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# SELECTIVE TRITYLATION AND MESITYLENESULPHONYLATION OF RAFFINOSE*†

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## ABSTRACT

Raffinose reacted with 3 molar equivalents of trityl chloride in pyridine to give a complex mixture of products from which 1′,6′,6″-tri-*O*-tritylraffinose‡ was isolated (20%) after chromatography, and characterised as the crystalline octa-acetate and octabenzoate. The octabenzoate was detritylated in methanolic 1% hydrogen chloride, without significant ester migration, to give the 1′,6′,6″-triol octabenzoate, from which 1′,6′,6″-trisulphonates were obtainable in high yields. Treatment of raffinose with 3 molar equivalents of mesitylenesulphonyl chloride in pyridine gave 1′,6′,6″-tri-*O*-mesitylenesulphonylraffinose (20%, after chromatography).

## INTRODUCTION

The non-reducing trisaccharide raffinose (1, 6-*O*-α-D-galactopyranosyl-α-D-glucopyranosyl β-D-fructofuranoside) is widely distributed in Nature and, after sucrose, is the most abundant, naturally occurring oligosaccharide in the plant kingdom. It is found in sugar-beet, together with sucrose from which it is separated by fractional crystallization. We have been concerned with the chemical modification of disaccharides with the view of synthesising materials possessing biological activity, and we now report an extension of this work to the trisaccharide raffinose, in which the three primary positions in the molecule have been selectively etherified and sulphonylated.

## RESULTS AND DISCUSSION

Trityl ethers of carbohydrates have been extensively used as intermediates in synthesis, because they are usually selectively introduced at primary hydroxyl groups, and can readily be removed by acetolysis, mild hydrolysis with acid, or hydro-

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*Dedicated to the memory of Sir Edmund Hirst, C.B.E., F.R.S.

†Raffinose Chemistry: Part I.

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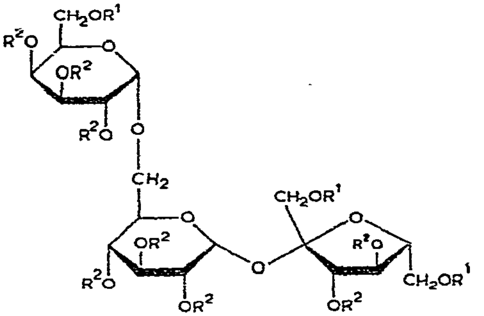
‡The unprimed, single-primed, and double-primed numbers refer to the carbon atoms in the D-glucosyl, D-fructosyl, and D-galactosyl rings, respectively.

genolysis[1]. Raffinose (1), which possesses eleven hydroxyl groups, three of which are primary, was expected to give a tritrityl derivative (2) upon treatment with 3 mol. of trityl chloride in pyridine. However, the reaction mixture was complex and gave 2 in 20% yield only after chromatography. Attempts to improve the yield by using more forcing conditions gave products having increased $R_F$ values in t.l.c. Isolation of one of the products and subsequent analysis suggested that it was a raffinose derivative containing five trityl groups. Its formation was not unexpected, as tritylation of secondary hydroxyl groups of carbohydrates can occur, albeit at a greatly diminished rate relative to that of primary hydroxyl groups[2].



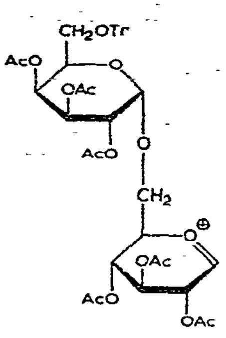
1 $R^1 = R^2 = H$
2 $R^1 = Tr, R^2 = H$
3 $R^1 = Tr, R^2 = Ac$
4 $R^1 = Tr, R^2 = Bz$
5 $R^1 = H, R^2 = Bz$
6 $R^1 = Ms, R^2 = Bz$
7 $R^1 = Ts, R^2 = Bz$
8 $R^1 = Mes, R^2 = Bz$
9 $R^1 = Mes, R^2 = H$
10 $R^1 = Mes, R^2 = Ac$

Mes = mesitylenesulphonyl

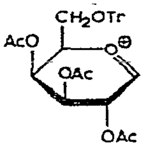
The tritrityl ether 2 was characterised as the crystalline octa-acetate (3) and octabenzoate (4). The $^1$H-n.m.r. spectrum of 3 in $C_6D_6$ clearly showed the presence of three trityl groups and eight separate acetyl signals. Furthermore, at 220 MHz, the spectrum was essentially first order and most of the resonances could be assigned from spin-decoupling experiments (see Experimental). The mass spectrum of 3 gave major ions arising from cleavage of interglycosidic linkages, namely *m/e* 819, 531, and 731, corresponding to the ions *A*, *B*, and *C*, resulting from the loss from 3 of the fructosyl, the glucosylfructosyl, and the galactosylglucosyl residues, respectively. Cleavages of this type appear to be typical of the behaviour in mass spectrometry of most raffinose derivatives so far studied, and these data are essential for the structural elucidation of reaction products. Ions *A–C* further fragmented by loss of acetic acid and ketene, and then a further loss of acetic acid for *A* and *B* as expected.

Detritylation of 1′,6′,6″-tri-*O*-tritylraffinose octabenzoate (4) with methanolic 1% hydrogen chloride proceeded smoothly to give the 1′,6′,6″-triol 5 in good yield. No migration of benzoyl groups took place during the detritylation step, as tritylation of 5 gave 4 in high yield. When 5 was mesylated, tosylated, or mesitylenesulphonylated in the usual way, the 1′,6′,6″-trisulphonates 6, 7, and 8 were obtained in high yields.

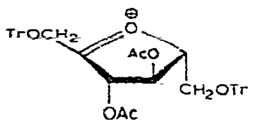
As an alternative and more economic method of preparing 1′,6′,6″-trisulphonates of raffinose, direct sulphonylation was investigated. Trimolar tosylation



*A* *m/e* 819



*B* *m/e* 531



*C* *m/e* 731

of raffinose has been reported[3] to give (after acetylation) a pure 1′,6′,6″-tritosylate in 40% yield. In our hands, attempts to selectively tosylate raffinose under various conditions resulted in the formation of complex mixtures of products (t.l.c.) and therefore was not investigated further. However, such bulky sulphonylating agents as tri-isopropyl and trimethylbenzenesulphonyl chlorides are much more selective[4] than toluene-*p*-sulphonyl chloride. Thus, the 6,1′,6′-trimesitylenesulphonate can be prepared directly from sucrose in 40% yield. Treatment of raffinose under similar conditions gave a mixture of at least eight products, with one major component. Isolation of this major product by column chromatography gave a trisulphonate (20%) which afforded an octabenzoate (**8**) identical to that prepared *via* 1′,6′,6″-tri-*O*-tritylraffinose, thereby confirming that the three sulphonyloxy groups were situated at the primary positions.

## EXPERIMENTAL

*General methods.* — Evaporations were carried out under reduced pressure below 45°. Optical rotations were determined on chloroform solutions (unless stated otherwise) with a Perkin–Elmer 141 polarimeter and 1-dm tubes. Melting points were determined on a Kofler hot-stage, and are uncorrected. Silica Gel 7731 (Merck) was used for t.l.c., detection being effected by charring with sulphuric acid. Column chromatography was performed on Silica Gel 7734 (Merck). Trityl ethers were fractionated on columns of silica gel that had been washed previously with the eluting solvent, because introduction onto dry columns caused detritylation. Anhydrous pyridine and anhydrous *N*,*N*-dimethylformamide were prepared by distillation from calcium hydride. Light petroleum (b.p. 60–80°) was used throughout. I.r. spectra were determined for Nujol mulls with a Perkin–Elmer 157 spectrometer. $^1$H-N.m.r. spectra were measured either on a Perkin–Elmer R-12B spectrometer operating at 60 MHz or on a Varian HA-100 instrument at 100 MHz. Selected regions of the spectra ($\tau$ 4–7) were then recorded at 220 MHz with a Varian HR-220 spectrometer; $Me_4Si$ was used as the internal standard. Mass spectra were determined with an A.E.I. MS-30 spectrometer at 70 eV. Raffinose pentahydrate was dried at 70°/8 mmHg for 24 h and was then dissolved in pyridine, and the solution was concentrated to azeotropically distil the remaining water. This process was repeated five times.

*1′,6′,6″-Tri-O-tritylraffinose* (**2**). — To a solution of anhydrous raffinose (10 g) in pyridine (100 ml), trityl chloride (16.57 g, 3 mol.) was added. The mixture was stirred for 30 h at 25°, and t.l.c. then showed a complex mixture of products with one major component. The solution was concentrated to dryness and residual pyridine removed by co-evaporation several times with toluene. A solution of the residue in dichloromethane was applied to a wet (dichloromethane) column of silica gel which was eluted with dichloromethane until tritanol had been removed and then with ethanol to remove the trityl ethers. The ethanol solution was concentrated to dryness and the resulting solid was re-chromatographed on a column of silica gel with ethyl acetate–ethanol (15:1). Fractions containing the tritrityl derivative were combined and concentrated to give a solid which crystallized from diisopropyl ether to afford **2** (4.88 g, 20%), m.p. 145–147°, $[\alpha]_D$ +31° (*c* 0.85) (Found: C, 73.5; H, 6.1. $C_{75}H_{74}O_{16}$ calc.: C, 73.2; H, 6.0%).

Acetylation (pyridine–acetic anhydride) of **2** gave the octa-acetate **3** (90%), m.p. 132–134° (from dichloromethane–methanol), $[\alpha]_D$ +59° (*c* 1) (Found: C, 70.1; H, 5.7. $C_{91}H_{90}O_{24}$ calc.: C, 69.7; H, 5.7%).

$^1$H-N.m.r. data ($C_6D_6$, 220 MHz, superscript letters indicate coupled signals determined by spin-decoupling): $\tau$ 2.3–3.1 (m, 9 Ph), $3.8^{a}$ (d, *J* 3.5 Hz, H-3′), $4.1^{b}$ (q, *J* 3 and <1 Hz, H-4″), $4.23^{c}$ (t, *J* 10 and 10 Hz, H-3), 4.25 (q, *J* 10.5 and 3.0 Hz, H-3″), $4.35$–$4.5^{a,d}$ (m, H-2″,4,4′), $4.53^{e}$ (d, *J* 3.5 Hz, H-1), $4.70^{d}$ (d, *J* 3.5 Hz, H-1″), $5.05^{c,e}$ (q, *J* 10.5 and 3.5 Hz, H-2), 5.52 (m, H-5), $5.62^{b}$ (t, *J* 6.0 and <1 Hz H-5″), 5.78 (m, H-5′), 6.2–6.8 (m, H-1′,6,6′,6″), 7.99, 8.16, 8.18, 8.28, 8.30, 8.40, 8.43, and 8.46 (8 s, 8 Ac).

Benzoylation (pyridine–benzoyl chloride) of **2** gave the octabenzoate **4** (90%), m.p. 138–140° (from ethanol), $[\alpha]_D$ +28.5° (*c* 1) (Found: C, 75.7; H, 5.1. $C_{131}H_{106}O_{24}$ calc.: C, 76.2; H, 5.1%).

*2,3,4-Tri-O-benzoyl 6-O-(2,3,4-tri-O-benzoyl-α-D-galactopyranosyl)-α-D-glucopyranosyl 3,4-di-O-benzoyl-β-D-fructofuranoside* (**5**). — To a solution of **4** (5 g) in dichloromethane (100 ml), methanolic 1% hydrogen chloride (5 ml) was added. The solution was kept at room temperature for 24 h; t.l.c. then indicated the formation of a single product. The solution was washed with saturated, aqueous sodium hydrogen carbonate at 0° to remove the acid, and then with water, dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was dissolved in dichloromethane, and chromatographed on a column of dry silica gel[5] with ether–light petroleum (1:1) to remove tritanol, and then with ethanol to give **5** (2.27 g, 70%), m.p. 121–123°, $[\alpha]_D$ +143° (*c* 0.5) (Found: C, 66.5; H, 4.79. $C_{74}H_{64}O_{24}$ calc.: C, 66.46; H, 4.79%).

A solution of **5** (0.1 g) in dry pyridine (4 ml) was treated with trityl chloride (0.13 g) for 40 h at 20°; t.l.c. then indicated the formation of a single product having $R_F$ identical with that of **4**. The reaction mixture was poured into water, and the resulting solid was collected and purified by elution from a short column of wet (ether) silica gel with ether. Concentration of the eluate and crystallization of the solid from ethanol afforded 1′,6′,6″-tri-*O*-tritylraffinose octabenzoate (**4**; 0.123 g, 80%), m.p. and mixture m.p. 138–140°. The i.r. spectrum was identical with that of **4** prepared above.

Conventional sulphonylation of **5** gave the following compounds: 1′,6′,6″-trimesylate **6** (60%), m.p. 120–122° (from ethanol), $[\alpha]_D$ +132° (*c* 1) (Found: C, 58.4; H, 4.5; S, 6.3. $C_{77}H_{70}O_{30}S_3$ calc.: C, 58.9; H, 4.5; S, 6.1%); 1′,6′,6″-tritosylate **7** (70%), m.p. 104–106° (from ethanol), $[\alpha]_D$ +116° (*c* 0.5) (Found: C, 62.2; H, 4.7; S, 5.5. $C_{95}H_{82}O_{30}S_3$ calc.: C, 63.4; H, 4.6; S, 5.3%); 1′,6′,6″-trimesitylenesulphonate **8** (80%), m.p. 111–113° (from ethanol), $[\alpha]_D$ +83° (*c* 1) (Found: C, 63.9; H, 5.3; S, 5.2. $C_{101}H_{94}O_{30}S_3$ calc.: C, 64.4; H, 5.0; S, 5.1%).

*1′,6′,6″-Tri-O-mesitylenesulphonylraffinose* (**9**). — To a solution of anhydrous raffinose (10 g) in pyridine at −30°, mesitylenesulphonyl chloride (13.1 g, 3 mol.) was added and the mixture was kept at −30° for 2 days; t.l.c. then indicated the formation of at least eight compounds with one major component. The mixture was poured into ice–water, the resulting syrup was extracted with dichloromethane, and the extract was dried ($MgSO_4$) and concentrated to a syrup from which toluene was evaporated several times to remove traces of pyridine. The syrup (17.6 g) was then dissolved in dichloromethane and applied to a dry column of silica gel, the top part of which (~10%) was mixed with activated charcoal, and eluted with chloroform–methanol (10:1). Fractions containing the major component were combined and concentrated to dryness to give **9** as a white, amorphous solid (4.34 g, 20%), m.p. 117–119° (from chloroform–methanol), $[\alpha]_D$ +83° (*c* 1) (Found: C, 49.4; H, 5.9; S, 8.6. $C_{45}H_{62}O_{25}S_3$ calc.: C, 49.2; H, 5.6; S, 8.7%).

Treatment of **9** with pyridine–acetic anhydride gave the octa-acetate **10** (90%), m.p. 88–90° (from ethanol–light petroleum at −30°), $[\alpha]_D$ +79° (*c* 1) (Found: C, 52.8; H, 5.4; S, 6.9. $C_{61}H_{72}O_{30}S_3$ calc.: C, 53.0; H, 5.2; S, 7.0%).

Treatment of **9** with pyridine–benzoyl chloride gave the octabenzoate **8** (90%), m.p. and mixture m.p. 111–113° (from ethanol), $[\alpha]_D$ +110° (*c* 1) (Found: C, 63.9; H, 5.3; S, 5.2. $C_{101}H_{94}O_{30}S_3$ calc.: C, 64.4; H, 5.0; S, 5.1%). The i.r. spectrum was identical with that of **8** prepared *via* **5** as described above.

## ACKNOWLEDGMENTS

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