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ACTION OF TITANIUM TETRACHLORIDE ON DERIVATIVES OF SUGARS. II. PREPARATION OF TETRA-ACETYL-BETA-NORMAL-HEXYLGLUCOSIDE AND ITS TRANSFORMATION TO THE ALPHA FORM[1,2]

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One of the difficulties which restricts the range of synthetical operations in the sugar series may be seen in the comparative inaccessibility of glycosides of the alpha configuration. No method has hitherto been described, that is, of general applicability in preparing such derivatives and most of the methods yield a product which is greatly contaminated by the isomeric beta form or other substances. A review of the literature shows that four methods have been proposed. The earliest of these was due to Emil Fischer,[3] who heated the reducing sugar with an alcohol in the presence of hydrogen chloride. Carried out, as this procedure was, with an acid medium and at an elevated temperature, it was obviously unsuitable for use with the compound reducing sugars and it also possessed the disadvantage of yielding from the simple sugars (except in the case of mannose) an equilibrium mixture of alpha and beta glycosides. Moreover, while Fischer obtained satisfactory results with alcohols of low molecular weight, the method was not applicable when the hydroxyl group to be esterified was attached to a long aliphatic chain or was of a phenolic nature. Another means of synthesizing alpha glycosides was discovered by the present author,[4] who found that the mercaptals of various monosaccharides yield these derivatives when decomposed by mercuric chloride dissolved in the appropriate alcohol. Like the method of Fischer, however, this also is restricted to the monosaccharides in its application, because the production of the mercaptals depends upon the interaction of a reducing sugar and a thioalcohol in strongly acid solution and mercaptals of the compound sugars obviously cannot be prepared in this way because of hydrolysis. Bourquelot and his co-workers[5] studied the action of the enzyme alpha glucosidase, present in yeast, and were able to show that it is capable of synthesizing alpha glycosides from a dilute alcoholic solution of certain reducing sugars. Their observations do not appear to have been developed into a method of practical importance and the same remark may be made con-

[1] Publication authorized by the Director of the Bureau of Standards, U. S. Department of Commerce.

[2] Part I was published in *Ber.*, **61**, 1508 (1928).

[3] Fischer, *ibid.*, **26**, 2400 (1893).

[4] Pacsu, *ibid.*, **58**, 509 (1925).

[5] Bourquelot and Verdon, *J. pharm. chim.*, [7] **8**, 19 (1913).

cerning the well-known synthesis of acetylated beta glycosides by Koenigs and Knorr[6] as modified by Fischer and Mechel[7] for the preparation of the alpha isomerides. The latter authors in some cases used quinoline, instead of silver oxide or carbonate, to neutralize the hydrobromic acid liberated when the aceto-halogeno sugar reacted with an alcohol and under these conditions obtained a mixture of both forms. The difficulty of separating the alpha and beta isomers seems to be responsible for the fact that the modified method has not come into general use.

A recent article by the present writer[8] described some experiments which were made with glucose β-penta-acetate and with tetra-acetyl-β-methyl-glucoside. These were allowed to interact, respectively, under various conditions of temperature and time, with equimolecular quantities of stannic chloride in chloroform and it was found that this reagent was capable of slowly transforming both the β-penta-acetate and the tetra-acetyl-β-methylglucoside into the corresponding alpha forms. Part I[2] of the present research describes the improvement that was observed when titanium tetrachloride was substituted for the stannic salt first used. Although the new reagent far excelled the old in promoting the same transformation, the mechanism of the reaction appeared to be essentially different in the two cases, for a yellow addition compound that was insoluble in chloroform was immediately produced when titanium tetrachloride was added to the solution of the glucose derivative. This phenomenon did not occur when stannic chloride was employed. Tetra-acetyl-α-methylglucoside was readily obtained in excellent yield by the improved method but it was worthy of note that glucose α-penta-acetate and similar substances underwent a secondary change and were smoothly transformed to the corresponding α-acetochloro sugars. Indeed, the use of titanium tetrachloride furnished in this way a means of preparing the latter derivatives that is as convenient as any that were previously known. This secondary reaction was also brought about by stannic chloride, though with much greater difficulty.

In view of the importance of acquiring a general method for preparing alpha glycosides of the reducing sugars, and having regard to the promising nature of the experiments of which a résumé has been given, the action of titanium tetrachloride upon the fully acetylated sugars and beta glycosides has been made the subject of further study. It seems necessary to submit suitable derivatives of the mono- and disaccharides to the action of the inorganic chloride in order to test the generality of the reaction. The present article forms a part of this general plan of research and describes the synthesis of tetra-acetyl-α-n-hexylglucoside from tetra-acetyl-β-n-

[6] Koenigs and Knorr, *Ber.*, **34**, 957 (1901).

[7] Fischer and Mechel, *ibid.*, **49**, 2814 (1916).

[8] Pacsu, *ibid.*, **61**, 137 (1928).

hexylglucoside by means of titanium tetrachloride. As the sugar residue in this particular glucoside is attached to an unbranched chain of six carbon atoms, the glucosidic linkage is probably somewhat similar in its reactivity to that which occurs in many disaccharides and the investigation may be regarded as a preliminary step in the development of this field.

Koenigs and Knorr's method was used to prepare tetra-acetyl-β-*n*-hexylglucoside from acetobromoglucose and *n*-hexyl alcohol. This acetylated glucoside, which is a new substance, is a crystalline solid melting at 51.5° and having a specific levo-rotation in chloroform of $[\alpha]_D^{20}$ −19.9° when pure. Although stable to Fehling's solution, it is very easily hydrolyzed by dilute acids and even by steam when in a neutral medium. The fatty character of the aglycon (*i. e.*, non-sugar component) dominated its physical properties and it quickly dissolved in all the common organic solvents, including even petroleum ether. It was insoluble in water.

In order to obtain the alpha form of tetra-acetyl-*n*-hexylglucoside, it was sufficient to heat the pure beta isomer with an equimolecular quantity of titanium tetrachloride in the presence of chloroform, as described in the experimental part. Control of the duration of heating was found to be quite important. When seventy-five minutes had elapsed, ice water was used to decompose the yellow solution. Both the water and the chloroform immediately became colorless and tetra-acetyl-α-*n*-hexylglucoside was recovered from the latter solvent by standard processes as a crystalline solid of m. p. 61° and with a specific dextro-rotation of $[\alpha]_D^{20}$ +116.5° in chloroform, after purification. The yield was 83% of the theoretical. The substance resembled the beta isomer in its solubilities and in its ready hydrolysis.

Although analysis showed that the new compound possesses the expected composition, the possibility remained that a change in the ring structure or stereochemical configuration, accompanied by a wandering of the acetyl groups, might have occurred during its preparation from tetra-acetyl-β-*n*-hexylglucoside. This question was examined in the following way. Hudson[9] has shown that it is permissible to regard the molecular rotation of a pair of acetylated glucosides possessing the same oxide bridge linking as composed of two quantities A and B, where A is the rotation due to the first asymmetric carbon atom of the sugar chain and B refers to the remainder of the glucose molecule. The latter portion, B, is independent of the particular pair of acetylated glucosides considered and has the value $B = +20{,}350$ in chloroform.[10] Writing the molecular rotation of the beta form of tetra-acetyl-*n*-hexylglucoside (mol. wt. 432) as $-A + B = (-19.9)(432) = -8597$ and subtracting the value of B gives $A = +28{,}947$ and hence $A + B = +49{,}297$. The last figure is the calculated molecular

[9] Hudson, THIS JOURNAL, **31**, 66 (1909).

[10] Hudson and Dale, *ibid.*, **37**, 1264 (1915).

rotation of a tetra-acetyl-α-*n*-hexylglucoside similar in ring structure to the original beta form. The calculated specific rotation $[\alpha]_D$ of the compound is accordingly 49,297/432 = +114° in chloroform. The close agreement between this computed value and that found by experiment for tetra-acetyl-α-*n*-hexylglucoside (+116.6°) furnishes definite proof that the alpha and beta forms of tetra-acetyl-*n*-hexylglucoside have like ring structures and, further, that this ring is the same as the ring of the alpha and beta forms of normal tetra-acetyl-methylglucoside. The last conclusion follows from the fact that the value of B used in the calculation is derived from the rotations of the normal tetra-acetyl-methylglucosides. It has recently been shown by Hudson[11] that the ring here referred to is of the 1,5 type.

Experimental

Preparation of Tetra-acetyl-β-*n*-hexylglucoside.—A solution of 30 g. of acetobromoglucose and 50 g. of pure *n*-hexyl alcohol in 500 cc. of absolute ether was shaken for five hours at room temperature with 18 g. of freshly prepared dry silver oxide. After the removal of the insoluble silver salts, the ethereal solution was evaporated under reduced pressure to a sirup, which was submitted to a steam distillation. The operation was cut short at the end of three hours, although the presence of a few oily drops in the distillate falling from the condenser showed that the excess of insoluble hexyl alcohol had not entirely passed into the receiver. The slight instability of the glucoside under the experimental conditions rendered this course advisable. A yellow sirup now lay underneath the water in the distilling flask. It was taken up in 250 cc. of ether and the solution was washed with dilute aqueous potassium bicarbonate solution and then twice with water, after which it was dried over anhydrous calcium chloride and evaporated under diminished pressure. The residue quickly crystallized and yielded about 15 g. of tetra-acetyl-β-*n*-hexylglucoside. Decolorizing carbon, used at room temperature, withdrew all the coloring matter from a solution of the crude product in petroleum ether and the acetylated glucoside then crystallized from the colorless filtrate on standing at 0° in the form of long prismatic needles of m. p. 51.5° and of specific levo-rotation $[\alpha]_D^{20}$ −19.3° in chloroform. After a second recrystallization from petroleum ether the substance showed $[\alpha]_D^{20}$ −19.9°, which is accepted as the rotation of the pure substance (0.4311 g. subs. in 25 cc. of $CHCl_3$ solution rotated 0.685° to the left in a 2-dm. tube).

In an acetyl estimation, made by the method of Kunz,[12] 0.4840 g. was dissolved in 50 cc. of pure acetone to which 103.8 cc. of 0.1 N potassium hydroxide was subsequently added. The acetylated glucoside neutralized 44.8 cc. of decinormal alkali, in excellent agreement with the calculated value of 44.78 cc.

Tetra-acetyl-α-*n*-hexylglucoside from Tetra-acetyl-β-*n*-hexylglucoside.—A solution of 1.9 g. of titanium tetrachloride in 50 cc. of absolute chloroform[13] was added to 4.3 g. of tetra-acetyl-β-*n*-hexylglucoside dissolved in 100 cc. of the same solvent. This mixture immediately became lemon-yellow in color although it remained clear, from which fact it is inferred that the addition product of this acetylated glucoside with titanium chloride is more soluble in chloroform than the compounds previously studied

[11] Hudson, THIS JOURNAL, **52,** 1680 (1930).

[12] Kunz and Hudson, *ibid.*, **48,** 1982 (1926).

[13] The chloroform used in this and the following experiments was pure U. S. P. chloroform which had been twice extracted with water, dried with anhydrous calcium chloride and distilled from phosphorus pentoxide.

(see the introduction). The solution was boiled gently for seventy-five minutes on a water-bath in a flask closed by a reflux condenser provided with a calcium chloride drying tube. No noticeable color change occurred during this operation and when it was over the liquid was poured into a separatory funnel containing ice water. After shaking, both the chloroform and water layers became colorless. The chloroform solution was washed with a dilute potassium bicarbonate solution and then thrice with water, after which it was dried with calcium chloride. Tetra-acetyl-α-n-hexylglucoside remained in the organic solvent and was isolated by concentrating the solution under reduced pressure to a sirup, which was dissolved in cold petroleum ether and purified with carbon at room temperature. The colorless solution was then concentrated under reduced pressure to a sirup, which soon crystallized when kept in the ice box and yielded after one day 3.6 g. of the fairly pure glucoside acetate. The recrystallization from about 100 cc. of petroleum ether in the ice box occupied several days and yielded 3.2 g. of long prismatic needles, melting sharply at 61° and having a specific dextrorotation in chloroform of $[\alpha]_D^{20}$ +116.6° (0.7345 g. in 25 cc. of $CHCl_3$ solution rotated 6.85° to the right in a 2-dm. tube). A second recrystallization from petroleum ether caused no significant change in this value of the specific rotation, which is accordingly accepted as correct for tetra-acetyl-α-n-hexylglucoside in chloroform solution.

An acetyl estimation was carried out by the method previously indicated, allowing three hours for the reaction; 0.4762 g. of the substance required 44.3 cc. of 0.1 *N* potassium hydroxide whereas the value calculated for tetra-acetyl-*n*-hexylglucoside is 44.1 cc.

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Summary

Tetra-acetyl-β-n-hexylglucoside, which has not been described before, was found to be a crystalline substance melting at 51.5° and having a specific levo-rotation in chloroform of $[\alpha]_D^{20}$ −19.9°. Under the influence of titanium tetrachloride in chloroform solution the substance was readily isomerized to the alpha form, which was isolated in 83% yield as a crystalline solid, m. p. 61° and $[\alpha]_D^{20}$ +116.6° in chloroform.

It follows that the action of titanium chloride in promoting the transformation of acetylated beta glycosides to their alpha isomers is not inhibited by the presence of a straight chain of six carbon atoms in the non-glucosidic portion of the molecule. Indeed, the hexylglucoside acetate is rearranged even more rapidly than the methylglucoside acetate. The sum of the rotations of the alpha and beta forms of tetra-acetyl-*n*-hexylglucoside conforms with Hudson's second isorotation rule and the rotation of either form may be calculated fairly accurately from that of the other, in conjunction with the rotations of the alpha and beta forms of tetra-acetyl-methylglucoside. The rotations of the two new substances thus show that they possess the same oxidic ring and that this ring is the ring of the known tetra-acetyl-methylglucosides, which has been found recently by Hudson to be of the 1,5 type.

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