Note

Chemical modification of trehalose
Part VII[1]. Rearrangement of 3,6:3′,6′-dianhydro-α,α-trehalose into the difuranoid form

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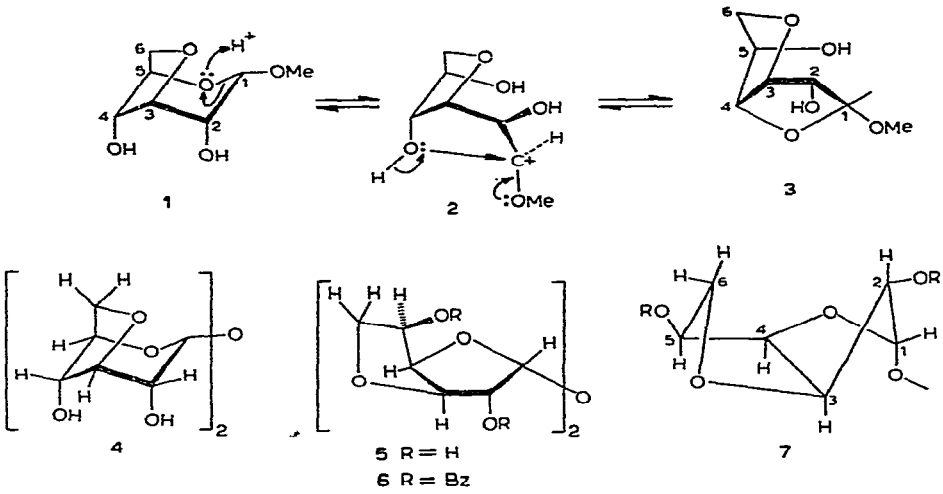
It has long been established that methyl 3,6-anhydro-α-D-glucopyranoside (**1**) and its β-anomer undergo acid-catalysed rearrangement to the corresponding furanosides[2] (*e.g.* **3**). The reaction may be rationalised on the basis of a thermodynamically controlled equilibrium between a highly strained dioxa[1.2.3]bicyclo-octane fused-ring system and the relatively strain-free dioxa[3.3.0]bicyclo-octane ring system via an intermediary carbonium/oxonium ion **2**. One remarkable aspect of this rearrangement is that the configuration at the anomeric carbon atom is retained, and only if the reaction is prolonged is there any anomerisation. This suggests that the lifetime of the intermediary carbonium/oxonium ion **2** must be short compared to the time taken for rotation about the C-1–C-2 bond. A concerted process, similar to an S_N2 transition state, in which the O-4–C-1 bond forms as the O-5–C-1 bond breaks is not sterically feasible and would lead to a change of configuration at C-1. The reaction mechanism has not previously been commented on in detail, but Lemieux[3] has pointed out that the "all-axial" configuration of **1** must be a driving force for the rearrangement.

The study of this rearrangement has only received scant attention, and it seemed of interest to investigate whether the reaction proceeded with glycosides containing more-complex aglycones. Consequently, we have applied the reaction to 3,6:3′,6′-dianhydro-α,α-trehalose[4] (**4**).

When an aqueous, ethanolic solution of the dianhydride **4** was adjusted to pH 1 and heated, conversion into the difuranoid compound **5** occurred, followed by hydrolysis. When the reaction was interrupted at the stage when hydrolysis was detected, a 35–45% yield of product **5** was isolated and characterised as the tetrabenzoate.

The relative simplicity of its ^1H n.m.r. spectrum (Fig. 1) showed that **5** was a symmetrical disaccharide. Assignments were made, in the usual manner, on the assumption that the low-field doublet was H-1,1′, followed by matching of splittings



in the various multiplets. The spectrum was in accord with the structure 3,6-anhydro-α-D-glucofuranosyl 3,6-anhydro-α-D-glucofuranoside (**5**). The presence of hydroxyl groups at the 2,2′,5,5′-positions was established by comparison of the ^{1}H n.m.r. spectrum with that of the tetrabenzoate **6**. The tetra-ester gave a spectrum very similar to that of **5**, except that the H-2,2′ and H-5,5′ resonances were deshielded by 0.89

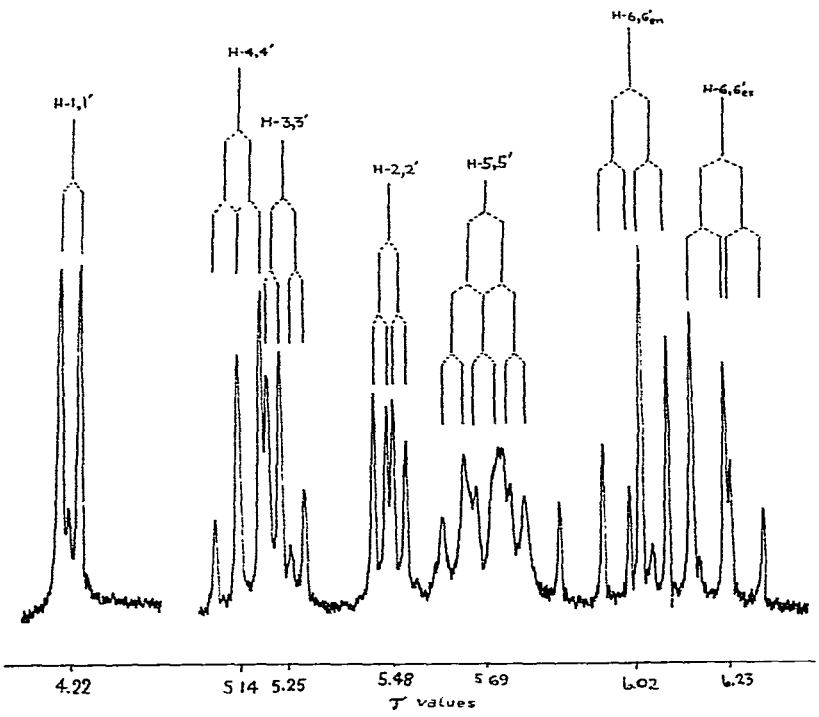


Fig. 1. ^{1}H n.m.r. spectrum at 100 MHz of 3,6-anhydro-α-D-glucofuranosyl 3,6-anhydro-α-D-glucofuranoside (**5**) in deuteriopyridine at 80°.

and 1.00 p.p.m., respectively, whereas the other resonances were deshielded only to the extent of 0.12–0.30 p.p.m. (Table I). This illustrates the way in which the deshielding effect of benzoyl groups can be used with advantage to determine the position of hydroxyl groups[5].

TABLE I

FIRST-ORDER CHEMICAL SHIFTS (τ VALUES) AND COUPLING CONSTANTS AT 100 MHz

Compound: *Solvent:*	**5**[a] *Pyridine*-d_5	**6**[b] *Chloroform*-d	**6** *Pyridine*-d_5
H-1,1′	4.22d	4.19d[c]	3.92d
H-2,2′	5.48q	4.91q[c]	4.59t
H-3,3′	5.25q	5.40q	5.13q
H-4,4′	5.14t	5.30t	4.96t
H-5,5′	5.69sx	4.83oc[c]	4.69oc
H-6,6′$_{en}$	6.02q	5.89q	5.84q
H-6,6′$_{ex}$	6.23q	6.15q[c]	6.04q
$J_{1,2}$	4.3	4.3	4.3
$J_{2,3}$	2.8	3.3	3.5
$J_{3,4}$	5.0	5.5	5.6
$J_{4,5}$	5.0	5.5	5.5
$J_{5,6en}$	7.3	7.1	6.7
$J_{5,6ex}$	5.9	5.9	5.9
$J_{6en,6ex}$	8.5	9.3	9.2

[a]At 80°. [b]Spectrum also determined at 220 MHz; signals were overlapped at 100 MHz. [c]Assignment confirmed by spin decoupling.

The observed coupling constants for **5** and **6** (Table I) suggest that each half of the molecule exists in a conformation in which the furanose ring adopts an E^2 (or a closely related twist) conformation and the anhydro ring an envelope (or related twist) conformation with C-6 out of plane and *endo* with respect to the bicyclic ring-system, as depicted in **7**. Such a conformation places O-1 in a quasi-axial position, favourable because of the anomeric effect, and O-2 and O-5 in quasi-equatorial positions. The approximate dihedral angles for this conformation, as ascertained from molecular models, are $\Phi_{1,2}$ 30°; $\Phi_{2,3}$ 130°; $\Phi_{3,4}$ 30°; $\Phi_{4,5}$ 30°; $\Phi_{5,6en}$ 150°; $\Phi_{5,6ex}$ 30°. In a related compound, 3,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose, the E^4 conformation has been proposed for the furanose ring, but, in this case, the fusion of the isopropylidene ring on to the furanose ring would have a marked influence on the conformation[6].

EXPERIMENTAL

3,6-Anhydro-α-D-glucofuranosyl 3,6-anhydro-α-D-glucofuranoside (**5**). — A solution of 3,6:3′,6′-dianhydro-α,α-trehalose[4] (**4**) (0.5 g) in ethanol (150 ml) was adjusted to pH ~1 by the addition of 2M hydrochloric acid (*ca.* 2 ml), and the solution was heated under reflux for 30 min. Thin-layer chromatography [silica gel G (Merck); butyl acetate–pyridine–water, 5:3:1 v/v] indicated the presence of unreacted starting material

and a slightly slower-moving compound. The reaction mixture was kept at room temperature for a further 2 h, and t.l.c. then indicated that a much faster-moving product was beginning to be formed, presumably by hydrolysis. At this stage, the reaction mixture was neutralised by the addition of Permutit Biodeminrolit mixed-bed, ion-exchange resin (carbonate form), and then concentrated to dryness. The crystalline residue was extracted with either cold water or cold ethanol (*ca.* 20 ml), and the mixture was quickly filtered. The insoluble residue was washed with a little of the solvent and dried to give starting material (*ca.* 40%). The filtrate and washings were concentrated to dryness, and the resulting solid was recrystallised from acetone to give the furanosyl furanoside **5** as clusters of needles (35–45%), m.p. 184–190°, $[\alpha]_D$ +178° (*c* 1.3, pyridine) (Found: C, 47.6; H, 5.9. $C_{12}H_{18}O_9$ calc.: C, 47.1; H, 5.7%).

Similar results were obtained by conducting the rearrangement in methanolic or ethanolic hydrogen chloride (prepared from acetyl chloride and the appropriate alcohol). The use of glacial acetic acid in ethanol resulted in a very slow reaction; the appearance of **5** occurred after 2–3 days and was accompanied by the formation of faster-moving materials (t.l.c.).

The tetrabenzoate **6** (75%), prepared from **5** in the usual way with benzoyl chloride–pyridine, had m.p. 125–128°, $[\alpha]_D$ −121° (*c* 0.3, chloroform) (Found C, 66.2; H, 4.6. $C_{40}H_{34}O_{13}$ calc.: C, 66.5; H, 4.7%).

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