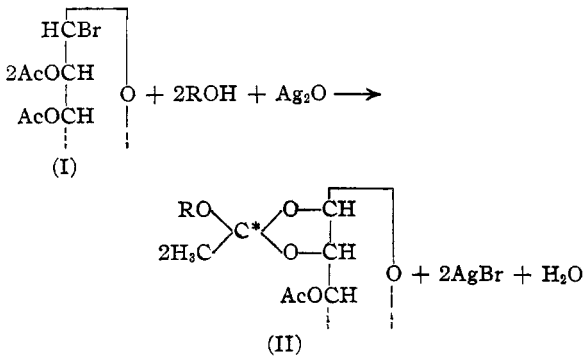
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Synthesis of Certain Disaccharide Acetates in the Mannose Series[1]

BY EUGENE A. TALLEY, DELBERT D. REYNOLDS AND WM. LLOYD EVANS

In 1930, Nishida and Hashima[2] reported that the acetolysis of the glucomannan from *Konjac* gave a trisaccharide hendecaacetate which could be hydrolyzed further to give two disaccharides, one containing two mannose units and the other containing a mannose unit and a glucose unit. The trisaccharide was thought to be a mannosido-mannosido-glucose with the hexose units joined together through 1–6 linkages. As the first step in checking this result by synthesis, the preparation of 6-β-D-mannosido-β-D-mannose octaacetate and 6-β-D-mannosido-β-D-glucose octaacetate was undertaken. These disaccharides can be prepared by the Koenigs and Knorr reaction from acetobromomannose and the corresponding 1,2,-3,4-tetraacetate.

A distinctive characteristic of the acetobromo compounds of the mannose series and other acetohalo sugars which are thought to have the halogen on carbon atom one *trans* to the acetyl group on carbon atom two (*cf.* Isbell[3]) is their tendency to form condensation products which possess an orthoester linkage of the type



The Koenigs and Knorr reaction has been applied to the synthesis of compounds of this type from the acetobromo derivatives of rhamnose,[4a] mannose,[4b] lyxose,[4c] ribose,[4d,h] talose,[4e] α-glucoheptose,[4f] 4-glucosidomannose,[4g] and α-guloheptose.[3b] In all of these cases, with the exception of one in which dihydroxyacetone monoacetate[4h] was used, the ROH compound has been either methyl or ethyl alcohol. Disaccharide acetates which possess two hexose units joined through an orthoester linkage have not been reported previously. Moreover, the condensation of acetobromomannose with another hexose unit by means of the Koenigs and Knorr reaction has never been applied to the synthesis of oligosaccharide acetates. These facts have led to the present work.

During the synthesis of an orthoester sugar derivative a new asymmetric carbon atom is formed, as illustrated in the structure (II), thus giving rise to two theoretically possible isomeric orthoester derivatives. Hence, when acetobromomannose is condensed with another hexose unit there are three possible structures which the product may possess. These possibilities are, first, a structure which contains a normal biosidic link and, second, two theoretically possible orthoester structures.

Instances are known[4c] where both the normal and the orthoester forms have been isolated from a single reaction mixture. However, in no previous cases have the two theoretically possible orthoester forms been isolated. In one case,[5] it was thought that two isomeric orthoester forms of turanose octaacetate had been isolated but later[6] these were found to be alpha and beta forms of octaacetyl-3-α-glucosido-fructopyranose.

Previous investigators[4a] have shown that the orthoester sugar acetates possess one alkali stable acetyl group. Moreover, Isbell[7] demonstrated that the orthoester sugar acetates exhibit a rapid rise in rotation when treated with absolute chloroform containing hydrogen chloride.

(1) Abstracted from theses presented by Delbert D. Reynolds and Eugene A. Talley to the Graduate School of The Ohio State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Kitsuji Nishida and Hideo Hashima, *J. Dept. Agr. Kyushu Imp. Univ.*, **2**, 277–360 (1930).

(3) (a) H. S. Isbell, *Ann. Rev. Biochem.*, **9**, 65–92 (1940); (b) Harriet L. Frush and Horace S. Isbell, *Bur. Standards J. Research*, **27**, 413–428 (1941).

(4) (a) Emil Fischer, Max Bergmann and Artur Rabe, *Ber.*, **53B**, 2362–2388 (1920); (b) J. K. Dale, THIS JOURNAL, **46**, 1046–1051, (1924); (c) P. A. Levene and M. L. Wolfrom, *J. Biol. Chem.*, **78**, 525–533 (1928); (d) P. A. Levene and R. S. Tipson, *ibid.*, **92**, 109 (1931); (e) William W. Pigman and Horace S. Isbell, *Bur. Standards J. Research*, **19**, 189–213 (1937); (f) Walter N. Haworth, Edmund L. Hirst and Maurice Stacey, *J. Chem. Soc.*, 2864–2872 (1931); (g) Horace S. Isbell, *Bur. Standards J. Research*, **7**, 1115–1131 (1931); and (h) Clarence W. Klingensmith and Wm. Lloyd Evans, THIS JOURNAL, **61**, 3012–3015 (1939).

(5) Eugene Pacsu, THIS JOURNAL, **54**, 3649–3661 (1932).

(6) Eugene Pacsu, E. Justin Wilson, Jr., and Ladislas Graf, *ibid*, **61**, 2675–2679 (1939).

(7) Horace S. Isbell, *Bur. Standards J. Research*, **7**, 1115–1131 (1931); THIS JOURNAL, **52**, 5298 (1930).

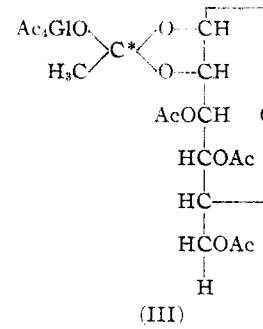
Evidence that the compound formed when acetobromomannose was condensed with β-D-mannose-1,2,3,4-tetraacetate possesses a normal biosidic linkage and not an orthoester linkage was borne out by the fact that eight acetyl groups were removed by alkali as well as by acid. If it were of the orthoester type, only seven acetyl groups would have been hydrolyzed by alkali. Moreover, the compound is stable when placed in chloroform containing dry hydrogen chloride.

When acetobromomannose was condensed with β-D-glucose-1,2,3,4-tetraacetate, a crystalline product which melted at 169° and which had a specific rotation $[\alpha]^{30}D$ +17.1°, was obtained. That it is a disaccharide octaacetate possessing an orthoester structure was shown by the fact that only seven acetyl groups were hydrolyzed by alkali, whereas eight acetyl groups were removed by acid. In addition, when this compound was dissolved in absolute chloroform containing dry hydrogen chloride the specific rotation changed to a value corresponding to $[\alpha]^{28}D$ +44°. This change was too rapid to be followed stepwise.

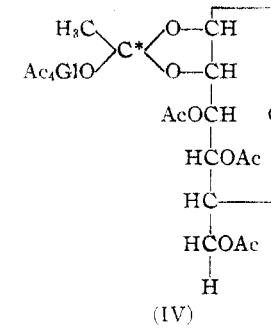
From the mother liquors of the above orthoester was isolated another crystalline compound (m. p. 174° and $[\alpha]^{32}D$ −27.6°). This compound is also a disaccharide octaacetate possessing an orthoester linkage as was shown by the fact that seven acetyl groups were removed by alkali, whereas eight acetyl groups were hydrolyzed by acid. When this compound was dissolved in absolute chloroform containing dry hydrogen chloride, the specific rotation changed to a value corresponding to $[\alpha]^{28}D$ +43°. This change was also too rapid to be observed stepwise. A mixed melting point of the two orthoesters showed a lowering of fifteen degrees.

In order to account for these two orthoester compounds the authors have concluded that they are isomers differing only in the configuration of the new asymmetric carbon atom formed during the condensation, *i. e.*, they represent *d* and *l* forms with respect to this particular asymmetric carbon atom. These isomers may be represented as shown for III and IV.

From the mother liquor of the two orthoester forms mentioned above, was obtained the third isomer (V) (softening range 90–95° and $[\alpha]^{19}D$ + 38.9°) expected, which has the normal biosidic linkage. That this compound possessed the normal biosidic linkage and not an orthoester

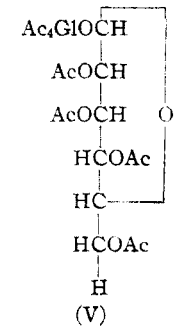


(III)



(IV)

(Gl = glucose residue)



(V)

linkage was shown by the fact that eight acetyl groups were removed by alkali. Also, it is stable when placed in absolute chloroform containing dry hydrogen chloride and it may be converted by the action of hydrogen bromide in glacial acetic acid into the corresponding crystalline acetobromomannosidoglucose (m. p. 172° and $[\alpha]^{30}D$ +151.5°) from which two crystalline trisaccharides were prepared. (These latter compounds will be described in a subsequent paper.) All attempts to crystallize (V) failed, but it was isolated as a reasonably pure compound. It was prepared both from acetobromomannose condensed with β-D-glucose-1,2,3,4-tetraacetate and from acetobromomannosidoglucose condensed with silver acetate and although the sirups obtained from the two reaction mixtures differed markedly in rotation ($[\alpha]_D$ +31–33° and +43°, respectively), the rotation of the product, after purification by chromatographic adsorption on a column of alumina, was the same within experimental error from the two sources.

During the course of the present work it was found that apparently the presence of iodine in the reaction mixture favored the formation of a normal biosidic link, whereas the absence of iodine favored the formation of an orthoester linkage. The reaction between acetobromomannose and β-D-mannose-1,2,3,4-tetraacetate in the presence of iodine gave a product which always

crystallized with great ease. If iodine were not added the product could be obtained only as a sirup which probably consisted largely of the orthoester derivatives. On the other hand, the reaction between acetobromomannose and β-D-glucose-1,2,3,4-tetraacetate in the presence of iodine often gave a sirupy product which could not be induced to crystallize. This sirup probably consisted chiefly of the normal form. In all cases where the iodine was omitted the orthoester (m. p. 169°) crystallized readily from the reaction mixture.

Experimental

β-D-Mannose Pentaacetate.—β-D-Mannose pentaacetate was prepared according to the procedure of Fischer and Oetker.[8] From 200 g. of dry β-D-mannose was obtained 294 g. of β-D-mannose pentaacetate (m. p. 116–117° (cor.)), 68%.

Acetobromomannose.—Seventy-five grams of β-D-mannose pentaacetate was added to 300 ml. of a solution of hydrogen bromide in glacial acetic acid containing a little acetic anhydride, saturated at 0°. After standing at room temperature for three hours (the mixture was stirred until solution was complete) the mixture was diluted with 600 ml. of U. S. P. chloroform and poured into a separatory funnel containing about three liters of crushed ice. The chloroform layer was separated, washed five times with ice water containing some ice, and then dried over anhydrous sodium sulfate. After filtration, the chloroform was evaporated under reduced pressure. The sirup was taken up in 250 ml. of anhydrous ether and high boiling petroleum ether added nearly to turbidity. Dried "Darco" (decolorizing charcoal) and anhydrous sodium sulfate were added and the mixture shaken. The solution was filtered directly into a 500-ml. round-bottomed flask through a layer of anhydrous sodium sulfate, a layer of "Darco" and a layer of "Filter-Cel," taking care to protect the solution from moisture during the filtration. The perfectly colorless filtrate was seeded with acetobromomannose. The flask was equipped with a stopcock, evacuated until the solution became turbid, and set in the refrigerator. Next day the mother liquor of the crystals was concentrated under reduced pressure to about 150 ml. Finally, 72 g. of crystals melting at 57–58° (cor.) was obtained; yield, 92%.

Purification of Chloroform.—The method used for purifying the chloroform has been described previously.[9]

β-D-Glucose-1,2,3,4-tetraacetate.—β-D-Glucose-1,2,3,4-tetraacetate was prepared by the method described in an earlier paper.[9]

β-D-Mannose-1,2,3,4-tetraacetate.—The preparation of β-D-mannose-1,2,3,4-tetraacetate is described in a recent paper.[10]

6-β-D-Mannosido-β-D-mannose Octaacetate (Normal).—The following materials were used in this preparation: β-D-mannose-1,2,3,4-tetraacetate (18 g.), "Drierite" (50 g.), dry alcohol-free chloroform (140 ml.), silver oxide (15 g.), iodine (2 g.), and acetobromomannose (18 g.). The apparatus and the procedure used were identical with that described for the preparation of β-gentiobiose octaacetate.[9]

The reaction product was crystallized from 95% ethanol; yield 11.7 g. (39%). After four recrystallizations from ethanol, the rotation and melting point were constant: $[\alpha]^{25}D$ +19.6° (*c*, 3.7; *l*, 2; $CHCl_3$); m. p. 152–153° (cor.).

Anal. Calcd. for $C_{12}H_{14}O_{11}(COCH_3)_8$: (a) acetyl, 11.79 ml. of 0.1 *N* sodium hydroxide for 100-mg. sample; found by the method of Kunz and Hudson[11] 11.79 ml. and 11.81 ml. Found by the Freudenberg[12] method, 11.70 ml. (b) Calcd.: C, 49.56; H, 5.65. Found: C, 49.2; H, 5.65.

6-β-D-Mannosidomannose.—6-β-D-Mannosido-mannose octaacetate (8.6 g.) was deacetylated according to the method of Zemplén.[13] The acetate dissolved within two minutes after the sodium methylate was added. After seven minutes the free sugar began to separate; yield of amorphous product, 2.7 g., which began to soften at 70° and caramelized at 90–95°. A solution of the disaccharide (1.1 g.), phenylhydrazine hydrochloride (2.4 g.) and sodium acetate (3.6 g.) in water (15 ml.) heated on steam-bath for one hour gave a crystalline product on cooling. Recrystallized from aqueous ethanol by slow evaporation with a current of air, m. p. 122–128°. *Anal.* Calcd. for $C_{24}H_{32}O_9N$: N, 10.76. Found: N, 10.75 (micro).

Acetylation of 6-β-D-Mannosido-D-mannose.—6-β-D-Mannosido-D-mannose (0.5 g.), obtained by deacetylation of the octaacetate, was dissolved in acetic anhydride (8 ml.) containing sodium acetate (0.5 g.). This mixture was heated on a steam-bath for two hours and then poured into ice water (200 ml.). A white amorphous solid separated. After standing in the refrigerator overnight, this solid was separated and crystallized from 95% ethanol. The crystalline product (0.1 g.) was identical with the original 6-β-D-mannosido-β-D-mannose octaacetate as was shown by mixed melting point.

Two Orthoester Forms of 6-Mannosidoglucose Octaacetate.—The following materials were used in this preparation: eighteen grams (1 mol) of β-D-glucose-1,2,3,4-tetraacetate, 15 g. of silver oxide, 50 g. of "Drierite," 200 ml. of dry, alcohol-free chloroform, 2 g. of iodine, and 21.5 g. (1 mol) of acetobromomannose. The apparatus and procedure was the same as that used for the preparation of 6-β-D-mannosido-β-D-mannose octaacetate except the acetobromomannose solution was added dropwise over a period of from four to six hours. The sirupy product thus obtained was dissolved in ethyl ether, evaporated to dryness and taken up again in 400 ml. of ether. Rosets of crystals separated out on standing overnight at room temperature. Then after standing about eight hours longer in the refrigerator, 3.5 g. of crystals was obtained (m. p. 165–167°; $[\alpha]^{22}D$ +16.6°). (These crystals may be obtained from 95% ethanol instead of ethyl ether.) Yields as high as 23% have been obtained without iodine in the reaction mixture. Recrystallization from 95% ethanol to constant rotation gives a product, *d*-(β-D-glucose-1,2,3,4-

(8) Emil Fischer and Rudolf Oetker, *Ber.*, **46**, 4034 (1913).

(9) Delbert D. Reynolds and Wm. Lloyd Evans, THIS JOURNAL, **60**, 2559–2561 (1938).

(10) Delbert D. Reynolds and Wm. Lloyd Evans, *ibid.*, **62**, 66–69 (1940).

(11) Alfons Kunz and C. S. Hudson, *ibid.*, **48**, 1982 (1926).

(12) Karl Freudenberg and Max Harder, *Ann.*, **433**, 230–233 (1923).

(13) Geza Braun, *Org. Syn.*, **17**, 34 (1937).

tetraacetate-D-mannose-3′,4′,6′-triacetate 6,1′,2′-orthoacetate), which has the following properties: m. p. 168–169° (cor.); $[\alpha]^{30}D$ +17.1° (*c*, 2.07; *l*, 2; $CHCl_3$).

Anal. Calcd. for $C_{12}H_{14}O_{11}(COCH_3)_8$: (a) acetyl, on basis of one alkali stable acetyl group, 10.32 ml. of 0.1 *N* sodium hydroxide for 100-mg. sample; found by the method of Kunz and Hudson[11] 10.35 ml., 10.34 ml. (b) Acetyl, on the basis that all acetyl groups are removed by acid, 11.79 ml. of 0.1 *N* sodium hydroxide for 100-mg. of sample; found by the Freudenberg[12] method; 11.71 ml., 11.70 ml.

The mother liquor from the above was left in the refrigerator four days longer and more needles crystallized out. These were filtered off and washed with ether: weight, 2.7 g.; m. p. 146–153°; $[\alpha]^{22}D$ −8°. This material was a mixture of the two orthoesters. Recrystallized to constant rotation the product, *l*-(β-D-glucose-1,2,3,4-tetraacetate-D-mannose-3′,4′,6′-triacetate 6,1′,2′-orthoacetate), has the following properties: m. p. 174.0–174.5° (cor.); $[\alpha]^{32}D$ −27.6° (*c*, 4.85; *l*, 2; $CHCl_3$).

Anal. Calcd. for $C_{12}H_{14}O_{11}(COCH_3)_8$: (a) acetyl, on the basis of one alkali stable acetyl group, 10.32 ml. of 0.1 *N* sodium hydroxide for 100-mg. sample; found by the method of Kunz and Hudson[11] 10.38 ml., 10.51 ml. (b) Acetyl, on the basis that all acetyl groups are removed by acid, 11.79 ml. of 0.1 *N* sodium hydroxide for 100-mg. sample; found by the Freudenberg[12] method; 11.95 ml.

The orthoester forms were found to be soluble in acetone, chloroform and warm alcohol. They are not very soluble in ethyl ether or cold alcohol.

The mother liquor left after all the crystalline material had been separated or, if the orthoester forms were not wanted, the sirup from the original reaction mixture after the solvent was removed, was treated with 100 ml. of boiling distilled water to which had been added 1 drop of 0.1 *N* hydrochloric acid (*cf.* Pacsu[14]). The mixture was vigorously stirred at the boiling point for ten minutes and then allowed to cool to room temperature with the stirrer going. Then the mixture was placed in the refrigerator. Later the water solution was poured off and the residue left was treated in the same manner with one or two 500-ml. portions of boiling distilled water. (The treatment with hot water containing a trace of hydrochloric acid serves to decompose most of the orthoester forms and then most of the decomposition products, mannose and glucose tetraacetates, are extracted with the water.) The residue obtained is quite hard and brittle at room temperature. After drying it may be converted to a white amorphous powder by rubbing with low-boiling petroleum ether. In one case, 11 g. of dried snow white material was obtained with a softening range of 83–87° and $[\alpha]^{23}D$ +33.5° but usually about 8 g. of material was obtained with approximately the same properties. It was found that this material can be used directly for the preparation of crystalline acetobromomannosidoglucose.

Acetobromo-6-β-D-mannosido-D-glucose.—The procedure for this preparation was a modification of that used by Brauns[15] in the preparation of acetobromogentiobiose. Eleven grams of dried, amorphous 6-β-D-mannosido-β-D-glucose octaacetate (obtained as above) was dissolved in 100 ml. of chloroform and cooled to −1°. To this was added 28 ml. of a saturated solution of hydrogen bromide in glacial acetic acid containing a small amount of acetic anhydride. The mixture was kept in a stoppered Erlenmeyer flask in an ice-salt bath for one and one-half hours (temperature about −2°). The solution was then poured into a liter separatory funnel about half-filled with crushed ice, shaken out, washed four times with ice water, dried over anhydrous sodium sulfate and filtered through "Darco." The colorless chloroform solution was evaporated to a thick sirup under reduced pressure, which was taken up in 200 ml. of anhydrous ether. The material crystallizes spontaneously in rosets of fine needles. After standing in the refrigerator overnight, 8.5 g. of crystals were filtered off and washed with anhydrous ether; m. p. 168–169°. After one recrystallization from chloroform and ethyl ether, 8.0 g. of material was obtained, m. p. 171–172°; $[\alpha]^{20}D$ +148° ($CHCl_3$); yield, 70%. After purification to constant rotation, $[\alpha]^{30}D$ +151.5° (*c*, 5.18; *l*, 2; $CHCl_3$); m. p., 172.0–172.5,° if heated very rapidly to within 10° of the melting point. The material melts clear and darkens about ten degrees higher.

Anal. Calcd. for $C_{12}H_{14}O_{10}Br(COCH_3)_7$: (a) bromine, 11.43%; determined gravimetrically as AgBr after hydrolyzing with sodium hydroxide and neutralizing with nitric acid; 11.68% and 11.63%. (b) Acetyl, Kunz and Hudson[11] procedure on the basis of one bromine and seven acetyl groups, 11.44 ml. of 0.1 *N* sodium hydroxide for 100-mg. sample; found, cooling base and acetone solutions to 5° before mixing and using a half an hour period of hydrolysis, 11.54 ml. and 11.48 ml. (The residue left after removing the bromine and the acetyl groups is very unstable in alkaline solutions, tending to form acids.)

Acetobromomannosidoglucose was found to be soluble in chloroform and acetone and insoluble in ethyl ether.

Acetylation of Acetobromomannosidoglucose.—The following materials were used: 14 g. of "Drierite," 1 ml. of C. P. glacial acetic acid, 35 ml. of dry, alcohol-free chloroform, 1 g. of silver acetate, 0.7 g. of iodine and 2 g. of acetobromomannosidoglucose. The apparatus and procedure were essentially the same as those used for the condensation of acetobromomannose and glucose tetraacetate. The chloroform solution, obtained after the reaction mixture was filtered, was colored with iodine, which was removed by extraction with a 10% solution of potassium iodide in water. The white amorphous powder obtained weighed 1.39 g. with a softening range of 90–94° and $[\alpha]^{25}D$ +43°. The product behaved almost exactly like that obtained from the acetobromomannose and glucose tetraacetate.

Purification of 6-β-D-Mannosido-β-D-glucose Octaacetate (Normal Form).—The method of chromatography was used to purify the 6-β-D-mannosido-β-D-glucose octaacetate in order to determine its properties. For discussions of the method, see Cassidy,[16a] Zechmeister and Cholnoky,[16b]

(14) Eugene Pacsu (THIS JOURNAL, **61**, 2673 (1939)) used a similar method to remove the orthoester forms in the preparation of normal β-ethylsorboside tetraacetate.

(15) D. H. Brauns, *ibid.*, **49**, 3174 (1927).

(16)(a) Harold G. Cassidy, THIS JOURNAL, **63**, 2735 (1941), and earlier articles. (b) L. Zechmeister and L. Cholnoky, "Principles and Practice of Chromatography," translated from the 2nd German ed. by A. L. Bacharach and F. A. Robinson, Chapman and Hall Ltd., London, 1941. (c) Harold H. Strain, "Chromatographic Adsorption Analysis," Interscience Publishers, Inc., New York, 1942.

and Strain.[16e] An examination of the literature indicated that alumina (ignited aluminum oxide) might be a very good adsorbent since it adsorbs compounds having free hydroxyl groups more strongly than if the same compounds have the hydroxyl groups esterified. The expected impurities have one free hydroxyl group each while the octaacetate wanted is completely esterified. Incidentally, it was found that certain activated grades of alumina are unsuited for sugar acetates. They contain free alkali which evidently partially deacetylates the sugar acetate. A reagent grade of ignited aluminum oxide which would pass through an 80-mesh screen rather easily and yet was not dusty was found to be satisfactory. This was stirred with a dilute solution of acetic acid (1700 g. of alumina in 2 liters of distilled water containing 20 ml. of glacial acetic acid) to remove any free alkali present and then washed twice with distilled water and dried. Just before use it was heated to 230–250° in an Erlenmeyer flask and allowed to cool with the flask lightly closed with a cork stopper.

The "flowing chromatogram" method was used in an apparatus essentially the same as that described by Fieser[17] for pressure filtration. After the column (3 cm. × 30 cm.) was moistened with anhydrous ethyl ether, about 4 g. of dried material in 50 ml. of anhydrous ethyl ether was added. The solvents used for eluants were mixtures of synthetic ether, acetone and ethanol; 95% ethanol (5% water) being the final solvent used. The rotation of each fraction of solvent was determined as it came through in order to obtain some idea as to the progress of the adsorption bands through the column. The glucose tetraacetate carried a trace of a triphenylmethane derivative which was adsorbed on the aluminum oxide column just below the normal form of mannosidoglucose octaacetate. This impurity fluoresces in ultraviolet light in a slightly darkened room; thus the progress of the corresponding band down the column may be followed easily. The receiver was changed each time when 50 ml. of the eluting agent was added to the column. The optical rotation of each of these fractions was determined and then the solvent was removed by evaporation under reduced pressure. If the amorphous material remaining was nearly pure mannosidoglucose octaacetate (normal form), a more or less characteristic deposit would form on the sides of an Erlenmeyer flask containing it, if low boiling petroleum ether were added and the lightly stoppered flask was warmed to the point where the petroleum ether evaporated off slowly. The deposit looked as if it might be crystalline to the naked eye, but showed no definite edges under the microscope except where it was broken. The fractions containing these characteristic deposits were powdered, filtered, washed with fresh petroleum ether and dried. Most of these fractions had specific rotations in the range of +37.5 to +39°, the results being the same within experimental error whether the material used was prepared from acetobromomannose and glucose tetraacetate or from acetobromomannosidoglucose. A second passage through a new column of aluminum oxide did not change the properties significantly. The material, 6-β-D-mannosido-β-D-glucose octaacetate, has a softening range of 90–95° and $[\alpha]^{19}D$ +38.9° (*c*, 4.02; *l*, 2; $CHCl_3$). The amorphous material is soluble in ethyl ether, benzene, dioxane, acetic anhydride, amyl acetate, methanol, acetic acid, pyridine, ethanol, chloroform and acetone. It is very slightly soluble in petroleum ether, water, propyl alcohol, and isoamyl alcohol.

Anal. Calcd. for $C_{12}H_{14}O_{11}(COCH_3)_8$: (a) acetyl, 11.79 ml. of 0.1 *N* sodium hydroxide for 100-mg. sample; found by the method of Kunz and Hudson[11]: 11.88 ml. and 11.90 ml. Molecular weight in benzene, 678.6 calculated; 618 found.

Discussion

Isbell[7] observed a rapid increase in rotation when an orthoester form of 4-glucosido-methylmannoside heptaacetate was dissolved in dry chloroform containing hydrogen chloride. For this reason a study has been made of the behavior of the newly synthesized orthoester forms of 6-mannosidoglucose octaacetate in various concentrations of hydrogen chloride in absolute chloroform.

Whereas Isbell noted only a rapid rise in rotation in the above case, we observed two distinct rotational changes when the orthoester disaccharides were subjected to this treatment. First, there was an initial rise in rotation which was too rapid to be followed stepwise under the experimental conditions. This did not appear to be greatly influenced by the concentration of the acid (although a molecular equivalent of hydrogen chloride must be present), but it was followed by a decrease in rotation, the rate of which was dependent upon the acid concentration. Figure 1, B and C, represent the changes observed

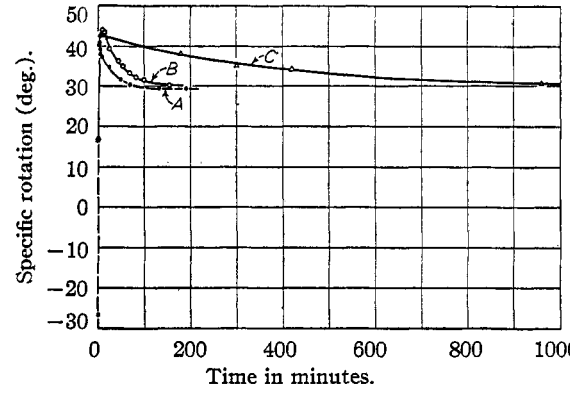
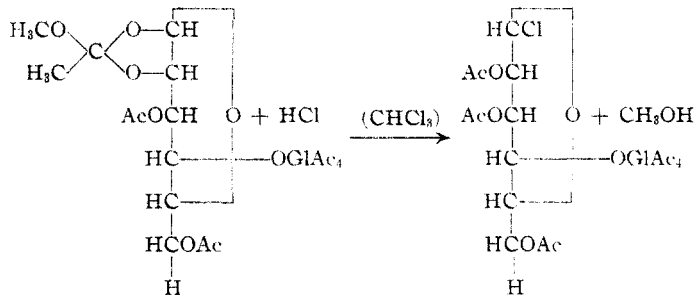


Fig. 1.—A, Specific rotation of the levorotating orthoester octaacetate (m. p. 174°) when dissolved in chloroform containing 0.19 g. of hydrochloric acid per 1 g. of orthoester octaacetate; initial $[\alpha]^{32}D$ −27.6°. B, Specific rotation of dextrorotating orthoester octaacetate (m. p. 169°) when dissolved in chloroform containing 0.37 g. hydrochloric acid per 1 g. of orthoester octaacetate; initial $[\alpha]^{30}D$ 17.10°. C, Specific rotation of the dextrorotating orthoester octaacetate (m. p. 169°) when dissolved in chloroform containing 0.088 g. hydrochloric acid per 1 g. of orthoester octaacetate, initial $[\alpha]^{30}D$ 17.10°

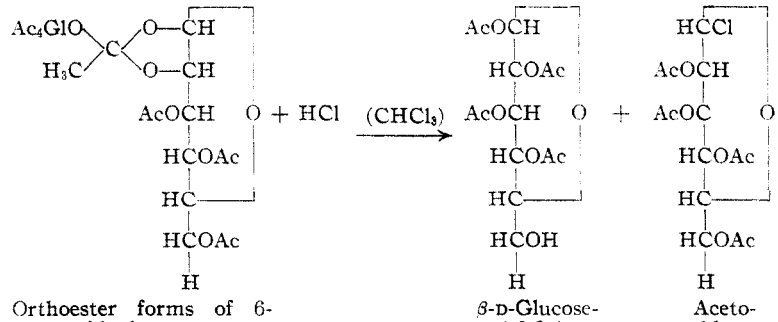
(17) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, 1941.

under different concentrations of acid using the orthoester having a specific rotation of + 17.1°. It is obvious that the decrease in rotation could be practically eliminated if the acid were of sufficiently low concentration. The orthoester with a specific rotation of −27.6° (Fig. 1, A) was found to react in the same general way, even showing practically the same maximum specific rotation followed by a fall to about the same value as shown by the positively rotating orthoester. These results might be expected on the basis of Isbell's observation.[3,7] When he treated the orthoester form of 4-glucosido-methylmannoside heptaacetate with hydrogen chloride in dry chloroform, he was able to isolate a small amount of acetochloro-4-glucosidomannose. In order to explain the formation of the acetochloro compound, he proposed a cleavage of the molecule, which may be represented by the equation



Equation 1

Assuming that the disaccharide orthoesters undergo a similar splitting and rearrangement, an analogous change in the orthoester forms of 6-mannosidoglucose octaacetate may be represented as illustrated in Equation 2.



Orthoester forms of 6-mannosidoglucose octaacetate
$[\alpha]^{30}D$ +17.1° and $[\alpha]^{32}D$ −27.6°

β-D-Glucose-1,2,3,4-tetraacetate
$[\alpha]^{20}D$ 12.1°[18]

Aceto-chloro-mannose
$[\alpha]^{20}D$ +90.5°[19]

Equation 2

Equation 2 explains the rise in rotation after treatment with dry hydrogen chloride in chloroform, but it does not explain the fall which follows. Attempts to isolate the products in crystalline condition were unsuccessful.

It seemed logical to believe that an analogous reaction should take place if hydrogen bromide were used instead of hydrogen chloride. In Fig. 2 are shown the rotational changes which took place under such treatment. It is of interest to note here that the change in rotation after the initial rise is an increase in rotation, whereas the second change was a decrease in rotation when hydrogen chloride was used: ($[\alpha]^{30}D$ + 131.57° for acetobromomannose.)[20] Since the acetobromo sugars in general are much more unstable than the corresponding acetochloro compounds, turning brown when they decompose, with the evolution of hydrogen bromide, we were able to obtain evidence that acetobromomannose was formed in the product from treatment with hydrogen bromide. After treating a sample of the positively rotating orthoester with hydrogen bromide–chloroform solution, removing the hydrogen bromide from the chloroform solution, evaporating the chloroform and taking the sirup up in anhydrous ether, the ether solution became dark brown on standing at room temperature a very short time and acid fumes were evolved as indicated by moist litmus paper. This would indicate that acetobromomannose was actually formed when the orthoester was treated with hydrogen bromide.

In order to account for the rotational changes which took place after the initial rise (Fig. 1), the following facts may be considered: (1) when Isbell treated an orthoester form of 4-glucosidomethylmannoside heptaacetate with a hydrogen chloride–chloroform solution, the initial rapid rise in rotation was the only change observed; (2) when an orthoester form of 6-mannosidoglucose octaacetate was treated with a chloroform–hydrogen chloride solution, the rapid initial rise in rotation was followed by a de-

(18) Burckhardt Helferich and Hellmut Jochinke, *Ber.*, **74B**, 719–725 (1941).

(19) Eugene Pacsu, *ibid.*, **61**, 1512 (1928).

(20) D. H. Brauns, *Bur. of Standards J. Research*, **7**, 581–582 (1931).

crease in rotation, the rate of which was directly dependent upon the hydrogen chloride concentration; and (3) when an orthoester form of 6-mannosidoglucose octaacetate was treated with a hydrogen bromide–chloroform solution, the rapid initial rise in rotation was followed by a slower rise in rotation, the rate of which was directly dependent upon the hydrogen bromide concentration (Fig. 2).

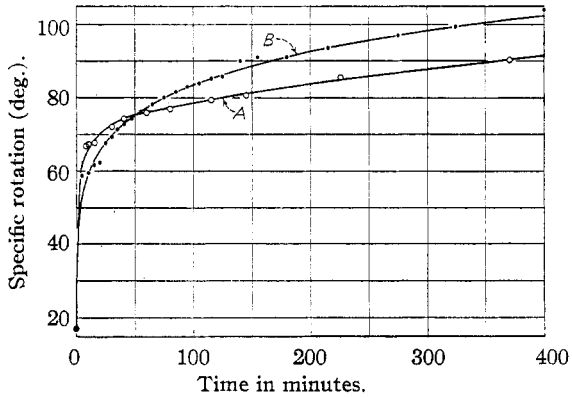


Fig. 2.—A, Specific rotation of the dextrorotating orthoester octaacetate (m. p. 169°) when dissolved in chloroform containing 0.28 g. of hydrogen bromide per 1 g. of orthoester octaacetate; initial $[\alpha]^{30}D$ 17.10°. B, Specific rotation of the dextrorotating orthoester octaacetate (m. p. 169°) when dissolved in chloroform containing 0.81 g. of hydrogen bromide per 1 g. of orthoester octaacetate; initial $[\alpha]^{30}D$ 17.10°.

Whereas the orthoester form of 4-glucosidomethylmannoside heptaacetate yielded methyl alcohol, the new orthoesters yielded β-D-glucose-1,2,3,4-tetraacetate (compare equations 1 and 2). From this fact it was concluded that the second change in rotation must be related in some way to this constitutional difference; perhaps, to the behavior of β-D-glucose-1,2,3,4-tetraacetate in the hydrogen halide-chloroform solutions. This was shown to be true when separate samples of β-D-glucose-1,2,3,4-tetraacetate were treated with a hydrogen chloride–chloroform solution and with a hydrogen bromide–chloroform solution. The results of these experiments are shown in Fig. 3. It becomes of great interest to compare these data with the second change in Fig. 1. Our experiments showed that the rate of change in rotation was a function of the hydrogen halide concentration as was true for the orthoester.

From these observations the authors believe they are correct in concluding that the decrease in rotation observed during the action of hydrogen chloride on a disaccharide orthoester of the type

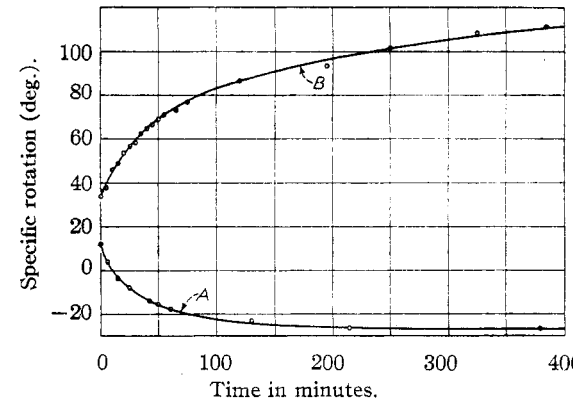


Fig. 3.—A, Specific rotation of β-D-glucose-1,2,3,4-tetraacetate (m. p. 128–129°) dissolved in chloroform containing 0.51 g. of hydrochloric acid per 1 g. β-D-glucose-1,2,3,4-tetraacetate; initial $[\alpha]^{30}D$ 12.1°. B, Specific rotation of β-D-glucose-1,2,3,4-tetraacetate (m. p. 128–129°) dissolved in chloroform containing 0.87 g. of hydrogen bromide per 1 g. of β-D-glucose-1,2,3,4-tetraacetate; first reading $[\alpha]^{30}D$ 33.8°.

studied in this report is caused by the action of hydrogen chloride on the β-D-glucose-1,2,3,4-tetraacetate which is formed by the reaction as indicated in equation 2. Likewise, the rise in rotation which follows the rapid initial rise when the disaccharide orthoester is treated with a hydrogen bromide–chloroform solution is due to the reaction of the hydrogen bromide with the glucose tetraacetate which is formed as previously indicated.

The approximate rotation of the normal form of 6-β-D-mannosido-β-D-glucose octaacetate was calculated on the basis of Hudson's isorotation rules according to the method described earlier,[10] from the known values for 6-β-D-mannosido-β-D-mannose octaacetate (B), β-D-glucose pentaacetate[21] (A′) and β-D-mannose pentaacetate (B′).[21] Thus

$$[\alpha_A]M_A{}^{22} = [\alpha_{A'}]M_{A'} - [\alpha_{B'}]M_{B'} + [\alpha_B]M_B$$
$$[\alpha_A]M_A = (+1482) - (-9828) + (+13357)$$
$$= +24667$$
$$[\alpha_A] = +36.4° \text{ (The observed value is } +38.9°)$$

The observed rotation agrees fairly well with that calculated by Hudson's rules.

Acknowledgment.—The authors wish to acknowledge the assistance given by William G.

(21) C. S. Hudson, "Relations Between Rotatory Power and Structure in the Sugar Group," *Scientific Papers of the Bureau of Standards*, Government Printing Office, Washington, 1926, No. 533 p. 379.

(22) $[\alpha_A]M_A$ = Molecular rotation of 6-β-D-mannosido-β-D-glucose octaacetate
$[\alpha_B]M_B$ = Molecular rotation of 6-β-D-mannosido-β-D-mannose octaacetate
$[\alpha_{A'}]M_{A'}$ = Molecular rotation of β-D-glucose pentaacetate
$[\alpha_{B'}]M_{B'}$ = Molecular rotation of β-D-mannose pentaacetate

Dauben and Harold D. McDowell[23] during the progress of the work.

Summary

1. Crystalline 6-β-D-mannosido-β-D-mannose octaacetate has been synthesized and characterized; m. p. 152–153° (cor.); $[\alpha]^{25}D$ +19.6°.

2. Amorphous 6-β-D-mannosido-mannose has been prepared from the corresponding octaacetate. This sugar began to soften at 70° and caramelized at 90–95°; $[\alpha]^{31}D$ +61.5°. The crystalline 6-β-D-mannosido-mannose phenylosazone has been prepared, m. p. 122–128°.

3. A series of two orthoester forms and one normal form of a glycoside (6-D-mannosido-β-D-glucose octaacetate) has been prepared for the first time.

4. The crystalline positively (m. p., 168–169° (cor.); $[\alpha]^{30}D$ + 17.1°) and negatively (m. p. 174.0–174.5° (cor.); $[\alpha]^{32}D$ −27.6°) rotating orthoester forms of 6-mannosido-β-D-glucose octaacetate have been synthesized and characterized. The action of dry hydrogen halide–chloroform on them has been studied.

5. The normal form of 6-β-D-mannosido-β-D-glucose octaacetate $[\alpha]^{19}D$ +38.9°) has been isolated and purified by chromatographic adsorption and its properties determined.

6. α - Acetobromo - 6 - β - D - mannosido - D - glucose has been prepared crystalline and its properties determined, m. p. 172.0–172.5° (cor.); $[\alpha]^{30}D$ +151.5°.

COLUMBUS, OHIO RECEIVED DECEMBER 17, 1942

(23) The Ohio State University W.P.A. project.

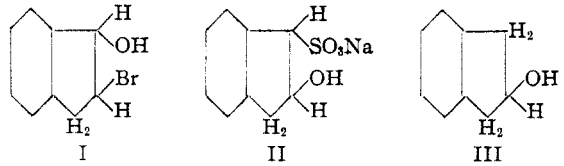
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Reaction of Indene and Styrene Bromohydrins with Sodium Sulfite. Cleavage of Alkali Sulfonates with Sodium in Liquid Ammonia

BY C. M. SUTER[1] AND H. BAYARD MILNE

Some time ago von Braun and co-workers[2] reported that the reaction of indene bromohydrin (1-hydroxy-2-bromoindane) with methylamine or dimethylamine gives a derivative of 2-hydroxy-1-aminoindane, presumably through the intermediate formation of indene oxide.[3] On the other hand, styrene bromohydrin (1-phenyl-1-hydroxy-2-bromoethane) reacts with ammonia without rearrangement,[4] and a third bromohydrin, 1-phenyl-1-hydroxy-2-bromopropane,[5] with methylamine yields a mixture of *pseudo* and *iso*-ephedrine.

The diverse behavior of these bromohydrins with ammonia and amines suggested the present study of the reaction of indene and styrene bromohydrins with sodium sulfite and other alkaline reagents. Indene bromohydrin, I, reacts rapidly with an excess of hot aqueous sodium sulfite solution to give a high yield of a sodium hydroxyindanesulfonate, II, together with a small amount of *trans*-indene glycol. The hydroxysulfonate undergoes rapid cleavage by sodium in liquid ammonia to give 2-indanol, III, thus indicating its structure.



The reaction of indene oxide with sodium bisulfite yields chiefly *cis*- and *trans*- indene glycols but the oxide and sodium sulfite give the same hydroxysulfonate that is obtained from the bromohydrin. Since in the bromohydrin reaction an excess of sodium sulfite was present the assumption that the oxide is an intermediate in the reaction is not contradicted. The hydroxysulfonate, II, is readily identified by its acetate which has a definite melting point.

The reaction of styrene bromohydrin, IV, with sodium sulfite gives a mixture of three products: styrene glycol, sodium 2-phenylethane-1-sulfonate, and sodium 1-hydroxy-1-phenylethane-2-sulfonate, V. The 2-phenylethane-1-sulfonate presumably comes from unchanged styrene or 1-phenyl-1-bromoethane present in the bromohydrin, as both of these yield this sulfonate.[6]

(1) Present address, Winthrop Chemical Company, Rensselaer, New York.

(2) von Braun and Weissbach, *Ber.*, **63**, 3052 (1930); von Braun, Braunsdorff and Kirschbaum, **55**, 3652 (1922).

(3) von Braun, Anton and Weissbach, *ibid.*, **63** 2847 (1930).

(4) Read and Reid, *J. Chem. Soc.*, 1488 (1928).

(5) Stevens, Allenby and Du Bois, THIS JOURNAL, **62**, 1424 (1940).

(6) Kharasch, May and Mayo, *J. Org. Chem.*, **3**, 188 (1938); Kharasch, Schenck and Mayo, THIS JOURNAL, **61**, 3092 (1939).