due common to the thioglycosides of both these disaccharides possessed an oxygen bridge linking in the normal position.

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[CONTRIBUTION FROM THE POLARIMETRY SECTION, BUREAU OF STANDARDS, U. S. DEPARTMENT OF COMMERCE]

RELATIONS BETWEEN ROTATORY POWER AND STRUCTURE IN THE SUGAR GROUP. XXIII. THE PREPARATION AND THE STRUCTURE OF BETA-THIOPHENOL MALTOSIDE AND OF ITS HEPTA-ACETATE[1,2]

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β-Thiophenol cellobioside and β-thiophenol lactoside, according to the evidence presented in the preceding paper,[2] may be regarded as derivatives of a β-thiophenol glucoside of the normal ring structure. The two compound thioglycosides were submitted to the action of aqueous acid in such a way that glucose, or galactose, and thiophenol glucoside formed the main products of the partial hydrolysis. On examination, the specimens of thiophenol glucoside so prepared were found to be identical in all respects with one derived from acetobromoglucose and potassium thiophenate. It was this fact which led to the above conclusion, although it will be noticed that the reasoning involved the assumption that the relatively great stability of the thioglycosides toward acid hydrolysis precluded any change in their ring structure during the course of the experiment.

The examination of maltose in similar fashion was beset with the difficulties found in obtaining an adequate supply of hepta-acetyl-β-thiophenol maltoside in a pure condition. These were largely due to the unsatisfactory nature of the reaction between hydrogen bromide in glacial acetic acid–chloroform solution and maltose β-octa-acetate, which fails to result in a crystalline acetobromo derivative. This compound formed the starting point in the preparation of the thiophenol glycoside acetate. When the action of the hydrogen bromide solution was limited to two and one-half hours at 0°, 60% of the octa-acetate was recovered unchanged after the remainder had been condensed with potassium thiophenate, in spite of the fact that a 500% excess of the gas had been used and that similar acetates, such as those of glucose or cellobiose, give almost quanti-

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

[2] The author has arranged with Dr. C. S. Hudson, under whose direction the research was carried out, that it will be included as No. XXIII in his series entitled "Relations between Rotatory Power and Structure in the Sugar Group." No. XXII was published in THIS JOURNAL, **51**, 3627 (1929).

tative yields of the acetobromo sugars under the same conditions. On another occasion a solution of maltose acetate and a 600% excess of hydrogen bromide were allowed to stand in solution at 20° for forty-eight hours with the result that twenty-six per cent. by weight of the acetate used was recovered as pure tetra-acetyl-β-thiophenol glucoside. The experimental conditions finally adopted for the preparation of acetobromo maltose were intermediate to those described above and were very similar to those used by Irvine and Black,[3] although the small scale to which the authors restricted the reaction was found to be unnecessary. When the directions cited in the experimental portion were adhered to with rigor, a chloroform solution of the amorphous derivative was obtained which gave a reliable yield of 49.5% by weight of crude, crystalline hepta-acetyl-β-thiophenol maltoside when condensed with potassium thiophenate in the usual way.

The crude acetylated glycoside could not be purified readily by recrystallization from chloroform and ether, and the fractions which separated from these solvents displayed a specific rotation which varied capriciously from $[\alpha]_D$ 43° to $[\alpha]_D$ 52° in chloroform. Reacetylation failed to give a homogeneous product and showed that the irregularities were not due to the partial removal of acetyl groups from the thioglycoside during the condensation. As sulfur and acetyl estimations tended to be high and low, respectively, the presence of tetra-acetyl thiophenol glucoside was inferred but whatever the nature of the impurity was, it was eventually eliminated by the careful fractional crystallization of the crude hepa-acetyl-β-thiophenol maltoside from absolute alcohol. The constants of the pure compound were found to be m. p. 93–95° and $[\alpha]_D^{27}$ −49.0° in chloroform.

The molecular rotation of hepta-acetyl β-thiophenol maltoside, M_D 35,660 in chloroform, may be expressed in the manner of Hudson[4] as $B - A_{SPh}$, where B refers to the rotation of the acetylated basal chain and has the value M_D 62,700. From this the rotation of the terminal asymmetric carbon atom, A_{SPh}, in the thioglycoside acetate is seen to be of a magnitude M_D 27,040 in chloroform, which is considerably lower than the average value of M_D 30,500 deduced from the molecular rotations of the fully acetylated β-thiophenol glycosides of glucose, xylose, lactose and cellobiose.[5] In the same article, moreover, it was shown that the deviations from the mean value of A_{SPh} for these four sugars were opposite in sign but similar in magnitude to those encountered in the quantity A_{Cl}, the rotation due to the terminal asymmetric center in the corresponding acetochloro derivatives. The sum $A_{SPh} + A_{Cl}$ was therefore remarkably constant throughout the series examined and amounted to M_D 69,200 in chloro-

[3] Irvine and Black, *J. Chem. Soc.*, 862 (1926).

[4] Hudson, THIS JOURNAL, **46**, 462 (1924).

[5] Purves, *ibid.*, **51**, 3619 (1929).

form. β-Thiophenol maltoside acetate and acetochloro maltose supply a further illustration of the principle, for the sum $A_{Cl} + A_{SPh}$ (41,400[4] + 27,040) is M_D 68,440 in this case and agrees well with the former value.

Two attempts were made to prepare a crystalline β-thiophenol maltoside from the hepta-acetate, alcoholic ammonia being used as the deacetylating agent on one occasion and sodium methylate on the other, but both methods yielded an amorphous white solid which could not be crystallized and which was not fermented by yeast. The specific rotation of the impure thioglycoside was of the order of $[\alpha]_D^{27}$ 38° in water but its extremely hygroscopic nature caused the determination to be of doubtful accuracy.

As thiophenol maltoside possessed such unsatisfactory physical properties, the crystalline acetate was submitted in its place to a partial hydrolysis with dilute sulfuric acid and yielded glucose and a thiophenol glucoside. This amorphous mixture was not readily separated by means of acetone or ethyl acetate and the amount of the thioglucoside recovered by the use of these solvents was only 55% of the theoretical yield. The insoluble portion was therefore fermented with yeast in order to remove the reducing sugar and when this was done a further quantity of β-thiophenol glucoside could be isolated, the total thus being increased to 71% of the theoretical. Acetylation of the material gave a pure tetra-acetyl-β-thiophenol glucoside, which was characterized with precision and found to be identical with a specimen prepared from acetobromoglucose.

β-Thiophenol maltoside, then, as well as the same derivative of cellobiose, must be regarded as β-thiophenol glucoside of the normal structure substituted in one hydroxy group by a second glucose residue. Haworth and his collaborators[6] have very recently elucidated the constitution of β-methyl maltoside by the methylation method and with the same result. Their more extended investigation shows that the methyl glycosides of cellobiose and maltose differ in a stereochemical sense only in that the former is a β-glucosido-glucoside while the latter possesses the α-configuration. Such a conclusion is in full accord with the properties of the glycosides of the two disaccharides but fails to explain the sharp distinction to be observed in the behavior of their acetates toward hydrogen bromide. The amorphous nature of acetobromo maltose, together with the low yields of crystalline β-glycosides which may be prepared from it, suggests that it is the product of a more complex reaction than that which results in acetobromo cellobiose. The reason for this anomalous behavior remains obscure.

Experimental

Preparation of β-Thiophenol Maltoside Acetate.—A 50-cc. graduated glass-stoppered flask held exactly 10 g. of pure β-maltose octa-acetate, 20 cc. of chloroform and 20 cc. of a glacial acetic acid solution which contained 340 g. of hydrogen bromide

[6] Haworth and Peat, *J. Chem. Soc.*, 3094 (1926).

per liter. After standing in a constant temperature room for eight hours at 20°, the mixture was made up to the mark with chloroform, shaken and found to have a positive reading of 74.1° on the polarimeter when observed in a 2-dm. tube. The specific rotation of the acetobromomaltose was therefore $[\alpha]_D$ 180.1°, when calculated on the basis that its formation from the octa-acetate had been quantitative. The acids were then removed from the solution by washing, thrice repeated, with ice water and the wet chloroform residue containing the acetobromo sugar was run into a mixture of 1.65 cc. (10% excess) of thiophenol and 21 cc. of 0.7 *N* alcoholic potassium hydroxide (the theoretical amount). Warming on the water-bath for forty minutes completed the condensation. After washing potassium bromide, thiophenol and alcohol from the liquor with very dilute aqueous sodium bicarbonate, the chloroform solution was dried over calcium chloride and evaporated to a thin sirup, which was straightway taken up in 30 cc. of cold alcohol. Hepta-acetyl-β-thiophenol maltoside readily crystallized in the presence of a nucleus when 5 to 6 cc. of water was added and the solution was steadily scratched; yield, 4.95 g., m. p. 90–93°, $[\alpha]_D^{19}$ 44.64° (0.3170 g. in 25 cc. of chloroform gave an observed reading of 1.132° to the right when in a 2-dm. tube).

In order to purify the thioglycoside acetate, the product from several condensations, 13 g., was allowed to separate from an initial volume of 160 cc. of absolute alcohol in five fractions, the properties of which were as follows.

FRACTION 1.—Slender felted needles, apparently homogeneous; weight, 5.31 g.; 0.3223 g. required 30.06 cc. of decinormal caustic soda in an acetyl determination, the calculated value being 30.99 cc.; 0.2942 g. gave 0.0984 g. of barium sulfate; found, S, 4.59.

FRACTION 2.—Similar in crystalline form to the above; weight, 4.40 g.; 0.3233 g. took 31.27 cc. of decinormal alkali in an acetyl estimation where theory demands 31.09 cc.; 0.5534 g. gave 0.1795 g. of barium sulfate; found, S, 4.46.

FRACTION 3.—Similar in crystalline form to the above; weight, 2.04 g.; 0.2841 g. required 27.56 cc. of decinormal alkali in place of 27.32 cc.

FRACTION 4.—A mixture of slender needles with shorter, stouter prisms; weight, 0.65 g.; 0.3065 g. took 27.74 cc. of decinormal alkali in place of 29.47 cc. required by theory; 0.3033 g. gave 0.1120 g. of barium sulfate; found, S, 5.07.

FRACTION 5.—A small, discolored residue which crystallized completely as short, pointed prisms some weeks later. Hepta-acetyl thiophenol maltoside requires S, 4.39.

Fractions 2 and 3, which possessed satisfactory analytical figures, also agreed in their specific rotation (found, $[\alpha]_D$ 48.83°, 48.85° in chloroform; 0.3072 g. in 25 cc. had α 1.200°; 0.2966 g. had α 1.159° to the right in a 2-dm. tube). These fractions were therefore recrystallized together from alcohol as fine clusters of square-ended very slender prisms, soluble in petroleum ether, readily so in other organic solvents and with a specific rotation in chloroform of $[\alpha]_D^{27}$ 49.09°, or substantially the same as before (0.2213 g. in 25 cc. gave an observed reading of 0.869° to the right in a 2-dm. tube). Pure hepta-acetyl-β-thiophenol maltoside therefore possessed a specific rotation in chloroform of $[\alpha]_D^{27}$ 49.0°.

Fraction 1, after recrystallization and rejection of the first portion of 1 g. to separate, also yielded the pure thioglycoside acetate with the correct melting point of 93–95° and an accurate specific rotation (found, $[\alpha]_D^{22}$ 48.59°; 0.5217 g. in 25 cc. of chloroform gave an observed reading of 2.028° to the right in a 2-dm. tube). Thus 10.4 g. of pure hepta-acetyl thiophenol maltoside was obtained from 13 g. of the crude material, or from 26.3 g. of pure maltose octa-acetate. The yield was therefore about 37% of the theoretical.

Thiophenol Glucoside from Hepta-acetyl β-Thiophenol Maltoside.—Exactly 4 g. of the acetate was heated at 90° in a 100-cc. flask with 50 cc. of normal sulfuric acid and about 30 cc. of alcohol, which was just sufficient to give a clear solution. As the acetyl groups were removed during the hydrolysis, it was possible to replace this alcohol

with distilled water as it evaporated, without causing the solution to become cloudy. Eight hours of heating sufficed to hydrolyze the thioglycoside, whereupon the volume was increased to the 100-cc. mark with water, a trace of thiophenol was extracted from the cold, cloudy solution with 1 cc. of chloroform and the clear aqueous portion was found to have a rotation of −0.66°, observed in a 2-dm. tube. This reading corresponds to a specific rotation of $[\alpha]_D$ −13.3° on the assumption that the hydrolysis to β-thiophenol glucoside and glucose had been quantitative and may be compared with the theoretical rotation of $[\alpha]_D$ −21.5° for this mixture, measured in distilled water.

After the neutralization of the free acids with calcium carbonate, the filtered liquor was evaporated to complete dryness at 60° and the residue was extracted three times with acetone. The extract deposited a stiff sirup when concentrated and the portion which remained dissolved was crystallized from ethyl acetate after its recovery; 0.823 g. of crystalline β-thiophenol glucoside was so obtained m. p. 121–127°, raised to 129–131° by several purifications from ethyl acetate. A mixture of the substance with authentic thiophenol glucoside, m. p. 133°, melted at 131°, while its specific rotation was $[\alpha]_D$ −64.0° in water (0.2016 g. in 25 cc. had α −1.032° when a 2-dm. tube was used). The whole of the original product which was not soluble in ethyl acetate was then united, freed from inorganic salts as far as possible by solution in methyl alcohol and fermented with yeast in 20 cc. of water after all traces of organic solvents had been removed. No glucose remaining in the solution four days later, a filtration through charcoal and a clarification with basic lead acetate were followed by the evaporation of the liquor to dryness under diminished pressure and by the extraction of the residue with ethyl acetate. The thiophenol glucoside which crystallized from the extract weighed 0.25 g. and increased the total yield of the crude material to 1.073 g., or 71.7% of the theoretical.

The acetylation of the thiophenol glucoside with acetic anhydride and pyridine, followed by recrystallization of the acetate from 95% alcohol, gave an almost quantitative yield of pure tetra-acetyl-β-thiophenol glucoside of the usual variety, m. p. 116°; mixed m. p. with an authentic specimen, 116° and $[\alpha]_D^{20}$ −18.4° in chloroform (0.4585 g. in 25 cc. and in a 2-dm. tube had a levorotation of 1.070°), thus agreeing with the standard constants, m. p. 117°, and $[\alpha]_D^{20}$ −17.5°, for this substance.

β-Thiophenol Maltoside.—A solution of 0.05 g. of metallic sodium in 5 cc. of absolute methyl alcohol was added to one of 8 g. of pure hepta-acetyl-β-thiophenol maltoside dissolved in 20 cc. of the same solvent.[7] The odor of methyl acetate was strong two days later, when the solution was evaporated to leave a colorless sirup which would not crystallize. The amorphous product was extremely soluble in water, methyl and ethyl alcohols, but dissolved sparingly in ethyl acetate and in cold propyl alcohol. Prior to analysis the β-thiophenol maltoside was heated at 100° (0.1 mm.) for several hours and assumed the form of an extremely hygroscopic glass with a specific rotation of $[\alpha]_D^{27}$ 38.12° in water (0.2339 g. in 25 cc. gave an observed reading of 0.357° to the right in a 1-dm. tube).

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Summary

1. Hepta-acetyl-β-thiophenol maltoside was synthesized from aceto-bromomaltose and potassium thiophenate and the constants of the pure compound were found to be m. p. 93–95° and $[\alpha]_D^{27}$ 49.0° in chloroform.

[7] Zemplén and Pacsu, *Ber.*, **62**, 1613 (1929).

2. When submitted to a partial hydrolysis with aqueous acid, hepta-acetyl-β-thiophenol maltoside yielded glucose and β-thiophenol glucoside of the normal ring structure. β-Thiophenol maltoside may accordingly be regarded as ordinary β-thiophenol glucoside substituted by a second glucose residue.

3. β-Thiophenol maltoside was obtained as a very hygroscopic glass with an approximate specific rotation of $[\alpha]_D^{27}$ 38° in water.

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PREPARATION OF BENZOYLACETIC ESTER

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The usual method given for the preparation of benzoylacetic ester is the Claisen condensation[1] of ethyl acetate with ethyl benzoate. A yield of 33% is reported but all attempts to duplicate this yield have failed. A study of this condensation was made by Marvel and Shiao[2] who found that the best yield obtainable by this method was 18%. In many runs the reaction mixture turned brown, puffed up and decomposed entirely giving very little or no product at all. A similar condensation with methyl piperonylate[3] gave yields ranging from 20 to 35%.

Since benzoylacetic ester would be an extremely useful reagent if it were readily obtainable, a search was made for other methods of preparation. The present communication is a report on the preparation of benzoylacetoacetic ester and its partial hydrolysis to benzoylacetic ester.

Benzoylacetoacetic ester was prepared in the usual way by the reaction between benzoyl chloride and the sodium derivative of acetoacetic ester. It was found possible to raise the yield of product from 50 to 75% and to shorten the time materially by using a slight excess of benzoyl chloride in benzene as the medium for the reaction.

The primary hydrolysis of benzoylacetoacetic ester may take place in three different ways

$$\left.\begin{matrix} C_6H_5CO \\ CH_3CO \end{matrix}\right\rangle CHCOOC_2H_5 + H_2O \longrightarrow \begin{cases} C_6H_5COCH_2COOC_2H_5 + CH_3COOH \\ CH_3COCH_2COOC_2H_5 + C_6H_5COOH \\ CH_3COCH_2COC_6H_5 + C_2H_5OH + CO_2 \end{cases}$$

Complete hydrolysis, of course, will lead to the formation of benzoic acid, acetophenone, acetone or acetic acid and the final products obtained will depend on the conditions of hydrolysis, which evidently must be carefully adjusted in order to favor the first reaction.

The different methods reported in the literature for accomplishing this

[1] Claisen, *Ber.*, **20**, 646 (1887).

[2] Shiao, B. S. "Thesis," University of Illinois, **1923**.

[3] Shriner and Kleiderer, THIS JOURNAL, **51**, 1269 (1929).