Carbohydrate Research
Elsevier Publishing Company, Amsterdam
Printed in Belgium

A NEW CHEMICAL SYNTHESIS OF α,α-TREHALOSE

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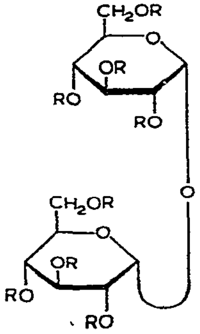
(Received June 7th, 1968; in revised form, July 17th, 1968)

ABSTRACT

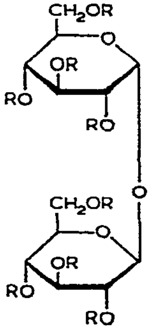
2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose has been treated with 2 equivalents of the corresponding glycosyl chloride under modified Koenigs–Knorr reaction conditions. Hydrogenolysis of the protecting groups of the syrupy product, followed by chromatography on Dowex-1 (HO^-) resin gave α,α-trehalose (α-D-glucopyranosyl α-D-glucopyranoside) and α,β-trehalose (α-D-glucopyranosyl β-D-glucopyranoside) in yields of 18 and 2%, respectively.

INTRODUCTION AND DISCUSSION

α,α-Trehalose[1] (α-D-glucopyranosyl α-D-glucopyranoside) (**1**), one of Nature's "reserve" sugars and the only naturally occurring isomer of the series, has been synthesised, but only in very low yield, by the acid reversion of D-glucose[2,3] and (together with α,β-trehalose) by condensation[4] of Brigl's anhydride with 2,3,4,6-tetra-*O*-acetyl-D-glucose (containing 65% of the α-anomer). Haq and Whelan[5,6] obtained a small proportion of trehalose during the synthesis of nigerose (3-*O*-α-D-glucopyranosyl-D-glucose). Recently[7], both α,α- (**1**) and α,β-trehalose (**2**) were isolated as by-products during the synthesis of some glucosides of glycerol and ribitol.



1 R=H
3 R=Ac



2 R=H
4 R=Ac

The main difficulty encountered in the synthesis of disaccharides of this type lies in specifically obtaining the α-D-glycosidic linkage. It has been shown that α-linked glycosides can be prepared in moderate yield by using per-*O*-benzylated glycosyl chlorides under modified Koenigs–Knorr conditions[7]. Glycosyl chlorides are not normally used in such reactions as they are relatively unreactive[8]. However, it has been demonstrated that removal of the halogen from these compounds by silver ions is much faster, if, instead of depending on the heterogeneous reaction with silver carbonate, a mixture of this salt and a small amount of soluble silver perchlorate is used[9]. The yields of α-D-glycosides[7] indicate that, in the presence of silver perchlorate, the glycosyl chloride largely dissociates into an ion pair[9,10] before reacting with an aglycon. Thus, the configuration of the glycosidic linkage in the product does not depend entirely upon the configuration at the anomeric centre in the chloride.

Under these conditions[7,9], 2,3,4,6-tetra-*O*-benzyl-D-glucose was treated with 2 mol of 2,3,4,6-tetra-*O*-benzyl-D-glucosyl chloride, which appears to be preponderantly the α-anomer[7]. Elution of the crude product from alumina with benzene–ether (20:1) gave a clear syrup, which was hydrogenated over palladium to give material having the same mobility on paper chromatograms as α,α-trehalose. Elution with ether–ethanol (9:1) gave 2,3,4,6-tetra-*O*-benzyl-D-glucose, some of which probably resulted from the hydrolysis of unreacted chloride during the isolation procedure.

Elution of the disaccharide fraction from Dowex-1 (HO^-) resin[11] with water gave α,α-trehalose (**1**), as the dihydrate, and α,β-trehalose (**2**), in yields of 18 and 2%, respectively, which were characterised as the octa-acetates (**3**) and (**4**). No β,β-trehalose seemed to be formed in the reaction.

The above result illustrates further the usefulness of 2,3,4,6-tetra-*O*-benzyl-D-glucosyl chloride–silver carbonate–silver perchlorate in the synthesis of α-D-glucosides which are normally difficult to prepare.

EXPERIMENTAL

I.r. spectra were determined on Nujol mulls. Evaporations were carried out *in vacuo* at 40°. Column chromatography was carried out on alumina (B.D.H. grade) and on Dowex-1 (HO^-) resin (2% cross-linked, 200–400 mesh). T.l.c. was performed on silica gel G (Merck) with benzene–ether (5:3) and detection with 3% ethanolic sulphuric acid at 140°. Light petroleum was the fraction having b.p. 60–80°. Paper chromatography was carried out on Whatman No. 1 paper with the organic phase of butyl alcohol–ethanol–water–conc. ammonia (40:10:49:1)[12], and the descending technique. The periodate–Schiff[13,14] and silver nitrate–sodium hydroxide[15] sprays were used as location reagents.

*Reaction between 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl chloride and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose.* — 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose[7] (3.0 g), silver carbonate[9] (10 g), and Drierite (20 g) were suspended in dry benzene (125 ml), and the mixture was stirred at room temperature in the dark for 18 h. Silver perchlorate (0.35 g), from which several portions (50 ml) of dry benzene had been evaporated, was then added, followed by a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl chloride[7] (3.1 g, 1.0 mol) in dry benzene (100 ml) during 8 h with continuous stirring. All operations were conducted in the dark. Stirring was continued for 24 h, and a further portion (3.1 g, 1.0 mol) of the chloride in dry benzene (100 ml) was added over 4 h. On completion of this final addition, stirring was continued for a further 8 days. The mixture was filtered through "Celite", the inorganic material was washed well with benzene (100 ml), and the combined filtrate and washings washed with water (4 × 250 ml), dried (Na_2SO_4, K_2CO_3), and evaporated. A solution of the resulting syrup (8.09 g) was eluted from alumina (300 g) with benzene–ether (20:1, 1200 ml), and concentration of the eluate gave a clear syrup (1.54 g). Elution with ether—ethanol (9:1), followed by evaporation, gave a thick, semi-crystalline residue which was recrystallized from ether–light petroleum to give 2,3,4,6-tetra-*O*-benzyl-D-glucose (3.47 g), m.p. 148–150°, $[\alpha]_D^{21}$ +20° (*c* 1.7, chloroform); lit.[16], m.p. 148°, $[\alpha]_D^{20}$ +21.2° (chloroform).

The material eluted with benzene–ether (20:1) was hydrogenolysed (310-ml uptake in 27 h) in the presence of palladium (from 2.5 g of the oxide) in ethanol–*p*-dioxane (150 ml, 1:1). Removal of the catalyst and evaporation of the filtrate gave material (0.49 g) which had the same mobility on paper chromatograms as authentic α,α-trehalose (R_G 0.48). It was dissolved in water (2 ml) and applied to a column (40 × 3.5 cm) of Dowex-1 (HO^-) resin; elution was carried out with CO_2-free water, and the eluate was collected in 20-ml fractions. Fractions 12–17 gave, on evaporation, and crystallization of the residue from aqueous ethanol, α,α-trehalose (**1**) as the dihydrate (378 mg, 18%), m.p. 98–105°, $[\alpha]_D^{22}$ +175° (*c* 1.4, water); lit.[4,17], m.p. 97–98°, $[\alpha]_D^{20}$ +178°; *cf.* β,β-trehalose[18], m.p. 135–140°, $[\alpha]_D^{17}$ −40°. With acetic anhydride–anhydrous sodium acetate, in the usual manner, compound **1** gave the known octa-acetate (**3**), m.p. and mixed m.p. 98–100°, $[\alpha]_D^{22}$ +160° (*c* 1.1, chloroform); lit.[4], m.p. 101°, $[\alpha]_D^{20}$ +163°.

Fractions 20–26 contained α,β-trehalose (**2**, 42 mg, 2%) which, after recrystallization from aqueous ethanol, had m.p. 138–145°, $[\alpha]_D^{22}$ +93° (*c* 0.78, water); lit.[19], m.p. 145–150°, $[\alpha]_D$ +95°. Acetylation as above gave the octa-acetate (**4**), m.p. and mixed m.p. 140–142°, $[\alpha]_D^{22}$ +84.5° (*c* 0.68, chloroform); lit.[19], m.p. 140–141°, $[\alpha]_D$ +85°.

On t.l.c., compounds **3** and **4** had R_F values (0.155 and 0.205, respectively) that were identical with those of the authentic compounds.

ACKNOWLEDGMENTS

The author thanks Dr. P. W. Austin for gifts of 2,3,4,6-tetra-*O*-benzyl-D-glucose and authentic samples of α,α- and α,β-trehalose octa-acetates, and Dr. J. G. Buchanan for helpful discussion.

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