REACTIONS OF THE PRODUCTS FORMED FROM
DIAZOMETHANE AND ACYCLIC SUGAR
DERIVATIVES

DISSERTATION

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By

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INTRODUCTION

The polyfunctional character of carbohydrates and the stereoisomeric possibilities represented by anomers, epimers, and diastereoisomers promotes mixtures as the products of the usual chemical reaction of a carbohydrate. The constituents of such mixtures, being very similar, are mutually soluble and lower the melting point of the mixture to below room temperature with the resultant formation of viscous solutions called "sirups". Nearly pure material will also frequently fail to crystallize, apparently due to the complexity of the molecules themselves. In the extreme case of absolute purity such a sirup would then be properly called a "supercooled liquid".

We might then have two classes of sirups called "supercooled liquids" and "solutions", or "pure" and "impure", or "definitive" and "not definitive". There could be no objection to working with the supercooled liquid type of sirup. However, sirups invariably have poor analyses indicating impurities and the modern chemist implicitly admits of their impurity by failing to record the refractive indices. Thus it is clearly recognized today that the supercooled sirup, or pure sirup, or definitive sirup does not exist and that the term "pure"
should be reserved for crystalline material.

The success of carbohydrate chemistry, based on crystalline compounds, rests on four factors: natural asymmetric syntheses, application of chemistry previously established in other fields, separation techniques, and the application of the LeBel-van't Hoff isomer number theory.

Of first importance is the occurrence in Nature of asymmetric syntheses, poorly understood and unduplicated by man, which provide us with pure, crystalline material. The chemistry of alcohols would surely have developed even in the absence of naturally occurring alcohols; aromatic chemistry would surely have developed in the absence of naturally occurring aromatics; but the field of carbohydrate chemistry would be unknown today if it were not for biologic processes which provide us with pure reference material.

Once provided with reference compounds, men undertook the study of these compounds. Lacking the means of separating sirups into their components, emphasis was placed on avoiding mixtures in order to avoid sirups. This was done by utilizing reactions whose course was well-known with simpler compounds and varying the conditions to obtain maximum yield of a single product.

In synthetic work this approach is that used today
where, for example, we would seldom consider subjecting glucose to the action of a reagent whose reactions with alcohols and aldehydes were unknown. The result is then that few new general synthetic methods originate in the carbohydrate field.

In degradative work, however, we no longer necessarily attempt to avoid mixtures but rather, utilizing chromatography, attempt to separate mixtures deliberately produced and thus obtain information previously unavailable. For example, an early approach to the structure of starch was to utilize a known reaction, the acid-catalyzed hydrolysis of acetals, using reaction conditions which gave a maximum yield of a single product, in this case D-glucose. The modern approach is still to utilize a known reaction, acid-catalyzed hydrolysis, but under conditions deliberately designed to yield a mixture. Separation of this mixture then yields compounds whose structures provide evidence for the fine structure of starch; evidence completely unavailable from the experimental fact that D-glucose is obtained on complete hydrolysis.

Experimental data must lend themselves to interpretation in order to be useful. Such interpretation, based on the tetrahedral carbon atom theory of LeBel and van't Hoff, was brilliantly initiated by Emil Fischer.
STATEMENT OF THE PROBLEM

The objectives of this work have been the following.

1. To prove the structure of the products obtained on treatment of keto-D-fructose tetraacetate with diazomethane (1,2,3).

(1) D. I. Weisblat, Ph.D. Dissertation, The Ohio State University, Columbus, Ohio (1941).


(3) A. R. Hange, Ph.D. Dissertation, The Ohio State University, Columbus, Ohio (1942).

2. To prove the structure of the product obtained on treatment of keto-L-sorbose pentacetate with diazomethane (3).

3. To study the reduction, with retention of nitrogen, of 1-deoxy-1-diazo-keto-acetates.
HISTORICAL

Reaction of Diazomethane with Hydroxyl Groups

The success of the conversion of $-\text{OH}$ to $-\text{OCH}_3$ by treatment with diazomethane depends primarily on the acidity of the hydroxyl hydrogen. The more acidic the hydrogen is the more rapid is the rate and extent of conversion to a methoxyl group.

In general, the methylation of alcohols by diazomethane is a sluggish and incomplete reaction and of little synthetic importance. Thus, attempts to use diazomethane as a methylating agent for cellulose (4,5,6),


cotton (7), wheat starch (8), and methyl $\alpha$-$D$-glucopyranos-
side (8) have given only low degrees of methylation. In the case of tartaric acid, however, it would appear that the neighboring carboxyl groups have imparted increased acidity to the hydroxyl hydrogens since treatment with diazomethane gives a 95 per cent yield of dimethyl 2,3-di-Q-methyl-Q-tartarate (9). It should be noted that


the nature of the solvent can influence the success of such methylations (10).


Hemiacetals might be expected to be somewhat more acidic than alcohols and in fact methyl glycosides have been prepared in yields up to 40 per cent by the action of diazomethane on the parent carbohydrate (11,12).


When the acidity becomes as high as that of the usual phenol or organic acid, then we find quantitative conversion of the -OH group to -OCH3 to give methyl phenyl
ethers and methyl esters, respectively. In the carbohydrate field this conversion of an acid to a methyl ester was first done indirectly by using a lactone in water (13,14) and then in a more direct manner by utilizing the acetylated, open chain glyconic acids (15-19).


(14) O. T. Schmidt and H. Kraft, Ber., 75B, 33 (1941).


Reaction of Diazomethane with Aldehydes

The known reactions of ethyl diazoacetate with carbonyl compounds (20) and the discovery of diazomethane (21),

(20) E. Buchner and T. Curtius, Ber., 18, 2371 (1885).

led to a large amount of work directed to the reaction of diazomethane with aldehydes and ketones (22-24) to give as the usual products homologous epoxides or carbonyl compounds.

In the case of an aldehyde we may expect the following reactions, where the superscript, ?, indicates the possibility of epimer formation.

\[
RCHO \xrightarrow{\text{CH}_2\text{N}_2} R?\text{CH}_2\text{CHO} + R?\text{CH}_2\text{CH}_2 + \text{RCOCH}_3
\]

In the carbohydrate field the action of diazomethane on an open chain aldehyde sugar was first reported by Brigl and coworkers (25) who obtained from 3,4,5,6-tetra-\( \text{Q-} \)

\[
\text{RCHO} \xrightarrow{\text{CH}_2\text{N}_2} \text{CH}_2\text{N}_2 \quad \text{CH}_2\text{N}_2
\]


benzoyl-\( \text{D-} \)glucose a product which was probably 4,5,6,7-tetra-\( \text{Q-} \)benzoyl-1-deoxy-\( \text{D-} \)gluco-heptulose. The only major effort in this field has been that of Wolf from and
coworkers who have treated aldehyde-D (and L)-arabinose tetraacetate, aldehyde-D-glucose pentaacetate, and aldehyde-D-galactose pentaacetate with diazomethane.

From the arabinose derivative there was obtained:

(a) 1-deoxy-keto-D (and L)-fructose tetraacetate (26),

(b) a compound which represented the addition of one methylene group to the starting material (1) and which had (26) m.p. 162-164° C. (dec.), \( \int_q \beta +41^\circ \) for the D isomer, \( \int_q \alpha -41^\circ \) for the L isomer, and (c) a "dimethylene" compound (1). On repeating this reaction some twenty times it was not possible to again obtain the "dimethylene" compound (27). The monomethylene compound,

(27) E. F. Evans, Ph.D. Dissertation, The Ohio State University, Columbus, Ohio (1943).

on reduction followed by acetylation and seeding with 2-deoxy-sorbitol pentaacetate, failed to crystallize (27).

This, together with the recently reported properties (28)


of 2-deoxy-aldehyde-D-glucose tetraacetate, m.p. 100°,
implies that the "monomethylene" compound is either 2-deoxy-aldehydo-D-idose tetraacetate or one of the two possible epoxides.

From aldehydo-D-glucose pentaacetate, on treatment with diazomethane, there was obtained a "dimethylene" compound having m.p. 90-91°, $\alpha_7+11.5^0$ (1) and a "monomethylene" compound having m.p. 91-92.5°C., $\alpha_7+10^0$ (27). The two substances are undoubtedly identical.

On treatment of aldehydo-D-galactose pentaacetate with diazomethane there was obtained a "dimethylene" compound (1).

**Reaction of Diazomethane with Ketones.**

Reaction of diazomethane with ketones may give the following products where the superscript, ?, indicates the possibility of epimer formation.

$$RCOR' + CH_2N_2 \rightarrow R'CH_2COR' + RCOCH_2R'^? + R-C?-R'$$

As in the case of the aldehydes, further reaction may occur between the carbonyl products of the initial reaction and additional diazomethane and, unlike the aldehydes, a cyclic ketone can give rise to ring expansion as shown below where the superscript, ?, indicates the possibility of inversion.
The successful application of this reaction to the carbohydrate field has been accomplished by Wolfrom and coworkers who used acetate blocking groups to obtain true ketonic starting material.

Thus, treatment of keto-2-fructose pentaacetate with diazomethane gave a material which was considered to be an epoxide (2) on the basis of analysis and its failure to give ketose color tests (1). A second product (3) was considered to be one of the possible deoxy-ketoses on the basis of analysis and its positive response to ketose color tests (3).

The epoxide product was deacetylated and gave a crystalline product (1,2) but the reverse reaction was not successful (1). Attempts to prove the epoxide nature
of the product obtained from the diazomethane reaction involved the addition of acetic anhydride, hydrogen bromide, acetyl chloride, and hydrogen but either sirups or starting material (1,3) were obtained. Vigorous acetolysis gave a small and variable yield of a crystalline material thought to be the other possible epoxide, that is, the epimer (3).

The supposed deoxy-ketose formed in the reaction of diazomethane with keto-D-fructose pentaacetate gave a sirup on saponification (3).

Wolfrom and coworkers have also obtained a crystalline product by the action of diazomethane on keto-L-sorbose pentaacetate which was thought to be an epoxide on the basis of its analysis and its negative response to ketose color tests (3). Saponification as well as repeated attempts to open the epoxide ring have given only sirups (3).

Posternak has shown that treatment of an inosose acetate, a compound closely related to the carbohydrate keto acetates, yields an epoxide (29) as shown below.

Reaction of Diazomethane with Acid Halides.

The initial products formed in the reaction of an acid halide with diazomethane are the diazomethyl ketone and hydrogen halide. This hydrogen halide will then react with the diazomethyl ketone unless excess diazomethane or an added base, such as triethylamine (29a), are present. We can thus obtain both diazomethyl ketones (30-32) and halo-methyl ketones from this reaction depending on the manner in which the reaction is carried out as indicated below.

\[
RCOX + CH_2N_2 \rightarrow RCOCHN_2 + HX \rightarrow RCOCH_2X + N_2 \quad \text{downward arrow}
\]

This subtlety of conditions escaped the notice of some early investigators and led to a published dispute in the American literature (33-34) by British authors.

(30) F. Arndt and J. Amende, Ber., 61, 1122 (1928).

In the carbohydrate field the reaction of diazo-methane with aldonyl chloride acetates to yield l-deoxy-l-diazo-keto-glycose acetates has been investigated in great detail by Wolfrom and coworkers and is discussed under "Reactions of Diazo Compounds."

Preparation of Diazo Compounds

Diazo compounds may be prepared in four ways: 
(a) by the diazotization of the group \( X=Z-\text{CHNH}_2 \) where \( X=Z \) may be C=C, O=C, N=C, or O=S (35), (b) by oxidation of hydrazones, (c) by the alkaline decomposition of the group \( RN(NO)CHR^+R^- \) where \( R \) is an electronegative group, and (d) by the reaction of acid halides with diazomethane (discussed previously). The von Pechmann (21) method, reaction of hydrazine with chloroform under alkaline conditions, is seldom used today as a source of diazomethane.

Historically, diazotization was the first method used, having been applied to 3-aminocamphor, a cyclic \( \alpha \)-amino ketone, by R. Schiff (36). Curtius extended

(35) A. Angeli, Ber., 27, 2080 (1904).

(36) R. Schiff, Ber., 14, 1375 (1881).
ethyl glycinatc to prepare ethyl diazoacetate and with this compound demonstrated much of the basic chemistry of the α-diazo-carbonyl group.

In 1891 Curtius and Thun found that oxidation of a hydrazone gave a diazo group (38) and that similar treatment of a 1,2-dihydrazone gave an acetylenic linkage (38, 39)

presumably by the decomposition of the initially formed 1,2-bis-diazo compound. This oxidation can be carried out in the indirect manner (39a, b) shown below.

R'

\[
\text{RCOC=NNHSO}_2\text{C}_7\text{H}_7 \xrightarrow{\text{NaOH}} \text{RCOCN}_2\text{R'} + \text{C}_7\text{H}_7\text{SO}_2\text{Na}
\]

In 1898 von Pechmann found that the alkaline decomposition of nitrosoethylurethane gave diazoethane (40).
This alkaline decomposition of a suitably constituted (as previously discussed) \(\text{N-nitroso} \) compound is the method most used for preparing \(\alpha\)-diazo hydrocarbons in general and diazomethane in particular. The best source of diazomethane at the present time is probably a commercial product, EXR-101 (DuPont, Explosives Dept.), whose active ingredient is \(\text{N,N'-dinitroso-N,N'-dimethylterephthalamide} \) shown below.

\[
\begin{align*}
{\text{H}_3\text{C-}} & \text{N-} \begin{array}{c}
\text{O} \\
\text{NO}
\end{array} \begin{array}{c}
\text{O} \\
\text{NO}
\end{array} \\
& \text{C-CH}_3
\end{align*}
\]

**The Structure of Diazo Compounds.**

The two nitrogen atoms of the diazo group and the carbon atom to which they are attached are now generally believed to be linear. In addition to physical measurements on diazomethane, a clever chemical proof of structure for ethyl diazoacetate has recently appeared (41) which demonstrates conclusively that the two nitrogen atoms are not equivalent and thus shows that a three-membered ring, \(\text{R-CH}^+\text{N}^\_\text{N}^\_\text{N}^- \), is not tenable.

---


For diazocarbonyls, however, another possible structure having non-equivalent nitrogen atoms might exist, namely, a 1,2,3-oxadiazole ring. This structure was first suggested by Schiﬀ (36) and was considered by Wolff who concluded the 1,2,3-oxadiazole structure to be that of compounds having, formally, a diazo group flanked by two carbonyl groups. These compounds he called "diazoanhydrides."

\[
\begin{align*}
&
RCO-CN_2-COR & \xrightarrow{H_2S} & RCO-C-COR + S \\
& \text{diazo} & & \text{NNH}_2
\end{align*}
\]

\[
\begin{align*}
&
RC - C-COR & \xrightarrow{H_2S} & RC - C-COR + H_2O \\
&  & &  \text{NNN} \quad \text{SSN}
\end{align*}
\]

1,2,3-oxadiazole or diazoanhydride

Wolff and associates found consistent differences between diazocarbonyl compounds and "diazoanhydrides" with respect to color and the nature of the product obtained on treatment with hydrogen sulfide (42), water (42), or

\[(42)\] L. Wolff, Ann., 294, 23 (1912).
primary amines (43).


Sidgwick considers the cyclic formula as improbable since the sodium ethoxide decomposition of a "diazoc-anhydride" proceeds in the same manner as in the case of the corresponding disubstituted β-ketoester (44).


\[
\begin{align*}
\text{R—CO}_2\text{Et} & \quad \text{NaOEt} \quad \text{EtOH} \\
\text{R—CN}_2—\text{CO}_2\text{Et} & \quad \text{NaOEt} \quad \text{EtOH} \\
\text{R—CON}_2—\text{CO}_2\text{Et} & \quad \text{NaOEt} \quad \text{EtOH}
\end{align*}
\]

Furthermore, although acetyl-benzoyl-diazomethane has been prepared in only one form (42,45), two isomeric 1,2,3-oxadiazoles might be expected, since hydrogen sulfide reduction yields two isomeric 1,2,3-thiadiazoles (46,47).

(45) L. Wolff, Ann., 325, 129 (1903).


(47) L. Wolff, Ann., 333, 1 (1904).
Dimroth pointed out that increasing stability toward acids is represented by the sequence, \( \text{CH}_2\text{N}_2 < \text{CH}_2\text{CH}-\text{CHN}_2 < \text{R-CO-CHN}_2 < \text{R-CO-CN}_2-\text{COR} \), and suggested that the observed differences between diazo carbonyl compounds and "diazocarbonyl anhydrides" was a constitutional effect related to the extent of conjugation rather than a structural effect (48).

---

(48) O. Dimroth, Ann., 373, 336 (1910).

---

An example of differing reactivity not related to the absence, or presence, of carbonyl groups but apparently related only to the amount of conjugation present in general, is provided by the action of lead tetraacetate (49). Thus, compounds of the types \( \text{R-CO-CN}_2-\text{aryl} \) and \( \text{aryl-CN}_2-\text{aryl} \) gave the diacetates, \( \text{R-CO-C(OAc)}_2-\text{aryl} \) and \( \text{aryl-C(OAc)}_2-\text{aryl} \), on treatment with lead tetraacetate whereas compounds of the type, \( \text{RGOCHN}_2 \), were stable to the same reagent (such a group is cleaved by periodic
acid, however (50).


It might be mentioned that the failure of 1-deoxy-l-diazo-D-gala-heptulose to mutarotate (51) although


D-gala-heptulose does mutarotate (51) would be explained if a 1,2,3-oxadiazole structure were present in the diazo sugar. However, D-glucose 1-(methylphenylhydrazone) also fails to mutarotate (52).

(52) H. Ohle, G. Hensenke, and A. Czyzewski, Ber., 86, 316 (1953).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Deoxy-l-diazo-(\text{D-gala})-heptulose</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>No mutarotation</td>
</tr>
<tr>
<td>D-gala-heptulose</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>Mutarotation</td>
</tr>
<tr>
<td>D-glucose 1-(methylphenylhydrazone)</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>No mutarotation</td>
</tr>
</tbody>
</table>

\(\text{D-gala}\)-heptulose
Perhaps further study may show this to be a general property of ketoses conjugated with carbon to nitrogen multiple bonds.

A linear structure then is generally accepted for all diazo groups although the "diazoanhydride" (1,2,3-oxadiazole) structure is apparently still accepted by some workers (53).


Reactions of Diazo Compounds.

In 1912 Wolff discovered the rearrangement of diazo-methyl ketones (42,54) which forms an essential part of the Arndt-Eistert method (55) for lengthening the carbon chain of an acid as shown below.

\[
\begin{align*}
\text{RCO}_2\text{H} & \rightarrow \text{RCOX} \xrightarrow{\text{CH}_2\text{N}_2} \text{RCOCH}_2\text{N}_2 \\
\left[\text{R-CH=COH}\xrightarrow{\text{H}_2\text{O}}\right] & \rightarrow \text{RCH}_2\text{CO}_2\text{H}
\end{align*}
\]

It has been proved that a true rearrangement occurs by isotopic labeling (56) and the suspected ketene intermediate has, in some cases (57,58), been isolated. A
homogeneous catalyst for the Wolff rearrangement has been developed (58a).


It has also been shown that where the migrating group is an asymmetric, tertiary carbon atom, retention of configuration can be expected (59,60) as indicated below.


(60) J. F. Lane and E. S. Wallis, J. Org. Chem. 6, 443 (1941).

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{C}_4\text{H}_9\text{C}-\text{COOHN}_2 + \text{C}_6\text{H}_5\text{NH}_2 & \rightarrow \text{C}_4\text{H}_9\text{C}-\text{CH}_2\text{C}-\text{NHNC}_6\text{H}_5 \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5
\end{align*}
\]
When, however, the migrating group is an asymmetric, secondary carbon atom, racemization may occur (60,61),


the extent of which is dependent on the conditions employed (62).


\[
\begin{align*}
\text{CH}_3\text{C-CH}_2\text{CO}_2\text{H} + \text{H}_2\text{O} & \rightarrow \text{CH}_3\text{C-CH}_2\text{CO}_2\text{H} \\
\text{CH}_2\text{C}_6\text{H}_5 & \quad \text{CH}_2\text{C}_6\text{H}_5
\end{align*}
\]

"D" and "DL"

In the carbohydrate field the Wolff rearrangement has also been successfully applied and the product was a 2-deoxylactone (63). This reaction would seem to hold promise of providing an excellent synthetic route to 2-deoxy sugar derivatives but requires a demonstration of configuration at C3 of the product since epimerization could occur at this point.


The action of iodine on diazomethyl ketones gives
1,1-diiodo derivatives as shown below.

\[ \text{RCOCHN}_2 + I_2 \rightarrow \text{RCOCHI}_2 + N_2 \]

This reaction has been applied in the carbohydrate field by Wolfrom and coworkers \((64)\) to prepare 1-deoxy-1,1-


diiodo-keto acetates.

In 1910, Forster and Zimmerli found that a diazo group may be reduced to a hydrazone with ammonium sulfide \((65)\) and thus demonstrated the complete reversibility of the diazo-hydrazone system as shown below.


\[ R_2CN_2 + (\text{NH}_4)_2S \rightarrow R_2C=N-NH_2 \]

Staudinger reports \((66)\) that hydrogen sulfide reduction is unsuccessful in the absence of ammonium hydroxide. One may infer then that the active reducing species is \(\text{HS}^-\). The hydrazones obtained from diazomethyl ketones are \((42)\) only slightly basic but will form azines and

slightly acidic acetates as shown below.

\[
\begin{align*}
\text{RCOCH} & \xrightarrow{\text{HS}^-} \text{RCOCH} = \text{NNH}_2 \\
\text{RCOCH} = \text{NNH}_2 & \xrightarrow{\text{Ac}_2\text{O}} \text{RCOCH} = \text{NNHAc}
\end{align*}
\]

Very slightly basic

Slightly acidic

These acid-base properties may be rationalized by considering the hydrazone to be analogous to the vinylog of an amide and the acetylated hydrazone to be analogous to the vinylog of an imide.

Hydrazones are also reported to be the product obtained by reduction with ferrous oxide (67) or ferrous sulfate (68).


sulfate (68).

(68) A. Darapsky and M. Prabhakar, Ber., 45, 1654 (1912).

Reduction of diazo compounds by dissolving metals gives a variety of products. Sodium amalgam has given hydrazino derivatives (68) and zinc with sodium hydroxide has given hydrazine plus undefined products (69). Aluminum amalgam is reported to give the following reactions (70).

(69) R. Jay and T. Curtius, Ber., 27, 775 (1894).
Zinc and acetic acid reduction apparently proceeds stepwise with the formation of a hydrazone, conversion to a hydrazino compound, and finally reduction to an amine and ammonia (36, 37, 65, 68, 71) as indicated below.

\[
\]

\[
\begin{align*}
(C_6H_5)_2CN_2 & \xrightarrow{Al/Hg} (C_6H_5)_2CHNH_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{Zinc and acetic acid reduction apparently proceeds stepwise with the formation of a hydrazone, conversion to a hydrazino compound, and finally reduction to an amine and ammonia (36, 37, 65, 68, 71) as indicated below.}
\end{align*}
\]

\[
\text{(71) T. Curtius, J. prakt. Chem., 238, 396 (1888).}
\]

\[
\begin{align*}
\text{R}_2\text{CH}_2 & \xrightarrow{\text{Zn}} \text{R}_2\text{C}=\text{NNH}_2 \xrightarrow{\text{Zn}} \text{R}_2\text{CH}_2\text{NH}_2 + \text{NH}_3 \\
\end{align*}
\]

\[
\text{Catalytic reduction with palladium adds two hydrogen atoms with the complete loss of nitrogen in some cases (70, 72, 73). In a very thorough study, Birkofer reports}
\]

\[
\text{(72) H. Wienhaus and H. Ziehl, Ber., 65B, 1461 (1932).}
\]

\[
\]
that in the reduction of RCOCHN₂ with a palladium oxide catalyst one obtains RCOCHNH₂ if R⁻ is aliphatic or alicyclic, RCOCH₂NH₂ + NH₃ if R⁻ is phenyl or benzyl, and RCOCH₃ or RCOCH₂CH₂COR regardless of the nature of R⁻ in the presence of copper oxide or hydrogen chloride (74).

(74) L. Birkofer, Ber., 80, 83 (1947).

The halogen acids add to diazo compounds with the elimination of nitrogen as shown below.

\[
R₂CN₂ + HX \rightarrow R₂CHX + N₂
\]

In the carbohydrate field Wolfrom and coworkers have used this reaction to prepare 1-deoxy-1-halo-keto acetates (64). The action of hydriodic acid on diazo-methyl ketones is of special interest since, depending on the acid concentration, one can obtain either the iodo compound or the methyl ketone (64). The methyl ketone can also be obtained by treatment of the 1-deoxy-1-iodo- or 1-deoxy-1,1-diiodo- compounds with hydriodic acid as shown below.

\[
\begin{align*}
& \text{RCOCHN₂} + \text{HI} \rightarrow \text{RCOCH₂I} + \text{N₂} \\
& \text{RCOCHN₂} + \text{I₂} \rightarrow \text{RCOCHI₂} + \text{N₂} \\
& \text{RCOCH₂I} + \text{HI} \rightarrow \text{RCOCH₃}
\end{align*}
\]
This then enables one to run the reverse of the haloform reaction as indicated below.

\[ \text{RCOCH}_3 \xrightarrow{\text{NaCl}} \text{RCO}_2\text{H} + \text{CH}_3 \text{I}_3 \quad \text{haloform reaction} \]

\[ \text{RCO}_2\text{H} \xrightarrow{\text{HI}} \text{RCOCH}_2\text{N}_2 \rightarrow \text{RCOCH}_3 \]

In 1883, Curtius found that the reaction of a diazo compound with an organic acid gave an ester, as indicated below.

\[ \text{R'}\text{CO}_2\text{H} + \text{R}_2\text{CN}_2 \rightarrow \text{R'}\text{CO}_2\text{CHR}_2 + \text{N}_2 \]

This reaction enables one to convert an aldehyde to a hydroxymethyl ketone by the following reactions.

\[ \text{RCHO} \rightarrow \text{RCO}_2\text{H} \rightarrow \text{RCOCl} \xrightarrow{\text{CH}_2\text{N}_2} \text{RCOCH}_2\text{N}_2 \xrightarrow{\text{RCO}_2\text{H}} \text{RCOCH}_2\text{OCOR} \xrightarrow{\text{base}} \text{RCOCH}_2\text{OH} \]

In order to utilize this sequence of reactions to prepare ketoses, it is necessary to obtain an acyclic form of the sugar. Gätsi and Reichstein did this as indicated below (75).

It should be noted that in this method the derivatives employed were not of general applicability.

In order to utilize this sequence of reactions to convert an aldose to the next higher ketose, it is necessary to convert the aldose to the aldonic acid. This is made difficult by the tendency for the aldonic acid to lactonize. Even in those cases where the unsubstituted aldonic acid can be prepared, the conversion to an acid halide requires that the hydroxyl groups be blocked, since any reagent which will convert an acid to an acid halide will also react with hydroxyl groups. The problem of converting an aldose to the next higher ketose through
the diastemethyI ketose route was solved by Wolfrom and coworkers as indicated below (see page 31) for a hexose.

This general preparative method for keto-acetates in conjunction with the aldehyde-acetate preparations by Wolfrom and coworkers represents two major advancements in carbohydrate chemistry originating from the same Laboratory. By the action of acetic acid on the diastemethyI ketoses there have been obtained all of the keto-acetates of the hexulososes (except tagatose) (15, 76-78)


together with examples of the corresponding derivatives of heptulososes (18, 51, 76, 79, 80), octulososes (16, 17, 81), and nonulososes (19). Deacetylation afforded the ketoses.

This general route has also been used to prepare
\[
\text{HOCH}_2\text{-CH-(CHOH)}_3\text{-CHOH}
\]
\[
\text{HOCH}_2\text{(CHOH)}_4\text{CH(SEt)}_2\quad \text{HOCH}_2\text{(CHOH)}_4\text{CO}_2\text{H}
\]
\[
\text{AcOCH}_2\text{(CHOAc)}_4\text{CH(SEt)}_2\quad \text{HOCH}_2\text{(CHOH)}_4\text{CHNH}_2
\]
\[
\text{AcOCH}_2\text{(CHOAc)}_4\text{CHO}
\]
\[
\text{AcOCH}_2\text{(CHOAc)}_4\text{CO}_2\text{H}
\]
\[
\text{AcOCH}_2\text{(CHOAc)}_4\text{COCH}_2\text{OAc}
\]
\[
\text{HOCH}_2\text{(CHOH)}_4\text{COH}_2\text{OH}
\]
1,3-di-β-acetyl-4-deoxy-β-erythulose (82), a key compound in the proof of structure of streptomycin. By substituting an α-acetylated aldonic acid for acetic acid some novel 1 → 1 ester linked disaccharides have been prepared (64).

Diazomethyl ketones will also react with sulfuric acid (82a) as shown below.


\[ 2\text{RCOCHN}_2 + \text{H}_2\text{SO}_4 \rightarrow (\text{RCOCH}_2)_2\text{SO}_4 + 2\text{N}_2 \]

With the proper acid catalysts (82a) alcohols react with diazomethyl ketones as shown below.

\[ \text{C}_6\text{H}_5\text{COCH}_2\text{N}_2 + \text{R'}\text{OH} \xrightarrow{\text{BF}_3\cdot\text{Et}_2\text{O}} \text{C}_6\text{H}_5\text{COCH}_2\text{OR'} + \text{N}_2 \]
DISCUSSION OF RESULTS

Unsuccessful Attempts to Obtain a Crystalline, Ring-Opened Product from 2-Acetoxyethyl-3,4,5,6-tetra-O-acetyl-1,2-anhydro-D-glucitol [mannitol].

In order to prove the epoxide nature of 2-acetoxyethyl-3,4,5,6-tetra-O-acetyl-1,2-anhydro-D-glucitol [mannitol], the product obtained by treatment of keto-D-fructose pentaacetate with diazomethane (1,2,3), it was necessary to obtain an addition reaction with opening of the epoxide ring. Either sirups or unreacted starting material were obtained in the present investigation on attempting: (a) the addition of acetic anhydride, ammonia, water, acetic acid, picric acid, nitrosyl chloride, and hydrochloric acid; (b) the conversion of the epoxide to an olefin using triphenylphosphine; and (c) the preparation of a phenylboronate from a sirup which was supposedly the branched chain heptitol.

An attempted quantitative epoxide determination by titration with a dilute acetic acid solution of hydrogen chloride failed to show any acid consumption.

The present work which did yield crystalline products is shown in Figure 1.
Figure 1. Reactions of 2-Acetoxymethyl-3,4,5,6-tetra-2-acetyl-1,2-anhydro-D-glucitol [mannotol].
Synthesis of 1-Chloro-1-deoxy-2-hydroxymethyl-\(D\)-glucitol [mannitol?] (III) by Epoxide Ring Opening.

By treatment of the epoxide pentaacetate, obtained by the action of diazomethane on keto-\(D\)-fructose pentaacetate \((1,2,3)\), with one per cent methanolic hydrogen chloride, a crystalline product was obtained which represented deacetylation and the addition of hydrogen chloride. This product was shown to be 1-chloro-1-deoxy-2-hydroxymethyl-\(D\)-glucitol [mannitol?] rather than 2-chloro-2-deoxy-2-hydroxymethyl-\(D\)-arabino-hexitol by periodate cleavage. Five moles of periodate were consumed and two moles of formaldehyde were liberated per mole of compound whereas the arabino-hexitol would have consumed only three moles of periodate and liberated one mole of formaldehyde per mole of compound.

It is of interest to note that the product obtained must necessarily have the same configuration as the starting material since no bonds to the asymmetric carbon atom were broken.

Course of Chlorohydrin Formation from the Epoxide.

In the reaction with methanolic hydrogen chloride one might expect, in addition to chlorohydrin formation, some products formed by the addition of methanol and of water to the epoxide ring. Paper chromatography of the crude product did show three components, the fastest
moving of which was shown to be the chlorohydrin. A sirup thought to be the branched chain heptitol obtained by the addition of water to the epoxide had an \( \text{R}_{\text{Glucose}} \) value identical with that of the slowest moving component of the crude chlorohydrin. An analysis of the crude chlorohydrin showed the presence of methoxyl groups and thus the third component of the crude chlorohydrin is thought to be the compound derived by the addition of methanol to the epoxide ring. Assigning to the middle spot, obtained on chromatographing the crude chlorohydrin, the methoxyl structure one finds the rate of migration, \( \text{RCl} > \text{ROMe} > \text{ROH} \), to be that expected on the basis of polarity. Furthermore, the intensity of the spots, \( \text{RCl} > \text{ROMe} > \text{ROH} \), is in agreement with a calculation of mole fraction composition based on carbon, hydrogen, chlorine, and methoxyl analyses and the hypothesis that the crude product represents a ternary mixture of \( \text{RCl} \), \( \text{ROMe} \), and \( \text{ROH} \). The mole fractions thus calculated are \( \text{N}_{\text{RCl}} = 0.9068 \), \( \text{N}_{\text{ROMe}} = 0.0905 \), and \( \text{N}_{\text{ROH}} = 0.0027 \).

The formation of the chlorohydrin involves two reactions: deacetylation by acid catalysed trans-esterification and addition of hydrogen chloride to the epoxide ring. The order in which these reactions occur has not been determined. Some inferences as to the mechanism of hydrogen chloride addition to the epoxide may be made, however, on the basis of product distribution. Assuming
that ring opening occurs after deacetylation (which in no way affects the argument to follow) we may consider chlorohydrin formation to occur in one of the two following ways.

\[
\begin{align*}
\text{CH}_2\text{O}^+ & \quad \text{slow} \quad \text{CH}_2^+ & \quad \text{fast} \quad \text{CH}_2\text{Cl} \\
\text{HOH}_2\text{C}-\text{C} & \quad \text{OH} \quad \text{HOH}_2\text{C}-\text{C} & \quad \text{OH} \quad \text{Cl}^- \quad \text{HOH}_2\text{C}-\text{C} & \quad \text{OH} \\
\end{align*}
\]

or

\[
\begin{align*}
\text{CH}_2\text{O}^+ & \quad \text{slow} \quad \text{CH}_2\text{Cl} \\
\text{HOH}_2\text{C}-\text{C} & \quad \text{Cl}^- \quad \text{HOH}_2\text{C}-\text{C} & \quad \text{OH} \\
\end{align*}
\]

The \( S_{N1oA} \) mechanism (83) is considered unlikely for two reasons: (a) the formation of a primary carbonium ion without attendant stabilization by, for example, resonance is improbable, and (b) the primary carbonium ion, if formed, should react with the nucleophiles present at rates largely dependent on the Mass Law rather than the nucleophilicity of the species present so that (assuming kinetic control) one might expect the methoxyl compound to be at least a major product of the reaction.

If, however, the $S_{N2oA}$ mechanism (83) is operative then one might expect (again assuming kinetic control) the product distribution to be primarily determined by the nucleophilicity of the species present and only secondarily determined by the Mass Law.

Although the experiments conducted were by no means designed to yield mechanistic data, it is interesting to consider a crude application of Swain's equation for bimolecular nucleophilic substitution (84):

$$\log \frac{\text{k}_Z}{\text{k}_{\text{MeOH}}} = S_n Z$$

Where: $k_Z$ is the second order rate constant for a nucleophilic displacement by reagent $Z$ whose nucleophilicity is $n_Z$ on a compound whose sensitivity to change in nucleophilicity is $S$, and $k_{\text{MeOH}}$ is the second order rate constant for nucleophilic attack by methanol.

then: rate of RCl formation = $k_{\text{Cl}} \left[ \frac{[\text{C}]}{[\text{MeOH}]} \right] [\text{Cl}^-]$

rate of ROMe formation = $k_{\text{MeOH}} \left[ \frac{[\text{C}]}{[\text{MeOH}]} \right] [\text{MeOH}]$

rate of RCl formation = $k_{\text{Cl}} \left[ \frac{[\text{MeOH}]}{[\text{MeOH}]} \right] [\text{Cl}^-]$

rate of ROMe formation = $k_{\text{MeOH}} \left[ \frac{[\text{MeOH}]}{[\text{MeOH}]} \right] [\text{MeOH}]$

If: $S \approx 1$ (84); $n_{\text{Cl}} \approx 3$ (84); $[\text{Cl}^-] \approx 0.23$ M in one per cent
methanolic hydrogen chloride (assume to be constant); and \([\text{MeOH}] = 25 \text{ M}\) in one per cent methanolic hydrogen chloride (nearly constant).

Then:

\[
\frac{\text{rate of RCl formation}}{\text{rate of ROMe formation}} \approx 10^{(1)(3)} \left(\frac{0.25}{25}\right)
\]

\[
\frac{\text{rate of RCl formation}}{\text{rate of ROMe formation}} \approx 10
\]

By analysis:

\[
\frac{N_{\text{RCl}}}{N_{\text{ROMe}}} = \frac{0.9068}{0.0905} \approx 10
\]

This equality of ratios of rates to the ratio of mole fractions of products would be expected for a kinetically controlled \(S_n^2\) reaction where the nucleophilic reagents are present in constant concentrations.

A similar application gives:

\[
\frac{\text{rate of ROH formation}}{\text{rate of ROMe formation}} = 10^{\frac{\text{SnH}_2\text{O}}{\text{MeOH}}} \frac{\text{H}_2\text{O}}{\text{MeOH}}
\]

If: \(S \approx 1 (84)\); \([\text{H}_2\text{O}] \approx 0.3 \text{ M}\) (nearly constant) and \([\text{MeOH}] \approx 25 \text{ M}\) (nearly constant), for commercial absolute methanol of the volume composition 99.5% methanol and 0.5% water; and

\[
\frac{\text{rate of ROH formation}}{\text{rate of ROMe formation}} = \frac{N_{\text{ROH}}}{N_{\text{ROMe}}} = 0.03
\]

Then:

\[
0.03 = 10^{\frac{\text{SnH}_2\text{O}}{25}} \frac{0.3}{25}
\]

\[
\text{nH}_2\text{O} = 0.4
\]
Although water is probably slightly less nucleophilic than methanol and might be expected to have $n_{H_2O} \approx 0.4$ where $n_{MeOH} = 0.84$ the order of magnitude obtained in this calculation of the nucleophilicity of water is interestingly close to that expected.

To summarize, it is suggested that the epoxide ring opened in one per cent methanolic hydrogen chloride at $15^\circ$ by an $S_N2$ mechanism to give primarily the halohydrin due to the high nucleophilicity of the chloride ion. As secondary products the methoxyl compound and the heptitol are believed to be formed in a ratio largely determined by the Mass Law due to the similarities in nucleophilicities of water and methanol.

When this synthesis is carried out in one per cent aqueous hydrochloric acid instead of one per cent methanolic hydrogen chloride almost none of the acetylated epoxide dissolves in six days time whereas three days reaction time was used with methanolic hydrogen chloride. After six days at refrigerator temperature ($15^\circ$) the aqueous mixture was refluxed for ten minutes. A homogeneous solution resulted from which there was isolated a sirup which resisted crystallization, gave a single spot, $R_{\text{glucose}} = 1$, on paper chromatography, and gave a negative Beilstein halogen test. This $R_{\text{glucose}}$ value is considered to be the value for ROH, the heptitol, and together with the negative Beilstein test infers the
formation of ROH to the exclusion of HCl, the chlorohydrin. On the other hand, following the treatment previously used, and assuming no loss of hydrochloric acid during reflux, we would expect the mole fraction ratio, \( \frac{N_{RCl}}{N_{ROH}} \), to be four. This tremendous disparity may be due to a change of mechanism from \( S_N2 \) to \( S_N1 \) due to the change in solvent and temperature.

Synthesis of 2-Acetoxymethyl-3,4,5,6-tetra-O-acetyl-1-chloro-1-deoxy-\( \beta \)-glucitol (mannitol) \( \beta \) (I).

By reaction with hydrogen chloride in acetic acid a crystalline chlorohydrin pentaacetate is obtained. The direction of ring opening was shown to be the same as with methanolic hydrogen chloride by conversion of the chlorohydrin pentaacetate to the free chlorohydrin.

The interconversion of the chlorohydrin and chlorohydrin pentaacetate could be done by either acetylation or deacetylation. To acetylate, however, requires that the tertiary carbinal remain unaffected and that basic conditions (i.e. pyridine or sodium acetate) which would cause epoxide formation be avoided. This direction of interconversion was not attempted.

To deacetylate under neutral or acid conditions suggests trans-esterification. An attempt to do this using methanol and an acid resin was unsuccessful. Mineral acids were next considered and sulfuric acid was chosen rather than hydrochloric acid to avoid any
possibility of the chlorohydrin product arising from any source other than the chlorohydrin starting material. The low yield (10%) suggests that methanolic hydrogen chloride would be a better reagent for preparative purposes.

The melting point of the chlorohydrin (132.5-133°C.) and the epoxide (133-135°C.) together with the melting point of the chlorohydrin pentaacetate (85-86°C.) and epoxide pentaacetate (86-87°C.) suggested the possibility that the chlorohydrins were being converted to the epoxides on heating. Mixed melting points served to demonstrate, however, that the crystalline material obtained from the chlorohydrin melt was still the chlorohydrin so that the melting point relations are coincidental.

**Synthesis of 2-Acetoxymethyl-3,4,5,6-tetra-O-acetyl-1-bromo-1-deoxy-D-glucitol (mannitol?) (IV), by the Action of Hydrogen Bromide on the Epoxide.**

On reaction of the epoxide obtained by the action of diazomethane on keto-D-fructose pentaacetate with hydrogen bromide in acetic acid for two minutes one obtains a crystalline bromohydrin pentaacetate whose direction of ring opening is assumed to be the same as that observed for hydrogen chloride in acetic acid. This view is consistent with the fact that treatment of the
bromohydrin pentaacetate with sodium acetate yields the original acetylated epoxide. The remarkably nearly identical X-ray powder diffraction patterns of the halo-hydrin pentaacetates reported here infers isomorphism. The slightly high bromine content of the bromohydrin pentaacetate suggests some dibromide pentaacetate (see below) as an impurity.

Synthesis of 2-Acetoxymethyl-3,4,5,6-tetra-O-acetyl-1,2-dibromo-1,2-dideoxy-β-glucitol (mannitol?) (V).

On reaction of the epoxide, obtained by treatment of keto-D-fructose pentaacetate with diazomethane, with hydrogen bromide in acetic acid overnight one obtains a dibromide plus traces of the bromohydrin. This dibromide reacts with sodium iodide to give iodine and sodium bromide and, in contrast to the bromohydrin, cannot be recrystallized from methanol probably due to the solvolytic instability of the bromine attached to the tertiary carbon atom. The slightly low bromine content of this dibromide suggests the presence of some bromohydrin as an impurity.

When reaction with sodium iodide was carried out as a preparative route to the olefin a crystalline product was obtained which, however, decomposed spontaneously with the formation of acid fumes and a dark red color.

The formation of an olefin would be of interest in that it would offer: (a) a possible means of preparing
the epimeric epoxides by epoxidation of the olefin and (b) a means of demonstrating epoxide epimerism (if it should be encountered) by conversion to a common compound as shown below.

Stereochemical Relation Between the Bromohydrin and the Dibromide as a Function of the Course of the Reaction.

It seems reasonable to assume that the dibromide is formed from the initially formed bromohydrin since a tertiary carbinal would be expected to be converted to a bromide under the conditions employed. The formation of this dibromide is of interest since under comparable conditions Posternak reported (29) only the following reaction.
Similarly in the steroid field the following bromohydrin formation is reported (85,86) under comparable conditions.


In these cases the tertiary carbinol is stable to the hydrogen bromide reagent.

In the present case it is probable that the formation of a halide from a tertiary carbinol flanked by three neighboring groups suitably situated and constituted to permit participation in the transition state (87) will

ensure an $S_{N1}loA$ mechanism. In this case, according to Ingold's "$S_{N1}$ Rule" (87), configuration is predominantly preserved.

It is of interest to apply the concept of neighboring group participation, which is the basis for the "$S_{N1}$ Rule," to a case which, to the best of the author's knowledge, has been previously unconsidered. This is the case of a molecule with two configuration-holding groups and one asymmetric center (see Figure 2).

Applying the steady state treatment and assuming the intermediates are present in low concentrations the following equations are obtained.

\[
\begin{align*}
\frac{dP}{dt} &= k_3(X)(A) + k_4(X)(B) \\
\frac{dP'}{dt} &= k_5(X)(A') + k_6(X)(B') \\
\frac{dA}{dt} &= k_4(R) + k_{-2}(B') + k_2(A) + k_3(X)(A) = 0 \\
\frac{dB}{dt} &= k_5(R) + k_{-1}(A') + k_1(B) + k_4(X)(B) = 0 \\
\frac{dA'}{dt} &= k_1(B) + k_{-1}(A') + k_5(A')(x) = 0 \\
\frac{dB'}{dt} &= k_2(A) + k_{-2}(B') + k_6(B')(X) = 0
\end{align*}
\]

Solving for $A$, $A'$, $B$ and $B'$ and substituting we obtain:

\[
\frac{dP}{dt} = R \left[ k_3k_A \left( \frac{k_{-2} + k_6X}{k_2k_6 + k_3k_6X} \right) + \frac{k_A}{k_B} \left( \frac{k_{-1} + k_5X}{k_1k_5 + k_4k_{-1} + k_4k_5X} \right) \right]
\]

\[
\frac{dP'}{dt} = R \left( \frac{k_1k_5k_B}{k_1k_5 + k_4k_{-1} + k_4k_5X} + \frac{k_2k_6k_A}{k_2k_6 + k_3k_{-2} + k_3k_6X} \right)
\]

Assume: $k_1 = k_2$, $k_{-1} = k_2$, $k_4 = k_6$, $k_3 = k_5$, then:
Figure 2. Hypothetical SN1 Reaction of an Asymmetric Molecule Having Two "Configuration Holding" Groups.
\[ r' = \frac{dP}{dt} = \frac{k_2k_3k_A + k_3k_6k_AX + k_2k_6k_B + k_3k_6k_BX}{k_{-2}k_3k_B + k_2k_6k_A} \]

Assume \( k_{-2} = k_2, k_3 = k_6, k_A = k_B \), then:

\[ \frac{r}{r'} = 1 + \frac{k_3}{k_1} X \]

A plot of \( r/r' \) versus \( X \) is a straight line with slope \( k_3/k_1 \) and intercept 1. This indicates that with a large excess of \( X \) we may expect essentially complete retention of configuration \( (X \rightarrow \infty, r/r' \rightarrow \infty) \). When, however, \( X \) is present in smaller amounts then the extent of racemization increases as the reaction proceeds becoming 50% when \( X = k_1/k_3 \) and 100% as \( X \) approaches zero.

Thus the presence of an additional configuration-holding group does not promote retention of configuration but rather provides a reaction path which, still passing through a bridged-ion of lower energy than the free carbonium ion, can lead to racemization analogous to that expected for the free carbonium ion.

Inability to estimate the relative magnitudes of the various specific rate constants involved prohibits a steady state treatment of a more ordinary molecule having a single asymmetric center and more than one configuration-holding group. Similarly, the case of a molecule having more than one asymmetric center, and more than one configuration-holding group, is likewise not amenable to a steady state treatment. It is
suggested, however, that the presence of more than one configuration-holding group may, in general, increase the extent of racemization occurring in a unimolecular reaction. For example, much racemization accompanies the predominating retention of configuration observed in the solvolysis of the phenylbromoacetate ion (87a). (87a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, New York (1953), p. 384.

This could be the result of the benzene ring acting as a second configuration-holding group although an alternate explanation is possible (87a).

It is suggested then that, contrary to the S_N1 Rule (87), the stereochemical relationship between the bromohydrin (IV) and the dibromide (V) is not predictable.

Synthesis of 2-Acetoxymethyl-3,4,5,6-tetra-O-acetyl-1-bromo-1-deoxy-D-glucitol [mannitol\(^2\)] (IV) by the Action of Magnesium Bromide on the Epoxide.

In the hope of obtaining a branched chain aldose a
Magnesium bromide isomerization (88-91) of the epoxide


was attempted. The product was, however, a bromohydrin identical with that obtained by the action of hydrogen bromide in acetic acid.

Conversion of the Halohydrins to the Epoxides.

Treatment of the halohydrins with bases has given the epoxides (IV → II and III → VI) as products but in low yield. We may suppose a major side reaction to be the formation of a product arising from a metathetical reaction or by the reopening of the epoxide once formed (see equations below).
The ideal base would be one of high basicity and low nucleophilicity since step (2) requires only a basic reagent while the unfavorable steps (1) and (4) will depend on nucleophilicity. Since these two properties are usually closely related it might be better to sacrifice basicity for lower nucleophilicity since the nucleophilic attack is harmful in two ways: (a) by providing an alternate reaction and (b) by providing a reaction path for the destruction of the product once formed.

A further complication is that step (5) may provide B$^-$ as a product and thus make steps (4) through (5) catalytic. The net result can be a leveling effect. Thus if we use aqueous sodium acetate as the base with the intent of minimizing steps (1) and (4) by avoiding highly nucleophilic species such as hydroxide ion the incursion of steps (4) and (5) will provide unwanted hydroxide ions.

The best yield obtained in this work (62%) was with sodium acetate as the base and acetic acid as the solvent.

**Deacetylation of the Epoxides.**

Deacetylation of the epoxide derived from keto-$D$-fructose pentaacetate has given low yields (less than 50 per cent) of the deacetylated epoxide. It is probable
that the major reaction is opening of the epoxide ring. It is of interest to consider how we might improve the yield of epoxide by suppressing ring opening.

Since both ring opening and deacetylation involve nucleophilic attack we are not in a position to choose a deacetylating reagent on the basis of nucleophilicity since we cannot predict the relative susceptibility to changes in nucleophilicity of the acetate and epoxide groups. Modifications in the deacetylating procedure could be made, however, by noting that ring opening, the undesired reaction, is a catalytic process with either aqueous sodium hydroxide or methanolic barium methoxide. This means that satisfactory yields of epoxide can only be obtained with these reagents by regulating the reaction time carefully. The use of catalytic amounts of barium methoxide in methanol in no way insures proper conditions. This is shown by the fact that drastic treatment with sodium hydroxide gave a yield almost as high as Weisblat’s overnight treatment with cold, catalytic amounts of barium methoxide in methanol (1).

We might expect more favorable yields from a reaction which will deacetylate without opening of the ring catalytically. Such a reaction medium would be methanolic ammonia. In practice, however, this reaction gave acetamide and a sirup (the amino compound?) which resisted crystallization.
Identification of a Supposed Second Product from the Reaction of Diazomethane with keto-D-Fructose Pentaacetate.

This compound, obtained by Hanze (3), has been shown in the present work to be β-D-fructose pentaacetate by melting point, specific rotation, analysis, and the absence of ketonic absorption in the ultraviolet. It is assumed that this material was an impurity in the keto-D-fructose pentaacetate starting material used by Hanze.

Unsuccessful Attempts to Obtain a Crystalline, Ring-Opened Product from 2-Acetoxymethyl-3,4,5,6-tetra-O-acetyl-1,2-anhydro-L-iditol [gulitol].

The action of methanolic hydrogen chloride, hydrogen chloride in acetic acid, hydrogen bromide in acetic acid, p-toluenesulfonic acid, periodic acid, nitric acid, nitrosyl chloride, hydroxide ion, sodium β-naphthoxide, 2,4-dinitrophenylmercaptan, 2,4-dinitrophenylhydrazine, and p-toluidine on the crystalline product obtained by Hanze (3) by treatment of keto-L-sorbose pentaacetate with diazomethane was unsuccessful in providing crystalline derivatives. Tritylation followed by acetylation of a sirup, supposedly the heptitol formed by addition of water to the epoxide, also failed to yield a crystalline derivative.
Synthesis of 2-Acetoxyethyl-3,4,5,6-tetra-O-acetyl-L-
chloro-1-deoxy-L-iditol [gulitol?].

The sirup formed by the action of hydrogen chloride
in acetic acid was chromatographed on Magnesol-Celite.
The sirup obtained on elution had a fair analysis for
the expected chlorohydrin pentaacetate.

Stereochemical Relationship Between
The Epoxides Formed From D-Fructose and L-Sorbose.

The epoxides in question may be related as C5
epimers or as diastereoisomers differing at C5 and C2.
An inference that they are, in fact, C5 epimers was ob­tained by treating the epoxide acetates with base followed
by excess sodium periodate. These final solutions had
identical (though very low) rotations as is expected for
C5 epimers (see Figure 3). This expectation involves
the assumptions that the action of base gives only epox­
ide and heptitol and that the yield of epoxide is the same
for both starting materials. The first assumption seems
sound; the second assumption, if in error, does not
invalidate the method since it merely turns our attention
from the sign and magnitude of rotation to the sign of
rotation only.

Unsuccessful Reductions of L-Deoxy-L-diazo-keto-D-gala-
heptulose Pentaacetate.

It was found that although zinc, ammonium chloride,
ammonium acetate, and ammonium hydroxide all failed to
Figure 2. Scheme for Establishing the Stereochemical Relationship between Two Epoxides.
give colors with 1-deoxy-l-diazo-keto-D-gala-heptulose pentaacetate, the combination of zinc with any of the above salts (not ammonium hydroxide) gave intense red colors. Attempts to isolate a crystalline product from zinc-ammonium chloride reductions were unsuccessful. Zinc-acetic acid reduction of 1-deoxy-l-diazo-keto-D-gala-heptulose pentaacetate gave a dark sirup which gave a negative ninhydrin test and a positive test for nitrogen.

Sodium borohydride reduction of both 1-deoxy-l-diazo-keto-D-gala-heptulose pentaacetate and diazoaceto-phenone gave sirups. On acetylation, both of these sirups again gave sirups.

No reduction of 1-deoxy-l-diazo-keto-D-gala-heptulose pentaacetate was observed using ferrous hydroxide or sodium sulfite.

Preparation of 1-Deoxy-keto-D-gala-heptulose Pentaacetate.

Reduction of 1-deoxy-l-diazo-keto-D-gala-heptulose pentaacetate to 1-deoxy-keto-D-gala-heptulose pentaacetate by aluminum amalgam was observed in the present work as shown below.

\[
\text{AcOCH}_2(\text{CHOAc})_4\text{COCH}_2 \xrightarrow{\text{Al/Hg}} \text{AcOCH}_2(\text{CHOAc})_4\text{COCH}_3
\]

The dimorphism previously reported (64) for this product was again encountered. The yield in this reaction is
inferior to that obtained using the hydrogen iodide reduction method of Wolfrom and Brown (64).

**Synthesis of 3,4,5,6,7-Penta-O-acetyl-D-gala-heptosone 1-Hydrazone by Hydrogen Sulfide Reduction.**

Reduction of 1-deoxy-1-diazo-keto-D-gala-heptulose pentaacetate proceeded smoothly at room temperature in ethanol as shown below.

\[
\text{AcOCH}_2(\text{CHOAc})_4\text{COCHN}_2 + \text{H}_2\text{S} \rightarrow \text{AcOCH}_2(\text{CHOAc})_4\text{COCH} = \text{NNH}_2
\]

Attempted recrystallization of the product from hot solvents caused darkening and recrystallization was best carried out by dissolving the compound in benzene and adding carbon disulfide to the saturation point.

Hydrogen sulfide failed to give reduction in the absence of added ammonium sulfide or at ice-salt bath temperature.

**Synthesis of 3,4,5,6,7-Penta-O-acetyl-D-gala-heptosone 1-Hydrazone by Sodium Dithionite Reduction.**

Reduction of 1-deoxy-1-diazo-keto-D-gala-heptulose by sodium dithionite gave the same hydrazone as was obtained by hydrogen sulfide reduction but in inferior yield.
Synthesis of 3,4,5,6-Tetra-α-acetyl-α-glucosone 1-Hydrazone.

Reduction of 1-deoxy-l-diazo-keto-D-fructose tetra-acetate with hydrogen sulfide gave the corresponding hydrazone which is, to the best of the writer's knowledge, the first acyclic glucosone derivative.

Chemistry of the α-Keto-Hydrazone.

The very slight basicity of the α-keto-hydrazone group has been previously noted (42) and in accord with this 3,4,5,6,7-penta-α-acetyl-D-gala-heptoseone 1-hydrazone failed to give a hydrobromide salt and gave only a very weak positive test with ninhydrin.

The same compound on reaction with nitrous acid and nitrous anhydride gave only sirups which after being chromatographed still failed to yield crystalline material.

An attempted exchange reaction between pyruvic acid and 3,4,5,6,7-penta-α-acetyl-D-gala-heptoseone 1-hydrazone gave a sirup which gave six zones on an exploratory chromatography column and was not further investigated.

An attempted exchange reaction between the above hydrazone after acetylation and buffered pyruvic acid (92)


gave only unchanged starting material. Use of β-hydroxy-
naphthaldehyde in an attempted exchange reaction gave a mixed aldazine discussed below.

Raney nickel catalytic hydrogenation of 3,4,5,6,7-penta-O-acetyl-D-gala-heptosone 1-hydrazone gave only sirup as did Raney nickel-ethanol reduction (93).


Zinc-acetic acid-acetic anhydride (94) reduction of 3,4,5,6,7-penta-O-acetyl-D-gala-heptosone 1-hydrazone gave a highly impure material in amounts too small to allow identification. It is of interest to note that although zinc-acetic acid-acetic anhydride reduction caused no color formation the same reaction omitting the acetic anhydride gave dark red colors.

Synthesis of β-Hydroxynaphthaldehyde 3,4,5,6,7-Penta-O-acetyl-D-gala-heptosone Aldazine.

From an attempted exchange reaction with β-hydroxynaphthaldehyde the crystalline, unsymmetrical aldazine (shown below) was isolated by chromatography. This compound was a bright golden-orange in color. It
undergoes irreversible color changes (cited in Experimental section) on treatment with acids and bases.

Product. Obtained on Acetylation of 3,4,5,6,7-Penta-O-acetyl-D-gala-heptosone 1-Hydrazone.

Acetylation of the hydrazone with hot acetic anhydride or with acetyl chloride at room temperature gave identical products, the acetyl chloride procedure providing better yields although the product was somewhat more difficult to purify than the product obtained using acetic anhydride. This product was considered pure on the basis of its very sharp melting point (195-195.2°C.) but the analysis does not agree with the N-acetate, the N,N-diacetate, a mixture of the two, or a mixture of the N-acetate and acetic acid. The nature of this product therefore remains in doubt although acetic anhydride acetylation of the group, \(-\text{CO-CH=NH}_2\), has been previously
reported to give the \( N \)-acetate (65,42).

Attempts to acetylate using \( N,N' \)-dichlohexlylcarbodi-imide and acetic acid, acetic anhydride and pyridine, and acetyl bromide were unsuccessful. Sodium acetate and acetic anhydride gave trace yields (4%) of the same material as described above.

Miscellaneous Syntheses, Results, and Observations.

Carcinolytic Evaluation of \( \text{l-Deoxy-\( l \)-diazo-keto-\( \text{D} \)-Fructose Tetraacetate} \).

In view of the reported carcinolytic activity of some diazo compounds together with the fact that the metabolism of \( \text{D} \)-glucose by cancer cells is more rapid than by normal cells, it was considered of interest to test a diazo sugar for carcinolytic activity. Evaluation of \( \text{l-deoxy-\( l \)-diazo-keto-\( \text{D} \)-fructose tetraacetate} \) by Eli Lilly & Co. showed no selective effect against three malignant cells and three normal cell controls at levels as high as 400 mcg. per cc. of culture media (see Appendix).

Detection of Carbohydrates on Paper Chromatograms.

During the course of the work reported herein, paper chromatography was used to separate mixtures of glycitols and their derivatives. To detect these materials, a sodium metaperiodate spray followed by a
potassium permanganate spray, a method used in this Laboratory at that time, was initially employed. The spots observed, however, soon became indistinguishable from the background as oxidation of the paper itself proceeded. In an effort to stabilize the chromatograms, the author rinsed the paper free of excess permanganate after the spots appeared. This treatment does not remove the spots and not only gives a more stable chromatogram but frequently reveals faint spots initially masked by the excess permanganate solution. A further improvement was made by spraying the washed chromatogram with an acidic benzidine solution (95) which instantly converts the brown spots to dark blue ones due to the oxidation of the benzidine by the manganese dioxide. This treatment will frequently reveal faint spots previously not seen. This method for detecting carbohydrates on paper chromatograms was subsequently published (96).


Preparation of Penta-α-acetyl-β-galactonic Nitrile.

The reported preparation of nitriles by the tosyl
chloride dehydration of amides (97) was successfully applied to penta-6-acetyl-6-galactonamide with the nitrile being obtained in 35 per cent yield. This represents the reversal of the Zemplen-Kiss nitrile to amide conversion (98).


(98) G. Zemplen and D. Kiss, Ber., 60, 165 (1927).

Attempts to apply this method to penta-6-acetyl-6-gluconamide, and tetra-6-acetyl-6-ribonamide were unsuccessful.

The Synthesis of Penta-6-acetyl-6-galactonic p-Toluidide and Tetra-6-acetyl-6-arabonic p-Toluidide.

The reaction of the aldonyl chloride acetates with excess p-toluidine in ether was found to give the p-toluidides. The p-toluidides possessed excellent crystallizing properties and it is believed that these may represent more convenient derivatives than the anilides since p-toluidine is easily purified by recrystallization whereas aniline must be distilled.

Action of Hydrazine on 2,3,4,6-Tetra-6-methyl-6-glucose.

Reaction of hydrazine with 2,3,4,6-tetra-6-methyl-
D-glucose in chloroform gives a clear, colorless, odorless sirup. This sirup still contains hydrazine after long periods of storage in a vacuum desiccator since on refluxing in methanol vapors basic to litmus are evolved. The sirup gradually acquires a yellow color and then becomes pasty after which a pure white crystalline compound can be isolated. The time required for this change varied from one and one-half to six months. The formulas given below agree with the analytical data obtained.

\[
\begin{align*}
\text{CH} &= \text{N} - \text{N} - \text{CH} \\
\text{CHO} &\quad \text{CH}_3 \\
\text{C} &= \text{O} \quad \text{CH}_2 \\
\text{MeO-C} &\quad \text{MeO-C} \quad \text{MeO-C} \\
\text{C-O} &\quad \text{C-O} \\
\text{C-OH} &\quad \text{C-OH} \\
\text{CH}_2\text{OMe} &\quad \text{CH}_2\text{OMe} \\
\end{align*}
\]

\[
\begin{align*}
\text{CH} &= \text{N} - \text{N} - \text{CH} \\
\text{CHO} &\quad \text{CH}_3 \\
\text{C} &= \text{O} \quad \text{MeO-C} \\
\text{MeO-C} &\quad \text{MeO-C} \quad \text{C-O} \\
\text{C-O} &\quad \text{C-O} \\
\text{C-OH} &\quad \text{C-OH} \\
\text{CH}_2\text{OMe} &\quad \text{CH}_2\text{OMe} \\
\end{align*}
\]
SUGGESTIONS FOR FURTHER WORK

1. To complete the structural assignment for 2-acetoxyethyl-3,4,5,6-tetra-O-acetyl-1,2-anhydro-β-glucitol \([\text{mannitol}]\) a proof of configuration is needed. This might be done by relating the epoxides to the fructo-cyanohydrins whose configurations are considered known (99). Figure 4 suggests several means of accomplishing this.

2. The sirupy 2-acetoxyethyl-3,4,5,6-tetra-O-acetyl-1-chloro-1-deoxy-\(\alpha\)-iditol \([\text{gulitol}]\) should be treated with sodium acetate to regenerate the crystalline epoxide pentaacetate as a further proof of structure.

3. The addition of water to the epoxides without deacetylation as, for example, in an acetic-acid-water-perchloric acid system should be attempted followed by periodate cleavage to give keto-\(\alpha\)-sorbose pentaacetate or keto-\(\beta\)-fructose pentaacetate.

4. An entry into the epimeric epoxide series should be sought. This might be accomplished by the selective hydrolysis of the tertiary bromine of the dibromide reported in this work. If the bromohydrin


Figure 4. Suggested Methods of Relating the Configuration of 1,2-Anhydro-2-β-hydroxymethyl-β-glucitol [mannitol?] to the Fructocyanohydrins.
obtained in this way should happen to be the epimer of the bromohydrin obtained on treatment of the epoxide with hydrogen bromide in acetic acid, then further treatment with sodium acetate would yield the epimeric epoxide.

Another method might be to convert the dibromide to the olefin and then epoxidize the olefin.

5. With the hope of obtaining 1-amino-1-deoxy-keto acetates, the zinc-acetic acid reduction of the diazomethyl-keto acetates should be attempted. Before this is done, however, the zinc-acetic acid reduction of keto-D-fructose pentaacetate should be investigated since this reducing system is known to reduce some ketol acetates (100), as shown below. Should the ketose acetate prove to be stable to these reducing conditions, then the zinc-acetic acid reduction of the diazomethylketoses should be reinvestigated. If, however, keto-D-fructose pentaacetate proves to be unstable to zinc-acetic acid reduction, then this reduction might be tried on the deacetylated diazomethylketoses where the carbonyl group

probably no longer exists as such.

6. The untried routes to diazo carbohydrate derivatives should be investigated. The following equations suggest some methods.

(a)
\[
\begin{align*}
\text{CH}_2\text{NH}_2 + \text{TsCl} &\rightarrow \text{CH}_2\text{-NHTs} \\
(\text{CHOH})_4 \text{NaOH} &\rightarrow (\text{CHOH})_4 \\
\text{CH}_2\text{OH} &\rightarrow \text{CH}_2\text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2\text{NH}_2 + \text{TsCl} &\rightarrow \text{CH}_2\text{-NHTs} \\
(\text{CHOH})_4 \text{NaOH} &\rightarrow (\text{CHOH})_4 \\
\text{CH}_2\text{OH} &\rightarrow \text{CH}_2\text{OH}
\end{align*}
\]

7. The hydrazones should be deacetylated. The mutarotation of these compounds, or the lack of it, would be of interest in view of the fact that l-deoxy-l-diazo-D-galacto-heptulose fails to mutarotate. Also, since glycosylamines are easily hydrolyzed, these deacetylated hydrazones might easily hydrolyze to give osones of high purity.
8. The structure of the acetylated 3,4,5,6,7-penta-α-acetyl-D-gala-heptose one 1-hydrazone should be established. The material should be re-analyzed for carbon, hydrogen, nitrogen, and total acetyl, an α-acetyl determination should be made, and a molecular weight determination is required. The infra-red spectrum should indicate whether the imine linkage is still present and the ultraviolet spectrum should indicate the presence, or absence, of the keto group and whether it is still conjugated with the imine link.

9. The structure of the product obtained by the action of hydrazine on 2,3,4,6-tetra-α-methyl-α-glucose should be investigated.

10. Phenyl diazomethane should be investigated as a benzylating agent for alcohols. The very mild conditions which could be used would be advantageous although poor yields may be encountered since diazomethane is usually a poor methylating agent for alcohols.
EXPERIMENTAL

Synthesis of 1-Chloro-1-deoxy-2-hydroxymethyl-\(\beta\)-glucitol \([\text{mannitol}]\) from the Epoxide obtained by the Action of Diazomethane on keto-\(\beta\)-fructose Pentaacetate.

An amount of 1.52 g. of 2-acetoxymethyl-3,4,5,6-tetra-\(\alpha\)-acetyl-1,2-anhydro-\(\beta\)-glucitol \([\text{mannitol}]\) (2) was covered with 50 ml. of a one per cent methanolic hydrogen chloride solution. After standing for three days in the refrigerator, all but a trace of material was in solution. The solvent was removed under reduced pressure at 60\(^\circ\)C. The resulting syrup was dissolved in ethanol and the solvent removed as before. This treatment was repeated followed by a similar one using benzene. The syrup was dissolved in water and the solution brought to neutrality with silver carbonate. After filtration, treatment with hydrogen sulfide, and refiltering, a neutral solution was obtained which gave a syrup upon solvent removal under reduced pressure. Crystallization was induced by the addition of a little ethanol and cooling in the refrigerator. After thorough washing with ethanol, the crystals had m.p. 126\(^\circ\)C. (dec.). A second crop was obtained from the combined washings and mother liquor; m.p. 107-122\(^\circ\) (dec.). The first crop of crystals, when recrystallized from ethanol, gave 210 mg.
of crystalline material, m.p. 127.5-130°C. (dec.).

Paper chromatography of this material, using butanol/ethanol/water (40/11/19 by vol.) as developer and NaIO₄/KMnO₄/benzidine (96) as the indicator, revealed two spots: R glucose 1.4 (very faint) and 1.9 (intense with tailing). For the purpose of interpreting the analytical results, the existence of a ternary mixture was assumed, the components of which, representing the opening of the epoxide ring by hydrogen chloride, methanol, and water, would be RCl, ROMe, and ROH (deacetylated in each case), respectively.

Anal. Calcd. for Nₐ₉Cl = 0.9068, Nₐ₉OMe = 0.0905, and Nₐ₉OH = 0.0027: C, 37.00; H, 6.72; Cl, 13.97; OMe, 1.22. Found (101): C, 36.93; H, 6.94; Cl, 13.97; OMe, 1.22.

(101) Huffman Microanalytical Laboratories, Wheatridge, Colorado.

In a succeeding preparation, using five g. of starting material and omitting the silver carbonate treatment, 2.16 g. of product (m.p. 122-130°C. dec.) was obtained from the strongly acidic sirup by adding a little ethanol, seeding, and refrigerating overnight. This material gave three spots on paper chromatography (as described above): R glucose = 0.95 (faint), 1.5 (faint), 1.9 (large and intense). The above material was chromatographed on
a 3 x 59 cm. powdered cellulose (Whatman Standard grade) column. The column had previously been prewashed continuously for two weeks with developer, butanol/ethanol/water (40/11/19 by vol.), and its performance checked by the separation of dyes (102-104). Methyl violet was placed on the column along with the sample to serve as a marker for the solvent front. Fractions were collected every 23 min. (about five ml.) after the methyl violet had been eluted from the column. The forerun, containing the methyl violet, gave a negative Beilstein halogen test (105). Fractions 1 through 19 gave positive Beilstein tests (105). Fractions 20 and above gave negative Beilstein tests and the presence of material in these fractions was detected by spotting a sample on paper and spraying with NaIO₄/KMnO₄/benzidine indicator (96). With this indicator, fractions 20 through 27 were
negative, fractions 28 through 36 weakly positive, and 37 through 76 negative.

Fractions 28 through 76 were combined and the solvent removed under reduced pressure to yield a sirup, \( R_{\text{glucose}} = 0.92 \), which has resisted crystallization but is believed to be the product obtained by opening of the epoxide ring with water.

Fractions 1-19 were combined and the solvent removed under reduced pressure to yield a crystalline product, m.p. 120-125°C. (dec.). Recrystallization from hot methanol gave 870 mg. (40% recovery) of a crystalline material, m.p. 127-130°C. (dec.), \( R_{\text{glucose}} = 1.9 \) and 1.6 (very weak). Recrystallization from hot butanol/ethanol/water (40/11/19 by vol.) followed by recrystallization from hot ethanol gave pure material, m.p. 132.5-133°C., \( \Delta T \simeq 25^\circ \text{D} \pm 8.5^\circ \text{C} \) (G 4.1, U.S.P. CHCl₃), chromatographically homogeneous, \( R_{\text{glucose}} = 1.89 \). The substance crystallized as white needles with a very sweet, followed by a bitter, taste; they were soluble in water, methanol, and hot ethanol; insoluble in acetone and ether.

Anal. Calcd. for \( \text{C}_7\text{H}_{15}\text{O}_6\text{Cl} \): C, 36.44; H, 6.57; Cl, 15.37. Found (106): C, 36.41; H, 6.53; Cl, 15.42.

(106) Galbraith Microanalytical Laboratories, Knoxville, Tennessee.
Proof of Structure of 1-Chloro-1-deoxy-2-hydroxymethyl-
D-glucitol \textit{[mannitol?]} by Periodate Oxidation.

The chlorohydrin obtained reduced five moles of periodate per mole of chlorohydrin and liberated two moles of formaldehyde per mole of chlorohydrin (see Table 1). This is consistent with the assigned structure and serves to differentiate the compound from the alternative structure, 2-chloro-2-deoxy-2-hydroxymethyl-
D-arabinohexitol, which would reduce only three moles of periodate and liberate only one mole of formaldehyde per mole of chlorohydrin.

Synthesis of 2-Acetoxymethyl-3,4,5,6-tetra-O-acetyl-1-
chloro-1-deoxy-D-glucitol \textit{[mannitol?]}. 

To a solution of 500 mg. of 2-acetoxymethyl-3,4,5,6-
tetra-O-acetyl-1,2-anhydro-D-glucitol \textit{[mannitol?] in}
1.8 ml. of acetic acid was added six ml. of acetic acid saturated with hydrogen chloride. The mixture was allowed to stand in the icebox for 23 hr. and then at room temperature for one and one-half hours. The solution was then poured into 30 ml. of a saturated sodium bicarbonate solution followed by the addition of small portions of solid sodium bicarbonate until the solution was neutral to litmus. The solution was then extracted four times with ten-ml. portions of chloroform, the combined extracts were dried with sodium sulfate, filtered, and the solvent
Table I

Periodate Oxidation of 1-Chloro-1-deoxy-2-hydroxymethyl-β-glucitol [mannitol?]

<table>
<thead>
<tr>
<th>Time, Min.</th>
<th>Moles of Periodate Reduced per Mole of Substrate* 25°C.</th>
<th>Moles of Formaldehyde Produced per Mole of Substrate at 25°C.**</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>4.99</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>5.03</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>5.51</td>
<td></td>
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<tr>
<td>27</td>
<td>5.24</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>5.24</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td>2.02</td>
</tr>
<tr>
<td>73</td>
<td>5.43</td>
<td></td>
</tr>
<tr>
<td>79</td>
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<tr>
<td>91</td>
<td>5.63</td>
<td>5.21</td>
</tr>
<tr>
<td>148</td>
<td>5.35</td>
<td>5.29</td>
</tr>
<tr>
<td>181</td>
<td>5.47</td>
<td></td>
</tr>
</tbody>
</table>


Analysis by Dr. D. S. Miyada.
removed under reduced pressure. The resulting sirup crystallized on scratching. Recrystallization from bensene/pet. ether (38-60° b.p.) gave 260 mg. of crystals, m.p. 82-85.5°C. Pure material was obtained after two recrystallizations from ether/pet. ether (30-60° b.p.), m.p. 85-87°C, [α]D +37.0° (c 2.1, U.S.P. CHCl₃).

Anal. Calcd. for C₁₇H₂₅O₁₁Cl: C, 46.32; H, 5.73; Cl, 8.04; OAc, 66.95. Found: (106) C, 46.34; H, 5.72; Cl, 7.92; OAc, 62-80. (Note: if hydrogen chloride were liberated during the acetyl determinations, then the apparent acetyl content would be 80.4%).


To a solution of 200 mg. of 2-acetoxymethyl-3,4,5,6-tetra-O-acetyl-l-chloro-l-deoxy-D-glucitol [mannitol] in 30 ml. of methanol was added one drop of dilute sulfuric acid and the mixture was allowed to stand in the icebox for nine days. The solution was then neutralized with IR-4B (107) and the solvent removed under reduced pressure.

to give a sirup which when covered with methanol and refrigerated, deposited sirupy crystals, m.p. 123°C. (dec.). Recrystallization from 1-butanol/ethanol/water (40/11/19 by vol.) and then from ethanol gave 10 mg. of crystals, m.p. 128.5°C (dec.), mixed m.p. with authentic 1-chloro-1-deoxy-2-hydroxymethyl-2-glucitol [mannitol] 130°C (dec.), R glucose identical with an authentic sample.

Synthesis of 2-Acetoxymethyl-3,5,6-tetra-O-acetyl-1-
bromo-1-deoxy-D-glucitol [mannitol] by the Action of

Hydrogen Bromide on the Corresponding Epoxide.

To a solution of two grams of 2-acetoxymethyl-3,4,5,6-
tetra-O-acetyl-1,2-anhydro-D-glucitol [mannitol] in
three ml. of acetic acid was added three ml. of acetic
acid saturated with hydrogen bromide. After two minutes
at room temperature, the solution was poured slowly into
40 ml. of a saturated sodium bicarbonate solution.
Solid sodium bicarbonate was then added in small portions
until the solution was slightly basic to litmus. The
mixture was extracted immediately with three ten-ml. por-
tions of chloroform, the combined extracts dried with
sodium sulfate, filtered, and the solvent removed under
reduced pressure to yield a thin sirup. Solution in
benzene followed by removal of the solvent under reduced
pressure gave a sirup which crystallized spontaneously.
Recrystallization from ether/pet. ether (b.p. 30-60°C.)
gave 1.06 g. of crystals, m.p. 91-98°C. Two additional recrystallizations from ether/pet. ether gave crystalline material of m.p. 99-101°C., \( [\alpha]^24.9_{D} +30.9^\circ \) (g. 3.9, U.S.P. CHCl₃), m.p. unchanged on recrystallization from methanol.

**Anal.** Calcd. for C₁₇H₂₅O₁₁Br: C, 42.07; H, 5.19; Br, 16.46. Found: C, 41.97; H, 5.15; Br, 17.01.

The X-ray powder diffraction pattern for this compound is nearly identical with that of the corresponding chloro compound and the two are probably isomorphous.

**Synthesis of 2-Acetoxymethyl-3,4,5,6-tetra-O-acetyl-1-bromo-1-deoxy-\( D \)-glucitol \( \text{[mannitol]} \) by the Action of Magnesium Bromide on the Corresponding Epoxide.**

To prepare active magnesium bromide, 10 mg. of magnesium in 50 ml. of benzene/ether (1/1 by vol.) was added to an excess of ethylene bromide (89). After all the magnesium had reacted 200 mg. of 2-acetoxymethyl-3, 4,5,6-tetra-O-acetyl-1,2-anhydro-\( D \)-glucitol \( \text{[mannitol]} \) was added and the solution was stirred overnight at room temperature. An equal volume of water was added, the ether/benzene layer separated, and the aqueous phase extracted with 20 ml. of chloroform. The combined ether/benzene and chloroform extracts were dried with sodium sulfate, filtered, and the solvent removed under reduced pressure to yield a sirup. Solution in benzene followed
by solvent removal as before gave a sirup which crystal-
ized spontaneously; yield 105 mg., m.p. 96.5-98°C.,
mixed m.p. with authentic bromohydrin undepressed, strongly positive Beilstein halogen test.

Synthesis of 2-Acetoxymethyl-3,4,5,6-tetra-O-acetyl-1,2-
dibromo-1,2-dideoxy-D-glucitol (mannitol).  

The synthesis of this compound follows that of the bromohydrin except that six ml. of acetic acid saturated with hydrogen bromide were used in a reaction time of 21 hr. at about 10°C. After pouring the reaction mixture into 40 ml. of saturated sodium bicarbonate solution, solid sodium bicarbonate was added in small portions until the solution was no longer acidic to Congo Red paper but was still acidic to litmus paper. The frothy white gum initially formed became crystalline after thorough trituration. Filtration followed by washing with water until the filtrate was no longer acidic to litmus gave, on drying, 2.39 g. of crystals, m.p. 79-82°C. Two re-
crystallizations from ether/pet. ether (30-60° b.p.) gave material of m.p. 81-84°C., [α]$_D$$^2$ +35.0° (a 3.3, U.S.P. CHCl$_3$), whose melting point was unchanged on recrystallization from 1,2-dimethoxyethane. (A small amount of the bromohydrin may be obtained from the mother liquors.)
Anal. Calcd. for C_{17}H_{24}O_{10}Br_{2}: C, 37.24; H, 4.41; Br, 29.16. Found (106): C, 37.94, 38.02; H, 4.94, 4.83; Br, 28.52, 28.65.

On attempted recrystallization of this compound from hot methanol there was obtained, on one occasion, a solid having m.p. 126° (dec.) which gave a strong positive Beilstein halogen test (105). On attempting to repeat this, however, only sirups were obtained.

This dibromide reacted with a 1,2-dimethoxyethane solution of sodium iodide to give sodium bromide (identified by X-ray powder diffraction pattern) and a brown solution (I_{2}) whose color was discharged by sodium sulfite.

Preparation of 1,2-Anhydro-2-hydroxymethyl-\(\alpha\)-glucitol

from 1-Chloro-1-deoxy-2-hydroxymethyl-\(\alpha\)-glucitol

by the Action of Sodium Hydroxide.

To 0.44 ml. of water containing 40 mg. of sodium hydroxide was added 110 mg. of the chlorohydrin. The solution was allowed to stand one day at room temperature at the end of which time the solution gave a positive halide test with silver nitrate/nitric acid. Deionization of the solution with MB-1 (107) resin gave a clear, colorless solution which gave a faintly positive Beilstein halogen test (105). Removal of the solvent under reduced pressure at 100°C gave a sirup which crystallized on scratching. Recrystallization from methanol gave 25 mg.
of crystals, m.p. 133.5-136°C., mixed m.p. with authentic 1,2-anhydro-2-D-hydroxymethyl-D-glucitol [mannitol\(^\oplus\)] (2) undepressed, Beilstein test negative (105).

Preparation of 1,2-Anhydro-2-hydroxymethyl-D-glucitol [mannitol\(\oplus\)] from the Chlorohydrin by the Action of Potassium Acetate - Potassium Iodide.

To ten ml. of absolute methanol containing 50 mg. of freshly fused potassium acetate and one very small crystal of potassium iodide was added 110 mg. of 1-chloro-1-deoxy-2-hydroxymethyl-D-glucitol [mannitol\(\oplus\)]. The solution was refluxed for one and one-quarter hour and then allowed to stand overnight at room temperature. Deionization of the solution with MB-1 (107) resin followed by removal of the solvent under reduced pressure yielded a sirup which gave a negative Beilstein halogen test (105). The sirup was dissolved in ethanol and benzene was added to the point of incipient crystallization. On standing, the solution deposited 20 mg. of crystals, m.p. 128-133°C., mixed m.p. with starting material 109-125°C. (dec.), mixed m.p. with authentic 1,2-anhydro-2-hydroxymethyl-D-glucitol [mannitol\(\oplus\)] (2) 130-136°C., \(R\) glucose identical with that of authentic anhydro sample.

Preparation of 1,2-Anhydro-2-hydroxymethyl-D-glucitol [mannitol\(\oplus\)] by the Deacetylation of the Parent Compound.

To 20 ml. of water containing 2 g. of sodium hydroxide
was added 2 g. of 2-acetoxyethyl-3,4,5,6-tetra-O-acetyl-1,2-anhydro-D-glucitol \textsuperscript{[mannitol\textregistered]} . The mixture was heated to reflux until complete solution resulted and was then maintained for 18 hr. at room temperature. Neutralization of the solution with MB-1 (107) resin followed by removal of the solvent under reduced pressure, yielded a sirup which crystallized on scratching. This material when recrystallized from boiling methanol gave 220 mg. of crystals; m.p. 133-135.5\degree C., mixed m.p. with authentic 1,2-anhydro-2-hydroxymethyl-D-glucitol \textsuperscript{[mannitol\textregistered]} (2) undepressed, \textit{R} \textsubscript{glucose} value identical with authentic material.

Preparation of 2-Acetoxyethyl-3,4,5,6-tetra-O-acetyl-1,2-anhydro-D-glucitol \textsuperscript{[mannitol\textregistered]} from 2-Acetoxyethyl-3,4,5,6-tetra-O-acetyl-1-bromo-1-deoxy-D-glucitol \textsuperscript{[mannitol\textregistered]} 

To a solution of 100 mg. of the bromohydrin in 60 ml. of ethanol was added 30 mg. of freshly fused sodium acetate. After refluxing for one hour, the solvent was removed under reduced pressure. The residue was extracted with chloroform and the chloroform removed under reduced pressure to yield a sirup. The sirup was dissolved in benzene and the solvent again removed under reduced pressure to yield a sirup which slowly crystallized. Recrystallization from benzene/pet. ether (30-60\degree b.p.) gave 50 mg. of crystals; m.p. 84-86\degree C., mixed m.p. with
authentic 2-acetoxymethyl-3,4,5,6-tetra-\(\alpha\)-acetyl-1,2-anhydro-\(\alpha\)-glucitol \(\text{mannitol}\) (2) undepressed.

Identification of a Supposed Second Product of the Reaction of Diazomethane with keto-\(\alpha\)-Fructose Pentaacetate.

Since any ketose resulting from such a reaction must be a keto-acetate, the author examined the ultraviolet spectrum of this compound and found no ketonic absorption. The constants of this compound are in excellent agreement with those of \(\beta\)-\(\alpha\)-fructose pentaacetate. Finally the reported analysis (3) gives \(C_{14}H_{29}O_{1},00\) as the simplest empirical formula which is equivalent to \(C_{16}H_{22}O_{11}\), the correct formula for \(\beta\)-\(\alpha\)-fructose pentaacetate. It is concluded, therefore, that this compound is \(\beta\)-\(\alpha\)-fructose pentaacetate which was present as an impurity in the keto-\(\alpha\)-fructose pentaacetate used as starting material by Hanze (3).

Synthesis of 2-Acetoxymethyl-3,4,5,6-tetra-\(\alpha\)-acetyl-1-chloro-1-deoxy-\(\alpha\)-iditol \(\text{gulitol}\).

To a solution of one g. of 2-acetoxymethyl-3,4,5,6-tetra-\(\alpha\)-acetyl-1,2-anhydro-\(\alpha\)-iditol \(\text{gulitol}\) (3) in four ml. of acetic acid was added 12 ml. of acetic acid saturated with hydrogen chloride. After four minutes at room temperature, the solution was slowly poured into 50 ml. of saturated sodium bicarbonate solution. Solid
sodium bicarbonate was added in small portions until the solution was slightly basic to litmus. Extraction with five 10-ml. portions of chloroform, drying with sodium sulfate, filtering, and solvent removal under reduced pressure, yielded a thin sirup. Solution in benzene followed by solvent removal again gave a sirup which resisted crystallization.

This sirup was divided in half and each half was chromatographed on a Magnesol (108)-Celite (109) (5/1 by wt.) column (17.5 x 3.5 cm.) using 350 ml. of benzene/1-butanol (100/1 by vol.) as developer. Extrusion of the columns and streaking with alkaline permanganate indicator revealed a single large zone, 1-8 cm. from the top of each column. The zones from the two columns were dissected, combined, and eluted with acetone. On evaporation of the solvent, a yellow sirup was obtained. This sirup was divided into thirds and each third chromatographed as before except that 700 ml. of developer was used for each column. Alkaline permanganate revealed a single zone on each column, 7-11 cm. from the top of

(108) A product of the Westvaco Chemical Division of Food Machinery and Chemical Corp., South Charleston, W. Va.

the column. The bottom half of each of these zones was dissected, combined, and eluted with acetone. Removal of the solvent under reduced pressure again gave a yellow sirup. The sirup was decolorized twice by treatment with Darco G60 (110) in ethanol. The sirup was then dried

(110) An activated carbon produced by the Darco Corporation, 60 E. 42nd St., New York.

at 78°C. in vacuum over phosphorus pentoxide; yield 110 mg., $\delta 24^2 +14.2^0$ (2 4.3, U.S.P. CHCl$_3$).

Anal. Calcd. for C$_{17}$H$_{25}O$_{11}Cl: C, 46.32; H, 5.73; Cl, 8.04. Found (111): C, 46.57; H, 5.52; Cl, 8.54.

(111) Schwarzkopf Microanalytical Laboratory, Woodside, New York.

Infrared Spectra of Epoxides

Epoxides are reported to show absorption in the 7.9 $\mu$ and 11.1 $\mu$ regions with the former being the more reliable (112). They are also reported to show absorption


in the 10.52-11.58 $\mu$ and 11.57-12.72 $\mu$ regions (113).
An examination of Table II indicates that three bands are associated with the carbohydrate epoxides: 7.9, 11.1, and 11.6 μ. The 7.9 μ band, however, which Bellamy regards as the most reliable, suffers here from acetyl absorption in the same region. Likewise, the 11.6 μ band does not appear to be without objection. We may expect then that epoxides of the sugar type will show 3 bands as indicated but we cannot say that these absorption bands prove the existence of an epoxide ring.

Stereochemical Relationship Between the Epoxide Derived from keto-D-Fructose Pentaacetate and that Derived from keto-L-Sorbose Pentaacetate.

An amount of 197.7 mg. of 2-acetoxymethyl-3,4,5,6-tetra-O-acetyl-1,2-anhydro-D-glucitol [mannitol] was placed in a flask with three ml. of N sodium hydroxide. The same procedure was followed with 196.9 mg. of 2-acetoxymethyl-3,4,5,6-tetra-O-acetyl-1,2-anhydro-L-iditol [gulitol]. The flasks were stoppered and heated on a boiling water bath for four minutes and then cooled. Four drops of acetic acid were added to each followed by five ml. of a saturated sodium metaperiodate solution. After 30 minutes at room temperature, the rotations were
Table II
Infrared Spectra of Some Carbohydrates

<table>
<thead>
<tr>
<th>Substance</th>
<th>Infrared Absorption Bands in Microns μμ</th>
<th>&quot;Solvent&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcOH₂C₂C₂C₂C₂CH₂</td>
<td>7.9 11.1 11.6</td>
<td>CHCl₃&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>AcOH₂C₂C₂C₂C₂CH₂</td>
<td>7.9 11.1 11.6</td>
<td>CHCl₃&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>HOH₂C₂C₂C₂C₂CH₂</td>
<td>7.9 11.1 11.6</td>
<td>Nujol mull</td>
</tr>
<tr>
<td>HOH₂C₂C₂C₂C₂CH₂Cl</td>
<td>- -</td>
<td>-11.3 Nujol mull</td>
</tr>
<tr>
<td>AcOH₂C₂C₂C₂C₂CH₂Cl</td>
<td>7.9 - -</td>
<td>CHCl₃&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Infrared recording spectrophotometer, Model B, Baird Associates, Inc., Cambridge, Mass.  <sup>b</sup> Compensated.
measured and the values obtained for the iditol derivative were corrected for concentration by multiplication by $0.1977/0.1969$. The results are shown in Table III. Assuming the same standard deviations, Student's t-test \((114)\) indicates the rotations for the blank and for the epoxide derived from fructose to be different at the five per cent level of significance and indicates no difference in the rotations of the fructose and the sorbose derivative at the five per cent level of significance. The statistical interpretation is then that the rotations observed for the blank and for the fructose derivative are different and that the rotations observed for the sorbose and the fructose derivatives are the same. The structural interpretation is that the starting materials in each case are C5 epimers (see Discussion).

Preparation of 1-Deoxy-keto-D-gala-heptulose Pentaacetate.

Amalgamated aluminum was prepared by covering 300 mg. of granular aluminum with a saturated solution of mercuric chloride acidified with hydrochloric acid. After sufficient amalgamation had occurred (about one minute) the solvent was decanted and the amalgam was washed by
### Table III
Rotations Observed After Saponification and Periodate Oxidation of Two Epoxides

<table>
<thead>
<tr>
<th>Compound</th>
<th>Average Observed Rotation at 5461 Å</th>
<th>Corrected for Blank</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Sorbose derivative</td>
<td>-1.812 ± 0.019°</td>
<td>-0.076 ± 0.045°</td>
</tr>
<tr>
<td>D-Fructose derivative</td>
<td>-1.836 ± 0.026°</td>
<td>-0.100 ± 0.052°</td>
</tr>
<tr>
<td>Distilled water</td>
<td>-1.736 ± 0.026°</td>
<td>0.000 ± 0.052°</td>
</tr>
</tbody>
</table>

*Visual readings with a Rudolph Photoelectric Polarimeter, Model 200. Crystallization of sodium iodate from solution prevented more accurate readings.*
décantation twice with acetone, twice with ether, and then twice with peroxide-free 1,2-dimethoxyethane.

The reaction was carried out by adding to the amalgam prepared above a solution of one gram of 1-deoxy-1-diazo-keto-D-gala-heptulose pentaacetate in 30 ml. of peroxide-free 1,2-dimethoxyethane. Immediate reaction occurred as evidenced by bubbling and the formation of an orange-gold color on the surface of the amalgam. One very small drop of water was added and the mixture was stirred at room temperature for 24 hr. The mixture was then filtered and the dark colored residue was thoroughly washed with chloroform. The combined filtrate and washings were stripped to a dark colored sirup. Some of the color was removed by passing a chloroform solution of the sirup through a column (0.9 x 8 cm.) of Magnesol (108)-Celite (109) (5/1 by wt.) followed by 15 ml. of pure chloroform. The yellow effluent was dissolved in ten ml. of methanol and again stripped to a sirup. This treatment was repeated. A solution of the sirup in ten ml. of methanol was then passed through a Darco G60 (110) column (0.9 x 8 cm.) followed by 15 ml. of methanol. The colorless effluent was evaporated in a desiccator over sulfuric acid under aspirator vacuum to a light yellow sirup. The addition of methanol to this sirup followed by refrigeration gave beautiful bright yellow crystals. Filtration followed by washing with
aqueous methanol (1/1 by vol.) gave, after drying, 560 mg. of crystals, m.p. 55-61°C. Four recrystallizations from ether/pet. ether (30-60° b.p.) gave crystals of m.p. 65.5-68.5°C, which on crystallizing from the melt then remelted at 78.5°C. Recrystallization from ether/pet. ether (30°-60° b.p.) and seeding with the higher melting polymorph of 1-deoxy-keto-D-gala-heptulose pentaacetate (64) gave crystals having m.p. 78-80°C., $\Delta_721.5^\circ$ $\Lambda_{D} +13.2^\circ +0.5^\circ$ (c 1.85, U.S.P. CHCl$_3$); lit. m.p. 78-79°C., $\Delta_7D +14^\circ$ (64). The X-ray powder diffraction pattern of this material was identical with that of an authentic sample of the higher melting polymorph of 1-deoxy-keto-D-gala-heptulose pentaacetate.

Silicate column chromatography of the crude reaction mixture from other preparations showed only one zone in addition to a highly colored zone at the column top. Isolation of material from this colorless zone gave 1-deoxy-keto-D-gala-heptulose pentaacetate. Although no attempt was made to determine optimum reaction conditions, it was found that without the addition of water less of the dark residue was formed and the deoxy compound was obtained in low yield together with some starting material, the two being separable by virtue of their solubility difference in ether - the starting material being the much less soluble. Larger amounts of water added to the reaction gave correspondingly larger amounts of dark color-
Synthesis of 3,4,5,6,7-Penta-O-acetyl-D-gala-heptosone 1-Hydrazone by Hydrogen Sulfide Reduction.

An amount of 840 mg. of l-deoxy-l-diazo-keto-D-galacto-heptulose pentaacetate was dissolved in 90 ml. of commercial absolute ethanol with warming. After cooling to room temperature, four drops of ammonium sulfide solution (Mallinkrodt, Analytical Reagent) were added. After bubbling hydrogen sulfide through the solution for two hours at the approximate rate of 100 ml/min. (S.T.P.), nitrogen was bubbled through for one hour. Removal of the solvent under reduced pressure at room temperature gave a sirup containing some crystalline material (Sg?). Upon scratching, the sirup crystallized. Two recrystallizations from benzene/carbon disulfide gave 740 mg. of crystals, m.p. 133-136°C. Recrystallization from benzene/pet. ether (30-60°C. b.p.) gave pure material; very slightly yellow crystals, m.p. 137-138.5°C., \[\alpha_{D}^{23} -28.46^\circ\] (2 3.40, U.S.P. CHCl₃).

Anal. Calcd. for C₁₇H₂₄O₁₁N₂: C, 47.22; H, 5.60; N, 6.48. Found (101): C, 47.30; H, 5.58; N, 6.41.

This hydrazone gives a weakly positive ninhydrin test on paper. The reduction of more concentrated solutions appears to enhance color formation and provides a precipitate of beautifully crystalline sulfur. Thus,
one gram of the diazo sugar in 30 ml. of ethanol gave a precipitate of sulfur corresponding to 86 per cent reduction and a 72 per cent yield of brown colored, crude hydrazone, m.p. 134-135.5°C. It was further determined that: (a) in the absence of ammonium sulfide no reduction occurred in 65 minutes, and (b) in the presence of ammonium sulfide at ice-salt bath temperature essentially no reduction occurred in 60 minutes time.

Synthesis of 3,4,5,6,7-Penta-O-acetyl-D-gala-heptosone 1-Hydrazone by Sodium Dithionite Reduction.

An aqueous ethanol solution saturated with sodium bicarbonate was prepared by mixing equal volumes of ethanol and a saturated sodium bicarbonate solution and filtering. The sodium dithionite solution was prepared by dissolving 1.01 g. of sodium dithionite in a minimum of water and then adding 20 ml. of the sodium bicarbonate solution as prepared above. The sodium dithionite solution thus prepared was added to 500 mg. of 1-deoxy-1-diazo-keto-D-gala-heptulose pentaacetate dissolved in 100 ml. of the sodium bicarbonate solution. At the end of 15 minutes, an excess of reducing agent remained as shown by the ability of the solution to bleach blue litmus paper. An equal volume of water was then added and the solution was extracted with four 20-ml. portions of
-94-

chloroform. The chloroform extracts were dried with sodium sulfate, filtered, and the solvent removed under reduced pressure to give a sirup. Solution in benzene and removal of the solvent when done twice gave a thick sirup which crystallized on scratching; yield 160 mg., m.p. 134-137.5°C. Recrystallization from benzene/carbon disulfide gave crystals having m.p. 138-140°C., mixed m.p. with authentic 3,4,5,6,7-penta-O-acetyl-D-gala-heptosone 1-hydrazone undepressed. X-ray powder diffraction patterns identical.

Synthesis of 3,4,5,6-Tetra-O-acetyl-D-glucosone 1-Hydrazone.

To a solution of 960 mg. of crude 1-deoxy-1-diazo-keto-D-fructose tetraacetate (m.p. 86.5-90.5°C., lit. m.p. 93-94°C. (63)) in 110 ml. of commerical absolute ethanol, was added four drops of ammonium sulfide solution (Mallinkrodt, Analytical Reagent). Hydrogen sulfide was bubbled through the solution for two hours at the approximate rate of 100 ml./min. (S.T.P.). Nitrogen was then bubbled through the solution for one hour. Removal of the solvent under reduced pressure at room temperature gave an orange colored, crystalline magma which was dissolved in benzene/ethanol and filtered. Carbon disulfide was added to the filtrate until crystallization began after which the solution was refrigerated
overnight. Filtration followed by washing with benzene gave 570 mg. of tiny, white crystals, m.p. 155-158°C.
Recrystallization from benzene/ethanol (1/1 by vol.)/
carbon disulfide, ethanol/pet. ether (30-60° b.p.), and
then ether/1,2-dimethoxyethane (2/1 by vol.)/pet.
ether (30-60° b.p.) gave pure material, m.p. 158.5-
160°C., \( \sqrt[\Delta q]{24.5} \) +76.1° (\( \alpha 3.9, \text{CHCl}_3 \)).

**Anal.** Calcul. for C\(_{14}\)H\(_{20}\)O\(_9\)N\(_2\): C, 46.67; H, 5.60;
N, 7.78. Found (106): C, 46.75; 46.82; H, 5.40, 5.64;
N, 7.70, 7.77.

**Infrared Spectra of Diazo Compounds and Their Hydrazone Derivatives.**

The infrared absorption peaks of some diazo compounds
and their corresponding hydrazone derivatives are given
in Table IV. Bellamy reports the following absorption
bands: C=N- , 5.92 - 6.10 \( \mu \); -N=N- , 6.14- 6.33 \( \mu \);
N=N , 4.63 - 4.72 \( \mu \) (115).

---


It is suggested that the diazo group exhibits two
absorption peaks in the infrared region: one at 4.75 \( \mu \)
due to nitrogen-to-nitrogen triple bonding and one at
6.1 \( \mu \) due to either carbon-to-nitrogen, or nitrogen-to-
nitrogen, double bonding. The hydrazones obtained on
Table IV
The Infrared Absorption Peaks of Certain Diazo Compounds and Hydrazones

<table>
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<th>Compound</th>
<th>Infrared Absorption Bands in Microns</th>
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<tr>
<td>Diazocetophenone hydrazone</td>
<td>4.85 6.2</td>
<td>KBr</td>
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<tr>
<td>Diphenyldiazo-methane hydrazone</td>
<td>4.95 6.2</td>
<td>Pet. ether</td>
</tr>
<tr>
<td>1-Deoxy-1-diazo-keto-D-galacto-heptulose penta-acetate hydrazone</td>
<td>4.75 6.05</td>
<td>Nujol mull</td>
</tr>
<tr>
<td>1-Deoxy-1-diazo-keto-D-erythro-L-manno-nonulose Heptaacetate (50)</td>
<td>4.75 6.10</td>
<td>CHCl₃</td>
</tr>
<tr>
<td>1-Deoxy-1-diazo-keto-D-erythro-L-gluco-nonulose Heptaacetate (50)</td>
<td>4.73 6.08</td>
<td>CHCl₃</td>
</tr>
</tbody>
</table>


** Infrared spectrophotometer, Model 21, Perkin-Elmer.

Compensated.
reduction of the diazo compounds will show only the 6.1 μ absorption.

Synthesis of 3,4,5,6,7-Penta-Q-acetyl-D-gala-heptosone.β-Hydroxynaphthaldehyde Aldazine.

To a solution of 100 mg. of 3,4,5,6,7-penta-Q-acetyl-D-gala-heptosone 1-hydrazone in 30 ml. of peroxide-free ether was added five drops of absolute ethanol followed by 80 mg. of β-hydroxynaphthaldehyde. The solution was allowed to stand overnight at room temperature and was then refluxed for one hour. Three drops of acetic acid were added and the solution was again allowed to stand overnight at room temperature after which it was again refluxed for one hour. Removal of the solvent under reduced pressure gave a bright yellow sirup which crystallized spontaneously. This was dissolved in five ml. of ethyl acetate, one ml. of acetic acid was added and the solution was refluxed for ten minutes. After standing overnight at room temperature, the solvent was removed under reduced pressure and a sirup was obtained. This sirup was chromatographed on a Magnesol (108)/Celite (109) (5/1 by wt.) column using one "column volume" of benzene/t-butanol (100/1 by vol.) as developer. Three zones were observed: a zone at the top of the column which was discarded, a broad middle zone (bright orange-yellow), and a lower zone (bright yellow) which
gave on elution five mg. of unidentified material, m.p. 55°C. to >250°C.

The middle zone was dissected and extracted with ethanol. Removal of the solvent under reduced pressure gave a bright yellow solid which after recrystallization from methanol gave 65 mg. of bright orange crystals, m.p. 112-118°C. Recrystallization from methanol, aqueous ethanol, and then methanol gave pure material, m.p. 116-119°C.

Anal. Calcd. for C$_{28}$H$_{30}$O$_{12}$N$_2$: C, 57.33; H, 5.16; N, 4.78. Found (106): C, 56.98; H, 5.07; N, 4.74.

This material gives a yellow ethanol solution which on being made slightly basic turns red. This red solution turns yellow on acidification or on being made more strongly basic. The original yellow solution gives no apparent color change on acidification. The yellow solutions obtained by the action of acid or excess base cannot be converted to the red solution by a change in pH.

It should be emphasized that the above experimental work was done with the intent of removing hydrazine from the sugar molecule by an exchange reaction with the excess β-hydroxynaphthaldehyde used. Successful reaction would have been indicated by the precipitation of the highly colored and highly insoluble bis(β-hydroxynaphthaldehyde) aldazine. When this failed to occur, progressively more drastic conditions were employed. For this
reason the above involved procedure in no way represents a method suggested for the synthesis of the product actually obtained.

The Product Obtained on Acetylation of 3,4,5,6,7-Penta-α-acetyl-D-gala-heptoseone 1-Hydrazone with Acetic Anhydride.

A mixture of five ml. of acetic anhydride and one gram of 3,4,5,6,7-penta-α-acetyl-D-gala-heptoseone 1-hydrazone was heated in a boiling water bath for three minutes. After cooling to room temperature, five grams of calcium carbonate was added and the slurry was taken to dryness at 80°C. under oil pump vacuum. The resulting solid was then extracted with three 15-ml. portions of chloroform. The chloroform extracts gave a solid upon removal of the solvent under reduced pressure. Recrystallization from 1,2-dimethoxyethane gave beautiful crystals; yield 430 mg., m.p. 182-197°C. A second crop of crystals was obtained from the mother liquor; yield 190 mg., m.p. 188-194°C. One more recrystallization from 1,2-dimethoxyethane gave pure material; m.p. 195-195.2°C., \( \Delta_{723}^0 -21.97 \pm 0.43^\circ \) (α 3.46, U.S.P. CHCl₃).

Anal. Calcd. for \( \text{C}_{17}\text{H}_{18}\text{O}_6\text{N}_2\text{Ac}_5 \): C, 48.10; H, 5.52; N, 5.90; Ac, 54.44. Calcd. for \( \text{C}_{17}\text{H}_{17}\text{O}_6\text{N}_2\text{Ac}_7 \): C, 48.84; H, 5.47; N, 5.42; Ac, 58.35. Found (111): C, 48.70, 48.70; H, 5.58, 5.35; N, 6.18, 6.04; Ac, 62.02, 63.15.
It will be seen that the analytical data are unsatisfactory for either the hexaacetate or the heptaacetate. Furthermore, calculations show the data do not represent a solvate of either the hexaacetate or the heptaacetate with acetic acid or any of the reasonably expected bi-molecular condensation products.

The Product Obtained on Acetylation of 3,4,5,6,7-Penta-\(\alpha\)-acetyl-D-gala-heptosone 1-Hydrazone with Acetyl Chloride.

To a solution of 400 mg. of 3,4,5,6,7-penta-\(\alpha\)-acetyl-D-gala-heptosone 1-hydrazone in 20 ml. of 1,2-dimethoxyethane was added 600 mg. of calcium carbonate followed by 0.5 ml. of acetyl chloride. After nine minutes of rapid stirring, 20 drops of ethanol were added and stirring was continued for five more minutes. The mixture was then filtered and the residue washed with five ml. of 1,2-dimethoxyethane. The solvent was removed from the combined filtrate and washings, under reduced pressure at room temperature, to yield a yellowish mass of crystals smelling strongly of ethyl acetate. This material, when recrystallized from 1,2-dimethoxyethane, gave 240 mg. of white platelets; m.p. 162-168°C. (dec.), X-ray powder diffraction pattern identical with that of the product obtained using acetic anhydride. Recrystallization from 1,2-dimethoxyethane gave crystals which gave a negative Beilstein halogen test (99); m.p. 162.5-164.5°C. (dec.),
Recrystallization from benzene/pet ether (30-60° b.p.) gave crystals of m.p. 186-189° C.

The specific rotation and X-ray powder diffraction pattern indicate this material to be identical with that obtained using acetic anhydride although there is apparently an impurity present which is difficult to remove and which does not occur in the acetic anhydride preparation.

Detection of Carbohydrates on Paper Chromatograms.

The production of blue spots results from the oxidation of benzidine to "benzidine blue" by manganese dioxide. The benzidine reagent has the following composition (95): 1 gram of benzidine, 8 grams of trichloroacetic acid, 20 ml. of anhydrous acetic acid, 12 ml. of water, and 160 ml. of absolute ethanol.

The air-dried chromatogram is first sprayed with a 1% aqueous solution of sodium metaperiodate. After 3 to 4 minutes, the chromatogram is sprayed with a freshly prepared 1% aqueous solution of potassium permanganate. In 5 minutes, sites of the largest amounts of material will show as green, yellow, or brown spots. The paper is then washed free of permanganate color with distilled water. This treatment will frequently reveal faint brown spots previously covered by the excess of permanganate
solution. After air-drying, the chromatogram is sprayed with the benzidine reagent, which instantly converts the brown spots to dark blue ones and frequently reveals spots not previously seen. The background is initially light blue, changing to white on drying and then to brown after about one week.

This method will detect 0.5% of mannitol, 2.4% of glucose, and 7.8% of sucrose, as 5x6 mm. oval spots, when these substances are placed directly on Whatman No. 1 paper. Distilled water on Whatman No. 1 paper may give a faint blue ring (not a spot).

Preparation of Penta-\(\alpha\)-acetyl-\(\alpha\)-Galactonic Nitrile.

To a solution of two grams of penta-\(\alpha\)-acetyl-\(\alpha\)-galactonamide in five ml. of dry pyridine was added 1.5 g. of tosyl chloride. After four hours at room temperature and 21 hours at about 10\(^\circ\)C., the solution was a red color. On pouring this solution into 100 ml. of water a pink solid was obtained which on recrystallization from aqueous ethanol gave 660 mg. of penta-\(\alpha\)-acetyl-\(\alpha\)-galactonic nitrile; m.p. 135-137\(^\circ\)C., lit. m.p. 138-139\(^\circ\)C. (116),


X-ray powder diffraction pattern identical with that of an authentic sample.
Attempts to apply this method to penta-\(\alpha\)-acetyl-\(\alpha\)-glucoamidamide and tetra-\(\alpha\)-acetyl-\(\alpha\)-ribonamide were unsuccessful.

**Synthesis of Penta-\(\alpha\)-acetyl-\(\alpha\)-Galactonic p-Toluidide.**

To an ether solution of penta-\(\alpha\)-acetyl-\(\alpha\)-galactonyl chloride was added an ether solution containing an excess of p-toluidine. A white precipitate (p-toluidine hydrochloride?) formed immediately. Sufficient water was added to dissolve the precipitate and the solution was made acid to litmus with hydrochloric acid. The ether layer was separated and removal of the solvent gave a solid, m.p. 39-125\(^\circ\)C. Two recrystallizations from 95 per cent ethanol gave pure material; m.p. 172-173\(^\circ\)C., \(\int_{\alpha}^{27\text{D}} +67.7^\circ\) (a 0.25, U.S.P. CHCl\textsubscript{3}).

**Anal.** Calcd. for \(C_{23}H_{29}O_1\text{N}:\ C, 55.74; H, 5.91; N, 2.83. Found (101): C, 56.06; H, 5.92; N, 2.84.

**Synthesis of Tetra-\(\alpha\)-acetyl-\(\beta\)-arabonic p-Toluidide.**

To an ether solution of tetra-\(\alpha\)-acetyl-\(\beta\)-arabonyl chloride was added an ether solution of an excess of p-toluidine. The white precipitate which formed immediately (p-toluidine hydrochloride?) was removed by filtration and crystalline material was obtained on removing the solvent under reduced pressure. The crystals were dissolved in warm benzene and petroleum ether (30-60\(^\circ\) b.p.) was added to incipient crystallization. On cooling
to room temperature, silky needles were obtained; m.p. 160.5-162.5°C. (dec.). Pure material was obtained after an additional reocrystallization from benzene/pet. ether (30-60°C b.p.); m.p. 165-165.5°C, $\sqrt{\alpha_{25}^D} = 17.93^\circ + 0.82^\circ$ ($\epsilon 1.84, \text{U.S.P. CHCl}_3$).

**Anal.** Calcd. for C$_{20}$H$_{25}$O$_8$N: C, 56.72; H, 5.96; N, 3.31. Found (101): C, 56.86; H, 5.89; N, 3.18.

**Reaction of Hydrazine with 2,3,4,6-Tetra-$\beta$-methyl-$\beta$-glucose.**

To a solution of 15 g. of 2,3,4,6-tetra-$\beta$-methyl-$\beta$-glucose in 120 ml. of chloroform was added six ml. of anhydrous hydrazine. After six hours at room temperature, the solution was shaken with anhydrous sodium sulfate, filtered, and the solvent removed at 80°C, under reduced pressure. The resultant sirup was placed in a vacuum desiccator over phosphorus pentoxide, potassium hydroxide, and paraffin chips. This gave a clear, colorless, odorless, very viscous sirup. The sirup still contained hydrazine, however, since on refluxing a benzene solution of the sirup, vapors basic to moist litmus paper were observed.

Sirups thus prepared gradually became yellow, then pasty, and then semi-solid, after which crystalline material can be obtained by dissolving the pasty material in hot ether or methanol and refrigerating. The mother
liquors from such crystallizations give sirups on removal of the solvent and these sirups then undergo the changes described for the original sirup after which a second crop of crystalline material can be obtained. The time required for these changes to occur is not reproducible and has varied from 1.5 to 6 months. Increased amounts of hydrazine, elevated temperatures for the initial reaction mixture, longer reaction times, and aeration of the sirup in refluxing benzene have failed to give crystalline material directly from the reaction mixture.

The pure material consists of white needles, has m.p. 149.5-150.5°C., and $\alpha-20^D +210.43\pm 0.67^\circ$ ($\alpha$ 2.97, 95% EtOH/U.S.P. CHCl$_3$, 1/1 by vol.) unchanged after 90 minutes.

**Anal. Found (106):** C, 50.95, 51.18; H, 8.04, 7.98; N, 6.50, 6.60; OMe, 46.96. Mol. wt. (ebullioscopic in CHCl$_3$), 385, 394 (101). Simplest empirical formula: C$_9$H$_{17}$O$_4$N or C$_5$H$_7$O$_1$N$_1$ (OCH$_3$)$_3$$_2$ (formula wt. 214). Probable mol. formula: C$_{18}$H$_{34}$O$_9$N$_2$ or C$_{12}$H$_{16}$O$_4$N$_2$ (OCH$_3$)$_6$ (mol. wt. 422).
SUMMARY

1. The known products obtained by the action of diazomethane on keto-D-fructose pentaacetate and keto-L-sorbose pentaacetate have been proven to be the epoxides, 2-acetoxymethyl-3,4,5,6-tetra-O-acetyl-1,2-anhydro-D-glucitol (mannitol\(^\text{I}\)) (I) and 2-acetoxymethyl-3,4,5,6-tetra-O-acetyl-1,2-anhydro-L-iditol (gulitol\(^\text{II}\)) (II), respectively.

2. Evidence was obtained that I and II are C\(_5\) epimers.

3. 1-Chloro-1-deoxy-2-hydroxymethyl-D-glucitol (mannitol\(^\text{II}\)) was synthesized by the action of methanolic hydrogen chloride on I and its structure was proven by periodate oxidation. Paper chromatography and analysis provided evidence for the addition of methanol and water, in addition to hydrogen chloride, to the epoxide ring. Ring opening probably occurs by an \(S_{N}2\) mechanism.

4. 2-Acetoxymethyl-3,4,5,6-tetra-O-acetyl-1-chloro-1-deoxy-D-glucitol (mannitol\(^\text{II}\)) was synthesized by the action of hydrogen chloride in acetic acid on I and its structure was proven by deacetylation.

5. 2-Acetoxymethyl-3,4,5,6-tetra-O-acetyl-1-bromo-1-deoxy-D-glucitol (mannitol\(^\text{II}\)) was synthesized by the action of hydrogen bromide in acetic acid, and by the action of magnesium bromide, on I. Its structure is
assigned on the basis of analogy with the chloro compound.

6. 2-Acetoxymethyl-3,4,5,6-tetra-O-acetyl-1,2-dibromo-1,2-dideoxy-\(\alpha\)-glucitol \(\text{[mannitol?]}\) was synthesized by the action of hydrogen bromide in acetic acid on I.

7. 1,2-Anhydro-2-hydroxymethyl-\(\alpha\)-glucitol \(\text{[mannitol?]}\) was prepared by: (a) the action of sodium hydroxide on I, and (b) by the action of either sodium hydroxide or potassium acetate/potassium iodide on 1-chloro-1-deoxy-2-hydroxymethyl-\(\alpha\)-glucitol \(\text{[mannitol?]}\).

8. Compound I was prepared by the action of sodium acetate on 2-acetoxymethyl-3,4,5,6-tetra-O-acetyl-1-bromo-1-deoxy-\(\alpha\)-glucitol \(\text{[mannitol?]}\).

9. 2-Acetoxymethyl-3,4,5,6-tetra-O-acetyl-1-chloro-1-deoxy-\(\alpha\)-iditol \(\text{[gulitol?]}\) was prepared by the action of hydrogen chloride on II. This derivative has failed to crystallize.

10. Infrared absorption peaks appear at 7.9, 11.1, and 11.6 \(\mu\) for the epoxide group in the molecules studied here.

11. A supposed second product from the reaction of diazomethane with keto-D-fructose pentaacetate has been shown to be \(\beta\)-D-fructose pentaacetate.

12. 1-Deoxy-keto-\(\alpha\)-galacto-heptulose pentaacetate has been prepared by the reduction of 1-deoxy-1-diaz-
keto-\(\text{D-gala}\)-heptulose pentaacetate (III) with aluminum amalgam.

13. 3,4,5,6,7-Penta-\(\text{D-gala}\)-heptosone 1-hydrazone (IV) has been synthesized by the reduction of III with either hydrogen sulfide or sodium dithionite.

14. Reaction of IV with \(\beta\)-hydroxynaphthaldehyde gave the crystalline mixed aldazine.

15. Acetylation of IV with either acetic anhydride or acetyl chloride gave the same crystalline product. This product is of unknown structure, the analysis not supporting a hexaacetate or a heptaacetate.

16. 3,4,5,6-Tetra-\(\text{D-gala}\)-glucosone 1-hydrazone has been synthesized by the hydrogen sulfide reduction of 1-deoxy-1-diazo-keto-\(\text{D-fructose}\) tetraacetate.

17. The diazo group shows infrared absorption bands at 4.73-4.95 \(\mu\) and 6.05-6.2 \(\mu\). After reduction to the hydrazones the 4.73-4.95 \(\mu\) band is eliminated but the 6.05-6.2 \(\mu\) band is retained.

18. The known penta-\(\text{D-gala}\)-galactonic nitrile has been prepared by the dehydration of penta-\(\text{D-gala}\)-galactonamide with tosyl chloride in a formal reversal of the Zemplen-Kiss nitrile to amide conversion. Attempts to extend this reaction were not successful.

19. Penta-\(\text{D-gala}\)-galactonic p-toluidide has been synthesized by the action of the corresponding acid chloride on p-toluidine.
20. Tetra-$\beta$-acetyl-$\beta$-arabonic p-toluidide has been synthesized by the action of the corresponding acid chloride on p-toluidine.

21. The action of hydrazine on 2,3,4,6-tetra-$\beta$-methyl-$\beta$-glucose has given a crystalline compound of unknown structure.

22. A new method for detecting carbohydrates on paper chromatograms has been developed and published (93).
APPENDIX

A facsimile of the Carcinolytic Evaluation Report
by Eli Lilly Co. on 1-Deoxy-1-Diazoketo-D-Fructose
Tetraacetate.
Research Records  
Source: Copy  
Dr. Rohrmann  

Submitter: Rohrmann  
Date: 6-7-56  
No. 25869  

Name of Compound: 1-Deoxy-1-diazo-keto-D-fructose tetraacetate  
M.p. ___  B.p. ___  
Prepared by: M. L. Wolfrom  
Date prepared: ____  
Ohio State Univ.  

Structural Formula or Description:  

Empirical Formula: C14H18N2O9  

New ___  Oldcompound. Stability ___  

Lit. Ref.  
Solubility __ H2O __ C2H5OH __ Dil. acid  
__ dil. alk. _________ other closely related products  
Comments:  

Testing Group Name of Test  Project No.  
Tissue culture Carcinolytic test  29  

Report:  
By: I. S. Johnson  
Date: 7-31-56  

This compound has been tested against three malignant cells and three normal cell controls at levels as high as 400 mcg/cc of culture media with no selective effect.
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I, Jerry Blair Miller, the son of Everette Jacob Miller and Dorothe Mae Miller (nee Blair), was born in Canton, Ohio on May 23, 1930. For the first eighteen years of my life my residence was in the wonderful home provided by my parents and my beloved grandparents, Charles Foster Blair and Anola Grace Blair (nee Dilley). During that time I received my elementary education at Baxter Grade School and my high school education at Lincoln High School from which I graduated in 1948. My undergraduate training was received at Cornell University where I was supported by my mother, a Cornell National Scholarship, a Westinghouse National Science Talent Search Scholarship, and the salary paid a pot washer. After graduating from Cornell University in June, 1952, I entered The Ohio State University Graduate School in September as a candidate for the degree of Doctor of Philosophy in Chemistry. The first nine quarters of my residence at The Ohio State University I was a teaching assistant in the Department of Chemistry, my most memorable student being Carol Irene Kendall. This same student became my wife on September 11, 1954; the mother of my son, Jerry Blair Miller, Jr., on October 28, 1955; and the mother of my daughter, Cynthia
Jana Miller on October 28, 1956. During my remaining residence at The Ohio State University it was my pleasure to hold the Procter and Gamble and Visking Co. predoctoral fellowships.