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II. THE OPTICAL ROTATORY DISPERSION OF SOME CARBOHYDRATE DERIVATIVES.

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II. THE OPTICAL ROTATORY DISPERSION OF SOME CARBOHYDRATE DERIVATIVES

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

Neal Edward Franks, B. A.

The Ohio State University
1963

Approved by

Adviser
Department of Chemistry
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PART I.

THE SYNTHESIS OF 2-DEOXY-\textit{d}-arabino-HEXONIC ACID 6-PHOSPHATE
INTRODUCTION

The major pathway of glucose metabolism in animals involves phosphorylation of \( \text{D}-\text{glucose} \) to form \( \text{D}-\text{glucose} \text{ 6-phosphate} \), transformation to \( \text{D}-\text{fructose} \text{ 6-phosphate} \), an additional phosphorylation to \( \text{D}-\text{fructose} \text{ 1,6-diphosphate} \), and cleavage to two three-carbon phosphate compounds. Woodward and Cramer (1) have shown that the anaerobic metabolism of \( \text{D}-\text{glucose} \) by Walker 256 rat carcinoma was inhibited 60 per cent by an equimolar quantity of 2-deoxy-\( \text{D}-\text{arabino-hexose} \). The same investigators (2) found that the anaerobic fermentation of glucose by living yeast was strongly inhibited by 2-deoxy-\( \text{D}-\text{arabino-hexose} \). The overall effect followed the laws of competitive inhibition of an enzyme.

A minor pathway of \( \text{D}-\text{glucose} \) metabolism is known as the hexose monophosphate oxidation shunt or the pentose phosphate pathway. In this pathway \( \text{D}-\text{glucose} \text{ 6-phosphate} \) is oxidized through \( \text{D}-\text{gluconolactone} \text{ 6-phosphate} \) to \( \text{D}-\text{gluconic acid} \text{ 6-phosphate} \). This product can also
arise by enzymic phosphorylation of \( D \)-gluconic acid. At this point there occurs an oxidative decarboxylation so that the product of this series of transformations is \( D \)-erythro-pentulose 5-phosphate. The \( D \)-erythro-pentulose 5-phosphate so arising can isomerize with enzymic help to \( D \)-ribose 5-phosphate and be incorporated into nucleic acids.

Evidence has been presented by Beck (3) that a greater proportion


of \( D \)-glucose metabolism occurs by means of the hexose monophosphate oxidation shunt in leucocytes of leukemia than in normal cells. Beck attributes this fact to a deficiency in the leukemic cells of hexokinase.

Calcium 2-deoxy-\( D \)-arabino-hexonate submitted for screening as a possible cancer chemotherapeutic agent to the National Institutes of Health had demonstrated some slight activity. It was desired to prepare a similar compound which could fit in at a point further along in the hexose monophosphate oxidation pathway.
It was desired in this problem to find a means of synthesis of 2-deoxy-D-arabino-hexonic acid 6-phosphate.
HISTORICAL

Carbohydrate phosphates

There is a great interest in carbohydrate phosphates and a large amount of published work in this area. Because of this, this discussion will necessarily be limited to some selected synthetic examples where the phosphate group has been introduced at the primary hydroxyl of the carbohydrate moiety. In addition, the means of introduction will be by chemical rather than enzymic means. Foster and Overend (4)


have published a review on carbohydrate phosphates including discussions on detection and estimation, isolation and enzymic preparation, and chemical synthesis of carbohydrate phosphates.

An article by Cramer (5) includes a general review of methods of


preparation of esters, amides, and anhydrides of phosphoric acid. Khorana (6) provides an extended review of the chemistry of a large number of carbohydrate phosphates.

Phosphorus oxychloride as a phosphorylating agent

Although earlier preparations of carbohydrate phosphates had been accomplished, Fischer (7) introduced the use of phosphorus oxychloride

(7) E. Fischer, Ber., 47, 3193 (1914).

at low temperatures by phosphorylating methyl α-D-glucopyranoside and theophyllin glucoside in this manner. Unfortunately the phosphate isolated from the methyl glucoside did not quite give the correct analytical values for the corresponding barium salt.

Raymond and Levene (8) succeeded in preparing D-fructose 1-phosphate


through phosphorylation of 2,3:4,5-di-O-isopropylidene-D-fructose using low temperatures (-40 to -50°C) and phosphorus oxychloride. At the same time Raymond and Levene cited evidence that phosphorylation of D-fructose, containing no blocking groups, with phosphorus oxychloride can be rather selective since they isolated a product that was supposedly D-fructose 1-phosphate.

Using 1,2-O-isopropylidene-α-D-glucofuranose as starting material, Levene and Raymond (9) were able to synthesize a phosphate ester

closely resembling the D-glucose 6-phosphate isolated from enzymic preparation. In a later paper (10) this preparation was repeated and


D-gluconic acid 6-phosphate was synthesized by hypiodite oxidation.

In attempting another method of synthesis of D-glucose 6-phosphate, Levene and Raymond (11) tried the use of 1,2,3,4-tetra-O-acetyl-β-


D-glucopyranose. The yield of the monophosphate ester was rather low and there was a considerable amount of barium phosphate found along with the product. Levene and Raymond attributed this to possible isomerization of the D-glucose tetraacetate used as starting material.

D-Galactose 6-phosphate was obtained by Levene and Raymond (12)


by phosphorylation of 1,2;3,4-di-O-isopropylidene-α-D-galactose at -30°C with phosphorus oxychloride. The product, after hydrolysis of the isopropylidene groups, was isolated in good yield and corresponded to a barium salt of a hexose monophosphate.

Levene and Stillor (13) were able to synthesize D-ribose 5-phosphate
by the phosphorylation of methyl 2,3-O-isopropylidene-α-D-ribofuranose with phosphorus oxychloride at -40°. These workers were able to crystallize the resulting barium salt which had the same properties as the barium salt of the phosphate ester isolated from inosinic acid.

Levene and Christman (14) prepared yet another pentose 5-phosphate

when they treated 1,2-O-isopropylidene-β-D-arabinofuranose with phosphorus oxychloride at a temperature of -40°. Although attempts to isolate a crystalline barium salt were unsuccessful, a crystalline dibrucine salt was isolated.

In each of the cases where phosphorus oxychloride was used as the phosphorylating agent the resulting phosphorodichloridate had to be hydrolyzed to the corresponding phosphate ester. In order to achieve milder conditions the following work arose.

Phosphorylation with diaryl phosphorochloridate

Bredereck (15) and Brigl and Müller (16) independently published


(16) P. Brigl and H. Müller, Ber., 72, 2121 (1939).
works synthesizing carbohydrate phosphates using diphenyl phosphorochloridate as the phosphorylating agent. Bredereck chose to cleave the phenyl residues from the resulting ester with alkali. Brigl and Müller chose conditions using acetic acid or platinum dioxide (Adams' catalyst) and hydrogen. In this manner Brigl and Müller phosphorylated 2,3-O-isopropylidene-D-fructofuranose with two moles of diphenyl phosphorochloridate to yield a crystalline tetraphenyl diphosphate ester. Hydrogenation with Adams' catalyst evidently yielded the D-fructose 1,6-diphosphate; however, the 6-phosphate hydrolyzed so readily that D-fructose 1-phosphate and inorganic phosphate were the products isolated.

The diphenyl phosphorochloridate used by Brigl and Müller was readily prepared and had a high degree of stability at room temperature. At higher temperatures it did disproportionate to phenyl phosphorodichloridate and triphenyl phosphate.

Ballou and MacDonald (17) discuss the general use of diphenyl phosphorochloridate with several specific synthetic applications being outlined by them.

Zervas (18) had introduced the use of silver dibenzyl phosphate

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and demonstrated that the benzyl groups were readily removed by hydrogenation in the presence of palladium. Atherton, Openshaw, and Todd (19) began using dibenzyl phosphorochloridate as a phosphorylating agent and in much of their later work they continued using it. Dibenzyl phosphorochloridate has the advantage that the benzyl residues are removed with a milder catalyst. Its disadvantages of difficult preparation and instability seem to outweigh the advantages so that the major portion of work has been done with diphenyl phosphorochloridate.

There are other aryl phosphorochloridates that have been used such as di(p-substituted benzyl) phosphorochloridates, mono-p-nitrophenyl phosphorodichloridate, and dianilino phosphorochloridate.

Until the time that diphenyl phosphorochloridate was introduced, most of the carbohydrates used for phosphorylation had been blocked with isopropylidene groups. Helfferich and Klein (20) had earlier demonstrated the utility of triphenylmethyl chloride as an easily removable blocking group for primary alcohols. Levene and Raymond (11) had been unable to synthesize D-glucose 6-phosphate using 1,2,3,4-tetra-O-acetyl-β-D-glucose described by Helfferich and Klein.
Phosphorylation of 1,2,3,4-tetra-O-acetyl-β-D-glucose with diphenyl phosphorochloridate was finally accomplished by Lardy and Fischer (21). These workers isolated a crystalline compound which they then treated with Adams' catalyst and hydrogen to yield the tetra-acetate of D-glucose 6-phosphate.

Using 1,2:3,4-di-O-isopropylidene-D-tagatose and phosphorylating it with diphenyl phosphorochloridate, Totton and Lardy (22) were able to synthesize D-tagatose 6-phosphate. Reductive cleavage of the phenyl groups with Adams' catalyst yielded a product (1,2:3,4-di-O-isopropylidene-D-tagatose 6-phosphate) that, when dissolved in water, hydrolyzed the isopropylidene groups without use of additional acid.

Mann and Lardy (23) were able to synthesize L-sorbose 1-phosphate by phosphorylating 2,3:4,6-di-O-isopropylidene-L-sorbose or dibenzylidene-L-sorbose with diphenyl phosphorochloridate. Reductive cleavage and hydrolysis of the blocking groups yielded the desired ester. Mann and Lardy also synthesized L-sorbose 6-phosphate through a rather
ingenious route. Phosphorylation of 2,3-0-isopropylidene-\(\text{L}\)-sorbose with two moles of diphenyl phosphorochloridate yielded the corresponding tetraphenyl 1,6-diphosphate ester. After reductive cleavage of the phenyl groups these workers were able to selectively hydrolyze the phosphate ester at carbon one and isolate \(\text{L}\)-sorbose 6-phosphate.

Foster, Overend, and Stacey (24) were able to prepare 2-deoxy-\(\text{D}\)-

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\(\text{D}\)-lyxo-hexose 6-phosphate using methyl 3,4-0-isopropylidene-2-deoxy-\(\text{D}\)-\(\text{L}\)-lyxo-hexopyranoside. These workers accomplished the synthesis using phosphorus oxychloride in one synthetic scheme and diphenyl phosphoro-chloridate in another. Hydrolysis of the isopropylidene and glycosidic methyl groups was accomplished in 0.01 N sulfuric acid at 100\(^\circ\) for thirty minutes. The final product was isolated as the amorphous free phosphate ester.

In a successful synthesis of 2,3,4,5-tetra-0-acetyl-aldehydo-\(\text{D}\)-galactose monomethanolate, Barclay, Foster, and Overend (25) used as

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starting material \(\text{D}\)-galactose diethyl dithioacetald. These workers isolated a crystalline 2,3,4,5-tetra-0-acetyl-6-0-trityl-\(\text{D}\)-galactose diethyl dithioacetald from which they were able to cleave the trityl group with hydrogen bromide in glacial acetic acid. Phosphorylation
with diphenyl phosphorochloridate and treatment of this compound in
the normal manner yielded 2,3,4,5-tetra-O-acetyl-aldehyde-D-galactose
6-(diphenyl phosphate). In a similar manner these workers synthesized
a tetrabenzoate which also yielded a crystalline 2,3,4,5-tetra-O-
benzoyl-D-galactose diethyl dithioacetal. Phosphorylation of this
compound required higher temperatures to achieve a product, and even
then the yield was only 56%. 2-Deoxy-D-lyxo-hexose and 2-deoxy-D-
arabinohexose were also investigated. A crystalline 3,4,5-tri-O-
acetyl-6-O-trityl diethyl dithioacetal was synthesized in both cases,
however, cleavage with hydrogen bromide in acetic acid yielded sirupy
products which were carried through the same scheme as was D-galactose.
The final products were sirups which could not be characterized as
crystalline derivatives.

Using a somewhat similar scheme, Ballou, Fischer, and MacDonald
(26) were able to synthesize D-erythrose 4-phosphate. They converted

\[
\text{(26) C. E. Ballou, H. O. L. Fischer, and D. L. MacDonald,}
\]

\[
\text{J. Am. Chem. Soc., 77, 5967 (1955).}
\]

4-O-trityl-D-erythrose diethyl dithioacetal to 4-O-trityl-D-erythrose
dimethyl acetal, acetylated, and catalytically removed the trityl
residue with palladium-on-carbon and hydrogen. Phosphorylation of
2,3-di-O-acetyl-D-erythrose dimethyl acetal with diphenyl phosphoro-
chloridate, catalytic removal of the phenyl groups, and deacetylation
yielded D-erythrose 4-phosphate dimethyl acetal.

Maley and Lardy (27) used diphenyl phosphorochloridate as a
selective phosphorylating agent when they successfully synthesized 2-amino-2-deoxy-D-glucose 6-phosphate and 2-acetamido-2-deoxy-D-glucose 6-phosphate. N-Anisylidene-2-amino-2-deoxy-D-glucose was phosphorylated at low temperature in pyridine and the resulting product was acetylated before isolation. Removal of the anisylidene group, reductive cleavage of the phenyl groups, and hydrolysis of the O-acetyl linkages completed the scheme. The product was isolated at pH 4 using barium hydroxide to prevent decomposition.

A similar selective phosphorylation using diphenyl phosphorochloridate was reported by Tenner and Khorana (28). Phosphorylation

of benzyl β-D-ribofuranoside, followed by mild alkaline treatment yielded benzyl β-D-ribofuranoside 6-(diphenyl phosphate). Their synthetic scheme continued on through the 2,3-carbonate derivative and finally to D-ribose 1,5-diphosphate characterized as the tetrakis(cyclohexylammonium) salt. The use of mild alkali to selectively remove phosphate esters on secondary hydroxyl groups is interesting to note.

Ukita and Nagasawa (29) phosphorylated methyl 2-deoxy-α- and

β-D-ribofuranoside with diphenyl phosphorochloridate and isolated a syrupy product identified as a mixture of the 5-(diphenyl phosphate) and the 3,5-bis(diphenyl phosphate). Reductive cleavage of the phenyl groups yielded the corresponding esters which were chromatographed on a cellulose column to separate the monoester from the diester. The monoester was crystallized as its dicyclohexylammonium salt and the diester isolated as its crystalline tricyclohexylammonium salt.

The synthesis of 3-deoxy-D-ribo-hexose 6-phosphate was accomplished by Dahlgard and Kaufmann (30) through the same scheme outlined by Lardy and Fischer (21).


3-Deoxy-D-ribo-hexose 6-phosphate was then oxidized by hypoiodite to yield 3-deoxy-D-ribo-hexonic acid 6-phosphate. The latter product was isolable as a crystalline tribrucine salt.

Remizov (31) attempted to prepare 2-deoxy-D-arabino-hexose 6-phosphate by tritylation and subsequent acetylation of 2-deoxy-D-arabino-hexose using mild conditions. Remizov was unable to isolate the corresponding pure acetylated trityl ether.

Using methyl 2-deoxy-α-D-arabino-hexopyranoside, tritylating, and acetylating, Remizov recovered a non-homogeneous product. After de-tritylating and phosphorylating, a low yield of methyl 3,4-di-O-acetyl-2-deoxy-α-D-arabino-hexopyranoside 6-phosphate was isolated as a
crystalline dicyclohexylammonium salt. Better results were obtained when methyl 2-deoxy-α-D-arabino-hexopyranoside was phosphorylated with diphenyl phosphorochloridate at -25° in pyridine. A product was obtained which was identical with that obtained using the preceding method. After hydrolysis of the glycosidic methyl group in 0.5 N hydrogen bromide, a product was obtained which was unstable above pH 9. Analytical values indicated that neutralization to pH 7.5 with barium hydroxide still failed to neutralize about 15 mole per cent of the acid.

Szabo' and Szabo' (32) were able to synthesize methyl α-D-glucopyranoside 6-(dicyclohexylammonium phosphate) by phosphorylation of methyl 2,3,4-tri-O-acetyl-α-D-glucopyranoside with diphenyl phosphorochloridate. After reductive cleavage of the phenyl groups and deacetylation with ammonia, the above product was isolated.

Several miscellaneous phosphorylating procedures

Another attempt to synthesize 2-deoxy-D-arabino-hexose 6-phosphate was reported by Brooks and Overend (33). Treating methyl 2,6-dideoxy-

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products yielded methyl 3,6-anhydro-2-deoxy-α-D-arabino-hexopyranoside
and crystalline dibenzyl phosphoric acid. The same results were ob­
tained when silver diphenyl phosphate was substituted for silver
dibenzyl phosphate.

The opening of epoxide rings with some form of phosphate has proved
to be a means of obtaining primary phosphate esters. Lampson and
Lardy (34) refluxed potassium monohydrogen phosphate with 1,2-0-

(34) G. P. Lampson and H. A. Lardy, J. Biol. Chem., 181, 693
(1949).

isopropylidene-5,6-anhydro-D-glucofuranose in water for 24 hours.
After hydrolysis of the isopropylidene groups, D-glucose 6-phosphate
was isolated. Although yields are not as good using this technique,
it does allow introduction of radioactive phosphates without requiring
complicated synthetic schemes.

Harvey, Michalski, and Todd (35) used dibenzyl hydrogen phosphate

Soc., 2271 (1951).

and 1,2-0-isopropylidene-5,6-anhydro-D-glucofuranose in carbon tetra-
chloride to open the 5,6-anhydro ring. Chromatography on neutral
alumina was necessary to isolate 1,2-0-isopropylidene-α-D-glucofuranose
6-(dibenzyl phosphate).
DISCUSSION OF RESULTS

Tritylation and acetylation of 2-deoxy-D-arabino-hexose

Since the work of Remizov (31) had not yet appeared and since no one else had described an attempt at tritylation and acylation of 2-deoxy-D-arabino-hexose, it was felt that this was a logical synthetic pathway.

In a number of trials 2-deoxy-D-arabino-hexose was treated with equimolar amounts of triphenylmethyl chloride in pyridine or N,N-dimethylformamide-pyridine. In several trials the mixture was heated to bring about solution, in others the mixture was shaken occasionally at room temperature to achieve solution of the reactants. Attempts to isolate crystalline 2-deoxy-6-O-trityl-D-arabino-hexose failed so the acylated derivatives were attempted.

To the solution of 2-deoxy-6-O-trityl-D-arabino-hexose in pyridine or N,N-dimethylformamide-pyridine was added acetic anhydride or benzoyl chloride at room temperature. After either heating on a steam bath for several hours or allowing to stand at room temperature for a day the solution was poured into ice water and the product isolated.

The only identifiable crystalline product obtained after isolation (in one instance) was triphenyl carbinol. The products obtained when acetic anhydride was used were sirups which refused to crystallize. Using benzoyl chloride, a solid with a wide melting point range was isolated, but attempts to crystallize this material were of no avail and the melting point could not be improved.

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Remizov (31) indicates that he thinks this behavior is due to the mixture of α- and β-anomers. This may very well be true, but without some means of isolating and identifying the product it is difficult to draw any sound conclusions.

**Tritylation and benzoylation of 2-deoxy-D-arabino-hexose diethyl dithioacetal**

In their unsuccessful attempt of synthesizing 2-deoxy-D-arabino-hexose 6-phosphate, Barclay, Foster, and Overend (25) had prepared 3,4,5-tri-O-acetyl-2-deoxy-6-O-trityl-D-arabino-hexose diethyl dithioacetal. Their attempt to cleave the 6-O-trityl residue was successful, but their product was sirupy.

Since benzoate esters are sometimes better crystallizing products than are the corresponding acetate esters, 2-deoxy-D-arabino-hexose diethyl dithioacetal in pyridine was treated with an equimolar amount of trityl chloride; after a day at room temperature it was reacted with a 10% excess of benzoyl chloride. The product obtained was highly crystalline and in the first preparation showed signs of dimorphism. Analysis indicated that the product was 3,4,5-tri-O-benzyol-2-deoxy-6-O-trityl-D-arabino-hexose diethyl dithioacetal.

One of the methods of cleavage of trityl residues is the method used by Helferich and Klein (20) wherein the trityl ether is dissolved in glacial acetic acid and hydrogen bromide in acetic acid is added at 0°. If a small enough volume of acetic acid is used the resulting trityl bromide will precipitate and can be removed by filtration.

Solution of 3,4,5-tri-O-benzyol-2-deoxy-6-O-trityl-D-arabino-
hexose diethyl dithioacetal in glacial acetic acid was accomplished at elevated temperature. On cooling to 0° the compound crystallized from the solution indicating a solubility at 0° of 0.2 g. in 10 ml. of glacial acetic acid. This is not a high enough solubility with which to carry out the cleavage in this manner.

In order to increase the solubility of the compound a mixture of N,N-dimethylformamide-glacial acetic acid (3:2 v/v) was used. After cooling to 0°, 10% hydrogen bromide in acetic acid was added and allowed to stand for 3-4 minutes. The normal course of this reaction finds the solution taking on a deep yellow color due to formation of the triphenylmethyl carbonium ion. In this instance no color appeared and after about five minutes, starting material began to crystallize out of solution. On processing the reaction mixture, 95% of starting material was recovered.

Failure to form trityl bromide here could be explained in several ways. It is possible that the N,N-dimethylformamide is complexing with the hydrogen bromide to form a weak hydrobromide. It is also possible that the additional bulk of the benzoate group at carbon five prevents attack by hydrogen bromide on the trityl ether linkage. It would appear that the first possibility is the more likely of the two.

Another method of trityl ether cleavage attempted was refluxing 3,4,5-tri-O-benzoyl-2-deoxy-6-O-trityl-D-arabino-hexose diethyl dithioacetal in 80% acetic acid for four hours. The odor of ethyl mercaptan could be noted during this period. A small amount of impure starting material was obtained and after a month a few crystals of triphenylcarbinol were obtained. Other than this the isolated product remained a sirup.
Reductive cleavage of the trityl ether.

Another possible means of removing trityl ether groups consists in the use of a palladium-on-carbon catalyst in the presence of hydrogen. Of course, the presence of ethylthio groups will interfere since sulfur poisons most noble metal catalysts.

In order to remove this source of catalyst poison, 3,4,5-tri-O-benzoyl-2-deoxy-6-O-trityl-aldehyde-D-arabinohexose was synthesized. The product was quite crystalline and gave a correct analysis.

The selection of a proper solvent for reductive detritylation presented an additional problem. The normal solvents used are ethanol or methanol; however, an aldehyde-derivative will form hemiacetals in these solvents creating additional problems. The solvent used in the first trial was tetrahydrofuran. Using 10% palladium-on-carbon with a hydrogen pressure of greater than two atmospheres, the hydrogenation was run for sixteen hours. Solution of the resulting sirup in toluene yielded a small amount of crystalline material (20 mg.) which decomposed before its identity was ascertained. The remaining sirup resisted attempts to crystallize it. Using dioxane as a solvent nothing but a sirup was isolated with the petroleum ether-soluble fraction failing to yield even triphenylmethane.

Using absolute ethanol as a solvent in the reductive detritylation, in one instance about 40% of the theoretical amount of triphenylmethane was isolated. The residual sirup failed to yield any crystalline material, so reductive detritylation was discounted as a possibility for providing a usable intermediate.
Selective phosphorylation of 2-deoxy-\(\beta\)-arabino-hexose diethyl dithioacetal

Zinner and co-workers (36) had accomplished selective acylation


of the primary hydroxyl of carbohydrate dithioacetals in pyridine at low temperatures by the slow addition of acylating agent.

Using this technique with diphenyl phosphorochloridate and 2-deoxy-\(\beta\)-arabino-hexose diethyl dithioacetal, an oil was obtained on processing of the reaction mixture. Attempts to crystallize this product failed, so efforts were changed to an attempt to isolate a crystalline acylated product.

Acylation after selective phosphorylation with either acetic anhydride or benzoyl chloride did not yield a crystalline product. Thin-layer chromatography was used to inspect the product obtained when acetic anhydride was used as the acylating agent. At least four compounds were found to be present, indicating that the reaction was not as selective as was hoped.

Selective phosphorylation of methyl 2-deoxy-\(\beta\)-arabino-hexopyranoside

In an interesting work, Inglis, Schwarz, and MacLaren (37)

investigated the methoxymercuration of tri-O-acetyl-D-glucal. The reaction is quite simple and is performed merely by reacting tri-O-acetyl-D-glucal in methanol with mercuric acetate for 70-90 minutes. Addition of sodium chloride in water yields 45% of the theoretical amount of methyl 2-chloromercuri-2-deoxy-β-D-arabinohexopyranoside triacetate.

Reduction of this material with sodium or potassium borohydride and acetylation of the anhydrous reaction mixture yields methyl 3,4,6-tri-O-acetyl-2-deoxy-β-D-arabinohexopyranoside in high yields. Catalytic deacetylation with sodium methoxide in methanol gives methyl 2-deoxy-β-D-arabinohexopyranoside. Since Ukita and Nagasawa (29) had been somewhat successful in phosphorylation of the methyl 2-deoxy-D-erythro-pentofuranosides, it appeared that this technique might be suitable with methyl 2-deoxy-β-D-arabinohexopyranoside. At about this time the report of Remizov's (31) successful synthesis of methyl 2-deoxy-α-D-arabinohexopyranoside 6-phosphate came to light. Selective or near selective phosphorylation was accomplished by Remizov by dissolving methyl 2-deoxy-α-D-arabinohexopyranoside in pyridine, cooling to -25°, and adding an equimolar amount of diphenyl phosphorochloridate in benzene over a period of 80-90 minutes. Methyl 2-deoxy-α-D-arabinohexopyranoside 6-(diphenyl phosphate) was isolated as a sirup which was then hydrogenated to cleave the phenyl groups.

Using this general technique, methyl 2-deoxy-β-D-arabinohexopyranoside was dissolved in pyridine, an equal volume of benzene added, and the mixture cooled to -15° using an ice-salt bath. An equimolar amount of diphenyl phosphorochloridate was added, with stirring, at
a rate of 1.2 ml. per hour. Processing of the product yielded a sirup (80-85% yield) which showed two major zones when examined by thin-layer chromatography.

It was feared that diphosphorylation had occurred, so the phosphorylation was repeated and the procedure changed to include two washings of the phosphorylated product in chloroform with 10% aqueous sodium hydroxide. This step was added because Tenner and Khorana (28) were able to free benzyl β-D-ribofuranoside 5-(diphenyl phosphate) of any secondary phosphate ester in this manner.

Isolation of a cyclic phosphate ester

Thin-layer chromatography of the reaction mixture after treatment with base showed three spots with $R_A$ 0.25, 0.5, and 0.95. Surprisingly, treatment of an ethereal solution of the sirup with petroleum ether yielded a small amount of crystalline material which proved to be homogeneous on thin-layer chromatography ($R_A$ 0.49). Analysis of the material clearly indicated that it was not methyl 2-deoxy-β-D-arabino-hexopyranoside 6-(diphenyl phosphate) or the corresponding monophenyl phosphate. Analytical values did indicate, however, that it could be methyl 2-deoxy-β-D-arabino-hexopyranoside 4,6-(monophenyl phosphate). In order to demonstrate that this was the correct assumption, methyl 2-deoxy-β-D-arabino-hexopyranoside was reacted with phenyl phosphoro-dichloridate using conditions similar to those used in the selective phosphorylation. The product isolated, in low yield, was identical with that obtained above.

The assignment of the 4,6-cyclic phosphate ring finds similarity
in work reported by Baddiley, Buchanan, and Szabó (38). These workers treated methyl α-D-glucopyranoside and benzyl β-D-glucopyranoside with phenyl phosphorodichloridate and in both instances isolated a product described as the corresponding 4,6-(monophenyl phosphate). Assignment of the 4,6 cyclic ring is not unreasonable if these compounds are considered as phosphorus analogs of the corresponding benzylidene derivatives.

The formation of methyl 2-deoxy-β-D-arabino-hexopyranoside-4,6-(monophenyl phosphate) can be explained by assuming that the diphenyl phosphorochloridate had disproportionated on standing (at room temperature) for an extended period of time. However, this does not explain why an attempt to recover crystalline products from a previous selective phosphorylation failed.

In an attempt to find a better explanation, freshly prepared diphenyl phosphorochloridate was used in repeating the selective phosphorylation. Any contact with base stronger than sodium bicarbonate was eliminated during the isolation procedure. Thin-layer chromatography of this sirupy product showed two discernible spots with $R_A$ 0.25 and 0.7-0.8. Visual estimation indicated these compounds were present in the ratio of 9:1. A barely discernible spot was present at $R_A$ 0.49 indicating that fractional distillation had not removed quite all of the phenyl phosphorodichloridate. The spot having $R_A$ 0.25 was methyl

2-deoxy-β-D-arabinopyranoside 6-(diphenyl phosphate) since it was present in the largest amount and had the slowest $R_A$. The other spot, $R_A 0.7-0.8$, was a result of diphosphorylation and was probably methyl 2-deoxy-β-D-arabinopyranoside 4,6-bis(diphenyl phosphate).

An amount of the above mixture was dissolved in chloroform and shaken with 10% aqueous sodium hydroxide for ten minutes. After washing the chloroform solution until neutral and removing the solvent, about 25% by weight of material was recovered. Thin-layer chromatography of the recovered material demonstrated three spots with $R_A 0.25$, 0.49, and 0.9-0.95. The spot at $R_A 0.49$ was identical with the $R_A$ of an authentic sample of methyl 2-deoxy-β-D-arabinopyranoside 4,6-(monophenyl phosphate). Intensities of the spots at $R_A 0.25$ and 0.49 were almost equal. The spot at $R_A 0.9-0.95$ was much less intense.

This evidence indicates that the secondary phosphate ester was completely hydrolyzed by treatment with base. The spot at $R_A 0.9-0.95$ was probably sodium diphenyl phosphate from this hydrolysis. The fact that methyl 2-deoxy-β-D-arabinopyranoside 4,6-(monophenyl phosphate) was produced in this reaction demonstrates that there is another route to formation of the cyclic ester. Moffatt and Khorana (39) investigated


a similar base cyclization. These workers treated 1,2-α-isopropylidene-α-D-xylofuranoside 5-(diphenyl phosphate) with sodium hydroxide and isolated 1,2-α-isopropylidene-α-D-xylofuranoside 3,5-(monophenyl
phosphate). Further hydrolysis cleaved the phenyl ester to 1,2-D-isopropylidene-α-D-xylofuranoside 3,5-phosphate.

On the basis of this information it appears that a similar situation occurs with methyl 2-deoxy-β-D-arabino-hexopyranoside 6-(diphenyl phosphate) and methyl 2-deoxy-β-D-arabino-hexopyranoside-4,6-bis(diphenyl phosphate). The reaction sequence from methyl 2-deoxy-β-D-arabino-hexopyranoside is outlined in Figure 1. Since only 25% of the original material was recovered it is entirely possible that the phenyl group was hydrolyzed from methyl 2-deoxy-β-D-arabino-hexopyranoside 4,6-(monophenyl phosphate) to form a water-soluble product. The aqueous solution was not investigated for this.

Catalytic cleavage of methyl 2-deoxy-β-D-arabino-hexopyranoside 4,6-(monophenyl phosphate) in absolute methanol with Adams’ catalyst and hydrogen was successful. The resulting product was isolated as crystalline methyl 2-deoxy-β-D-arabino-hexopyranoside 4,6-(cyclohexyl-ammonium phosphate).

Reductive cleavage of phenyl groups from methyl 2-deoxy-β-D-arabino-hexopyranoside 6-(diphenyl phosphate)

An amount of the sirupy selective phosphorylation mixture was dissolved in absolute methanol, boiled for 5-10 minutes with acid-washed charcoal, and filtered. Adams’ catalyst was suspended in the methanolic solution and shaken in the presence of hydrogen. The rate of hydrogen uptake was dependent upon the activity of the catalyst and whether or not any catalyst poisons were present in the methanolic
Fig. 1.—Synthetic sequences leading to 2-deoxy-D-arabino-
hexonic acid 6-phosphate and to methyl 2-deoxy-β-D-arabino-hexo-
pyranoside 4,6-(monophenyl phosphate).
Fig. 1
solution. The mixture was allowed to shake on the Parr apparatus for a further 12-16 hours after this rapid hydrogen uptake had ceased. On occasion the catalyst was removed and fresh catalyst was added with additional reaction time allowed. After filtration to remove the catalyst, cyclohexylamine (preferably freshly distilled) was added to the methanolic solution to pH 8-9. Addition of one to two volumes of ethyl acetate and standing in the refrigerator brought out a crystalline product which was only slightly soluble in ethanol. After several recrystallizations the product yielded the proper analytical values for methyl 2-deoxy-β-D-arabino-hexopyranoside 6-(dicyclohexylammonium phosphate). Remizov (31) indicated that methyl 2-deoxy-α-D-arabino-hexopyranoside 6-(dicyclohexylammonium phosphate) showed $[\alpha]_D^{42.8\circ}$. Using this fact and Hudson's isorotation rules, methyl 2-deoxy-β-D-arabino-hexopyranoside 6-(dicyclohexylammonium phosphate) should have had $[\alpha]_D^{-29\circ}$. The observed value of $[\alpha]_D^{-30\circ}$ agrees very well with this calculated value.

For methyl 2-deoxy-D-arabino-hexopyranosides

$$2\alpha = 326\circ \text{ (mol. rot.)}$$

$$[\alpha]_{D} - [\alpha]_{B} = 2\alpha = 326\circ$$

$$[\alpha]_{B} = [\alpha]_{D} - 326\circ$$

$[\alpha]_{D} \text{ (for the 6-phosphate salt)} = \frac{456 \times 42.8}{100}$

$$[\alpha]_{B} = \frac{456 \times 42.8}{100} - 326\circ = 131\circ$$

$$[\alpha]_{B} = \frac{100 \times (-131\circ)}{456} = -29\circ$$
Hydrolysis of methyl \(2\text{-deoxy-}\beta\text{-D-arabino-hexopyranoside 6-phosphate}\)

In order to remove the glycosidic methyl group from methyl \(2\text{-deoxy-}\alpha\text{-D-arabino-hexopyranoside 6-phosphate}\) Remizov (31) had heated the starting compound in a slightly more than equivalent amount of 0.5 N hydrogen bromide on a boiling water bath for 30-40 minutes. However, after isolation of the 6-phosphate as its barium salt, paper chromatography (2-propanol-15% trichloroacetic acid, 8:2) of the isolated product showed some inorganic phosphate. Remizov credited this to hydrolysis during chromatography, but offered no substantiation for it.

In attempting to prevent any possible inorganic phosphate formation, a solution of methyl \(2\text{-deoxy-}\beta\text{-D-arabino-hexopyranoside 6-(dicyclohexylammonium phosphate)}\) was treated with the acid form of a cationic exchange resin to remove the cyclohexylamine. After removal of the ion exchange resin the solution (pH < 3) was heated at 65-70° with samples being removed at half-hour intervals for 3.5 hours. Descending paper chromatography (2-propanol-15% trichloroacetic acid, 8:2) of the hydrolyzate samples indicated that methyl \(2\text{-deoxy-}\beta\text{-D-arabino-hexopyranoside 6-phosphate}\) \(\left(\text{RA} 0.63\right)\) was changing to \(2\text{-deoxy-}\beta\text{-D-arabino-hexose 6-phosphate}\) \(\left(\text{RA} 0.49\right)\). The 3.5 hour period at 65-70° was not long enough to bring about complete hydrolysis, but after 8.5 hours there was only a trace of methyl \(2\text{-deoxy-}\beta\text{-D-arabino-hexopyranoside 6-phosphate}\) remaining. No inorganic phosphate was visible on the papergrams indicating that hydrolysis in Remizov's work (31) could have occurred in his attempt to isolate barium \(2\text{-deoxy-}\beta\text{-D-arabino-hexose}\)
6-phosphate. Since 2-deoxy-\(\text{D-arabino}\)-hexose 6-phosphate served only as an intermediate in this synthesis, there was no attempt made to isolate it.

**Oxidation of 2-deoxy-\(\text{D-arabino}\)-hexose 6-phosphate**

Dahlgard and Kauffman (30) had used a modification of the hypoiodite oxidation used by Levene and Raymond (10) in their synthesis of 3-deoxy-\(\text{D-ribo}\)-hexonic acid 6-phosphate. Dahlgard and Kauffman were able to take advantage of the difference of solubilities of barium iodide and the acid salt in a water-ethanol mixture to effect separation of these compounds.

The solution of 2-deoxy-\(\text{D-arabino}\)-hexose 6-phosphate from the hydrolysis was treated with an equimolar amount of iodine (with barium iodide). Saturated barium hydroxide was added until the solution attained pH 8. The barium salt of 2-deoxy-\(\text{D-arabino}\)-hexonic acid 6-phosphate was then isolated by precipitation with 1 to 1.5 volumes of ethanol. The product obtained was a white powder which required some effort to re-dissolve it in water. The powder did demonstrate absorption peaks in the infrared at 1550 and 1400 cm\(^{-1}\) attributable to the ionized carboxyl group.

The barium ion was removed using ion exchange resin (Dowex 50-X, \(\text{H}^+\)), and the resulting solution was neutralized to pH 6.5 with cyclohexylamine. The product isolated by removal of the water was crystallized from ethanol-acetone. The analysis of this product indicated that it was the bis(cyclohexylammonium) salt of 2-deoxy-\(\text{D-arabino}\)-hexonic acid 6-phosphate. One millimole of the free acid (generated by treatment of the bis(cyclohexylammonium) salt with
Dowex 50-X, H⁺) required 2.9 milliequivalents of sodium hydroxide (phenolphthalein used as indicator). Attempts to convert this material to the tris(cyclohexylammonium) salt of 2-deoxy-D-arabino-hexonic acid 6-phosphate yielded products which failed to give the proper analytical results.

The fact that 2-deoxy-D-arabino-hexonic acid 6-phosphate gives a stable bis(cyclohexylammonium) salt rather than a tris(cyclohexylammonium) salt is unusual, but not without precedent. Ballou and MacDonald (40) indicate that the stability of phosphate ester cyclo-

(40) Ref. 17, page 274.

hexylamine salts vary. In some cases the phosphate monooester crystallizes with less than two moles of amine. Ukita and Nagasawa (29) showed that methyl 2-deoxy-D-erythro-pentofuranoside 3',5'-diphosphate was isolated as the tris rather than the tetrakis(cyclohexylammonium) salt.

Paper chromatography (formic acid-water-95% ethanol, 1:29:60) of the free 2-deoxy-D-arabino-hexonic acid 6-phosphate demonstrated one major zone and one minor zone. The minor zone was faster moving and was assumed to arise from lactone formation either during application of the material to the chromatogram or during the course of elution. When the ammonium salt was treated in the same manner, only one zone was found.
EXPERIMENTAL

Preparation of tri-O-acetyl-D-glucal

Tetra-O-acetyl-D-glucopyranosyl bromide (290 g.) was dissolved in 4.2 liters of 50% acetic acid with stirring. This solution was then placed in an ice-bath and allowed to cool; 790 g. zinc dust was added in 100 g. portions every 15-20 minutes. At intervals during the reaction several drops of 3% chloroplatinic acid were added (41).


The reaction mixture was stirred an additional two hours, and the zinc acetate and unreacted zinc was then filtered and washed with an additional amount of water. Care (do not allow to dry) was taken in handling the filter cake since it was pyrophoric. The filtered solution was then extracted with ethylene dichloride (four 500-ml. portions) and the ethylene dichloride was then washed several times with half its volume of water. After drying the ethylene dichloride with anhydrous sodium sulfate and treatment of the solution with decolorizing carbon, the ethylene dichloride was removed under reduced pressure to yield a colorless sirup. When a solution of the sirup in ethanol or ether was treated with petroleum ether to incipient opalescence, subsequent cooling and scratching of the wall of the flask induced crystallization to occur; yield 150 gm., m.p. 51-53° (reported m.p. 55°).
Deacetylation of tri-0-acetyl-D-glucal (42)


Tri-0-acetyl-D-glucal (250 g.) which had been dried overnight in a vacuum desiccator over sodium hydroxide was dissolved in 2.5 liters of methanol and placed in the refrigerator. To the above solution at 10° was added a solution of sodium methoxide (0.5 g. sodium in 30 ml. methanol); it was then shaken and allowed to stand for 30 minutes. Neutralization of the solution with glacial acetic acid and removal of the methanol under reduced pressure yielded a sirup. This sirup was extracted by adding a volume of ethyl acetate, heating to the boiling point, agitating, cooling the flask in running tap water, and decanting. After 4 to 6 of these extractions the resulting ethyl acetate solution was cooled to 10° in the refrigerator and crystallization generally occurred. If crystallization failed to occur, the volume of the solution was reduced under reduced pressure and the solution again placed in the refrigerator with scratching used to induce crystallization.

The product was filtered. The best yield obtained was 125 g. or about 85% of the theoretical amount, m.p. 50-55°.

Preparation of 2-deoxy-D-arabino-hexose

D-Glucal (50 g.) was added to 400 ml. of 5% sulfuric acid (w/w) at between 0° and -4°. After stirring, the solution was allowed to remain at that temperature overnight. The solution, still at 0°, was neutralized with dilute barium hydroxide (using phenolphthalein as an indicator), treated with decolorizing carbon, and suction-filtered
through a Celite (43) pad. Removal of the water under reduced pressure

(43) A product of the Johns Manville Corp.

yielded a sometimes yellow-gold sirup.

The above sirup was taken up in as small an amount of methanol as possible and cooled. The resulting product crystallized. The crystals were then filtered, washed with a small amount of methanol, and dried. The mother liquors were concentrated and several more crops of material were obtained; total yield 31.8 g. (57%), m.p. 143-145°.

Attempted tritylation and acylation of 2-deoxy-D-arabino-hexose

A. To a solution of 1 g. of 2-deoxy-D-arabino-hexose in 10 ml. of dry pyridine and 10 ml. of dry N,N-dimethylformamide, at room temperature, was added 1.6 g. (less than 1 equivalent) of trityl chloride. The mixture was agitated until solution occurred and then allowed to stand an additional 36 hours. The solution was then heated on a steam bath for 20 minutes and subsequently cooled to 0°.

Pyridine (2 ml.) and 5 ml. of acetic anhydride were then added to the cooled solution and the solution was allowed to stand for 6 hours at room temperature. An additional 2 ml. of acetic anhydride was added; the solution was then heated at 90° for 15 minutes and afterward cooled to room temperature. The reaction mixture was poured, with stirring, into 200 ml. of iced water. Stirring was continued until the ice melted. The solution was then placed in the refrigerator overnight, and a sirupy product separated.
The aqueous solution was decanted from the sirup and the sirup was taken up in methanol. After treatment with decolorizing carbon, the methanol solution was filtered and the volume reduced to 25 ml. Triphenylcarbinol, which crystallized from this solution while in the refrigerator, was removed by filtration; the methanol was then removed under reduced pressure. This methanol-soluble material was dissolved in ethanol and petroleum ether added to incipient opalescence. Placing this solution in the refrigerator failed to yield anything but a reddish sirup.

B. Trityl chloride (3.2 g) was added to a solution of 2 g. of 2-deoxy-D-arabino-hexose in 12 ml. of dry N,N-dimethylformamide and 5 ml. of dry pyridine. The mixture was heated 90 minutes at 80° and allowed to stand overnight at room temperature. An additional 15 ml. of pyridine was added, the solution cooled to 0°, and 6 g. of benzoyl chloride added. The solution was removed from the ice-bath, allowed to stand at room temperature for 90 minutes, and then heated at 70° for 1 hour. After cooling, the solution was poured into 300 ml. of ice and water. Extraction with two 100-ml. portions of ethylene dichloride was carried out after most of the ice melted.

Pyridine was removed from the ethylene dichloride solution by washing it with two 200-ml. portions of dilute cadmium chloride and filtered to remove the resulting precipitate. After an additional washing with dilute sodium bicarbonate and two washings with water, the ethylene dichloride solution was dried with anhydrous sodium sulfate. Removal of the ethylene dichloride under reduced pressure yielded a mixture of sirup and solid.
Solution of this material in warm ethanol provided a colored solid after the solution was placed in the refrigerator. This solid was then filtered, with the amount recovered being less than one gram. The melting point range of this material was quite wide, the observed value being between 50–80°. Recrystallization was attempted immediately with about half the material going into solution. The remainder changed to a gummy material which required a considerably longer time to reach solution. No material with an improved melting point was recovered.

Preparation of 2-deoxy-D-arabino-hexose diethyl dithioacetal (44,45)


2-Deoxy-D-arabino-hexose (1.7 g.) and 1.4 g. of ethanethiol were placed in a test tube on a mechanical shaker. Concentrated hydrochloric acid (1.6 ml.) was added, the test tube stoppered, and shaking begun immediately. The reaction mixture warmed slightly and then solidified. Another milliliter of concentrated hydrochloric acid was added and the mixture was shaken for an additional 30 minutes. The product was then transferred to a filter funnel and washed with 50 ml. of water, followed by a washing with a small amount of ether. The solid was dissolved in 50 ml. of warm methanol, 10 ml. of water was added and the solution was then allowed to stand uncapped overnight. A portion of the methanol had evaporated by morning, leaving a
crystalline mass of material. This material was filtered, washed with
water, then washed with ether, and finally dried. Processing of the
mother liquors yielded another crop of crystals which was also air-
dried; total yield of air-dried material 2.3 g. (82%), m.p. 134-135.5°
(uncorrected).

The order of addition of reactants is rather important since
adding the ethanethiol before addition of the acid prevents any blacken-
ing of the sugar.

**Synthesis of 3,4,5-tri-O-benzoyl-2-deoxy-6-O-trityl-D-arabino-
hexose diethyl dithioacetal**

2-Deoxy-D-arabino-hexose diethyl dithioacetal (2 g.) was dissolved
in pyridine and to this solution was added 2.1 g. of trityl chloride.
After standing for 40 hours at room temperature, the solution was
cooled to 0°. An additional 10 ml. of pyridine was added, followed by
the drop-wise addition of 4 g. of benzoyl chloride. After attaining
room temperature, the solution was allowed to stand for 48 hours.

The solution was then poured, with stirring, into 200 ml. of iced
water. A gum immediately formed at the bottom, after which the solu-
tion was stirred for 10 minutes. This mixture was then extracted with
three 80-ml. portions of ethylene dichloride. The ethylene dichloride
solution was washed twice with portions of dilute sodium bicarbonate
and water. After drying the ethylene dichloride with anhydrous sodium
sulfate, it was treated with decolorizing carbon; after filtering, the
ethylene dichloride was removed under reduced pressure.

In order to remove any pyridine present in the resulting sirup,
two 20-ml. portions of toluene were added and removed under reduced
pressure. The sirup was then dissolved in ethanol and almost immediately a substance began to crystallize. The solution was placed in the refrigerator for several hours, removed and filtered. Recrystallization from 45 ml. of absolute ethanol yielded 3.8 g. of product, m.p. 123-124.5° (uncorrected).

After allowing the product to stand at room temperature, another melting point determination was taken. A slight change was noted at 123°, but the material melted at 145-146°. In none of the other syntheses of this compound was any of the lower-melting material obtained; [α]_D^26 +35.5° (c 2, CHCl₃).

Anal. Calcd. for C₉₀H₄₈O₇S₂: C, 72.81%; H, 5.83%; S, 7.76%.

Found: C, 72.76%; H, 5.81%; S, 7.91%.

**Attempted acid cleavage of the 6-0-trityl group from 3,4,5-tri-0-benzoyl-2-deoxy-6-0-trityl-D-arabino-hexose diethyl dithioacetal**

3,4,5-Tri-0-benzoyl-2-deoxy-6-0-trityl-D-arabino-hexose diethyl dithioacetal (2 g.) was dissolved with heating in a solution of 10 ml. of glacial acetic acid and 15 ml. of N,N-dimethylformamide. The solution was cooled to 0° and 2 g. of 10% hydrogen bromide in glacial acetic acid then added. The solution was agitated and allowed to stand at 0° for 3 to 4 minutes. The solution failed to assume any yellow-gold color, but some material began to crystallize out of solution. The mixture was filtered onto a mixture of 100 g. of ice and 5 g. of sodium bicarbonate. The resulting solid was washed with water and recrystallized from absolute ethanol. The recovered material amounted
to 1.88 g., m.p. 143-145°. This is an almost quantitative recovery of starting material.

Synthesis of 3,4,5-tri-O-benzoyl-2-deoxy-6-O-trityl-aldehydo-D-arabino-hexose

A suspension of 12 g. of mercuric chloride, 20 g. of neutral finely-ground cadmium carbonate, 4 ml. of water, and 150 ml. of acetone was prepared and stirred for 10 minutes. To this was added, with stirring, 6 g. of 3,4,5-tri-O-benzoyl-2-deoxy-6-O-trityl-D-arabino-hexose diethyl dithioacetal in 100 ml. of acetone. The suspension was stirred for 26 hours at room temperature with occasional additions of fresh cadmium carbonate.

The suspension was then filtered through a sintered-glass funnel onto 15 g. of fresh cadmium carbonate. The residue was washed with an additional 100 ml. of acetone, and then the acetone was removed under reduced pressure (bath temp. 50°). The resulting solid was extracted with three 100-ml. portions of warm ethylene dichloride. The ethylene dichloride solution was washed once with 250 ml. of water, twice with 100-ml. portions of 10% aqueous potassium iodide and twice again with water. After drying the ethylene dichloride solution over anhydrous sodium sulfate, the ethylene dichloride was removed under reduced pressure. The resulting sirup was dissolved in 100 ml. of ether and as small an amount of acetone as required. Petroleum ether was added to make the final volume of the solution 500 ml. After 2.5 days a crystalline product was recovered (3.6 g., m.p. 142°) and the mother liquors yielded more crystalline product (0.6 g.,
m.p. 139-140°). Recrystallization of the material yielded pure material; m.p. 147-148° (uncorr.), [α]_D^{23} +36° (c 2, CHCl₃).

Anal. Calcd. for C_{46}H_{38}O₆: C, 76.90%; H, 5.29%.

Found: C, 78.15%; H, 5.35%.

**Attempted reductive cleavage of the 6-O-trityl group**

3,4,5-Tri-O-benzoyl-2-deoxy-6-O-trityl-aldehydo-D-arabino-hexose (1 g.) was dissolved in 50 ml. of absolute ethanol and treated with 0.5 g. of palladium-on-carbon in the presence of 50 lbs./in.² of hydrogen for 14 hours. A second portion of 0.5 g. of palladium-on-carbon was then added and the reduction continued for an additional 12 hours.

The palladium-on-carbon was removed by centrifugation and the ethanol removed under reduced pressure. The resulting sirup was extracted with four 50-ml. portions of petroleum ether. Evaporation of the petroleum ether and solution of the petroleum ether soluble material in ethanol, after cooling, yielded 0.125 g. material, m.p. 84-95°. This was assumed to be triphenylmethane and corresponded to a 40% yield of the product.

The portion of the reaction mixture that was not soluble in petroleum ether failed to yield a crystalline product.

**Attempted selective phosphorylation of 2-deoxy-D-arabino-hexose diethyl dithioacetal**

2-Deoxy-D-arabino-hexose diethyl dithioacetal (1 g.) was dissolved in 25 ml. of dry pyridine; 15 ml. of benzene was then added and the mixture was next cooled to -10°. Diphenyl phosphorochloridate (1 g.)
was added to this cooled mixture, with stirring, during a half-hour period. The mixture was allowed to stir an additional 1.5 hours and the temperature approached 0°. The mixture was then placed in the refrigerator for 21 hours at 10°. The reaction mixture was then removed and allowed to stand at room temperature for 4 hours. The mixture was cooled to 0° and 6 ml. of acetic anhydride was added.

After standing at room temperature overnight, the mixture was cooled to 0° and 10 ml. of methanol was added. After allowing the mixture to stand at room temperature for 3 hours, the solvents were removed under reduced pressure. The resulting sirup was dissolved in 100 ml. of chloroform, was washed twice with 100-ml. portions of 3% sulfuric acid, once with 100 ml. of dilute sodium bicarbonate, and once with 100 ml. of water. Drying the chloroform solution with anhydrous sodium sulfate and removal of the chloroform under reduced pressure yielded 1.34 g. of a pale yellow sirup.

Examination of the sirup by thin-layer chromatography on Brinkman Silica Gel G (46) using diethyl ether as a solvent, demonstrated the

(46) Brinkmann Instruments, Inc., Great Neck, N. Y.

presence of four components in the sirup. Location of these components was accomplished by spraying the plate with a solution of 1% potassium permanganate in 10% sodium hydroxide.

Attempts to crystallize a product using diethyl ether-petroleum ether were unsuccessful.
Methoxymercuration of tri-O-acetyl-D-glucal

This is a larger scale procedure of the work of Inglis, Schwarz, and MacLaren (37). Tri-O-acetyl-D-glucal (5 g.) in 20 ml. of anhydrous methanol was added to a solution of 6.18 g. of mercuric acetate in 50 ml. of anhydrous methanol; it was allowed to stir for 90 minutes. A solution of 1.13 g. of sodium chloride in 20 ml. of water was added and allowed to stir for a short time. Another 40 ml. of water was added, and the solution was suction filtered before placing it in the refrigerator overnight. A crystalline product appeared and was filtered and air-dried. The yield of product was 2.82 g. or about 30% of the theoretical. The melting point of the resulting material was 166-170°. Inglis, Schwarz, and MacLaren (37) report a melting point of 172° for methyl 3,4,6-tri-O-acetyl-2-chloro-mercuri-2-deoxy-β-D-arabino-hexopyranoside.

The corresponding α-D anomer was obtained in a syrupy form by removing the methanol-water solution under reduced pressure and further washing with water. The α-D anomer was then crystallized from ethyl acetate-petroleum ether.

Preparation of methyl 2-deoxy-β-D-arabino-hexopyranoside (37)

Methyl 3,4,6-tri-O-acetyl-2-chloromercuri-2-deoxy-β-D-arabino hexopyranoside (6.68 g.) in a solution of 105 ml. of dioxan and 35 ml. of N sodium hydroxide was treated with a solution of 0.25 g. of sodium borohydride in 25 ml. of N sodium hydroxide; it was stirred for several hours. A small crystal of sodium borohydride was added, but no further
darkening of the solution occurred. The supernatant liquid was de-
canted from the mercury formed during the reaction. This supernatant
solution was concentrated under reduced pressure and was further dried
by the addition of anhydrous ethanol which was again removed under re-
duced pressure. The resulting solid was placed in a vacuum desiccator
over sodium hydroxide pellets for 1.5 days. Dry pyridine (10 ml.) was
then added and the resulting slurry made as homogeneous as possible.
The slurry was cooled to 0°; 14 ml. of acetic anhydride was added in
several portions with agitation. The slurry was shaken mechanically
for 6 hours and allowed to stand overnight. Ethylene dichloride
(100 ml.) was added to the slurry, shaken, and then poured onto 600 g.
of ice. After occasional stirring while the ice melted, the aqueous
solution was decanted and extracted with 75 ml. of ethylene dichloride.
The ethylene dichloride solutions were combined and washed with water
(three 75-ml. portions), dilute sodium bicarbonate (two 75-ml. portions),
and water (two 75-ml. portions). The ethylene dichloride solution was
dried with anhydrous sodium sulfate. The ethylene dichloride was removed
under reduced pressure, and any residual pyridine was removed by addition
of toluene and removal under reduced pressure. The crystalline product
was dissolved in a small amount of anhydrous ethanol, treated with de-
colorizing carbon, and filtered. Crystallization began immediately and
the solution was placed in the refrigerator at -10°. Filtration of the
crystalline material yielded 3 g. (80%) of methyl 3,4,6-tri-O-acetyl-2-
deoxy-β-D-arabinohexopyranoside; m.p. 100-102°. Inglis, Schwarz, and
MacLaren (37) report m.p. 96-98°.

Deacetylation of 5 g. of methyl 3,4,6-tri-O-acetyl-2-deoxy-β-D-
arabino-hexopyranoside in methanol with a catalytic amount of sodium methoxide yielded 2.5 g. of methyl 2-deoxy-β-D-arabino-hexopyranoside, m.p. 122-124°; reported m.p. 121-122° (37). This product was crystallized from a small amount of methanol.

Selective phosphorylation of methyl 2-deoxy-β-D-arabino-hexopyranoside

A. Methyl 2-deoxy-β-D-arabino-hexopyranoside (1 g.) was dissolved in 20 ml. of dry pyridine. Benzene (25 ml.) was then added and the mixture was cooled, with stirring, to -15° with an ice-salt bath. Precautions were taken to protect the mixture from atmospheric moisture.

Diphenyl phosphorochloridate (1.5 g.) was added drop-wise using a hypodermic syringe, with stirring, over a period of 50-60 minutes. The syringe was washed with several milliliters of benzene which was flushed into the reaction flask. The reaction mixture was allowed to stir for another hour, and then was placed in the refrigerator (10°) overnight.

After removal of the mixture from the refrigerator, it was allowed to stand at room temperature for 3 hours before the solvents were removed under reduced pressure (bath temperature 40°). The sirup was dissolved in 125 ml. of chloroform, after which the chloroform solution was washed with 5% sulfuric acid (two 50-ml. portions), water (50 ml.), dilute sodium bicarbonate (50 ml.), and again with water (50 ml.). The chloroform solution was dried with anhydrous sodium sulfate and treated with carbon; the chloroform was then removed under reduced pressure. Yield of the resulting sirup was 1.91 g. or 85%.

The above sirup was examined by thin-layer chromatography using Brinkmann Silica Gel G (46) and ethyl acetate-diethyl ether (1:1 v/v).
After spraying the chromatogram with 1% potassium permanganate in 10% sodium hydroxide, three zones were visible. They were as follows:

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<th>RA</th>
<th>Amount*</th>
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<tr>
<td>0.25-0.3</td>
<td>85-90%</td>
</tr>
<tr>
<td>0.7-0.8</td>
<td>10-15%</td>
</tr>
<tr>
<td>0.9</td>
<td>Trace</td>
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*Estimated visually.

The zone of RA 0.25-0.3 was then assigned to methyl 2-deoxy-β-D-arabino-hexopyranoside 6-(diphenyl phosphate), and the zone at RA 0.7-0.8 was assigned to methyl 2-deoxy-β-D-arabino-hexopyranoside 4,6-bis(diphenyl phosphate).

B. (31) Diphenyl phosphorochloridate (2.6 g.) in 16 ml. of dry benzene was added, with stirring, to a solution of 1.8 g. of methyl 2-deoxy-β-D-arabino-hexopyranoside in 15 ml. of pyridine at -20°.

Addition of the benzene solution required 90 minutes. The solution was allowed to stir for an additional hour at 0°, and was then placed in the refrigerator overnight. The solution was allowed to stand at room temperature for 4 hours, and then the solvents were removed under reduced pressure (bath temperature 40°). The remainder of the procedure was quite similar to that in section A (above), except that the wash solutions used were saturated with sodium sulfate. After drying the chloroform solution with anhydrous sodium sulfate, the chloroform was removed under reduced pressure to yield a sirup. Thin-layer chromatographic examination of this sirup, using the procedure outlined above, demonstrated but one zone, RA 0.25-0.3. This agrees with the assignment of this zone to methyl 2-deoxy-β-D-arabino-hexopyranoside 6-(diphenyl phosphate).
Base cyclization of the selectively phosphorylated product

A mixture of 1 g. of sirupy methyl 2-deoxy-β-D-arabinohexopyranoside 6-(diphenyl phosphate) and methyl 2-deoxy-β-D-arabinohexopyranoside 4,6-bis(diphenyl phosphate) (9:1 by visual estimation) was dissolved in 100 ml. of chloroform. The chloroform solution was shaken for 10 minutes at room temperature with 50 ml. of 10% sodium hydroxide solution. The chloroform solution was then washed with 50-ml. portions of saturated sodium sulfate solution until the washings were neutral (3 times). The chloroform solution was dried over anhydrous sodium sulfate, and the chloroform was removed under reduced pressure. The solid material recovered amounted to 0.26 g. Examination of this material by thin-layer chromatography, as performed in the previous section, indicated three zones of Rf 0.25, 0.49, and 0.95. The starting material showed three zones of Rf 0.25-0.3 (≈90% of the total), 0.49 (trace), and 0.7-0.8 (≈10% of the total). An authentic sample of methyl 2-deoxy-β-D-arabinohexopyranoside 4,6-(monophenyl phosphate) (see following section) was also run; Rf 0.49. Crystallization of the solid material from ether-acetone-petroleum ether yielded 0.078 g. of material, m.p. 168-174°.

Synthesis of methyl 2-deoxy-β-D-arabinohexopyranoside 4,6-(monophenyl phosphate)

Methyl 2-deoxy-β-D-arabinohexopyranoside (1 g.) was dissolved in 20 ml. of dry pyridine. Benzene (10 ml.) was added and the solution was subsequently cooled to -10° in an ice-salt bath. Monophenyl phosphorodichloridate (16) (1.19 g.) was added with a syringe over a
45 minute period. Care was taken to exclude any extraneous moisture.

After stirring an additional 45 minutes, the mixture was placed in the refrigerator overnight. The mixture was then removed and allowed to stand at room temperature for several hours. Removal of the solvent under reduced pressure yielded a material which was dissolved in 150 ml. of ethylene dichloride. The ethylene dichloride solution was washed with 5% sulfuric acid (two 50-ml. portions), dilute sodium bicarbonate (50 ml.), and with water (50 ml.). After drying, the ethylene dichloride was removed under reduced pressure to yield a solid material.

Crystallization of this material was achieved by dissolving it in a mixture of acetone-diethyl ether and adding petroleum ether to opalescence. The material crystallized as fine needles; yield 0.425 g., 25% of the theoretical; m.p. 174-175° (decomp., uncorr.). Recrystallization was effected in the same manner; m.p. 182-183° (decomp.), $[\alpha]^D_{24} = -58°$ (c 1, CHCl$_3$).

Anal. Calcd. for C$_{13}$H$_{17}$O$_7$P: C, 49.36%; H, 5.38%.

Found: C, 49.66%; H, 5.43%.

Acetylation of 0.425 g. of the above compound in pyridine yielded 0.32 g. of material crystallized from 95% ethanol; m.p. 191-192° (uncorr.), $[\alpha]_D^{23} = -27°$ (c 1, CHCl$_3$).

Anal. Calcd. for C$_{15}$H$_{19}$O$_8$P: C, 50.28%; H, 5.30%.

Found: C, 50.05%; H, 5.43%.
Catalytic cleavage of the phenyl residue from methyl 2-deoxy-β-D-arabino-hexopyranoside 4,6-(monophenyl phosphate)

Methyl 2-deoxy-β-D-arabino-hexopyranoside 4,6-(monophenyl phosphate) (0.5 g.) was refluxed for 10 minutes in anhydrous methanol with about 0.5 g. of acid-washed decolorizing carbon. The solution was suction-filtered and washed with another 10 ml. of methanol. Adams* catalyst (0.1 g.) was then added. This mixture was shaken on a Parr apparatus in the presence of hydrogen (15 lbs./in.²). Rapid hydrogen uptake ceased after one half-hour, but the shaking was continued for 16 hours more. The catalyst was then removed from the solution by filtering, and the solution was neutralized (pH 8-9) with cyclohexylamine. The methanol was removed under reduced pressure and the resulting material was dissolved in a small amount of ethanol. The ethanol solution was treated with carbon and filtered; ether was added to incipient opalescence. Placing the solution in the refrigerator gave a total yield of crystalline product of 0.33 g., m.p. 202-203° (decomp., uncorr.; browning occurs above 190°). Recrystallization of the material gave a product with the following constants: m.p. 197-198° (decomp., browning occurs prior to melting), [α]D⁰ -60.5° (c 2, abs. ethanol).

Anal. Calcd. for C₁₃H₂₆O₇NP: C, 46.01%; H, 7.67%; N, 4.13%.

Found: C, 46.12%; H, 7.65%; N, 4.02%.
Catalytic cleavage of the phenyl residue from methyl 2-deoxy-β-D-arabino-hexopyranoside 6-(diphenyl phosphate)

A sirupy mixture (1.5 g.) of methyl 2-deoxy-β-D-arabino-hexopyranoside 6-(diphenyl phosphate) and methyl 2-deoxy-β-D-arabino-hexopyranoside 4,6-bis(diphenyl phosphate) was dissolved in 25 ml. of anhydrous methanol and refluxed with a small amount of acid-washed carbon. The carbon was removed by filtration and washed with a small amount of methanol. Adams' catalyst (0.2-0.3 g.) was then added and the mixture was shaken in the presence of hydrogen (30 lbs./in.²). Hydrogen uptake was generally rapid for the first half-hour or hour.

After shaking for 12 to 16 hours, the catalyst was removed by filtration and fresh catalyst was added to the solution. This was shaken in the presence of hydrogen for 4 to 6 hours and the catalyst was again removed by filtration. The methanol solution was neutralized with cyclohexylamine, and ethyl acetate was added to just short of the point where the product began coming out in a gelatinous form.

The solution was placed in the refrigerator and a product appeared after the wall of the flask was scratched with a glass rod. After several recrystallizations from methanol-ethyl acetate, 0.7 g. of material was obtained. Constants observed were m.p. 183-184° (decomp.) with softening of the product observed above 175°, [α]²²_D -30° (c 2, H₂O).

Anal. Calcd. for C₁₉H₂₄O₈N₂P: C, 50.00%; H, 9.00%; N, 6.14%.

Found: C, 49.81%; H, 9.28%; N, 6.30%.
Hydrolysis and oxidation of methyl 2-deoxy-β-D-arabino-hexopyranoside 6-phosphate

Methyl 2-deoxy-β-D-arabino-hexopyranoside 6-(dicyclohexylammonium phosphate) (0.1 g.) was dissolved in 5 ml. of water; 2 g. of Dowex 50-X (H⁺) (47) was added and the mixture was shaken to remove the cyclo-

hexylamine. The ion exchange resin was then removed by filtration and washed with more water. The final volume of solution was 10 ml.

A sample (<0.01 ml.) was removed and spotted on a paper chromatogram. The solution was then placed in a water bath at 65-70 °. Samples were removed each half-hour for 3.5 hours and spotted on the papergram. Descending elution of the papergram with 2-propanol-15% trichloroacetic acid (8:2 v/v) and subsequent development with the ammonium molybdate-perchloric acid spray reagent of Hanes and Isherwood (48) allowed a

qualitative check of the hydrolysis. Prior to heating the solution there was but one spot at RA 0.63. Samples taken during hydrolysis show a spot at RA 0.49 that grew more intense as time passed. At the end of 3.5 hours there is still a trace of material having RA 0.63. The solution was heated an additional 5 hours at 65-70 °. The corresponding papergram showed no material having RA 0.63 nor any trace of inorganic phosphate.

The technique of developing the papergram deserves some
explanation. After spraying with the Hanes-Isherwood reagent, the papergram was air-dried. It was then placed in an oven at about 85°.

In 5 to 7 minutes the spots generally were visible. Removal of the papergram from the oven and exposure to light formed a blue background. Inorganic phosphate demonstrated a yellow color on heating which changed to a green color on exposure to light. Methyl 2-deoxy-β-D-arabinohexopyranoside 6-phosphate and 2-deoxy-D-arabinohexose 6-phosphate yielded dark brown spots. The oxidized product (see later) gave little or no indication of a spot on heating, but after exposure to light gave a blue spot against a lighter blue background.

Methyl 2-deoxy-β-D-arabinohexopyranoside 6-((dicyclohexylammonium phosphate) (1.0 g.) was dissolved in 8 ml. of water and treated with 15 g. of Dowex 50-X (H⁺). The solution was filtered and the resin was washed with water. The solution and washings were combined and the total volume was about 25 ml. After hydrolysis at 68° for 12 hours, a solution of 0.56 g. of iodine and 1.2 g. of barium iodide in 4 ml. of water was added.

The drop-wise addition of saturated barium hydroxide solution was commenced with vigorous stirring of the solution. The addition of barium hydroxide was halted when the solution attained pH 8 and remained at that value. Stirring was allowed to continue for an additional 15 to 30 minutes. Decolorizing carbon was added; the mixture was then filtered and washed. The total volume of the solution was 60 ml.

Ethanol (90 ml.) was added and the product was collected by centrifugation. The supernatant solution was tested for additional product by adding more ethanol; however, nothing more precipitated.
The product was redissolved and reprecipitated with ethanol. A last washing with absolute ethanol was followed by drying the product under reduced pressure (12-15 mm. Hg) and at room temperature for an hour. Washing this with absolute ether yielded 0.8 g. (80%) of the barium salt of 2-deoxy-D-arabino-hexonic acid 6-phosphate. The infrared spectrum (KBr pellet) of this compound demonstrated strong peaks at 1550 and 1400 cm.⁻¹.

The barium salt was converted to the free acid by dissolving it in 50 ml. of water, cooling it, and adding 10 g. of Dowex 50-X (H⁺). The resin was removed by filtration and washed with a small amount of water. The resulting solution (showing a slight red color) was neutralized to pH 6.5-7 with cyclohexylamine.

Evaporation of the solution under reduced pressure yielded a sirup which was dried by azeotropic distillation under reduced pressure with absolute ethanol. The resulting solid was dissolved in absolute ethanol, treated with carbon, and filtered. This solution was heated to 40-45° and acetone was added to opalescence. Scratching and cooling yielded a product which crystallized in clusters of fine, short needles. Recrystallization of this material from the above solvent system showed the product had m.p. 145-146° (decomp., [α]D25 +60° (c 1, 95% EtOH). The melting point observed was quite dependent on the rate of temperature change.

*Anal. Calcd. for C18H39O9N2P: C, 47.16%; H, 8.52%; N, 6.11%.
Found: C, 47.14%; H, 8.53%; N, 6.12%.

Attempts were made to convert the dicyclohexylammonium salt to the tricyclohexylammonium salt of 2-deoxy-D-arabino-hexonic acid
6-phosphate. This was done by treating an ethanol solution of the
dicyclohexylammonium salt with an excess of cyclohexylamine. A
product was precipitated on addition of acetone, which had a melting
point of 158-160° (decomp., uncorr.). The analysis of this compound
failed to give the proper values for the tricyclohexylammonium salt of
2-deoxy-D-arabino-hexonic acid 6-phosphate.
SUMMARY

Attempts to prepare 2-deoxy-D-arabino-hexose 6-phosphate by routes utilizing properly blocked derivatives were unsuccessful. Selective phosphorylation of methyl 2-deoxy-β-D-arabino-hexopyranoside with diphenyl phosphorochloridate was successful. Reductive cleavage of the phenyl residues on methyl 2-deoxy-β-D-arabino-hexopyranoside 6-(diphenyl phosphate) yielded a crystalline dicyclohexylammonium derivative.

Hydrolysis of the glycosidic methyl group was possible using no additional acid. Oxidation of the resulting free phosphate ester with barium hypoiodite yielded an amorphous barium salt. A crystalline bis(cyclohexylammonium) salt of 2-deoxy-D-arabino-hexonic acid 6-phosphate was isolated.

Base treatment of a sirupy mixture of methyl 2-deoxy-β-D-arabino-hexopyranoside 6-(diphenyl phosphate) and methyl 2-deoxy-β-D-arabino-hexopyranoside 4,6-bis(diphenyl phosphate) produced methyl 2-deoxy-β-D-arabino-hexopyranoside 4,6-(monophenyl phosphate). This compound was synthesized by treatment of methyl 2-deoxy-β-D-arabino-hexopyranoside with phenyl phosphorodichloridate.
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<td>11</td>
<td>7</td>
<td>P. A. Levene and A. L. Raymond, <strong>J. Biol. Chem.</strong>, 92, 757 (1931).</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>P. A. Levene and A. L. Raymond, <strong>J. Biol. Chem.</strong>, 92, 765 (1931).</td>
</tr>
<tr>
<td>13</td>
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<td>P. A. Levene and E. T. Stiller, <strong>J. Biol. Chem.</strong>, 104, 299 (1934).</td>
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<td>14</td>
<td>8</td>
<td>P. A. Levene and C. C. Christman, <strong>J. Biol. Chem.</strong>, 123, 607 (1938).</td>
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<td>15</td>
<td>8</td>
<td>H. Bredereck, <strong>Angew. Chem.</strong>, 52, 576 (1939).</td>
</tr>
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<td>16</td>
<td>8</td>
<td>P. Brigl and H. Müller, <strong>Ber.</strong>, 72, 2121 (1939).</td>
</tr>
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<td>18</td>
<td>9</td>
<td>L. Zervas, <strong>Naturwiss.</strong>, 27, 317 (1939).</td>
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PART II.

THE OPTICAL ROTATORY DISPERSION OF

SOME CARBOHYDRATE DERIVATIVES
INTRODUCTION

The first report of rotatory dispersion was made by Biot (1) in 1812. In it he observed that quartz had the property of rotating the plane of plane polarized light, and that this property was dependent on the thickness of the quartz plate used. In the same communication he also reported that he had discovered a form of quartz having the opposite rotatory power and that when equal thicknesses of both forms were included in the light path, no rotation was observed.

Although Biot had no source of monochromatic light at his disposal, in a later paper (2) he measured the rotation of quartz at eight different colors. Using only the rough wave-length values for these colors, he was able to postulate his law of inverse squares:

$$\alpha = \frac{K}{\lambda^2}$$

Another contribution of Biot was made in 1838 (3) when he estab-

lished a definition or standard of rotatory power with the relationship

$$[\alpha] = \frac{\alpha}{18} \quad \text{or} \quad \frac{\alpha}{15} \quad \text{or} \quad \frac{\alpha}{61}$$
where $\alpha$ is the observed rotation in degrees,

1 is the column length in decimeters,

$\delta$ is the density of the liquid, and

$\xi$ is the weight-fraction of optically active substance.

Several significant developments occurred in the half-century after Biot's work. Pasteur (4) explained optical activity by intro-

(4) L. Pasteur, Annales de Chimie et de Physique, [iii], 24, 443 (1848).

ducing the concept of molecular dissymmetry. He contended that mole-
cules must be grouped into two classes, those with superposable images
and those with non-superposable images. With his separation of the
two crystalline forms of a racemic mixture of sodium ammonium tartrate,
Pasteur (5) demonstrated that his idea of molecular dissymmetry was

(5) L. Pasteur, Alembic Club Reprints, 14, 21.

correct.

In 1874 LeBel (6) and Van't Hoff (7) independently postulated


(7) J. H. Van't Hoff, "A Suggestion Looking to the Extension
into Space of the Structural Formulas at Present Used in Chemistry and
a note Upon the Relation Between the Optical Activity and the Chemical
Constitution of Organic Compounds," Utrecht, 1874; See G. M. Richardson,
theories which explained dissymmetry in chemical compounds. LeBel explained it by the substitution of four different radicals around the carbon atom. Van't Hoff did essentially the same thing except that he pictured the spatial requirements of an asymmetric carbon and deduced the tetrahedral arrangement still in use after nearly a century.

Although not of direct interest in this paper, it should be noted that Werner (8) then applied the ideas of LeBel and Van't Hoff in the field of inorganic complexes.

Since Biot's law of inverse squares was formulated using light of only approximate wave-lengths, it was inevitable that re-examination would bring some change. Broch (9) determined the rotatory power of quartz and found that the quantity $\alpha \lambda^2$ was not constant as the law of inverse squares predicted. von Lang (10) was the first to attempt to correct this oversight by proposing a two term equation:

$$\alpha = A + B/\lambda^2$$
Applied to Broch's data for quartz, the relationship (for quartz) became:

\[ \alpha = -3.40 + \frac{8.5706}{10^6 \lambda^2} \]

Stefan (11) also attempted to find the correct relationship, using observations of his own, and arrived at the same type of equation used by von Lang:

\[ \alpha = -1.753 + \frac{8.1624}{10^6 \lambda^2} \]

Biot's formula erred in terms of two degrees, while Stefan's was accurate to tenths of a degree.

Boltzmann (12), in 1874, criticized the work of both Stefan and von Lang and proposed a relationship of his own. Using Broch's data for quartz, Boltzmann represented its rotatory power in the following fashion:

\[ \alpha = \frac{7.07018}{10^6 \lambda^2} + \frac{0.14983}{10^{12} \lambda^4} \]

Boltzmann then concluded that equations for rotatory dispersion do not contain a consistent term, but could be extended by use of terms of higher order.

Drude (13) then made what was the first adequate study of natural light dispersion.
and magnetic rotatory power. His explanation includes consideration of a "dissymmetrically isotropic medium" or a situation in which the molecules are all irregular tetrahedra of the same kind. Using this idea, the relationship for rotation of plane polarized light is:

\[ \alpha = \frac{K}{\lambda^2 - \lambda_0^2} \]

where \( \lambda_0 \) is the wave-length corresponding to a characteristic frequency of vibration, and

\( K \) is a constant dependent on the compound.

Drude's equation indicates that when \( \lambda^2 = \lambda_0^2 \) the rotation should be infinity, with a reversal of sign in crossing the wave-length of absorption. Use of this equation is now limited to wave-lengths in the region of transparency, where it applies with a high degree of accuracy.

In actuality, if the optical rotation is plotted as a function of the wave-length, the resulting idealized curve reaches a maximum, then reaches a minimum after intersecting the zero line. At this point of intersection Cotton (14) discovered that the difference in

\[ \lambda_0 \]

(14) A. Cotton, Ann. chem. phys., [7], 8, 347-432 (1896); Compt. rend., 153, 245 (1911).

the index of refraction and absorption for right and left circularly polarized light was at a maximum. This difference, though small, is measurable in termed ellipticity or circular dichroism.

In order to overcome the limitations imposed by Drude's equation, Natanson (15) modified it with the help of a "damping factor" such
that it could be used in a region of absorption. His relationship is stated as:

$$\alpha = \frac{D (\lambda^2 - \lambda_0^2)}{(\lambda^2 - \lambda_0^2) + T^2 \lambda^2}$$

where $D$ is a constant characteristic of the compound involved,

$\lambda_0$ is the wave-length of the absorption, and

$T$ is the "damping factor" and equal to the half-width of the absorption band.

More recent treatments of this type are due to the work of Kuhn and Braun (16); Lowry and Hudson (17); Kirkwood (18); Condon, Altar, and Eyring (19); and Moffitt and Moscowitz (20).

Optical rotatory dispersion studies have become commonplace only in the past ten years, due to the most part from introduction of spectropolarimeters able to measure rotations in the ultraviolet.
Refinements made on the manual instrument described by Rudolph (21)


have led to the development of a recording instrument which now promises measurements as far into the ultraviolet as 185 m\(\mu\) (22).


General references to optical rotatory dispersion must include Lowry (23), Wolf from (24), Djerassi (25), Klyne and Parker (26), and Elie l (27).


STATEMENT OF THE PROBLEM

It is the purpose of this work to investigate the optical rotary properties of a number of carbohydrate compounds, and where possible, to correlate these results with findings already published.
HISTORICAL

Sucrose

The first recorded instance of the measurement of optical rotatory dispersion of a member of the carbohydrate series was made by Biot (2). He measured the optical rotation of a solution of sucrose through the visible region by compensating the observed rotation with quartz having an opposite rotatory power. In this way he deduced that sucrose followed his law of inverse squares, and also that this law was general.

Lowry and Richards (28) and Harris, Hirst, and Wood (29) re-examined the optical rotatory dispersion of sucrose into the ultraviolet portion of the spectrum (235.6 μ) and found that sucrose did obey a single term Drude equation. The center of the optically active absorption band was located at 146 μ.

Optical rotatory dispersion curves of this type (those that can be represented by a single Drude equation) are termed simple curves. The constant k is called the rotation constant and λ₀ the dispersion constant. One of the more widespread graphical methods for

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determining whether or not a compound exhibits "simple" optical rotatory dispersion is by a plot of \( \frac{1}{[\alpha]} \) vs. \( \lambda^2 \). Caution must be taken to use rotation values outside the region of absorbency. If a straight line results from this plot, it is assumed that the rotatory dispersion curve is simple and due to one optically active absorbing center or a collection of absorbing centers spaced closely together. In a plot of this kind the values of \( k \) and \( \lambda_0^2 \) can also be determined from the slope of the line and the intercept, respectively.

Yang and Doty (30) have criticized this so-called "Biot-Lowry"


plot since it tends to concentrate the shorter wave-length regions into a disproportionately small portion of the graph. Determination of \( \lambda_0^2 \) from the intercept requires close observation leading to the possibility of error. They prefer instead to plot \( \lambda_0^2[\alpha] \) as a function of \( [\alpha] \). This means that \( \lambda_0^2 \) is the slope of the resulting line. A straight line will result if a simple curve is being analyzed. On the other hand, it should be pointed out that Lowry always used the method of least squares to find the best straight line and its intercept; he never depended upon graphic extrapolation.

If the points in a Biot-Lowry plot do not fit a straight line, the optical rotatory dispersion curve can be classed as complex, because it would appear that a complex Drude equation is needed to fit the data. Caution must be used here since this is not universally true, as shown in the next section.
Methyl glycosides

Lowry and Abram (31) measured methyl α- and β-D-glucopyranoside,


using two sets of pure spectral lines (mercury and cadmium) and calculating \( k \) and \( \lambda_0^2 \) for each set of lines using the Drude equation. Agreement between the mercury lines and cadmium lines was excellent for the methyl α-D-glucopyranoside (\( k = 25.87 \) and \( \lambda_0^2 = 0.0234 \)). There was some difference in the values derived from the methyl β-D-glucopyranoside, the greatest difference being in the values of \( \lambda_0^2 \). Lowry and Abram indicated that the difference \( \lambda_0^2 = 0.0017 \) was not significant.

This work could very easily be questioned since there was no effort to attain a series of values in the ultraviolet. In 1932 Harris, Hirst, and Wood (29) attempted to correct this oversight and reported optical rotatory dispersion studies on ten carbohydrate compounds.

Upon studying the optical rotatory dispersion data of methyl α-D-glucopyranoside in the region 240-671 μ, they found that it did not obey a simple Drude equation, but that the value of \( \lambda_0^2 \) was 0.022. This does not differ a great deal from the value found by Lowry, so that this work might also be questioned.

Table 1 gives a sampling of the results reported by Harris, Hirst, and Wood (29). The data in Table 1 were analyzed by means of the Drude equation, and by mathematical means rather than by the graphical method. They attempted to use two widely separated points from the rotatory dispersion curve, calculate a value of \( k \) and \( \lambda_0^2 \),
<table>
<thead>
<tr>
<th>Compound</th>
<th>Wave-length range (mμ)</th>
<th>Type of dispersion</th>
<th>(\lambda^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl α-D-glucopyranoside</td>
<td>240-671</td>
<td>complex</td>
<td>0.022</td>
</tr>
<tr>
<td>Methyl α-D-glucofuranoside</td>
<td>241-671</td>
<td>complex</td>
<td>0.018</td>
</tr>
<tr>
<td>Methyl α-D-mannopyranoside</td>
<td>238-671</td>
<td>complex</td>
<td>0.022</td>
</tr>
<tr>
<td>Methyl α-D-mannofuranoside</td>
<td>302-671</td>
<td>simple</td>
<td>0.019</td>
</tr>
<tr>
<td>Methyl α-D-glucopyranoside tetaacetate</td>
<td>319-671</td>
<td>complex</td>
<td>0.026</td>
</tr>
<tr>
<td>Methyl β-D-glucopyranoside tetaacetate</td>
<td>298-671</td>
<td>complex</td>
<td>0.030</td>
</tr>
<tr>
<td>Methyl α-D-mannopyranoside tetaacetate</td>
<td>298-671</td>
<td>complex</td>
<td>0.030</td>
</tr>
<tr>
<td>Methyl β-D-mannopyranoside tetaacetate</td>
<td>261-752</td>
<td>simple</td>
<td>0.022</td>
</tr>
<tr>
<td>α-cellobiose octaacetate</td>
<td>298-671</td>
<td>complex</td>
<td>0.017</td>
</tr>
</tbody>
</table>
recalculate the curve, and compare it with the original. If deviation occurred, this indicated that they were dealing with a complex Drude curve.

It is difficult to understand why complex dispersion here seems to be the rule rather than the exception, particularly when the rotatory dispersion measurements stop 100 or more μ above the calculated active absorption band. These dispersion constants are consistent with what is known about the position of absorption bands in the ultraviolet.

In 1934 Herbert, Hirst, and Wood (32) published their findings on


the optical rotatory dispersion of methyl tetra-α-methyl-α-D-glucopyranoside and methyl tetra-α-methyl-α-D-mannopyranoside. The glucopyranoside differed even more from a simple Drude plot than did its unmethylated derivative, while the mannopyranoside gave a simple Drude plot.

Sørenson and Trumpy (33) then reported measurements in the visible


region for methyl α- and β-D-glucopyranoside, methyl α- and β-D-galactopyranoside, and methyl α- and β-L-rhamnopyranoside. The only instance of complex behavior is that of methyl β-D-galactopyranoside.
The values of $\lambda_0^2$ in these cases were in the range of 0.0179 to 0.0249.

In an effort to bring about some constancy, Sørenson and Trumpy, using the Drude-Natanson equation, re-evaluated some of the earlier published data. Evaluation in this manner, using data appearing in the original papers, leads to the conclusion that only three of twenty cases re-evaluated by Sørenson and Trumpy demonstrate complex behavior.

The value of $\lambda_0$ of eleven simple or fully methylated glycosides ranged from 134-173 μ with the mean value about 155 μ. Values of $\lambda_0$ of the six acetate derivatives demonstrating simple dispersion is between 142 and 192 μ with a mean value of 172 μ.

It appeared that, for free sugars, methyl glycosides, methylated sugars, and acetylated sugars containing no absorption band outside the Schumann region, simple rotatory dispersion is the rule rather than the exception.

**Polysaccharides**

Wolff, Watson, and Rist (34) studied a number of starch derivatives in the visible region and were able to analyze their results using a simple Drude plot. Table 2 gives their results.

---

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>k</th>
<th>$\lambda_0^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn amylose</td>
<td>KOH</td>
<td>50.86</td>
<td>0.0215</td>
</tr>
<tr>
<td>Corn amylopectin</td>
<td>KOH</td>
<td>54.63</td>
<td>0.0107</td>
</tr>
<tr>
<td>Corn starch triacetate</td>
<td>CHCl$_3$</td>
<td>56.48</td>
<td>0.0162</td>
</tr>
<tr>
<td>Corn amylose triacetate</td>
<td>CHCl$_3$</td>
<td>55.86</td>
<td>0.0224</td>
</tr>
<tr>
<td>Corn amylopectin triacetate</td>
<td>CHCl$_3$</td>
<td>56.31</td>
<td>0.0111</td>
</tr>
<tr>
<td>Corn starch tricarbanilate</td>
<td>C$_5$H$_5$N</td>
<td>-16.49</td>
<td>0.1125</td>
</tr>
<tr>
<td>Corn amylose tricarbanilate</td>
<td>C$_5$H$_5$N</td>
<td>-21.60</td>
<td>0.0926</td>
</tr>
<tr>
<td>Corn amylopectin tricarbanilate</td>
<td>C$_5$H$_5$N</td>
<td>-15.81</td>
<td>0.1069</td>
</tr>
</tbody>
</table>
The first interesting thing to be noticed from Table 2 is that the sign of \( k \) changes in going from the simple derivatives to the carbanilate. It is hard to postulate why this should happen unless the steric demands of the carbanilate molecule require a conformational change in the \( \text{D}-\text{glucose} \) residues of the polysaccharide chain.

The second item of interest is that \( \lambda_0^2 \) becomes much larger in the tricarbanilate derivatives. This is explained by the fact that the aromatic ring can be affected by the asymmetric centers through the \(-\text{C-NH-}\) group, shifting the optically active band to longer wavelengths.

Neely (35) investigated the optical rotatory dispersion of a


partially methylated cellulose (1.8 methoxyl groups per anhydroglucose residue) and an approximate molecular weight of 35,000. This particular compound has the unusual property of being more soluble in cold water than in warm water. Neely's main interest was the use of rotatory dispersion to investigate whether or not some of the properties of aqueous solutions of this material could be explained by aggregate formation.

By using different means of preparing his solutions he was able to obtain a wide range of line shapes using a plot of \( \lambda^2[a] \) as a function of \([a]\). In accord with findings in the peptide field (30) it appeared that the methylated celluloses solubilized at higher temperatures demonstrated complex Drude behavior, indicating that they had a
more organized structure. Those solutions prepared at a higher temperature, but then cooled, demonstrated a simple behavior leading Neely to the conclusion that in this case the O-methylcellulose molecules were randomly dispersed.

In a later work Neely (36) ventured outside the area of O-methyl-

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cellulose as shown in the following table:

**TABLE 3**

SOLVENT EFFECTS ON POLYSACCHARIDES (36)

<table>
<thead>
<tr>
<th>Polysaccharide</th>
<th>Solvent</th>
<th>$\lambda_o$ (μm)</th>
<th>$[\alpha]_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylose (0.4 g./100 ml.)</td>
<td>H$_2$O</td>
<td>135</td>
<td>+200</td>
</tr>
<tr>
<td></td>
<td>0.5 M KCl</td>
<td>134</td>
<td>+201</td>
</tr>
<tr>
<td></td>
<td>8 M urea</td>
<td>132</td>
<td>+200</td>
</tr>
<tr>
<td></td>
<td>1 M NaOH</td>
<td>132</td>
<td>+162</td>
</tr>
<tr>
<td></td>
<td>Dimethyl sulfoxide</td>
<td>210</td>
<td>+175</td>
</tr>
<tr>
<td>Amylopectin (0.4 g./100 ml.)</td>
<td>H$_2$O</td>
<td>135</td>
<td>+200</td>
</tr>
<tr>
<td></td>
<td>1 M NaOH</td>
<td>134</td>
<td>+163</td>
</tr>
<tr>
<td>O-Methylcellulose (2 g./100 ml.)</td>
<td>H$_2$O</td>
<td>Complex behavior</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 M urea</td>
<td>235</td>
<td>-7.44</td>
</tr>
</tbody>
</table>

In all cases, excepting O-methylcellulose in water, the rotatory dispersion obeyed the simple Drude equation. The constancy of $\lambda_o$ of amylose in 0.5 M KCl and 8 M urea indicates that the polysaccharide undergoes no conformational change. The change of the $\lambda_o$ of amylose in dimethyl sulfoxide to a higher value could mean that the amylose has assumed an ordered conformation similar to the change noted in polypeptides.
Use of \( \lambda_0 \) values to detect branching differences in polysaccharides would not appear to be a promising analytical method, since in this case the values of \( \lambda_0 \) of the aqueous solutions are the same for amylose and amylopectin.

As demonstrated in Neely's previous work, \( \beta \)-methylcellulose could give a complex Drude plot. However, with 8 M urea this behavior changed and it obeyed a simple Drude equation. This would indicate that the addition of urea tended to disrupt hydrogen bonding in the \( \beta \)-methylcellulose system.

One last observation was concerned with the decrease of \( [\alpha]_D \) when molar sodium hydroxide was used as a solvent for amylose and amylopectin. Neely explained this by proposing that the hydroxyl groups are ionized in this medium causing axially oriented ring hydroxyls to shift to an equatorial position where less hindrance would be encountered.

**Aromatic glycosides**


D line for a large number of aromatic glycosides and compared their results with alkyl glycosides. Their findings indicated that by attaching an aromatic nucleus to an asymmetric carbon through an oxygen link, other asymmetric carbon atoms attached to the carbon involved in this linkage make a larger rotatory contribution than is the case in
the aliphatic series. Also, aromatic \( \beta-D \)-glucosides are more levo-
rotatory than the aliphatic \( \beta-D \)-glucosides.

Later Pigman (38) studied the optical rotatory dispersion of some


free and acetylated aromatic glucosides in the visible region. Sur-
prisingly enough, most of the compounds fitted the one term Drude

equation. As might be expected, the values of \( \lambda_0 \) came at longer wave-
lengths than with aliphatic glucosides. \( \beta-D \)-Dinitrophenyl \( \beta-D \)-gluco-
pyranoside tetraacetate had a \( \lambda_0 \) value of 370 \( \text{m} \mu \). This was the highest
value of \( \lambda_0 \) recorded in the series with \( \lambda_0 \) values of the unacetylated
compounds ranging between 219 and 242 \( \text{m} \mu \).

In yet another study of this type, Bonner (39) investigated the

\[ (39) \text{W. A. Bonner, J. Am. Chem. Soc., 71, 3384 (1949).} \]

optical rotatory dispersion of \( \beta-D \)-phenylazophenyl \( \beta-D \)-glucopyranoside,
\( \beta-D \)-galactopyranoside and \( \beta-D \)-galactopyranoside tetraacetate. Earlier
work by Zelinski and Bonner (40) had indicated two distinct absorption

\[ (40) \text{R. P. Zelinski and W. A. Bonner, J. Am. Chem. Soc., 71,}
1791 (1949). \]

bands between 240 and 800 \( \text{m} \mu \). One was a relatively low intensity
"R-band" at approximately 436 \( \text{m} \mu \) and the other was a high intensity
"K-band" at about 338 \( \text{m} \mu \). The R-band had been attributed to the
isolated azo linkage and the K-band to the p-phenylazo chromophore as a whole.

The major difficulty in polarimetry of this type of compound is that it is colored and this makes accurate determinations extremely difficult. Bonner was able to study the rotation, using dioxane as a solvent, only in the region from 524 to 667 μm. Nonetheless, both the p-phenylazophenyl β-D-glucopyranoside and galactopyranoside obeyed a simple Drude plot in this region with a λ₀ of 339 μm for the glucoside and 342 μm for the galactoside. Bonner reapplied the constants derived from the Drude plot of the glucoside and recalculated the rotations, finally comparing these values with his observed values. He found that from about 572 μm downward there was a divergence between the calculated and the observed values. Their explanation of these results was that the optically active band was in the K-band with the R-band having some slight effect in the area where it occurred. The calculated and observed values for the galactoside differed appreciably, and the galactoside tetraacetate was even worse. Bonner felt that the galactosides exhibited complex behavior.

Levedahl and Jones (41) made a study of the optical rotatory dispersion of adenine, adenosine, adenosine 5'-monophosphate, adenosine 5'-diphosphate, and adenosine 5'-triphosphate at four pH values (2.2, 5.5, 7.1, and 10.2). The purpose of the study was to better elucidate

the conformation of these compounds. Measurements extended into the ultraviolet as far as 320 mµ and analysis using the simple Drude equation was possible. The same chromophoric center controlled the optically active absorption band in all cases. It was concluded that addition of a second phosphate group to adenosine 5'-monophosphate somehow created a more symmetrical molecule.

Compounds containing the \(-\text{C}-\) and \(-\text{S-C}-\) chromophores

If optical rotatory dispersion is dependent upon the presence of an absorption band somewhere in the ultraviolet, compounds with a keto or aldehydo group should serve as excellent specimens for study.

Wolf from and Brode (42) investigated the first instance of this type when they measured the rotatory dispersion of aldehydo-\(\text{D}-\)glucose pentaacetate, aldehydo-\(\text{D}-\)galactose pentaacetate, and aldehydo-\(\text{L}-\)arabinose tetraacetate in chloroform from 423 to 656 mµ. Using a Biot-Lowry plot the dispersions of the galactose and arabinose derivatives provided straight lines while the glucose derivative strayed in the ultraviolet region. Thus galactose and arabinose were assumed to have simple behavior and glucose complex behavior.

Hudson, Wolf from, and Low ry (43) extended optical rotatory dispersion


measurements of these compounds in chloroform into the ultraviolet (254 μm), as well as measuring their circular dichroism and ultraviolet absorption. By extending the rotatory dispersion measurements this far into the ultraviolet, they observed the Cotton effect curve. Although they were able to represent the dispersion of aldehyde-D-arabinose tetraacetate by a simple Drude equation, it was necessary to resort to a two term equation to represent both the aldehyde-D-glucose pentaacetate and aldehyde-D-galactose pentaacetate.

In all cases the rotation constant (k) of the first or long wavelength term was negative in sign. This was due to the "induced dissymmetry" of the aldehydic group stemming from asymmetry at carbon two. The second positive term in the case of glucose and galactose arises from the summation of the effects in the far ultraviolet. The lack of this term in arabinose indicates that there was some sort of cancellation or compensation occurring in the far ultraviolet, with the resultant observed rotation due supposedly to the induced dissymmetry of the aldehydic group.

There was excellent agreement observed in the values of the center of the ultraviolet and circular dichroism bands with the values ranging from 290 to 292 μm. The observed value of λₒ of the optical rotatory dispersion curve for aldehyde-D-glucose tetraacetate was 297 μm, while the value calculated from the complex Drude equation was 302 μm. For aldehyde-D-arabinose tetraacetate the observed value of λₒ was 292 μm with the calculated value being 299 μm. For aldehyde-D-arabinose tetraacetate the observed value was 290 μm while the calculated value was 293 μm. As mentioned by these authors, there was marked divergence in the values of dispersion constants between the observed and calculated values.
In a later paper (44) the same measurements were carried out on


keto-D-fructose pentaacetate and aldehyde-L-fucose tetraacetate. It
would be expected that the fructose derivative would be similar to
arabinose since a $\text{H}_2\text{C}-\text{O}-\text{COCH}_3$ has replaced the aldehydic hydrogen.
Likewise, the fucose compound is merely galactose with a hydrogen
replacing the $-\text{O}-\text{COCH}_3$ at carbon six.

The ultraviolet absorption maximum for keto-D-fructose penta-
acetate occurred at 283 m$\mu$ and the circular dichroism maximum at
280 m$\mu$. The transition from an aldehydo- to a keto- derivative has
thus shifted both of these values to shorter wave-lengths. The optical
rotatory dispersion of this compound demonstrates the same type of
optical cancellation as evidenced by the corresponding arabinose
derivative, obeying a simple Drude equation between 411 and 671 m$\mu$.
The value of $\lambda_o$ of the rotatory dispersion constant conforms to the
pattern of the ultraviolet and circular dichroism maxima and shifts
to a shorter wave-length (283 m$\mu$).

Ultraviolet absorption and circular dichroism maxima for aldehyde-
L-fucose tetraacetate shift to slightly longer wave-lengths than the
corresponding galactose derivative. The rotatory dispersion is complex,
requiring a two term Drude equation to approximately represent it with
an observed value of $\lambda_o$ of 298 m$\mu$.

Lowry and Krieble (45) investigated the rotatory dispersion of
D-galactono-1,4-lactone in water through the visible region. Using a simple Drude plot they calculated a value of $\lambda_0$ of 242 m\u. In the same paper Lowry and Kriple also measured D-galactonic acid and sodium D-galactonate. Neither compound conformed to a simple Drude equation with the sodium D-galactonate demonstrating a maximum in the visible blue region.

The effect of various solvents on the rotatory dispersion of tetra-O-methyl-D-mannono-1,4-lactone was investigated by Harris, Hirst, and Wood (46). In water the D-mannonolactone obeyed a simple Drude equation with $\lambda_0^2$ of 0.049. In dioxan, ethanol, and chloroform, it exhibited a maximum and reversal of sign, while in ether, benzene, and acetone it failed to obey a simple Drude equation.

Harris, Hirst, and Wood (47) observed the optical rotatory dispersion of tetra-O-methyl-D-glucono-1,5-lactone and tetra-O-methyl-D-galactono-1,5-lactone. These two cases could be described by a single...
term Drude-Natanson equation with the value of $\lambda_0$ falling in the region of 200 m\(\mu\). It is feasible that this could represent induced dissymmetry of the lactonic carbonyl.

Horton and Wolfrom (48) have used optical rotatory dispersion to accomplish a configurational correlation of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-\(\beta\)-D-glucopyranosyl ethylxanthate with 2,3,4,6-tri-O-acetyl-\(\beta\)-D-glucopyranosyl ethylxanthate. Both compounds showed the same shaped Cotton curves with the reversal in sign occurring at a weak ultraviolet absorption band near 360 m\(\mu\).

Miscellaneous carbohydrate derivatives

Harris, Herbert, Hirst, Wood, and Woodward (49) investigated the optical rotatory dispersion of di-\(\alpha\)-acetyl-\(\beta\)-xylal, tri-\(\alpha\)-acetyl-\(\beta\)-glucal, hexa-\(\alpha\)-acetyllactal, hexa-\(\alpha\)-acetylellobial, lactal, and cellobial. Di-\(\alpha\)-acetyl-\(\beta\)-xylal was the only member of the group obeying a single term Drude-Natanson equation. The value of $\lambda_0$ fell in the range where C=C absorption occurs.

Measurements of D-xylal and D-glucal triacetate have been repeated at this university (50).
The D-xylal gave a simple Drude plot whereas the D-glucal triacetate gave a complex Drude plot. Also investigated in this work was the rotatory dispersion of a number of nitrate esters, most of them esters of D-mannitol. The results demonstrated both complex and simple Drude behavior.
EXPERIMENTAL

All optical rotatory dispersion data were obtained using a Rudolph Automatic Recording Spectropolarimeter, Model No. 260/655/850/810-614, Rudolph Instruments Engineering Co., Little Falls, New Jersey.

The technique used in all cases studied in this work consisted of measurement of the optical rotatory dispersion, using a one-decimeter polarimeter tube with fused silica endplates and a monochromator slit width of 0.50 mm. Measurements with the one-decimeter tube were carried into the ultraviolet until absorption of available light made further measurement impossible. At this point, or at slightly longer wave-lengths, a 0.1 decimeter polarimeter tube was substituted and measurement was continued.

Although the polarimeter contains a quartz reference, it was found that with a monochromator slit width of 0.50 mm. use of the quartz reference was unnecessary.

**Methyl β-celllobioside and methyl β-celllobioside heptaacetate**

Using samples of these two compounds provided by Dr. S. Haq, the rotatory dispersion of methyl β-celllobioside in water (g 3) was measured between 280 and 650 m\(\mu\) (curve B, Figure 2). The rotatory dispersion of methyl β-celllobioside heptaacetate in chloroform (g 4) between 250 and 650 m\(\mu\) was also measured (curve A, Figure 2). Table 4 contains the data from these compounds.
Fig. 2.—Optical rotatory dispersion of (A) methyl β-cellobioside heptaacetate in chloroform (c 4) and (B) methyl β-cellobioside in water (c 3).

Fig. 3.—A plot of $[\alpha]_\lambda^2$ as a function of $[\alpha]$ of (A) methyl β-cellobioside heptaacetate and (B) methyl β-cellobioside.
### TABLE 4

**METHYL β-CELLOBIOSIDES**

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Imferon and dextran isolated from Imferon

A sample of Imferon, the iron-dextran complex manufactured by Benger Laboratories Limited, Holmes Chapel, Cheshire, England, was diluted 25:1 (v/v) with water and the rotatory dispersion was measured in a 0.1 decimeter cell at 0, 24, 48, and 72 hours. There was no appreciable difference in the values over this time range. Because of the color and corresponding intense light absorption, it was possible to measure the rotatory dispersion of Imferon only from 525 to 700 μm. The rotatory dispersion curve, calculated on the basis of dextran present, can be seen in Figure 4 (curve A). A qualitative check run to 350 μm with a 0.01 decimeter tube indicated a normal dispersion pattern.

In order to isolate the dextran present to measure its rotatory dispersion, a 5-ml. vial of Imferon was diluted to 1000 ml. and refluxed for 20 hours. The solution was filtered and the residue washed with a further 100-150 ml. of warm water. The filtrate was taken to dryness under reduced pressure (12-15 mm. Hg) at a bath temperature of 50-55°C. The dry residue was extracted with 50 ml. of warm water, carbon (Darco G-60) added, and filtered. Dilution (by further washing of the residue) to 100 ml. yielded the solution used to determine the optical rotatory dispersion of the isolated dextran (curve B, Figure 4). In this instance the quartz reference was used.

Dextran concentration was established by pipetting 3 x 10 ml. of the solution of isolated dextran into pre-ignited, pre-weighed crucibles. The crucibles were dried to a constant weight in an oven at 85°C. After igniting the crucibles to a constant weight the difference between the
Fig. 4.—The optical rotatory dispersion of dextran in Imferon (c 0.86, water) calculated on the basis of dextran present (A) and of dextran isolated from Imferon (c 1.01, water) (B).

Fig. 5.—(A) Ultraviolet absorption of tetra-β-acetyl-2-deoxy-aldehydo-D-arabino-hexose (10^{-2} M, abs. CHCl_3). (B) Optical rotatory dispersion of tetra-β-acetyl-2-deoxy-aldehydo-D-arabino-hexose (c 2, abs. CHCl_3).
TABLE 5
TETRA-O-ACETYL-2-DEOXY-ALDEHYDO-D-arabino-HEXOSE

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oven-dried and ignited material was assumed to be the amount of dextran in 30 ml. of the solution. This value was 0.303 g. (two determinations), giving a concentration of 1.02 g. dextran per 100 ml. of solution.

The value for the specific rotation of the isolated dextran at the sodium D line determined by the recording spectropolarimeter and on a manual polarimeter differed by only 3°, an experimental error of about 2%.

Tetra-O-acetyl-2-deoxy-aldehyde-D-arabino-hexose

The preparation of this compound was carried out using the method of Barclay, Cleaver, Foster, and Stacey (51). The physical constants (melting point and specific rotation) of the first preparation failed to agree with those reported in the original article.

The work was repeated dissolving 1.36 g. of tetra-O-acetyl-2-deoxy-D-arabino-hexose diethyl dithioacetal in 10 ml. of acetone and 4 ml. of water in which was suspended 7 g. of neutral, finely-ground cadmium carbonate. After the addition of 6 g. of mercuric chloride in 8 ml. of acetone, the slurry was shaken for 24 hours with several further additions of fine cadmium carbonate. After filtering this solution into a flask containing a small amount of fine, neutral cadmium carbonate, it was taken to dryness under reduced pressure. The
residue was extracted with 100 ml. of warm chloroform and this was washed twice with 100 ml. of water, once with 50 ml. of 5% aqueous potassium iodide, and again with water. After drying the chloroform solution over anhydrous sodium sulfate, the chloroform was removed under reduced pressure and the product crystallized from ether-acetone-petroleum ether (b.p. 30-60°). After two recrystallizations, 0.56 g. of crystalline material was recovered, m.p. 107-108° (uncorrected), $[\alpha]_D^{23} +13.5^\circ$ (c 2, abs. CHCl$_3$). Barclay, Cleaver, Foster, and Stacey indicated m.p. 100°, $[\alpha]_D + 23$ (c 1.5, CHCl$_3$).

Anal. Calcd. for C$_{14}$H$_{20}$O$_4$: C, 50.6%; H, 6.02%.
Found: C, 50.49%; H, 6.03%.

The optical rotatory dispersion and ultraviolet absorption measurements of this compound were carried out in absolute chloroform.

The ultraviolet absorption study used a Perkin-Elmer Model 202 Recording Spectrophotometer, manufactured by Instrument Division, Perkin-Elmer Corporation, Norwalk, Connecticut.

Table 5 contains both sets of data in tabular form and Figure 5 contains a graphical representation.

**Derivatives of keto-$D$-psicose tetraacetate**

1-Deoxy, 1-chloro, and 1-bromo-keto-$D$-psicose tetraacetate were prepared from 1-diazo-1-deoxy-keto-$D$-psicose tetraacetate according to the directions of Wolf from, Thompson, and Evans (52). 1-Iodo-keto-$D$-

Psicose tetraacetate was prepared from the 1-chloro derivative also using the procedure of Wolfrom, Thompson, and Evans.

Optical rotatory dispersion and ultraviolet absorption measurements were carried out in absolute chloroform and data are reported in Tables 6 and 7, respectively. Ultraviolet data were obtained using a Perkin-Elmer Model 202 Recording Spectropolarimeter.

The optical rotatory dispersion is graphically represented in Figure 6 and ultraviolet absorption in Figure 7.

An attempt to synthesize 1-fluoro-keto-D-psicose tetraacetate by dissolving 1 g. of 1-diazo-1-deoxy-keto-D-psicose tetraacetate in 30 g. of anhydrous diethyl ether, cooling it to 0°C, adding 4-5 ml. of anhydrous HF, and allowing it to stand overnight, failed to yield a crystalline product after removal of the residual ether and attempted crystallization from ether-petroleum ether or ethanol-water.

Synthesis of 1-diazo-1-deoxy-keto-D-psicose tetraacetate involves solution of 1 mole of tetra-O-acetyl-D-ribonol chloride in ether and in the cold, and addition of 2 moles of diazomethane in ether.

Phenylhydrazones, substituted phenylhydrazones, and some "anhydros"-phenylhydrazones

In the course of the structure determination of some olefinic derivatives of acetylated sugar phenylhydrazones (53) optical rotatory dispersion measurements were made on penta-O-acetyl-aldehyde-D-galactose
Fig. 6.—Optical rotatory dispersion of 1-deoxy-keto-\(\text{D}\)-psicose tetraacetate (A) in chloroform (c 2), 1-chloro-keto-\(\text{D}\)-psicose tetraacetate (B) in chloroform (c 1), 1-bromo-keto-\(\text{D}\)-psicose tetraacetate (C) in chloroform (c 2), and 1-iodo-keto-\(\text{D}\)-psicose tetraacetate (D) in chloroform (c 2).
Fig. 7.—Ultraviolet absorption spectra in chloroform of 1-deoxy-keto-D-psicose tetraacetate (A), 1-chloro-keto-D-psicose tetraacetate (B), 1-bromo-keto-D-psicose tetraacetate (C), and 1-iodo-keto-D-psicose tetraacetate (D).

Fig. 8.—A plot at $[\alpha]_2^\lambda$ as a function of $[\alpha]$ of 1-deoxy-keto-D-psicose tetraacetate (A) in chloroform (c 2), 1-chloro-keto-D-psicose tetraacetate (B) in chloroform (c 1), 1-bromo-keto-D-psicose tetraacetate (C) in chloroform (c 2), and 1-iodo-keto-D-psicose tetraacetate (D) in chloroform (c 2).
TABLE 6
OPTICAL ROTATORY DISPERSION OF C-1 DERIVATIVES
OF keto-\(\beta\)-PSICOSE TETRAACETATE IN ABSOLUTE CHCl\(_3\)

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**TABLE 7**

**DERIVATIVES OF keto-\(\text{D}\)-PSICOSE TETRAACETATE**

**IN ABSOLUTE CHCl\(_3\)**

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<td>24.2</td>
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<td>18.3</td>
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<td>300</td>
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<td>17</td>
<td>10</td>
<td>40</td>
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<td>330</td>
<td>9</td>
<td>8</td>
<td>23.6</td>
<td>175</td>
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* Center of absorption
phenylhydrazone, \( \text{penta-O-acetyl-aldehyde-D-galactose p-nitrophenyl hydrazone} \), \( \text{penta-O-acetyl-aldehyde-D-mannose p-nitrophenyl hydrazone} \), \( \text{D-lyxo-3,4,5,6-tetraacetoxy-1-phenylazo-trans-1-hexene} \), \( \text{D-glucose \( \alpha \)-phenylhydrazone pentaacetate} \), (see Figure 9), \( \text{D-arabino-3,4,5,6-tetraacetoxy-1-phenylazo-trans-1-hexene} \), and \( \text{D-arabino-3,4,5,6-tetraacetoxy-1-(p-bromophenyl)azo-trans-1-hexene} \), (see Figure 10). The solvent used in all cases was acetonitrile. The color and corresponding high ultraviolet absorption made it difficult to penetrate the region below 400 nm.

Ultraviolet absorption spectra were measured in 95% ethanol on a Beckman DU spectrophotometer. Table 8 gives the location of ultraviolet absorption maxima and the intensity of these maxima.
Fig. 9.—Optical rotatory dispersion of penta-0-acetyl-aldehydo-
D-galactose phenylhydrazone (A) in acetonitrile solution (c 1.0),
penta-0-acetyl-aldehydo-D-galactose p-nitrophenylhydrazone (B) in
acetonitrile solution (c 1.0), penta-0-acetyl-aldehydo-D-mannose
p-nitrophenylhydrazone (C) in acetonitrile solution (c 1.0), D-lyxo-
3,4,5,6-tetraacetoxy-1-phenylazo-trans-1-hexene (D) in acetonitrile
solution (c 0.5), and D-glucose "α"-phenylhydrazone pentaaceta
te (E) in acetonitrile solution (c 1.0).

Fig. 10.—Optical rotatory dispersion of D-arabino-3,4,5,6-
tetraacetoxy-1-phenylazo-trans-1-hexene (lower curve) in acetonitrile
solution (c 0.5) and D-arabino-3,4,5,6-tetraacetoxy-1-(p-bromophenyl)azo-trans-1-hexene (upper curve) in acetonitrile solution (c 0.5).
TABLE 8

ULTRAVIOLET ABSORPTION OF PHENYLHYDRAZONES IN 95% ETHANOL

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<tr>
<th>Compound</th>
<th>$\lambda_{\text{max}}$ (nm)</th>
<th>$\epsilon$</th>
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<tr>
<td>Penta-O-acetyl-aldehydo-D-galactose phenylhydrazone</td>
<td>280</td>
<td>$1.82 \times 10^4$</td>
</tr>
<tr>
<td></td>
<td>305 (shoulder)</td>
<td>$1.14 \times 10^4$</td>
</tr>
<tr>
<td></td>
<td>373</td>
<td>$3.4 \times 10^2$</td>
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<tr>
<td></td>
<td>550</td>
<td>$2.3 \times 10^2$</td>
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<tr>
<td>Penta-O-acetyl-aldehydo-D-galactose p-nitrophenyl-hydrazone</td>
<td>375</td>
<td>$2.34 \times 10^4$</td>
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<tr>
<td></td>
<td>550</td>
<td>$2.66 \times 10^2$</td>
</tr>
<tr>
<td>Penta-O-acetyl-aldehydo-D-mannose p-nitrophenyl-hydrazone</td>
<td>370 (shoulder)</td>
<td>$1.1 \times 10^3$</td>
</tr>
<tr>
<td></td>
<td>540</td>
<td>$1.66 \times 10^2$</td>
</tr>
<tr>
<td>D-Glucose &quot;a&quot;-phenylhydrazone pentaacetate</td>
<td>280</td>
<td>$1 \times 10^3$</td>
</tr>
<tr>
<td>D-Lyxo-3,4,5,6-Tetraacetoxy-1-phenylazo-trans-1-hexene</td>
<td>303</td>
<td>$2.28 \times 10^4$</td>
</tr>
<tr>
<td>D-arabino-3,4,5,6-Tetraacetoxy-1-phenylazo-trans-1-hexene</td>
<td>303</td>
<td>$2.42 \times 10^4$</td>
</tr>
<tr>
<td>D-arabino-3,4,5,6-Tetraacetoxy-1(p-bromophenyl)azo-trans-1-hexene</td>
<td>312</td>
<td>$3.38 \times 10^4$</td>
</tr>
</tbody>
</table>
DISCUSSION OF RESULTS

Methyl β-cellobioside and methyl
β-cellobioside heptaacetate

The optical rotatory dispersion patterns demonstrated by methyl
β-cellobioside and methyl β-cellobioside heptaacetate are shown in
Figure 2. It can be readily discerned that no Cotton effect occurs
in the wave-length region studied.

Figure 3 shows a plot of \([\alpha]\lambda^2\) as a function of \([\alpha]\) for each of
the two compounds. Methyl β-cellobioside heptaacetate conforms to a
straight line relationship indicating that it obeys a one-term Drude
equation in the observed portion of the rotatory dispersion curve.
The value of \(\lambda_0\) for methyl β-cellobioside heptaacetate, calculated
from the shape of this line is 196 m\(\mu\). This value is at the upper
limit of the values for acetates quoted by Sørenson and Trumpy (33).

Methyl β-cellobioside obeys a one-term Drude relationship. The
best straight line indicates an approximate \(\lambda_0\) of 182 m\(\mu\). This value
is somewhat higher (10 m\(\mu\)) than the highest \(\lambda_0\) value of simple
glycosides quoted by Sørenson and Trumpy (33).

Imferon and its dextran

Inspection of Figure 4 indicates that the presence of the ferric
iron in the dextran solution does definitely enhance the rotation of
the dextran. This is indicative of some type of bonding or true
complexing between the ferric iron and the dextran. This could be
comparable to the heightened rotations observed in carbohydrates when borate is added.

It is unfortunate that measurements were limited to the use of the 0.1 dm. tube in studying the Imferon. With tube lengths of this type there can be little confidence in a Biot-Lowry plot. Assuming that a one-term Drude relationship is obeyed and using values from Figure 4 at 600 and 525 mp, a $\lambda_0$ value of 283 mp is obtained. Applying the same procedure to the isolated dextran, from values at 600 and 525 mp, a $\lambda_0$ value of 134 mp is derived. Although this could be coincidental, Neely (36) quotes values for amylose and amyllopectin (Table 3) between 132 and 135 mp.

**Tetra-0-acetyl-2-deoxy-aldehydo-D-arabinohexose**

The optical rotatory dispersion behavior of tetra-0-acetyl-2-deoxy-aldehydo-D-arabinohexose (I) is such that a complex Cotton effect is observed. This of course is due to absorption by the aldehydic carbonyl function. Absorption by the solvent (chloroform) prevents worthwhile measurements at wave-lengths below 250 mp.

The center of the optically active absorption band falls at 305 mp while the center of the ultraviolet absorption band is at 296 mp. This 9 mp shift to longer wave-lengths for the center of the optically active band is greater (4 mp) than that observed for the corresponding D-glucose derivative (43). A means of explanation is that substitution of a hydrogen at carbon two for the $-\text{OCOCH}_3$ group was responsible.

The shape of the rotatory dispersion curve for the 2-deoxy compound
also deserves attention. Normally when such a curve intersects the zero axis it is assumed that this is the effect of an absorption band in the near vicinity. Here tetra-α-acetyl-2-deoxy-aldehyde-D-arabinohexose demonstrates an intersection at 370 μ which is 75 μ above the observed ultraviolet absorption maximum. This fact alone makes it evident that the rotatory dispersion is not obeying a simple Drude relationship. In addition there is a great difference in the amplitude of the maximum and minimum.

Providing there is no difference in conformation of the remainder of the molecule of tetra-α-acetyl-2-deoxy-aldehyde-D-arabinohexose and penta-α-acetyl-aldehyde-D-glucose, the difference in molecular rotation, [M], should show the contribution of the asymmetric center at carbon two. The resultant curve of the difference is a negative Cotton effect curve with [M]_D^0 = -66°. The minimum occurs at 310 μ with [M] of -1560°. The crossover point, λ_o, occurs at 284 μ, with the maximum occurring at 270 μ; [M] = +1200-1300°. It should be emphasized that these values are but an approximation using data from Table 5 and from Hudson, Wolfson, and Lowry (43).

The optical rotatory dispersion behavior of tetra-α-acetyl-2-deoxy-aldehyde-D-arabinohexose does seem to resemble the behavior of penta-α-acetyl-aldehyde-D-glucose, and although the elimination of asymmetry at carbon two removed a part of the induced dissymmetry, it is evident that the observed Cotton effect curve must arise from dissymmetry induced in the carbonyl chromophore by centers other than carbon two.
keto-D-Psicose tetraacetate series

Djerassi and co-workers (54,55) have reported the effect on the

\[ \text{CH}_2X \]

\[ \text{C}=\text{O} \]

rotatory dispersion of steroidal ketones of placing a halogen atom in a position alpha to the carbonyl group. The resultant effect led Djerassi to formulate what is called the "axial haloketone rule."

However, in substituting the halogen atom in the steroidal ketones a center of asymmetry was generated by the act of substitution.

More recently Djerassi, Wolf, and Bunn inberg (56) have measured

\[ \text{CH}_2X \]

\[ \text{C}=\text{O} \]

the optical rotatory dispersion, ultraviolet absorption, and circular dichroism of steroidal \( \alpha \)-bromo and \( \alpha \)-iodo-ketones in which the halogen atom was not adjacent to an asymmetric center.

The effect of such substitution in the series 1-deoxy (IVa), 1-chloro (IVb), 1-bromo (IVc), and 1-iodo-keto-D-psicose tetraacetate (IVd) was investigated in this study.
Ultraviolet absorption studies on this series show that the maximum for the 1-deoxy derivative falls 10 m\(\mu\) higher than observed in \textit{keto-}D-fructose pentaacetate (44). The maximum for the 1-chloro derivative is shifted to a shorter wave-length (285 m\(\mu\)). The absorption maximum for the 1-bromo compound is shifted to a longer wave-length (297 m\(\mu\)) while the 1-iodo derivative is shifted to a lower wave-length (287 m\(\mu\)) than 1-deoxy-\textit{keto-}D-psicose tetraacetate.

The intensity of the ultraviolet absorption maxima also fails to follow a definite pattern with the intensity of the 1-chloro derivative being less than that of the 1-deoxy compound. However, the intensity of the 1-bromo and 1-iodo maxima increase in order, with the observed intensity of the 1-iodo compound being ten times greater than that of 1-deoxy-\textit{keto-}D-psicose tetraacetate.

The intensity of the maximum for 1-iodo-\textit{keto-}D-psicose tetraacetate is not unwarranted. Its location is unusual since Djerassi (56) indicates that in steroidal iodo ketones the absorption maximum near 290 m\(\mu\) is masked by a more intense absorption maximum occurring at about 258 m\(\mu\). Figure 7 indicates that there is little indication of such a maximum occurring in 1-iodo-\textit{keto-}D-psicose tetraacetate. Since chloroform was
the solvent used to measure ultraviolet absorption in the keto-D-psicose tetraacetates, it is possible that any maximum occurring at 258 μ was obscured by absorption by the solvent. The intense absorption by l-iodo-keto-D-psicose tetraacetate prevented measurement of its rotatory dispersion below 330 μ.

The results of the optical rotatory dispersion measurements can be summarized very readily. The 1-deoxy, 1-chloro and 1-bromo-keto-D-psicose tetraacetates all exhibited negative Cotton effect curves that intersected the zero axis at the same point (283 μ). The minima observed in these three cases diminished in the order named. The maxima and minima observed in the case of 1-deoxy and 1-bromo-keto-D-psicose tetraacetate were nearly symmetrical with the 1-chloro compound demonstrating near symmetry.

l-Iodo-keto-D-psicose tetraacetate differed in that in the region observed it demonstrated a positive maxima with an intersection at the zero axis at a wave-length 50 μ longer than that observed in the other members of this series.

It is possible that the rotatory dispersion data could be used to calculate the angle between the \( \mathrm{C=O} \) and the \( \mathrm{-C-X} \) bond as suggested by Djerassi, but since this work has been limited to steroids, more data should be collected on the acyclic series before such calculations are made.

A plot of \([\alpha] \lambda^2\) as a function of \([\alpha]\) for this series provides some interesting facts. The rotatory dispersion data for each of the compounds obeys a straight line relationship outside the area where anomalies are exhibited. After choosing two points that fall on this
line, the values of $\lambda_0$ were calculated. For 1-deoxy, 1-chloro, and 1-bromo-keto-D-psicose tetraacetate these values were close, being between 296 and 304 $\mu\text{m}$. This fails to agree with the observed $\lambda_0$ value of 283 $\mu\text{m}$.

1-Iodo-keto-D-psicose tetraacetate also follows a straight line relationship with a calculated $\lambda_0$ value of 342 $\mu\text{m}$. This is remarkably close to the point at which the observed intersection of the zero axis occurred and leads to some speculation about the observed $\lambda_0$. Although there was no ultraviolet absorption maximum observed at this point, there is a possibility of an optically active center in this area. If the results for 1-iodo-keto-D-psicose tetraacetate are real, it means that the absorbing center is masked by another center or centers and that the optically active center is shifted to longer wave-lengths than observed in steroidal iodo ketones (56).

**Phenylhydrazones and phenylhydrazone derivatives**

Ultraviolet absorption data in Table 8 indicate that all of the compounds listed have ultraviolet absorption maxima within the wave-length range accessible to the Rudolph recording spectropolarimeter. The only difficulty lies in the fact that the absorption bands are all of sufficient intensity as to make rotatory dispersion measurements into them almost impossible. Nonetheless, it was possible using short cell lengths and medium concentrations to approach some of these absorption bands.

The ultraviolet absorption maxima in the instance of penta-$\alpha$-acetyl-aldehyde-D-galactose $p$-nitrophenylhydrazone and
penta-O-acetyl-aldehydo-D-mannose p-nitrophenylhydrazone are somewhat similar to each other and also similar to the instance of p-phenylazophenyl \( \beta \)-D-glycosides studied by Zelinski and Bonner (40). They found an ultraviolet absorption maximum at 338 \( \mu \) (\( \epsilon = 24,000 \)) and another at 436 \( \mu \) (\( \epsilon = 890 \)). In the p-nitrophenylhydrazones the absorption maxima are shifted to longer wave-lengths, but the intensities of the maxima are of the same order. The ultraviolet absorption maxima of the trans-l-hexene derivatives coincide very closely.

The rotatory dispersion measurements indicate that penta-O-acetyl-aldehydo-D-galactose phenylhydrazone and p-nitrophenylhydrazone each demonstrate a positive maximum. This is opposite to the directing influence demonstrated by the D-galactose configuration in aldehydo-\( \beta \)-galactose pentaacetate (43). Why the change in chromophore should bring about such a drastic change is difficult to comprehend.

It appears that the absorption band governing the optical activity in penta-O-acetyl-aldehydo-D-galactose phenylhydrazone is the maximum occurring at 305 \( \mu \) while in the p-nitrophenylhydrazones the 375 \( \mu \) center seems to control the optical activity.

The penta-O-acetyl-aldehydo-D-mannose p-nitrophenylhydrazone demonstrates a simple curve over the region studied and analysis by a Biot-Lowry plot indicates a value for \( \lambda_0 \) of 363 \( \mu \). This is close enough to the ultraviolet maximum at 370 \( \mu \) to assume that this band is controlling the optical activity.

The D-lyxo-3,4,5,6-tetraacetoxy-1-phenylazo-trans-l-hexene (V) also yields a simple curve in the range observed. A Biot-Lowry plot
yields a $\lambda_0$ value of 312 m$\mu$ close to the observed ultraviolet maximum of 303 m$\mu$.

The positive curves demonstrating a maximum in the range observed might be expected in the cases of D-arabino-3,4,5,6-tetraacetoxy-l-phenylazo-trans-l-hexene (VI) and the l-(p-bromophenyl)azo-trans-l-hexene derivative since aldehyde-D-arabinose tetraacetate would give a positive Cotton effect curve. However, the fact that these compounds intersect the zero line a good distance from the observed ultraviolet absorption maximum is puzzling. This at least indicates that in measurement of optical rotatory dispersion theoretical considerations are not always obeyed to the letter.

D-Glucose "a"-phenylhydrazone gives a simple appearing rotatory dispersion curve, but analysis with a Biot-Lowry plot fails to yield a straight line indicating that a simple Drude relationship is not obeyed.
SUMMARY

Analysis of the optical rotatory dispersion of methyl β-cellobioside and methyl β-cellobioside heptaacetate, using the Moffitt technique (30), indicates that both of these compounds follow a one-term Drude relationship. Introduction of the acetate radical causes a shift of the calculated optically active center of absorption to a longer wave-length.

The increased rotatory power of a ferric iron-dextran complex over the isolated dextran was taken to be a sign of chemical combination present in the complex. The isolated dextran demonstrated a calculated \( \lambda_0 \) close to that reported by Neely (36) for amylose.

Elimination of an optically active center at C-2 of an aldehydohexose, as in tetra-O-acetyl-2-deoxy-aldehydo-D-arabino-hexose, does not completely eliminate induced asymmetry (43) in this compound as evidenced by the complex optical rotatory dispersion observed.

1-Deoxy, 1-chloro, and 1-bromo-keto-D-psicose tetraacetate provide a family of negative Cotton effect curves yielding identical observed centers of optical activity. Outside the region of absorption these compounds follow a one-term Drude relationship with the calculated centers of absorption occurring at a longer wave-length than the observed centers. 1-Iodo-keto-D-psicose tetraacetate fails to fit the pattern demonstrated by the other members of the series. This compound has an apparent positive, complex rotatory dispersion curve with an observed center of optical activity at a considerably longer wave-length.
than the other members of the series. Outside its region of absorption the 1-iodo compound follows a one-term Drude relationship with the calculated center of optical activity close to the observed.

The optical rotatory dispersion measurements of the phenylhydrazone derivatives fail to indicate any consistent rotatory dispersion behavior.
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ADDENDUM
The Reaction of Tetra-\(\beta\)-acetyl-\(\beta\)-ribonyl Chloride

with Two Sodio \(\beta\)-Keto Esters

The preparation of 1-diazo-1-deoxy-\(\beta\)-keto-\(\beta\)-psicose tetraacetate (52) was discussed in another place in this work. In a somewhat similar reaction tetra-\(\beta\)-acetyl-\(\beta\)-ribonyl chloride (from 12.2 g. of tetra-\(\beta\)-acetyl-\(\beta\)-ribonic acid) was dissolved in 350 ml. of anhydrous ether, and 25 g. of sodio diethyl oxalacetate was suspended in the solution and stirred overnight. The ether solution was then filtered, washed several times with water, and dried over anhydrous sodium sulfate. Most of the ether was removed under reduced pressure and petroleum ether added. A yield of 9.4 g. of crude crystalline material was recovered, which, after recrystallization, showed m.p. 77-77.5\(^\circ\) (uncorrected), \([\alpha]_D^{24} = -3^\circ\) (c 2.32, CHCl\(_3\)). Molecular weight determination using the method of Childs (57) gives a value of 542; the calculated value is 504.


Anal. Calcd. for C\(_{21}\)H\(_{28}\)O\(_4\): C, 50.00\%; H, 5.55\%.

Found: C, 50.06\%; H, 5.73\%.

The resulting product (I), diethyl (tetra-\(\beta\)-acetyl-\(\beta\)-ribonyl)oxalacetate, (0.5 g.) yielded 0.23 g. of a finely crystalline 2,4-dinitrophenylhydrazone, m.p. 147-148\(^\circ\) (uncorrected).

Anal. Calcd. for C\(_{33}\)H\(_{36}\)O\(_{20}\)N\(_8\): C, 45.83\%; H, 4.16\%; N, 13.0\%.

Found: C, 45.94\%; H, 4.06\%; N, 15.42\%.

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Attempted deacetylation of the condensation product in methanol with a catalytic amount of sodium methoxide caused the solution to take on a dark color indicating that decomposition was occurring. Neutralization with Amberlite IR 120 ($\text{H}^+$), removal of methanol under reduced pressure and consequent treatment with ethyl acetate failed to yield a crystalline product.

Attempted decarbonylation with powdered soft glass at 4 mm. Hg and 200° for 8 hours merely lowered the melting point a very small amount.

At this time Reist, Hart, Baker, and Goodman (58) reported the


synthesis of 1-deoxy-keto-$\text{D}$-psicose tetraacetate by condensation of tetra-$\text{O}$-acetyl-$\text{D}$-ribonyl chloride with dibenzylmalonate, hydrogenation, and decarboxylation. With diethyl malonate and tetra-$\text{O}$-acetyl-$\text{D}$-arabonyl chloride they recovered the expected product but could not remove the ethyl groups by base hydrolysis because of extreme sensitivity to base. In an attempt to circumvent the sensitivity of diethyl (tetra-$\text{O}$-acetyl-$\text{D}$-ribonyl)oxalacetate toward base, 6 g. of tetra-$\text{O}$-acetyl-$\text{D}$-ribonyl chloride in 150 ml. of anhydrous ether was treated with 8.2 g. of soda ethyl ethoxalylpropionate (59) and stirred overnight. After


filtration of the ether solution, several washings with water and drying
with anhydrous sodium sulfate, the ether was removed under reduced pressure. Attempted crystallization of the resulting sirup from ether-petroleum ether at 10° for several months yielded no product other than a sirup. The ether-petroleum ether was finally removed and the sirup taken up in a small amount of 95% ethanol. After several days at room temperature a small crystal had formed and the solution was then placed in the refrigerator for several more days. Approximately 2.5 g. of crystalline material (II) was then recovered; m.p. 80-85°. After three recrystallizations from 95% ethanol and drying over P₂O₅ at 3 mm. Hg, there was found m.p. 88-89° (uncorr.), [α]D²⁵ +2.8° (c 2; CHCl₃).

**Anal.** Calcd. for C₂₂H₃₀O₁₄: C, 50.97%; H, 5.97%.

Found: C, 51.08%; H, 5.69%.

Deacetylation of this compound (diethyl methyl(tetra-O-acetyl-D-ribosyl)oxalacetate) in methanol using catalytic amounts of sodium methoxide at 10°, neutralization with Amberlite 120 (H⁺), and removal of the methanol under reduced pressure yielded a green-yellow sirup which failed to crystallize from ethyl acetate.
AUTOBIOGRAPHY

I, Neal E. Franks, was born in Canton, Ohio, on July 24, 1936. My secondary school education was obtained in the Marlboro Township Schools, Stark County, Ohio. Manchester College, North Manchester, Indiana, granted me the Bachelor of Arts degree in chemistry in 1958. My graduate work began the same year in the chemistry department of The Ohio State University. Shortly after beginning graduate work I married Betty Royer, a former Manchester College classmate. From 1958 to 1960 I served as a teaching assistant in this department. From 1960 to the completion of this work I have been fortunate enough to hold a Research Foundation Fellowship.

I have accepted a position with American Enka Corporation, Enka, North Carolina.