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.

The author expresses his thanks to the International Education Board, whose support has made this investigation possible, and also wishes to thank Dr. C. S. Hudson for his helpful suggestions.

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.

WASHINGTON, D. C.

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

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]

BY EUGEN PACSU

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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).

extension of the method to the production of alpha glycosides of the reducing disaccharides from their beta forms, which are easily accessible through the Koenigs–Knorr synthesis, was next undertaken and the results in the case of methylcellobioside, where the alpha form has now been synthesized, are reported in this article.

Beta-hepta-acetyl-methylcellobioside, first described by Hudson and Sayre,[2] was prepared from cellobiose octa-acetate through the acetobromo derivative. Certain modifications of their directions gave an increased yield, as will be described in the experimental part. Titanium chloride caused beta-hepta-acetyl-methylcellobioside to rearrange in chloroform solution in the course of six hours' heating and the main product was the alpha form of this substance, of m. p. 185° and $[\alpha]_D^{20}$ +55.7° in chloroform, when pure. Consideration of the rotatory powers, as will presently be discussed, shows that this substance has the same ring structure as the original beta form. There was also isolated from the reaction mixture a small quantity of a second crystalline substance, showing a sharp melting point of 174° and $[\alpha]_D^{20}$ +23.8° in chloroform. Its hydrolysis by acids yielded *d*-glucose as the sole sugar component and it thus appears to be a derivative either of cellobiose or some other di-glucose disaccharide. The de-acetylation of alpha-hepta-acetyl-methylcellobioside gave a good yield of crystalline alpha-methylcellobioside, of m. p. 144–145 and $[\alpha]_D^{20}$ +96.8° in water, when pure.

The rotations of the alpha and beta forms of methylcellobioside and their hepta-acetates may be compared through Hudson's isorotation rule in the way that has been indicated in the two preceding articles.

TABLE I

ROTATIONS OF THE ALPHA AND BETA FORMS OF METHYLCELLOBIOSIDE (MOL. WT. 356) AND THEIR HEPTA-ACETATES (MOL. WT. 650)

Substance	M. p., °C.	$[\alpha]_D$	$[M]_D$	Solvent
α-Methyl cellobioside	144–145	+96.8	$+34{,}460 = +A' + B'$	H_2O
β-Methyl cellobioside	193	−18.9	$-\ 6{,}730 = -A' + B'$	H_2O
Hepta-acetates of				
α-Methyl cellobioside	185	+55.7	$+36{,}200 = +A + B$	$CHCl_3$
β-Methyl cellobioside	187	−25.4	$-13{,}260 = -A + B$	$CHCl_3$

Hudson and Johnson[3] have shown that the value of B, which is obtained from the rotation of the alpha and beta forms of cellobiose octa-acetate, is +8,800 and from this value it was predicted by Hudson and Sayre[2] fifteen years ago that the specific rotations of the alpha and beta forms of hepta-acetyl-methylcellobioside in chloroform would be +56 and −28, respectively. They synthesized the beta form and its rotation (−25.4) agreed satisfactorily with the calculated value. The alpha form could not

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[2] Hudson and Sayre, THIS JOURNAL, **38**, 1867 (1916).

[3] Hudson and Johnson, *ibid.*, **37**, 1278 (1915).

be made at that time because of the lack of a suitable method. The substance has now been synthesized and its rotation (+55.7) agrees closely with their calculation. The agreement proves that the primary ring structure of the methylcellobioside hepta-acetate is the same as that of alpha and beta forms of cellobiose octa-acetate, since the value of B that is used in the calculations was obtained from the rotations of the latter substances. The value of A from these acetylated methylcellobiosides is $(36{,}200 + 13{,}260)/2 = 24{,}730$, which is in good agreement with previous measurements of this value by Hudson and Dale[4] from the rotations of the acetylated methylglucosides, galactosides and xylosides. The value of A' from the methylcellobiosides is $(34{,}460 + 6730)/2 = 20{,}595$, in comparison with the average value of about 18,500 that was found by Hudson[5] from the rotations of the methylglucosides, galactosides, xylosides and arabinosides. The difference corresponds to about 6° in the specific rotation of the methylcellobiosides. The value of B' is $(34{,}460 - 6730)/2 = 13{,}865$; this is the first measurement of the rotation of the cellobioside chain. If one now combines it with the rotation of beta-cellobiose ($B' - a_{\text{OH}} = 5470$) there results $a_{\text{OH}} = 8395$, in good agreement with the value of a_{OH} from the glucose series (8440). It is evident from these agreements that all these substances of the cellobiose series possess the same kind of primary ring, which has been shown by Hudson[6] to be of the 1,5 type.

Experimental

Preparation of Alpha-Acetobromocellobiose and Beta-Methylcellobioside Hepta-acetate.—Forty grams of cellobiose octa-acetate was digested with 100 cc. of glacial acetic acid for a few minutes on the water-bath and the mixture was then cooled to 20° and 20 g. of acetic anhydride was added, followed by 130 g. of a solution of hydrobromic acid in glacial acetic acid, prepared by saturation with hydrogen bromide gas at 0°. The octa-acetate slowly dissolved during one and one-half hours at room temperature and the mixture was then kept overnight in the ice box. In the morning the crystalline mass was shaken with 2 liters of water and ice and some chloroform. The chloroform layer was washed with ice-cold dilute potassium bicarbonate solution, then several times with cold water and dried with calcium chloride. It was decolorized with activated carbon and concentrated to 100 cc. under reduced pressure. On the addition of 200 cc. of ether, 39.2 g. of alpha-acetobromocellobiose crystallized immediately; yield, 95% of the theoretical.

A solution of the acetobromocellobiose in 500 cc. of methyl alcohol was shaken for a few minutes with 25 g. of freshly prepared silver carbonate and then gently refluxed on the steam-bath, with frequent shaking, during one hour. The hot solution was filtered by suction through a layer of decolorizing carbon, which was then washed with hot methyl alcohol. The filtrate crystallized quickly on cooling and the crystals were washed with methyl alcohol followed by ether. A second crop was obtained from the mother liquor and the total yield was 34.7 g. (95% of the theoretical) of beta-methylcellobioside hepta-acetate. The product was recrystallized once from 40% methyl

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[4] Hudson and Dale, THIS JOURNAL, **40**, 997 (1918).

[5] Hudson, *ibid.*, **47**, 268 (1925).

[6] Hudson, *ibid.*, **52**, 1707 (1930).

alcohol; yield, 32.4 g. of substance of $[\alpha]_D$ −24.0 in chloroform. The value found by Hudson and Sayre is −25.4.

Transformation of Beta-Methylcellobioside Hepta-acetate to the Isomeric Alpha Form.—On mixing a solution of 6 g. of titanium tetrachloride in 50 cc. of absolute[7] chloroform with one of 20 g. of beta-methylcellobioside hepta-acetate in 300 cc. of the same solvent, a lemon yellow amorphous halochromic compound immediately separated but rapidly redissolved on shaking. The solution was gently refluxed for six hours with exclusion of moisture by a calcium chloride tube; the color slowly changed to grayish brown. After the usual treatment with ice water, potassium bicarbonate solution, etc., the dextrorotation of the slightly colored chloroform solution corresponded to about $[\alpha]_D$ 50 for the solute. Concentration of the solution under reduced pressure yielded a thick sirup which soon crystallized; the mass was dissolved in 250 cc. of hot 95% alcohol and on cooling there separated globular masses of crystals (10.5 g.) showing $[\alpha]_D$ 45.8 in chloroform. The material is a mixture and by successive recrystallizations from absolute alcohol a small quantity of a substance was obtained of sharp melting point at 174° and $[\alpha]_D^{20}$ 23.8 (0.4537 g. in 25 cc. of chloroform solution rotated 0.865 to the right in a 2-dm. tube), which did not change on further recrystallization. This appears to be a by-product of the reaction, as its rotation indicates that it is not the expected alpha isomer; since its hydrolysis by acids yields glucose as the sole sugar, it seems to be a derivative of cellobiose or of some similar di-glucose disaccharide which has been produced from cellobiose. It will be investigated further. The mother liquor from which the 10.5 g. of crystals, previously mentioned, had separated was kept for one day in the ice box and 5 g. of long flexible needles separated, showing $[\alpha]_D^{20}$ 54.4 and after one recrystallization 55.7 (0.303 g. in 25 cc. of chloroform solution rotated 1.35 to the right in a 2-dm. tube), a value which was not changed by two further recrystallizations. The rotation of this substance, its analysis and de-acetylation to give what is evidently alpha-methylcellobioside (as shown by the rotation and analysis of the latter) show that it is the expected alpha-methylcellobioside hepta-acetate, and it was obtained in about 25% yield from its beta isomer. Its melting point is 185° and in its solubility in organic solvents it closely resembles the beta isomer except that it is more soluble in absolute alcohol.

An acetyl estimation by the method of Kunz[8] corresponded with the composition of a hepta-acetate of methylcellobioside; 0.5126 g. of substance in acetone solution at 0° neutralized 55.4 cc. of 0.1 *N* potassium hydroxide in comparison with the calculated value, 55.17 cc.

Preparation of Alpha-Methylcellobioside by the De-acetylation of its Hepta-acetate.—The acetate was de-acetylated by Zemplén's[9] method, with slight modifications. Forty cubic centimeters of a 0.5 *N* solution of sodium methylate in absolute methyl alcohol was slowly added from a buret to an ice cold solution of 8.3 g. of pure alpha-methylcellobioside hepta-acetate in 60 cc. of absolute chloroform and the mixture was kept for one hour in an ice and salt bath. The sodium methylate addition product separated as a gelatinous mass. Ten cubic centimeters of water were then added and after fifteen minutes at room temperature 200 cc. of 0.1 *N* sulfuric acid was added to convert the sodium acetate to sulfate. The water layer was then concentrated under reduced pressure to a thin sirup which was taken up in absolute alcohol and the sodium sulfate filtered off. The filtrate was concentrated similarly to dryness, the residue was extracted with hot absolute alcohol and the solution was decolorized with carbon. After one day it yielded 4.15 g. of microscopic needles (92% of the theoretical) showing

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[7] Prepared as described in Footnote 13, Part II.

[8] Kunz and Hudson, This Journal, **48**, 1892 (1926).

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

$[\alpha]_D^{20}$ 96.6 in water (0.244 g. of substance in 25 cc. of chloroform solution rotated 1.73 to the right in a 2-dm. tube). Successive recrystallizations gave the values 97.1, 96.8 and 96.7 and the value 96.8 is accepted for pure alpha-methylcellobioside. The pure substance melts at 144–145°, tastes faintly sweet and does not reduce Fehling's solution. The crystals which had been dried in a desiccator at room temperature did not lose weight appreciably when kept at 110° in vacuo for four hours.

Anal. Subs., 0.155: CO_2, 0.249; H_2O, 0.096. Calcd. for $C_{13}H_{24}O_{11}$: C, 43.79; H, 6.79. Found: C, 43.5; H, 6.93.

The author expresses his thanks to the International Education Board for the grant of a fellowship which enabled him to carry out this investigation. He also thanks Dr. C. S. Hudson for helpful suggestions.

Summary

Alpha-methylcellobioside has been synthesized through the transformation of the known beta-methylcellobioside hepta-acetate to its new alpha isomer by the action of titanium tetrachloride, followed by de-acetylation. The rotations of the various substances agree in first approximation with the values predicted by Hudson's rules of isorotation and the results indicate that the primary ring in all of them is of the 1,5 type. The titanium tetrachloride transformation yielded along with alpha-methylcellobioside hepta-acetate a second crystalline substance which showed in a pure condition $[\alpha]_D$ 23.8 in chloroform and m. p. 174; it is being studied further.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

A SYNTHESIS OF METHIONINE

BY WALLACE WINDUS AND C. S. MARVEL

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Several years ago Mueller[1] isolated from the hydrolytic products of casein a new amino acid which contained sulfur. He determined its composition and prepared some derivatives. More recently Barger and Coyne[2] have demonstrated that this amino acid was γ-methylthiol-α-amino-*n*-butyric acid and succeeded in synthesizing the racemic compound from methylthiolpropionaldehyde by use of the Zelinsky–Stadnikoff modification of the Strecker method. The yields were not very satisfactory and the starting materials are not readily available.

A new synthesis of this interesting amino acid has been accomplished which seems to be more satisfactory as a method of preparation than the original method of Barger and Coyne. The reactions involved are represented by the following outline

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[1] Mueller, *J. Biol. Chem.*, **56**, 157 (1923).

[2] Barger and Coyne, *Biochem. J.*, **22**, 1417 (1928).