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Note

Synthesis of methyl ether derivatives of sucrose*

MICHAEL G. LINDLEY, GORDON G. BIRCH,

National College of Food Technology, St. George's Avenue, Weybridge, Surrey KT13 0DE (Great Britain)

AND RIAZ KHAN

Tate & Lyle Ltd., Group Research & Development, Philip Lyle Memorial Research Laboratory, University of Reading, P.O. Box 68, Reading RG6 2BX (Great Britain)

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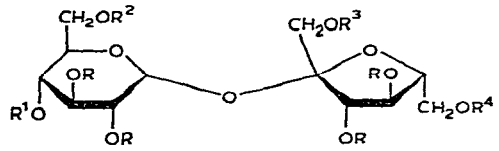
Sucrose is one of the sweetest known sugars and is by far the most widely used food-sweetening agent. However, no attempts have been made to ascertain why it is so sweet. Recognising that the sweetness is a function of hydroxyl groups[2], the obvious way to identify the saporogenic groups of the sucrose molecule is to prevent selected hydroxyl groups from participating in the sensory response. This may be achieved by utilising suitable blocking-groups, such as *O*-methyl. The preparation of selected methyl ethers of sucrose is described, though the results of their sensory evaluation will appear elsewhere.

Octa-*O*-methylsucrose[3], 1′,2,3,3′,4,4′,6- and 1′,2,3,3′,4,4′,6′-hepta-*O*-methylsucrose[4], 1′,6,6′-tri-*O*-methylsucrose[5], and 1′,4,6′-tri-*O*-methylsucrose[6] were, hitherto, the only known methyl ethers of sucrose. Methylation of carbohydrates containing base-labile substituents using a combination of diazomethane in dichloromethane and boron trifluoride etherate (reagent *A*) is known to proceed readily, without migration of acyl groups[7,8]. Consequently, this method of methylation was chosen for preparing various methyl ethers of sucrose.

Methylation of 2,3,3′,4,4′-penta-*O*-acetylsucrose[9] with reagent *A* gave the 1′,6,6′-trimethyl ether[5] **1** in 88% yield. In the p.m.r. spectrum of **1**, the resonances due to H-1, H-2, H-3, H-3′, H-4, and H-4′ (τ 4.36, 5.16, 4.57, 4.44, 5.0, and 4.61) had the expected coupling constants and chemical-shift values. The three methyl resonances were clearly identified as singlets at τ 6.57, 6.64, and 6.86. The structure of **1** was also supported by its mass spectrum. Conventional de-esterification of **1** afforded 1′,6,6′-tri-*O*-methylsucrose (**2**). Similar methylation of 2,3,3′,4′,6-penta-*O*-acetylsucrose[6] gave the 1′,4,6′-trimethyl ether[6] **3**. The structure of **3** was indicated by its p.m.r. spectrum. The resonance due to H-4 was shifted upfield to the region τ 5.75–5.96, because of the methyl substituent. The signals due to H-2, H-3, H-3′, and H-4′

*Sucrochemistry: Part XVIII. For Part XVII, see Ref. 1.

appeared in their usual positions (τ 5.25, 4.57, 4.42, and 4.66), suggesting that the two remaining methyl groups were located at primary positions. This conclusion was substantiated by the mass spectrum of **3**, which contained a strong peak at *m/e* 275 and a weaker peak at *m/e* 303, due to ketofuranosyl and hexopyranosyl cations, respectively. De-esterification of **3**, in the usual way, gave the known[5] 1′,4,6′-trimethyl ether **4**.



1 R = R¹ = Ac, R² = R³ = R⁴ = Me
2 R = R¹ = H, R² = R³ = R⁴ = Me
3 R = R² = Ac, R¹ = R³ = R⁴ = Me
4 R = R² = H, R¹ = R³ = R⁴ = Me
5 R = R¹ = R² = Ac, R³ = R⁴ = Me
6 R = R¹ = R² = H, R³ = R⁴ = Me
7 R = R³ = R⁴ = Ac, R¹ = R² = Me
8 R = R³ = R⁴ = H, R¹ = R² = Me
9 R = R² = R³ = Ac, R¹ = R⁴ = Me
10 R = R² = R³ = H, R¹ = R⁴ = Me
11 R = R¹ = R³ = Bz, R² = R⁴ = Me
12 R = R¹ = R³ = H, R² = R⁴ = Me
13 R = R² = R³ = R⁴ = Ac, R¹ = Me
14 R = R² = R³ = R⁴ = H, R¹ = Me
15 R = R¹ = R² = R³ = Ac, R⁴ = Me
16 R = R¹ = R² = R³ = H, R⁴ = Me

Methylation of 2,3,3′,4,4′,6-hexa-*O*-acetyl[10], 1′,2,3,3′,4′,6′-hexa-*O*-acetyl[11], 1′,2,3,3′,4′,6-hexa-*O*-acetyl[12], and 1′,2,3,3′,4,4′-hexa-*O*-benzoyl[13] derivatives of sucrose with reagent *A* gave the corresponding 1′,6′-dimethyl (**5**), 4,6-dimethyl (**7**), 4,6′-dimethyl (**9**), and 6,6′-dimethyl ethers. The structures of **5**, **7**, **9**, and **11** were established on the basis of p.m.r. and mass spectrometry. In the p.m.r. spectrum of **5**, the chemical-shift values for H-1, H-2, H-3, H-3′, H-4, and H-4′ were as expected, which indicated that the two methyl groups were located on primary positions. The mass spectrum of **5** contained a strong peak at *m/e* 275 due to ketofuranosyl cation and a weaker peak at *m/e* 331 due to hexopyranosyl cation, and thus confirmed the structure **5**. The presence of a methyl group at C-4 in **7** was indicated by the absence of an H-4 signal in the region τ 4.5–5.4 of the p.m.r. spectrum, where it usually occurs in acylated derivatives of sucrose. The mass spectrum of **7** showed peaks at *m/e* 331 and 275 due to ketofuranosyl and hexopyranosyl cations, respectively. The signals for H-4 in the p.m.r. spectrum of **9** occurred at an upfield position (τ 5.79), because of the deshielding effect of the methyl substituent. The mass spectrum of **9** confirmed that the two methyl substituents were not located on the same ring, as a strong peak was observed at *m/e* 303. The p.m.r. spectrum of **11** indicated that the two methyl groups were primary-hydroxyl substituents.

De-esterification of **5**, **7**, **9**, and **11** with sodium methoxide in methanol afforded the corresponding methyl ethers **6**, **8**, **10**, and **12**.

Methylation of 1′,2,3,3′,4′,6,6′-hepta-*O*-acetylsucrose[14] and 1′,2,3,3′,4,4′,6-hepta-*O*-acetylsucrose[15] gave the expected 4-methyl (**13**) and 6′-methyl (**15**) ethers, the structures of which were confirmed on the basis of p.m.r. and mass spectroscopy. The p.m.r. spectrum of **13** confirmed the location of the methyl substituent at C-4.

The structure of **13** was also supported by its mass spectrum. In the p.m.r. spectrum of **15**, the signals due to H-1, H-2, H-3, H-3′, and H-4′ appeared below τ 5.4, which suggested that the *O*-methyl substituent was at a primary position. The mass spectrum of **15** showed peaks at *m/e* 331 and 303 due to hexopyranosyl and ketofuranosyl cations, respectively. The absence of a weak peak at *m/e* 96 ($-CH_2OCH_3$) supported[16] the location of the methyl group at C-6′.

De-esterification of **13** and **15** afforded the corresponding 4-methyl (**14**) and 6′-methyl (**15**) ethers.

EXPERIMENTAL

For details of the general procedure, see Part VI[17].

1′,6,6′-Tri-O-methylsucrose (**2**). — 2,3,3′,4,4′-Penta-*O*-acetylsucrose[9] (2 g) was treated with a freshly prepared solution of diazomethane in dichloromethane (80 ml) and boron trifluoride etherate (0.2 ml) with stirring at −5° for 0.5 h. Polymethylene was filtered off and the pale-yellow solution was washed successively with aqueous acetic acid, saturated aqueous sodium hydrogen carbonate, and water. The solution was dried (Na_2SO_4) and concentrated, and the residue was eluted from a column of silica gel (50 g), using ether–light petroleum (5:1), to give 1′,6,6′-tri-*O*-methylsucrose penta-acetate (**1**) as a syrup (1.9 g, 88%), $[\alpha]_D$ +68.6° (*c* 3.4, chloroform); lit.[5] $[\alpha]_D^{20}$ +52° (*c* 1, acetone). N.m.r. data: τ 4.36 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1); 5.16 (q, 1 H, $J_{2,3}$ 10.5, H-2); 4.57 (d, 1 H, $J_{3,4}$ 10.0 Hz, H-3); 5.0 (t, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 4.44 (d, 1 H, $J_{3',4}$ 7.0 Hz, H-3′); 4.61 (t, 1 H, $J_{4',5'}$ 7.0 Hz, H-4′); 6.59, 6.61, and 6.65 (3 s, 9 H, 3Me). Mass-spectral data [(a) and (b) refer to hexopyranosyl and ketofuranosyl cations, respectively]: *m/e* 303a, 275b, 243a, 215b, 201a, 183a, 173b, 141a, and 109a,b.

Anal. Calc. for $C_{25}H_{38}O_{16}$: C, 50.5; H, 6.4. Found: C, 50.4; H, 6.7.

De-esterification of **1** (1 g), using sodium methoxide in methanol to pH 10 at room temperature for 2 h, afforded, after deionisation with Amberlyst 15 (H^+) resin and concentration, **2** (500 mg, 77%), $[\alpha]_D$ +69° (*c* 1.7, water).

Anal. Calc. for $C_{15}H_{28}O_{11}$: C, 46.9; H, 7.3. Found: C, 46.7; H, 7.4.

1′,4,6′-Tri-O-methylsucrose (**4**). — 2,3,3′,4′,6-Penta-*O*-acetylsucrose[6] (1.8 g) was treated with a solution of diazomethane (80 ml) and boron trifluoride etherate (0.15 ml), and worked up as described previously. The syrupy residue was eluted from a column of silica gel (60 g), using ether–light petroleum (5:1), to give 1′,4,6′-tri-*O*-methylsucrose penta-acetate (**3**; 1.6 g, 82%), $[\alpha]_D$ +60.1° (*c* 1.4, chloroform); lit.[6] $[\alpha]_D$ +57.7° (*c* 3.72, chloroform). N.m.r. data: τ 4.46 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1); 5.25 (q, 1 H, $J_{2,3}$ 10.5 Hz, H-2); 4.57 (q, 1 H, $J_{3,4}$ 10.0 Hz, H-3); 5.75–5.96 (H-4); 4.42 (d, 1 H, $J_{3',4'}$ 7.0 Hz, H-3′); 4.66 (t, 1 H, $J_{4,5'}$ 7.0 Hz, H-4′). Mass-spectral data [(a) refers to hexopyranosyl and (b) to ketofuranosyl cations]: *m/e* 303a, 275b, 243a, 215b, 201a, 183a, 173b, 169a, 141b, and 109a,b.

Anal. Calc. for $C_{25}H_{38}O_{16}$: C, 50.4; H, 6.4. Found: C, 50.5; H, 6.7.

Conventional de-esterification of **3** (1 g), using sodium methoxide in methanol, gave **4** (500 mg, 77%), $[\alpha]_D$ +67.1° (*c* 0.7, water); lit.[6] $[\alpha]_D^{24}$ +67.6° (*c* 1.74, water).

Anal. Calc. for $C_{15}H_{28}O_{11}$: C, 46.9; H, 7.3. Found: C, 46.7; H, 7.4.

1′,6′-Di-O-methylsucrose (**6**). — Methylation of 2,3,3′,4,4′,6-hexa-*O*-acetylsucrose[10] (700 mg) with diazomethane (45 ml) and boron trifluoride etherate (0.05 ml) gave, after processing as described previously, 1′,6′-di-*O*-methylsucrose hexa-acetate (**5**; 700 mg, 95.4%) as a syrup, $[\alpha]_D$ +59.8° (*c* 1.4, chloroform). N.m.r. data: τ 4.36 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1); 5.14 (q, 1 H, $J_{2,3}$ 10.0 Hz, H-2); 4.94 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4); 4.4 (d, 1 H, $J_{3',4'}$ 7.0 Hz, H-3′); 4.62 (t, 1 H, $J_{4',5'}$ 7.0 Hz, H-4′); 6.6 and 6.62 (2 s, 6 H, 2Me). Mass-spectral data [(a) and (b) indicate ions due to hexopyranosyl and ketofuranosyl cations, respectively]: 331a, 275b, 271a, 229a, 215b, 173b, 169a, 141b, 127a, 109a, and 109a,b.

Anal. Calc. for $C_{14}H_{26}O_{11}$: C, 45.4; H, 7.0. Found: C, 45.4; H, 7.5.

De-esterification of **5** (500 mg), in the usual way, afforded **6** (200 mg, 67%) as a syrup, $[\alpha]_D$ +70° (*c* 2.56, water).

Anal. Calc. for $C_{14}H_{26}O_{11}$: C, 45.4; H, 7.0. Found. C, 45.4; H, 7.5.

4,6-Di-O-methylsucrose (**8**). — 1′,2,3,3′,4′,6′-hexa-*O*-acetylsucrose[11] (2 g) was treated with diazomethane (20 ml) and boron trifluoride etherate (0.2 ml), and processed as described previously, to give 4,6-di-*O*-methylsucrose hexa-acetate (**7**; 2 g, 95.5%) as a syrup, $[\alpha]_D$ +63° (*c* 1.4, chloroform). N.m.r. data: τ 4.41 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1); 5.2 (q, 1 H, $J_{2,3}$ 10.5 Hz, H-2); 4.61 (t, 1 H, $J_{3,4}$ 10.5 Hz, H-3); 4.52 (d, 1 H, $J_{3',4'}$ 6.5 Hz, H-3′); 6.53, 6.56 (2 s, 6 H, 2Me). Mass-spectral data [(a) and (b) indicate ions due to hexopyranosyl and ketofuranosyl cations, respectively]: *m/e* 331b, 275a, 215a, 211b, 173a, 169b, 141a, and 109a,b.

Anal. Calc. for $C_{26}H_{38}O_{17}$: C, 50.1; H, 6.1. Found: C, 50.0; H, 6.3.

De-esterification of 7 (500 mg), using sodium methoxide in methanol, afforded **8** (200 mg, 67%) as a syrup, $[\alpha]_D$ +61.4° (*c* 1.7, water).

Anal. Calc. for $C_{14}H_{26}O_{11}$: C, 45.4; H, 7.0. Found: C, 45.2; H, 7.1.

4,6′-Di-O-methylsucrose (**10**). — Methylation of 1′,2,3,3′,4′,6-hexa-*O*-acetylsucrose[12] (3.3 g) with diazomethane (140 ml) and boron trifluoride etherate (0.3 ml) at −5° for 0.5 h gave, after processing in the usual way, a syrupy residue. The product, on elution from a column of silica gel (50 g) with ether–light petroleum (2:1), afforded 4,6′-di-*O*-methylsucrose hexa-acetate (**9**; 3 g, 87%) as a syrup, $[\alpha]_D$ +61.9° (*c* 1.1, chloroform). N.m.r. data: τ 4.45 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1); 5.23 (q, 1 H, $J_{2,3}$ 10.5 Hz, H-2); 4.67 (t, 1 H, $J_{3,4}$ 10.5 Hz, H-3); 5.79 (t, 1 H, $J_{4,5}$ 10.5 Hz, H-4); 4.6 (d, 1 H, $J_{3',4'}$ 6.0 Hz, H-3′); 4.7 (t, 1 H, $J_{4',5'}$ 6.0 Hz, H-4′); 6.55, 6.60 (2 s, 6 H, 2Me); 7.75–7.94 (m, 18 H, 6Ac). Mass-spectral data: *m/e* 303, 243, 201, 183, 169, 141, 109, and 101.

Anal. Calc. for $C_{26}H_{38}O_{17}$: C, 50.1; H, 6.1. Found: C, 50.7; H, 5.9.

Conventional de-esterification of **9** (1 g), using sodium methoxide in methanol, gave **10** (480 mg, 80.6%) as a syrup, $[\alpha]_D$ +44.8° (*c* 2.83, water).

Anal. Calc. for $C_{14}H_{26}O_{11}$: C, 45.4; H, 7.0. Found: C, 45.0; H, 6.9.

6,6′-Di-O-methylsucrose (**12**). — Methylation of 1′,2,3,3′,4,4′-hexa-*O*-benzoyl-

sucrose[13] (2.5 g), using diazomethane (85 ml) and boron trifluoride etherate (0.15 ml), gave a syrupy residue, which was eluted from a column of silica gel (50 g) with ether–light petroleum to afford 6,6′-di-*O*-methylsucrose hexabenzoate (**11**; 2.3 g, 87.8%) as a syrup, $[\alpha]_D$ +21.5° (*c* 2.3, chloroform). N.m.r. data: τ 3.88 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1); 4.55 (q, 1 H, $J_{2,3}$ 10.0 Hz, H-2); 3.77 (t, 1 H, $J_{3,4}$ 10.0 Hz, H-3); 4.31 (t, 1 H, $J_{4,5}$ 10.0 Hz, H-4); 4.03 (t, 1 H, $J_{4',5'}$ 7.0 Hz, H-4′); 6.55, 6.67 (2 s, 6 H, 2Me); 1.7–2.8 (m, 30 H, 6Bz).

Anal. Calc. for $C_{56}H_{50}O_{17}$: C, 67.6; H, 5.0. Found: C, 67.9; H, 5.3.

De-esterification of **11** (2 g), using sodium methoxide in methanol, gave **12**. (800 mg, 67%) as a syrup, $[\alpha]_D$ +63.6° (*c* 0.94, water).

Anal. Calc. for $C_{14}H_{26}O_{11}$: C, 45.4; H, 7.0. Found: C, 44.9; H, 7.2.

4-O-Methylsucrose (**14**). — Methylation of 1′,2,3,3′,4′,6,6′-hepta-*O*-acetylsucrose[14] (1 g), as described previously with diazomethane (75 ml) and boron trifluoride etherate (0.05 ml), afforded a syrupy product, which was eluted from a column of silica gel (30 g) with ether–light petroleum (3:1) to give 4-*O*-methylsucrose hepta-acetate (**13**; 1 g, 97.8%) as a syrup, $[\alpha]_D$ +49.4° (*c* 1.5, chloroform). N.m.r data: τ 4.44 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1); 5.22 (q, 1 H, $J_{2,3}$ 10.0 Hz, H-2); 4.58 (t, 1 H, $J_{3,4}$ 10.0 Hz, H-3); 4.6 (d, 1 H, $J_{3',4'}$ 7.0 Hz, H-3′); 4.66 (t, 1 H, $J_{4',5'}$ 7.0 Hz, H-4′); 6.56 (s, 3 H, Me); 7.75–7.92 (m, 21 H, 7Ac). Mass-spectral data [(a) and (b) represent ions due to hexopyranosyl and ketofuranosyl cations, respectively]: *m/e* 331b, 303a, 271b, 243a, 201a, 183a, 169b, 141a, 127b, and 109a,b.

De-esterification of **13** (500 mg), using sodium methoxide, afforded **14** (240 mg, 85.7%) as a syrup, $[\alpha]_D$ +49.6° (*c* 0.74, water).

Anal. Calc. for $C_{13}H_{24}O_{11}$: C, 43.8; H, 6.7. Found: C, 43.9; H, 7.3.

6′-O-Methylsucrose (**16**).—Treatment of 1′,2,3,3′,4,4′,6-hepta-*O*-acetylsucrose[15] (5 g) with diazomethane (50 ml) and boron trifluoride etherate (0.25 ml), as described previously, gave a syrupy product, which was eluted from a column of silica gel (100 g) with ether–light petroleum to afford 6′-*O*-methylsucrose hepta-acetate (**15**; 5 g, 97.8%) as a syrup, $[\alpha]_D$ +59.1° (*c* 0.3, chloroform). N.m.r. data: τ 4.15 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1); 5.1 (q, 1 H, $J_{2,3}$ 10.0 Hz, H-2); 4.53 (t, 1 H, $J_{3,4}$ 10.0 Hz, H-3); 4.89 (t, 1 H, $J_{4,5}$ 10.0 Hz, H-4); 4.38 (d, 1 H, $J_{3',4'}$ 6.0 Hz, H-3′); 4.66 (t, 1 H, $J_{4',5'}$ 6.0 Hz, H-4′); 6.54 (s, 3 H, Me); 7.76–9.5 (m, 21 H, 7Ac). Mass-spectral data [(a) and (b) refer to hexopyranosyl and ketofuranosyl cations, respectively]: *m/e* 331a, 303b, 271a, 243b, 229a, 201b, 183b, 169a, 141b, 127a, and 109a,b.

Anal. Calc. for $C_{27}H_{38}O_{18}$: C, 49.8; H, 5.8. Found: C, 50.0; H, 6.0.

De-esterification of **15** (5 g), as described previously, gave **16** (2.6 g, 92.9%) as a syrup, $[\alpha]_D$ +53.4° (*c* 1, water).

Anal. Calc. for $C_{13}H_{24}O_{11}$: C, 43.8; H, 6.7. Found: C, 43.5; H, 7.1.

REFERENCES

1 R. Khan and K. S. Mufti, *Carbohyd. Res.*, 43 (1975) 247–253.
2 R. S. Shallenberger, *J. Food Sci.*, 28 (1963) 584–589.
3 H. Bredereck, G. Hagelloch, and E. Hambsch, *Chem. Ber.*, 87 (1954) 35–37.

4 T. OTAKE, *Bull. Chem. Soc. Jap.*, 43 (1970) 3199–3205.
5 E. G. V. PERCIVAL, *J. Chem. Soc.*, (1935) 648–653.
6 G. G. MCKEOWN, R. S. E. SERENIUS, AND L. D. HAYWARD, *Can. J. Chem.*, 35 (1957) 28–36.
7 E. G. GROS AND S. M. FLEMATTI, *Chem. Ind. (London)*, (1966) 1556–1557.
8 E. G. GROS AND I. O. MASTRONARDI, *Carbohyd. Res.*, 10 (1969) 318–321.
9 H. BREDERECK, H. ZINNER, A. WAGNER, G. FABER, G. GREINER, AND W. HUBER, *Chem. Ber.*, 91 (1958) 2824–2829.
10 J. G. BUCHANAN AND D. A. CUMMERSON, *Carbohyd. Res.*, 21 (1972) 293–296.
11 R. KHAN, *Carbohyd. Res.*, 32 (1974) 375–379.
12 R. KHAN, *Carbohyd. Res.*, 25 (1972) 232–236.
13 L. HOUGH, K. S. MUFTI, AND R. KHAN, *Carbohyd. Res.*, 21 (1972) 144–147.
14 R. KHAN AND K. J. PARKER, *British Patent Application* (1973).
15 J. G. BUCHANAN, D. A. CUMMERSON, AND D. M. TURNER, *Carbohyd. Res.*, 21 (1972) 283–292.
16 W. W. BINKLEY, R. C. DOUGHERTY, D. HORTON, AND J. D. WANDER, *Carbohyd. Res.*, 17 (1971) 127–144.
17 L. HOUGH AND K. S. MUFTI, *Carbohyd. Res.*, 25 (1972) 497–503.