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Action of Strong Acids on Acetylated Glycosides

X.* Synthesis of 4,6-β-Glucose α,β-Diglucoside Hendecaacetate

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In Part IX of this series the synthesis of a potential *limit dextrin*, 6-glucose α-maltoside, although in an impure state, was reported. The aim of the present work was to prepare another disaccharide of this type, 4,6-glucose α,α-diglucoside. The synthesis was, however, only carried out as far as 4,6-β-glucose α,β-diglucoside hendecaacetate, since the yield of this substance was so low that attempts to transform it into the α,α-diglucoside seemed to be without any prospect of success.

The synthesis followed the following scheme:

1. Phenyl β-maltoside heptaacetate was prepared in a yield of 45 % from β-maltose octaacetate and phenol, with *p*-toluene sulfonic acid as catalyst, using the fusion procedure of Helferich and Schmitz-Hillebrecht [1]. The substance melted at 154—155° ** and showed $[\alpha]_D^{20}$ + 42°. Fischer and Armstrong [2] report the melting point as 155—156° but give no value for the optical rotation.

From the mother liquors of the phenyl β-maltoside heptaacetate another substance of m.p. 181—182° and $[\alpha]_D^{20}$ + 164° was isolated in 5 % yield. This liberated phenol on acid hydrolysis and gave an analysis corresponding to a phenyl maltoside heptaacetate. From the high specific rotation it seemed probable that the substance was an α-maltoside and this was supported by the fact that it could also be prepared as the chief product by condensing β-maltose octaacetate and phenol with zinc chloride as condensing agent according to the general procedure for the preparation of phenyl α-glycosides [2]. Although it is generally supposed that a small amount of the α-glycoside is formed when a sugar acetate and a phenol are condensed in the presence of *p*-toluene sulfonic

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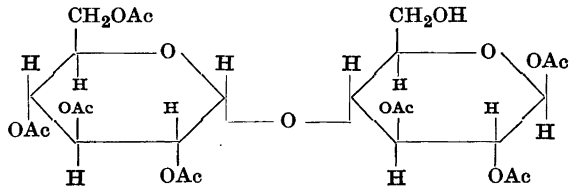
** All melting points uncorrected. All specific rotations in chloroform, $C = 2$.

acid [2], this appears to be the first occasion that such a product has been isolated. The phenyl α-maltoside heptaacetate has a higher melting point and a lower solubility than the β-maltoside, whereas the reverse is true for most pairs of glycosides, and this, together with the high crystallization tendency of the substance, undoubtedly, facilitated its isolation.

2. In one step the phenyl β-maltoside heptaacetate was deacetylated and degraded by alkali to 4-levoglucosan β-glucoside (maltosan), following in principle the methods of Montgomery, Richtmeyer and Hudson [3] for the synthesis of similar disaccharide derivatives. Subsequent acetylation gave a 72 % yield of maltosan hexaacetate, m.p. 182—183°, $[a]_D^{20}$ + 48°. Karrer and Kamienski [4] report the melting point as 184° but give no value for the optical rotation.

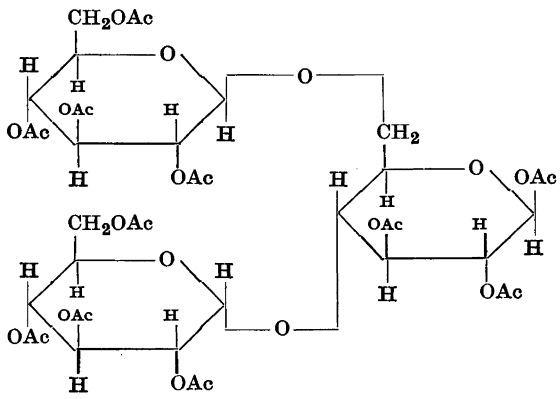
3. Zemplén and Csürös [5] have prepared 2,3,4-triacetyl glucosyl chloride by the action of titanium tetrachloride upon levoglucosan triacetate in chloroform. An analogous reaction was carried out with maltosan hexaacetate, followed by treatment of the reaction product with mercuric acetate in order to replace the chlorine atom by an acetoxyl group. From the reaction mixture β-maltose heptaacetate and unchanged starting material were obtained in yields of 25 % and 40 % respectively. The heptaacetate melted at 140—141° and showed $[a]_D^{20}$ + 65°. By acetylation with pyridine-acetic anhydride it yielded β-maltose octaacetate. It was easily tosylated and the tosyl group was readily replaced by iodine, which facts indicate the presence of a primary hydroxyl group in the heptaacetate. There are only two possible heptaacetates of maltose containing a primary hydroxyl group, and there is little doubt that the substance in question is 1,2,3,2′3′4′6′-β-maltose heptaacetate.



1,2,3,2′,3′,4′,6′-β-Maltose heptaacetate

4. The Koenigs-Knorr reaction, with the improvements of Reynolds and Evans [6], did not succeed very well with maltose heptaacetate and acetyl glucosyl bromide. Several attempts were made but the yield of 4,6,-β-glucose α,β-diglucoside hendecaacetate did not exceed 6 %.

The product melted at 181—182° and showed $[\alpha]_D^{20}$ + 47°. The reason for this unusually low yield is at present obscure, the usual reference to sterical hindrance might be justified. A similar effect perhaps operates in the reaction between acetyl glucosyl bromide and α,γ-dichlorohydrin where the yield is only 7 % by the Koenigs-Knorr reaction [7] and 14 % by the mercuric acetate method [8]. As only rather small amounts of the trisaccharide were available it was not practicable to attempt to transform it into the potential *limit dextrin*. Several branchedchain polysaccharides have been obtained from natural sources but this trisaccharide, as far as is known, is the only example of a synthetic trisaccharide where the "branch" is actually represented, *i.e.* one glucose unit is the bivalent aglucon of the two others. The substance and its synthesis are therefore of some interest.



4,6-β Glucose α,β-diglucoside hendecaacetate

EXPERIMENTAL

Phenyl β-maltoside heptaacetate. *p*-Toluenesulfonic acid (0.7 g) was dissolved in molten phenol (50 g) and β-maltose octaacetate (48 g) and acetic anhydride (2.5 ml) were added. The mixture was heated for 1 hour on the steam bath under water pump vacuum and whilst still hot dissolved in benzene (400 ml). The benzene solution was washed with water, several times with 2 *N* sodium hydroxide and again with water, dried over calcium chloride and concentrated under reduced pressure. The crystalline residue was recrystallized from methanol (120 ml). The yield of phenyl β-maltoside heptaacetate was 23 g (45 %). Its melting point, 152—153° could be raised to 154—155° by one further recrystallization, but the first material was sufficiently pure for the next step in the synthesis. The recrystallized substance showed $[\alpha]_D^{20}$ + 42°.

Phenyl α-maltoside heptaacetate. a. When the methanolic mother liquors from the first recrystallization mentioned above were kept at 0° overnight, crystals (3 g) of m.p. 168—169° were precipitated. After further recrystallizations from ethanol the substance

was obtained pure with m.p. 181—182° and $[\alpha]_D^{20}$ + 164°. When a small amount of the substance was heated in ethanolic sulfuric acid and the ethanol then evaporated a distinct smell of phenol was detected.

$C_{32}H_{40}O_{18}$ (712.7)	Calc.	C 53.9	H 5.66
	Found	» 53.8	» 5.68

b. A mixture of β-maltose octaacetate (10 g), phenol (9 g) and anhydrous zinc chloride (1.5 g) was stirred at 120° for 2 hours. Whilst still hot the mixture was dissolved in benzene (300 ml) and worked up as described above for the β-maltoside. After two recrystallizations from ethanol the product (4.9 g) was pure and melted at 181—182°, alone or in admixture with the specimen described above.

Maltosan hexaacetate. A mixture of phenyl β-maltoside heptaacetate (46 g) and 2.6 *N* aqueous potassium hydroxide (800 ml) was heated on the steam bath for 40 hours. After about half an hour the mixture had become homogenous. The rotation of the solution in a 2 dm tube changed from + 2.4° to + 4.5° during the first 24 hours and thereafter remained constant. The solution was neutralized with 4 *N* sulfuric acid and concentrated under reduced pressure. The distillation was interrupted twice and precipitated salts removed by filtration. The remaining sirup was dried overnight in vacuo over sulfuric acid and thereafter mixed with acetic anhydride (250 ml) and anhydrous sodium acetate (25 g) and heated on the steam bath for 2 hours. The mixture was poured into ice water (1 500 ml) and extracted with chloroform (2 × 200 ml). The light-brown extract was washed with sodium hydrogen carbonate solution, dried over calcium chloride and decolorized by filtration through a column of aluminium oxide. The chloroform solution was then evaporated under reduced pressure and the crystalline residue recrystallized from ethanol (250 ml). The yield of maltosan hexaacetate, m.p. 181—182°, was 27 g (72 %). By further recrystallizations the pure substance, m.p. 182—183°, $[\alpha]_D^{20}$ + 48°, could be obtained.

1,2,3,2',3',4',6'-β-Maltose heptaacetate. Maltosan hexaacetate (25 g) was dissolved in chloroform (300 ml) and ethanol (5 ml) and titanium tetrachloride (40 g) were added. The mixture was refluxed for 3 hours on a glycerol bath kept at 70°. When cold the yellow mixture was poured into ice water (1 000 ml). The chloroform solution was separated and washed with water (4 × 250 ml), then concentrated under reduced pressure at a bath temperature not exceeding 30°. The sirupy residue was dissolved in a solution of mercuric acetate (25 g) in acetic acid (250 ml). After 2 hours at room temperature the solution was poured into ice water (2 500 ml) and extracted with chloroform (2 × 500 ml). The chloroform solution was washed with sodium hydrogen carbonate solution and water, dried over calcium chloride and concentrated under reduced pressure. The residue was dissolved in hot ethanol (125 ml) and on cooling almost pure maltosan hexaacetate (8.0 g) of m.p. 178—179° precipitated. The mother liquors were concentrated to 50 ml and a second crop (1.7 g) of less pure starting material of m.p. 163—165° was recovered. The mother liquors from this crop were poured into water (450 ml) and kept overnight at 0°, when maltose heptaacetate (5.8 g), m.p. 135—137°, precipitated. From the aqueous residues a further amount (1.7 g) of maltose heptaacetate could be obtained. Further recrystallizations from ethanol-water (1 : 9) yielded the pure substance, m.p. 140—141°, $[\alpha]_D^{20}$ + 65°.

$C_{12}H_{15}O_{11}(OCCH_3)_7$ (636.5)	Calc.	$OCCH_3$ 47.3
	Found	» 47.6

A small amount of the heptaacetate was acetylated with acetic anhydride and pyridine. β-Maltose octaacetate, m.p. 157—158° alone or in admixture with an authentic specimen, was obtained in an almost quantitative yield.

6-Tosyl 1,2,3,2',3',4',6'-β-maltose heptaacetate. β-Maltose heptaacetate (250 mg) was dissolved in absolute pyridine (1 ml) and tosyl chloride (300 mg) was added. After 17 hours at room temperature the mixture was poured into water (15 ml). The tosyl derivative precipitated immediately and was filtered off, washed with water and dried in vacuo over sulfuric acid. The yield was 300 mg (96 %). After two recrystallizations from ethanol the product had a constant melting point of 140—141° and showed $[\alpha]_D^{20}$ + 50°.

$C_{33}H_{42}O_{20}S$ (790.7) Calc. S 4.03
Found » 3.88

6-Iodo 1,2,3,2',3',4',6'-β-maltose heptaacetate. The tosyl derivative (100 mg) and sodium iodide (100 mg) were dissolved in dry acetonylacetone (3 ml) and the solution was kept at 100°. Sodium *p*-toluene sulfonate was deposited after a few minutes. After 1.5 hours the mixture was poured into water (15 ml), whereupon the salt dissolved while the iodo compound precipitated out. The latter was collected on the centrifuge and recrystallized from 70 % ethanol. The substance (44 mg), which had m.p. 88—90° and $[\alpha]_D^{20}$ + 50° was not purified further.

$C_{26}H_{35}O_{17}I$ (746.5) Calc. I 17.0
Found » 16.2

4,6-β-Glucose α,β-diglucoside hendecaacetate. A mixture of maltose heptaacetate (6.36 g), silver oxide (3.0 g) and Drierite (5 g) in absolute chloroform (30 ml) was shaken mechanically for 1 hour with the exclusion of direct light. A solution of acetyl glucosyl bromide (4.11 g) and iodine (0.5 g) in absolute chloroform (30 ml) was then added in 4 portions at 15 minutes intervals. Shaking was continued for 29 hours, after which the solution was filtered through a layer of Celite, washed with dilute sodium thiosulfate solution and water, dried over calcium chloride and concentrated under reduced pressure. The residual sirup was crystallized from methanol (20 ml), giving a product (1.0 g) of m.p. 153—155°. After two further recrystallizations from the same solvent the substance (0.6 g) had a constant melting point of 181—182° and showed $[\alpha]_D^{20}$ + 47°.

$C_{40}H_{54}O_{27}$ (966.8) Calc. C 49.7 H 5.63
Found » 50.2 » 5.57

Correction to the text added in proof. We have observed that the substance believed above to be 4,6-β-glucose α,β-diglucoside hendecaacetate is actually maltosan hexaacetate, which gives approximately the same analyses and the presence of which is due to the fact that unpurified maltose heptaacetate was used in the Koenigs-Knorr synthesis. The real trisaccharide should be found in the non-crystalline material from the mother liquors. The discussion on the bad yield of the Koenigs-Knorr synthesis has thus no significance.

SUMMARY

1,2,3,2',3',4',6'-β-Maltose heptaacetate has been prepared by the action of titanium tetrachloride in chloroform-ethanol upon maltosan hexaacetate and subsequent treatment with mercuric acetate in acetic acid.

4,6-β-Glucose α,β-diglucoside has been prepared from this maltose heptaacetate and acetyl glucosyl bromide by the Koenigs-Knorr reaction.

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