[CONTRIBUTION FROM THE POLARIMETRY SECTION, BUREAU OF STANDARDS, UNITED STATES DEPARTMENT OF COMMERCE]

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

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In the preceding article the employment of titanium tetrachloride for the synthesis of acetylated alpha glycosides was extended from the case of α-methylglucoside tetra-acetate, previously studied,[3] to that of tetra-acetyl-α-*n*-hexylglucoside. Cyclohexylglucoside may be regarded as very similar to the same derivative of *n*-hexyl alcohol, indeed, as having been formed from it by the removal of one hydrogen atom from each end of the carbon chain and closure of the ring by the valences so set free. On the other hand, cyclohexanol is the simplest member of the hydro-aromatic alcohols, the beta glycosides of many of which are known, while only one representative of the corresponding alpha forms (α-*l*-menthyl-*d*-glucoside)[4] has yet been prepared. The present paper describes the rearrangement of tetra-acetyl-β-cyclohexylglucoside to tetra-acetyl-α-cyclohexylglucoside by means of titanium tetrachloride in chloroform, the isolation of the pure substance and its conversion to the alpha glucoside by de-acetylation.

Having prepared the acetylated beta glucoside by the directions of Fischer and Helferich[5] but on a somewhat larger scale, the pure compound was found to melt at 120–121° and to have a specific rotation of $[\alpha]_D^{20}$ $-23.8°$ in chloroform; the values found by the former workers are m. p. 120–121° and $[\alpha]_D^{22}$ $-29.74°$ in alcohol. As was expected, titanium chloride readily rearranged the compound to tetra-acetyl-α-cyclohexylglucoside, but trial experiments showed that it was very necessary to restrict the action of the reagent closely to seventy-five minutes under the conditions employed. Unless this was done, the golden yellow color of the chloroform solution quickly changed to deep red and the product decomposed. Pure crystalline tetra-acetyl-α-cyclohexylglucoside has a low melting point, 40–41°, a specific rotation of $[\alpha]_D^{20}$ $+121.7°$ in chloroform and is easily distinguished from the beta isomer by its ready solubility in petroleum ether, in which solvent the beta form is nearly insoluble.

As has been mentioned, relatively few alpha glucosides are available for

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[2] Part II was published in THIS JOURNAL, **52,** 2563 (1930).

[3] Pacsu, *Ber.*, **61,** 1508 (1928).

[4] Fischer and Bergmann, *ibid.*, **50,** 711 (1917).

[5] Fischer and Helferich, *Ann.*, **383,** 68 (1911).

study and the opportunity was therefore taken to de-acetylate tetra-acetyl-α-cyclohexylglucoside and so add another member to the series. The new compound, α-cyclohexylglucoside, crystallized from acetone, melted at 126° and had a specific dextro-rotation in aqueous solution of $[\alpha]_D^{20}$ +133.2° after careful purification. It was very bitter in taste.

In order to show that the action of titanium chloride on tetra-acetyl-β-cyclohexylglucoside was restricted to the terminal asymmetric carbon atom of the glucosidic chain, the specific rotations of α-cyclohexylglucoside and its tetra-acetate were calculated from those of the corresponding beta isomers by the second isorotation rule of Hudson as described in detail in Part II for a similar case. The data for the comparisons are recorded in the following table, those for β-cyclohexylglucoside being quoted from Fischer and Helferich. Let it be assumed that the ring of β-cyclohexylglucoside is 1,5, as in the methylglucosides, and that the second rule of isorotation holds for the new glucosides. The value of B is obtained from Riiber's[6] recent measurements of the rotations of the methylglucosides ($[M]_D$ = 30,830 and −6630) as (30,830 − 6600)/2 = 12,100, and the value of A is then obtained from the rotation of β-cyclohexylglucoside as 12,100 + 10,850 = 22,950. The rotation of the α-cyclohexylglucoside is then calculated to be $[\alpha]_D$ = (12,100 + 22,950)/262 = 134, in excellent agreement with the observed value (133.2). Similarly, in the case of the tetra-acetates of these glucosides, B' = 20,350[7] and A' = 20,350 + 10,230 = 30,580; the rotation of tetra-acetyl-α-cyclohexylglucoside is then calculated to be $[\alpha]_D$ = (20,350 + 30,580)/430 = 118, which is quite near the observed value (121.7). These two agreements between theory and observation prove that the cyclohexylglucosides and their tetra-acetates possess the same ring as the methylglucosides, namely, 1,5, as allocated recently by Hudson.[8]

TABLE I

ROTATIONS OF THE PURE ALPHA AND BETA CYCLOHEXYLGLUCOSIDES (MOL. WT. 262) AND THEIR TETRA-ACETATES (MOL. WT. 430)

Compounds	M. p., °C.	$[\alpha]_D$	$[M]_D$	Solvent
α-Cyclohexyl-*d*-glucoside	126	133.2	$+34{,}900 = +A + B$	H_2O
β-Cyclohexyl-*d*-glucoside	133–137	−41.4	$-10{,}850 = -A + B$	H_2O
Tetra-acetates of				
α-Cyclohexyl-*d*-glucoside	40–41	121.7	$+52{,}330 = +A' + B'$	$CHCl_3$
β-Cyclohexyl-*d*-glucoside	120–121	−23.8	$-10{,}230 = -A' + B'$	$CHCl_3$

Experimental

Tetra-acetyl-β-cyclohexylglucoside.—Sixty grams of acetobromoglucose, 800 cc. of absolute ether, 200 g. of pure cyclohexanol and 30 g. of dry freshly prepared silver oxide were allowed to react as described by Fischer and Helferich.[5] The crude producr

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[6] Riiber, *Ber.*, **57**, 1797 (1924).

[7] Hudson and Dale, THIS JOURNAL, **37**, 1264 (1915).

[8] Hudson, *ibid.*, **52**, 1680 (1930).

weighed 42 g. and was twice recrystallized from hot alcohol before its rotation became constant at the value $[\alpha]_D^{20}$ −23.8° in chloroform (1.326 g. in 25 cc. of solution gave a reading of 2.53° to the left in a 2-dm. tube). This determination, together with the melting point of 120–121°, was accepted as referring to the pure compound.

Transformation of Tetra-acetyl-β-cyclohexylglucoside to the New Isomeric Alpha Form.—A solution of 13.5 g. of titanium tetrachloride in absolute chloroform[9] was added to a solution of 30 g. of tetra-acetyl-β-cyclohexylglucoside in 350 cc. of the same solvent at room temperature, whereupon the mixture assumed a golden yellow color and became perceptibly warm. The reaction was hastened by boiling the solution gently under a reflux condenser in the absence of atmospheric moisture, and experience showed that the transformation was practically complete after seventy-five minutes. Ice water removed the inorganic constituents from the cooled liquid and also caused its deep yellow color instantly to disappear, leaving a colorless chloroform solution which was washed with aqueous potassium bicarbonate and thrice with water and then dried over anhydrous calcium chloride and evaporated under reduced pressure. The residual sirup (29 g.) soon crystallized and the crude acetylated glucoside which was extracted from it by cold petroleum ether was allowed to crystallize in the ice box from the extract after the latter had been filtered through carbon. Four days later the long needles or star-like clusters of stout prisms were isolated, preferably in a cool room on account of their low melting point, and were stored in an evacuated desiccator. The yield of the once recrystallized substance was 80% of the theoretical (24 g.). Its specific rotation was $[\alpha]_D^{20}$ +121.7° in pure chloroform (0.6561 g. in 25 cc. of solution rotated 6.39° to the right in a 2-dm. tube) and a second recrystallization did not change this value. The pure substance melts at 40–41°. It is stable to Fehling's solution and is soluble in most organic solvents, including petroleum ether, but is insoluble in water.

In an acetyl estimation, carried out by Kunz's method,[10] 0.528 g. was equivalent to 23.8 cc. of 0.2 N potassium hydroxide solution, the reaction time being two hours, in comparison with 24.5 cc. calculated for tetra-acetyl-cyclohexylglucoside.

α-Cyclohexylglucoside.—The method of Zemplén[11] was used to de-acetylate tetra-acetyl-α-cyclohexylglucoside. One hundred cc. of absolute methyl alcohol in which 1.5 g. of metallic sodium had been dissolved was added to a solution of 18 g. of the acetylated glucoside in 250 cc. of absolute chloroform. Both solutions were well cooled in an ice and salt bath prior to their mixing and the temperature of the mixture did not rise much above 0° for the first half hour. Water (15 cc.) was then added and the liquid was allowed to stand for another half hour before the addition of a considerable quantity of water. The chloroform layer, which proved to be without optical rotation, was rejected but the aqueous portion which contained the product was made slightly acid with acetic acid and evaporated under reduced pressure to a sirup, which was extracted repeatedly with acetone. The substance was isolated in crystalline form and with a 90% yield by concentrating the acetone solution after decolorizing it with carbon. After two recrystallizations from acetone, the specific rotation of the glucoside was $[\alpha]_D^{20}$ +131.7° in water. After the third, $[\alpha]_D^{20}$ was +133.2° (0.3622 g. in 25 cc. rotated 3.86° to the right in a 2-dm. tube) while the second fraction which separated from the solution had $[\alpha]_D^{20}$ +132.9°. A specific rotation of $[\alpha]_D^{20}$ +133.2° was accordingly accepted as correct for an aqueous solution of α-cyclohexylglucoside. The same specimen was carefully dried in a vacuum before analysis.

Anal. Subs., 0.1486: CO_2, 0.2987; H_2O, 0.1138. Calcd. for $C_{12}H_{22}O_6$ (cyclohexylglucoside): C, 54.92; H, 8.45. Found: C, 54.82; H, 8.56.

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[9] For preparation of the chloroform, see note 13 to Part II.

[10] Kunz and Hudson, THIS JOURNAL, **48**, 1982 (1926).

[11] Zemplén, *Ber.*, **59**, 1254 (1926).

The new glucoside, which crystallized as small, stout prisms or as thick prismatic needles, had a melting point of 125–126° and was very soluble in cold water, acetone or alcohol, rather less so in hot ethyl acetate and benzene, but was insoluble in chloroform, ether and petroleum ether. It failed to reduce Fehling's solution. It is very bitter in taste.

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Summary

Tetra-acetyl-β-cyclohexylglucoside was readily rearranged by titanium tetrachloride to the isomeric alpha form and the use of this inorganic chloride in promoting such a transformation has therefore been extended to the acetylated glucoside of a hydro-aromatic alcohol. α-Cyclohexylglucoside was prepared from the acetate by de-acetylation. The observed rotations of the new α-glucoside and its acetate agree well with values calculated by Hudson's second isorotation rule and the agreement shows that the oxidic ring in the cyclohexylglucosides and their acetates is the same as the ring of the normal methylglucosides, namely, 1,5, as recently allocated by Hudson.

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ACTION OF TITANIUM TETRACHLORIDE ON DERIVATIVES OF SUGARS. IV. TRANSFORMATION OF HEPTA-ACETYL-BETA-METHYLCELLOBIOSIDE TO THE ALPHA FORM AND THE PREPARATION OF ALPHA-METHYLCELLOBIOSIDE[1]

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It has been shown in the previous articles that the preparation of alpha glucosides from the respective beta compounds by the action of titanium tetrachloride can be accomplished with various types of beta glucosides. Transformations were obtained where the aglycon (*i. e.*, non-sugar component) of the glucoside was a single methyl group, an unbranched chain of six carbon atoms or a hydrogenated benzene ring. The mechanism of the reaction appears to consist in the formation of a halochromic double compound of titanium tetrachloride with the fully acetylated beta glucoside in absolute chloroform solution and the rapid isomerization of this compound on heating the solution, with the resulting production of acetylated alpha glucosides. All the transformations have been made so far with derivatives of only one sugar, *d*-glucose, a representative of the monosaccharides; the

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[1] Publication authorized by the Director of the Bureau of Standards. Part III was published in THIS JOURNAL, **52**, 2568 (1930).