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Action of Strong Acids on Acetylated Glycosides

VIII *. A New Synthesis of Melibiose

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Melibiose, or 6-glucose α-galactopyranoside, has been prepared by Helferich and Bredereck [1] by the action of galactose bromide tetraacetate upon 1,2,3,4-glucose tetraacetate with quinoline as condensing agent. From these same carbohydrate derivatives, but using silver carbonate as condensing agent, Helferich and Rauch [2] obtained another disaccharide, different from melibiose. As β-galactosides are the usual products when the Koenigs-Knorr synthesis is applied to galactose bromide tetraacetate, these results indicated that melibiose had an α-glycosidic structure. Helferich and Bredereck [1] also condensed galactose bromide tetraacetate with phenol in the presence of quinoline, and were able to isolate phenyl α-galactoside from the reaction mixture.

Melibiose is structurally related to *iso*-maltose, 6-glucose α-glucopyranoside. The latter disaccharide has been prepared from the corresponding β-glucoside, gentiobiose, by transglycosidation (Part V [3]). As the transglycosidation reaction has been successfully performed in the galactose series (Part VI [4]), it seemed possible that melibiose might be prepared from the 6-glucose β-galactoside mentioned above. This synthesis has now been carried out, by the same procedure as was employed for the synthesis of *iso*-maltose. The β-glycosidic disaccharide, in the form of the octaacetate, was treated with titanium tetrachloride in chloroform. In the reaction product, a mixture of disaccharide chloride heptaacetates, the chlorine was replaced by acetoxyl with the aid of mercuric acetate in acetic acid. From the resulting mixture a small amount of almost pure β-melibiose octaacetate could be isolated by successive recrystallizations. Helferich and Bredereck had considerable difficulty in obtaining the

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melibiose octaacetate in a pure state. This was probably due to the fact that β-melibiose octaacetate and β-6-glucose β-galactoside octaacetate have rather similar solubilities and crystallization tendencies and therefore are not easily separated. In the present case there is a further complication, due to the strongly acidic nature of the catalyst, titanium tetrachloride.

It is known that in the presence of aluminium chloride, also a strong acid, the octaacetates of cellobiose and lactose are partly isomerized into other disaccharides [5], two of which, celtrobiose and neolactose, have been isolated. In these cases the glycosidically linked glucose unit has been transformed into the altrose configuration. Now titanium tetrachloride, although not so strong an acid as aluminium chloride (at least it is not as active when used as catalyst in the Friedel-Crafts synthesis [6]), might also be able to catalyze this isomerization; there are moreover no reasons why the effect should be restricted to lactose and cellobiose.

It is in fact reasonable to assume that the acetates of all reducing saccharides, at least those in which the reducing part of the molecule is a glucose unit, may undergo this type of isomerization in the presence of aluminium chloride or titanium tetrachloride. This would be a most undesirable reaction in the synthesis of α-glycosidic saccharides, and it may well be responsible for the low yields obtained in the synthesis of *iso*-maltose and melibiose.

EXPERIMENTAL

β-Melibiose octaacetate

To a solution of β-6-glucose β-galactoside octaacetate (2.3 g) in anhydrous chloroform (70 ml), titanium tetrachloride (3 g) was added. A yellow precipitate was formed, which did not dissolve when the mixture was refluxed for four hours on a glycerol bath, kept at 70°. After cooling, the mixture was poured into ice water (400 ml), whereupon the precipitate dissolved and the chloroform phase became almost colorless. The latter was separated, washed with water, dried over calcium chloride and concentrated to a sirup under reduced pressure. This sirup, together with mercuric acetate (2 g), was dissolved in acetic acid (20 ml) and kept at room temperature. After four hours the solution was poured into ice water (250 ml) and extracted with chloroform (2 × 30 ml). The chloroform solution was washed with sodium carbonate and water, dried over calcium chloride and concentrated under reduced pressure. The residual sirup was dissolved in methanol (5 ml) and the solution kept at 0°, when crystals slowly separated. Three crops of somewhat sticky crystals (total yield 0.95 g), melting between 140—150° and showing $[\alpha]_D^{20}$ + 50° (chloroform, c = 2), were collected. The first crop (0.25 g) was subjected to successive recrystallizations from methanol, and after eight such operations, the product had m. p. 171—172° (uncorr.) and $[\alpha]_D^{20}$ + 100°. One further recrystallization did not change these values. An authentic sample of β-melibiose octaacetate melted at 173—174° and showed $[\alpha]_D^{20}$ + 102°; an admixture with the synthetic product melted at 172—173°. As only a

small amount (25 mg) of the synthetic material remained after the final recrystallization, further purification was not attempted. The specific rotation and melting point values, however, showed that it was substantially pure β-melibiose octaacetate.

SUMMARY

β-Melibiose octaacetate has been prepared from β-6-glucose β-galactoside octaacetate by the transglycosidation method.

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