufti[1] from sucrose octamethanesulphonate. The H^1-n.m.r. spectral data for **9** confirmed the 1',4,6'-triazido structure proposed for **8**.



7 R=Ms, R'=Ac
10 R=Bz, R'=Ac
11 R=R'=H



8 R=Ac
9 R=Ms

EXPERIMENTAL

The general experimental data are as in Part I[2].

1',4,6'-Tri-O-mesylsucrose penta-acetate (**2**). — A solution of 2,3,3',4',6-penta-*O*-acetylsucrose[1] (**1**; 10.0 g) in dry pyridine (100 ml) was cooled to 0°, and mesyl chloride (3 mol., 5.0 ml) was added during a period of 10 min. The reaction mixture was allowed to attain room temperature and then stirred for 16 h. T.l.c. (chloroform–acetone, 2:1) showed one product running faster than the starting material. The reaction mixture was poured into ice–water, the precipitated syrup was extracted with chloroform, and the chloroform extract was washed successively with water, dilute hydrochloric acid, water, and saturated, aqueous sodium hydrogen carbonate, and dried ($MgSO_4$). Concentration gave a syrup which crystallised from ethanol to give the trisulphonate **2** (13.0 g, 91.2%), m.p. 56–58°, $[\alpha]_D^{31}$ +36.1° (*c* 0.5, acetone). N.m.r. data: τ 4.38 (*d*, 1 proton, $J_{1,2}$ 3.5 Hz, H-1), 5.16 (*q*, 1 proton, $J_{2,3}$ 11.0 Hz, H-2), 4.5 (*d*, 1 proton, $J_{3',4'}$ 6.0 Hz, H-3'), 4.66 (*t*, 1 proton, $J_{4',5'}$ 6.0 Hz, H-4'), 7.8-7.96 (*m*, 15 protons, 5Ac), 6.86–6.92 (*m*, 9 protons, 3Ms).

Anal. Calc. for $C_{25}H_{38}O_{22}S_3$: C, 38.3; H, 4.8; S, 12.2. Found: C, 38.2; H, 5.1; S, 11.9.

Reaction of 1',4,6'-tri-O-mesylsucrose penta-acetate (**2**) *with sodium benzoate in hexamethylphosphoric triamide.* — (*a*) Sodium benzoate (7.0 g) was added to a solution of **2** (3.5 g) in $(Me_2N)_3PO$ (20 ml), and the mixture was heated at 90° for 72 h. T.l.c. (ether–light petroleum, 5:1) showed two spots, both running faster than the starting material. The cooled mixture was poured into ice–water, the white precipitate was filtered off, washed well with water, and taken up in dichloromethane, and the solution was dried (Na_2SO_4), filtered, and then concentrated to a syrup. The resulting

syrup was eluted from a column of silica gel (200 g) with ether–light petroleum (2:1) to give the following products. (*a*) 3′,4′-Di-*O*-acetyl-1′,6′-di-*O*-benzoyl-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-*O*-benzoyl-α-D-galactopyranoside (**3**), as a syrup (1.8 g, 46.7%), $[\alpha]_D$ +14.9° (*c* 1.3, chloroform). N.m.r. data: τ 4.1 (*d*, 1 proton, $J_{1,2}$ 3.5 Hz, H-1), 4.74 (*q*, 1 proton, $J_{2,3}$ 10.5 Hz, H-2), 4.34 (*q*, 1 proton, $J_{3,4}$ 3.5 Hz, H-3), 4.44 (*q*, 1 proton, $J_{4,5}$ 1.5 Hz, H-4), 4.32 (*d*, 1 proton, $J_{3',4'}$ 9.5 Hz, H-3′), 4.36 (*t*, 1 proton, $J_{4',5'}$ 9.5 Hz, H-4′), 1.84–2.7 (*m*, 15 protons, 3Bz), 7.82–8.08 (*m*, 15 protons, 5Ac).

Anal. Calc. for $C_{43}H_{44}O_{19}$: C, 59.7; H, 5.1. Found: C, 58.9; H, 5.1.

(*b*) 3′,4′-Di-*O*-acetyl-6′-*O*-benzoyl-1′-*O*-mesyl-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-*O*-benzoyl-α-D-galactopyranoside (**4**), as a syrup (1.0 g, 23.4%), $[\alpha]_D$ +15.6° (*c* 1.7, chloroform). N.m.r. data: τ 4.12 (*d*, 1 proton, $J_{1,2}$ 3.5 Hz, H-1), 4.78 (*q*, 1 proton, $J_{2,3}$ 11.0 Hz, H-2), 4.56 (*q*, 1 proton, $J_{3,4}$ 3.0 Hz, H-3), 4.46 (*q*, 1 proton, $J_{4,5}$ 1.0 Hz, H-4), 4.28 (*d*, 1 proton, $J_{3',4'}$ 5.5 Hz, H-3′), 4.46 (*t*, 1 proton, $J_{4',5'}$ 5.5 Hz, H-4′), 6.9 (*s*, 3 protons, Ms), 7.8–8.08 (*m*, 15 protons, 5Ac).

Anal. Calc. for $C_{37}H_{42}O_{20}S$: C, 52.3; H, 5.1; S, 3.7. Found: C, 52.5; H, 5.1; S, 3.7.

1′-O-mesyl-β-D-fructofuranosyl α-D-galactopyranoside (**6**). — M Methanolic sodium methoxide was added dropwise to a solution of the monosulphonate **4** (800 mg) in dry methanol (25 ml) until the pH reached 9. The solution was then stored overnight at room temperature, neutralised with Amberlite-15(H^+) resin to pH 7.0, and concentrated to a syrup which immediately crystallised from hot ethanol to give **6** (0.3 g, 90%), m.p. 158–161°, $[\alpha]_D$ +70.1° (*c* 0.8, water).

Anal. Calc. for $C_{13}H_{24}O_{13}S$: C, 37.1; H, 5.7; S, 7.6. Found: C, 36.5; H, 5.7; S, 7.6.

A solution of **6** (50 mg) in 50% aqueous formic acid (10 ml) was heated at 100° for 16 h and then concentrated to a small volume. T.l.c. of the hydrolysate with chloroform–methanol (3:1) or methyl sulphoxide–ethyl acetate–acetic acid–water (30:68:1:1), using D-galactose and D-fructose as reference substances, revealed two products; the slower moving had the same R_F value (0.544) as galactose and the faster moving had an R_F value (0.830) higher than that of fructose (0.614).

β-D-Fructofuranosyl α-D-galactopyranoside (**5**). — A solution of **3** (500 mg) in dry methanol (25 ml) was treated dropwise with M methanolic sodium methoxide until the pH was 9.0, and was then left at room temperature for 16 h. After neutralisation with Amberlite-15(H^+) resin to pH 7, the solution was concentrated to a syrup which crystallised from aqueous ethanol–acetone at 0° to give **5** (0.157 g, 80%), m.p. and mixed m.p. 174–177°, $[\alpha]_D^{25}$ +77° (*c* 0.9, water); lit.[5] m.p. 179°, $[\alpha]_D^{20}$ +81.5 ±0.5° (*c* 1, water).

Reaction of 1′,4,6′-tri-O-mesylsucrose penta-acetate (**2**) *with sodium azide in hexamethylphosphoric triamide.* — Sodium azide (1.0 g) was added to a solution of **2** (1.0 g) in $(Me_2N)_3PO$ (5 ml), and the reaction mixture was stirred at 85° for 20 h. T.l.c. (benzene–ethyl acetate, 9:4) showed the presence of four products. The reaction was worked up as usual by pouring into ice–water, and the resulting precipitate was

dissolved in acetone. This solution was dried ($MgSO_4$), filtered, and concentrated to a syrup which was taken up in dry pyridine (10 ml), and acetic anhydride (10 ml) was added. The reaction mixture was stirred at room temperature for 16 h, and t.l.c. (benzene–ethyl acetate, 9:4) then showed two spots, both having R_F values lower than that of starting material. The reaction mixture was concentrated, and pyridine was removed from the syrupy residue by co-distillation with toluene. The resulting syrup was subjected to p.l.c. (benzene–ethyl acetate, 9:4) to give the following fractions. (*a*) 3′,4′-Di-*O*-acetyl-1′,6′-diazido-1′,6′-dideoxy-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-azido-4-deoxy-α-D-galactopyranoside (**8**), as the faster-moving fraction (355 mg, 44.5%), m.p. 57–59° (from ethanol), $[\alpha]_D^{26}$ +40.1° (*c* 1.0, chloroform); lit.[6] m.p. 55–57°, $[\alpha]_D^{12}$ +37° (*c* 0.5, chloroform). N.m.r. data: τ 4.31 (*d*, 1 proton, $J_{1,2}$ 4.0 Hz, H-1), 4.54 (*q*, 1 proton, $J_{2,3}$ 11.0 Hz, H-2), 4.42 (*q*, 1 proton, $J_{3,4}$ 3.5 Hz, H-3), 6.3 (*q*, 1 proton, $J_{4,5}$ 1.5 Hz, H-4), 4.32 (*d*, 1 proton, $J_{3',4'}$ 10.0 Hz, H-3′), 5.72 (*t*, 1 proton, $J_{4',5'}$ 10.0 Hz, H-4′), 8.12–8.5 (*m*, 15 protons, 5Ac). (*b*) 3′,4′-Di-*O*-acetyl-6′-azido-6′-deoxy-1′-*O*-mesyl-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-azido-4-deoxy-α-D-galactopyranoside (**7**) (210 mg, 24.2%), m.p. 135–138° (from ethanol), $[\alpha]_D^{26}$ −7.1° (*c* 0.7, acetone). N.m.r. data: τ 4.38 (*d*, 1 proton, $J_{1,2}$ 3.5 Hz, H-1), 4.8 (*q*, 1 proton, $J_{2,3}$ 11.0 Hz, H-2), 4.68 (*q*, 1 proton, $J_{3,4}$ 3.5 Hz, H-3), 4.56 (*d*, 1 proton, $J_{3',4'}$ 6.5 Hz, H-3′), 6.02 (*t*, 1 proton, $J_{4',5'}$ 6.5 Hz, H-4′), 7.8–7.96 (*m*, 15 protons, 5Ac), 6.96 (*s*, 3 protons, Ms).

Anal. Calc. for $C_{23}H_{32}N_6O_{16}S$: C, 40.5; H, 4.7; N, 12.1. Found: C, 40.4; H, 4.7; N, 12.3.

Sodium benzoate (80 mg) was added to a solution of **7** (80 mg) in $(Me_2N)_3PO$ (3 ml), and the mixture was heated at 85° for 20 h with stirring. T.l.c. (benzene–ethyl acetate, 9:4) then showed one major product with an R_F value greater than that of the starting material, and a number of slower-moving products probably due to partial deacetylation during the reaction. The reaction was worked up by pouring into ice–water, and a solution of the resulting precipitate in acetone was dried ($MgSO_4$) and concentrated to a syrup (**10**; 45 mg, 54.0%).

The pH of a solution of **10** (45 mg) in dry methanol (10 ml) was brought to 9.0 by the dropwise addition of M methanolic sodium methoxide at room temperature. The solution was left at room temperature for 2 h, and t.l.c. (1-butanol–acetic acid–water, 12:3:5) then showed a single spot. The solution was neutralised with Amberlite IRC-50(H^+) resin (previously washed with methanol) and concentrated to give a syrup (**11**; 22.3 mg, 90%), which showed only one spot on t.l.c. (chloroform–methanol, 5:3).

A solution of **11** (22.3 mg) in M hydrochloric acid (8 ml) was stirred at room temperature for 36 h, and then neutralised with Amberlite IR-45(HO^-) resin and concentrated to a small volume.

Ascending-front paper chromatography of the hydrolysate was carried out (Whatman No. 1; 1-propanol–ammonia–water, 6:3:1) with D-glucose, D-galactose, and D-fructose as reference compounds. After two developments, detection with a solution of *p*-aminophenol (0.5 g) and orthophosphoric acid (2.0 g) in ethanol (150 ml)

at 105–110° for 10 min revealed only two products, R_F 0.838 (dark brown) and 0.911 (brown); *cf.* D-galactose, R_F 0.735 (very dark brown); D-fructose, 0.764 (lemon yellow); D-glucose, 0.735 (brown).

1′,6′-Diazido-1′,6′-dideoxy-3′,4′-di-O-mesyl-β-D-fructofuranosyl 4-azido-4-deoxy-2,3,6-tri-O-mesyl-α-D-galactopyranoside (**9**). — Ammonia gas was passed for 30 min into a cooled solution of 3′,4′-di-*O*-acetyl-1′,6′-diazido-1′,6′-dideoxy-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-azido-4-deoxy-α-D-galactopyranoside (**8**, 300 mg) in dry methanol (50 ml), and the solution was then stored in the refrigerator for 12 h. T.l.c. (chloroform–ethanol, 5:3) then showed one product with an R_F value smaller than that of starting material. The solution was concentrated, the syrupy residue was dissolved in dry pyridine (10 ml), and the solution was cooled to 0°. Mesyl chloride (0.25 ml) was added during 15 min and the reaction mixture was left at room temperature overnight. T.l.c. (chloroform–acetone, 3:1) then showed one product. Pyridine was removed on a rotary evaporator by co-distillation with toluene. A solution of the brown, syrupy residue in chloroform was washed with water, dried ($MgSO_4$), decolourised with charcoal, and concentrated to a syrup which crystallised from hot methanol to give **9** (150 mg, 64.3%), m.p. 63–65°, $[\alpha]_D^{23}$ +73.3° (*c* 0.2, acetone). N.m.r. data: τ 4.02 (*d*, 1 proton, $J_{1,2}$ 3.5 Hz, H-1), 5.06 (*q*, 1 proton, $J_{2,3}$ 11.0 Hz, H-2), 4.68 (*q*, 1 proton, $J_{3,4}$ 3.25 Hz, H-3), 4.5 (*d*, 1 proton, $J_{3',4'}$ 8.0 Hz, H-3′), 4.62 (*t*, 1 proton, $J_{4',5'}$ 8.0 Hz, H-4′), 6.08–6.80 (*m*, 15 protons, 5Ms).

Anal. Calc. for $C_{17}H_{29}N_6O_{18}S_5$: C, 25.3; H, 3.6; N, 15.6. Found: C, 25.3; H, 3.8; N, 15.5.

ACKNOWLEDGMENTS

We thank the International Sugar Research Foundation (Washington, U.S.A.) for a grant-in-aid (to K.S.M.), the Director of the Tate and Lyle Research Centre for his support, and Dr. A. C. Richardson, Dr. K. J. Parker and Dr. R. A. Khan for useful discussions.

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