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6′-SUBSTITUTED AND 6′,6″-DISUBSTITUTED DERIVATIVES OF RAFFINOSE*

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ABSTRACT

The reaction of 6′-chloro-6′-deoxyraffinose deca-acetate with a variety of nucleophilic anions (Br^-, I^-, N_3^-) gave the corresponding 6′-substituted raffinoses. The 6′-azide was further converted into 6′-amino-6′-deoxyraffinose, isolated as its *N*-acetyl derivative, and silver fluoride-induced elimination of hydrogen iodide from the 6′-iodide gave the 6′-deoxy-5′-ene. Treatment of 6′-chloro-6′-deoxyraffinose and 6′,6″-dichloro-6′,6″-dideoxyraffinose with base afforded, respectively, 3′,6′-anhydro- and 3′,6′;3″,6″-dianhydro-raffinose in high yields. In addition, the dichloride was converted into 6′,6″-diazido-6′,6″-dideoxyraffinose.

INTRODUCTION

Although raffinose (**1**) is the only readily available trisaccharide, few efforts have been made to study its chemistry with a view to its structural modification. Some syntheses of mono- and tri-substituted derivatives have been described recently, either *via* the 1′,6′,6″-tritrityl ether[2,3] or the corresponding tritosylate[4]. In addition, the reaction of raffinose with sulphuryl chloride at −20° afforded a mixture of 6′-chloro-6′-deoxyraffinose and 6′,6″-dichloro-6′,6″-dideoxyraffinose, isolated as their acetates **2** and **13**, respectively, in 43% and 7% yields[1]. We now report on the conversion of **2** and **13** into other mono- and di-substituted derivatives of raffinose.

RESULTS AND DISCUSSION

The reaction of 6′-chloro-6′-deoxyraffinose deca-acetate[1] (**2**) with either lithium bromide, sodium iodide, or sodium azide in hexamethylphosphoric triamide gave the respective bromide **3**, iodide **5**, and azide **7** in good yields. The structures of these compounds were indicated by m.s., in which oxycarbonium ions at *m/e* 331 (Galp^+)

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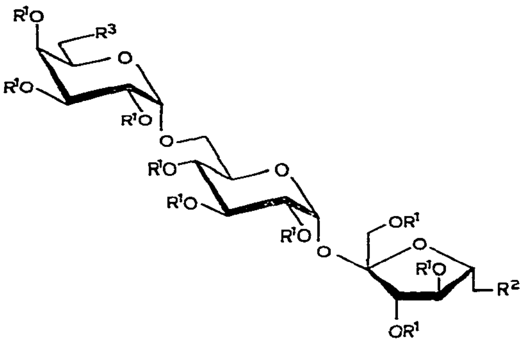
*Raffinose Chemistry: Part III. For Part II, see ref. 1. The unprimed, single-primed, and double-primed numbers refer to the carbon atoms of the D-glucosyl, D-fructosyl, and D-galactosyl residues, respectively.

and 619 (Gal*p*–Glc*p*$^+$) were common to all three[1]. In addition, the appropriate fructofuranosyl oxycarbonium ion was observed at *m/e* 351, 353 (Br), 391 (I), and 314 (N_3), respectively. Substitution at C-6′ was indicated for each compound by the ^{13}C-n.m.r. spectra of the corresponding *O*-deacetylated derivatives (see Table I), in which upfield shifts of the C-6′ resonances were observed, relative to raffinose, of 28.7 (for Br), 56.0 (for I), and 9.3 p.p.m. (for N_3).



1 $R^1 = H$, $R^2 = R^3 = OH$
2 $R^1 = Ac$, $R^2 = Cl$, $R^3 = OAc$
3 $R^1 = Ac$, $R^2 = Br$, $R^3 = OAc$
4 $R^1 = H$, $R^2 = Br$, $R^3 = OH$
5 $R^1 = Ac$, $R^2 = I$, $R^3 = OAc$
6 $R^1 = H$, $R^2 = I$, $R^3 = OH$
7 $R^1 = Ac$, $R^2 = N_3$, $R^3 = OAc$
8 $R^1 = H$, $R^2 = N_3$, $R^3 = OH$
9 $R^1 = H$, $R^2 = NH_2$, $R^3 = OH$
10 $R^1 = H$, $R^2 = NHAc$, $R^3 = OH$
11 $R^1 = Ac$, $R^2 = NHAc$, $R^3 = OAc$
12 $R^1 = Ac$, $R^2 = N(CO)_2C_6H_4$, $R^3 = OAc$
13 $R^1 = Ac$, $R^2 = R^3 = Cl$
14 $R^1 = Ac$, $R^2 = R^3 = N_3$
15 $R^1 = H$, $R^2 = R^3 = N_3$

TABLE I

^{13}C-CHEMICAL-SHIFT DATA[a]

Carbon atom	1	4	6	8	9	10	15	17
C-2′	106.4	106.6	106.5	106.6	106.6	106.5	106.6	111.7
C-1″	101.1	101.3	101.4	101.3	101.1	101.2	101.2	100.9
C-1	94.7	94.9	95.0	95.0	94.9	94.7	94.9	95.7
C-4′	83.9	83.4	83.6	82.4	82.3	81.6	82.4	80.1
C-3′	79.0	79.1	79.7	79.1	79.0	79.1	79.1	83.9
C-5′	76.6	79.6	80.8	78.0	78.0	78.8	78.0	78.5
C-2	75.3	75.2	75.3	75.5	75.3	75.3	75.3	75.6
C-3	74.0	74.1	74.2	74.1	74.1	74.0	74.0	74.2
C-5	73.6	73.6	73.6	73.7	73.6	73.5	73.6	73.5
C-5″	72.1	72.1	72.2	72.3	72.0	72.1	72.3	72.1
C-2″	71.9	71.9	71.9	72.0	71.0	71.0	72.0	71.8
C-4	71.9	71.9	71.9	71.9	71.9	71.9	71.9	71.9
C-4″	71.1	70.9	71.1	71.2	69.3		70.8	71.0
C-3″	69.1	69.2	69.3	69.0	68.2	68.7	68.9	68.7
C-6	68.5	69.2	69.3	69.0	68.2	68.7	68.9	68.7
C-6′	65.0	36.3	9.0	55.7	45.2	45.0	55.7	70.8
C-1′	64.0	64.0	63.8	64.1	64.0	64.1	64.0	63.7
C-6″	63.7	63.6	63.8	63.8	63.7	63.6	53.7	63.3

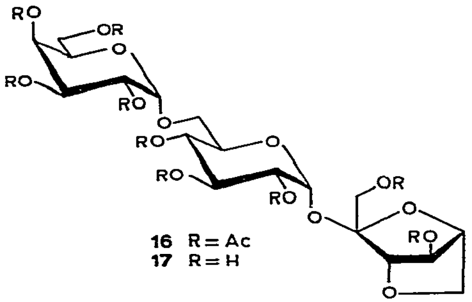
[a] P.p.m. downfield from DSS, at 15.08 MHz in D_2O.

Similarly, the reaction of 6′,6″-dichloro-6′,6″-dideoxyraffinose nona-acetate (**13**) with sodium azide under the same conditions afforded the corresponding 6′,6″-diazide **14** in 69% yield. In this case, the ^{13}C-n.m.r. spectrum of the *O*-deacetylated derivative **15** showed upfield shifts of the C-6′ and C-6″ resonances by 9.3 and 10 p.p.m., respectively.

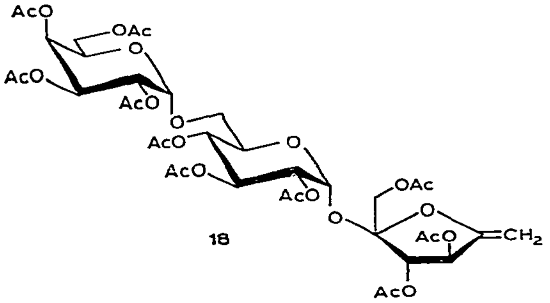
Hydrogenation of 6′-azido-6′-deoxyraffinose (**8**) afforded the 6′-amine **9** as a hygroscopic solid, which was best isolated as the crystalline *N*-acetyl derivative **10**. An attempt to introduce a 6′-amine function into raffinose by treatment of the 6′-chloride **2** with potassium phthalimide in hexamethylphosphoric triamide was partially successful, but the yield (11%) of the 6′-phthalimide **12** made the method unattractive.

The reaction of the 6′-iodide **5** with silver fluoride in pyridine[5] afforded an 85% yield of crystalline α-melibiosyl 6-deoxy-β-D-*threo*-hex-5-enulofuranoside deca-acetate (**18**).

When the 6′-chloride **2** was treated with boiling, methanolic sodium methoxide, it was transformed into a single compound, which was isolated as its nona-acetate **16**. The mass spectrum of **16** showed oxycarbonium ions at *m/e* 331 (Galp^{+}), 619 (Gal$p$–Glcp^{+}), and 229, the latter corresponding to an anhydrofructosyl oxycarbonium ion. The ^{13}C-n.m.r. spectrum of the *O*-deacetylated anhydride **17** (Table I) showed downfield shifts for the signals of C-6′ and C-3′ by 5.8 and 4.9 p.p.m., respectively, compared with raffinose, which indicated the formation of a 3′,6′-anhydride ring. Notably, most of the other carbons of the fructosyl ring in **17** were also shifted by relatively large amounts. For example, the C-2′ and C-5′ resonances, which could not have been involved in anhydro-ring formation, were shifted downfield by 5.3 and 1.9 p.p.m., respectively, and that for C-4′ was shifted upfield by 3.8 p.p.m. These shifts have



16 R = Ac
17 R = H



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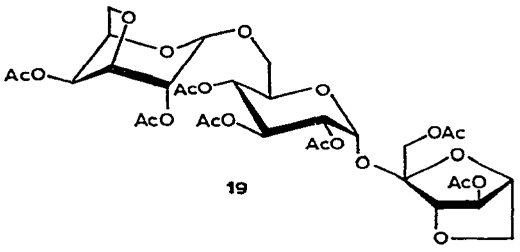

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also been observed in the ^{13}C-n.m.r. spectra of anhydrosucroses[6] and are attributable to steric compression in the formation of these bridged-ring compounds.

Similarly, when the 6′,6″-dichloride **13** was treated with sodium methoxide, the 3′,6′:3″,6″-dianhydride was formed, and isolated as the hepta-acetate **19**. The mass spectrum of **19** was indicative of the structure, displaying oxycarbonium ion fragments at *m/e* 229 (anhydro-Gal*p*$^+$ and anhydro-Fru$^+$) and 517 (anhydro-Gal*p*–Glc*p*$^+$).

EXPERIMENTAL

For general procedures, see ref. 1. Hexamethylphosphoric triamide was dried by storage over molecular sieve for several days and subsequent distillation *in vacuo*.

Nucleophilic displacement reactions of 6′-chloro-6′-deoxyraffinose deca-acetate (**2**). — (*a*) *With bromide*. A solution of the 6′-chloride[1] **2** (0.2 g, 0.21 mmol) and lithium bromide (0.5 g, 5.8 mmol) in hexamethylphosphoric triamide (2 ml) was heated at 100–105° for 24 h. T.l.c. (ether–light petroleum) then revealed a product that moved slightly faster than **2**. The mixture was cooled and treated with ice–water, and the product isolated by ether extraction. The resulting, yellow solid (0.21 g) was decolourised by passage through a short column of charcoal–silica gel, with elution by ether–light petroleum (8:1), to give **3** as a white, amorphous solid (0.17 g, 80%), m.p. 78–80°, $[\alpha]_D$ +98.6° (*c* 0.5) (Found: C, 45.9; H, 5.2; Br, 8.1. $C_{38}H_{51}BrO_{25}$ calc.: C, 46.2; H, 5.2; Br, 8.1).

O-Deacetylation of **3** with a catalytic amount of sodium methoxide in methanol afforded 6′-bromo-6′-deoxyraffinose (**4**) as a white, hygroscopic solid, m.p. 121–123°, $[\alpha]_D$ +61.6° (*c* 0.5, methanol); a satisfactory analysis could not be obtained due to its hygroscopic nature.

(*b*) *With iodide*. The reaction in (*a*) was repeated, using sodium iodide. T.l.c. of the product showed a major component and minor, slower-moving components, possibly arising from *O*-deacetylation. The mixture was acetylated in the usual way (acetic anhydride–pyridine), to give the 6′-iodide **5** (65%), m.p. 68–72° (from ethanol–light petroleum), $[\alpha]_D$ +90.8° (*c* 1) (Found: C, 43.8; H, 5.1; I, 11.2. $C_{38}H_{51}IO_{25}$ calc.: C, 44.1; H, 4.9; I, 12.3).

O-Deacetylation of **5** afforded 6′-deoxy-6′-iodoraffinose (**6**), m.p. 116–118° (from water), $[\alpha]_D$ +89° (*c* 0.3, methanol) (Found: C, 35.6; H, 5.05; I, 19.8. $C_{18}H_{31}IO_{15}$ calc.: C, 35.2; H, 5.05; I, 20.7).

(*c*) *With azide*. The reaction in (*a*) was repeated, using sodium azide at 70° for 17 h. The product was purified by passage through a short column of silica gel, by elution with ether–light petroleum (12:1), to give the 6-azide **7** (70%) as a white, amorphous solid, m.p. 66–68°, $[\alpha]_D$ +112° (*c* 1) (Found: C, 48.7; H, 5.1; N, 3.8. $C_{38}H_{51}N_3O_{25}$ calc.: C, 48.1; H, 5.3; N, 4.4).

O-Deacetylation of **7** gave 6′-azido-6′-deoxyraffinose (**8**) as a white, amorphous solid, m.p. 86–89°, $[\alpha]_D$ +126° (*c* 0.5, methanol) (Found: C, 40.2; H, 5.8; N, 7.1. $C_{18}H_{31}N_3O_{15}$ calc.: C, 40.8; H, 5.8; N, 7.9).

(*d*) *With potassium phthalimide.* A mixture of the 6′-chloride **2** (0.52 g, 0.53 mmol) and potassium phthalimide (0.3 g, 1.6 mmol) was heated in dry hexamethylphosphoric triamide (2 ml) at 95° for 48 h. The product was isolated by ether extraction as in (*a*), and purified on a short column of silica gel, by elution with ethanol–light petroleum (1:3), to give the phthalimide **12** as an amorphous solid (60 mg, 11%), m.p. 77–80°, $[\alpha]_D$ +111° (*c* 0.5) (Found: C, 51.8; H, 4.9; N, 1.0. $C_{46}H_{55}NO_{27}$ calc.: C, 52.4; H, 5.2; N, 1.3).

6′-Acetamido-6′-deoxyraffinose (**10**) *and its deca-acetate* **11**. — A solution of 6′-azido-6′-deoxyraffinose (**8**, 0.56 g) in methanol (100 ml) was hydrogenated with 10% palladium-on-charcoal for 108 h. After filtration, the reaction mixture was evaporated to dryness. T.l.c. (ethanol–water, 1:1) indicated some fast-moving, minor components and one slower moving, major component. The mixture was fractionated on a short column of silica gel by elution with ethanol–water (1:1). The first few fractions containing the faster-moving components were discarded, and the 6′-amine **9** was obtained as a white, hygroscopic solid (0.35 g, 58%), m.p. 157–159°, $[\alpha]_D$ +127° (*c* 0.5, water).

A sample (0.15 g, 0.26 mmol) of **9** was dissolved in methanol (10 ml) and treated with acetic anhydride (0.5 ml, 5.3 mmol). After 6 h, the solution was evaporated to dryness and the product fractionated on a column of silica gel by elution with ethanol. The acetamido derivative **10** was obtained (0.09 g, 59%) as a hygroscopic, white solid, m.p. 118–121°, $[\alpha]_D$ +119.3° (*c* 0.3, methanol); a satisfactory analysis could not be obtained.

A sample (0.2 g, 0.35 mmol) of the 6′-amine **9** was acetylated in the usual way with acetic anhydride (0.7 ml) in pyridine (5 ml), to give the deca-acetate **11** (48%), m.p. 83–85° (from ether–light petroleum), $[\alpha]_D$ +98° (*c* 0.5) (Found: C, 50.2; H, 5.8; N, 1.5. $C_{40}H_{55}NO_{26}$ calc.: C, 49.7; H, 5.7; N, 1.5).

6′,6″-Diazido-6′,6″-dideoxyraffinose nona-acetate (**14**). — A mixture of the 6′,6″-dichloride[1] **13** (0.5 g, 0.54 mmol), sodium azide (0.5 g, 7.7 mmol), and hexamethylphosphoric triamide (10 ml) was heated at 100° for 5.5 h; t.l.c. (ether–light petroleum, 8:1) then indicated completion, with a small amount of concomitant *O*-deacetylation. The product was isolated as described above and acetylated in the usual way, to give the diazide **14** as a white solid (0.35 g, 69%), m.p. 64–66°, $[\alpha]_D$ +109° (*c* 0.5) (Found: C, 46.6; H, 5.0; N, 9.1. $C_{36}H_{48}N_6O_{23}$ calc.: C, 46.4; H, 5.2; N, 9.0).

O-Deacetylation of **14**, in the usual way, gave 6′,6″-diazido-6′,6″-dideoxyraffinose (**15**) as an amorphous solid, m.p. 112–114°, $[\alpha]_D$ +60° (*c* 0.5, methanol) (Found: C, 39.2; H, 5.3; N, 14.8. $C_{18}H_{30}N_6O_{14}$ calc.: C, 39.0; H, 5.4; N, 15.1%).

3′,6′-Anhydroraffinose nona-acetate (**16**). — A solution of the 6′-chloride[1] **2** (0.5 g, 0.53 mmol) in 0.02M methanolic sodium methoxide (100 ml) was boiled under reflux for 24 h and then evaporated to dryness, and the residue acetylated in the usual manner (acetic anhydride–pyridine), to give the nona-acetate **16** as a white, amorphous solid (0.32 g, 70%), m.p. 80–83°, $[\alpha]_D$ +125° (*c* 1) (Found: C, 50.2; H, 5.7. $C_{36}H_{48}O_{24}$ calc.: C, 50.0; H, 5.5).

O-Deacetylation afforded 3′,6′-anhydroraffinose (**17**) as a white, hygroscopic, amorphous powder, m.p. 136–139°, $[\alpha]_D$ +79° (*c* 0.5, methanol), which did not analyse correctly due to its hygroscopic nature.

3′,6′:3″,6″-Dianhydroraffinose hepta-acetate (**19**). — The 6′,6″-dichloride[1] **13** (0.18 g, 0.2 mmol) was treated, as described above, with 0.02M methanolic sodium methoxide (50 ml). The product was acetylated, to give **19** (84 mg, 56%), m.p. 80–83° (from ethanol–light petroleum), $[\alpha]_D$ +97° (*c* 0.5) (Found: C, 50.4; H, 5.2. $C_{32}H_{42}O_{21}$ calc.: C, 50.4; H, 5.5). ^{1}H-N.m.r. data (C_6D_6, 220 MHz): δ 3.95 (t, $J_{2,3} = J_{3,4} = 9$ Hz, H-3), 4.25 (d, $J_{1,2}$ 3.0 Hz, H-1), 4.4 (d, $J_{3'',4''}$ ~2, $J_{4'',5''}$ ~0 Hz, H-4″), 4.56 (t, $J_{4,5}$ 10 Hz, H-4), 4.58 (dd, $J_{1'',2''}$ 3, $J_{2'',3''}$ 5 Hz, H-2″), 4.72 (dd, H-2), 5.00 (d, H-1″), 5.13 (d, *J* 2.5 Hz, ?), 5.41 (d, $J_{1'a,1'b}$ 12 Hz, H-1′a), 5.59 (d, H-3″), 5.75–6.48 (complex, overlapped multiplets), 8.01 (CH_3), 8.20 (CH_3), 8.21 (2 × CH_3), 8.24 (CH_3), and 8.48 (CH_3).

*α-Melibiosyl 6-deoxy-β-*D-threo-*hex-5-enulofuranoside deca-acetate* (**18**). — A solution of 6′-deoxy-6′-iodoraffinose deca-acetate (**5**; 0.204 g, 0.2 mmol) in pyridine (20 ml) was stirred with anhydrous silver fluoride (0.23 g, 1.8 mmol) for 4.5 h; t.l.c. then indicated that only one product had been formed. The reaction mixture was poured into ice–water, and the product was isolated as a black syrup by extraction with dichloromethane in the usual way. Fractionation on a small column of silica gel–charcoal, by elution with ether–light petroleum (10:1), gave the deca-acetate **18** as a white, amorphous solid (0.14 g, 83%), m.p. 67–70°, $[\alpha]_D$ +113° (*c* 0.5) (Found: C, 50.5; H, 5.6. $C_{38}H_{50}O_{25}$ calc.: C, 50.3; H, 5.5).

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