SUGAR ACETATES, HALOGENO-ACETATES, AND ORTHOESTERS IN RELATION TO THE WALDEN INVERSION

By

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I INTRODUCTION

The sugar acetates and their derivatives are among the most important sugar compounds from the standpoint of their general usefulness for analytical purposes, in synthesis, and in the elucidation of structure. Methods for the preparation of the fully acetylated derivatives were discovered early in the history of sugar chemistry, and several of the acetates were soon obtained in crystalline form. In some cases two crystalline acetates were obtained for the same sugar, and it became apparent that these were alpha and beta modifications analogous to the glycosides. Today, a large number of the crystalline sugar acetates are known, in both alpha and beta modifications, and are widely used in the characterization of the sugars and their derivatives. Because the acetyl linkage can be removed readily, and yet is comparatively stable, acetylation has frequently been employed to protect part of the hydroxyls in the sugar molecule, in the course of reactions involving the remaining groups. Thus the acetylated sugars have proved to be valuable starting materials in the synthesis of other derivatives.

Even more useful than the sugar acetates in synthetic processes are their halogen derivatives, prepared by reaction of the hydrogen halide upon the acetate, and having the halogen attached to the glycosidic carbon. Since this halogen is particularly reactive in comparison to the acetyl groups, the halogeno-acetates may be used in a wide variety of reactions

involving replacement on the glycosidic carbon. Thus a halogeno-acetate may be condensed with alcoholic hydroxyl groups in the presence of a basic condensing agent, (e.g., silver oxide or carbonate, or quinoline), to form glycosides, substances which are widely distributed in plant and animal life. Consequently, the halogeno-acetates of the sugars have an essential part in the synthesis of compounds which are important in biochemical research and have practical applications in the fields of pharmacy and medicine. Numerous syntheses of natural glycosides have already been carried out, generally thru the reaction of the non-saccharide constituent with a halogeno-acetyl sugar.

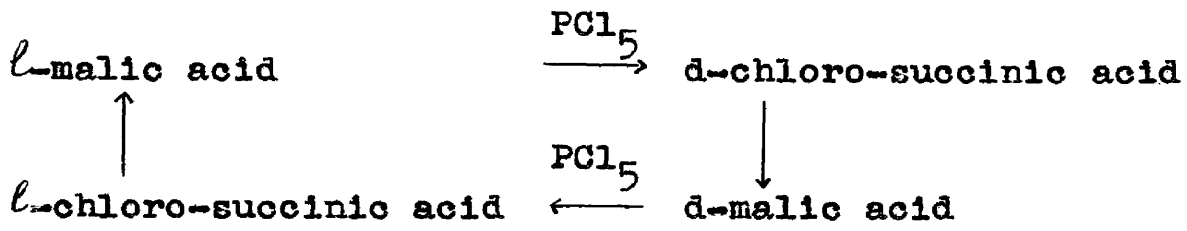
In a special group of glycosides, the disaccharides, several syntheses have been accomplished by essentially the same methods. For instance, by treating α-bromo-tetraacetyl-d-glucose with tetraacetyl-d-glucose in the presence of silver carbonate, Fischer synthesised isotrehalose, (β,β -trehalose), (1), and by condensing α-bromo-tetraacetyl-d-glucose with levoglucosan and carefully hydrolysing the 1,6 ring, Freudenberg and Nagai (2) obtained cellobiose. In the hands of Helferich and co-workers this condensation method has resulted in the synthesis of a number of other disaccharides, including gentiobiose (3). In these condensations, the alpha halogeno-acetyl sugar is combined with another sugar having one free hydroxyl group, and the resulting disaccharide is formed with a Walden inversion on carbon one, so that these syntheses generally lead to disaccharides with a beta type of union. One might anticipate that the alpha type of union could be

obtained by use of the beta halogeno-acetate, but the preparations have not generally been successful. A few beta chloro-acetates have been obtained by treatment of the alpha bromo-acetate with an especially prepared silver chloride, (4) but these beta compounds are frequently unstable, and in condensation reactions give complex mixtures from which crystalline products are not readily separable.

Since replacement occurs with inversion at carbon one, the difference in behavior of the alpha and beta halogeno-acetates is, no doubt, related to the mechanism of the Walden inversion. A brief review of the Walden inversion, and its various interpretations will afford a basis for its application to the replacement reactions of the halogeno-acetyl sugars.

II THE WALDEN INVERSION

In 1896, Walden first reported a novel inversion of rotation in the conversion of malic to chloro-succinic acid by reaction with PCl_5 (5).



Since this first brief report, the phenomenon, which has come to be known as the Walden inversion, has been extensively studied with numerous reactants and optically active substances (6, 7). Several hypotheses for the mechanism have been advanced, but modifications of two assumptions have most frequently been made, namely that there is a removal of one of the attached groups before inversion (8), or that there is some sort of intermediate addition compound or complex formation (9, 10). In 1911 Werner, (11, p. 881) suggested an "opposite face" mechanism for the Walden inversion. He pointed out that in the tetrahedron formed by the groups A,B,D, and X attached to a carbon, there are four positions at which an entering group may become attached, with the extrusion of group X, namely the four faces ABX, BDK, DAX, or ABD. Substitution for X at one of the first three of these faces will cause no change in configuration, but when the entering group approaches the face opposite X, (ABD), with simultaneous withdrawal of X, a shift to the enantiomorphic configuration

must occur. Garner, (12) clarified the Werner concept by means of an ingenious mechanical model showing this shift in valencies, which is comparable to the turning inside out of an umbrella.

In 1940, Isbell, (13) applied the opposite face concept in the explanation of many reactions in the field of sugar chemistry. The sugars and their derivatives are uniquely adapted to the study of the inversion mechanism since, with the carbons bound in a ring, rotation about the carbon-carbon bonds is largely restricted, and the spheres of influence of the various groups are oriented in space. For the purpose of obtaining more information concerning the derivatives of the sugar acetates, and their reactions, it seemed advantageous to study the Walden inversion and its interpretation by the opposite face concept in reactions of the halogeno-acetyl sugars.

III REPLACEMENT REACTIONS OF THE HALOGENO-ACETYL SUGARS

In the course of several years' work, Dr. H. S. Isbell had prepared a number of the heptose sugars, (14, 15, 16) of which the acetates, halogeno-acetates and glycosides had not been studied. These sugars were available for investigation, and offered an excellent opportunity for the preparation of new acetate derivatives, and for testing the opposite face mechanism as applied to the replacement reactions of the halogeno-acetyl sugars.

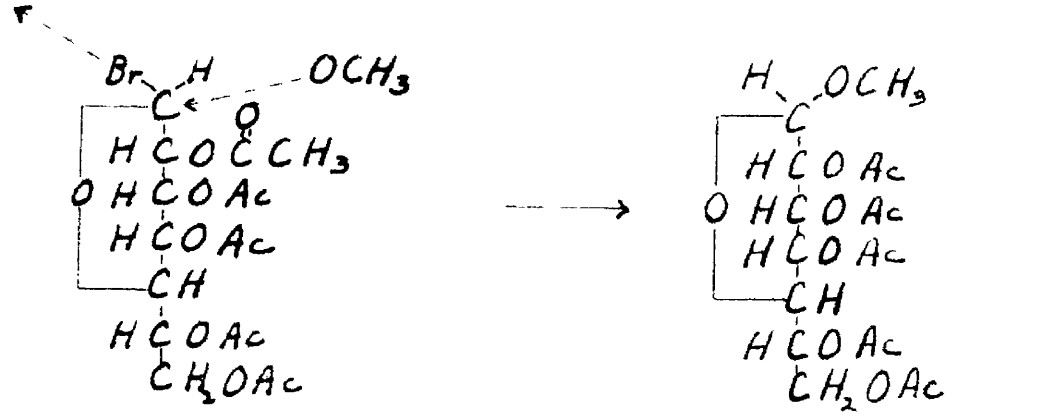
The replacements studied in this investigation have involved the reaction between certain halogeno-acetyl sugars and methyl alcohol in the presence of silver carbonate, a reaction first used almost simultaneously by Koenigs and Knorr, (17), and by Fischer, (18), and commonly referred to as the Koenigs-Knorr reaction. In a number of cases this reaction has led to the formation of compounds in which one of the acetyl groups is joined to the glycosidic carbon and the adjacent one in an orthoacetic ester structure, and the normal glycoside, if produced, is obtained only in small yield. According to Isbell, (13) the orthoester seems to be formed by an intramolecular reaction in which an acetyl group adjacent to the glycosidic carbon approaches the face of carbon one opposite the departing halogen, and combines with inversion. Presumably, as the bromine is removed by combination with the silver carbonate or other suitable reagent, the carbonyl oxygen is attracted to the opposite face

of carbon one, leaving the acetyl carbon deficient in electrons. The deficiency is satisfied by the attraction of a negative group, in this case, methoxyl, from the environment. Electronically, the reaction may be considered to consist in a flow of electrons from the hydrogen of the methyl alcohol to the methoxyl, from the methoxyl to the acetyl carbon, to the oxygen, to the glycosidic carbon, and finally to the bromine. This results in the formation of a hydrogen ion, a bromide ion, and the methyl orthoacetate.

The orthoester is formed only when the carbonyl oxygen of an acetyl group can approach the face of the carbon opposite the halogen. This is possible when the acetyl and halogen atoms lie on opposite sides of the plane of the sugar ring. As shown by the diagrams, when the halogen and the acetyl group of carbon two are on the same side of the ring, the carbonyl oxygen of the acetyl group is unable to approach carbon one at the face opposite the departing halogen, and therefore it cannot form the orthoester. Under these circumstances the halogen is replaced with inversion by a negative group from the environment, (OCH_3 in this case). This is the ordinary Koenigs-Knorr reaction which leads to the formation of normal glycosides. However, when the halogen and the adjacent acetyl group are on opposite sides of the ring, either the acetyl group of the adjacent carbon, or the methoxyl group from the environment is capable of approaching the face of carbon one opposite the departing halogen, and combining with inversion. One of these reactions gives the normal glycoside, the other the orthoester, and the two reactions may be conceived as

FIGURE I

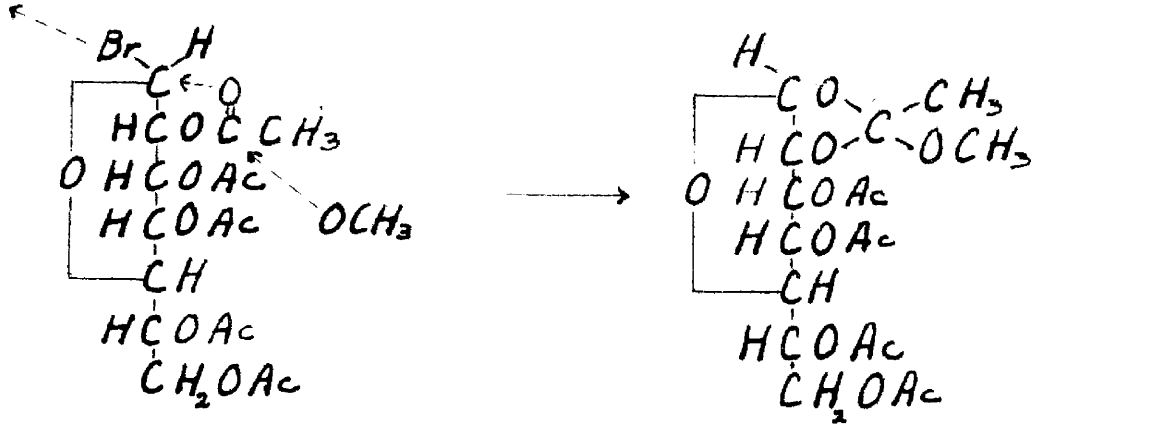
NORMAL GLYCOSIDIC REACTION



Bromo-pentaacetyl-
α-d-α-guloheptose

Methyl pentaacetyl
β-d-α-guloheptoside

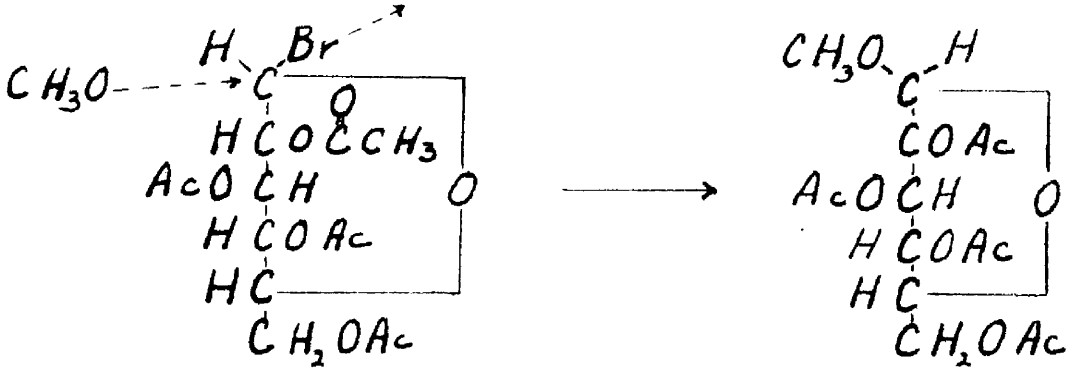
ORTHOESTER FORMATION



Bromo-pentaacetyl-
α-d-α-guloheptose

Tetraacetyl-d-α-guloheptose
methyl orthoacetate

NORMAL GLYCOSIDIC REACTION



Bromo-tetraacetyl-
α-d-glucose

Methyl tetraacetyl-
β-d-glucoside

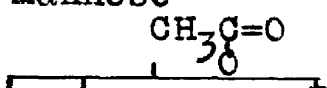
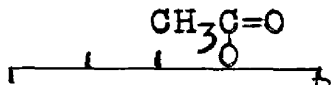
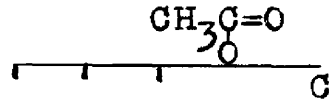
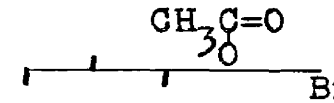
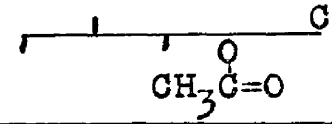
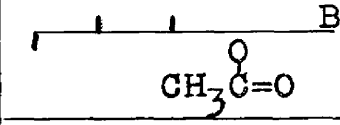
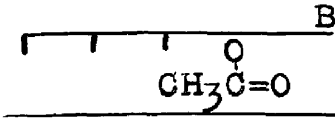
Acetyl group cannot approach carbon one
on side opposite departing halogen

occurring in competition, so that ordinarily both products are formed. The separation of crystalline isomers from this mixture is frequently difficult, and consequently the lack of a crystalline derivative is not satisfactory evidence for the lack of orthoester formation.

Crystalline orthoesters have been prepared for rhamnose, lyxose, mannose, 4-glucosido-mannose, α-glucoheptose, ribose, fructose, sorbose, turanose, and maltose. The structure and configuration of the parent halogeno-acetyl derivatives are known for all of these compounds with the exception of maltose. Since the orthoester of maltose was prepared from a chloro-acetylmaltose which supposedly has a chloro-orthoester structure, (19, 20) the formation of the methyl orthoester of maltose presumably involves merely the replacement of the chlorine in a structure already existing, but not the formation of an entirely new orthoester, the reaction being considered here. Inasmuch as carbon one of the ketoses is free to rotate about the carbon-carbon axis, the acetyl group of carbon one can always be brought into a favorable position for the ortho-ester reaction, and all ketoses are therefore capable of orthoester formation. Aside from the derivatives of maltose and the ketoses, the orthoesters so far prepared have been formed from halogeno-acetates in which the acetyl groups of both carbons two and three are trans to the halogen. Although the configuration of carbon three may to some extent influence orthoester formation, it is believed that it plays only a limited part, according to the mechanism outlined, and that the essential configuration is a trans relationship between

TABLE I

Aldose sugars which have yielded methyl orthoacetates

Hexose Configuration	Sugars	Orthoacetate prepared
A. From the alpha halogeno-acetate		
Mannose 	rhamnose	Fischer, Bergmann, and Rabe (21)
	lyxose	Levene and Wolfrom, (22)
	mannose	Dale, (23)
	glucosido-mannose	Isbell, (24)
Talose 	talose	Pigman and Isbell, (25)
	α-guloheptose	This investigation
Altrose 	neolactose	This investigation
Idose 	not investigated	
B. From the beta halogeno-acetate		
Gulose 	α-glucoheptose	Haworth, Hirst and Stacey, (4)
Galactose 	not investigated	
Allose 	not investigated	
Glucose 	not investigated	

carbons one and two. As may be observed from the compilation of data on orthoester formation shown in Table I, only halogeno-acetyl sugars having the α-mannose, α-talose, or β-gulose configuration have previously been reported to give orthoesters. In the course of this investigation the reactions of chloro-acetylneolactose, (altrose structure), have been studied, and the heretofore unknown bromo-acetyl-α-d-α-gulcheptose (talose structure) has been prepared. The application of the Koenigs-Knorr reaction to these compounds lead to the preparation of new crystalline orthoesters of neolactose and α-gulcheptose. These new compounds show all of the reactions and properties of other orthoesters, including stability of the orthoacetyl group toward alkaline hydrolysis, and formation of the normal halogeno-acetate by the reaction of dry hydrogen chloride in chloroform solution, (24).

In addition to confirming the opposite face mechanism for orthoester formation, this investigation has lead to the synthesis of a number of sugar acetates and bromo-acetates which are of value for the preparation of other sugar derivatives, and for the study of structure, configuration, and optical rotation.

IV EXPERIMENTAL DETAILS

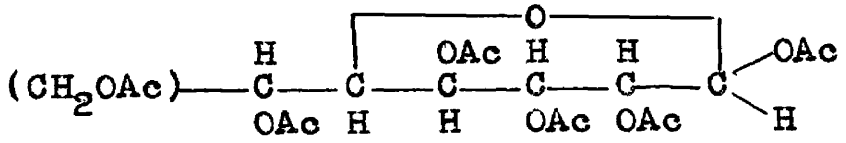
A. The preparation and properties of the acetyl sugars.

With the exception of chloro-acetylneolactose, the halogeno-acetyl sugars used in this investigation were prepared from the corresponding fully acetylated sugars. Several methods are available for the preparation of acetyl sugars, and these give different products, depending upon whether equilibrium is established between the alpha and beta pyranose, furanose and open chain forms of the sugar before or after acetylation. When the crystalline sugar is treated with pyridine and acetic anhydride at low temperature there is very little interconversion of the isomeric forms of the sugar either before or after acetylation, and consequently this method ordinarily leads to a product which has the same structure and configuration as the parent sugar. Because of the simplicity of the method and the purity of the resulting product, the low temperature pyridine method was used whenever crystalline sugars were at hand. In most cases crystalline acetates were obtained, but with α-d-gulose-$CaCl_2.H_2O$, (26) the acetylation product obtained by the pyridine method failed to crystallize, and it was necessary to try other methods. Unsuccessful attempts were made to prepare a crystalline gulose pentaacetate by the high temperature sodium acetate method, (27) and the low temperature sulphuric acid method, (28, 29). A small quantity of crystals, had been obtained previously by the low temperature zinc chloride method. This

preparation was repeated with large quantities of the d-gulose calcium chloride, and 60g of the crude acetate was obtained by use of a unique method for separating the product, which consisted in dissolving the crude acetate in a large volume of water and allowing the water to evaporate in air. As evaporation took place, a scum of sirupy acetate formed on top of the water. This scum was removed from day to day, until finally crystals separated from the aqueous solution.

The process for converting the sugar to the acetate even by the pyridine method frequently causes considerable isomerization, and the formation of other ring isomers. (furanosides), of aldehydo derivatives and partially acetylated products. Crystalline mixtures are difficult to separate, and since the percentages of carbon and hydrogen in the various compounds do not differ widely, analyses for these elements are not reliable criteria for the purity of the product. However, the analyses in conjunction with acetyl determinations, and comparisons of optical rotations provide a fairly reliable means for the assignment of structure to the products.

1. Hexaacetyl-α-d-α-galaheptopyranose



Twenty grams of α-d-α-galaheptose.H_2O, (30), was acetylated by the low temperature pyridine method. After the acetylation mixture had been stirred in an ice bath for 2 days, it was poured into ice water and formed an amorphous mass. The water

was decanted and the acetate was stirred with a fresh quantity of ice water. When the process was repeated, the acetate crystallized, and crystals also separated from the first two liquors upon addition of seed. The total weight of crystalline acetate was 29 g, m.p. 120-128°, and $(\alpha)_D^{20} = -7.6°$ approximately. A chloroform extraction of the watery solutions yielded a sirup which crystallized slowly upon standing, but these crystals, (about 9 g) were evidently a different product, for they melted at 110-115°C, and were dextrorotatory, ($[\alpha]_D^{20} = +10°$ approximately). Some difficulty was experienced in the purification of the levorotatory product. Although the compound crystallized well, and from a number of solvents, purification was slow. Carbon tetrachloride, ether, isopropyl alcohol, and ethyl alcohol were successively used, and 7 recrystallizations were given the compound before it was considered pure. The last two recrystallizations were from ethyl alcohol. Hexaacetyl-α-d-α-galaheptopyranose melts at 132°C and gives $[\alpha]_D^{20} = -25.8°$. Analysis: Calculated for $C_{19}H_{26}O_{13}$: C, 49.35; H, 5.67. Found: C, 49.42; H, 5.99.

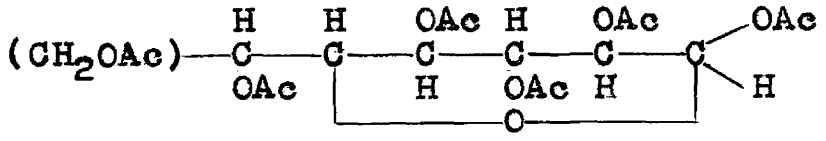
The dextrorotatory fraction was dissolved in ethyl alcohol from which about 2 g of button-like clusters of needles separated, m.p. 108-109°C, $[\alpha]_D^{20} = +19°$ approximately. The mother liquor was poured off from these, and nearly solidified at once in a mixture of crystalline forms. Aside from the 2 g of this compound, no more material has been obtained by recrystallizing mixtures of the two acetates, and these products will be held for further investigation.

Assignment of the alpha pyranose structure to the levorotatory acetate is based upon its preparation from the alpha pyranose form of the sugar, (*14, p. 519*) and upon agreement with the optical rotation as calculated from the analogous compounds listed below. (d-α-Galaheptose has the *l*-mannose configuration).

	M
(1) Methyl tetraacetyl-α-*l*-mannopyranoside	-17,800
(2) Methyl pentaacetyl-α-d-α-galaheptopyranoside	-8,900
(3) Pentaacetyl-α-*l*-mannopyranose	-21,500
(4) Hexaacetyl-α-d-α-galaheptopyranose	X

$$(1) - (2) = (3) - (4)$$
$$-17,800 - (-8,860) = -21,500 - X$$
$$X = -12,600$$
$$[\alpha] = -12,600/462.4$$
$$= -27.2^\circ \text{ (calculated)}$$
$$[\alpha] = -25.8^\circ \text{ (observed)}$$

2. Hexaacetyl-β-d-β-glucoheptopyranose



Crystals of this acetate were obtained by Dr. Isbell several years ago, but the properties of the compound were not studied. In this investigation, twenty-five grams of crystalline *d*-β-glucoheptose (*31*) was acetylated by the low temperature pyridine method, using 300 ml of acetic anhydride and 250 ml of pyridine. After the acetylation mixture had been mechanically stirred in an ice bath for 2 days, and rotated at room temperature for 3 days, during which time it turned dark, it

was poured into ice water and extracted with chloroform. The chloroform extracts were washed several times with copper nitrate solution, then with water, and after drying and filtering, were concentrated in vacuo to a sirup, which crystallized in the flask. Ether was added, the crystals were separated, and together with a second crop which was obtained by concentrating the mother liquor, weighed 36.7 g, m.p. 130-136°C. The crude acetate was recrystallized several times from warm ethyl alcohol. Hexaacetyl-β-d-β-glucoheptopyranose crystallizes in short prisms m.p. 136°C, and gives $[\alpha]_D^{20} = -9.1°$

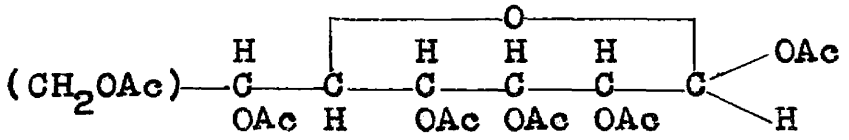
Analysis: Calculated for $C_{19}H_{26}O_{13}$: C, 49.35; H, 5.67. Found: C, 49.21; H, 5.64.

The preparation of the hexaacetyl-d-β-glucoheptopyranose from crystalline β-d-β-glucoheptose by the low temperature pyridine method, which is comparatively mild, appears to support its classification as a beta acetate. However, the rapid complex mutarotation of β-d-β-glucoheptose makes this classification less certain. (*14, p. 518*) A comparison of molecular rotations of the acetate and the bromo-acetate, with those of the epimeric compounds of α-glucoheptose is of interest.

	M
Hexaacetyl-β-d-α-glucoheptopyranose	+2,200
Hexaacetyl-d-β-glucoheptose (β-glucoheptose)	-4,200
Difference	+6,400
Bromo-pentaacetyl-β-d-α-glucoheptopyranose	+75,400
Bromo-pentaacetyl-d-β-glucoheptose	+69,600
Difference	+5,800

While these differences are in harmony, it is not invariably true that the difference in molecular rotation between a pair of acetates is of the same order of magnitude as the difference between the analogous halogeno-compounds. The beta configuration is tentatively assigned, but conclusive comparisons cannot be drawn in this case because hexaacetyl-d-β-glucoheptose has the rare idose structure, and virtually no derivatives having the idose structure are known. When the structures of these new compounds are established, they will provide a basis for allocating structure to derivatives in the gulose-idose series.

3. Hexaacetyl-α-d-α-guloheptopyranose



Five grams of the finely powdered α-d-α-guloheptose (15) was acetylated by the low temperature pyridine method, using 28 ml of acetic anhydride and 35 ml of pyridine. The acetylation mixture was stirred in an ice bath for 2 days, then poured into ice water from which the acetate separated as a gum. The water solution was decanted and a fresh quantity of ice water was added, from which the compound crystallized in an hour. The crude acetate weighed 7.5 g, and melted at 115°C, approximately. A total of 13.2 g of crude material from two acetylations was recrystallized several times from ethyl alcohol, in which the compound is quite soluble. Hexaacetyl-α-d-α-guloheptopyranose melts at 126°C, and gives $[\alpha]_D^{20} = -62.8°$.

Analysis: Calculated for $C_{19}H_{26}O_{13}$: C, 49.35; H, 5.67. Found: C, 49.47; H, 5.64.

The preparation of the d-α-guloheptose acetate from crystalline α-d-α-guloheptose by the low temperature pyridine method supports the classification of the acetate as the alpha pyranose modification, analogous to the sugar. Inasmuch as d-α-guloheptose has the *l*-talose configuration, one might expect a parallelism between the properties of the derivatives of d-α-guloheptose and *l*-talose. The following comparisons show the similarity in molecular rotations of derivatives of the two sugars.[1]

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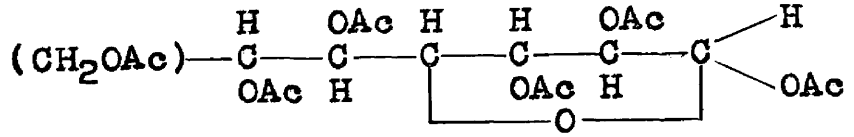
[1] The molecular rotations of the *l*-talose derivatives have been obtained from those of the d-talose derivatives by reversing the signs.

	M
Pentaacetyl-α-*l*-talopyranose	-27,400
Hexaacetyl-d-α-guloheptose	-29,000
Bromo-tetraacetyl-α-*l*-talopyranose	-68,100
Bromo-pentaacetyl-d-α-guloheptose	-60,000
Triacetyl-*l*-talose methyl orthoacetate	-1,340
Tetraacetyl-d-α-guloheptose methyl orthoacetate	+1,400

4. Hexaacetyl-α-d-β-guloheptofuranose



Finely powdered α-d-β-guloheptose (32) (1.35 g), was acetylated at 0°C, in 9 ml of acetic anhydride and 14 ml of

pyridine.[2] The mixture darkened, and the sugar went into

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[2]This sugar was originally named by La Forge, d-α-gulo-heptose. However, using the nomenclature for the heptoses suggested by Isbell, (33) in which the alpha and beta represent not the order of discovery, but the configuration of carbon two, this sugar is named d-β-guloheptose.

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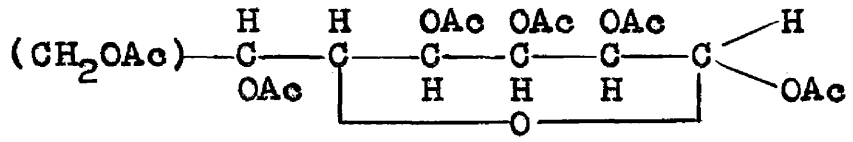
solution slowly. After one week in an ice bath, the mixture was removed to a refrigerator and kept for two weeks longer. It was then worked up by pouring it into ice water, with stirring, and treating the precipitated sirup with two additional quantities of ice water. The compound crystallized in short needles, and a second crop separated from the benzene extracts upon removal of the solvent. The total yield was almost quantitative. After several recrystallizations from ethyl alcohol, hexaacetyl-α-d-β-guloheptofuranose melted at 117-118°C, and gave $[\alpha]_D^{20} = -54.1°$. Analysis: Calculated for $C_{19}H_{26}O_{13}$: C, 49.35; H, 5.67. Found: C, 50.09; H, 5.77.

The preparation of hexaacetyl-d-β-guloheptose from crystalline α-d-β-guloheptose by the pyridine method might be expected to give hexaacetyl-α-d-β-guloheptopyranose. (14, p. 518) d-β-Guloheptose has the ring configuration of l-galactose, and d-α-guloheptose has the configuration of l-talose. A comparison of the optical rotations of the new acetates of d-β-guloheptose and d-α-guloheptose with the previously known acetates of galactose and talose reveals that the difference in the molecular rotations of hexaacetyl-d-β-guloheptose, (-25,000), and hexaacetyl-d-α-guloheptose, (-29,000), is +4,000, while the difference in the molecular rotations of pentaacetyl-α-l-galactofuranose, (-23,900), and pentaacetyl-α-l-talopyranose,

(-27,400), is +3,500. This agreement may be fortuitous but it is probable that a ring shift occurred in the preparation of the new hexaacetyl-d-β-guloheptose and that it is an alpha furanose, instead of an alpha pyranose.

5. Hexaacetyl-α-d-β-mannoheptopyranose



Finely powdered α-d-β-mannoheptose.H_2O (*16, 14, p. 527*) (2.35 g), was acetylated with 13 ml of acetic anhydride and 20 ml of pyridine at 0°C. The sugar went into solution overnight, and the reaction solution was poured into ice water from which it crystallized readily in small needles or short prisms, weighing 3.6 g, m.p.128-132°C. A benzene extraction of the water solution yielded a sirup which failed to crystallize. The acetate, after several recrystallizations from warm ethyl alcohol, melts at 137°C, and gives $[\alpha]_D^{20}$ = +88.8°. Analysis: Calculated for $C_{19}H_{26}O_{13}$: C, 49.35; H, 5.67; Found: C, 49.56; H, 5.72.

The assignment of the alpha pyranose structure to hexaacetyl-d-β-mannoheptose is based upon its preparation from crystalline α-d-β-mannoheptose and upon the agreement of its optical rotation with that calculated from the rotations of compounds, affording a comparison of epimeric differences. (d-α-Mannoheptose has the d-galactose structure, and the epimeric sugar, d-β-mannoheptose has the d-talose structure)

	M
(1) Hexaacetyl-α-d-α-mannoheptopyranose	+55,900
(2) Hexaacetyl-α-d-β-mannoheptopyranose	X
(3) Pentaacetyl-α-d-galactopyranose	+41,770
(4) Pentaacetyl-α-d-talopyranose	+27,400

(1) -(2)= (3) - (40

+55,900 - X = +41,770 - 27,400

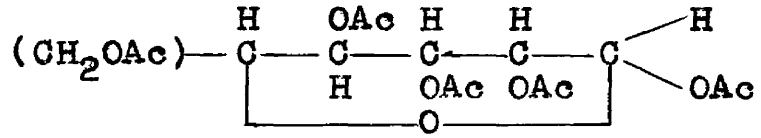
X = +41,530

$[\alpha]$ = +41,530/462.4

= +89.8° (calculated)

$[\alpha]$ = +88.8° (observed)

6. Pentaacetyl-α-d-gulopyranose



In 1932, Dr. Isbell obtained crystals of an acetate of d-gulose, and mentioned the fact in a footnote, N.B.S. Jour. Research, 8, 8 (1932). In the course of this investigation, attempts have been made to find a better method of acetylation, since the low temperature zinc chloride method originally used yielded largely sirupy acetates. However, several other methods gave only traces of the crystalline acetate, (low temperature pyridine method, low temperature sulfuric acid method, and high temperature sodium acetate method), and the zinc chloride method was again used on relatively large amounts of crystalline d-gulose calcium chloride. (26) In the largest acetylation run, 150 g of α-d-gulose.$CaCl_2.H_2O$, finely powdered, was added to 700 ml of acetic anhydride containing 225 g of

freshly fused zinc chloride. The mixture was mechanically stirred in an ice bath for 5 days, and the flask was then rotated at room temperature for another 5 days, after which the sirup was poured into 8 liters of ice and water, and then extracted with a total of 1.6 liters of benzene, in 3 portions. The extracts were concentrated to a sirup, and dissolved in 10 liters of boiling water. Several grams of seed were added to the partially cool solution, and it was allowed to evaporate under a stream of air. The sirupy acetate was skimmed off the surface of the water from time to time, and the crude crystals, when finally removed from the bottom of the beaker weighed 50 g.

When this compound was recrystallized from warm ethyl alcohol, it formed slender needles, m.p. 113°C, $[\alpha]_D^{20} = +86.2°$. However, the needle crystals were quite unstable, and upon standing, or, occasionally even during a filtration were converted to chunky prisms, m.p. 105-106°C. Because of the difficulty in obtaining a single crystalline modification, alcohol was finally abandoned as a solvent for recrystallization, and the acetate was recrystallized from water. The material was dissolved in hot water, the solution was concentrated to approximately one-fourth of its volume, in vacuo, and when cooled, gave the chunky prisms, exclusively, in good yield. They melt at 105-106°C, give $[\alpha]_D^{20} = +86.2°$, and do not lose weight upon prolonged heating at 60°C in vacuo. Analysis: Calculated for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.68. Found for needle crystals, m.p. 113°C: C, 49.31; H, 5.60. Found for prisms m.p. 105-106°C: C, 49.44; H, 5.63.

Assignment of structure is based upon the comparison of the optical rotations of gulose compounds with those of analogous compounds, (A), of galactose, and (B) of glucose. (Gulose differs from galactose in the configuration of carbon three, and from glucose in the configuration of carbons three and four).

(A)

	M
(1) Methyl tetraacetyl-α-d-galactopyranoside	+48,200
(2) Methyl tetraacetyl-α-d-gulopyranoside	+35,300
(3) Pentaacetyl-α-d-galactopyranose	+41,770
(4) Pentaacetyl-α-d-gulopyranose	X

(1) - (2) = (3) -(4)

+48,200 - 35,300 = +41,770 - X

X = +28,870

[α] = +28,870/390.3

= +74 (calculated).

[α] = +86.2, (observed).

(B)

	M
(1) Methyl tetraacetyl-α-d-glucopyranoside	+47,280
(2) Methyl tetraacetyl-α-d-gulopyranoside	+35,300
(3) Pentaacetyl-α-d-glucopyranose	+39,700
(4) Pentaacetyl-α-d-gulopyranose	X

(1) - (2) = (3) -(4)

+47,200 - 35,300 = +39,700 - X

X = +27,780

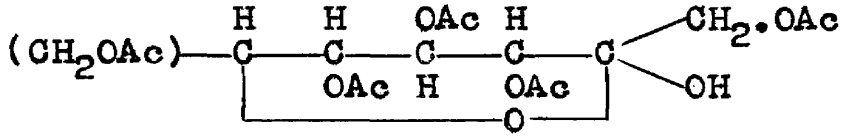
[α] = +27,780/390.3

= +71.1° (calculated)

[α] = +86.2° (observed)

The difference between the observed optical rotation of the gulose acetate (+86.2°), and the calculated values, (+74° and +71°), is larger than might be anticipated for substances of closely related structures. This may find explanation in the existence of different ring comformations which have been postulated by Isbell to account for other variations in the optical rotations of substances in the gulose and α-glucoheptose series, (*34*).

7. Pentaacetyl-α-d-glucoheptulopyranose



In the course of this investigation, an acetylation of d-glucoheptulose (*35*) was carried out by the low temperature pyridine method. W. C. Austin had reported the preparation of hexaacetyl-α-d-glucoheptulose by the hot sodium acetate method of acetylation, (*34*) and it was expected that the same acetate would be formed by the milder method. However, the acetylated sugar proved to be a mixture from which has been isolated, in addition to Austin's acetate, a pentaacetyl-d-glucoheptulose, and a crude fraction having a rotation different from either.

Twenty grams of powdered glucoheptulose was added to 92 ml of acetic anhydride and 140 ml of pyridine, and the acetylation mixture was stirred at 0°C. for 3 days, and rotated at room temperature for 2 days. It was then poured into ice water, and the precipitated gum was treated with successive quantities of ice water, with stirring, but it failed to crystallize. All water solutions were combined and extracted with chloroform,

and after addition of the gum, the chloroform solution was concentrated in vacuo to a thick sirup, which was brought to crystallization by the addition of ether and petroleum ether. The crude acetate weighed about 30 g, and the melting point was approximately 80°C. This material was given several recrystallizations from aqueous alcohol, (50:50), but appeared to be a mixture. During one recrystallization a second crop of very different appearance separated, (slender prisms, $[\alpha]_D^{20}$ = +48° approximately, whereas Austin's compound forms silky needles, $[\alpha]_D^{20}$ = +87°). Attempts to separate more of the prisms by use of various solvents lead only to mixtures, but it was found that in crystallization from carbon tetrachloride there was some separation. This solvent was now used in numerous recrystallizations, and the rotation of each fraction was checked. The material of high rotation proved to be the hexaacetyl-α-d-glucoheptulose prepared by Austin, and a fraction of low rotation (+10° approximately) will be investigated later. The prisms of specific rotation +48° approximately, were recrystallized several times from carbon tetrachloride and finally from alcohol. In pure condition this acetate gives $[\alpha]_D^{20}$ = +45.9°, m.p. 114-115°C. Analysis showed it to be a pentaacetate. The more polar nature of this hydroxyl-containing compound accounts for the suitability of a non-polar solvent such as carbon tetrachloride in crystallization.

Analysis: Calculated for $C_{17}H_{24}O_{12}$: C, 48.57; H, 5.74.
Found: C, 48.40; H, 5.64.

One gram of the pentaacetate was acetylated at room temperature by the pyridine method, and the product crystallized when poured into ice water, with stirring. After one recrystallization from 95% alcohol, the compound gave $[\alpha]_D^{20} = +86°$. Hexaacetyl-α-d-glucoheptulose has a specific rotation of +87.0°.

Since the new pentaacetate may thus be acetylated to give the known 1,2,3,4,5,7-hexaacetyl-α-d-glucoheptulose, (prepared by Austin), it must be a pentaacetyl-α-d-glucoheptulopyranose. The position of the acetyl groups and the configuration of the glycosidic carbon may be allocated by comparison of the optical rotation of the new compound with that calculated from the optical rotations of certain derivatives in the sorbose series. (Glucoheptulose and sorbose differ principally in the group attached to carbon six, which is CH_2OH, and H, respectively).

	M
(1) Methyl pentaacetyl-α-d-glucoheptulopyranoside	+34,100
(2) 1,3,4,5,7-pentaacetyl-α-d-glucoheptulopyranose	X
(3) Methyl tetraacetyl-α-d-sorbopyranoside	+18,800
(4) 1,3,4,5-tetraacetyl-α-d-sorbopyranose	+7,400

$$(1) - (2) = (3) - (4)$$

$$+34,100 - X = +18,800 - 7,400$$

$$X = +22,700$$

$$[\alpha] = +22,700/420.4$$

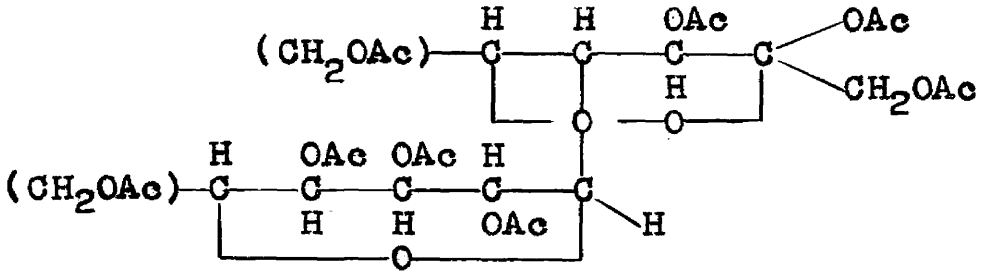
$$= +54°, \text{ (calculated).}$$

$$[\alpha] = +45.9° \text{ (observed).}$$

Although the agreement between the calculated rotation, (+54°), and the observed value, (+45.9°), is not very close, there is better agreement than would be expected for substances having

the acetyl groups on different carbons, or for substances having different ring forms. For this reason the new compound appears to have the structure and configuration characteristic of 1,3,4,5-tetraacetyl-α-d-sorbose, and should be called 1,3,4,5,7-pentaacetyl-α-d-glucoheptulose.

8. Octaacetyl-β-lactulofuranose.



Twenty grams of crystalline lactulose, (4-β-d-galactoside-d-fructose), (37), was acetylated at approximately -15°C by the pyridine method. The mixture was mechanically stirred in an ice and salt bath for two days, and was then poured into ice water and extracted with chloroform. Treatment by stirring with several fresh quantities of ice water failed to bring about crystallization, but after the sirupy acetate had been dissolved in acetone, concentrated to a thin sirup, and treated with ethyl alcohol, bulky needle-like crystals formed, which when separated, weighed 7.5 g. The mother liquor, although light-colored, has not crystallized. The crude acetate was recrystallized several times from warm ethyl alcohol, and once from isopropyl alcohol. The fine needles are difficult to filter, tend to occlude the mother liquor, and when pure and dry, electrify and scatter badly, thus causing some loss in handling. Pure octaacetyl-β-lactulofuranose melts at 138°C, and gives

$[\alpha]_D^{20}$ =-6.6°. Analysis: Calculated for $C_{28}H_{38}O_{19}$: C, 49.56; H, 5.64. Found: C, 50.01; H, 5.69.

The crystalline lactulose used in preparing the new crystalline octaacetyllactulose probably contains a furanose modification of the sugar, (38), and consequently the resulting acetate by mild acetylation might also be expected to contain the furanoid ring. Unfortunately there are no rotational data available for use in assigning the furanoid ring to derivatives in this series. However, a comparison of rotations indicates that the compound is neither the α- nor the β-pyranoid modification. Thus the optical rotation of octaacetyl-α-d-lactulopyranose may be calculated to be +22.3°, from the following values:

	M
(1) Octaacetyl-α-lactopyranose	+36,300
(2) Octaacetyl-α-lactulopyranose	X
(3) Pentaacetyl-α-d-glucopyranose	+39,700
(4) Pentaacetyl-α-d-fructopyranose	+18,500

Since lactose is a substituted glucose, and lactulose a similarly substituted fructose, then

$$(1) - (2) = (3) - (4)$$

$$+36,300 - X = +39,700 - 18,500$$

$$X = +15,100$$

$$[\alpha] = +15,100/678.6$$

$$= +22.3°$$

Similarly, the optical rotation of octaacetyl-β-d-lactulopyranose may be calculated to be -76.5°

	M
(1) Octaacetyl-β-lactopyranose	-3,200
(2) Octaacetyl-β-lactulopyranose	X
(3) Pentaacetyl-β-d-glucopyranose	+1,480
(4) Pentaacetyl-β-d-fructopyranose	-47,200

$$(1) - (2) = (3) - (4)$$

$$-3,200 - X = +1,480 - (-47,200)$$

$$X = -51,800$$

$$[\alpha] = -51,800/678.6$$

$$= -76.5°$$

The new octaacetate did not reduce Schiff's reagent, and hence is not an open chain compound but must be a derivative of either the alpha or the beta furanose since its specific rotation (-6.6°) differs greatly from either of the values calculated for the pyranoses. The ring in lactulofuranose lies to the right in the usual projectional formula, and hence according to the Drew and Haworth modification[3] of Hudson's

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[3] Generally, an equimolecular mixture of the alpha and beta forms of the sugar possesses a dextro-rotation when the ring lies to the right in the projectional formula, and a levo-rotation when the ring lies to the left. That is, the direction of the rotatory contribution of the molecule, except the glycosidic carbon, is dextro or levo depending upon whether the ring lies to the right or the left, respectively.

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lactone rule (*39*), the optical rotation of the lactulose structure not including the glycosidic carbon should be dextrorotatory. Since the new compound is levorotatory, it must be the more levorotatory member of the alpha-beta pair, and hence it is octaacetyl-β-lactulofuranose.

B. The preparation and properties of the halogeno-acetyl sugars.

After the preparation of a number of new acetates, and the determination of their properties, several of them were converted to the halogeno-acetates, in order that the replacement reactions of the halogen might be studied. Ordinarily, the alpha halogeno-acetates of the sugars are obtained by treating the sugar acetate with the corresponding hydrogen halide in acetic acid solution, or by treatment with phosphorus pentachloride, titaniun tetrachloride, or other suitable halide. Prolonged treatment of the sugar acetates with these reagents at high temperature leads to further substitution, and to complex reactions involving configurational changes which give new sugars. For instance, when octaacetyllactose is treated with aluminum chloride and phosphorus pentachloride, under suitable conditions, chloroacetyl-α-neolactose is obtained. In this process lactose, (4-β-d-galactosido-d-glucose) is converted to neolactose, (4-β-d-galactoside-d-altrose), (40). The chloro-acetyl-α-neolactose used in this investigation was prepared in the manner described. The other halogeno-acetates were prepared from the corresponding acetate by treatment with hydrogen bromide in acetic acid solution.

The bromo-acetyl-d-β-glucoheptose proved to be rather unstable. In purified chloroform it showed a gradual mutarotation and upon standing overnight the solution darkened and decomposed. A more stable halogeno-acetate of d-β-glucoheptose was obtained in small quantity by much the same method,

but this compound has not yet been thoroughly investigated. Bromo-acetyl-d-α-guloheptose was fairly stable and showed only a slight mutarotation in chloroform. When hexaacetyl-α-d-α-galaheptose was brominated by the method used on the other acetates, a crystalline compound containing bromine was obtained, which was mixed with considerable hexaacetyl-α-d-α-galaheptose. Attempts to separate the pure bromo-acetate from this mixture were unsuccessful, and consequently this acetate must be rebrominated by a more drastic method, possibly at room temperature and for a longer time. Attempts to prepare the unknown bromo-acetyl-d-gulose by the hydrogen bromide method lead to the formation of a sirupy product. Various attempts to crystallize the compound, for instance, by use of different solvents, and of extremely low temperatures, were unsuccessful, and the sirup decomposed even in the refrigerator over sodium hydroxide.

1. Bromo-pentaacetyl-β-d-β-glucoheptopyranose.

One gram of the new hexaacetyl-β-d-β-glucoheptopyranose was brominated by treating it with 5 ml of a cold, saturated solution of hydrogen bromide in acetic acid, to which 0.5 ml of acetic anhydride had been added. The sugar dissolved in about ten minutes, and the solution was kept at 0°C, for 3 hours, after which time it was poured into ice water, and extracted quickly with benzene. The benzene extract was washed six times with ice water, dried with "drierite", and after filtration, concentrated in vacuo to a thin sirup which crystallized upon addition of ether. The preparation was

repeated on several 5-gram quantities of the hexaacetyl-β-d-β-glucoheptopyranose, which yielded about 4 g each of the crude bromo-acetate. The compound was recrystallized several times by dissolving it in ether, and adding petroleum ether to saturation. When pure, the compound melts at 114°C.

When the optical rotation of bromo-pentaacetyl-d-β-glucoheptopyranose was read in chloroform, there was found to be a slow mutarotation, with gradual discoloration of the solution. $[\alpha]_D^{20}$ (initial) = +144°, approximately. The compound could not be reclaimed from the chloroform solution, which turned black upon standing overnight, as did also the mother liquors of the recrystallizations. However, the compound crystallizes readily from ether upon addition of petroleum ether, and keeps fairly well when stored in a flat dish over sodium hydroxide in a vacuum desiccator at a low temperature. Without these precautions, even the pure substance soon decomposes with the liberation of hydrogen bromide. Analysis: Calculated for $C_{17}H_{23}O_{11}Br$: C, 42.25; H, 4.80; Br, 16.54. Found: C, 42.92; H, 4.82 ; Br, 16.30.

When 1 g of the hexaacetyl-β-d-β-glucoheptopyranose was brominated by the same method, but the extraction was made with chloroform, and the extract was washed once with sodium bicarbonate solution, a more stable halogen-containing compound melting at 145°C (crude) was obtained. The crude product, which gave $[\alpha]_D^{20}$ = +20° approximately, is being investigated further.

It was shown on page 16, that bromo-pentaacetyl-d-β-glucoheptose gives approximately the same epimeric difference

from bromo-pentaacetyl-β-d-α-glucoheptose, as that which is obtained from the corresponding acetates. In the light of this comparison, bromo-pentaacetyl-d-β-glucoheptose may be tentatively assigned the beta pyranose configuration, but the subject needs further study, since very few data are available for making comparisons in the idose series.

2. Bromo-pentaacetyl-α-d-α-guloheptopyranose.

The new hexaacetyl-α-d-α-guloheptopyranose, (6.8 g) was treated at 0°C, with 35 ml of a saturated solution of hydrogen bromide in acetic acid, and with 3.5 ml of acetic anhydride. After the acetate had dissolved, the solution was kept in ice for 3 hours, and was then poured into ice water. The extraction was made rapidly with benzene, and the benzene extract was washed six times with ice water, dried with "drierite", and after a filtration, concentrated in vacuo. When crystals began to separate from the sirup during evaporation, ether was added, and the crystalline product was collected on a filter. The first crop weighed 4.0 g, and an additional 0.7 g was obtained by concentrating the mother liquor. The crude halogeno-acetate was recrystallized at once from benzene by the addition of ether. When pure, bromo-pentaacetyl-α-d-α-guloheptopyranose melts at 139-140°C, and gives $[\alpha]_D^{20} = -124°$, approximately. There is a slight mutarotation, but it is not so great as in the case of bromo-pentaacetyl-β-d-β-glucoheptopyranose and the compound was readily reclaimed from the chloroform solution. The bromo-acetate is fairly stable when pure, and has been kept at room temperature for several weeks in a flat dish over sodium hydroxide. Analysis: Calculated

for $C_{17}H_{23}O_{11}Br$: C, 42.25; H, 4.80; Br, 16.54. Found: C, 42.81; H, 4.92; Br, 16.47.

As shown on page 18, the rotation of bromo-pentaacetyl-d-α-guloheptose parallels the rotation of bromo-tetraacetyl-α-l-talopyranose, and hence it should be classified tentatively as the alpha pyranose modification.

C. The Koenigs-Knorr reaction.

The Koenigs-Knorr reaction, in which a halogeno-acetate is combined with a hydroxyl-containing compound, frequently an alcohol, in the presence of silver carbonate or other condensing agent, has been used since 1901 (17) as a convenient and most useful means for the synthesis of glycosides, disaccharides, and related substances. In the course of the reaction, water is formed, and reacts further to give objectionable by-products. This factor was not taken into account until relatively recently when Helferich and coworkers used a dessicant to absorb the water as it was formed. Helferich, Bohm and Winkler, (41) used calcium chloride, and Reynolds and Evans (42) introduced the use of powdered "drierite", (calcium sulfate), which has been used in all of the Koenigs-Knorr reactions conducted in the present investigation. In each case the finely powdered halogeno-acetyl derivative was added to alcohol containing powdered drierite and freshly prepared silver carbonate in suspension. All moisture was excluded and the solution was mechanically stirred while reaction took place.

As a result of the preparations carried out in this research, two halogeno-acetates were made available for use

in the Koenigs-Knorr reaction. One of these, (bromo-penta-acetyl-d-α-guloheptose) possesses a configuration which should be favorable for orthoester formation, and, in fact, it gave the orthoester in good yield. The other compound, bromo-pentaacetyl-d-β-glucoheptose, exhibits mutarotation, and appears to resemble the beta acetyl derivatives. If the compound be a beta pyranose derivative, it would not have the configuration favorable for orthoester formation, but actually, the solution gave by analysis, a 30% yield of a product which is resistant to alkaline hydrolysis, and appears to be an orthoester. The formation of this substance might involve the change in configuration which must be postulated to explain the mutarotation reaction. In any case the uncertainty in our knowledge concerning the structure and configuration of the bromo-pentaacetyl-d-β-glucoheptose precludes the interpretation of its behavior in the Koenigs-Knorr reaction.

According to the premise on which this investigation is based, chloro-heptaacetyl-α-neolactose, first prepared by Kuhn and Hudson, should be capable of forming an orthoester. In order to test this hypothesis, chloro-heptaacetyl-α-neolactose was prepared, and as anticipated, it gave a good yield of the orthoester. Inasmuch as chloro-acetyl-α-neolactose has a configuration, (α-altrose), which differs markedly from any previously investigated, (table I), the formation of the new orthoester demonstrates the utility of the investigation.

1. The preparation and properties of tetraacetyl-d-α-guloheptose methyl orthoacetate.

Two grams of powdered drierite and 4 g of freshly prepared silver carbonate were added to 50 ml of methyl alcohol, and the mixture was mechanically stirred in an ice bath for ten minutes. One gram of the finely powdered bromo-pentaacetyl-d-α-guloheptose was added, and the reaction mixture was mechanically stirred at 0°C for 44 hours. It was then filtered, and a part of the filtrate was pipetted into small glass stoppered flasks for analysis. The remainder crystallized completely when the alcohol was evaporated in air, and the sirup was stirred with ethyl alcohol. The crude material melted at approximately 100°C, and gave no test for halogen. In the analysis of the solution for normal acetate and orthoester, advantage was taken of the fact that tenth normal alkali at room temperature hydrolyses the normal acetyl, without disturbing the orthoacetyl group ([21], [23]), whereas all of the attached acetyl groups are removed by tenth normal acid. The excess alkali was titrated at the end of three hours, and the acid after standing overnight. Upon the basis of the difference in alkali and acid consumed, the conversion to orthoester was calculated to be nearly quantitative.

In a second preparation, the analysis was omitted, and all of the product was crystallized and purified. The compound is quite soluble in ether and in alcohol, but nearly insoluble in petroleum ether. It was recrystallized several times from alcohol by careful addition of petroleum ether. When pure, tetraacetyl-d-α-guloheptose methyl 1,2-orthoacetate

melts at 106°C, and gives $[\alpha]_D^{20} = +3.2°$. Analysis: Calculated for $C_{18}H_{26}O_{12}$: C, 49.77; H, 6.03. Found: C, 49.83; H, 6.09.

When treated with an anhydrous, tenth normal solution of hydrogen chloride in chloroform, this compound reacted in a manner characteristic of orthoesters, (24, p. 1117) presumably to form the normal chloro-pentaacetyl-α-d-α-guloheptose. The reaction was too rapid to be measured polarimetrically, and the specific rotation four minutes after dissolution was -38.1°, whereas the specific rotation of the orthoester in chloroform is +3.2°. The solution, when evaporated, gave a residue containing crystals, which will be investigated further. The mechanism of this reaction was discussed earlier in this paper.

2. The preparation and properties of hexaacetylneolactose methyl orthoacetate and methyl heptaacetyl-β-neolactopyranoside.

Five grams of chloro-acetyl-α-neolactose was used in the Koenigs-Knorr reaction under conditions identical with those described for bromo-acetyl-α-d-α-guloheptose. The methyl alcoholic solution, when evaporated to a sirup in air, and stirred with a little ethyl alcohol, yielded slender prismatic crystals melting at 118-121°C, and having a specific rotation of approximately +25°. Acid and alkaline hydrolyses of the reaction solution showed that only about 70% of the original sugar was present, and this was almost completely in the form of the orthoester. It was at first supposed that undissolved chloro-acetyl-α-neolactose remained in the silver residues, but when these were treated with chloroform, and the filtered solvent was evaporated, a halogen-free sirup was obtained which crystallized in short rectangular prisms, when stirred with

methyl alcohol. This crude material melted at 168-174°C, and gave $[\alpha]_D^{20} = -13.7°$. It thus appeared that the Koenigs-Knorr reaction on chloro-acetyl-α-neolactose yielded, besides the crystalline orthoester, a second crystalline product, difficultly soluble in methyl alcohol, and differing widely from the orthoacetate in optical rotation and melting point.

The hexaacetyl neolactose methyl 1,2-orthoacetate was recrystallized several times by dissolving it in absolute alcohol, concentrating the solution in vacuo to about one third of its volume, and rotating the flask at room temperature for an hour before separating the crystals. When thoroughly dried, the crystals melt at 121-122°C, but melting points several degrees lower have been obtained with the pure material. Prolonged drying in vacuo always raised the melting point to the value given. For the pure compound, $[\alpha]_D^{20} = +25.3°$. Analysis: Calculated for $C_{27}H_{38}O_{18}$: C, 49.84; H, 5.89. Found: C, 49.75; H, 5.77.

When the new compound was treated with a tenth normal solution of hydrogen chloride in purified chloroform, it gave the rapid reaction characteristic of orthoesters. The specific rotation of hexaacetylneolactose methyl orthoacetate is +25.3°, but the acid-treated material gave a specific rotation of +62.7°, which had become constant before the solution could be read in the polarimeter. The solution yielded crystals, and these, after recrystallization from ethyl acetate contained halogen, melted at 178°, and showed no depression of melting point when mixed with the original chloro-acetyl-α-neolactose, ($[\alpha]_D^{20} = +71.2$, and m.p. 178-180°C).

The second crystalline substance separated in the Koenigs-Knorr reaction, m.p. 168-174°C, was recrystallized from chloroform by the addition of ether, and finally from a large volume of methyl alcohol. When pure, the compound melted at 179°C, and gave $[\alpha]_D^{20} = -14.5°$. Unlike the ortho-ester, when this compound was treated with hydrogen chloride in chloroform, there was no change of rotation, and the solution after evaporation yielded crystals which are identical with the original compound. Analysis: Calculated for $C_{27}H_{38}O_{18}$: C, 49.84; H, 5.89. Found: C, 49.70; H, 5.91.

Since the ring in the altrose unit of neolactose lies to the right in the projectional formula, and the rotatory contribution of the molecule except the glycosidic carbon is positive, this compound must be the more levorotatory of an alpha-beta pair. Neolactose is 4-β-d-galactosido-d-altrose, and position four in the altrose unit is blocked. Hence, the compound cannot be a furanoside, and must therefore be methyl heptaacetyl-β-neolactopyranoside.

3. The Koenigs-Knorr reaction on bromo-pentaacetyl-β-d-β-glucoheptopyranose.

Although the structure of this compound was uncertain, the Koenigs-Knorr reaction was run by the method described before, and the difference between the acid and the alkaline hydrolysis indicated about 30% of orthoester. Upon evaporation, the alcoholic solution, yielded a mixture of crystals, which will be investigated further.

TABLE II

New compounds prepared in the course of this investigation

Compound[a]	Formula	Molecular Weight	Melting Point, °C.	$[\alpha]_D^{20}$[b]	(M)
Hexaacetyl-α-d-α-galaheptopyranose	$C_{19}H_{26}O_{13}$	462.40	132	-25.8	-11,900
Hexaacetyl-β-d-β-glucoheptopyranose	$C_{19}H_{26}O_{13}$	462.40	136	-9.1	-4,200
Hexaacetyl-α-d-α-guloheptopyranose	$C_{19}H_{26}O_{13}$	462.40	126	-62.8	-29,000
Hexaacetyl-α-d-β-guloheptofuranose	$C_{19}H_{26}O_{13}$	462.40	117-118	-54.1	-25,000
Hexaacetyl-α-d-β-mannoheptopyranose	$C_{19}H_{26}O_{13}$	462.40	137	+88.8	+41,100
Pentaacetyl-α-d-gulopyranose	$C_{16}H_{22}O_{11}$	390.34	105-106[c] 113[d]	+86.2[e]	+33,600
Pentaacetyl-α-d-glucoheptulopyranose	$C_{17}H_{24}O_{12}$	420.36	114-115	+45.9	+19,300
Octaacetyl-β-lactulofuranose	$C_{28}H_{38}O_{19}$	678.58	138	-6.6	-4,500
Bromo-pentaacetyl-β-d-β-glucoheptopyranose	$C_{17}H_{23}O_{11}Br$	483.27	114	+144[f]	+69,600
Bromo-pentaacetyl-α-d-α-guloheptopyranose	$C_{17}H_{23}O_{11}Br$	483.27	139-140	-124	-60,000
Tetraacetyl-α-guloheptose methyl orthoacetate	$C_{18}H_{26}O_{12}$	434.39	106	+3.2	+1,400
Hexaacetylneolactose methyl orthoacetate	$C_{27}H_{38}O_{18}$	650.57	121-122	+25.3	+16,500
Methyl heptaacetyl-β-neolactopyranoside	$C_{27}H_{38}O_{18}$	650.57	179	-14.5	-9,400

[a] Ring structures were assigned by comparisons of optical rotations.

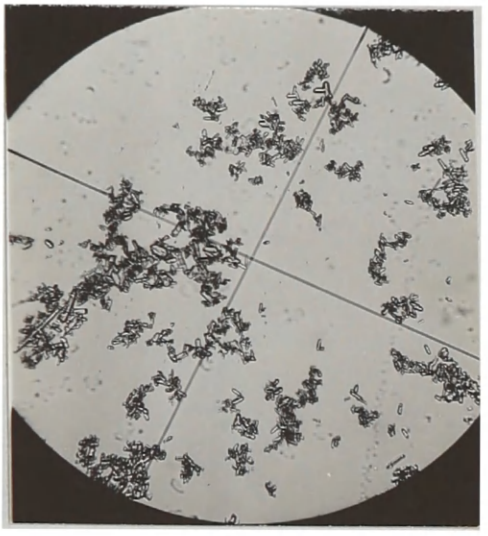
[b] Chloroform was used as the solvent for all rotational measurements.

[c] Melting point of stable prisms.

[d] Melting point of unstable needles.

[e] Rotation of either prisms or needles.

[f] Approximate rotation.



E

F

G

H

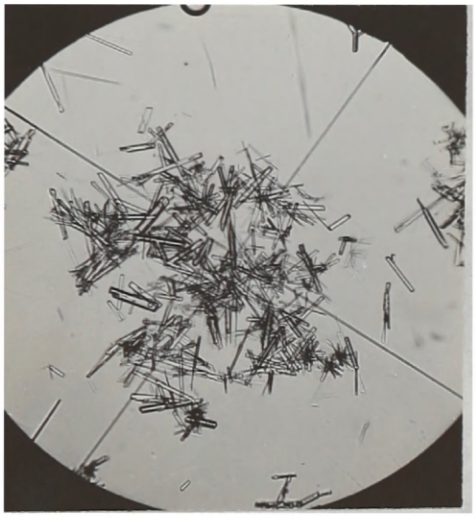
E. Hexaacetyl-α-d-β-mannoheptopyranose

F. Pentaacetyl-α-d-gulopyranose, (needles).

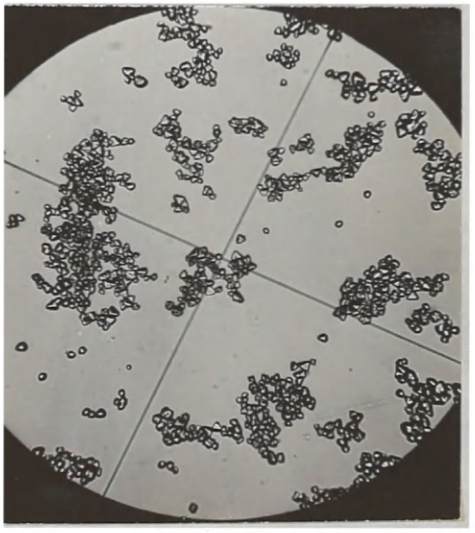
G. Pentaacetyl-α-d-gulopyranose, (prisms).

H. Pentaacetyl-α-d-glucoheptulopyranose

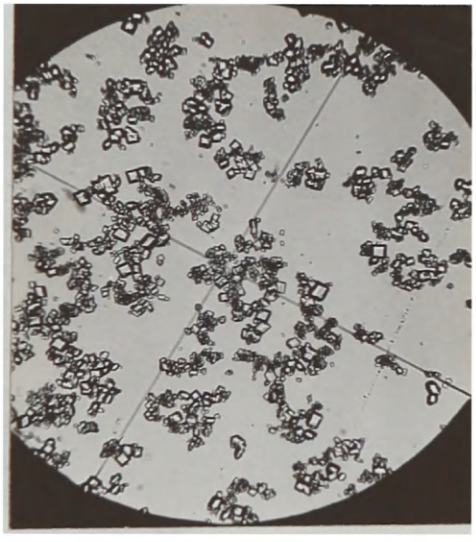
D. Photomicrographs of New Crystalline Compounds



A



B



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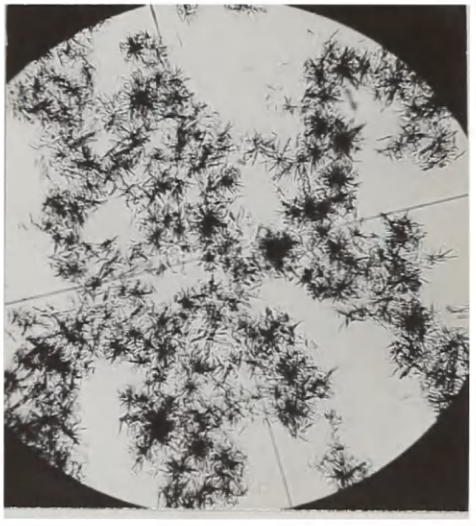


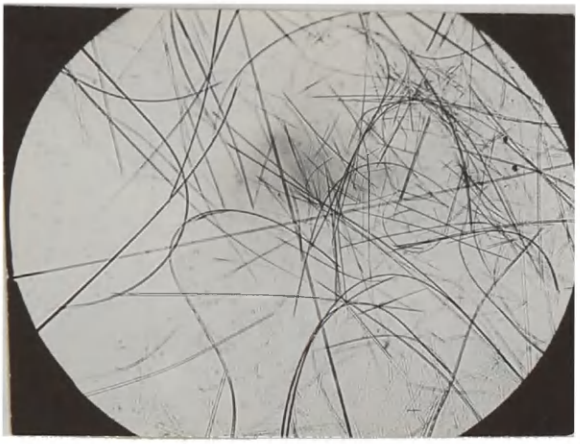
D

A. Hexaacetyl-α-d-α-galaheptopyranose

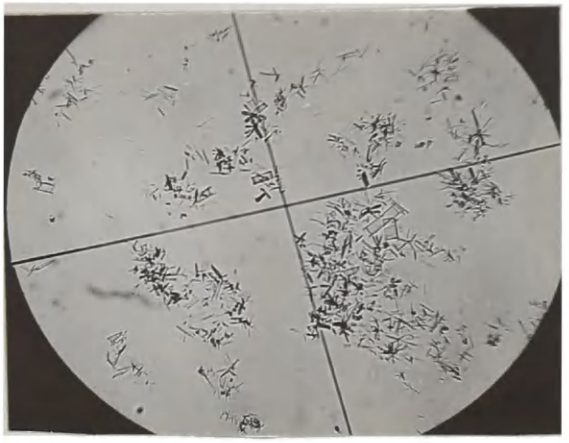
B. Hexaacetyl-β-d-β-glucoheptopyranose

C. Hexaacetyl-α-d-α-guloheptopyranose

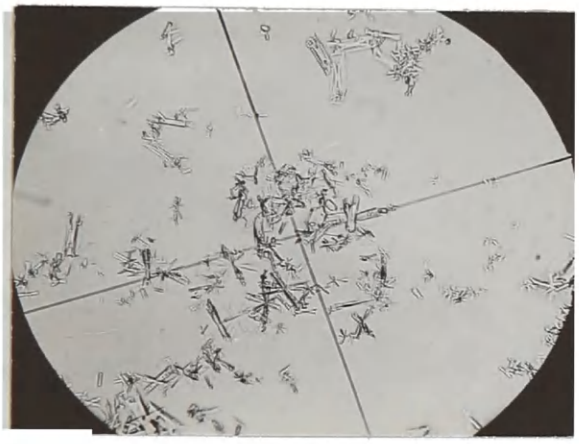
D. Hexaacetyl-α-d-β-guloheptofuranose



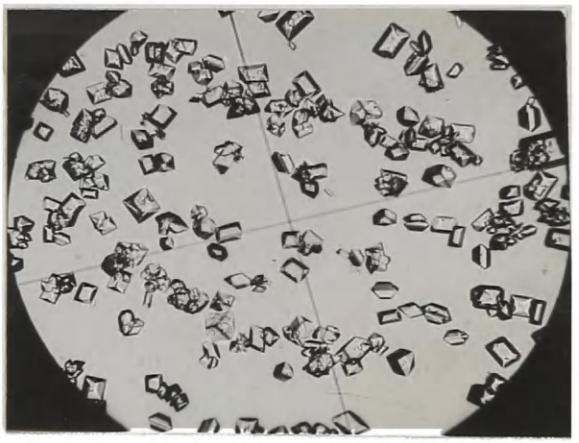
I



J



K



L

M

N

I. Octaacetyl-β-lactulofuranose

J. Bromo-pentaacetyl-β-d-β-glucoheptopyranose

K. Bromo-pentaacetyl-α-d-α-guloheptopyranose

L. Tetraacetyl-α-guloheptose methyl orthoacetate

M. Hexaacetylneolactose methyl orthoacetate

N. Methyl heptaacetyl-β-neolactopyranoside

V SUMMARY

The new crystalline compounds prepared in the course of this investigation are listed in table II. They include eight acetates, two bromo-acetates, two methyl orthoacetates, and one methyl acetyl glycoside. Five aldoheptose acetates have been prepared which have the mannose, idose, talose, (two), and galactose configurations, respectively. One of these compounds, (hexaacetyl-d-β-glucoheptose) is the first crystalline acetate to be prepared, having the rare idose configuration, and for this reason considerable significance attaches to its properties. The optical rotation of this substance, in conjunction with that of the corresponding bromo-pentaacetyl-d-β-glucoheptose provides the first definite information on the optical rotations in the acetylated idose series. In harmony with the conclusion drawn from mutarotation studies by Isbell and Pigman, that lactulose probably is a furanose sugar, it was shown from rotational comparisons that the new octaacetyl-lactulose likewise contains a furanose ring.

From the acetates, two crystalline bromo-acetyl sugars have been obtained, having respectively, the idose and talose structures. The bromo-pentaacetyl-d-β-glucoheptose, having the rare idose structure, is relatively unstable, although it crystallizes readily. It may be that greater lability of the halogen atom attached to the glycosyl carbon will be found to be a characteristic property of the idose configuration. Because of the large number of possible syntheses which may

be carried out starting with the halogenoacetate, these two compounds open up an entire field of possibilities in synthesis and research.

The Koenigs-Knorr reaction was applied to the two new bromo-acetyl sugars, and to chloro-acetylneolactose. Two of these compounds, (bromo-pentaacetyl-α-d-α-guloheptose, and chloro-heptaacetyl-α-neolactose) have configurations which should give orthoesters according to the opposite face mechanism for orthoester formation previously suggested by Isbell. In both cases the crystalline orthoester was obtained in the Koenigs-Knorr reaction, in good yield. In the case of neolactose, the orthoester reaction was accompanied by formation of the normal beta glycoside, indicating the existence of the extra-molecular glycoside reaction in competition with the orthoester reaction, as postulated earlier. The yield of the tetraacetyl-d-α-guloheptose methyl orthoacetate was nearly quantitative. Chloro-acetyl-α-neolactose gave, in addition to about 70% of crystalline hexaacetylneolactose methyl orthoacetate, nearly one third of this amount of crystalline methyl heptaacetyl-β-neolactoside.

VI. LITERATURE CITED

1. E. Fischer and K. Delbrück, Ber. deut. chem. Ges. 42, 2776 (1909).
2. K. Freudenberg and W. Nagai, Naturw. 20, 578 (1932); Ber. deut. chem. Ges. 66, 27 (1933).
3. B. Helferich and others, Ann. 447, 27 (1926); 450, 219 (1926).
4. W. N. Haworth, E. L. Hirst, and M. Stacey, J. Chem. Soc. (1931) 2864.
5. P. Walden, Ber. deut. chem. Ges. 29, 133 (1896).
6. P. Walden, J. Chim. phys. 9, 160 (1911).
7. P. F. Frankland, J. Chem. Soc. (1913) 103 722.
8. T. M. Lowry, Chem. and Ind. 43, (2) 1128 (1924).
9. E. Fischer, Ann. 381, 132 (1911).
10. J. Gadamer, Chem. Zeit. (1910) 34, 1004; (1912) 36, 1327.
11. A. Werner, Ber. deut. chem. Ges. 44, 873 (1911).
12. W. E. Garner, Proceed. Chem. Soc. 29, 198 (1913).
13. H. S. Isbell, Ann. Rev. Biochem. IX, 65 (1940).
14. H. S. Isbell, J. Research N.B.S. 18, 505 (1937) RP990.
15. H. S. Isbell, J. Research N.B.S. 19, 639 (1937) RP1052.
16. H. S. Isbell, J. Research N.B.S. 20, 97 (1938) RP1069.
17. W. Koenigs and E. Knorr, Ber. deut. chem. Ges. 34, 957 (1901).
18. E. Fischer and E. F. Armstrong, Ber. deut. chem. Ges. 34, 2885 (1901).
19. K. Freudenberg and H. Scholz, Ber. deut. chem. Ges. 63, 1969 (1930).
20. E. Pacsu, J. Am. Chem. Soc. 57, 537 (1935)

21. E. Fischer, M. Bergmann, and A. Rabe, Ber. deut. chem. Ges. 53, 2362 (1920).

22. P. A. Levene and M. L. Wolfrom, J. Biol. Chem. 78, 525 (1928).

23. J. K. Dale, J. Am. Chem. Soc. 46, 1046 (1924).

24. H. S. Isbell, B. S. J. Research 7, 1115 (1931) RP392.

25. W. W. Pigman and H. S. Isbell, J. Research N.B.S. 19, 189 (1937) RP1021.

26. H. S. Isbell, B.S. J. Research 5, 741 (1930) RP226.

27. E. Erwig and W. Koenigs, Ber. deut. chem. Ges. 22, 2207 (1889).

28. Zd. H. Skraup and J. Koenig, Ber. deut. chem. Ges. 34, 1115 (1901).

29. C. S. Hudson and D. H. Brauns, J. Am. Chem. Soc. 37, 1283 (1915).

30. R. M. Hann, A. T. Merrill, and C. S. Hudson, J. Am. Chem. Soc. 57, 2100 (1935).

31. H. S. Isbell, J. Am. Chem. Soc. 56, 2789 (1934).

32. F. B. LaForge, J. Biol. Chem. 4, 251 (1920).

33. H. S. Isbell, J. Chem. Ed. 12, 96 (1935).

34. H. S. Isbell and H. L. Frush, J. Research N.B.S. 24, 125 (1940)

35. W. C. Austin, J. Am. Chem. Soc. 52, 2106 (1930).

36. W. C. Austin, J. Am. Chem. Soc. 54, 1925 (1932).

37. E. Montgomery and C. S. Hudson, J. Am. Chem. Soc. 52, 2101 (1930).

38. H. S. Isbell and W. W. Pigman, J. Research N.B.S. 20, 773 (1938) RP1104.

39. H. D. K. Drew and W. N. Haworth, J. Chem. Soc. 1926, 2303.

40. A. Kunz and C. S. Hudson, J. Am. Chem. Soc. 48, 1978, 2435 (1926).

41. B. Helferich, E. Bohm, and S. Winkler, Ber. deut. chem. Ges. 62, 990 (1930).

42. D. D. Reynolds and W. L. Evans, J. Am. Chem. Soc. 60, 2559 (1938).