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Note

Synthesis of a 3-keto derivative of trehalose*

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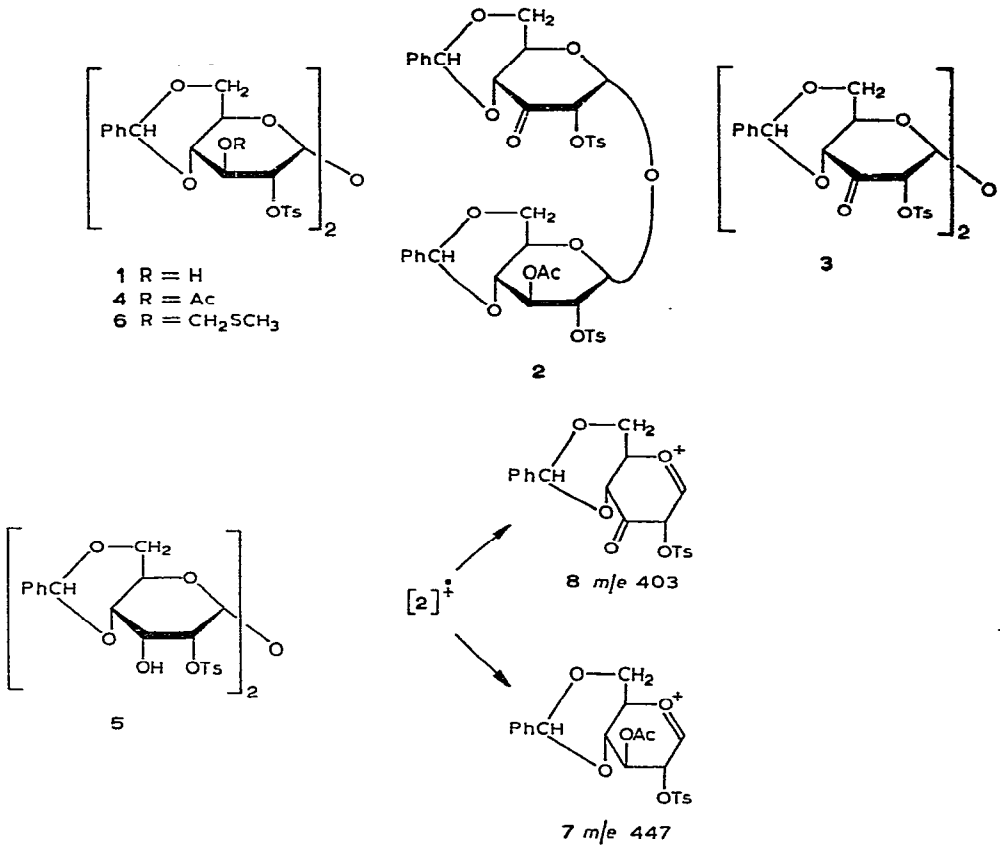
In seeking new analogues of α,α-trehalose for studies of the chemical basis of sweetness of sugars, the oxidation of a particular secondary hydroxyl group followed by reduction of the product offers an attractive route, particularly where inversion of configuration by nucleophilic substitution is not facile due to steric and polar factors[2]. Thus, the conversion of the *arabino* into the *ribo* analogue of 3,3′-dideoxy-α,α-trehalose has been effected in good yields[3]. In continuing this study, the synthesis of α,α-*allo*,*allo*-trehalose was examined.

Oxidation of HO-3 in methyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucopyranoside with methyl sulphoxide occurs readily in the presence of activating, electrophilic reagents, such as acetic anhydride[4], phosphorus pentaoxide[5], and dicyclohexylcarbodi-imide[6]. However, the oxidation of HO-3 and HO-3′ in the trehalose analogue did not occur readily using methyl sulphoxide–acetic anhydride. Thus, treatment of 4,6:4′,6′-di-*O*-benzylidene-2,2′-di-*O*-tosyl-α,α-trehalose[7] (**1**) with methyl sulphoxide (3–4 mol) and acetic anhydride (excess) at room temperature for 20 h gave three crystalline compounds, *A* (major), *B*, and *C* (trace). Component *A*, isolated in 65–85% overall yield, was identified as 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucopyranosyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-*ribo*-hexopyranosid-3-ulose (**2**). The n.m.r. spectrum fully supported the structure (**2**), and the assignments were confirmed by analogy with the ^{1}H-n.m.r. parameters (Table I) for the symmetrical 3,3′-diulose and 3,3′-diacetate (**3** and **4**, respectively). The lack of symmetry in **2** was clearly shown by the multiplicity of resonances. The methyl resonances of the two tosyl groups were not coincident (τ 7.64 and 7.69). Likewise, one of the two H-2 resonances was a double doublet at τ 5.37, and the other was a doublet (τ 4.73) because of its proximity to the 3-keto grouping. Furthermore, there was only one H-3 resonance (a triplet at τ 4.51, $J_{2,3}$ and $J_{3,4}$ = ~9.2 Hz, typical of the *gluco* configuration) and one acetate resonance (τ 8.14).

Mass spectrometry of trehalose derivatives has shown[8] that the major fragmentation pattern involves the cleavage of the C-1–O-1 bonds to give two glycosyloxy carbonium ions (identical in symmetrical derivatives). Subsequent fragmentation then

*Chemical Modification of Trehalose: Part XVI[1].



involves the stepwise elimination of substituents in a manner essentially similar to that of the monosaccharides. The mass spectrum of *A* contained a significant peak at *m/e* 824.2306, corresponding to $C_{40}H_{40}O_{15}S_2$, which must have been formed from the molecular ion by elimination of ketene, a process characteristic of *O*-acetyl derivatives. This suggested that *A* has the proposed structure **2**. The structure was further substantiated by the presence of a weak peak at *m/e* 866.1200, corresponding to the molecular ion $[C_{42}H_{42}O_{16}S_2]^{\cdot+}$, and a pair of ions, *m/e* 447 and 403, corresponding to the two oxycarbonium ions **7** and **8**, formed by the fragmentation of one or the other of the two glycosidic bonds. Further fragments arising from this pair of ions are identical to those obtained from the symmetrical 3,3′-diulose and 3,3′-diacetate (Schemes 1 and 2, respectively).

Components *B* and *C* were isolated (3–5%) as crystalline solids by dry-column chromatography. The simplicity of the n.m.r. spectra indicated that these compounds were symmetrically substituted trehalose derivatives. The first-eluted component (*B*) was identical to 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-tosyl-α-D-gluco-pyranosyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucopyranoside (**3**), prepared by acetylation (pyridine–acetic anhydride) of 4,6:4′,6′-di-*O*-benzylidene-2,2′di-*O*-

TABLE I

P.M.R. PARAMETERS[a] OF 3-KETO AND 3-*O*-ACETYL DERIVATIVES

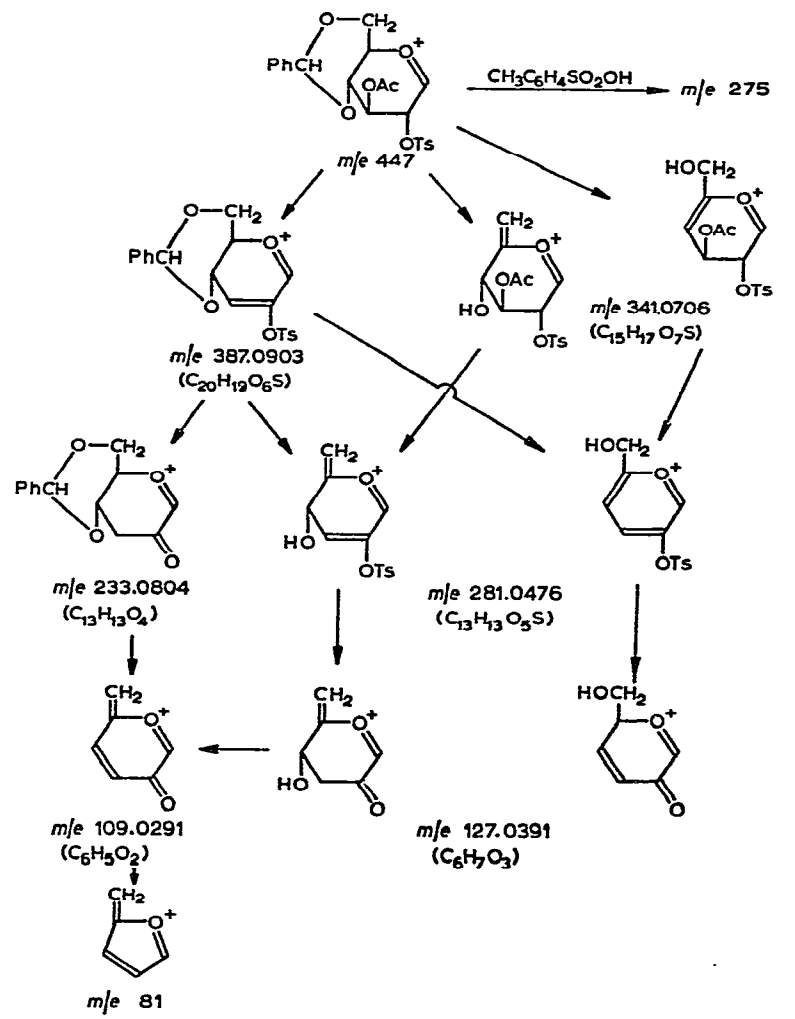
Compound	2[b]	3[b,d]	4[b,d]	4[c,d]
H-1	4.52(d)	4.53(d)	4.25(d)	4.19(d)
H-1′	4.25(d)			
H-2	5.37(dd)	5.27(dd)	4.83(d)	4.46(d)
H-2′	4.73(d)			
H-3	4.47(t)	4.55(t)		
H-3′				
H-4	5.45–6.50(m)	6.35(t)	5.85(d)	5.32(d)
H-4′				
H-5		6.22(m)	6.25(m)	6.06(m)
H-5′				
H-6		5.61(q)	5.55(q)	5.60(q)
H-6′		5.91(q)	5.74(q)	5.72(q)
CHPh	4.51, 4.54(s)	4.54(s)	4.50(s)	4.36(s)
OAc	8.13(s)	8.22(s)		
CH_3Ar	7.64, 7.69(s)	7.69(s)	7.66(s)	7.63(s)
$J_{1,2}$	4.0	4.0	4.2	4.3
$J_{1',2'}$	4.2			
$J_{2,3}$	9.6	9.5		
$J_{2',3'}$				
$J_{2,4(2',4')}$				1.1
$J_{3,4}$	9.0	9.5		
$J_{3',4'}$				
$J_{4,5}$		9.5	9.6	9.5
$J_{4',5'}$				
$J_{5,6a(5',6a')}$		4.6	4.0	4.5
$J_{5,6b(5',6b')}$		5.4	5.0	5.5
$J_{6a,6b(6a',6b')}$		11.0	10.5	12.0

[a]First-order chemical shifts (τ values) and coupling constants at 100 and 220 MHz; multiplicity of resonances: d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet. [b]In deuteriochloroform. [c]In deuterioacetone. [d]At 220 MHz.

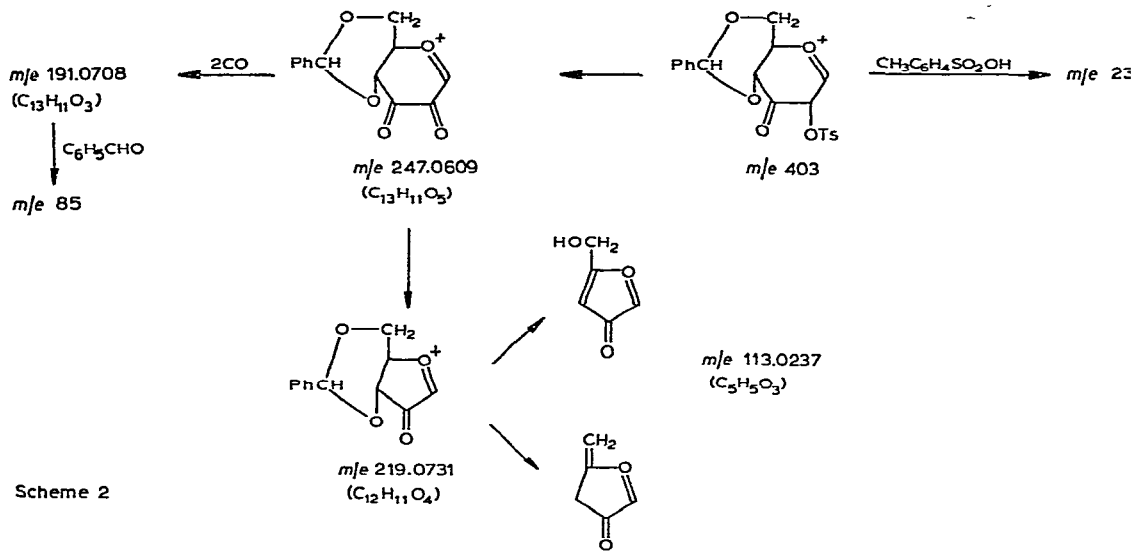
tosyl-α,α-trehalose (**1**). The two benzylic hydrogen resonances in the ^{1}H-n.m.r. spectum were coincident and readily recognised at τ 4.56. The H-1 and H-1′ doublet (τ 4.51) slightly overlapped the broad-limbed triplet (τ 4.54) due to H-3 and H-3′, while the resonances due to H-2 and H-2′ occurred as a double doublet at τ 5.26. The mass-spectral fragmentation pattern (Scheme 1) was relatively simple compared to that of component *A*. A sizeable peak at *m/e* 910.2169 corresponded to the molecular ion $[C_{44}H_{46}O_{17}S_2]^{\cdot+}$. The base peak (*m/e* 447) was due to the glycosyloxy carbonium ion derived from the fragmentation of the disaccharide into two monosaccharide moieties.

Component *C*, which was identical to the product obtained (in 86% yield) by treating **1** with methyl sulphoxide (3–4 mol) and phosphorus pentaoxide (1.5 mol)

in *N,N*-dimethylformamide for 2.5 h at 60°, was expected to be the symmetrical 3,3'-diketo derivative **4** by analogy with the oxidation of methyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucopyranoside[5]. Confirmation of the structure was obtained from ^{1}H-n.m.r. and m.s. data. The n.m.r. assignments (Table I) were confirmed by decoupling experiments. Furthermore, reduction of the diulose **4** with sodium borohydride gave the *allo* analogue of α,α-trehalose (**5**) through approach of the borohydride anion from the equatorial direction[9]. This conclusion was clearly indicated by the small $J_{2,3}$ and $J_{3,4}$ values (~4 Hz)[10]. The mass spectrum of **4** contained a major peak at *m/e* 403, corresponding to the oxycarbonium ion **8**. The fragmentation is rather complex (Scheme 2). Precise mass measurement, however, indicated fragments at *m/e* 172.0125 ($C_7H_8O_3S$, toluene-*p*-sulphonic acid) and *m/e* 155.0168



Scheme 1



Scheme 2

($C_7H_7O_2S$, tosyl radical). These peaks were also abundant in the spectra of **1**, **2**, and **4**).

Mitera *et al.*[11] reported that the occurrence of a mass-spectral peak at *m/e* 179 ($C_{10}H_{11}O_3$) appears to be characteristic of benzylidene glycosides. This peak was observed in the spectra of the four trehalose derivatives analysed. It was further reported[11] that with the MeO-2 derivatives of 4,6-*O*-benzylideneglycosides, the ions *m/e* 179 were accompanied by the ions *m/e* 193. This fragmentation pattern was not found for the C-2 toluene-*p*-sulphonates studied, as no ions *m/e* 334 (in **4**), 335 (in **1**), and 377 (in **3**) were observed. As reported by Mitera *et al.*[11], no metastable transitions for the formation or decomposition of these ions were observed. From the evidence available, we are also unable to suggest the pattern of formation or the detailed structure of the ion *m/e* 179.

As expected, the compounds studied contained ions of the aromatic type *m/e* 77 ($C_6H_5^+$), 79 ($C_6H_7^+$), 91 ($C_7H_7^+$), 105 ($C_6H_5CO^+$), and 106 ($C_6H_5CHO^+$).

Traces of a fourth compound were also obtained (2%), as a slightly impure syrup, on oxidation of **1**. Though no analyses were carried out, this is most probably the methylthiomethyl ether **6**, which is a common side-product of this type of reaction.

Compound **3** showed strong i.r. absorption at 1220 and 1235 cm^{-1} (presumably arising from the C–O stretching vibrations of acetyl groups[12]), while compound **4** showed a substantial peak at 1775 cm^{-1} (C=O stretching vibration of the keto grouping). These peaks were also given by **2**.

The origin of the non-symmetrical derivative seems obscure. We have earlier[1,13] proposed that formation of non-symmetrical analogues of trehalose proceeded *via* two consecutive first-order reactions, the asymmetric component rising to ~50% in the early stages of the reaction. The presence of the 3-mono-keto derivative (**2**) in such

high yields in the reaction mixture suggested that the reaction did not strictly follow the proposed two-stage mechanism. The oxidation procedure using methyl sulphoxide–acetic anhydride (or phosphorus pentaoxide) is particularly well-suited to the oxidation of relatively hindered hydroxyl groups, since with less-hindered compounds, substantial amounts of acetate are formed due to the competing acetylation reaction[14]. Thus, it appears that **2** may be the result of simultaneous oxidation and acetylation reactions. It is significant that only 50–55% of the 3-keto derivative was obtained when methyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucopyranoside was treated with this reagent[15,16]. Examination of the reaction mixture (t.l.c.) showed the presence of considerable amounts of two other (faster-moving) compounds, one of which (the slower of the two) corresponded with the 3-acetate.

EXPERIMENTAL

All evaporations were carried out under diminished pressure. Melting points were determined on a Kofler hot-stage apparatus and were uncorrected. Optical rotations were measured on a Bendix automatic photoelectric polarimeter, Type 143, in a 1-cm cell at ~20°. Column chromatography was carried out at room temperature using Merck Kieselgel-7734 (70–230 mesh). Thin-layer or preparative layer chromatography was performed at room temperature on silica gel (Merck 7731). Detection was effected with 10% ethanolic conc. H_2SO_4 at ~120° for 2–5 min. Recrystallisations with dichloromethane in conjunction with another solvent were normally carried out at the boiling point of dichloromethane; the product usually separated out after much of the dichloromethane had boiled off.

*Treatment of 4,6-*O*-benzylidene-2-*O*-tosyl-α-*D*-glucopyranosyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-*D*-glucopyranoside* (**1**) *with methyl sulphoxide–acetic anhydride.* — A solution of **1** (7.6 g) in a mixture of methyl sulphoxide (75 ml) and acetic anhydride (45 ml) was monitored by t.l.c. (benzene–ethyl acetate, 8:1). The reaction was complete after 20 h at room temperature; one major and 3 minor compounds were formed. The mixture was poured into ice–water, and the solid was filtered off and washed well with 10% aqueous ethanol. Three recrystallisations from ethanol gave **2** (65–80%), m.p. 202–203°, $[\alpha]_D$ +2.3° (*c* 0.6, chloroform) (Found: C, 57.6; H, 5.4; S, 8.1. $C_{42}H_{42}O_{16}S_2$ calc.: C, 58.2; H, 4.9; S, 7.4%); ν_{max}^{Nujol} 1770 (C=O), 1235 and 1220 cm^{-1} (C–O stretching in acetyl groups[12]).

The combined filtrates from the recrystallisations were evaporated to a syrup, dried over P_2O_5, and chromatographed on a column of silica gel (100 g) with benzene–ethyl acetate (10:1) to give, in sequence: (*a*) a syrupy, slightly impure fraction (~2% yield), which is probably 4,6:4′,6′-di-*O*-benzylidene-3,3′-bis(methylthiomethyl)-2,2′-di-*O*-tosyl-α,α-trehalose (**6**); (*b*) 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucopyranosyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-*ribo*-hexopyranosid-3-ulose (**2**, 4.8%); (*c*) 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucopyranosyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucopyranoside (**3**, 2–3% yield), m.p. 231–233° (from dichloromethane–ethanol), $[\alpha]_D$ +80.3° (*c* 0.75, chloroform) (Found: C, 58.3;

H, 5.3; S, 7.4. $C_{44}H_{46}O_{17}S_2$ calc.: C, 58.0; H, 5.0; S, 7.0%), identical with the product obtained by acetylation of **1** (see below); (*d*) 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-*ribo*-hexopyranosyl-3-ulose 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-*ribo*-hexopyranosid-3-ulose (**4**, 2–3% yield), m.p. 207–209°, $[\alpha]_D$ +32.5° (*c* 0.45, chloroform) (Found: C, 57.9; H, 5.0; S, 8.6. $C_{40}H_{38}O_{15}S_2$ calc.: C, 58.3; H, 4.6; S, 7.8%), identical with the product obtained by direct oxidation of **1** (see below).

4,6-O-Benzylidene-2-O-tosyl-α-D-ribo-hexopyranosyl-3-ulose 4,6-O-benzylidene-2-O-tosyl-α-D-ribo-hexopyranosid-3-ulose (**4**). — To a stirred solution of **1** (15 g) in *N,N*-dimethylformamide (300 ml), phosphorus pentaoxide (25 g) and methyl sulphoxide (75 ml) were added. The solution was heated with continuous stirring for 2 h at 60–65°, and t.l.c. (benzene–ethyl acetate, 6:1) then showed that the reaction was complete. The reaction mixture was poured into ice–water (1 litre) containing ethanol (~100 ml). The white precipitate was filtered off, and washed thoroughly with water and alcohol to give the crude product (12.9 g, 86% yield). Three recrystallisations from dichloromethane–ethanol gave **4** (12.0 g, 80%), m.p. 207–208°, $[\alpha]_D$ +32.5° (*c* 0.35, chloroform) (Found: C, 58.0; H, 4.9; S, 8.2. $C_{40}H_{38}O_{15}S_2$ calc.: C, 58.3; H, 4.6; S, 7.8%), ν_{max}^{Nujol} 1775 cm^{-1} (C=O).

3-O-Acetyl-4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranosyl 3-O-acetyl-4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranoside (**3**). — The diacetate **3** (95%), prepared in the usual way from **1**, had m.p. 231.5–233° (from dichloromethane–ethanol), $[\alpha]_D$ +80.5° (*c* 0.9, chloroform) (Found: C, 57.9; H, 5.1; S, 6.9. $C_{44}H_{46}O_{17}S_2$ calc.: C, 58.0; H, 5.0; S, 7.0%).

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