Carbohydrate Research, 50 (1976) 152–157

Note

Synthesis of α-D-glucopyranosyl α-D-galactopyranoside*

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(Received November 26th, 1975; accepted for publication, December 8th, 1975)

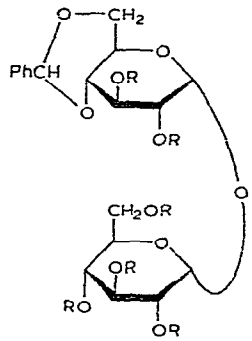
The simple two-fold axis of symmetry through the glycosidic oxygen atom of trehalose[2] makes both the D-glucose residues chemically and physically indistinguishable. Thus, introduction of certain functional substituents into both glycosyl units, leading to symmetrical analogues, by conventional monosaccharide reactions is relatively facile[1–4]. Selective modification of one glycosyl unit to give non-symmetrical analogues is more difficult[3,5–7], but under carefully controlled reaction conditions, yields of up to 50% of non-symmetrical products are theoretically possible[4,7] for a reaction occurring *via* two consecutive first-order reactions. An instance where the reaction did not follow this mechanism was recently reported[8] and a non-symmetrical trehalose derivative was synthesised in 65–80% yield.

Non-symmetrical analogues of trehalose, particularly those containing one unmodified glycopyranosyl unit, may be of biological interest[5]. 2-Amino-2-deoxy-α-D-glucopyranosyl α-D-glucopyranoside[9] and 2-amino-2-deoxy-α-D-glucopyranosyl α-D-mannopyranoside[10] possess some biological activity. Furthermore, non-symmetrical analogues of trehalose are of interest in studies of the chemical basis of sweetness and bitterness of sugars. Only one half of the trehalose molecule is involved in binding to the taste receptor site to elicit the sweet or bitter taste[11], and asymmetrical derivatives may be of value in structure–activity determinations.

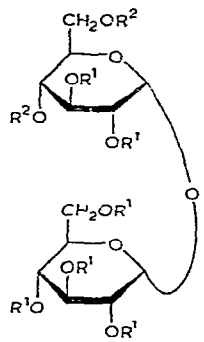
2,3-Di-*O*-benzoyl-α-D-glucopyranosyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside was recently prepared (47%) by acid-catalysed methanolysis of the symmetrical diacetal[5] followed by chromatography. By using appropriate amounts of benzaldehyde and zinc chloride, and suitable reaction times (48–72 h), direct, selective benzylidenation of trehalose yielded 35–40% of the monoacetal **1**; chromatography was not necessary.

Acid catalysed methanolysis of hexa-acetate **2** and hexabenzoate **3** of **1** gave the respective 4,6-diols (**4** and **5**) which were converted into the 4,6-dimesylates **6** and **7**, respectively. The benzoylated 4,6-dimesylate **7** underwent replacement of both sulphonate groups very readily when treated with sodium benzoate in hexamethylphosphoric triamide to give α-D-glucopyranosyl α-D-galactopyranoside octabenzoate

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



1 R = H
2 R = Ac
3 R = Bz



4 R^1 = Ac, R^2 = H
5 R^1 = Bz, R^2 = H
6 R^1 = Ac, R^2 = Ms
7 R^1 = Bz, R^2 = Ms

(**10**, 74.8%). The proposed structure was in accord with the n.m.r. data (Table I). The narrow double-doublet for one H-4 at τ 4.14 ($J_{3,4}$ 3.5 and $J_{4,5}$ ~1.5 Hz) was indicative of an *ax,eq,ax* arrangement of H-3, H-4, and H-5, *i.e.*, the *galacto* configuration, whereas the resonance for the other H-4 was a triplet at τ 4.32 with splittings of 10.0 Hz, characteristic of the *gluco* configuration.

TABLE I

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

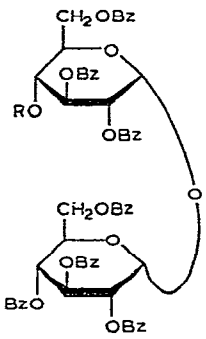
Compound	**6**	**7**	**8**	**10**[b]
H-1	4.64 (d)	4.32 (d)	4.03 (d)	4.07 (d)
H-1′	4.71 (d)	4.35 (d)	4.06 (d)	4.23 (d)
H-2	4.71 (dd)	4.57 (dd)	4.15 (dd)	4.08 (dd)
H-2′	4.99 (dd)	4.66 (dd)	4.19 (dd)	4.48 (dd)
H-3	4.41 (t)	3.77 (t)	3.43 (t)	3.72 (t)
H-3′	4.42 (t)	3.81 (t)	3.58 (t)	3.77 (t)
H-4	4.95 (t)	4.34 (t)	4.08 (t)	4.32 (t)
H-4′	5.28 (t)	5.00 (t)	4.19 (t)	4.14 (dd)
H-5,5′–H-6,6′	5.5–6.1 (cm)	5.6–6.3 (cm)	5.3–5.8 (cm)	5.3–6.2 (cm)
OMs	6.91 (s)	7.07 (s)		
	6.94 (s)	7.20 (s)		
$J_{1,2}$	4.0	3.7	3.5	3.6
$J_{1',2'}$	3.5	3.7	3.5	3.5
$J_{2,3}$	10.0	10.0	10.0	9.5
$J_{2',3'}$	10.0	10.0	10.0	10.0
$J_{3,4}$	9.5	10.0	9.5	10.0
$J_{3',4'}$	10.0	9.5	9.5	3.5
$J_{4,5}$	10.0	9.5	9.5	10.0
$J_{4',5'}$	10.0	9.5	9.5	~1.5

[a]First-order chemical shifts (τ values) and coupling constants at 100 MHz for solutions in deuteriochloroform. Key: s, singlet; d, doublet; dd, double doublet; t, triplet; cm, complex multiplet. The non-primed numbers refer to the pyranosyl ring which is more highly acylated; the ring protons are thus more deshielded.

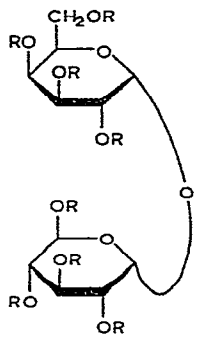
[b]The primed numbers refer to the galactopyranosyl ring and the non-primed numbers to the glucopyranosyl ring.

On the other hand, the acylated 4,6-dimesylate **6** underwent only partial replacement when similarly treated, and considerable deacetylation occurred (t.l.c.). After reacetylation, at least three major products were detected (t.l.c.) and isolation was not attempted.

An alternative precursor to α-D-*gluco*,α-D-*galacto*-trehalose octabenzoate (**10**), 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl 2,3,6-tri-*O*-benzoyl-4-*O*-mesyl-α-D-glucopyranoside (**9**), was prepared from the heptabenzoate **8** which, in turn, was obtained (30%) by selective benzoylation of 2,2′, 3,3′-tetra-*O*-acetyl-α,α-trehalose[12] in the cold. Nucleophilic displacement of the sulphonate group in **9** with sodium benzoate in hexamethylphosphoric triamide readily yielded **10** (67%).



8 R = H
9 R = Ms



10 R = Bz
11 R = H

The optical rotations of non-symmetrical derivatives of trehalose are averages of the rotations of the two related symmetrical derivatives[5]; compounds **5**, **7**, **10**, and **11** further illustrate this trend (Table II).

EXPERIMENTAL

For details of the general procedure, see Ref. 1.

α-D-*Glucopyranosyl 4,6-O-benzylidene-α-D-glucopyranoside* (**1**). — A mixture of α,α-trehalose (40 g, dried at 70° *in vacuo* for 5 h), freshly distilled benzaldehyde (200 ml), and freshly crushed zinc chloride (50 g) was vigorously shaken for 48–72 h. T.l.c. then showed that equilibrium had been attained. The mixture was poured into light petroleum (200 ml) and stirred for 30 min. Ice-cold water (1 litre) was added and stirring was continued till precipitation occurred. The white solid was collected, washed well with water and light petroleum, and recrystallised from ethanol to give 4,6:4′,6′-di-*O*-benzylidene-α,α-trehalose (36.9 g, 42%), m.p. 197–198°, $[\alpha]_D$ +93° (*c* 0.4, chloroform); lit.[3] m.p. 198–199°, $[\alpha]_D$ +92.4° (acetone).

The aqueous layer of the foregoing filtrate and washings was neutralised with sodium hydroxide, filtered, and concentrated. The residue was extracted with ethanol, and the extract was filtered, and concentrated to dryness. This process was

TABLE II

COMPARISON BETWEEN THE CALCULATED AND OBSERVED SPECIFIC ROTATIONS FOR NON-SYMMETRICAL TREHALOSE DERIVATIVES

Compound	$[\alpha]_D$ (*calc.*) (*degrees*)	*Ref.*	*Solvents*	$[\alpha]_D$ (*obs.*) (*degrees*)	*Ref.*	*Solvent*
2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl 2,3-di-*O*-benzoyl-α-D-glucopyranoside	+243	12	MeOH $CHCl_3$	+225		$CHCl_3$
2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl 2,3-di-*O*-benzoyl-4,6-di-*O*-mesyl-α-D-glucopyranoside	+204	12	$CHCl_3$ $CHCl_3$	+217		$CHCl_3$
2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranoside	+221	12	$CHCl_3$ $CHCl_3$	+228		$CHCl_3$
α-D-Glucopyranosyl α-D-galactopyranoside	+201	12	H_2O H_2O	+183		H_2O
α-D-Glucopyranosyl β-D-glucopyranoside	+79.5	13,14	H_2O H_2O	+70	15	H_2O
2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside	+73	14,15	$CHCl_3$ $CHCl_3$	+79.6	14	$CHCl_3$
α-D-Glucopyranosyl 6-deoxy-α-D-glucopyranoside	+192	7	H_2O H_2O	+202.9	7	MeOH
2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-glucopyranoside	+186	7	$CHCl_3$ $CHCl_3$	+184.5	7	$CHCl_3$
α-D-Glucopyranosyl 6-bromo-6-deoxy-α-D-glucopyranoside	+197	7	H_2O MeOH	+180.8	7	MeOH
2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-α-D-glucopyranoside	+144.5	7	$CHCl_3$ $CHCl_3$	+141.3	7	$CHCl_3$
2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl 2,3,4-tri-*O*-acetyl-6-chloro-6-deoxy-α-D-glucopyranoside	+148.5	7	$CHCl_3$ $CHCl_3$	+147.9		$CHCl_3$
2,3-Di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranosyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside	+199.5	1,12	$CHCl_3$ $CHCl_3$	+202	1	$CHCl_3$
2,3-Di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranosyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose	+152.7	1	$CHCl_3$ $CHCl_3$	+155	1	$CHCl_3$
4,6-Dichloro-4,6-dideoxy-α-D-galactopyranosyl 3,6-anhydro-4-chloro-4-deoxy-α-D-galactopyranoside	+177.9	4	EtOH EtOH	+133	4	EtOH
2,3-Di-*O*-acetyl-4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl 2-*O*-acetyl-3,6-anhydro-4-chloro-4-deoxy-α-D-galactopyranoside	+155.9	4	$CHCl_3$ $CHCl_3$	+195	4	$CHCl_3$

repeated twice, and the final, ethanolic solution was deionised with Biodeminrolit mixed-bed (CO_3^{2-}) resin and concentrated to small volume. Addition of light petroleum precipitated **1** (22 g, 30%) as an amorphous, hygroscopic powder, m.p. 133–140°, $[\alpha]_D$ +140° (*c* 0.5, ethanol); lit.[5] m.p. 135–139°, $[\alpha]_D$ +141° (ethanol).

Benzoylation and acetylation of **1** gave products identical (m.p., $[\alpha]_D$) to those described by Richardson and Tarelli[5].

2,3,4,6-Tetra-O-*acetyl*-α-D-*glucopyranosyl 2,3-di*-O-*acetyl*-α-D-*glucopyranoside* (**4**). — To a solution of **2**[5] (5 g) in dichloromethane (50 ml), methanolic 1% hydrogen chloride (50 ml) was added and the mixture was stored at room temperature for 7 h. The mixture was deionised using Biodeminrolit mixed-bed (CO_3^{2-}) resin and concentrated to dryness. Recrystallisation of the crude product (35 g, 92%) twice from ethanol gave **4**, m.p. 106–108°, $[\alpha]_D$ +134° (*c* 0.75, chloroform) (Found: C, 48.5; H, 6.0. $C_{24}H_{34}O_{17}$ calc.: C, 48.5; H, 5.7).

2,3,4,6-Tetra-O-*benzoyl*-α-D-*glucopyranosyl 2,3-di*-O-*benzoyl*-α-D-*glucopyranoside* (**5**). — Deacetalation of **3**[5] was carried out as described above for **2** to give **5** (90%), as a syrup, $[\alpha]_D$ +225° (*c* 0.45, chloroform) (Found: C, 67.5; H, 5.0. $C_{54}H_{46}O_{17}$ calc.: C, 67.1; H, 4.75).

2,3,4,6-Tetra-O-*acetyl*-α-D-*glucopyranosyl 2,3-di*-O-*acetyl-4,6-di*-O-*mesyl*-α-D-*glucopyranoside* (**6**). — A solution of **4** (2.7 g) in pyridine (15 ml) was treated with mesyl chloride (2 ml) at room temperature for 3 h. Isolation of the product in the usual way gave **6** (3.3 g, 95%), m.p. 93–95° (from propan-2-ol), $[\alpha]_D$ +102° (*c* 0.45, chloroform) (Found: C, 41.4; H, 5.2; S, 8.65. $C_{26}H_{38}O_{21}S_2$ calc.: C, 41.6; H, 5.1; S, 8.5%).

2,3,4,6-Tetra-O-*benzoyl*-α-D-*glucopyranosyl 2,3-di*-O-*benzoyl-4,6-di*-O-*mesyl*-α-D-*glucopyranoside* (**7**). — Treatment of a solution of 2,2′, 3,3′-tetra-*O*-acetyl-α,α-trehalose[12] (5 g) in pyridine (15 ml) with mesyl chloride (5 ml) at room temperature for 3 h, followed by the usual work-up, gave **7** (2.1 g, 90%), m.p. 105–108° (from propan-2-ol), $[\alpha]_D$ +218° (*c* 0.3, chloroform) (Found: C, 59.4; H, 4.45; S, 5.7. $C_{56}H_{50}O_{21}S_2$ calc.: C, 59.9; H, 4.45; S, 5.7%).

2,3,4,6-Tetra-O-*benzoyl*-α-D-*glucopyranosyl 2,3,6-tri*-O-*benzoyl*-α-D-*glucopyranoside* (**8**). — To a solution of **5** (2 g) in pyridine (15 ml) at −20°, benzoyl chloride (2 ml) was added dropwise. The reaction was monitored by t.l.c. (benzene–ethyl acetate, 8:1). After 1.5 h, the solution was poured into cold water, and the precipitate was collected, dried, and eluted from a column (100 ml) of silica gel with benzene–ethyl acetate (20:1). Recrystallisation of the product from ethanol yielded **8** (1.9 g, 30%), m.p. 154–159°, $[\alpha]_D$ +208° (*c* 0.35, chloroform) (Found: C, 68.55; H, 4.8. $C_{61}H_{50}O_{18}$ calc.: C, 68.4; H, 4.7%).

2,3,4,6-Tetra-O-*benzoyl*-α-D-*glucopyranosyl 2,3,4,6-tetra*-O-*benzoyl*-α-D-*galactopyranoside* (**10**). — (*a*) A mixture of **7** (7 g) and sodium benzoate (7 g) in hexamethylphosphoric triamide (25 ml) was stirred at 70° for 54 h. T.l.c. (benzene–ethyl acetate, 15:1) then indicated that the reaction was complete and that one major product was formed. The mixture was poured into ice–water, and the precipitate was collected and, without drying, dissolved in chloroform. The solution was washed with distilled water,

dried (Na_2SO_4), and concentrated. Two recrystallisations of the residue (5.2 g, 76%) from propan-2-ol gave **10**, m.p. 104–106°, $[\alpha]_D$ +228.5° (*c* 0.3, chloroform) (Found: C, 70.1; H, 4.8. $C_{68}H_{54}O_{19}$ calc.: C, 69.5; H, 4.6%).

(*b*) To a solution of **8** (2 g) in pyridine (10 ml), mesyl chloride (2 ml) was added, and the mixture was stored at room temperature for 2 h and then worked-up in the usual way.

A portion (1.5 g) of the crude product (**9**; 1.6 g, 76%) was stirred with sodium benzoate (1.5 g) in hexamethylphosphoric triamide (5 ml) at 60° for 48 h, and t.l.c. (benzene–ethyl acetate, 15:1) then showed only one product. The addition of alcohol (5 ml) and water (150 ml) to the mixture gave a white solid which was collected and, without drying, dissolved in dichloromethane. The solution was washed well with water, dried (Na_2SO_4), and concentrated to dryness to give **10** (1.1 g, 67%), identical with the product from (*a*)

α-D-Glucopyranosyl α-D-galactopyranoside (**11**). — To a solution of **10** (1 g) in methanol (10 ml), methanolic M sodium methoxide (1 ml) was added. The solution was stored at room temperature for 2 h, and t.l.c. (propan-2-ol–water, 7:1) then showed that the reaction was complete. The solution was deionised with Biodeminrolit mixed-bed (CO_3^{2-}) resin and concentrated. A solution of the residue in water was washed with light petroleum (to remove methyl benzoate) and concentrated to give syrupy **11** (0.25 g, 83%), $[\alpha]_D$ +183° (*c* 0.6, water) (Found: C, 42.1; H, 6.2. $C_{12}H_{22}O_{11}$ calc.: C, 42.1; H, 6.5%).

ACKNOWLEDGMENTS

The author thanks J. Sainsbury for financing this research, the P.C.M.U., Harwell, for the 100-MHz p.m.r. spectra, and the S.R.C. for a grant. He is also deeply indebted to the late Miss Sundrawattee Elizabeth Mattai for her encouragements.

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