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SELECTIVE SUBSTITUTION REACTIONS OF α,α-TREHALOSE: PREPARATION OF 6-MONOFUNCTIONAL DERIVATIVES*†

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ABSTRACT

Procedures are described that lead, by action of triphenylphosphine–*N*-halosuccinimide, from α,α-trehalose to 6-deoxy-6-halo-α,α-trehalose heptaacetates in one step. The 6-bromo-6-deoxy derivative, isolated in 37% overall yield as the crystalline heptaacetate has been converted in high yield into 6-deoxy-α,α-trehalose, a known substrate for trehalase. The crystalline 6-chloro and 6-iodo analogs are also reported.

INTRODUCTION

The relevance of α,α-trehalose and some of its analogs to diverse biological problems has been known for some time[1]. In particular, the specificity of trehalases and related hydrolytic enzymes for trehalose and its analogs is of interest[2]. The synthesis of functionalized trehaloses has been investigated by several groups[3–5] concerned with evaluating their properties as substrates and/or inhibitors of trehalases. Trehalose is unusual in having a symmetrical disposition of α-D-glucosyl groups about the central oxygen atom; this feature and the α-D-linkage undoubtedly have a strong bearing on its behavior toward enzymes. From the standpoint of chemical modification, the presence of an α-linkage can be a structural asset, particularly if modifications aimed at antibiotics[6] of the aminoglycoside type are envisaged. One of the structurally simplest members of the aminoglycoside group of antibiotics is the antitubercular substance trehalosamine[7] (2-amino-2-deoxy-α-D-glucopyranosyl α-D-glucopyranoside), a naturally occurring amino analog of α,α-trehalose.

The introduction of certain functional groups into both glucosyl groups of α,α-trehalose by conventional monosaccharide reactions is relatively facile and leads to symmetrical analogs[4,8,9]. The selective introduction of a functional group on only one of the two glucosyl groups, to give non-symmetrical analogs, is more difficult[10,11]. Only recently have the mono-*O*-benzylidene[12] and monoepoxide[13] derivatives of α,α-trehalose been prepared and subjected to various transformations.

*Dedicated to Dr. Louis Long, Jr., in honor of his 70th birthday.
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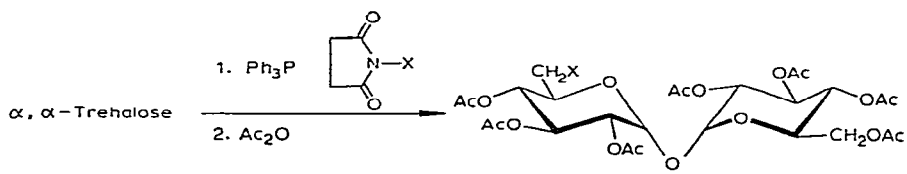
The 6-deoxy[5] and 6-deoxyiodo[11] derivatives have also been recently reported, but their preparation is hampered by low yields of intermediates. However, the available biochemical data indicate that the non-symmetrical analogs of α,α-trehalose, and in particular, the 6-substituted derivatives, are potentially of greater interest than the corresponding symmetrical analogs; thus 6-deoxy-α,α-trehalose, but not the 6,6'-dideoxy analog, has been shown to be a substrate for trehalases[5]. The need for devising newer methods for the selective functionalization of α,α-trehalose is therefore apparent. This paper is concerned with the preparation of 6-halo and 6-deoxy-α,α-trehalose derivatives.

DISCUSSION

In previous reports[14] from this laboratory, it has been shown that carbohydrates and certain nucleosides can be efficiently halogenated by treatment with triphenylphosphine–*N*-halo(bromo, chloro, or iodo)succinimide. This reaction affords selectivity of halogenation in polyhydroxy compounds and is compatible with commonly used *O*- and *N*-protecting groups. Thus, bromination of methyl α-D-glucopyranoside with Ph_3P–*N*-bromosuccinimide in *N*,*N*-dimethylformamide gave, after acetylation of the product, methyl 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-α-D-glucopyranoside in 66% overall yield. In this paper, we report on the application of this reaction to α,α-trehalose and the formation of 6-deoxy-6-halo-α,α-trehalose derivatives (Scheme I).

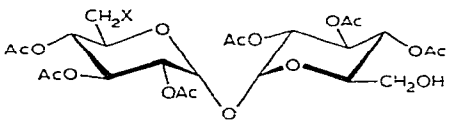


SCHEME 1

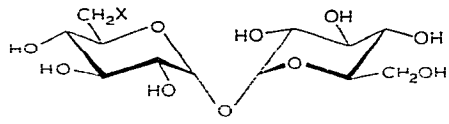
Preliminary experiments indicated that the ratio of halogenating mixture (Ph_3P–*N*-bromosuccinimide) and the reaction time and temperature are important in determining whether mono- or dibromination occurs at the primary positions of the disaccharide. Although the formation of a certain proportion of dibromo derivative could not be avoided, even with a deficiency of halogenating agent, a reproducible procedure was developed that gives acceptable yields (37–40% based on the starting disaccharide) of crystalline 6-bromo-6-deoxy-α,α-trehalose (**1**), isolated as its crystalline heptaacetate **2**. When the amount of halogenating mixture was changed from two equivalents to four equivalents relative to trehalose, the major product was 6,6'-dibromo-6,6'-dideoxy-α,α-trehalose (**4**), isolated in 62% overall yield as the crystalline hexaacetate **3**. Thin-layer chromatographic solvent systems were found that clearly differentiated the acetylated monobromo and dibromo derivatives from α,α-trehalose octaacetate. Because of their similar solubility proper-

ties, it was not possible to eliminate entirely traces of one of these compounds from the other during attempted recrystallizations, but they could be separated by column chromatography on silica gel. A definitive proof for the location of the bromine atom(s) in these products was afforded by reduction to the corresponding deoxy and dideoxy analogs (see later). In addition, deacetylation of **3** gave the 6,6′-dibromo derivative **4**, which on benzoylation gave the known[9] crystalline 6,6′-dibromo-6,6′-dideoxy-α,α-trehalose hexabenzoate **11** in 80% yield. In an effort to increase the yield of the monobromo derivative **2**, the selective displacement of one of the two bromine atoms in the dibromo derivative **3** was examined. Thus treatment of **3** with two equivalents of sodium acetate in *N*,*N*-dimethylformamide under controlled conditions gave a mixture of products from which the desired monobromo derivative **2** was isolated in 43% yield. Other products were α,α-trehalose octaacetate (43%) formed by an unavoidable double-displacement, and a small amount of starting dibromide **3**. Thus, by effecting such a selective displacement, compound **3** could be recycled and utilized effectively as another source of the desired monobromide **2**. These procedures, alone or in combination, provide easy access to mono-6-substituted α,α-trehalose derivatives, and the 6-bromo derivative **2** was used as the starting material for a variety of standard transformations. The reduction of **2** and **3** to the respective deoxy and dideoxy derivatives was of interest in view of the potential biological importance of the products. Reduction of **2** with hydrogen in the presence of 20% palladium-on-charcoal[15] and sodium acetate in methanol was complete within 24 h at room temperature, and the known[5] crystalline 6-deoxy-α,α-trehalose heptaacetate (**5**) was obtained in 81% yield. Similarly, reduction of the dibromo derivative **3** gave the known[8] crystalline, 6,6′-dideoxy-α,α-trehalose hexaacetate (**6**) in 86% yield. It is noteworthy that such 6-deoxyhexoses give a characteristic greenish color[14] on thin-layer chromatograms, when sprayed with an acidic solution of ammonium molybdate[16]. Deacetylation of **5** afforded the known[5] 6-deoxy-α,α-trehalose **7** as an amorphous solid in quantitative yield. Although the deoxy analogs **5** and **6** have been described in the literature, their preparation by sulfonate displacement methods is plagued by low yields of precursors. For example, monomesylation of α,α-trehalose gives the 6-*O*-methylsulfonyl derivative in yields of 2.6% (ref. 10) and 6% (ref. 5) after column chromatography. The 6-deoxy-6-iodo derivative **8** was obtained from the acetylated 6-methanesulfonate by displacement with sodium iodide[5,11]. Initial attempts to reduce this product by catalytic methods to the monodeoxy derivative **5** were unsuccessful[11], but in subsequent work[5], the desired deoxy derivative (59% yield) was obtained by reduction with Raney nickel or by photolysis (55% yield). In the first report (by Birch[8]) of 6,6′-dideoxy-α,α-trehalose, a five-step procedure was used to obtain the diiodide **9**, which was reduced (Raney nickel, 58% yield) and the product deacetylated. Access to such 6,6′-disubstituted α,α-trehaloses has been made easy by the action of *N*-bromosuccinimide on appropriate benzylidene acetals[9]. In our previous report[14], the combination Ph_3P–*N*-halosuccinimide (where halide = Cl, Br, I), was shown to give in high yield the 6-chloro and iodo derivatives of various carbohydrates originally containing primary hydroxyl groups. Treatment

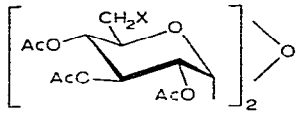
of α,α-trehalose with two equivalents each of triphenylphosphine and *N*-iodosuccinimide in *N*,*N*-dimethylformamide at 50°, followed by acetylation of the product and chromatographic purification, gave the crystalline 6-deoxy-6-iodo-α,α-trehalose heptaacetate[11] **8** in 21% yield. The crystalline 6,6′-diiodo derivative **9** could be obtained in 55% yield when a large excess of halogenating agent was used. When *N*-chlorosuccinimide was used as the halogenating agent, again a somewhat longer reaction time was required to effect halogenation and only low yields (13%) of crystalline 6-chloro-6-deoxy-α,α-trehalose heptaacetate **10** could be obtained after acetylating the initial mixture. The relatively lower yields of the iodo and chloro derivatives (**9** and **10**, respectively), compared with the bromo analog **2**, can certainly be circumvented by using the latter as substrate for nucleophilic displacement reactions with iodide and chloride ions, respectively. Indeed displacements of this type have many precedents in the chemistry[8–10] of α,α-trehalose. Such an approach was used to transform α,α-trehalose into its 6-amino analog[17], which is a positional isomer of trehalosamine.



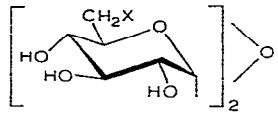
2 X = Br
8 X = I
10 X = Cl
5 X = H



1 X = Br
7 X = H



3 X = Br
9 X = I
12 X = Cl
6 X = H



4 X = Br

SCHEME 2

EXPERIMENTAL

General. — Melting points were obtained on a Reichert apparatus and are uncorrected. N.m.r. spectra were recorded for solutions in chloroform-*d* at 60 or 100 MHz with tetramethysilane as internal standard. I.r. spectra were recorded with a Beckman IR-8 spectrophotometer. Mass spectra were obtained with Hitachi–Perkin–Elmer medium-resolution and A.E.I. MS-902 high-resolution mass spectrometers. Optical rotations were measured with a Perkin–Elmer Model 141 automatic polarimeter. T.l.c. was performed with plates coated with Silica Gel GF_{254} and the spots were detected with a 20% (in ethanol) sulfuric acid spray. 6-Deoxy sugars were detected[14,16] by spraying the plates with an aqueous solution containing ammonium

molybdate (5 g), sulfuric acid (5 ml) and phosphoric acid (5 ml) and heating the plates at 110°. Column chromatography was conducted with short columns of the same silica gel by application of moderate suction. *N,N*-Dimethylformamide (analytical grade) was dried over Linde 4A molecular sieve for 1 week followed by distillation prior to use.

6,6'-Dibromo-6,6'-dideoxy-α,α-trehalose hexaacetate (**3**). — To a homogeneous solution of anhydrous α,α-trehalose[18] (0.684 g, 2 mmoles) and triphenylphosphine (2.16 g, 8.25 mmoles) in 75 ml of *N,N*-dimethylformamide was added *N*-bromosuccinimide (1.42 g, 8 mmoles) slowly and with stirring in an ice bath. The color of the solution changed from pale-yellow to orange and back to pale-yellow upon completion of the addition. The reaction mixture was left for 60 h at room temperature, after which time t.l.c. (chloroform–methanol, 10:3) indicated the formation of the maximal yield of the dibromo derivative **4**. Methanol (20 ml) was added to decompose excess reagent, and the solvent was removed by azeotropic evaporation with 1-butanol at 50°. The oily residue was taken up in toluene, and then chloroform was added and the solution was evaporated to give a solid. Water (200 ml) was added and the solution was extracted four times with 50 ml of chloroform and the combined organic extracts were washed with water (60 ml). Evaporation of the combined aqueous phases (under diminished pressure or by lyophilization) and evaporation of toluene from the residue gave a solid that was acetylated with acetic anhydride (5 ml) in pyridine (20 ml). After 24 h at room temperature, the solution was poured slowly into 300 ml of ice–water to give a crystalline product (1.24 g) that was contaminated with small amounts of the acetylated monobromo derivative **2** and α,α-trehalose octaacetate (t.l.c., dichloromethane–ethyl acetate, 4:1). Column chromatography with the foregoing solvent system gave the title compound (0.89 g, 62%), which was recrystallized from ethanol, m.p. 165–166°. A second recrystallization from the same solvent afforded an analytical sample, m.p. 166–167°, $[\alpha]_D^{25}$ +126° (*c* 3.4, chloroform); *m/e* 353, 351 $[(C_{12}H_{16}BrO_7)^+]$.

Anal. Calc. for $C_{24}H_{32}Br_2O_{15}$: C, 40.01; H, 4.61. Found: C, 40.05; H, 4.50.

6-Bromo-6-deoxy-α,α-trehalose heptaacetate (**2**). — *Method* A, *with* Ph_3P–*N-bromosuccinimide*. To a cooled and homogeneous solution of anhydrous trehalose (0.684 g, 2 mmoles) and triphenylphosphine (1.07 g, 4 mmoles) in *N,N*-dimethylformamide (100 ml) was slowly added *N*-bromosuccinimide (0.714 g, 4 mmoles) with stirring. The reaction mixture was kept for ~43 h at room temperature when t.l.c. indicated the formation of the maximal amount of **1** (chloroform–methanol, 10:3). The product was isolated as described for **3** by addition of methanol to give a solid residue, that was dissolved in water (100 ml), and the solution was extracted four times with chloroform (50 ml). The aqueous layer was separated and evaporated (coevaporation with ethanol). Traces of water were removed by evaporation of toluene from the residue, which was acetylated with acetic anhydride (4 ml) in pyridine (20 ml). The resultant solution was poured after 24 h at ~25° into 300 ml of ice–water. The resulting precipitate (1.18 g) was a mixture of acetylated bromo derivatives **3** and **2** and α,α-trehalose octaacetate, as shown by t.l.c. (dichloromethane–

ethyl acetate, 4:1, R_F ~0.67, 0.58, and 0.48, respectively on a 5×10-cm plate). Separation by column chromatography with the same solvent system gave the dibromo derivative **3** (11%) and the title compound (0.528 g, 37%). Recrystallization of the latter from chloroform–hexane or from ethanol gave in both cases, chromatographically homogeneous crystals (m.p. 75–90°) that contained occluded solvent as indicated by weight losses upon drying and by microanalytical data. Recrystallization from isopropyl alcohol gave a sharp-melting product, m.p. 121–123°, $[\alpha]_D^{25}$ +141.3° (*c* 1.2, chloroform); *m/e* 353, 351 $[(C_{12}H_{16}BrO_7)^+]$ and *m/e* 331 $[(C_{14}H_{19}O_9)^+]$.

Anal. Calc. for $C_{26}H_{35}BrO_{17}$: C, 44.64; H, 5.04. Found: C, 44.74; H, 4.96.

Method B, *via nucleophilic displacement.* A solution of **3** (0.187 g, 0.26 mmoles) and anhydrous sodium acetate (34 mg, 0.4 mmoles) in *N*,*N*-dimethylformamide (15 ml) was heated for 2.5 h at 85°, at which time another portion of sodium acetate (20 mg) was added. After 1.5 h of further heating, the solution was kept overnight at room temperature and then neutralized with Dowex-50 (H^+). Filtration and azeotropic evaporation of the filtrate with 1-butanol gave a solid residue that was chromatographed on a short column of silica gel with dichloromethane–ethyl acetate (4:1) as developing solvent. The following fractions were obtained: unreacted **3** (40 mg, m.p. 166–167°); 6-bromo-6-deoxy-α,α-trehalose heptaacetate (**2**) (87 mg) which was recrystallized from chloroform–hexane giving 75 mg (43%) of product, m.p. 117–119°; and α,α-trehalose octaacetate (44 mg), which was recrystallized from ethanol, m.p. 78–80° (needles), [lit.[11] m.p. 99° (hexagons) and m.p. 76–78° (needles)].

6,6'-Dibromo-6,6'-dideoxy-α,α-trehalose (**4**). — To a solution of **3** (0.36 g, 0.5 mmoles) in methanol (75 ml) were added a few drops of a freshly prepared solution of sodium methoxide. The solution was kept overnight at 5° and then neutralized with Dowex-50 (H^+). Filtration and evaporation of the filtrate afforded a chromatographically homogeneous (t.l.c. chloroform–methanol, 10:3) solid in quantitative yield (0.23 g). The product was dissolved in warm ethanol and the amorphous, colorless solid that separated out showed a decomposition point of 155° and $[\alpha]_D^{25}$ +195° (*c* 2.5, methanol). Acetylation of a portion gave the crystalline hexaacetate **3** in high yield.

6,6'-Dibromo-6,6'-dideoxy-α,α-trehalose hexabenzoate (**11**). — To a solution of **4** (0.1 g) in 8 ml of pyridine was added dropwise 0.5 ml of benzoyl chloride at 0° and the solution was kept overnight at ~25°. The reaction mixture was poured slowly into 50 ml of ice–water, the resulting precipitate was filtered off, washed with water, and dried. Crystallization from acetone–ether–pentane gave the title compound (0.25 g, 80%), m.p.111–113° (needles), undepressed when mixed with an authentic sample[9], $[\alpha]_D^{25}$ +218° (*c* 1, chloroform). Recrystallization from acetone–ether–petroleum ether (b.p. 30–60°) gave a dimorphic form of **11**, m.p. 168–169° (cubes); $[\alpha]_D^{25}$ +217° (*c* 1.24, chloroform). Recrystallization of the authentic sample[9] (needles) from the same mixture, and seeding with the new dimorphic form, gave cube-shaped crystals, m.p. 168–169°.

6-Deoxy-α,α-trehalose heptaacetate (**5**). — To a solution of chromatographically

homogeneous **2** (0.175 g,0.25 m moles) in 50 ml of methanol were added 0.15 g of 20% palladium-on-charcoal[15] and 0.2 g of sodium acetate. The mixture was hydrogenated during 24 h at room temperature, at which time t.l.c. (5 × 10 cm plate) of an aliquot indicated complete transformation into the title compound; it gave a green spot when the plate was sprayed with the acidic molybdate reagent[16] and heated at 110°. Filtration of the suspension through a bed of Celite and evaporation of the filtrate gave a solid that was partitioned between 60 ml of dichloromethane and 20 ml of water. Drying and evaporation of the organic phase gave an oil that crystallized on standing; yield 0.125 g (81%), m.p. 84–85°. Two recrystallizations from ethanol gave the pure product, m.p. 88.5–90°, $[\alpha]_D^{25}$ +184.5° (*c* 1.45, chloroform); (lit[5]. m.p. 89–90°, $[\alpha]_D^{25}$ +185° in chloroform); n.m.r. spectral data in accord with literature values[5].

6-Bromo-6-deoxy-α,α-trehalose (**1**). — To a solution of **2** (0.175 g, 0.25 mmole) in methanol (50 ml) were added a few drops of a freshly prepared solution of sodium methoxide and the solution was kept overnight at 5°. Neutralization with Dowex-50 (H^+), filtration, and evaporation of the filtrate afforded a chromatographically homogeneous solid in quantitative yield (0.10 g) that was dissolved in hot ethanol. The amorphous, colorless solid that separated out had m.p. 148–151° and $[\alpha]_D^{25}$ +180.8° (*c* 0.7, methanol). Acetylation of a portion gave the crystalline heptaacetate **2** in high yield.

6,6'-Dideoxy-α,α-trehalose hexaacetate **6**. — A solution containing **3** (0.36 g, 0.5 mmoles), 0.45 g of anhydrous sodium acetate, and 0.37 g of 20% palladium-on-charcoal[15] in 60 ml of methanol was hydrogenated during 30 h. Filtration of the suspension through a bed of Celite and evaporation of the filtrate gave a solid residue that was dissolved in chloroform (80 ml) and the solution was washed with water (3 × 20 ml). The organic phase was dried, filtered, and evaporated to give a solid (0.28 g) that crystallized from ethanol to afford the title compound in two crops; yield 0.24 g (80%), m.p. 195–196°. A second recrystallization from ethanol did not change the m.p.; $[\alpha]_D^{25}$ +209° (*c* 1.2, chloroform) (lit.[8] m.p. 197–198.5°, $[\alpha]_D^{25}$ +106° in chloroform; the discrepancy with the literature rotation remains unexplained).

6-Deoxy-α,α-trehalose (**7**). — To a solution of **5** (1.27 g, 2.05 mmoles) in 125 ml of methanol were added a few drops of a freshly prepared solution of sodium methoxide and the solution was kept overnight at 5°. Neutralization with Dowex-50 (H^+), filtration, and evaporation of the filtrate gave a colorless oil that was dissolved in 10 ml of water. Lyophilization gave **7** as a colorless, chromatographically homogeneous powder in quantitative yield. A sample was dried at 80°/0.02 torr during 12 h and had m.p. 115–117°, $[\alpha]_D^{25}$ +202.9° (*c* 1.2, methanol); [lit.[5] m.p. 116–118°, $[\alpha]_D^{25}$ +116.5° (*c* 0.5, water)]. This compound gave a characteristic greenish color on chromatograms sprayed with the acidic molybdate reagent[16].

6-Deoxy-6-iodo-α,α-trehalose heptaacetate (**8**). — To a cooled and homogeneous solution of anhydrous trehalose (0.684 g, 2 mmoles) and finely powdered triphenylphosphine (1.05 g, 4 mmoles) in 75 ml of *N*,*N*-dimethylformamide was added *N*-iodosuccinimide (0.9 g, 4 mmoles), slowly and with stirring. After 48 h at room

temperature and another 48 h at 50°, the solution was processed as previously described for **2**. The acetylated residue was purified by column chromatography to give the 6,6'-diiodo derivative **9** (82 mg, 5%) and the title compound[11] **8**, yield 0.35 g (21%). Recrystallization of the latter product from isopropyl alcohol gave a pure sample, m.p. 82–83°, $[\alpha]_D^{25}$ +118.1° (*c* 0.65, chloroform); *m/e* 399 $[(C_{12}H_{16}IO_7)^+]$ and m/e 331 $[(C_{14}H_{19}O_9)^+]$; [lit.[11] m.p. 80–82, $[\alpha]_D^{25}$ +121.5 (chloroform)].

Anal. Calc. for $C_{26}H_{35}IO_{17}$: C, 41.83; H, 4.73. Found: C, 42.04; H, 4.70.

6,6'-Dideoxy-6,6'-diiodo-α,α-trehalose hexaacetate (**9**). — To a cooled and homogeneous solution of anhydrous trehalose (0.342 g, 1 mmole) and finely powdered triphenylphosphine (1.05 g, 4 mmoles) in 30 ml of *N,N*-dimethylformamide was added *N*-iodosuccinimide (0.90 g, 4 mmoles), slowly and with stirring. The solution turned red, and it was heated for 50 h at 50°. After the addition of methanol (20 ml) the solution was evaporated in the presence of 1-butanol, and toluene, and then chloroform was repeatedly evaporated from the resulting oil. The residue was dissolved in water (100 ml) and the solution was extracted with chloroform (4 × 20 ml). Processing of the aqueous solution as previously described, followed by acetylation, gave a solid that was purified by column chromatography to give the desired product **9** (0.442 g, 55%). Recrystallization from 30 ml of ethanol gave material having m.p. 197–198° and $[\alpha]_D^{25}$ +90.7° (*c* 1, chloroform); *m/e* 399 $[(C_{12}H_{16}IO_7)^+]$; [lit.[19] m.p. 191–193°, $[\alpha]_D^{19}$ +92.2° (chloroform)].

Anal. Calc. for $C_{24}H_{32}I_2O_{15}$: C. 35.40; H, 3.96. Found: C, 35.48; H, 3.87.

6-Chloro-6-deoxy-α,α-trehalose heptaacetate (**10**). — To a cooled solution of anhydrous trehalose (0.684 g, 2 mmoles) and finely powdered triphenylphosphine (1.05 g, 4 mmoles) in 75 ml of *N,N*-dimethylformamide was added *N*-chlorosuccinimide (0.544 g, 4 mmoles), slowly and with stirring. After stirring for 48 h at ~25° and a further 48 h at 50°, the solution was processed as described for **2** or **8**. Column chromatography of the acetylated product gave the 6,6'-dichloro derivative **12** [20 mg (1,6%), as needles from isopropyl alcohol]; m.p. 165.5–166, $[\alpha]_D^{25}$ +133.3° (*c* 0.12, chloroform), and the title compound **10** (0.175 g, 13%); m.p. 124–125° (from isopropyl alcohol), $[\alpha]_D^{25}$ +147.9° (*c* 0.57, chloroform); *m/e* 309, 307 $[(C_{12}H_{16}ClO_7)^+]$; *m/e* 331 $[(C_{14}H_{19}O_9)^+]$.

Anal. Calc. for $C_{26}H_{35}ClO_{17}$: C, 47.63; H, 5.39. Found: C, 47.78; H, 5.38.

6,6'-Dichloro-6,6'-dideoxy-α,α-trehalose hexaacetate (**12**). — To a cooled solution of anhydrous trehalose (0.684 g, 2 mmoles) and finely powdered triphenylphosphine (2.2 g, 8.1 mmoles) in 60 ml of *N,N*-dimethylformamide, was added *N*-chlorosuccinimide (1.07 g, 8 mmoles), slowly and with stirring. After one h the reaction temperature was raised to 50° and the solution was stirred for 70–75 h. After this period the solution was processed as described previously. Column chromatography of the acetylated product gave 6,6'-dichloro-6,6'-dideoxy-α,α-trehalose hexaacetate (**12**, 0.53 g, 42%); m.p. 165–166° (needles from isopropyl alcohol), $[\alpha]_D^{25}$ +134° (*c* 0.6, chloroform); *m/e* 309, 307 $[(C_{12}H_{16}ClO_7)^+]$.

Anal. Calc. for $C_{24}H_{32}Cl_2O_{15}$: C, 45.65; H, 5.11. Found: C, 45.38; H, 5.00.

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