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Note

6,6′-Diamino-2,3,4,2′,3′,4′-hexa-*O*-benzyl 6,6′-dideoxy-α,α-trehalose

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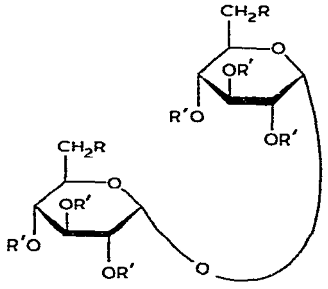
A recent report[1] from this laboratory described the synthesis of diamide pseudo-cord-factors from (α-D-glucopyranosyluronic acid) (α-D-glucopyranosiduronic acid) and various amines. An alternative class of diamide pseudo-cord-factors may also be prepared from lipid carboxylic acids and a suitably protected, 6,6′-diamino derivative of trehalose. We sought to prepare and to employ for this purpose 2,3,4,2′,3′,4′-hexa-*O*-acetyl-6,6′-diamino-6,6′-dideoxy-α,α-trehalose, a compound whose preparation from the corresponding 6,6′-diazido derivative was earlier described[2]. However, we observed[3] that catalytic hydrogenation of the diazide led, not to the 6,6′-diamine reported, but to 6,6′-diacetamido-2,3,2′,3′-tetra-*O*-acetyl-6,6′-dideoxy-α,α-trehalose, presumably *via* O→N acetyl migration. In order to overcome this difficulty, we utilized a hexa-*O*-benzyltrehalose[4] to synthesize 6,6′-diamino-2,3,4,2′,3′,4′-hexa-*O*-benzyl-6,6′-dideoxy-α,α-trehalose. This is a protected diamine not subject to O to N migration and is currently being successfully employed in the synthesis of "amide" pseudo-cord-factors.

Treatment of 2,3,4,2′,3′,4′-hexa-*O*-benzyl-6,6′-di-*O*-(methylsulfonyl)-α,α-trehalose (**1**) with sodium azide in *N*,*N*-dimethylformamide gave the corresponding 6,6′-diazido derivative **2** in high yield. Catalytic hydrogenation of **2** in the presence of platinum oxide proceeded smoothly, and the 6,6′-diamino derivative **3** was isolated in very good yield as a practically homogeneous syrup. The product was ninhydrin-positive, and it was also characterized as the di-*N*-acetyl derivative **4**.

Compound **3** could also be prepared from 6,6′-diazido-6,6′-dideoxy-α,α-trehalose[3,5] (**5**) by benzylation of the latter with benzyl chloride in 1,4-dioxane, and subsequent hydrogenation. In this case, the benzylated diazido derivative was contaminated with dibenzyl ether, which could not be removed by either high-vacuum distillation or by chromatography. However, the diamine obtained by this route could be readily purified by treating it with ion-exchange resin. In spite of this difficulty, synthesis of the benzylated 6,6′-diamino derivative **3** from the diazide **5** is preferred, owing to the ease of formation of the latter from trehalose.



	R	R'
1	OMs	CH$_2$Ph
2	N$_3$	CH$_2$Ph
3	NH$_2$	CH$_2$Ph
4	NHAc	CH$_2$Ph
5	N$_3$	H

EXPERIMENTAL

General methods. — Optical rotations were determined with a Jasco DIP-4 polarimeter for whose use we thank Dr. John Stewart. Thin-layer chromatograms were run on Eastman Kodak silica gel plates. Chromatography columns were packed with silica gel (E. Merck, No. 7734). Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

*6,6'-Diazido-2,3,4,2',3',4'-hexa-*O*-benzyl-6,6'-dideoxy-α,α-trehalose* (**2**). — A mixture of 2,3,4,2',3',4'-hexa-*O*-benzyl-6,6'-di-*O*-(methylsulfonyl)-α,α-trehalose[4] (0.52 g) and sodium azide (0.35 g) in *N*,*N*-dimethylformamide (10 mL) was heated with stirring for 15 h at 130–135°. The mixture was cooled to room temperature and the insoluble material was filtered off. The filtrate was evaporated and the residue was extracted with chloroform. Evaporation of the solvent gave a syrup (0.44 g, 93%) that was chromatographically homogeneous. A portion of the product was further purified by column chromatography. Elution with 3:1 hexane–ethyl acetate gave an analytically pure sample, $[\alpha]_D^{24}$ +122° (c 1.48, chloroform).

Anal. Calc. for $C_{54}H_{56}N_6O_9$: C, 69.51; H, 6.04; N, 9.00. Found: C, 69.37; H, 6.05; N, 8.91.

*6,6'-Diamino-2,3,4,2',3',4'-hexa-*O*-benzyl-6,6'-dideoxy-α,α-trehalose* (**3**). — The 6,6'-diazido derivative **2** was dissolved in 1:1 ethyl acetate–ethyl alcohol (40 mL) and hydrogenated in the presence of platinum oxide (60 mg) at 25 lb.in.$^{-2}$ for 2 h. The catalyst was filtered off and washed with ethyl alcohol, and the filtrate was evaporated to a syrup (77 mg, 89%) that was practically pure. For microanalysis, a portion of the product was purified by column chromatography. Elution with 9:1 chloroform–methanol removed the by-products (trace amounts). Continued elution with the same solvent system afforded an analytically pure sample; $[\alpha]_D^{24}$ +76° (*c* 1.3, chloroform).

Anal. Calc. for $C_{54}H_{60}N_2O_9$: C, 73.61; H, 6.86; N, 3.17. Found: C, 73.41, H, 7.04; N, 3.08.

*6,6'-Diacetamido-2,3,4,2',3',4'-hexa-*O*-benzyl-6,6'-dideoxy-α,α-trehalose* (**4**). — The diamino derivative (**3**, 85 mg) was acetylated conventionally with acetic anhydride and pyridine. Evaporation of the mixture gave a syrup that showed one major spot in t.l.c. The mixture was applied to a column of silica gel, and elution was performed with 9:1 ethyl acetate–methanol. The first fractions, which were found to contain a minor by-product, were discarded. Continued elution with 7:1 ethyl acetate–methanol gave pure **4**: yield 62 mg (64%), $[\alpha]_D^{24}$ +57° (*c* 1.04, chloroform).

Anal. Calc. for $C_{58}H_{64}N_2O_{11}$: C, 69.86; H, 6.46; N, 2.80. Found: C, 69.76; H, 6.70; N, 2.85.

6,6'-Diamino-2,3,4,2',3',4'-hexa-O-benzyl-6,6'-dideoxy-α,α-trehalose (**3**) (from **5**). — A mixture of 6,6'-diazido-6,6'-dideoxy-α,α-trehalose (**5**, 0.6 g) and powdered potassium hydroxide (7 g) in 1,4-dioxane (6 mL) was boiled gently under reflux. To the mixture was added benzyl chloride (8 mL) dropwise, and heating was continued for 1 h after completion of the addition. The 1,4-dioxane was distilled off, and the residue was cooled to room temperature. Water was added to the residue, and the mixture was extracted with ether. Evaporation of the ether, followed by high-vacuum distillation, left a residue that consisted of the hexabenzylated diazide and some dibenzyl ether. Without further purification, this mixture was dissolved in 1:1 ethyl acetate–ethyl alcohol (80 mL) and hydrogenated in the presence of platinum oxide as already described. The catalyst was filtered off, and washed with ethyl alcohol, and the filtrate was evaporated. The residue was stirred with a cation-exchange resin [AG MP-50(H$^+$), 10 g] suspended in 1:1 chloroform–methanol. The resin was filtered off, and washed thoroughly with 1:1 chloroform–methanol. The 6,6'-diamino derivative **3** was then recovered by washing the resin with 5:5:1 chloroform–methanol–ammonia. Evaporation of the effluent gave the practically pure product, which was identical with **3** already described; yield, 0.727 g (54%).

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