Chemical Modification of Trehalose. Part XII.[1] Synthesis of Azido- and Amino-trehaloses *via* Epoxide Derivatives

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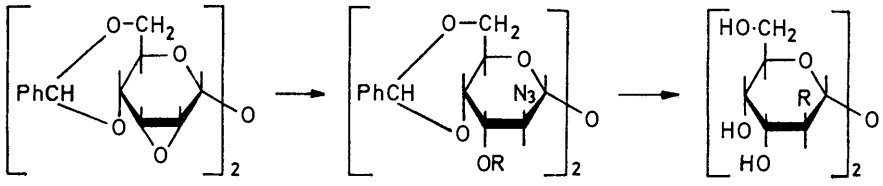
2,3-Anhydro-4,6-*O*-benzylidene-α-D-mannopyranosyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside, and the corresponding isomeric *allo,allo*- and non-symmetrical *allo,manno*-diepoxides all undergo predominant *trans*-diaxial ring opening with azide anion to give diazides of altropyranosyl altropyranosides. Likewise, ring opening of the monoepoxide, 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranosyl 4,6-*O*-benzylidene-α-D-glucopyranoside gave 3-azido-3-deoxy-α-D-altropyranosyl 4,6-*O*-benzylidene-α-D-glucopyranoside.

OUR studies of the chemical modification of trehalose have led to the synthesis, from the 4,6:4′,6′-dibenzylidene diacetal,[2] of three 2,3:2′,3′-diepoxide derivatives,[3] namely 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranosyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (1), the corresponding mannopyranosyl mannopyranoside (7), and the non-symmetrical *allo,manno*-isomer (11). We have now explored the synthesis of diamino-derivatives of the disaccharide by treatment of these diepoxides with sodium azide in the presence of ammonium chloride.

By analogy with the ring opening of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside and -allopyranoside,[4] the diepoxides (1), (7), and (11) should undergo *trans*-diaxial nucleophilic ring opening with azide anion to give diazido-derivatives of altropyranosyl altropyranosides. Diaxial ring opening of the two



(1) (2) R = H (3) R = Ms (4) R = Bz (5) R = N_3 (6) R = NH_2

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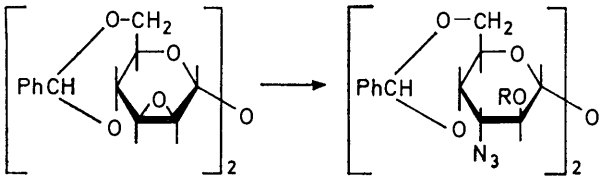
[3] L. Hough, P. A. Munroe, and A. C. Richardson, *J. Chem. Soc.* (*C*), 1971, 1090.
[4] R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 1963, 5288.

symmetrical epoxides, (1) and (7), with hydride ion (from lithium aluminium hydride) has previously been observed.[5,6] Reaction of the *allo,allo*-diepoxide (1) with azide anion afforded a crystalline diazide in 71% yield; t.l.c. indicated that at least two minor components were present which we could not isolate. The three products

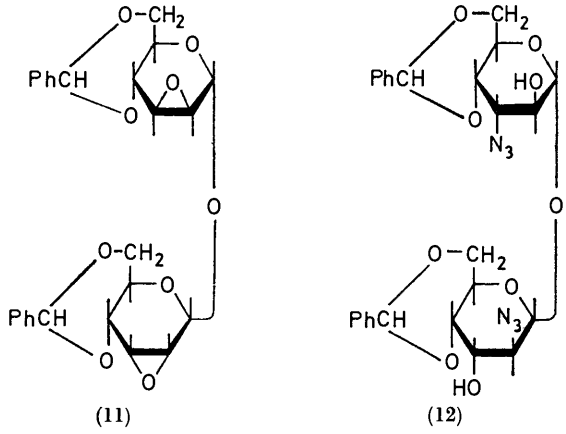


(7) (8) R = H (9) R = Ms (10) R = Bz

were estimated visually to be in the approximate ratio of 80 : 15 : 5, and the minor products must presumably be those resulting from diequatorial ring opening on one and both rings, respectively. The ^{1}H n.m.r. spectrum of the major diazide showed that it was a symmetrical product. The resonances attributable to the benzylic protons and to H-1 and H-1′ appeared as two singlets at τ 4·44 and 5·00, respectively. Furthermore, the observed small (<1 Hz) coupling between H-1 and H-2 is a characteristic feature of altropyranosides[5,7] and is consistent with the product being the expected 2,2′-diazido-*altro,altro*-isomer (2). The structure of the diazide (2) was confirmed by the ^{1}H n.m.r. spectrum of the derived 3,3′-dibenzoate (4) in which the H-3,H-3′ resonance was observed at low field as a narrow triplet (τ 4·49; $J_{2,3} = J_{3,4} = ca.$ 2·5 Hz) owing to the deshielding effect of the adjacent benzoyloxy-groups.[2,3,5-7] A similar result was obtained with the 3,3′-dimesylate (3) (see Table).

Reaction of the *manno,manno*-diepoxide (7) with sodium azide and ammonium chloride in hexamethylphosphoric triamide gave a diazide in 89% yield. Again the *altro*-configuration of both pyranosyl rings of the 3,3′-diazide (8) was indicated by its ^{1}H n.m.r. spectrum, in which both the benzylic and H-1,H-1′ resonances appeared as singlets (Table). In the ^{1}H n.m.r. spectrum of the derived syrupy 2,2′-dibenzoate (10) the anomeric protons (H-1,H-1′) resonated as a singlet at τ 4·80 and, as a result of deshielding by the benzoyloxy group, the H-2,H-2′ signal appeared at lower field (τ 4·67) as a doublet (*J* 2·5 Hz), consistent with the 3,3′-diazido-*altro,altro*-structure (10).

The non-symmetrical diepoxide 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranosyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (11) was treated similarly with azide to give a major crystalline product in 76% yield. A minor product was detected by t.l.c. (<5%) but all efforts to isolate and characterise it failed. In this case, and in contrast to the foregoing symmetrical diazido-derivatives [(2) and (8)], the major product (12) was non-symmetrical as suggested by the appearance of two benzylic resonances in the ^{1}H n.m.r. spectrum at τ 4·16 and 4·20. The *altro*-stereochemistry of the two pyranosyl rings was shown by the appearance of both anomeric proton signals as singlets at τ 4·43 and 4·46. Hence the product was identified as the 2,3′-diazido-*altro,altro*-isomer (12).



(11) (12)

We have previously[3] described the synthesis, from trehalose, of a monoepoxide, namely 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranosyl 4,6-*O*-benzylidene-α-D-glucopyranoside (13). Reaction of the epoxide (13) with azide anion afforded a single syrupy product, which had the predicted *altro*-configuration in one of the pyranosyl rings as shown by its ^{1}H n.m.r. spectrum. This contained two benzylic resonances at τ 4·48 and 4·54 and two resonances attributable to H-1 and H-1′; the proton attached to the *gluco*-ring gave a doublet at τ 4·87 (*J* 3·8 Hz) and that attached to the *altro*-ring gave a singlet at τ 5·08.

The conversions of the 2,2′-diazide (2) and the 3-mono-azide (14) into the corresponding amino-disaccharides were then studied. The acetal protecting groups were removed from the diazide (2) by acid-catalysed methanolysis and the syrupy product (5) was reduced catalytically to the amorphous 2,2′-diamino-2,2′-dideoxy-disaccharide (6). Methanolysis of the mono-azide (14) gave the crystalline 3-azido-3-deoxy-α-D-altropyranosyl α-D-glucopyranoside (15), which was reduced to the crystalline 3-amino-3-deoxy-α-D-altropyranosyl α-D-glucopyranoside (16), a positional and stereochemical isomer of the antibiotic trehalosamine (2-amino-2-deoxy-α-D-glucopyranosyl α-D-glucopyranoside).[8] Neither the diamine (6) nor the monoamine (16) showed antibacterial activity.

All ^{1}H n.m.r. data are summarised in the Table. In the spectra of the altropyranosides (2), (3), (4), (8), (10), (12), and (14) the H-1,H-1′ and H-3,H-3′ resonances were not sufficiently resolved to permit measurement of the long-range coupling $J_{1,3}$, which is normally less than 1 Hz.[7]

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[6] L. Hough, A. C. Richardson, and E. Tarelli, *J. Chem. Soc.* (*C*), 1971, 2122.

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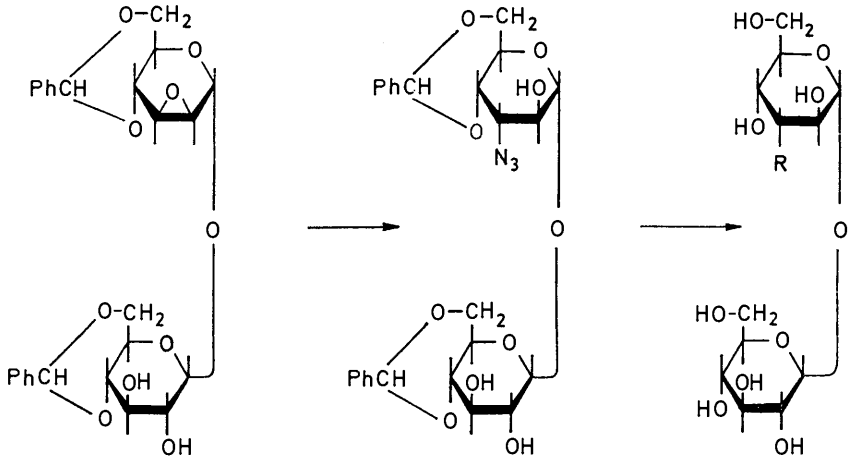
[8] F. Arcamone and F. Bizioli, *Gazzetta*, 1957, **87**, 896; S. Umezawa, K. Tatsuta, and R. Muto, *J. Antibiotics, Ser. A*, 1967, **20**, 388.



(13) (14) (15) R = N_3 (16) R = NH_2

EXPERIMENTAL

For general procedures see ref. 3. Optical rotations were taken, unless otherwise stated, for chloroform solutions at 20—25°.

2-Azido-4,6-O-benzylidene-2-deoxy-α-D-altropyranosyl 2-Azido-4,6-O-benzylidene-2-deoxy-α-D-altropyranoside (2).—The *allo,allo*-diepoxide [3] (1) (5 g) dissolved in hot *NN*-dimethylformamide (200 ml) was treated with a slurry of sodium azide (10 g) and ammonium chloride (10 g) in water (10 ml). The mixture was heated under reflux for 12—14 h; t.l.c. [ethyl acetate–light petroleum (4 : 6)] then indicated that reaction was complete and one major product had been formed along with two minor products, visually estimated to be in the approximate ratio of 80 : 15 : 5. The cooled mixture was poured slowly into stirred ice–water (200 ml) and the resulting white solid was filtered off, washed with water, and recrystallised from ether. A further recrystallisation from ethanol, afforded the *diazide* as an *ethanolate* (4·2 g, 71%), m.p. 114—115°, $[\alpha]_D$ +120° (*c* 1·25) (Found: C, 54·7; H, 5·1; N, 14·2. $C_{26}H_{28}N_6O_9,C_2H_5OH$ requires C, 54·75; H, 5·5; N, 13·7%). The presence of ethanol of crystallisation was revealed by a triplet (3H) at τ 8·86 in the ^1H n.m.r. spectrum.

Attempts to isolate the two minor products by silica gel chromatography failed to give a homogeneous product.

The *dibenzoate* (4) (73%) had m.p. 64—66° (from methanol), $[\alpha]_D$ +52° (*c* 1) (Found: C, 62·1; H, 4·7; N, 10·8. $C_{40}H_{36}N_6O_{11}$ requires C, 61·9; H, 4·6; N, 10·8%).

The *dimesylate* (3) had m.p. 110°, $[\alpha]_D$ +79° (*c* 2·1) (Found: C, 46·2; H, 4·7; N, 11·2; S, 8·9. $C_{28}H_{32}N_6O_{13}S_2$ requires C, 46·4; H, 4·4; N, 11·6; S, 8·8%).

2-Amino-2-deoxy-α-D-altropyranosyl 2-Amino-2-deoxy-α-D-altropyranoside (6).—To the diazide (2) (1·0 g) dissolved in hot methanol (50 ml) was added methanolic 1% hydrogen chloride (10 ml). The reaction was monitored by t.l.c. [chloroform–methanol (4 : 1 v/v)], which indicated that reaction was complete within 4—5 min. The solution was immediately neutralised with basic lead carbonate and filtered. To the filtrate was added Adams catalyst (25 mg) and the mixture was hydrogenated at 30 lb in^{-2} for 1 h. Filtration and evaporation gave the *diamine* as a glass (0·2 g, 33%), $[\alpha]_D$ +109° (H_2O) (Found: C, 42·2; H, 7·1; N, 8·1. $C_{12}H_{24}N_2O_9$ requires C, 42·3; H, 7·0; N, 8·2%).

3-Azido-4,6-O-benzylidene-3-deoxy-α-D-altropyranosyl 3-Azido-4,6-O-benzylidene-3-deoxy-α-D-altropyranoside (8).—A solution of the diepoxide [3] (7) (5 g) in hexamethylphosphoric triamide (20 ml) was heated to 80° and treated with a paste of powdered sodium azide (10 g) and ammonium chloride (10 g) with water (10 ml). The mixture was stirred at 80° for 48 h, after which t.l.c. [benzene–acetone (4 : 1 v/v)] indicated that the reaction was complete. The mixture was cooled and poured into stirred ice–water (500 ml). The precipitate was filtered off, washed with water, and dissolved in ether (100 ml). The ethereal layer was washed with water, dried ($MgSO_4$), filtered, and evaporated to a stiff syrup which crystallised from ethanol–chloroform. A

^1H N.m.r. parameters: first-order coupling constants (Hz) and chemical shifts (τ values) at 100 MHz

Compound	(2) [a]	(3) [a]	(4) [a]	(8) [b]	(10) [a]	(12) [b]	(14) [a]
H-1,H-1′	5·00(s)	4·92(s)	4·78(s)	4·46(s)	4·80(s)	{4·43(s) 4·46(s)	{4·87(d) 5·08(s)
H-2,H-2′		5·91(d) *	6·03(d)		4·67(d)		
H-3,H-3′		4·90(t) *	4·49(t)				
H-4,H-4′		6·01(q) *	5·92(q)				
C*H*Ph	4·44(s)	4·38(s)	4·40(s)	4·25(s)	4·35(s)	{4·20(s) 4·16(s)	{4·48(s) 4·54(s)
$J_{1,2}$	<1	<1	<1	<1	<1	{<1 <1	{*ca.* 3·8 <1
$J_{2,3}$		2·9	2·5		2·5		
$J_{3,4}$		*ca.* 2·5	2·8				
$J_{4,5}$		8·5	*ca.* 8·5				

[a] In [^2H]chloroform. [b] In [$^2H_5$]pyridine.

* Assignments verified by spin decoupling.

further recrystallisation, from ethanol, afforded the *diazide* (5·3 g, 89%), m.p. 108—110°, $[\alpha]_D$ +336° (*c* 1·1 in MeOH) (Found: C, 54·9; H, 4·8; N, 14·2. $C_{26}H_{28}N_6O_9$ requires C, 54·9; H, 4·9; N, 14·7%). The *dimesylate* (9) (79%) had m.p. 197—200°, $[\alpha]_D$ +27° (*c* 2) (Found: C, 46·2; H, 4·3; N, 11·2; S, 8·9. $C_{28}H_{32}N_6O_{13}S_2$ requires C, 46·4; H, 4·4; N, 11·6; S, 8·8%). The *dibenzoate* (10) was a colourless glass (85%), characterised by its ^{1}H n.m.r. spectrum (see Table).

3-*Azido*-4,6-O-*benzylidene*-3-*deoxy*-α-D-*altropyranosyl* 2-*Azido*-4,6-O-*benzylidene*-2-*deoxy*-α-D-*altropyranoside* (12).—A solution of the *allo,manno*-diepoxide [3] (11) (1 g) in hexamethylphosphoric triamide (10 ml) was heated to 70°, and a slurry of ammonium chloride (1·5 g), sodium azide (1·5 g), and water (1·5 ml) was added. The mixture was stirred for 24 h; t.l.c. (ether) then indicated that the starting material had been converted into a major product and a minor one (<5%). The mixture was cooled and poured on ice (150 g). The precipitate was filtered off, washed with water, and partitioned between water and ether. The ethereal solution was dried ($MgSO_4$) and evaporated to a hard glass which crystallised from ethanol–chloroform, to give a chromatographically homogeneous *product* (0·9 g, 76%), m.p. 103°, $[\alpha]_D$ +61° (*c* 0·6) (Found: C, 55·1; H, 5·0; N, 14·8. $C_{26}H_{28}N_6O_9$ requires C, 54·9; H, 4·9; N, 14·8%). Attempts to isolate the minor component by chromatography were unsuccessful.

3-*Azido*-4,6-O-*benzylidene*-3-*deoxy*-α-D-*altropyranosyl* 4,6-O-*Benzylidene*-α-D-*glucopyranoside* (14).—The monoepoxide (13) (5 g) was dissolved in hexamethylphosphoric triamide (20 ml) and a slurry of sodium azide (5 g) and ammonium chloride (5 g) and water (2·5 ml) was added. The mixture was heated in an oil-bath at 85° for 12 h; t.l.c. [chloroform–acetone (9 : 1 v/v)] then indicated that the reaction was complete. The mixture was cooled and poured on crushed ice (250 g); the precipitate was filtered off, washed with water, and partitioned between water and ether. Evaporation of the dried ($MgSO_4$) ether layer gave the *monoazide* as a hard glass (4·8 g, 90%), $[\alpha]_D$ +44·6° (*c* 1 in MeOH) (Found: C, 57·4; H, 5·4; N, 7·2. $C_{26}H_{29}N_3O_{10}$ requires C, 57·5; H, 5·3; N, 7·7%).

3-*Azido*-3-*deoxy*-α-D-*altropyranosyl* α-D-*Glucopyranoside* (15).—The di-*O*-benzylidene derivative (14) (1·5 g) dissolved in anhydrous methanol (20 ml) was treated with methanolic 1% hydrogen chloride (5 ml). T.l.c. [chloroform–methanol (9 : 1 v/v)] indicated that the reaction was complete within 5—6 min. The mixture was immediately neutralised with lead carbonate and, after filtration, evaporated to a syrup which was washed with light petroleum to remove benzaldehyde dimethyl acetal. Crystallisation from methanol–chloroform gave the *monoazide* (0·6 g, 59%), m.p. 105—108° (crystal transition 74—76°), $[\alpha]_D$ +155° (*c* 1·0 in MeOH) (Found: C, 39·0; H, 5·7; N, 11·8. $C_{12}H_{21}N_3O_{10}$ requires C, 39·2; H, 5·7; N, 11·5%).

3-*Amino*-3-*deoxy*-α-D-*altropyranosyl* α-D-*Glucopyranoside* (16).—The monoazide (15) (1·0 g) in methanol (50 ml) was hydrogenated over palladium–charcoal (20 mg) at 3 atm for 2 h. T.l.c. [chloroform–methanol (3 : 2 v/v)] then showed that the reaction was complete. After filtration, the solution was evaporated to a syrup which crystallised from methanol–chloroform to give the *amine* (0·65 g, 70%), m.p. 130—133°, $[\alpha]_D$ +170° (*c* 1·0 in MeOH) (Found: C, 42·2; H, 6·7; N, 4·1. $C_{12}H_{23}NO_{10}$ requires C, 42·2; H, 6·7; N, 4·2%).

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