

## SOME OBSERVATIONS ON THE SYNTHESIS OF SOPHOROSE

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## ABSTRACT

Condensation of tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl bromide with 1,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-glucopyranose in acetonitrile solution containing mercuric cyanide and mercuric bromide affords the octa-acetates of both kojibiose (2-*O*- $\alpha$ -D-glucopyranosyl-D-glucose) and sophorose (2-*O*- $\beta$ -D-glucopyranosyl-D-glucose). Each of these products can be isolated in approximately 28% yield. Although this method results in a lower over-all yield of sophorose from D-glucose than an alternative procedure, it has the advantage of being more rapid and direct, and is particularly well-suited to preparation of the acetylated glycosyl bromide.

## INTRODUCTION AND DISCUSSION

Previous authors<sup>1-3</sup> have employed the Koenigs-Knorr procedure for the synthesis of sophorose (2-*O*- $\beta$ -D-glucopyranosyl-D-glucose). The original method<sup>1</sup> involved condensation of methyl 4,6-*O*-benzylidene- $\alpha$ -D-glucopyranoside with tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl bromide to form methyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl)- $\alpha$ -D-glucopyranoside. The free sugar was only obtained from this compound *via* a series of intermediate derivatives, and the over-all yield of sophorose was less than 5%. A 65% yield of sophorose octa-acetate was obtained<sup>2</sup> by condensation of 1,3,4,6-tetra-*O*-acetyl-D-glucose with tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl bromide. More recently, a modification<sup>3</sup> of the Freudenberg procedure<sup>1,4</sup> gave a 30% yield of crystalline sophorose from the benzylidene compound.

The 1,3,4,6-tetra-*O*-acetyl-D-glucose employed by Gakhokidze<sup>2</sup> would appear to be the inaccessible  $\beta$ -anomer. However, 1,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-glucose can be readily prepared<sup>5</sup>, and a simple and direct synthesis of sophorose from this compound therefore appeared possible. Condensation with tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl bromide was carried out by the improved<sup>3</sup> Koenigs-Knorr procedure, but t.l.c. revealed that only a small amount of disaccharide was formed. This was recovered, in 3-5% yield, as the relatively insoluble and readily crystallizable glycosyl bromide hepta-acetate (" $\alpha$ -acetobromosophorose"). Contrary to expectation and to the findings of Gakhokidze<sup>2</sup>, use of the anomeric tetra-*O*-acetyl- $\beta$ -D-glucose gave

essentially the same results. No  $\beta$ -sophorose octa-acetate could be crystallized from the reaction mixture, and bromination did not lead to a higher yield of  $\alpha$ -acetobromosophorose. Control experiments with methyl 4,6-*O*-benzylidene- $\alpha$ -D-glucopyranoside always gave the expected product in the reported<sup>3</sup> 40% or higher yield.

In view of the above results, further experiments were directed towards a synthesis of sophorose by the method of Helferich and Zirner<sup>6</sup>, involving reaction in the presence of mercuric cyanide and mercuric bromide in acetonitrile solution. Reaction under these conditions has been reported<sup>6</sup> to result in the formation of the  $\alpha$ -octa-acetate of kojibiose (2-*O*- $\alpha$ -D-glucopyranosyl-D-glucose), which was isolated in 21% yield. However, as condensation proceeds *via* an intermediate glycosyl cation formed by loss of halogen from the acetylated glycosyl halide, formation of both  $\alpha$ - and  $\beta$ -D-glycosides must be considered possible<sup>6</sup>. Examination by t.l.c. of the reaction mixture from the condensation of 1,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-glucopyranose and tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl bromide under the exact conditions of Helferich and Zirner<sup>6</sup> revealed that two major products, differing only slightly in chromatographic behaviour, were formed.  $\alpha$ -Kojibiose octa-acetate crystallized from ethanolic solution in the expected 21% yield, and bromination of the dry residue from the mother liquor led to the isolation of  $\alpha$ -acetobromosophorose in 25% yield. Modification of the reaction conditions, by employing a 30% excess of glycosyl halide instead of the molar equivalent and extending the reaction period from 2 to 6 h, increased the yield of  $\alpha$ -kojibiose octa-acetate to 27.6% and that of  $\alpha$ -acetobromosophorose to 31.3%. The non-crystalline  $\alpha$ -sophorose octa-acetate could also be converted *via* the bromide to the  $\beta$ -octa-acetate which was isolated in an over-all yield from D-glucose of 28.2%. Deacetylation of this compound gave  $\alpha$ -sophorose monohydrate in 62.8% yield. Since pure 1,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-glucopyranose can be prepared from D-glucose in 28% yield<sup>5,6</sup>, the over-all yield of sophorose from D-glucose is calculated to be 4.96%. Sophorose can also be prepared by direct deacetylation of the  $\alpha$ -octa-acetate in the kojibiose mother liquor, the yield in this case being slightly lower (4.27% from D-glucose) owing to the presence of various impurities which interfere with crystallization. If it is considered that methyl  $\alpha$ -D-glucopyranoside can be prepared in 50% yield from D-glucose<sup>7</sup> and that the yield<sup>8</sup> of the 4,6-*O*-benzylidene derivative from the methyl glycoside is 70%, the over-all yield of sophorose from D-glucose by the method of Coxon and Fletcher<sup>3</sup> is 10.5%. However, despite the lower yield by the Helferich and Zirner procedure<sup>6</sup>, its directness and simplicity make it the method of choice. In addition, the acetylated glycosyl halide is of particular value for the synthesis of glycosides, and this compound is very readily preparable by the latter procedure.

#### EXPERIMENTAL

All m.ps. are uncorrected and were determined by the Kofler method. Merck Kieselgel G was employed for t.l.c., with 15% (v/v) methanol in benzene as irrigant and sulphuric acid as spray reagent.

*1,3,4,6-Tetra-O-acetyl-2-O-(2,3,4,6-tetra-O-acetyl- $\alpha$ -D-glucopyranosyl)- $\alpha$ -D-glucopyranose ( $\alpha$ -kojibiose octa-acetate).* — 1,3,4,6-Tetra-O-acetyl- $\alpha$ -D-glucopyranose<sup>6</sup> (1.75 g) was dissolved in a solution of mercuric cyanide (0.64 g) and mercuric bromide (0.90 g) in acetonitrile (14 ml), and 2,3,4,6-tetra-O-acetyl- $\alpha$ -D-glucopyranosyl bromide (2.75 g) was added. After 6 h at room temperature, the solvent was evaporated, and the residue was treated with chloroform (50 ml). The filtered extract was washed with aqueous M potassium bromide (3  $\times$  10 ml) and water (2  $\times$  20 ml). The chloroform was evaporated, and the residue was crystallized from ethanol to yield  $\alpha$ -kojibiose octa-acetate (0.94 g, 27.6%), m.p. 168–169°,  $[\alpha]_D^{22} + 153.2^\circ$  (c 2.5, chloroform); lit.<sup>6</sup>, m.p. 168–168.5°,  $[\alpha]_D^{18} + 152.5^\circ$  (chloroform).

*3,4,6-Tri-O-acetyl-2-O-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyl)- $\alpha$ -D-glucopyranosyl bromide ( $\alpha$ -acetobromosophorose).* — The ethanolic mother liquor from the preparation of  $\alpha$ -kojibiose octa-acetate was evaporated to dryness, and the residue was dissolved in dichloromethane (2 ml) and treated with a solution of 40% hydrogen bromide in glacial acetic acid (15 ml) for 20 min at room temperature. The solution was diluted with chloroform (75 ml), washed with iced water, saturated aqueous sodium hydrogen carbonate, and water until the washings were neutral to litmus, filtered through anhydrous sodium sulphate, and evaporated to dryness at 30°. Crystallization of the residue from dichloromethane–ether yielded  $\alpha$ -acetobromosophorose (1.1 g, 31.3%), m.p. 189–191°,  $[\alpha]_D^{26} + 97.7^\circ$  (c 1.6, chloroform); lit.<sup>3</sup>, m.p. 190–191°,  $[\alpha]_D^{20} + 97.4^\circ$  (chloroform).

*1,3,4,6-Tetra-O-acetyl-2-O-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyl)- $\beta$ -D-glucopyranose ( $\beta$ -sophorose octa-acetate).* — The chloroform solution of crude  $\alpha$ -acetobromosophorose, prepared as described above, was evaporated to dryness at 30° and treated with a solution of mercuric acetate (3.0 g) in glacial acetic acid (40 ml) for 2 h at room temperature. The solution was diluted with chloroform (150 ml), washed with water (4  $\times$  50 ml), and evaporated to dryness. Crystallization of the residue from ethanol afforded  $\beta$ -sophorose octa-acetate (0.96 g, 28.2%), m.p. 191–192°,  $[\alpha]_D^{22} - 3.5^\circ$  (c 2.5, chloroform); lit.<sup>4</sup>, m.p. 192°,  $[\alpha]_D^{20} - 4^\circ$  (chloroform).

*2-O- $\beta$ -D-Glucopyranosyl- $\alpha$ -D-glucopyranose ( $\alpha$ -sophorose).* —  $\beta$ -Sophorose octa-acetate (0.96 g) in absolute methanol (10 ml) was treated with 1.2% methanolic sodium methoxide (6 ml) for 30 min at room temperature. The solution was adjusted to pH 7.0 with dilute hydrochloric acid, desalted electrolytically (Shandon Mark II desalter), and evaporated almost to dryness at 35°. The residue was crystallized from aqueous ethanol–ether to yield  $\alpha$ -sophorose monohydrate (0.32 g, 62.8%), m.p. 195–197°,  $[\alpha]_D^{22} + 33.6 \rightarrow + 19.0^\circ$  (equil.; c 3.2, water); lit.<sup>9</sup>, m.p. 196–198°,  $[\alpha]_D^{18} + 19^\circ$  (equil., water).

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