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Note

Synthesis of dimethyl ethers of α,α-trehalose*

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α,α-Trehalose has a two-fold axis of symmetry[2] which makes the D-glucopyranosyl residues chemically and physically indistinguishable, and is an ideal model for taste studies. The synthesis of symmetrical derivatives is relatively facile[1–4] and generally, in their use in taste studies, the question as to which half of the disaccharide interacts *via* intermolecular hydrogen bonding between an AH,B unit[5] and a similar bifunctional unit of the receptor site, to elicit the sweet-taste response, does not arise.

The location of the saporogenic AH,B group(s) of trehalose might be determined by selective and suitable blocking of hydroxyl groups[6,7]. Methylation has proved to be suitable, and the sensory properties of some methyl ethers of α,α-trehalose have been reported[8]. We now describe the preparation of these derivatives.

Because of the tendency for ester migration[9] under the mildly basic conditions used for *O*-alkylation, acetyl derivatives were avoided in the synthesis of the desired methyl derivatives of trehalose. Treatment of 2,2′-di-*O*-benzoyl-4,6:4′,6′-di-*O*-benzylidene-α,α-trehalose[4] (**4**) and 4,6:4′,6′-di-*O*-benzylidene-2,2′-di-*O*-tosyl-α,α-trehalose[3] (**5**) with methyl iodide and silver oxide gave the respective 3,3′-dimethyl ethers **6** and **7** in yields of over 80%. The n.m.r. data (Table I) for **6** and **7** show the expected chemical shifts and coupling constants for H-1,1′, H-2,2′, and H-4,4′. The resonance due to H-3,3′ of **6** is shifted upfield (τ 6.06) because of the methyl substituent; in α-D-glucopyranosyl structures having $^4C_1$ conformations, the resonance due to H-3 usually occurs downfield relative to those of the other ring-proton resonances, due to deshielding[2] by O-1. Treatment of **4** with diazomethane in dichloromethane and boron trifluoride etherate, a reagent that does not cause acyl migration, also gave **6**.

Reaction[10] of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with methyl

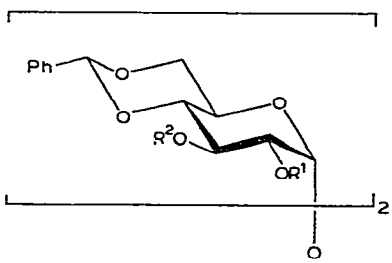
*Chemical Modification of Trehalose: Part XIX. For Part XVIII, see Ref. 1.

TABLE I

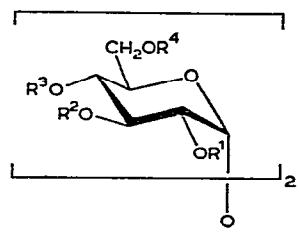
^{1}H-N.M.R. DATA[a]

Compounds:	6	7[b]	9	12	13	17[b]	18	21
H-1,1′	4.61(d)	4.60(d)	4.74(d)	4.75(d)	4.53(d)	4.48(d)	4.35(d)	4.73(d)
H-2,2′	4.91(dd)	5.80(dd)	5.14(dd)	5.08(dd)	5.62(dd)	4.68(dd)	4.79(dd)	4.96(dd)
H-3,3′	6.06(t)	5.3–	6.17(t)	6.20(t)	6.33(t)	3.86(t)	4.12(t)	4.51(t)
H-4,4′	6.09(t)	5.6(cm)	6.30(t)	5.02(t)	5.03(t)	6.39(t)	6.24(t)	4.95(t)
H-5,5′	6.3–		6.02(m)	6.11(m)	5.9–			5.8–
	6.4(cm)	6.2–			6.0(cm)	5.7–		6.0(cm)
H-6a6′a	6.5–	6.5(cm)	5.83(dd)	5.83(dd)	5.7–	6.2(cm)		6.5–
H-6b6′b	6.6(cm)		6.25(t)	5.99(dd)	5.8(cm)			6.6(cm)
OCH_3	6.39(s)	6.67(s)	6.37(s)	6.50(s)	6.85(s)	6.65(s)	7.02(s)	6.70(s)
$J_{1,2}$	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
$J_{2,3}$	10.0	10.0	9.0	10.0	10.0	10.5	10.5	10.5
$J_{3,4}$	10.0		9.0	10.0	10.0	10.5	9.5	10.0
$J_{4,5}$	9.0		9.0	9.5	9.5	10.0	9.5	10.0
$J_{5,6a}$			4.5	7.0				
$J_{5,6b}$			9.0	2.0				
$J_{6a,6b}$			10.5	12.5				

[a]First-order chemical shifts (τ values) and coupling constants at 220 MHz in deuteriochloroform. Key: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; cm, complex multiplet. [b]100 MHz.



1 $R^1 = R^2 = H$
2 $R^1 = R^2 = Bz$
3 $R^1 = Me, R^2 = H$
4 $R^1 = Bz, R^2 = H$
5 $R^1 = Ts, R^2 = H$
6 $R^1 = Bz, R^2 = Me$
7 $R^1 = Ts, R^2 = Me$
8 $R^1 = H, R^2 = Me$
9 $R^1 = Ac, R^2 = Me$



10 $R^2 = Me, R^1 = R^3 = R^4 = H$
11 $R^1 = Ts, R^2 = Me, R^3 = R^4 = H$
12 $R^2 = Me, R^1 = R^3 = R^4 = Ac$
13 $R^1 = Ts, R^2 = Me, R^3 = R^4 = Ac$
14 $R^1 = R^2 = Bz, R^3 = R^4 = H$
15 $R^3 = H, R^1 = R^2 = R^4 = Bz$
16 $R^3 = H, R^1 = R^2 = Bz, R^4 = Tr$
17 $R^3 = Me, R^1 = R^2 = R^4 = Bz$
18 $R^3 = Me, R^1 = R^2 = Bz, R^4 = Tr$
19 $R^3 = Me, R^1 = R^2 = R^4 = H$
20 $R^4 = H, R^1 = R^2 = R^3 = Ac$
21 $R^4 = Me, R^1 = R^2 = R^3 = Ac$
22 $R^4 = Me, R^1 = R^2 = R^3 = H$

iodide in *N,N*-dimethylformamide, in the presence of barium oxide, afforded mainly the 2-*O*-methyl derivative. However, application of this method to 4,6:4′,6′-di-*O*-benzylidene-α,α-trehalose (**1**) gave the 3,3′-di-*O*-methyltrehalose derivative **8** as the major product. Treatment of **1** with methyl iodide and silver oxide also gave **8** as the major product (55%), from which the diacetate **9** was obtained.

Debenzylidenation of **7** and **8** with methanolic hydrogen chloride gave crystalline **11** and **10**, respectively, which were further characterised as their acetates **12** and **13**. The ^{1}H-n.m.r. data (Table I) for **12** and **13** show that the resonance due to H-3,3′ has a relatively upfield position. The mass spectrum of **13** contained a peak at *m/e* 864.2025 corresponding to $C_{36}H_{46}O_{19}S_2$, and another at *m/e* 415 corresponding to the glycosyloxy carbonium ion formed by cleavage of the C-1–O-1 bond.

Methylation of 2,3,6,2′,3′,6′-hexa-*O*-benzoyl-α,α-trehalose (**15**, prepared by selective benzoylation of the 2,3,2′,3′-tetrabenzoate **14**) and 2,3,2′,3′-tetra-*O*-benzoyl-6,6′-di-*C*-trityl-α,α-trehalose (**16**, prepared by tritylation of **14**) with methyl iodide and silver oxide yielded the 4,4′-di-*O*-methyl derivatives **17** and **18**, respectively, in yields of over 85%. The presence of MeO-4,4′ in **17** and **18** was indicated by the absence of the signal for H-4,4′ in the region (τ 4.5–5.4) of the ^{1}H-n.m.r. spectra (Table I) where it usually occurs in benzoylated derivatives of trehalose. De-esterification of **17** gave 4,4′-di-*O*-methyl-α,α-trehalose (**19**).

Methylation of 2,3,4,2′,3′,4′-hexa-*O*-acetyl-α,α-trehalose[11] (**20**) with diazomethane in dichloromethane and boron trifluoride etherate gave the 6,6′-di-*O*-methyltrehalose derivative **21** (92%); the ^{1}H-n.m.r. spectrum of **21** (Table I) contains resonances for the ring protons which are not shifted upfield, suggesting that the methyl groups must be attached at C-6,6′. Zemplén deacetylation of **21** afforded syrupy 6,6′-di-*O*-methyl-α,α-trehalose (**22**).

EXPERIMENTAL

For details of general procedures, see Ref. 8.

2-O-Benzoyl-4,6-O-benzylidene-3-O-methyl-α-D-glucopyranosyl 2-O-benzoyl-4,6-O-benzylidene-3-O-methyl-α-D-glucopyranoside (**6**). — (*a*) A mixture of 2,2′-di-*O*-benzoyl-4,6:4′,6′-di-*O*-benzylidene-α,α-trehalose[4] (**4**, 1 g), dry acetone (30 ml), and Drierite (3 g) was heated under reflux with methyl iodide (30 ml) and silver oxide (10 g) for 5 h. T.l.c. (benzene–ethyl acetate, 8:1) then revealed that methylation was complete and that one product was formed. The mixture was filtered and concentrated, and the syrupy residue (1.85 g, 86%) was crystallised from ethanol. Two further recrystallisations gave **6**, m.p. 202–204°, $[\alpha]_D$ +197° (*c* 0.5, chloroform).

Anal. Calc. for $C_{42}H_{42}O_{13}$: C, 66.8; H, 5.6. Found: C, 66.3; H, 5.4.

(*b*) Compound **4** (2 g) was stirred with a freshly prepared solution of diazomethane in dichloromethane (80 ml) and boron trifluoride etherate (0.2 ml) at −5° for 0.5 h. The mixture was filtered and the pale-yellow solution was washed successively with aqueous acetic acid, saturated, aqueous sodium hydrogen carbonate, and water,

dried (Na_2SO_4), and concentrated to a syrup. Crystallisation from ethanol gave **6** (2.0 g, 96%), identical with the product in (*a*).

4,6-O-Benzylidene-3-O-methyl-2-O-tosyl-α-D-glucopyranosyl 4,6-O-benzylidene-3-O-methyl-2-O-tosyl-α-D-glucopyranoside (**7**). — A mixture of 4,6:4′,6′-di-*O*-benzylidene-2,2′-di-*O*-tosyl-α,α-trehalose[3] (**5**, 1 g), methyl iodide (25 ml), and silver oxide (5 g) was stirred and boiled under reflux for 2.5 h. T.l.c. (benzene–ethyl acetate, 8:1) then showed only one product. The mixture was filtered and concentrated, and the syrupy residue was crystallised twice from ethanol to give **7** (0.85 g, 76%), m.p. 180–182°, $[\alpha]_D$ +32° (*c* 0.2, chloroform).

Anal. Calc. for $C_{42}H_{46}O_{15}S_2$: C, 59.0; H, 5.4; S, 7.5. Found: C, 59.1; H, 5.4; S, 7.4.

4,6-O-Benzylidene-3-O-methyl-α-D-glucopyranosyl 4,6-O-benzylidene-3-O-methyl-α-D-glucopyranoside (**8**). — (*a*) A mixture of 4,6:4′,6′-di-*O*-benzylidene-α,α-trehalose (**1**, 4 g), dry acetone (20 ml), freshly distilled methyl iodide (50 ml), and silver oxide (8 g) was boiled under reflux for 2 h. T.l.c. (benzene–ethyl acetate, 3:2) then showed a major and three minor products. The mixture was filtered and concentrated, and the syrupy residue was crystallized from chloroform–light petroleum to give **8** (2.6 g, 48%), m.p. 203–205°, $[\alpha]_D$ +42° (*c* 0.3, chloroform).

Anal. Calc. for $C_{28}H_{34}O_{11}$: C, 61.5; H, 6.2. Found: C, 61.3; H, 6.7.

(*b*) A mixture of **1** (4 g), *N,N*-dimethylformamide (15 ml), freshly distilled methyl iodide (8 ml), and barium oxide (5 g) was stirred and boiled under reflux for 0.5 h. T.l.c. (benzene–ethyl acetate, 3:2) then showed a major and several minor products. The mixture was filtered and concentrated, and the syrupy residue was eluted from a column of silica gel (75 g) with benzene–ethyl acetate (5:1) to give **8** (1.9 g), which was identical with the product in (*a*).

The diacetate **9** (82%), prepared from **8** in the usual way with acetic anhydride–pyridine, had m.p. 211–215° (from ethanol), $[\alpha]_D$ +28° (*c* 0.15, chloroform).

Anal. Calc. for $C_{32}H_{38}O_{13}$: C, 60.95; H, 6.0. Found: C, 60.6; H, 6.3.

3-O-Methyl-α-D-glucopyranosyl 3-O-methyl-α-D-glucopyranoside (**10**). — A solution of **8** (1 g) in dichloromethane (10 ml) was treated with methanolic 1% hydrogen chloride (25 ml) for 1 h at room temperature, deionised with Biodeminrolit mixed-bed (CO_3^{2-}) resin, and concentrated to dryness. An aqueous solution of the syrupy residue was extracted with light petroleum and then concentrated, and the syrupy residue (0.58 g, 85%) was crystallised from ethyl acetate to give **10**, m.p. 154–155°, $[\alpha]_D$ +173° (*c* 0.65, water).

Anal. Calc. for $C_{14}H_{26}O_{11}$: C, 45.4; H, 7.3. Found: C, 45.2; H, 7.3.

The hexa-acetate (**12**) of **10** had m.p. 153–155°, $[\alpha]_D$ +119° (*c* 0.45, chloroform).

Anal. Calc. for $C_{26}H_{38}O_{17}$: C, 50.2; H, 6.1. Found: C, 50.5; H, 6.4.

3-O-Methyl-2-O-tosyl-α-D-glucopyranosyl 3-O-methyl-2-O-tosyl-α-D-glucopyranoside (**11**). — Debenzylidenation of **7** (1 g), as described above for **10**, gave crude **11** (0.56 g, 89%) which, after two recrystallisations from ethanol, had m.p. 127–129°, $[\alpha]_D$ +130° (*c* 0.4, acetone).

Anal. Calc. for $C_{28}H_{38}O_{15}S_2$: C, 49.6; H, 5.6; S, 9.4. Found: C, 49.4; H, 5.8; S, 9.9.

The tetra-acetate (**13**) of **11** had m.p. 189–195°, $[\alpha]_D$ +93° (*c* 0.5, chloroform).

Anal. Calc. for $C_{36}H_{46}O_{19}S_2$: C, 51.1; H, 5.4; S, 7.5. Found: C, 50.8; H, 5.5; S, 8.0.

*2,3,6-Tri-*O*-benzoyl-α-*D*-glucopyranosyl 2,3,6-tri-*O*-benzoyl-α-*D*-glucopyranoside* (**15**). — A solution of 2,3,2′,3′-tetra-*O*-benzoyl-α,α-trehalose[2] (**14**, 5 g) in pyridine (50 ml) was stirred at −10°, and benzoyl chloride (1.65 ml) was added during 0.5 h. The solution was stored at room temperature and the reaction, which was monitored by t.l.c. (benzene–ethyl acetate, 6:1), was complete in ~0.5 h. The mixture was poured into ice–water, and the precipitate was collected, dried, and eluted from silica gel (70 g) with ether–light petroleum (2:1). Two recrystallisations from ether–light petroleum gave **15** (4.0 g, 64%), m.p. 95–99°, $[\alpha]_D$ +175° (*c* 0.5, chloroform).

Anal. Calc. for $C_{54}H_{46}O_{17}$: C, 67.1; H, 4.8. Found: C, 67.8; H, 5.0.

*2,3-Di-*O*-benzoyl-6-*O*-trityl-α-*D*-glucopyranosyl 2,3-di-*O*-benzoyl-6-*O*-trityl-α-*D*-glucopyranoside* (**16**). — To a solution of **14** (5 g) in pyridine (50 ml) was added a solution of trityl chloride (7.0 g) in pyridine (25 ml). The solution was kept at room temperature for 24 h, and t.l.c. (benzene–ethyl acetate, 18:1) then showed only one product. The mixture was poured into ice–water, and the product was collected, dried, and eluted from silica gel (20 g), first with light petroleum (to remove trityl alcohol) and then with acetone to give a syrup which crystallised from aqueous methanol to yield **16** (7.3 g, 88%), m.p. 136–138°, $[\alpha]_D$ +94° (*c* 0.35, chloroform).

Anal. Calc. for $C_{79}H_{68}O_{15}$: C, 75.5; H, 5.4. Found: C, 75.9; H, 5.2.

*2,3-Di-*O*-benzoyl-4-*O*-methyl-6-*O*-trityl-α-*D*-glucopyranosyl 2,3-di-*O*-benzoyl-4-*O*-methyl-6-*O*-trityl-α-*D*-glucopyranoside* (**18**). — Purdie methylation of **16** (2 g), as described above for **5**, gave **18** (1.75 g, 89%), m.p. 130–132°, $[\alpha]_D$ +86° (*c* 0.4, chloroform).

Anal. Calc. for $C_{80}H_{70}O_{15}$: C, 75.6; H, 5.5. Found: C, 76.15; H, 5.75.

*2,3,6-Tri-*O*-benzoyl-4-*O*-methyl-α-*D*-glucopyranosyl 2,3,6-tri-*O*-benzoyl-4-*O*-methyl-α-*D*-glucopyranoside* (**17**). — (*a*) Methylation of **15** (2.8 g) with diazomethane, as described above for **4**, gave **17** (2.6 g, 90%), m.p. 96–97° (from ether–light petroleum), $[\alpha]_D$ +174° (*c* 0.5, chloroform).

Anal. Calc. for $C_{56}H_{50}O_{17}$: C, 67.1; H, 4.8. Found: C, 67.5; H, 5.1.

(*b*) Purdie methylation of **15** (2 g), as described above for **5**, gave **17** (1.7 g, 81%), which was identical with the product from (*a*).

(*c*) To a solution of **18** (1 g) in dichloromethane (5 ml) at 5° were added glacial acetic acid (10 ml) and 45% hydrogen bromide in glacial acetic acid (3 ml). Trityl bromide was removed, and the filtrate was washed successively with dilute sulphuric acid, saturated, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and concentrated. To a solution of the syrupy residue in pyridine (10 ml) at 0°, benzoyl chloride (5 ml) was added dropwise. After 2 h at room temperature, the solution was poured into ice–water, and the precipitate was collected, washed well

with water, dried, and recrystallised from ether–light petroleum to give **17** (0.5 g, 65%), identical with the product obtained from (*a*).

4-O-Methyl-α-D-glucopyranosyl 4-O-methyl-α-D-glucopyranoside (**19**). — Treatment of **17** (1.0 g) with M sodium methoxide (5 ml) in methanol (15 ml) at room temperature for 2 h, followed by deionisation with Biodeminrolit mixed-bed (CO_3^{2-}) resin and concentration, gave **19** (0.28 g, 76.8%), m.p. 104–108° (from ethanol), $[\alpha]_D$ +186° (*c* 0.2, water).

Anal. Calc. for $C_{14}H_{26}O_{11}$: C, 45.4; H, 7.0. Found: C, 45.7; H, 7.1.

2,3,4-Tri-O-acetyl-6-O-methyl-α-D-glucopyranosyl 2,3,4-tri-O-acetyl-6-O-methyl-α-D-glucopyranoside (**21**). — Methylation of 2,3,4,2′,3′,4′-hexa-*O*-acetyl-α,α-trehalose[14] (**20**, 2.2 g) with diazomethane, as described above for **4**, and two recrystallisations of the product from methanol gave **21** (2.1 g, 92%), m.p. 158–161°, $[\alpha]_D$ +165° (*c* 0.54, chloroform).

Anal. Calc. for $C_{26}H_{38}O_{17}$: C, 50.2; H, 6.1. Found: C, 49.9; H, 6.3.

6-O-Methyl-α-D-glucopyranosyl 6-O-methyl-α-D-glucopyranoside (**22**). — Deacetylation of **21** (1.75 g), with M sodium methoxide (5 ml) in methanol (30 ml), gave **22** (0.84 g, 80.5%) as a syrup, $[\alpha]_D$ +184° (*c* 1.8, water).

Anal. Calc. for $C_{14}H_{26}O_{11}$: C, 45.4; H, 7.0. Found: C, 45.1; H, 7.4.

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