

Synthetic Methods for Carbohydrates

The colophon on the book cover is a simplified representation of a reaction process involving a blocking group indicated as a chord of the upper circle.

Synthetic Methods for Carbohydrates

Hassan S. El Khadem, EDITOR
Michigan Technological University

A symposium sponsored
by the Division of
Carbohydrate Chemistry
at the Centennial Meeting
of the American Chemical
Society, New York, N. Y.,
April 5–6, 1976.

A C S S Y M P O S I U M S E R I E S

39

AMERICAN CHEMICAL SOCIETY
WASHINGTON, D. C. 1976



Library of Congress CIP Data

Synthetic methods for carbohydrates.
(ACS symposium series; 39 ISSN 0097-6156)

Includes bibliographical references and index.

1. Carbohydrates—Congresses. 2. Organoboron compounds—Congresses. 3. Chemistry, Organic—Synthesis—Congresses.

I. el Khadem, Hassan Saad, 1923- II. American Chemical Society. Division of Carbohydrate Chemistry. III. Series: American Chemical Society. ACS Symposium series: 39.

QD320.S93 547'.78 76-58888
ISBN 0-8412-0365-2

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American Chemical Society

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PRINTED IN THE UNITED STATES OF AMERICA

American Chemical
Society Library
1155 16th St. N. W.

Washington, D. C. 20036

In Synthetic Methods for Carbohydrates, El Khadem, H.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1977.

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FOREWORD

The ACS SYMPOSIUM SERIES was founded in 1974 to provide a medium for publishing symposia quickly in book form. The format of the SERIES parallels that of the continuing ADVANCES IN CHEMISTRY SERIES except that in order to save time the papers are not typeset but are reproduced as they are submitted by the authors in camera-ready form. As a further means of saving time, the papers are not edited or reviewed except by the symposium chairman, who becomes editor of the book. Papers published in the ACS SYMPOSIUM SERIES are original contributions not published elsewhere in whole or major part and include reports of research as well as reviews since symposia may embrace both types of presentation.

PREFACE

The symposium on new synthetic methods was organized by the Carbohydrate Division of the American Chemical Society to commemorate the 100th anniversary of the society. Chemists from the USA and six other countries presented 16 papers during three sessions of the symposium. The invited speakers were all involved in elaborate synthetic work or had developed new and innovative techniques. They were either established authorities in the field or younger chemists who had recently produced significant developments worth reporting on such a solemn occasion.

Successful syntheses in the field of carbohydrates usually require a desired change to occur in a chosen site of the polyfunctional sugar molecule. This naturally necessitates extensive use of selective blocking groups, and it is not surprising that two of the chapters in this text are devoted to the study of the applications of new blocking groups. In the course of the rapid development of the chemistry of natural products, certain striking similarities became apparent between carbohydrate molecules and their corresponding homocyclic or heterocyclic analogs. This led to a closer interaction between natural product chemists and carbohydrate chemists. A conceptual treatment of the synthetic reactions used by both groups and a close study of the relationship between these carbohydrate molecules and their non-carbohydrate analogs was highly desirable at this time.

Stereochemistry has always played an important role in carbohydrate chemistry and is an ever present concern to the synthetic chemist. With the advent of readily accessible ORD and CD instruments, greater use has been made of the correlations between optical properties and the configuration and conformation of the products of synthesis to develop stereospecific isomerization that could lead to desired products. Other chapters in the present text deal with the synthetic application of reactive starting materials such as glycols, and others review the methods available for the preparation of biologically important derivatives such as thio sugars and heterocyclic compounds.

The significance of this book is that it is authored by a large number of prestigious chemists and active younger ones; it is contemporary and, judging from the attendance of the symposium, deals with topics that are both interesting and current.

Houghton, Michigan
December 1976

HASSAN S. EL KHADEM

Applications of Ethylboron Compounds in Carbohydrate Chemistry

R. KÖSTER and W. V. DAHLHOFF

Max-Planck-Institut für Kohlenforschung, Mülheim-Ruhr, Germany

The fundamental work of Böeseken (1) in the first half of this century showed that the element boron has different affinities towards the various polyhydroxy compounds. The early investigations demonstrated the stereospecificity of the various polyols and saccharides towards boric acid. One analytical application that developed from this work was the quantitative determination of boron based on the interaction of boric acid with certain hydroxy compounds. However, it is the preparative aspects that are of interest to carbohydrate chemists, and we will present here some of the uses of organoboron compounds in synthetic work and show the advantages they offer over conventional blocking groups.

The most important and well known application of organoboron compounds in sugar chemistry was, and is still, the use of the bifunctional *O*-phenylboranediyl ligand as a protective group. Some *O*-phenylboranediyl derivatives of monosaccharides have been described in the literature (2,3). They have been prepared from phenylboric acid, which is neither as easy to react nor as easy to remove as the *O*-ethylboron group. The products are often not volatile and cannot be purified by distillation. Usually crystallisation is used to purify the products, but this is often difficult to achieve.

In the past three years we have discovered new methods for the preparation of boron derivatives of hydroxy compounds and in particular *O*-ethylboron compounds. We were thus able to apply our 20 years of experience in the field of organoboranes to carbohydrate chemistry. The combination of two separate fields of research often brings about new impetus to the development of science. We believe that by combining our expertise in the field of sugars and

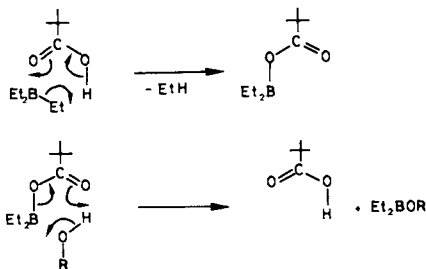


Figure 1. The catalytic cycle of the O-diethylborylation

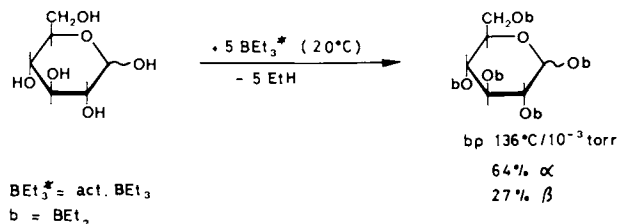


Figure 2. Per-O-diethylborylation of D-glucose

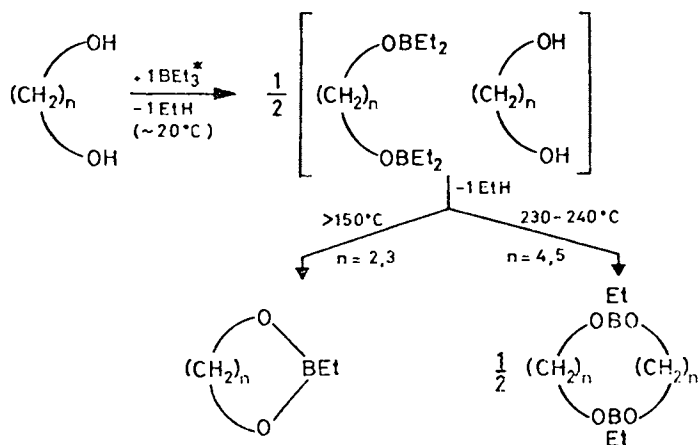


Figure 3. Formation of intra- and intermolecular O-ethylboranediyl compounds

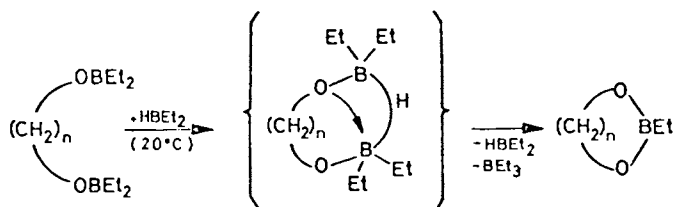


Figure 4. Ligand exchange in the presence of BH compounds

organoboranes we have contributed to the development of both.

This review includes some results we have obtained in our work on the preparation of O-ethylboron derivatives of polyhydroxy compounds. In addition to discussing the preparative routes and the properties of the new derivatives we will outline some possible applications of the new protective groups.

Some years ago we found that O-dialkylborylation of nearly all hydroxy groups took place with trialkylboranes in the presence of special new catalysts (4). The best promotor was a mixed anhydride of a carboxylic acid and a dialkylboric acid R_2BOCOR' . We also found that the diethylborylation of hydroxy groups could be achieved with, the easily obtainable, triethylborane (5) in the presence of small amounts of diethylborylpivalate $Et_2BOCOtBu$. The following two equations illustrate the proposed catalytic cycle of the O-diethylborylation.

Since each hydroxy-group of a polyol reacts with liberation of exactly one mole of ethane, we use this reaction as a simple analytical method for the determination of hydroxy groups (5). It could also be used as means of determining the purity of carbohydrates and their derivatives. D-Glucose, for example, reacts with activated triethylborane, at room temperature exothermically, with the evolution of exactly five moles of ethane (6) (see fig. 2). A mixture of about 64 % α -anomer and 27 % β -anomer of the pentakis-O-diethylboryl-D-glucopyranose is formed. The remaining 9 % is an α/β -D-glucofuranose mixture.

No difficulties are encountered in preparative per-O-diethylborylations. The per-O-diethylboryl derivatives of polyalcohols (7-12) and saccharides (6,13) have been prepared in nearly quantitative yield in all cases. The products are usually liquids which are miscible with hydrocarbons in all proportions. The per-O-diethylborylated monosaccharides and hexitols can be vacuum distilled without decomposition. The compounds are very water-sensitive and can therefore easily be deborylated with methanol or with acetylacetone at room temperature.

Beside the monofunctional O-diethylboryl group, we also have the bifunctional O-ethylboranediyl group. This group can be introduced into hydroxy compounds either directly or indirectly. The indirect method involves the per-O-diethylboryl derivatives as intermediates (fig. 3 and 4).

The O-ethylboranediyl derivatives are also obtained in high yields at room temperature in the presence of BH-boranes.

The direct method of O-ethylboranediylation works with a special reagent. Bis(ethylpivaloyloxy)-diboroxane (BEPDIB) [(EtBOCotBu)₂O] reacts at room temperature with hydroxy compounds to give the O-ethylboranediyl compounds (11-13). Water and pivalic acid are formed as sideproducts. One obtains pure isomer-free anomers from monosaccharides in excellent yield. The O-ethylboranediylgroup can link two intra- or intermolecular hydroxygroups (see fig. 5).

In the ¹H-n.m.r. spectra of the per-O-diethylborylated monosaccharides (14), the anomeric protons are well separated from the non-anomeric ring protons. The range for the anomeric protons is larger than that found for the trimethylsilyl analogous. This makes the per-O-diethylboryl derivatives suitable for structural identifications. The preparation of n.m.r. samples is extremely easy. A very small sample of the compound to be investigated is put into an n.m.r.-tube and activated triethylborane is added at room temperature. After measurement, the sugar can be regenerated quantitatively by simply adding methanol.

It is often possible to assign structures to the O-ethylboranediyl derivatives with the help of ¹¹B-n.m.r.- (15) and ¹³C-n.m.r.- (16) spectra. The five-membered 1,3,2-dioxaborolan-ring has a characteristic resonance signal at $\delta = +34.5$ ppm (relative to the external standard Et₂O-BF₃), whereas the ¹¹B-signal of the six- and higher membered OBO-rings lies at $\delta = +30.5$ ppm (see fig. 6) (8).

The next part of this review will deal with some specific hydroxy compounds.

The trihydroxyalkane glycerol (9) (see fig. 7) reacts with activated triethylborane at room temperature to give 3 moles of ethane and tris-O-diethylborylglycerol.

The latter compound on heating to 170° eliminates one mole of triethylborane to give quantitatively a glycerol derivative having one five membered O-ethylboranediyl-ring and one O-diethylborylgroup in the 1-position. The structure of this compound was determined with the help of the ¹¹B-n.m.r.-spectrum ($\delta = +34.4$ ppm and $\delta = +54.2$ ppm) and was verified by a study of its ¹³C-n.m.r.-spectrum (15), which showed three separate ¹³C-signals. Further, it could be selectively deborylated with methanol to give the 1,2-O-ethylboranediyl-glycerol, which was O-acylated in

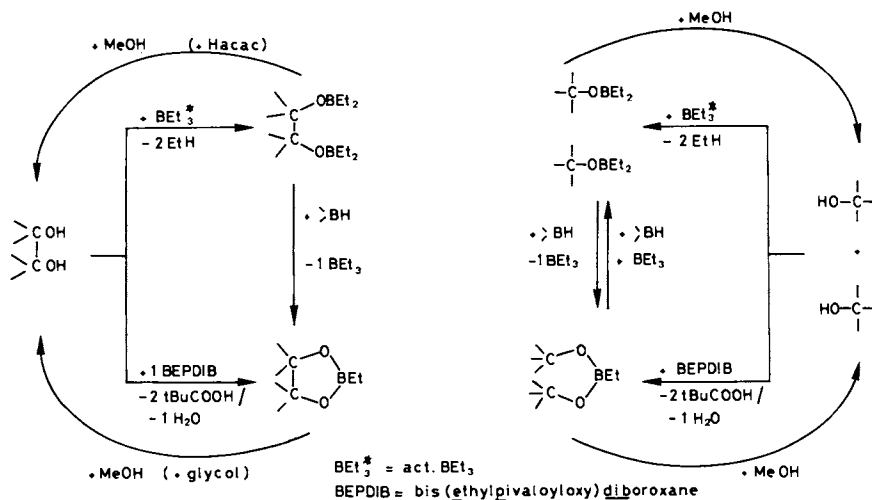


Figure 5. Formative and transformation of O-ethylboron protective groups

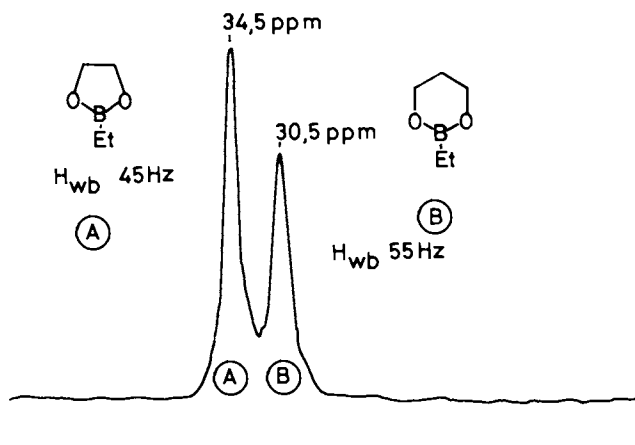


Figure 6. ^{11}B -nmr spectrum of an equimolar mixture of A and B in 2,2-dimethylbutane (standard: $\text{Et}_2\text{O}\text{-BF}_3$ with $\delta = 0 \text{ ppm}$; deshielding: $\delta > 0 \text{ ppm}$)

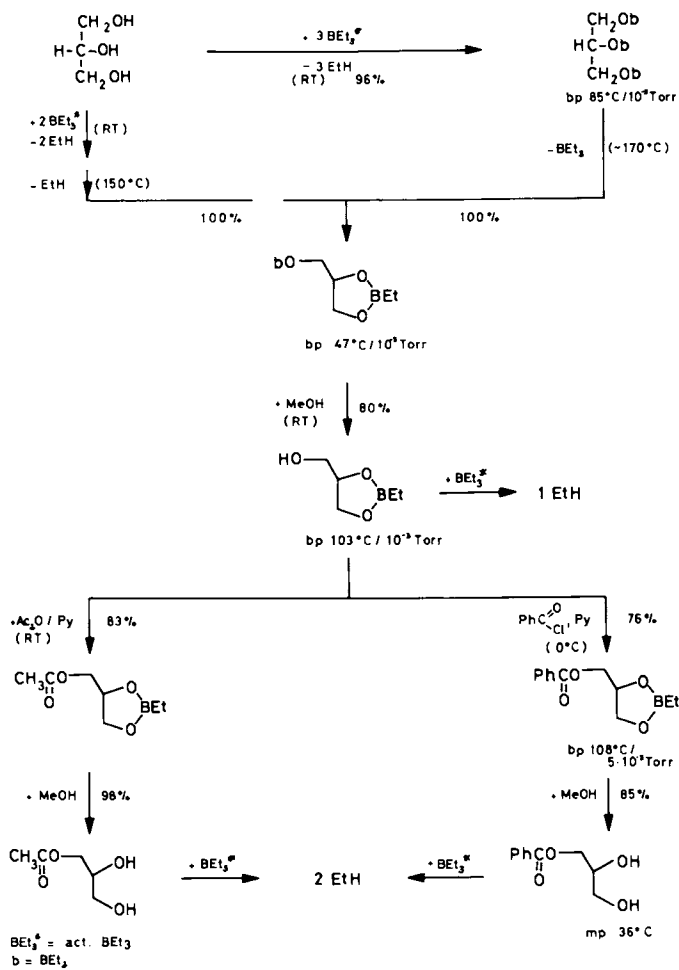


Figure 7. 1-O-Acyl-glycerols via ethylboron intermediates

the usual manner, then deborylated to give 1-O-acetyl- or 1-O-benzoylglycerol in high yields (see fig. 7).

The O-ethylboronation of butan-1,2,4-triol is the second example (17). This alkanetriol yielded on O-ethylboronation a gas chromatographically (17) pure, isomer-free compound in high yield which had one 2-ethyl-1,3,2-dioxaborinan-ring ($\delta = +31$ ppm) and one O-diethylborylgroup ($\delta = +54$ ppm). After selective deborylation with methanol, subsequent O-acetylation and finally total deborylation, pure 1-O-acetylbutane-1,2,4-triol was obtained (see fig. 8).

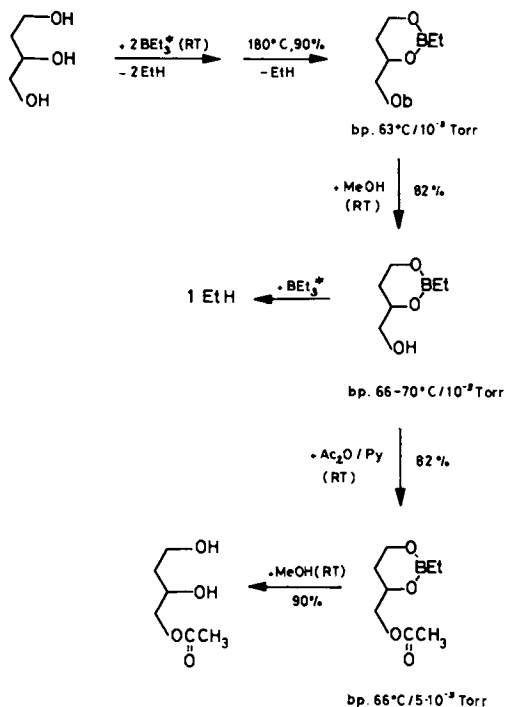
The behaviour of the alkanetetraols was similar, but specific for each compound. Meso erythritol formed a bis-O-ethylboranediyl derivative having two membered OBO-rings, whereas pentaerythritol yielded a compound with two six membered rings (see fig. 9).

Each polyhydroxy-compound seems to have its own stable O-ethylboron derivative. In fact, we found for example, that the three hexitols dulcitol, D-mannitol and D-sorbitol gave three different O-ethylboranediyl derivatives. Five routes were used to the mannitol derivative (see fig. 10).

Pentitols, such as xylitol and ribitol, reacted with BEPDIB, or via the per-O-diethylboryl, to give derivatives containing two O-ethylboranediyl rings. In the presence of an excess of BEPDIB dimeric pentitols with an intermolecular O-ethylboranediylgroup, were obtained.

An example of an O-ethylboranediyl derivative of a simple saccharide, which is incapable of isomerisation, is the 4,6-O-ethylboranediyl derivative of methyl α -D-glucopyranoside. This was prepared by two methods (see fig. 11).

In the first route, methyl α -D-glucopyranoside was per-O-diethylborylated with activated triethylborane. One mole triethylborane was then eliminated at room temperature in the presence of a catalytic amount of ethyldiborane. Finally, the two O-diethylboryl groups are removed with acetylacetone to yield the crystalline, vacuum distillable methyl 4,6-O-ethylboranediyl- α -D-glucopyranoside. The same compound was also prepared, in 99 % yield, by reacting two moles of the methyl α -D-glucopyranoside with one mole BEPDIB in the presence of pyridine at room temperature. Normal conditions for the O-acylations, followed by deborylations with methanol at room temperature, led to the known 2,3-di-O-acyl derivatives of methyl α -D-glucopyranoside (see Fig. 11).



$\text{BEt}_3^* = \text{act. BEt}_3$

$\text{b} = \text{BEt}_2$

Figure 8. 1-O-Acetylbutane-1,2,4-triol via o-ethylboron intermediates

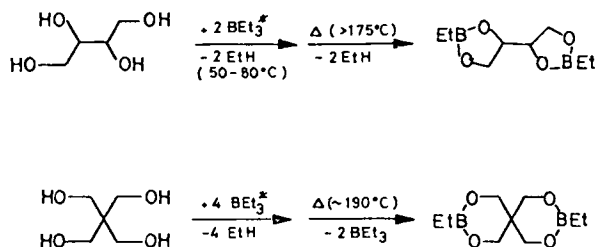


Figure 9. O-ethylboronediyl derivatives of mesoerythritol and pentaerythritol

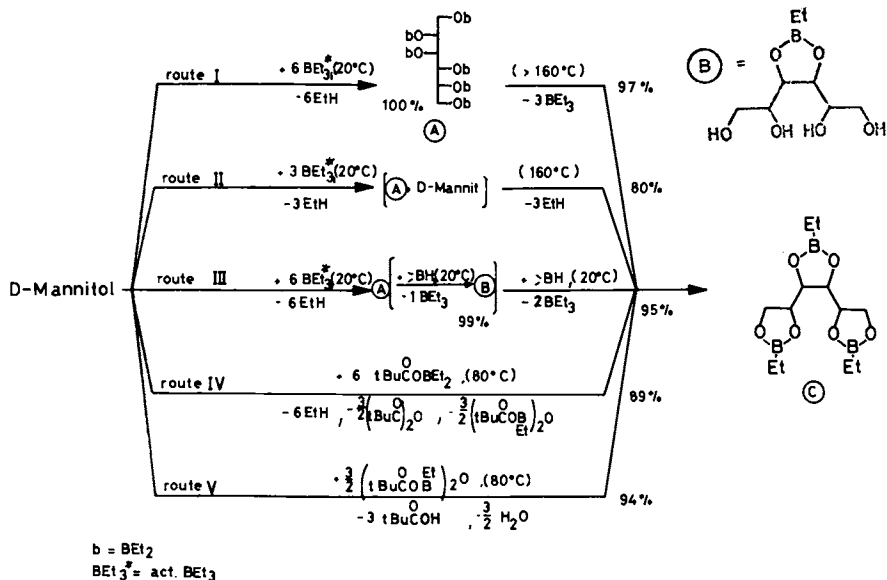


Figure 10. Five routes to prepare 1,2:3,4:5,6-tris-O-ethylboranediyl-D-mannitol

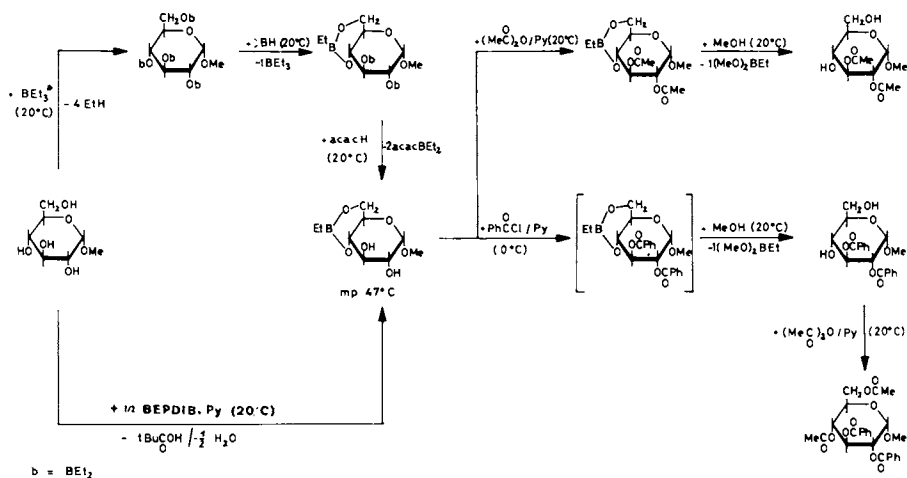


Figure 11. 2,3-Di-O-acyl derivatives of methyl α -D-glucopyranoside via O-ethylboranediyl intermediates

More complications are possible in the boronation of those free sugars which can form α - and β -anomers having pyranose or furanose-rings. The O -ethylboron derivatives of D -xylose and methyl β - D -xylopyranoside are shown in figures 12 and 13. Reaction of D -xylose with BEPDIB yielded the 1,2:3,5-bis- O -ethylboranediyl- α - D -xylofuranose derivative as shown in fig. 12. On the other hand the O -ethylboranediylation of methyl β - D -xylopyranoside afforded the 2,4- O -ethylboron derivative in excellent yield. Two independent routes for the preparation of this compound may be used (see fig. 13).

The reaction of free D -xylose with the intermediates of the per- O -diethylboryl- α - β -mixture via our indirect route was somewhat more complicated. The addition of catalytic amounts of $>BH$ to the per- O -diethylboryl-mixture of xyloses resulted in the formation of the two O -ethylboron α - and β -anomers (see fig. 14).

Distillation yielded about 65 % of the bis-boron α -furanose derivative and 35 % of a β -furanose derivative having two O -diethylboryl groups at C-1 and C-2. The rate of reduction of these two anomers with alkyl-diboranes at 90° was different. The β -anomer reacted 7 times faster than the α -anomer. The vacuum distillable bis-1,2:3,5- O -ethylboranediyl-4- O -diethylboryl-xylitol was the end-product in each case (see fig. 14). The same compound was obtained nearly quantitatively from xylitol via the three independent indirect routes (see fig. 15). With BEPDIB in excess, by the direct route, one obtains a compound with a intermolecular O -ethylboranediyl-group.

The next monosaccharide example, 2-deoxy- D -ribose, illustrates the high yields of the O -ethylboron derivatives that can be obtained. Reaction of the 2-deoxy- D -ribose with 0.5 mole BEPDIB at room temperature affords, after distillation, pure 3,4- O -ethylboranediyl-2-deoxy- β - D -ribofuranose in 97 % yield (see fig. 16).

The 1H -n.m.r.-spectrum of this crystalline derivative in d_6 -dmsO verifies the structural assignments (see fig. 17).

The doublet at $\tau \sim 3.8$ ppm with $J(HOHH^1) = 5$ is characteristic of an anomeric hydroxy group. H^1 appears as a well resolved signal (ddd) at $\tau \sim 5$ ppm due to coupling with HOH, H^2 and $H^{2'}$. The remaining protons are also well separated multiplets in this spectrum (see fig. 17).

This compound can easily be acetylated to give a colourless, vacuum distillable liquid in 98 % yield. When this 3,4- O -ethylboranediyl-1- O -acetyl-2-deoxy- D -ribose is deborylated with methanol at room tempera-

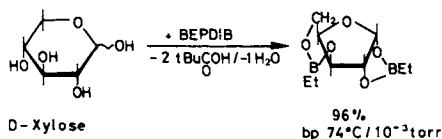


Figure 12. 1,2:3,5-Bis-O-ethylboranediyl α -D-xylofuranose from D-xylose and BEPDIB

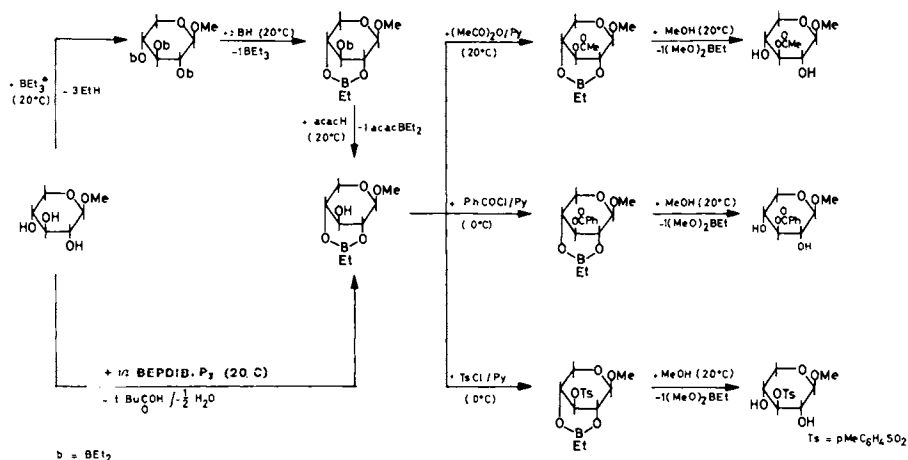


Figure 13. 3-O-Acyl derivatives of methyl β -D-xylopyranoside via O-ethylboranediyl intermediates

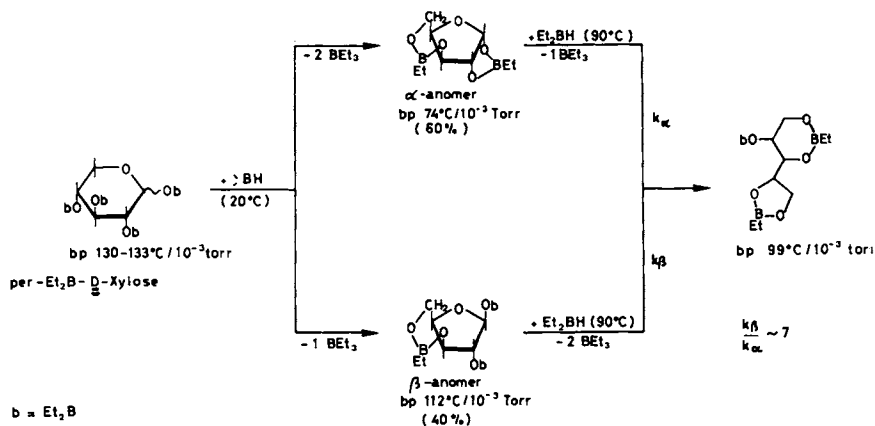


Figure 14. Selective reduction of α - and β -D-xyloses via O-ethylboron intermediates

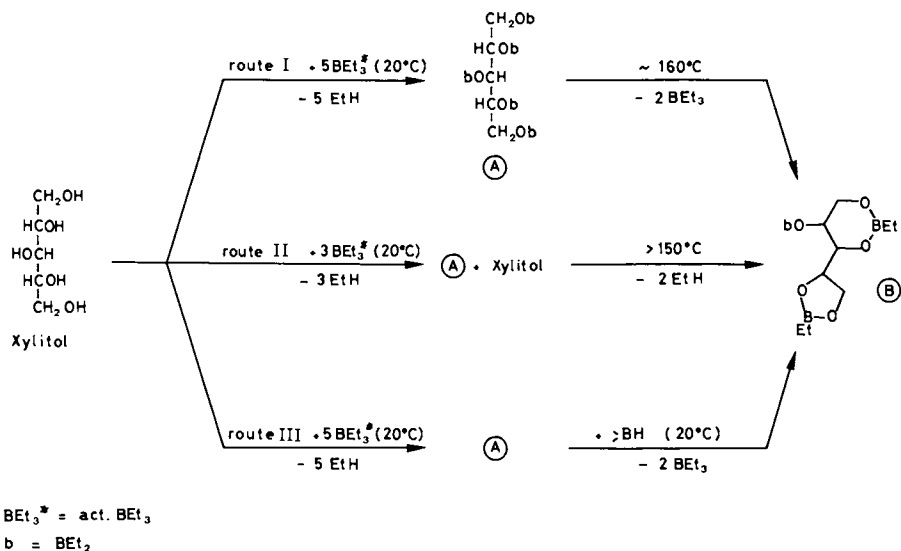


Figure 15. Preparation of 1,2:3,5-bis-O-ethylborane-diyl-4-O-diethylboranyl-xylitol B

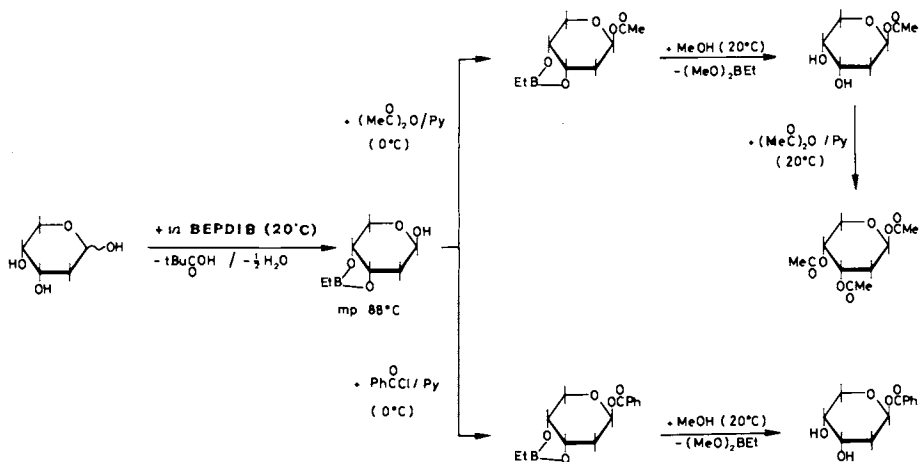


Figure 16. Preparation of 1-O-acyl derivatives of 2-deoxy-D-ribose via O-ethylborane diyl intermediates

ture it gives pure 1-O-acetyl-2-deoxy-D-ribofuranose in an overall yield of 80 %.

The reactions of 6-deoxy-L-mannose (L-rhamnose) with ethylboron compounds are rather complicated and somewhat surprising. A simplified scheme of some of the reactions that have been carried out with L-rhamnose is shown in the fig. 18.

The reaction with one mole of BEPDIB, at room temperature, yielded the vacuum distillable, pure bis-1,2:3,5-O-ethylboranediylfuranose derivative. The structure of this compound was determined with the help of ^1H -, ^{11}B - and ^{13}C -n.m.r. spectra. We found this reaction rather surprising since L-rhamnose formed only a mono-2,3-O-isopropylidene derivative with a 50 to 100 fold excess of acetone. No trace of a bis-O-isopropylidene product could be detected (18).

Treatment of the bis-O-ethylboranediyl derivative with methanol, at room temperature, did not yield mono-1,2-O-ethylboranediyl- or a mono-3,5-O-ethylboranediyl-L-rhamnofuranose. Instead 2,3-O-ethylboranediyl-L-rhamnofuranose was formed by an intramolecular transesterification. This compound could not be vacuum distilled and a disproportionation reaction occurred at the temperature required for distillation yielding L-rhamnose and its bis-1,2:3,5-O-ethylboranediyl derivative. The 2,3-O-ethylboranediyl derivative of L-rhamnose could be O-acetylated in good yield. The total deborylation with ethylene glycol led to 1,5-di-O-acetyl-L-rhamnofuranose, which could not be prepared via the O-isopropylidene intermediates.

The reactions of the new reagent BEPDIB with the aldopentoses L-arabinose, D-ribose and D-xylose, and the deoxy-sugars D-fucose, L-rhamnose and 2-deoxy-D-ribose, as well as the aldohexoses D-glucose, D-mannose and D-galactose are depicted in figures 19 - 21. L-Arabinose and D-ribose reacted to give bis-O-ethylboranediyl-pyranose derivatives in over 90 % yield.

On the other hand, D-xylose formed a bis-O-ethylboronfuranose derivative. The structural assignments were based on ^1H -, ^{11}B - and ^{13}C -n.m.r. data. The formation of the bis-O-ethylboranediyl derivatives of D-fucose, L-rhamnose and the mono-O-ethylboranediyl derivative of 2-deoxy-D-ribose (shown in fig. 20) is of interest since each saccharide behaved differently.

6-Deoxy-D-galactose (D-fucose) reacted with an excess of BEPDIB to form an α -pyranose derivative, whereas 6-deoxy-L-mannose (L-rhamnose) gave a β -furanose derivative. 2-Deoxy-D-ribose reacted with an

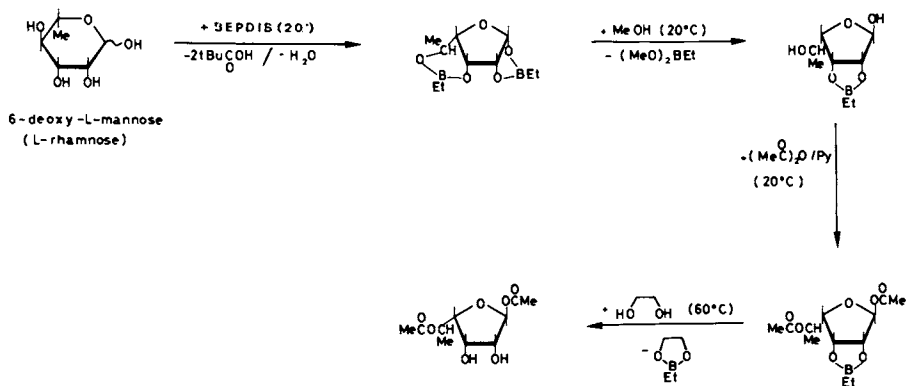


Figure 17. $^1\text{H-nmr}$ spectrum (100 MHz, d_6 -dmsO) of 3,4-O-ethylboranediyl-2-deoxy- β -D-ribofuranose

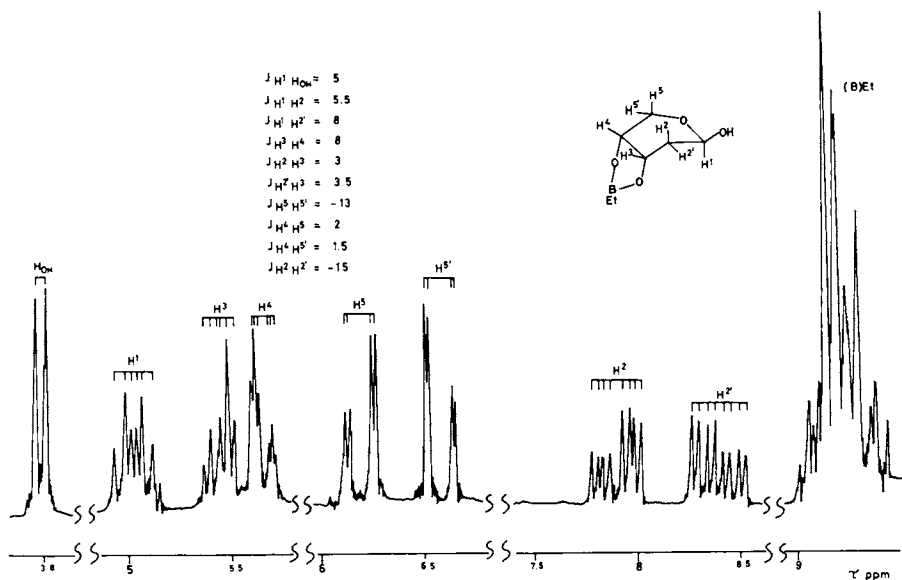


Figure 18. 1,5-Di-O-acetyl-6-deoxy- α -L-mannofuranose via O-ethylboranediyl intermediates

excess of BEPDIB forming a product containing an intermolecular O-ethylboranediyl group. A vacuum distillable β -pyranose derivative with a free hydroxy group on C-1 was obtained by reacting 2-deoxy-D-ribose with exactly 0.5 mole of BEPDIB.

Finally, when one mole of the aldohexoses D-glucose, D-mannose and D-galactose was allowed to react with one mole BEPDIB at room temperature a vacuum distillable bis-O-ethylboranediyl derivative was obtained (see fig. 21). The D-mannose derivative had a furanose ring and the D-galactose derivative a pyranose ring. Both structures were analogous to the O-isopropylidene derivatives. The D-glucose derivative, on the other hand, forms an unusual 1,2:3,5-furanose ring system. The free hydroxy groups in each of the above mentioned bis-boron derivatives reacted with an excess of BEPDIB at room temperature to form non-distillable intermolecular O-ethylboranediyl products. The structures of these products are shown in figure 21. The properties of these intermolecular derivatives may be used for separation purposes.

We would now like to give some examples of separations that were carried out with the help of the O-ethylboronation-deboronation procedures. These reactions were carried out under mild neutral conditions.

We found that many saccharides can be purified via ethylboron intermediates, one application was the preparation of pure amylose. It was possible to separate the high molecular linear amylose part of native starch from the branched amylopectin part by using the simple borylation-deborylation method (see fig. 22).

Anhydrous corn starch was O-diethylborylated with activated triethylborane in hexane at room temperature. The insoluble component, composed of non-borylated amylopectin, was filtered off and the soluble portion, composed of per-O-diethylborylated amylose, was treated with methanol to give pure amylose.

The ethylboronation-deboronation procedure was also used to purify other carbohydrates. The hydrocarbon insoluble inorganic impurities being removed by filtration after O-diethylborylation or O-ethylboranediylation.

Further, it is possible to dehydrate sugar hydrates using triethylborane. This reagent reacts with water at room temperature to give two moles of ethane and one mole of the volatile tetraethyldiboroxane from each mole of water. The procedure was used to obtain anhydrous raffinose, pure 5-deoxylactobionic acid and absolutely dry cycloamyloses.

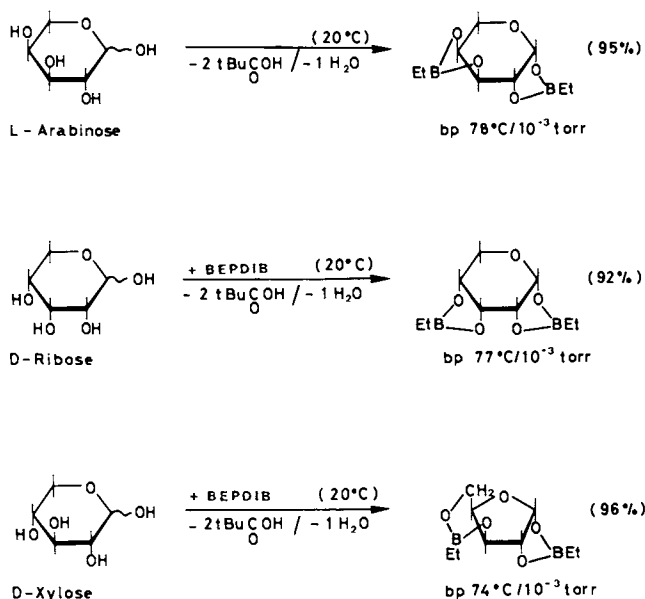
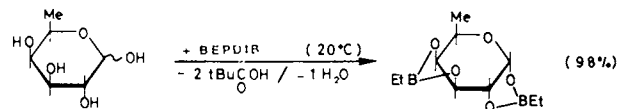


Figure 19. Bis-O-ethylboranediyl derivatives of some pentoses

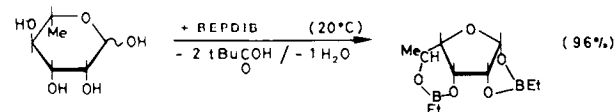
The volatile O-ethylboron derivatives of mono-saccharides can easily be separated from di- and higher saccharides. Thus, after reacting a mixture of glucose and sucrose with activated triethylborane, the pentakis-O-diethylborylglucose can be distilled off from the per-O-diethylborylated disaccharide. Treatment of distillate and residue with methanol affords pure glucose and sucrose.

The special property of the O-ethylboranediyl-group to form intra- and intermolecular products can be used for the separation of polyhydroxy compounds. Thus, xylitol and D-mannitol can be converted to their respective O-ethylboranediyl compounds with BEPDIB or via the per-O-diethylboryl derivatization with BH-catalysts (see fig. 23).

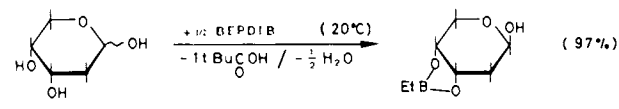
Intra- and intermolecular reactions with triethylborane occur with xylitol, whereas D-mannitol forms intramolecular O-ethylboranediyl groups only. The mannitol derivative can therefore be distilled off quantitatively from the mixture and the xylitol "dimer", remains as a residue. Pure D-mannitol and xylitol can then be regenerated by deboronation with ethylene glycol.



6-Deoxy-D-galactose

bp $65^\circ\text{C}/10^{-3}$ torr

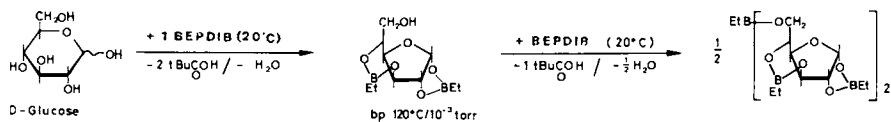
6-Deoxy-L-mannose

bp $78^\circ\text{C}/10^{-3}$ torr

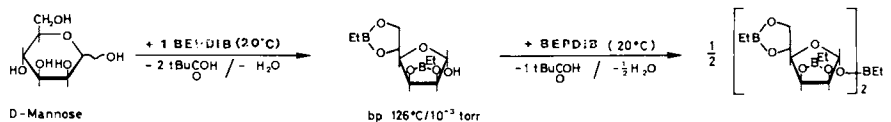
2-Deoxy-D-ribose

bp $98^\circ\text{C}/10^{-3}$ torrmp 88°C

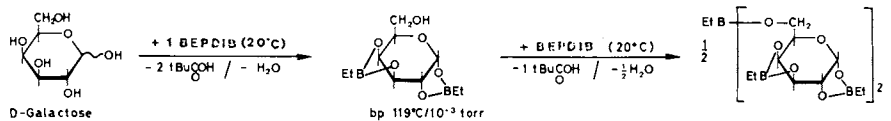
Figure 20. Intramolecular O-ethylboranediyl derivatives of some deoxy sugars



D-Glucose

bp $120^\circ\text{C}/10^{-3}$ torr

D-Mannose

bp $126^\circ\text{C}/10^{-3}$ torr

D-Galactose

bp $119^\circ\text{C}/10^{-3}$ torr

Figure 21. Intra- and intermolecular O-ethylboranediyl derivatives of some hexoses

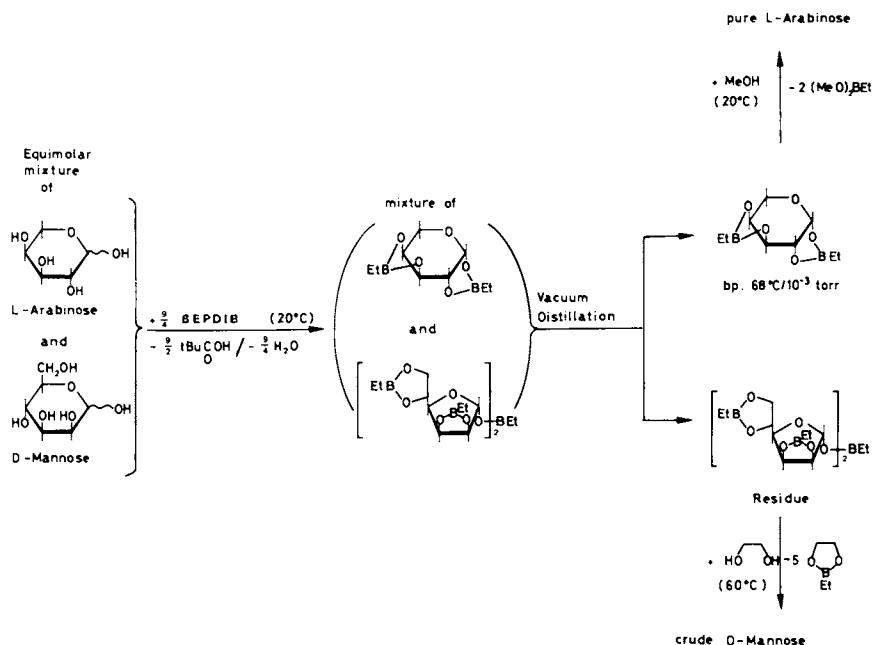


Figure 24. The separation of L-arabinose and D-mannose via O-ethylboron intermediates

The same separation method can be carried out with a mixture of pentoses and hexoses (see fig. 24).

L-Arabinose and D-mannose react with an excess of BEPDIB at room temperature to give O-ethylboranediyl-derivatives. The bis-O-ethylboranediyl-L-arabinose can be distilled off and will yield on methanolysis pure L-arabinose. Pure D-mannose can also be regenerated from the distillation residue by treatment with ethylene glycol. Mixtures of compounds having odd and even numbered hydroxygroups can be subjected to this type of separation. There exist however some compounds with an even number of OH groups which form intermolecular O-ethylboranediyl-derivatives. One such example is methyl α -D-glucopyranoside.

To summarize some of the most important results obtained in our investigation with the O-ethylboranediyl protective group one can say the following:

1. The O-ethylboranediyl group can be introduced and removed under milder conditions than any of the commonly used protective groups in carbohydrate chemistry.

2. The O-ethylboranediyl group is capable of forming both intra- and intermolecular linkages in excellent yields.

3. The bifunctional protective group can be introduced via two monofunctional O-diethylboryl groups.

4. Intermolecular O-ethylboranediyl groups can be broken to give two O-diethylboryl groups.

5. Most of the intramolecular O-ethylboranediyl-derivatives of monosaccharides can be vacuum distilled without decomposition and are quite often crystalline.

6. Several of the bis-O-ethylboranediyl-derivatives can be partially and selectively deborylated with methanol at room temperature. Such selective deborylations have not been observed for any O-phenylboranediyl derivatives.

7. The structures of many but not all of the products resemble those of the analogous O-isopropylidene compounds.

8. The O-ethylboranediyl group can be removed under far milder conditions than the O-isopropylidene group. Thus, for example, we have been able to prepare some 1-O-acyl derivatives via O-ethylboranediyl intermediates.

Because of these facts, the use of the O-ethylboron protective groups offers new possibilities for the purification, the separation and many O-derivatizations of polyhydroxy compounds.

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2

New Aspects of Synthesis with Benzylidene Acetals

DEREK HORTON and WOLFGANG WECKERLE

Department of Chemistry, Ohio State University, Columbus, Ohio 43210

In conjunction with esters and ethers, acetals play an important role as protecting groups in carbohydrate chemistry. Moreover, benzylidene acetals offer an elegant route to halogen-substituted derivatives by means of a ring-opening reaction (Figure 1), whereby the acetal is treated with *N*-bromosuccinimide in hot carbon tetrachloride. The process presumably involves bromination at the benzylic position followed by ionic rearrangement, and yields the primary bromide benzoylated at the secondary position. This reaction was applied in the carbohydrate field by Hanessian (1) in 1966 with examples illustrated in Figure 1, and was further extended in the same year by Hullar and coworkers (2). Since then, the reaction has found wide utility in numerous applications.

A recent application of acetals novel in the carbohydrate field was described in 1974, when Klemer and Rodemeyer (3) reported the reaction of methyl 2,3,4,6-di-O-benzylidene- α -D-mannopyranoside (1) with two molar equivalents of butyllithium at -30° in tetrahydrofuran (Figure 2). They showed that the dioxolane ring reacts selectively and the dioxane ring is unaffected. Furthermore, the reaction led regiospecifically to the 2-deoxy-3-ketone 2; the only side-product was a trace of a 2,3-unsaturated compound.

The foregoing reaction is a specific illustration of a general type of process observed with dioxolanes derived from benzaldehyde, as illustrated in Figure 3. Removal of a proton from 3 by the strong base initiates the reaction, and the subsequent course depends on which proton has been abstracted. If the benzylic proton is removed, the resultant anion 10 then collapses with elimination of benzoate anion to give the alkene 11, as shown in the lower portion of Figure 3. The benzoate anion subsequently reacts with the excess of alkyllithium reagent. If, on the other hand, abstraction of the hydrogen atom attached to one of the other carbon atoms of the dioxolane 3 occurs, the subsequent process leads to an enolate anion (5 or 8), with elimination of benzaldehyde (which then reacts with a second

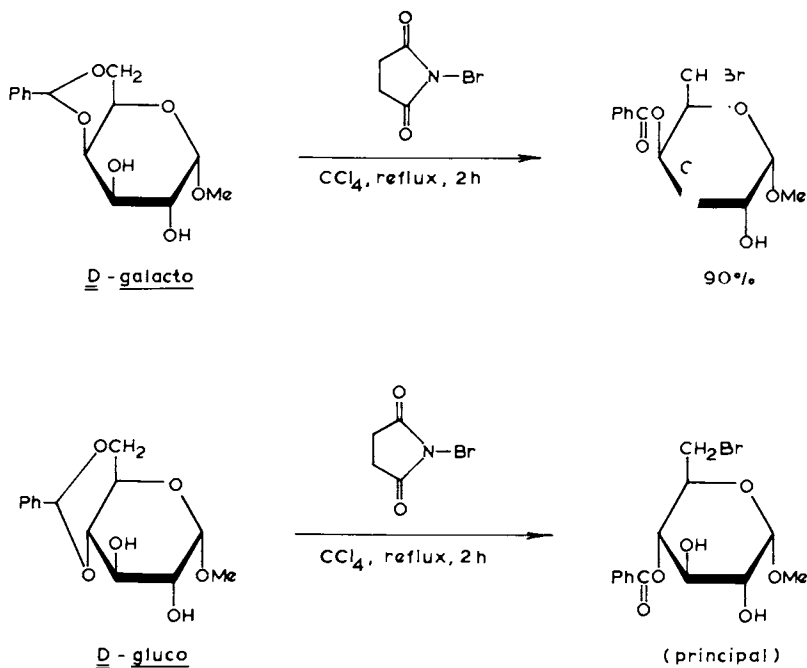


Figure 1. Ring-opening reaction of benzylidene acetals with N-bromosuccinimide

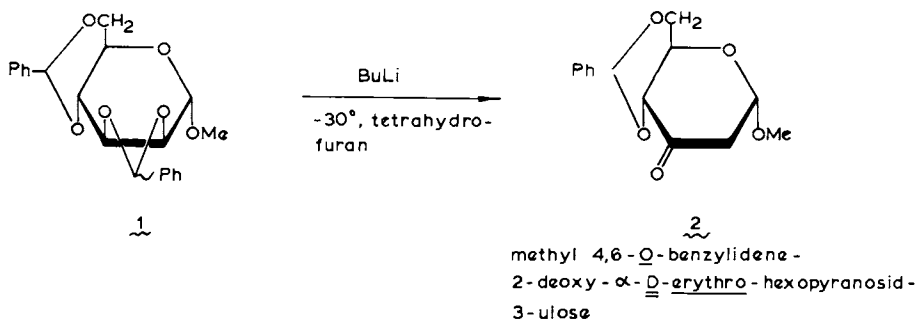


Figure 2. Opening of a 1,3-dioxolane ring: reaction of methyl 2,3:4,6-di-O-benzylidene- α -D-mannopyranoside (1) with butyllithium

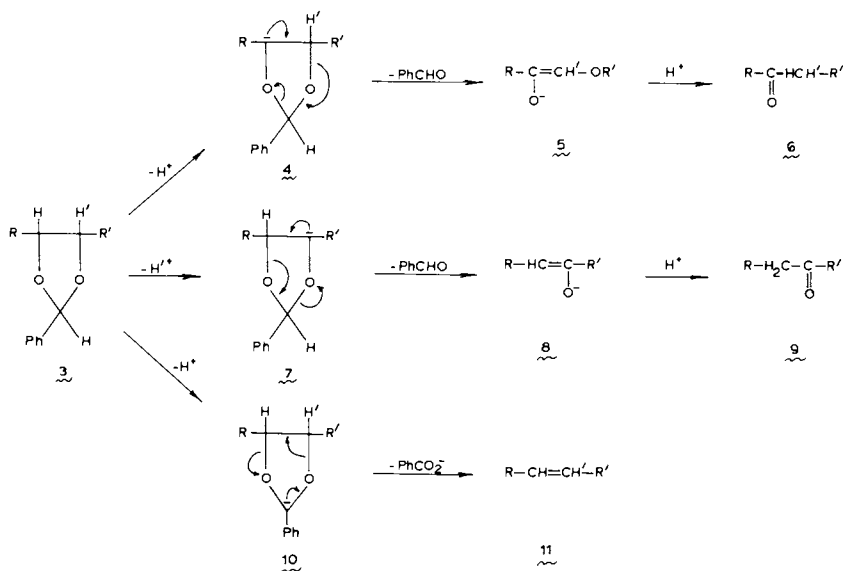
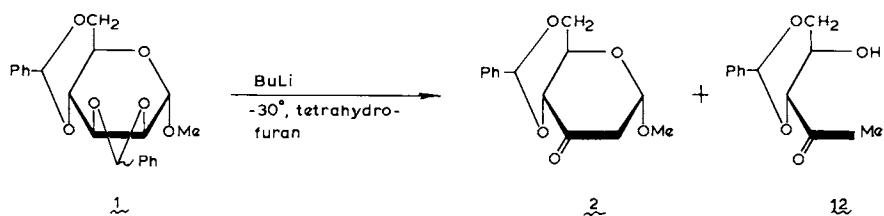


Figure 3. Possible pathways and products of the butyllithium reaction with 2-phenyl-1,3-dioxolane derivatives



Large-scale operations		
Isolation conditions	yield	
	2	12
strongly alkaline (ref. 3)	traces	10-20% (+ complex mixture)
ammonium chloride-buffered	91%	traces

Figure 4. Preparative synthesis of the deoxy ketone 2

molecule of the reagent). After conventional processing, one or other of the corresponding deoxygenated keto products (6 or 9) is isolated, as shown in the upper half of Figure 3. The outcome of the reaction depends on which of the three hydrogen atoms in 3 is the more-readily abstracted, and this step determines which of the three possible products (6, 9, or 11) is formed.

The great potential utility of this reaction by Klemer and Rodemeyer prompted our evaluation of it on a large scale, as the ketone 2 was required as an intermediate in a proposed synthesis of daunosamine and related compounds. As shown in Figure 4, some difficulties were encountered in the scale-up of the reaction as originally described. Although small-scale preparations proceeded satisfactorily, attempts to use quantities of 50 grams or more of compound 1 did not lead to the desired ketone 2, but to complex mixtures containing a wide range of other products besides 2, as indicated by t.l.c. From this mixture, a crystalline compound was isolated in relatively low yield that was subsequently identified as a product (12) of chain degradation. The difficulty was traced to decomposition of compound 2 during the isolation procedure when water was added to the solution. Under these conditions, the mixture becomes strongly alkaline, permitting base-catalyzed degradation of 2, as will be shown later. A modified isolation procedure, whereby the cold reaction mixture (-40°) is poured into well-stirred, ice-cold, aqueous ammonium chloride permitted the successful, large-scale conversion of 1 into 2. The tetrahydrofuran was evaporated off and the crystalline product then filtered off directly from the aqueous mixture. By this modification, the ketone 2 could be obtained crystalline in 91% yield (4). The reaction is quite regiospecific, and no 3-deoxy-2-keto product could be detected.

A major objective in our laboratory has been the development of a high-yielding synthesis of the amino sugar daunosamine (3-amino-2,3,6-trideoxy-L-lyxo-hexose, 21), a constituent of the important antitumor antibiotics daunorubicin (5,6), carminomycin (7), and adriamycin (8). The synthesis of this amino sugar from D-mannose as starting material requires deoxygenation at C-2, amination with inversion at C-3, and inversion at C-5 together with deoxygenation at C-6. Having in hand a high-yielding route to the ketone 2 allowed the development of a very convenient synthesis for this amino sugar, as illustrated in Figure 5, affording it in a net yield of 40% from methyl α -D-mannopyranoside (4).

The ketone 2 is oximated, and the resultant oxime 13 is reduced and the product acetylated, to give a mixture of the D-ribo (14) and D-arabino (15) acetamido derivatives. The reduction strongly favors the ribo compound, and separation of the two products is readily achieved by exploiting the very low solubility of the arabino derivative (15) in most organic solvents, especially in toluene. The ribo product (14) is very soluble in this and most other solvents. By this simple separation, pure compounds 14

and 15 were obtained in 87% and 12%, respectively. These products were subjected separately to the action of *N*-bromosuccinimide to generate the 6-bromides (16 and 17) benzoylated at O-4. The *D*-ribo isomer (16) was then treated with technical silver fluoride to bring about elimination of hydrogen bromide and generate the exocyclic enol derivative 18, which was then converted into the debenzoylated analogue 19. The latter undergoes stereospecific reduction with hydrogen in the presence of palladium to give the corresponding C-5-inverted product 20, which is the *N*-acetylated, methyl glycoside of daunosamine. The hydrochloride (21) of the free reducing sugar is obtained by removal of the *N*-substituent and hydrolysis of the glycosidic group (4).

This synthesis also provides a versatile general method for related amino sugars (9, 10), as illustrated in Figure 6. If the elimination-inversion sequence at C-5 is omitted, compound 16 (*D*-ribo) can be converted into the corresponding 6-deoxy derivative 22 and, likewise, the *D*-arabino derivative 17 gives its corresponding 6-deoxy analogue 23. In the ribo series, O-deacylation to compound 24 and subsequent hydrolysis affords 3-amino-2,3,6-trideoxy-*D*-ribo-hexose (26), the optical antipode of the antibiotic constituent ristosamine (11). By a similar sequence, the corresponding *D*-arabino derivative (27) is obtained; this compound is the enantiomorph of acosamine (12). Compound 27, upon *N,N*-dimethylation, gives angolosamine, which is a component of the macrocyclic lactone antibiotic angolomycin (13).

The feasibility of the butyllithium reaction with compounds having a different mode of substitution was next examined, and the results of reactions performed on derivatives of *L*-rhamnose (14) are illustrated in Figure 7.

Although the first derivative chosen, methyl 2,3-O-benzylidene- α -*L*-rhamnopyranoside (28) has formal similarity to the foregoing compound 1 in that both 1 and 28 have the dioxolane ring derived from benzaldehyde attached to a 6-membered sugar ring, there are substantial differences, most importantly because 28 possesses a labile proton. Treatment of 28 with butyllithium did not lead to a deoxy ketone, but to a mixture of products containing a small proportion of the 2,3-unsaturated product 29 (presumably arising from the 4-oxyanion of 28 by abstraction of the benzylic hydrogen atom and subsequent elimination of a benzoate anion), together with larger proportions of two branched-chain products (30 and 31) that are apparently formed by attack of the butyllithium reagent upon the keto sugar derivative. The reaction with compound 28 is more sluggish than with the di-O-benzylidenemannoside 1. No reaction took place at all at -30° , but at 0° the products shown were formed. The fact that the reaction must take place by way of an initial oxyanion at C-4 may influence the outcome of the reaction. Under the more-vigorous conditions required to separate a second proton and generate a doubly-charged species (32), the enolate (33) of the desired 2-deoxy-3-ketone evidently eliminates the glycosidic methoxyl group

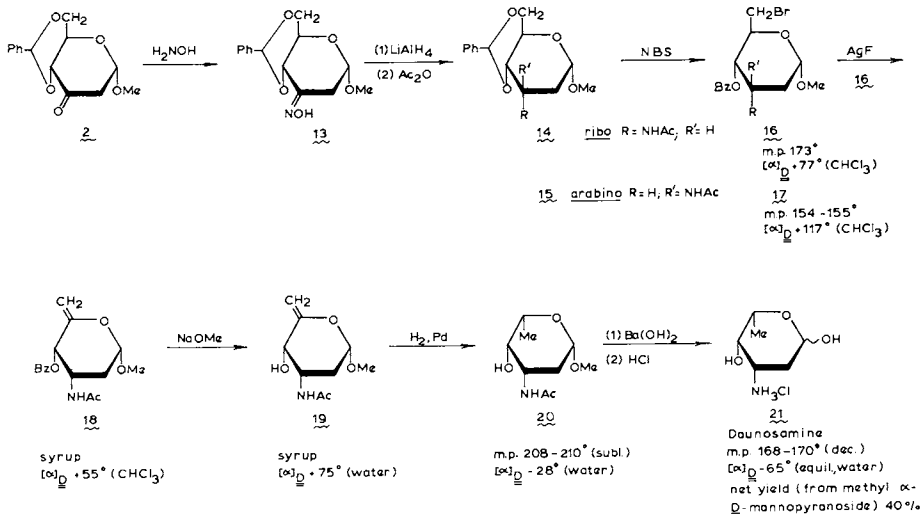


Figure 5. Synthesis of daunosamine

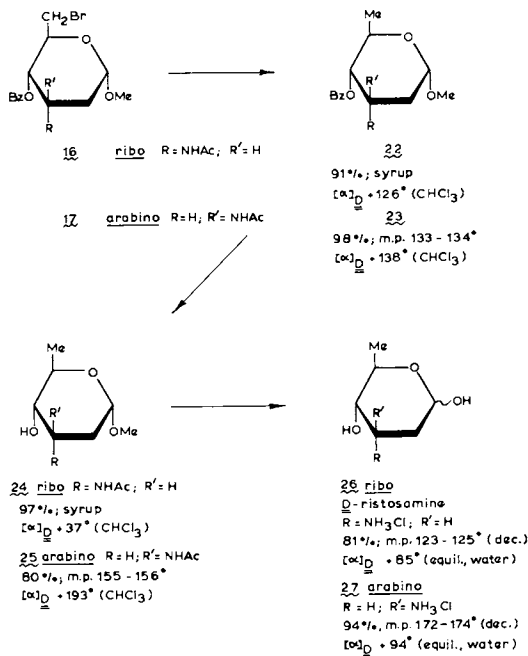


Figure 6. Synthesis of 3-amino-2,3,6-trideoxy-D-ribo- and D-arabino hexoses

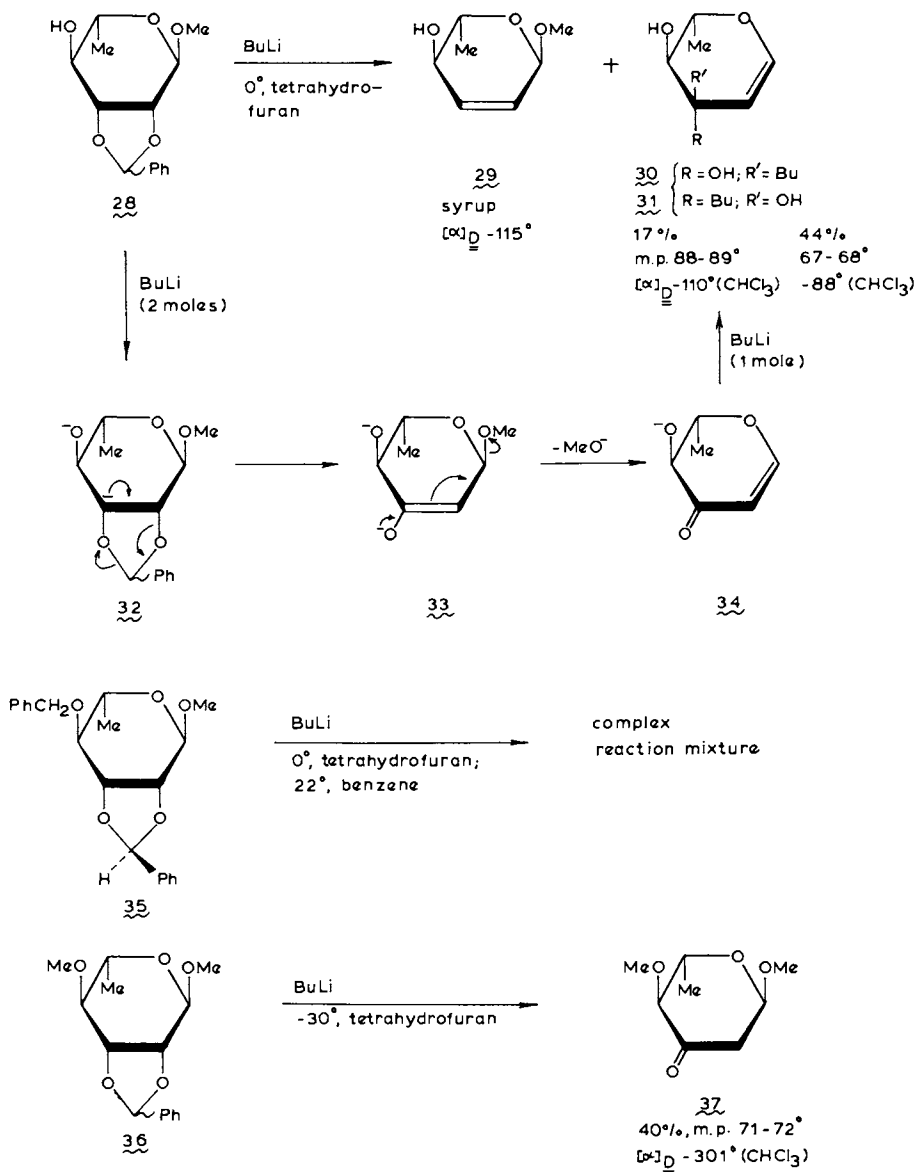


Figure 7. Reactions of methyl 2,3-O-benzylidene- α -L-rhamnopyranosides with butyllithium

readily to form the corresponding 1-ene-3-one 34, which would predictably react with the reagent to give a mixture of products (30 and 31), formed by addition of butyllithium to the carbonyl group.

In order to impede this competing process, it was considered necessary to protect the hydroxyl group in the rhamnose derivative 28 by means of a base-stable group. This was achieved by preparation of both the 4-benzyl (35) and 4-methyl (36) ethers. However, butyllithium failed to effect a straightforward transformation of the benzylated benzylidene acetal 35, even under a variety of conditions explored; at low temperature (-30°) no reaction occurred, and more-vigorous conditions led to a complex mixture of products. Evidently, the reagent abstracts a proton from the 4-O-benzyl group (as indicated by a change of the solution to a yellow-red color), thus hindering removal of a second proton from the dioxolane ring.

In contrast, the methyl ether 36 reacted readily with butyllithium at -30° and the reaction was complete after 30 minutes. The product is the 2-deoxy-3-ketone 37, whose structure is fully supported by conventional characterization data as well as by n.m.r. - and mass-spectral data. A sequence involving oximation, reduction, and hydrolysis thus offers a route from 37 to the L-ribo (enantiomer of 26) and L-arabino (enantiomer of 27) analogues of daunosamine (21), ristosamine (11), and acosamine (12).

In a further effort to demonstrate the generality of the butyllithium reaction with benzylidene acetals having the dioxolane ring-structure, additional examples (15) have been examined. The allo analogue 38 of the previously studied manno dibenzylidene acetal 1 was subjected to the same type of treatment with butyllithium in tetrahydrofuran (Figure 8). The compound reacted readily to generate a deoxy keto sugar 39 having the keto group in the 2-position and deoxygenation at C-3. Only traces of the 2,3-unsaturated glycoside (40) were formed. It is thus evident that compound 38 reacts by exactly the reverse of the steric mode observed with the manno derivative 1; the course may be ascribed to initial abstraction of the axially oriented hydrogen atom (H-2) of 38. In the case of 1, it is the adjacent hydrogen atom (H-3) that is axially disposed and whose abstraction initiates elimination in the direction observed.

The ketone 39 is a useful intermediate in synthesis. Thus, its reduction to a pair of epimers at C-2, followed by the opening of the dioxane ring with N-bromosuccinimide, subsequent reduction of the corresponding primary halide, and hydrolysis leads (16) to the deoxy sugars paratose (3,6-dideoxy-D-ribo-hexose) and tyvelose (the D-arabino analogue). Furthermore, reductive amination of compound 39 provides a simple route to a range of 2-amino-2,3-dideoxy sugars (15).

The next application of the butyllithium reaction was made (15) with compounds having the same general structure as the mannose and allose derivatives already described, but lacking the

glycosidic methoxyl group that leads to complications in some instances. Thus (Figure 9), 1,5-anhydro-2,3:4,6-di-O-benzylidene-D-mannitol (41) was found to react with butyllithium at 0° (at -30° the reaction proceeded insufficiently rapidly) to give the crystalline 3-ketose 42 in 66% yield by the same process that was observed with the glycosides 1 and 36. A dimeric side-product (44) was also encountered, and this presumably arises from self-addition of 42. A very minor side-product was the glucal derivative 43, whose assigned structure is supported by analytical and spectroscopic data as well as by comparison with an authentic sample (17). Although the desired ketose was contaminated with the dimer 44, the two could be separated readily because chromatography on silica gel (with 4:1 ether-petroleum ether as eluant) gives the pure 1,5-anhydroketose (42), whereas the dimer (44) remains on the column.

The reverse course of the foregoing reaction is observed when 1,5-anhydro-2,3:4,6-di-O-benzylidene-D-allitol (45) is treated with butyllithium at 0° in tetrahydrofuran. In this instance, the principal product is the 3-deoxy-2-ketose 46, fully in line with the observations with the corresponding allose derivative 38. Again a glycal derivative (47) is encountered in very low yield, together with a product that has not yet been firmly identified, but which probably arises from self-addition of the 2-ketose 46.

As mentioned earlier, scaled-up experiments with methyl 2,3:4,6-di-O-benzylidene- α -D-mannopyranoside (1) and butyllithium initially led to a degradation product, 3,5-O-benzylidene-1-deoxy-keto-D-erythro-2-pentulose (12), instead of the desired ketone 2. It was assumed that 2 was initially present, and that the pentulose 12 was produced only under the strongly alkaline conditions of the isolation procedure. This hypothesis is supported by the fact that 2 could be detected while monitoring the reaction mixture by t.l.c., and that simple modification of the isolation procedure (by use of a buffer) overcame the problem. Later on, it was of interest to devise a practical procedure for obtaining this pentulose derivative (12) as a precursor for other synthetic studies. The best results were obtained (15) with a two-phase system utilizing stoichiometric amounts of lithium hydroxide, with shaking overnight at room temperature (Figure 10). The structure of 12 was fully supported by infrared (OH, C=O), n.m.r., and mass-spectral data, as well as by the preparation of the corresponding acetate 48, the benzoate 49, and the 2',4'-dinitrophenylhydrazone 50. The product was further identified by direct comparison with literature data for compound 12 prepared in a different way (18).

A possible mechanism for the chain degradation is illustrated in Figure 11. Under basic conditions, the corresponding enolate (51) of 2 may eliminate the glycosidic methoxyl group to give the enone 52. Hydration of this product and subsequent attack on 53 by hydroxide ion would lead, with elimination of formate, to the

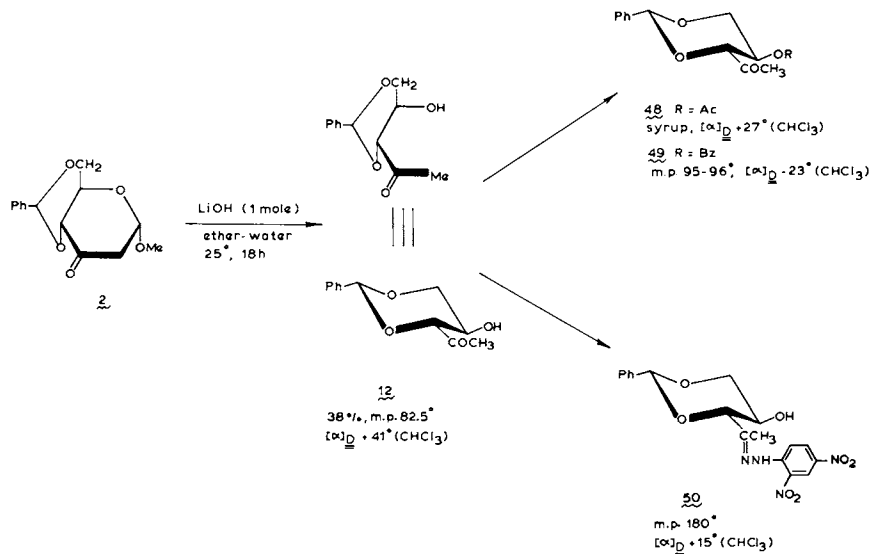
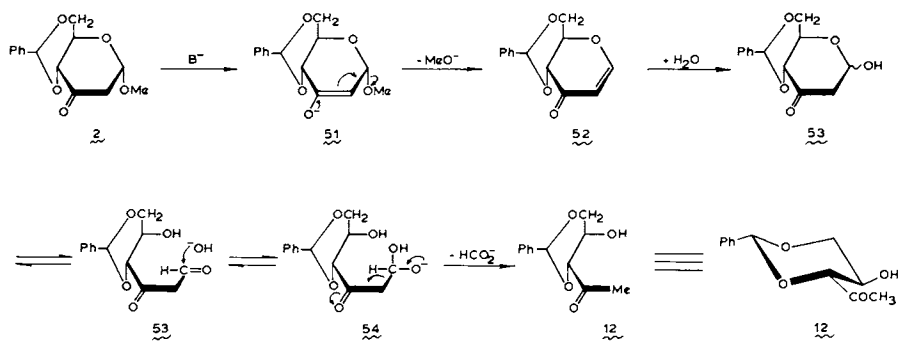
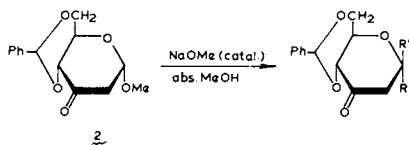


Figure 10. Base-promoted chain degradation of **2** to 3,5-O-benzylidene-1-deoxy-keto-D-erythro-2-pentulose (**12**)



Supported by



	R'	R	m.p.	$[\alpha]_D^{25}$
2	α	H	170-171°	+150° (AcOEt)
55	β	OMe	194-195°	-51° (CHCl ₃)

ratio ~1:1 (estimated from n.m.r. data)

Figure 11. Proposed mechanism for the chain degradation

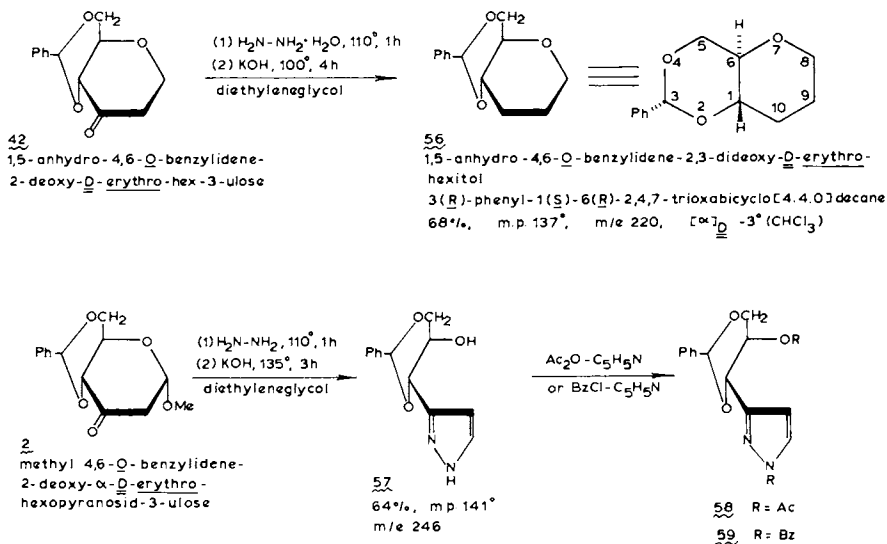


Figure 12. Wolff-Kishner reduction (Lock modification)

pentulose derivative **12**. The reaction does require a stoichiometric amount of base, together with an excess of water, to afford the product. The idea of elimination of the glycosidic group, possibly in a reversible manner, is supported by studies on the behavior of the ketone **2** under alkaline conditions in anhydrous methanolic solution; it was shown that **2** anomerizes readily, and gives an approximately equimolar ratio of the two anomers **2** and **55**; no degradation product **12** could be detected under these conditions. The β -anomer **55** was isolated by column chromatography and has been fully characterized.

In a further extension designed to develop additional synthetic methods useful in carbohydrate chemistry, the feasibility of reductions of the Wolff-Kishner type (**19**) was explored (**20**) with the ketose **42** obtained from a 1,5-anhydroalditol precursor (**41**). As shown in Figure 12, the reaction of this ketone with hydrazine hydrate and subsequent treatment with potassium hydroxide in 2,2'-oxybis(ethanol) gave a 68% yield of the expected product of the Wolff-Kishner reaction, namely the 3-deoxygenated derivative **56**, whose structure is fully supported by analytical and spectroscopic data. However, it should be kept in mind that the Wolff-Kishner reaction, even under the conditions of Lock (namely a two-step modification, **21**) that were used, and with temperatures far below those usually applied, is incompatible with the fragility of most carbohydrate

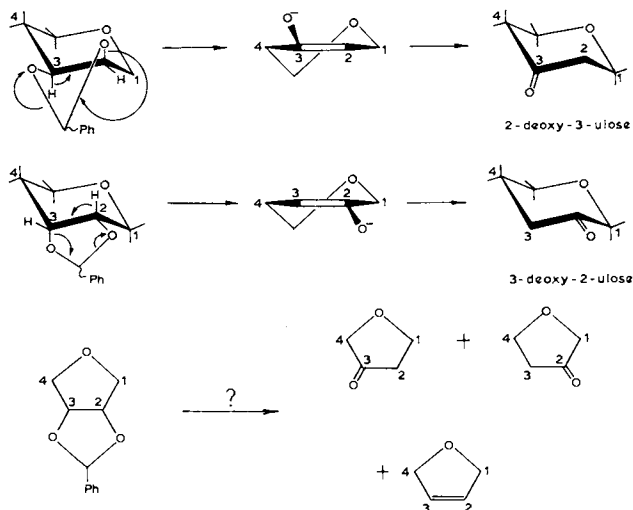


Figure 13. Net steric course of the reaction of butyllithium with benzylidene acetals. The top two sequences present a 5-membered benzylidene acetal ring fused to a pyranose ring. The bottom one shows a 5-membered benzylidene acetal ring fused to a furanose ring.

molecules. In contrast to the successful conversion of the robust alditol derivative **42** into **56**, the reaction with the methyl glycosidulose **2** did not lead to the desired product deoxygenated at C-3 (prepared earlier by another route in this laboratory, **22**), but to the pyrazole derivative **57**, presumably through opening of the pyranose ring by a mechanism similar to that shown for the chain degradation mentioned before. Condensation of the C-1 aldehyde group with the second nitrogen atom of the hydrazono group gives the product having the indicated structure (**57**). The latter structure accords with all spectroscopic evidence and analytical data, and was further supported by preparation of the diacetate **58** and dibenzoate **59**.

In summary (Figure 13), the usefulness of the reaction of butyllithium with a variety of 5-membered benzylidene acetal rings fused to a pyranose ring has been demonstrated. Provided that there is no interference by an acidic proton, such as is present in a hydroxyl or benzyl ether group, the reaction generally leads to deoxy ketones. The initial step is the abstraction of the axial proton of the original diol, with subsequent expulsion of benzaldehyde to give a product having the ketone function at the position of the former axial proton. No other isomer is formed. A very minor side-reaction may be encountered, in which abstraction of the benzylidene proton initiates expulsion of a benzoate anion, leading to the corresponding alkene from the original diol. In some instances, secondary reactions such as aldol additions, may take place.

Further extensions of this study to encompass 5-membered benzylidene acetal rings fused to furanoid sugars are under investigation.

Acknowledgments

This work was supported, in part, by Grant No. GM-11976 from the National Institute of General Medical Sciences, and by Contract No. N01-CM-57015 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare, Bethesda, Md. 20014.

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3

Innovations in Synthetic Carbohydrate Chemistry— Practical and Conceptual Approaches to Glycoside Synthesis

STEPHEN HANESSIAN and JOSEPH BANOUB

Department of Chemistry, University of Montreal, Montreal, Quebec, Canada

The continued discovery of new antibiotics and of other, biologically important substances, containing glycosidically-linked sugars, has provided much impetus to the problems associated with glycoside synthesis (1). With the advent of sophisticated methodology, it has been possible to probe the biological effects of these substances at the molecular level, and to gain better insight into their respective roles. It is now clear that biological specificities are dependent not only on the nature of the sugars present in the substrate, but also on the type of glycosidic linkages that are involved. This feature is in turn, closely related to the molecular shape in solution, and to preferred rotamer populations of the aglycon and the oxygen atom involved in the glycosidic linkage (2). The functional, stereochemical, conformational and spatial characteristics of carbohydrates are therefore of utmost significance within a particular biological environment. The primordial importance of many carbohydrate biopolymers in life processes at all levels, has been recognized for many years even though their precise functions, and modes of interaction are, in many cases, as yet to be unravelled. Great strides have been made in recent years in the chemistry and biology of nucleic acids and proteins, which have led to the present state of development of molecular biology as we know it. Studies on equally important classes of macromolecules comprising carbohydrates, are harvesting a similar wealth of knowledge. The immediate future will witness a surging effort in the area of carbohydrate-containing natural products, particularly antibiotics and biopolymers. Intensive research work on the biological front is presently concerned with various aspects of bacterial polysaccharides, cell-surface carbohydrates including glycoproteins, glycolipids and other complex carbohydrates

of immunological significance among many more related biopolymers. Many of the crucial biochemical phenomena associated with these substances are centered around the glycosidic linkage (3). Indeed, complex glycosides as well as polysaccharides and related polymers containing carbohydrates, are systematically assembled in remarkable enzymatic reactions, which, unlike the biosynthesis of nucleic acids, do not require a template. Nature has therefore found the means to specifically activate the anomeric carbon atom, and to effect the synthesis of complex glycosides and polysaccharides, via the intermediacy of glycosyl transferases, with remarkable stereocontrol and at rates that defy the most sophisticated chemical method. For these and other reasons that have evolved with the times, the chemical synthesis of glycosides has been a challenging area of research work over the years. This has, by necessity, led to the development of a large number of temporary protecting groups for hydroxyl and amino functions, and to methods of activation of the anomeric center. As a result, considerable advances have been made in the stereocontrolled synthesis of 1,2-*cis*, and 1,2-*trans*-linked glycosides, including those with complex aglycons, such as can be found in some antibiotics containing sugars (4). Greater emphasis on the biological role of carbohydrate biopolymers requires the development of glycosylation methods that are applicable to the preparation of di-, tri-, and oligosaccharides, as well as polysaccharides (5,6). The complex structures of the target products, and the inherent polyfunctional nature of carbohydrates, present some formidable synthetic, as well as practical problems. The chemical synthesis of an oligosaccharide for example, requires the stereocontrolled and systematic attachment of sugars at specific hydroxyl groups. This feature necessitates the availability of preferentially substituted aglycons, since glycosylations of sugars containing more than one free hydroxyl group may lead to mixtures in some cases. Figure 1 illustrates the partial structures of some carbohydrate-containing substances of biological interest, such as the aminoglycoside antibiotics (7), determinant, and repeating units in the blood group substances (5,8) and O-specific lipopolysaccharides (9,10), and a monosialoganglioside (11). The nature of the glycosidic linkages, the unique sites of attachment, and the specific sequences of the various sugar units in these substances, have a profound bearing on their biological specificities. These features are in fact, among the important prerequisites for recognition phenomena associated with biological processes at the cel-

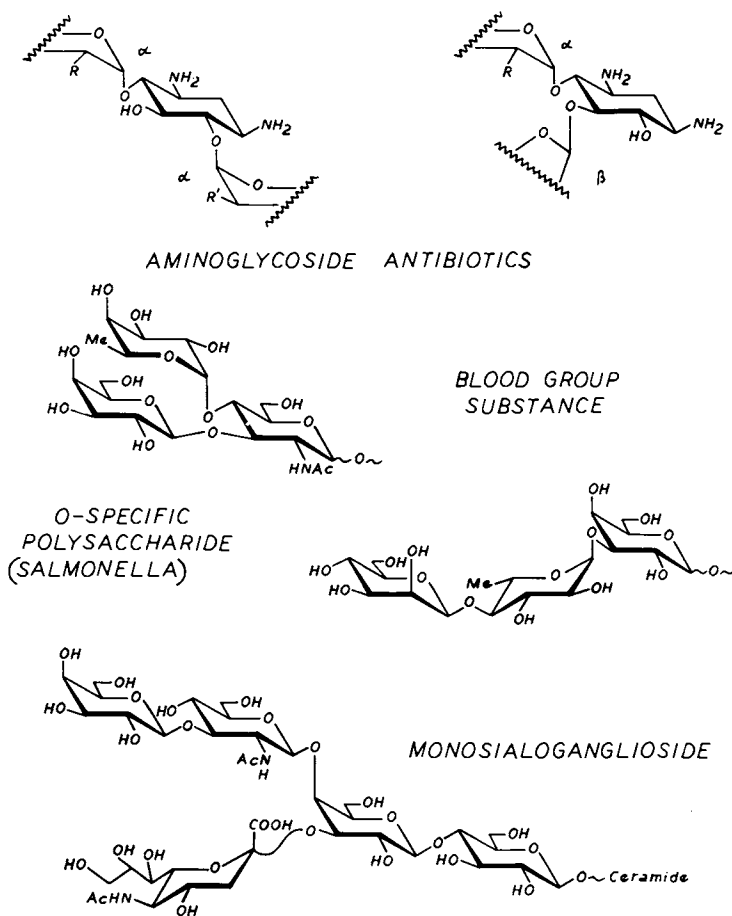


Figure 1

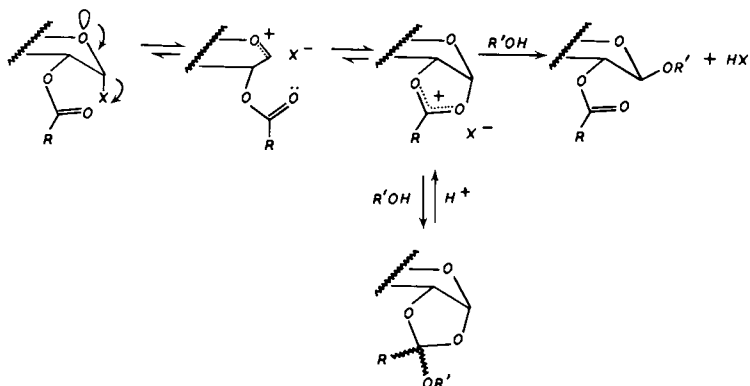


Figure 2

lular level. A seemingly trivial functional, stereochemical, or positional modification of their natural arrangement, can therefore have dramatic biochemical consequences.

With these features in mind, and being acutely aware of the ever-increasing demand for newer, and more practical methods for glycoside synthesis, we embarked upon a synthetic program for the stereocontrolled formation of 1,2-cis, and 1,2-trans-linked glycosides. In this article, we discuss several approaches to the stereocontrolled synthesis of 1,2-trans-linked glycosides, pseudodisaccharides, and disaccharides.

Synthesis of 1,2-trans-linked glycosides - a brief overview

The subject of glycoside synthesis in general has been extensively reviewed (1,12,13,14,15). The synthesis of 1,2-trans-linked glycosides in particular, has been the object of a large number of studies, since, historically, this type of glycoside has been experimentally more accessible. Recently however, several routes have been described for the synthesis of α -glycosides, and these methods have been extended to the synthesis of di- and oligosaccharides as well (5). Simple alkyl 1,2-trans-linked glycosides (e.g. alkyl β -D-glycosides) can be frequently prepared by the classical Fischer synthesis (16,17). For more complex aglycons including sugars, the Koenigs-Knorr glycosylation, involving the use of a peracylated glycosyl halide, an acid acceptor, and an alcohol (aglycon) has been in use since its discovery (18). Many modifications of the original method, particularly with regard to the use of both soluble and insoluble acid acceptors and a variety of solvents, have been introduced over the years (1). Another method that has been extensively used for the synthesis of 1,2-trans-linked glycosides, is based on the acid-catalyzed rearrangement of 1,2-orthoester derivatives (19). This method is also applicable to the synthesis of di- and oligosaccharides (14,19). In addition, there are a significant number of other less frequently used procedures that lead to the above mentioned type of linkage (1,12,13,14).

Mechanistic aspects of the formation of glycosides have been discussed in detail (1,20). It is now generally accepted that in the presence of an acid acceptor a glycosyl halide derivative containing a participating group at C-2, will lead to a 1,2-trans-glycoside, via the intermediacy of a 1,2-acyloxonium ion intermediate, Figure 2. Taking a 2,3,4,6-tetra-O-acetyl- α -D-aldopyran-

osyl bromide as example, it can be appreciated that the initially formed transient oxonium ion is rapidly transformed into the more stable 1,2-acetoxonium ion as a result of an interaction of the electron deficient anomeric carbon atom with the p orbitals of the favorably disposed carbonyl oxygen atom. The stereospecificity of glycosylation results therefore from an attack of the alcohol from the " β " side, leading in this case, to the thermodynamic product. Attack of the alcohol at the dioxolenium carbon atom, would, on the other hand, lead to an orthoester derivative, which can be considered to be the kinetic product. In neutral or basic media, O-acylglycosyl halides and alcohols may lead preponderantly to the corresponding orthoesters (19). Treatment of the latter with acid catalysts, under anhydrous conditions, leads to the formation of the corresponding 1,2-trans-glycosides, via the intermediacy of 1,2-acyloxonium ions.

In spite of our understanding of the apparent mechanistic aspects of these reactions, it has not been possible to devise a general method of glycoside synthesis in this series. Glycosylation reactions using glycosyl halides or orthoester derivatives are, dependent on several parameters, such as the nature of the alcohol, and the catalyst, etc. A successful, high yielding, stereospecific glycosylation of one alcohol, may lead to variable if not disappointing results with another. Thus the quest for procedures having general applicability continues. Ideally, the formation of glycosides should satisfy the following basic criteria:

- a. the reaction should involve a minimum number of reagents,
- b. a favorable stoichiometry between the substrate (glycosyl halide or its equivalent), alcohol (aglycon), and catalyst, (usually in combination with an acid acceptor) should be maintained,
- c. the manipulative part should be simple and the yields should be high,
- d. the glycosylation reaction should be stereocontrolled, and potentially applicable to a wide variety of glycosides.

The exploration of novel methods of glycosylation invariably deals with simple alcohols at the outset. Successful extension of these methods to more complex alcohols, including sugars, will generally lead to wide and rapid acceptance, particularly if a number of the above mentioned criteria are satisfied.

Formation of glycosides with lactim ethers

In previous work from this laboratory (21) it was shown that in the presence of a Lewis acid such as

stannic chloride, and O-TMS enol ethers or O-TMS ketene acetals, 1-O-acetyl-2,3,5-tri-O-benzoyl- β -D-ribofuranose 1, was transformed into the corresponding C- β -D-ribofuranosyl derivatives 3 (21). The mild reaction conditions and the high yields of C-glycosides reflect the inherent reactivity of the aglycons and the sugar derivative. The stereospecificity of the reaction could be explained by invoking the formation of a 1,2-O-benzoxonium ion intermediate 2, Figure 3. It is of interest that no acetal-type products such as 5, were formed under these conditions in contrast to the reaction between 2,3,5-tri-O-benzoyl- β -D-ribofuranosyl chloride 4 with carbanionic reagents (22). It is apparent that in addition to the important role of the solvent, the nature of the counter-ion species present in solution, and their ion-pairing tendencies will strongly dictate the reaction pathway to be followed from the 1,2-benzoxonium ion intermediate.

Our interest in the synthesis of a series of β -D-ribofuranosyl lactams (23) led us to investigate the reaction between 1 or 4 and various lactim ethers, in the presence of stannic chloride or antimony pentachloride as Lewis acids. Treatment of 1 or 4 individually with 2-ethoxy-3,4,5-dihydropyrrole, 2-ethoxy-3,4,5,6-tetrahydropyridine, and 7-ethoxy-3,4,5,6-tetrahydro-2H-azepine, in the presence of a Lewis acid in dichloromethane at room temperature led to the formation of the corresponding 2,3,5-tri-O-benzoyl- β -D-ribofuranosyl lactams 6. The same products were also formed when the individual N-trimethylsilyl lactams were used instead of the lactim ethers. The reactions, and possible mechanistic pathways are illustrated in Figure 4.

Treatment of 1 with 2-ethoxy-3,4,5,6-tetrahydro-2H-azepine in the presence of antimony pentachloride in refluxing dichloromethane, did not give the expected lactam derivative, but led instead, to the formation of ethyl 2,3,5-tri-O-benzoyl- β -D-ribofuranoside 7 in high yield. Since the only source of ethoxyl group was the lactim ether, it appeared that glycoside formation had occurred via attack of an initially formed benzoxonium ion by ethoxide ion or an (SbCl₅OEt) anion complex, either directly at C-1, or at the dioxolenium carbon atom to give an orthoester derivative, initially, that could subsequently rearrange, Figure 5. Intrigued by the facile formation of a glycoside under these aprotic conditions, we sought to further exploit the chemistry of imino ethers and related compounds as potential sources of "alkoxide" donors, in conjunction with Lewis acids as complexing agents.

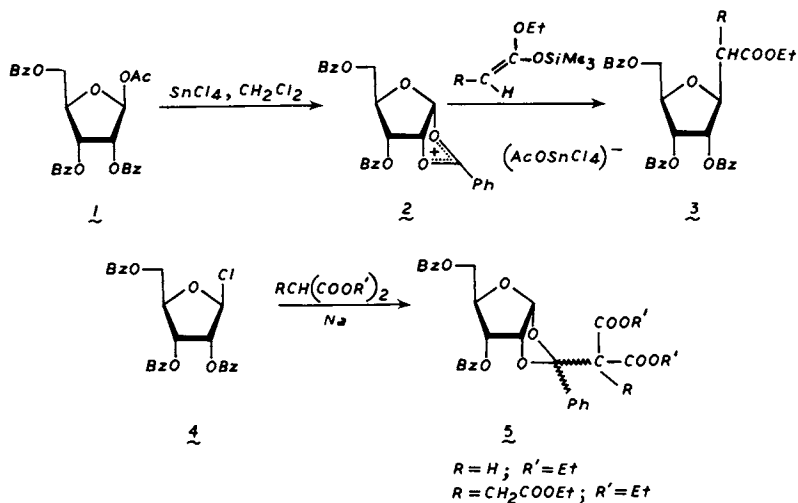


Figure 3

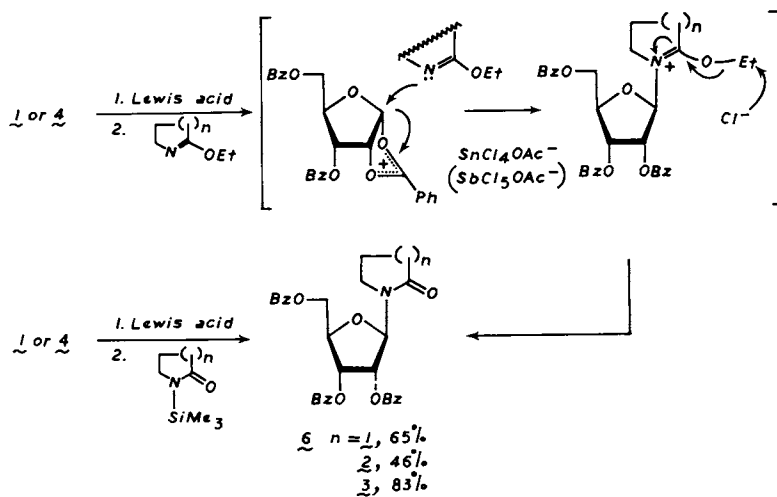


Figure 4

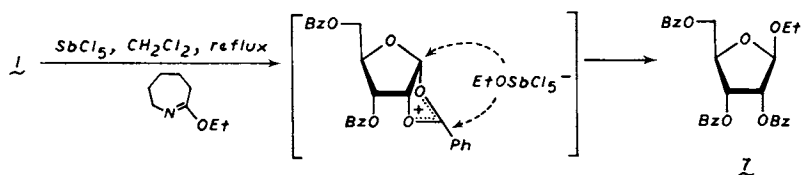


Figure 5

Formation of glycosides with amide acetals

Since their discovery by Meerwein and coworkers (24) amide acetals have been known to be powerful electrophilic reagents, whose reactivity is largely due to the existence of ionic species in solution (24,25,26), Figure 6. Amide acetals, such as the well known and commercially available *N,N*-dimethylformamide dimethylacetal, undergo facile exchange reactions with higher alcohols (27) and with appropriate 1,2- and 1,3-diols (24), Figure 6. The resulting (dimethylamino)alkylidene acetals are structurally related to cyclic orthoesters, and they undergo a variety of synthetically useful transformations (28). Amide acetals have also found applications in the chemistry of nucleosides and nucleotides (29,30), among other fields. Because of their tendency to exist in their ionic forms in solution, amide acetals were expected to be an excellent source of sustained amounts of alkoxide ions, hence, their potential utility in glycoside synthesis. It was therefore of interest to study the chemical behavior of this class of compounds toward sugar derivatives capable of generating 1,2-acyloxonium ions in the presence of a Lewis acid such as stannic chloride. Treatment of 1, successively with stannic chloride and *N,N*-dimethylformamide dimethylacetal in dichloromethane at 0°, led to the formation of methyl 2,3,5-tri-*O*-benzoyl- β -D-ribofuranoside 8 in 95% yield, Figure 7. The corresponding isopropyl, benzyl, cyclohexyl and neopentyl glycosides were similarly prepared in over 90% yield, from 1 and the appropriate *N,N*-dimethylformamide dialkylacetal (31). It is highly probable that the reaction leads first to the rapid formation of 1,2-orthoester derivatives, which are known from related work in this series to spontaneously rearrange to 1,2-trans glycosides in the presence of stannic chloride. Experiments are now in progress with the objective of trapping the possible orthoester derivative by performing the reaction at much lower temperatures. The possibility of a direct " β "-attack on an oxonium ion intermediate in which the " α "-side is shielded cannot be excluded at this time.

The glycosylation reaction was also extended to the D-gluco series. Thus, treatment of β -D-glucopyranose pentaacetate 9 with stannic chloride and *N,N*-dimethylformamide dimethylacetal in dichloromethane, gave methyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside 10 in over 80% yield. The corresponding benzyl glycoside was similarly prepared, Figure 8. However, the cyclohexyl or neopentyl glycosides could not be obtained under the same conditions, and prolonged reaction times led to

the recovery of 9 and the formation of varying amounts of 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl chloride 11. This may be due to the decreased reactivity (ionic) of N,N-dimethylformamide dialkylacetals having bulky, secondary alkoxy groups - a condition that is compensated by the much higher reactivity of 1, compared to 9. Although the formation of a 1,2-acyloxonium ion (32) in the pyranose series may, a priori, be considered as a favored process, and aided by the electronic interaction of the π system of the oxonium ion with the p orbitals of the C-2 acetoxy carbonyl oxygen atom, such an acyloxonium ion will have considerable ring strain. It should also be pointed out that the formation, and relative reactivities of such 1,2-acyloxonium ions are critically related to the nature of the Lewis acid, consequently to that of the counterionic species, and the situation may be different in going from antimony pentachloride (32) to stannic chloride. To explore this idea further, the known acetoxonium salt 13 was prepared, and subsequently treated with N,N-dimethylformamide dimethylacetal in dichloromethane. Surprisingly, methyl 1,2,3,4-tetra-O-acetyl- β -D-glucopyranuronate 12, was formed, resulting most likely from the complexation of the amide acetal with the Lewis acid, and stereospecific return of acetate ion. Identical results were obtained with the acetoxonium salt derived from β -D-xylose pentaacetate. These results led us to study the interaction between N,N-dimethylformamide dimethylacetal and antimony pentachloride and stannic chloride individually. In the first case an oily substance separates out from dichloromethane almost instantly. In the case of stannic chloride, a white solid was obtained, that was surprisingly stable to air. Treatment of 9 with this solid complex, in the presence of a catalytic amount of stannic chloride gave the glycoside 10, indicating that the complex contains the dimethylaminomethoxycarbonyl and methoxy species, and that it can dissociate in the reaction medium. In view of these results, it is believed that the glycosylation reaction is dependent on: a. the extent of ionization of the amide acetals and on the effect of catalytic amounts of the Lewis acid on this process, b. on the availability in solution, of reactive species such as oxonium and acetoxonium ions having ion-pairing relationships with the counter-ions that are favorable to glycoside (or orthoester) formation. It is of interest therefore, that no reaction occurred between 11 and amide acetals, even in the presence of added stannic chloride (compare with the D-ribo series in a later section on orthoesters). Efforts are in progress to

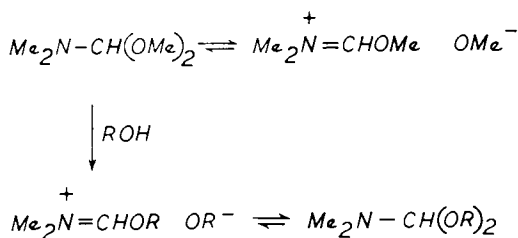


Figure 6

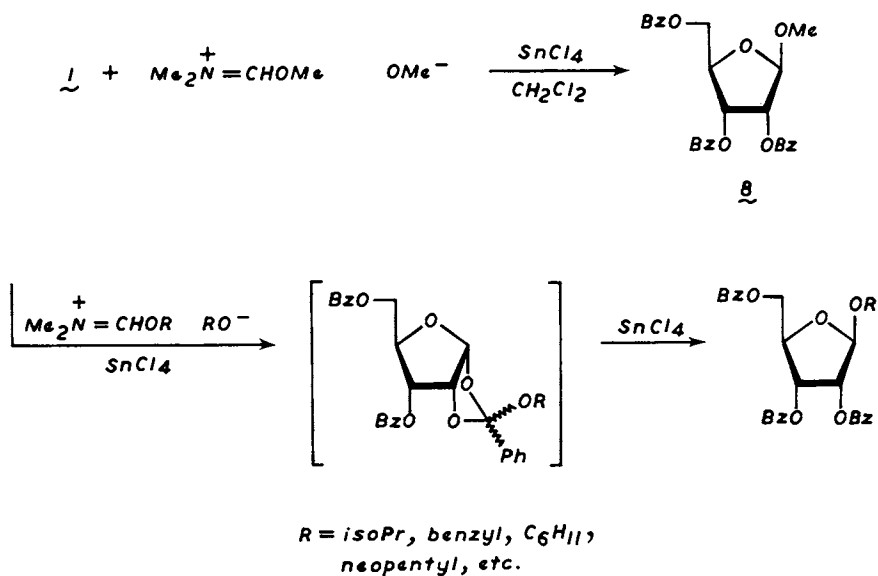


Figure 7

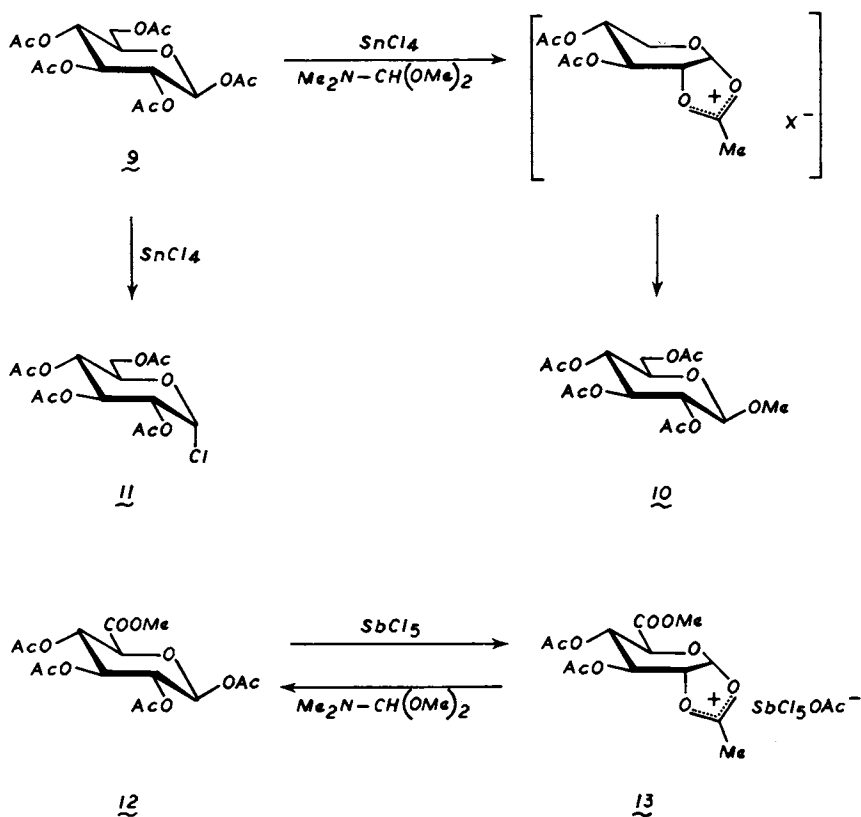


Figure 8

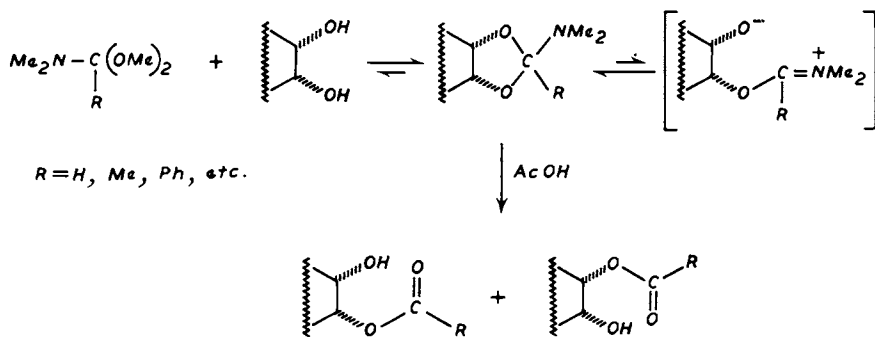


Figure 9

find methods of activation of amide acetals and of sugar derivatives, in order to provide higher concentrations of the reactive alcoholate species and acyloxonium ions.

The Lewis acid catalyzed glycosylation reaction using amide acetals as the source of the aglycon has several advantages, particularly when applied to the pentofuranose series. The reaction requires quasi-stoichiometric quantities of reagents, and leads to anomerically pure 1,2-*trans*-glycosides in high yield. In addition, the use of ester derivatives, rather than the often unstable glycosyl halide derivatives, coupled with the mild conditions, and the simplicity of operation contribute significantly to the practical aspects of the reactions. It is of interest to comment on the combination of reagents. In spite of the fact that stannic chloride and the amide acetals are, individually acidic and basic reagents respectively, in protic media, little, if any degradation occurs during the reaction.

The remarkable ability of amide acetals as alkoxide donors and their proven utility in the synthesis of alkyl β -D-ribofuranosides and alkyl β -D-glucopyranosides, urged us to extend these reactions to the possible formation of disaccharides (33). The anticipated success of the reaction was based on the premise that cyclic amide acetals [e.g. 1-(dimethylamino)alkylidene acetals], formed by an exchange reaction with appropriate diols, may be sufficiently reactive as glycosidating agents toward anomerically activated sugar derivatives, by virtue of the existence in solution of finite proportion of open iminium forms, particularly in the presence of a Lewis acid. Previous work in this laboratory had demonstrated the facile formation and synthetic utility of 1-(dimethylamino)ethylidene, and α -(dimethylamino)benzylidene acetals of a variety of sugar derivatives (28). For example, such acetals are suitable temporary protecting groups for vicinal, *cis*-diols. In addition, they undergo acid catalyzed ring opening reactions to give the corresponding esters, by what is now generally recognized as a stereoelectronically controlled process (34), Figure 9.

The 1-(dimethylamino)methylene derivative of *cis*-1,2-cyclohexanediol 14 (35) appeared to be a suitable model for exploring glycoside synthesis with cyclic amide acetals. Based on mechanistic arguments, it was anticipated that the resulting glycoside would be preferentially O-formylated in the aglycon portion, as a result of the hydrolysis of an initially formed dimethylaminoiminium (dimethylaminoalkoxycarbonyl) ion

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intermediate. Such an indirect temporary protection of a specific hydroxyl group, would give added preparative significance to the method. Indeed, treatment of 1 successively with stannic chloride (1.5 mmole equivalents) and the cyclic acetal derivative (1 mmole equivalent) in dichloromethane, followed by addition of aqueous sodium bicarbonate and usual manipulation gave a diastereomeric mixture of 2-O-formyl-1-cyclohexyl(2,3,5-tri-O-benzoyl- β -D-ribofuranoside) 16, (60%), as a colorless syrup, Figure 10. Methanolysis of the formate ester, simply by refluxing in methanol, gave the corresponding 2-hydroxy derivative 17 in over 90% yield. Finally debenzoylation led to a mixture of the two diastereomeric glycosides 18 and 19 that were isolated in crystalline form. The formation of 17 can be rationalized on the basis of the existence in solution, of the iminium salt intermediate 15, which would be expected to undergo hydrolysis during the processing of the reaction mixture. Monitoring the reaction mixture by thin layer chromatography showed the presence of a strong U.V. absorbing substance at the origin of the plates, presumably the salt 15, together with the gradual disappearance of starting material 1 and only traces of 16. Upon treatment of an aliquot with aqueous sodium bicarbonate however, this U.V. absorbing substance was replaced by the product 16, indicating that the latter is formed only upon aqueous hydrolysis of 15. To further confirm this hypothesis, 1 was treated with stannic chloride and with *cis*-1,2-cyclohexanediol, essentially under the same conditions as with the amide acetals. Monitoring the reaction revealed the formation of 16 directly, again lending support to the existence of the polar iminium ion intermediate in the original reaction mixture.

Encouraged by these results, we sought to extend the reaction to the synthesis of disaccharides containing the β -D-ribofuranosyl unit. Thus, with methyl 3,4-O-[1-(dimethylamino)methylene]-2-O-methanesulfonyl β -D-arabinopyranoside 21, prepared in quantitative yield by acetal exchange with 20 and N,N-dimethylformamide dimethylacetal, there was formed the crystalline disaccharide derivative 22 in 70% yield, Figure 11. Methanolysis of 22, led to the deformylated disaccharide derivative 23, which upon treatment under hydrolytic conditions (acetolysis, methanolysis) led to the formation of the component sugar derivatives. Additional evidence in favor of the structure of 22 was obtained by treatment of 23 with sodium methoxide in methanol (at 25° or reflux), whereupon the disaccharide derivative 24 was formed. This established the substitution

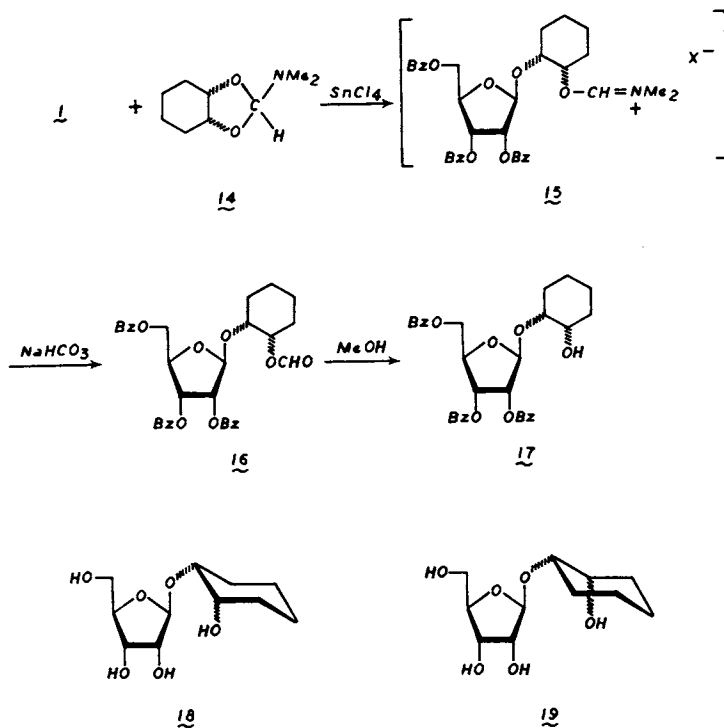


Figure 10

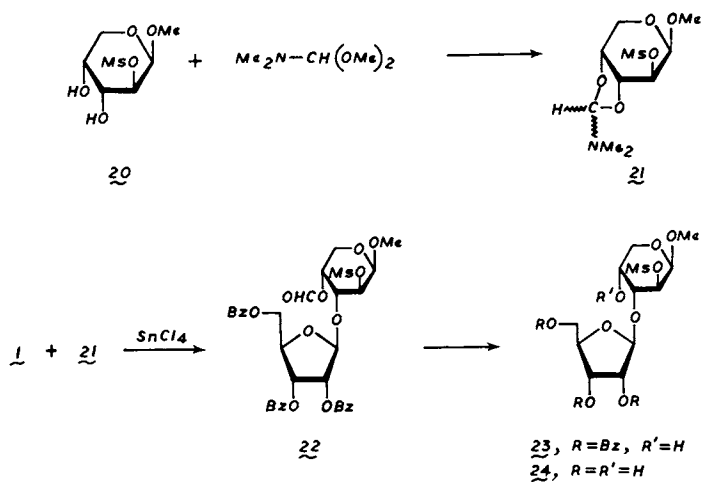


Figure 11

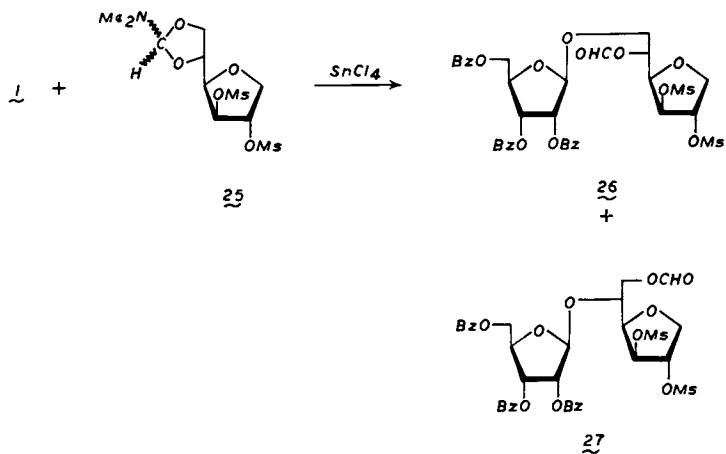


Figure 12

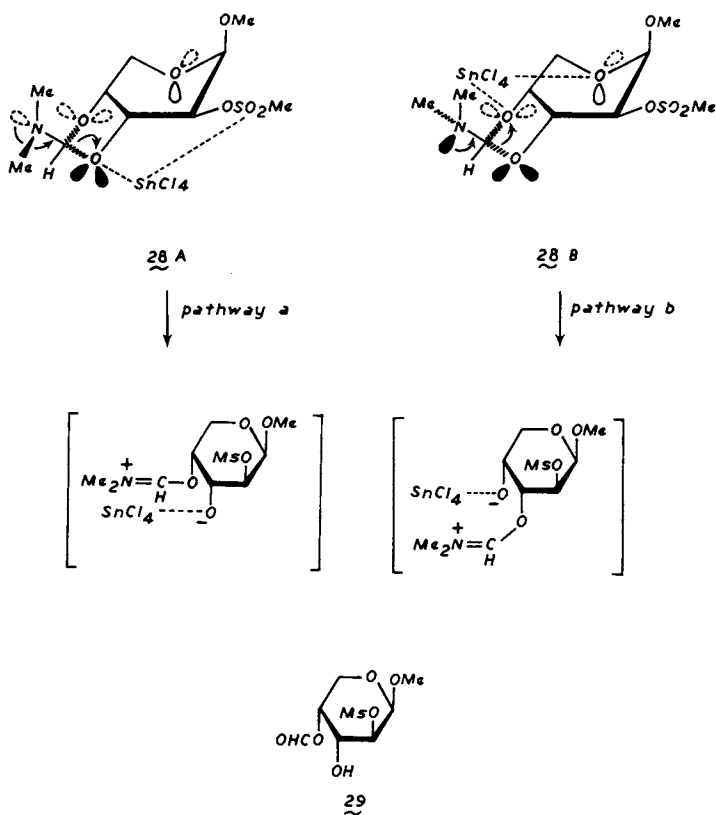


Figure 13

pattern in the disaccharide as being 1→3, since the alternative 4-O-substituted analog would have formed an epoxide derivative under these conditions, as shown in model experiments with methyl 2-O-methanesulfonyl-β-D-arabinopyranoside 20.

In another example, 1 was treated with 1,4-anhydro-5,6-O-[1-(dimethylamino)methylene]-2,3-di-O-methanesulfonyl-D-glucitol 25, in the presence of stannic chloride to give in this case, a mixture of the disaccharide derivatives 26 and 27 in a ratio of 3:1, Figure 12. These were conveniently separated, and their structures determined by sequential methanolysis, and tritylation, whereupon the 1→6-linked disaccharide was obtained as an amorphous powder (70%).

A priori, it would be expected that glycoside synthesis with unsymmetrical cyclic acetals such as 21 and 25, would lead to the formation of two positional isomers much the same way as two diastereomers were obtained in the case of 14. The reaction appears to be dependent on steric and stereoelectronic factors, which may vary in relative importance, depending on the type of cyclic acetal derivative. Let us assume that the conformation of 21 in solution is one approaching the half-chair structure 28 (represented as 28A and 28B), Figure 13, in which the C-O bonds of the dioxolane ring are quasi axial and quasi-equatorial with respect to the sugar ring. In this, and other conformations, the lone pair on the nitrogen atom can assume a *trans* periplanar orientation with respect to either of the two C-O bonds of the central orthoamide carbon atom such as in 28A and 28B, thus facilitating ring opening in both directions (pathways "a" and "b"). The apparent stereoselective formation of 22 can be better explained on the basis of a preferential cleavage of the C-O bond by pathway "a" (possibly assisted by a more effective complexation of the Lewis acid with the sulfonate group and the oxygen atom). This will lead to a more favorable steric outcome, while taking advantage of a possible stereoelectronic enhancement. The reactivity of the 1-(dimethylamino)methylene ring system in similar reactions, may, therefore be much more dependent on steric rather than stereoelectronic factors. A similar situation appears to exist in the hydrolysis of orthoesters (5). In fact, treatment of 21 with stannic chloride (1 equiv), and hydrolysis of the mixture with aqueous sodium bicarbonate gave the formate ester derivative 29, indicating the preferential ester formation at C-4. In the presence of stannic chloride, equimolar amounts of 1 and 29 led to the same disaccharide derivative 22, apparently without any detectable amounts of the

positional isomer, thus excluding the possibility of ester migration. Again, it should be pointed out that, in the original reaction (Figure 11), the reaction most likely proceeds by initial formation of an iminium ion intermediate, since none of 22 could be detected prior to aqueous hydrolysis of the reaction mixture. An authentic sample of 22 remained unaffected after treatment with stannic chloride. These reactions demonstrate the utility of 1-(dimethylamino)methylene acetals as precursors to selectively O-formylated diol derivatives, and the possibility of effecting Lewis acid-catalyzed glycoside syntheses with such derivatives.

Some unique features are associated with this novel synthesis of saccharides in the D-ribofuranose series. a. The reaction occurs under very mild condition with amide acetals derived from simple diols as well as from those of sugar derivatives, b. There appears to be an apparent regioselectivity in the glycosylation reaction, as indicated by the preponderance, or exclusive formation of one of two possible disaccharide derivatives, c. The reactions are stereocontrolled, leading to β -D-ribofuranosyl disaccharides, and they require quasi stoichiometric amounts of reagents, d. The hydroxyl group that is vicinal, and *cis*-disposed relative to the newly formed glycosidic bond in the aglycon portion, is protected as the formyl ester in the final product; subsequent selective hydrolysis of this group liberates an isolated hydroxyl group in the molecule, which can be subjected to further chemical manipulations. This feature could have important preparative applications, particularly in a synthetic scheme that calls for the stepwise assembly of pseudosaccharide units of the aminoglycoside type (7) and of oligosaccharides in general. For example, 5-O-(β -D-ribofuranosyl)deoxystreptomamine (36) constitutes an important pseudodisaccharide present in a number of clinically important aminoglycosides.

The synthesis of pseudo- and oligosaccharides by the presently described method may thus be of further preparative value, particularly if the reaction can be successfully extended to the pyranose series, and to amide acetals (imidates or iminium salts) derived from sugars derivatives (37). Efforts in this direction are now in progress in our laboratory.

Lewis acid catalyzed formation of glycosides and disaccharides

The facile formation of glycosides from anomeric-ally activated sugar derivatives and amide acetals, in

the presence of Lewis acids such as stannic chloride, prompted an investigation of the same reaction in the presence of an alcohol rather than the amide acetal. Lewis acid catalyzed glycosylations are not without precedent. Lemieux and Shyluk (38) had shown that β -D-glucose pentaacetate and methanol gave methyl 2,3,4,6-tetra-O-acetyl- β -D-glucoside (benzene, reflux). Apart from some applications in the synthesis of nucleosides (39,40) and C-glycosyl compounds, (21,22,41,42,43), the method has been largely neglected for the synthesis of O-glycosides (44). Our studies have shown that rapid and efficient glycoside formation takes place when peracylated sugar derivatives, in which the C-1 and C-2 ester groups bear a *trans* relationship, are allowed to react with various alcohols, including sugars, in the presence of stannic chloride. The stereospecific formation of β -D-ribofuranosides and β -D-glucopyranosides, suggests the intermediate formation of the corresponding 1,2-orthoesters, followed by stannic chloride catalyzed rearrangement. No anomerization is observed under the mild reaction conditions. Figure 14 illustrates some typical glycosides prepared by this method. It is of interest, for example that the crystalline 6-O-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)1,2:3,4-di-O-isopropylidene- α -D-galactopyranose is formed from 1 and 1,2:3,4-di-O-isopropylidene- α -D-galactopyranose in high yield. As previously discussed, glycosides such as 16, and the disaccharide derivative 22 were also prepared from 1 and the respective sugar derivatives in the presence of stannic chloride as catalyst. We note also that both *cis* and *trans* 1,2-cyclohexane diol form a solid complex with stannic chloride, that is insoluble in dichloromethane. The complex is hydrolyzed in aqueous sodium bicarbonate liberating the diol. The complexing property of stannic chloride and other Lewis acids have already been shown in the case of lactim ethers and amide acetals in earlier discussion. Studies in this area are continuing with the aim of enhancing the reactivity of the oxygen atom in polyols, cyclic amide acetals and imino ethers.

Formation of 1,2-Orthoesters with Amide acetals

Carbohydrate 1,2-orthoesters have been known for a long time (45), and they have been used for the synthesis of 1,2-*trans* glycosides (19), including some with complex aglycons. As previously mentioned, 1,2-orthoesters result from the trapping of 1,2-acyloxonium ion intermediates with appropriate alcohols, and are therefore considered as kinetic products. Their formation

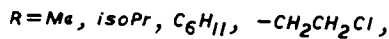
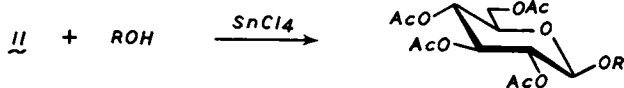
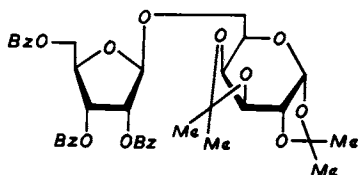
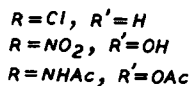
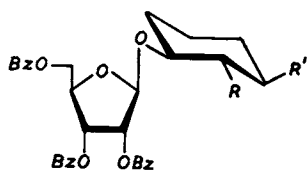
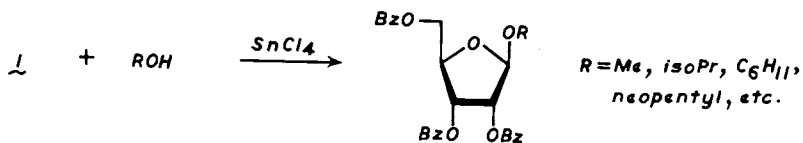


Figure 14

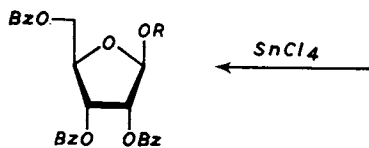
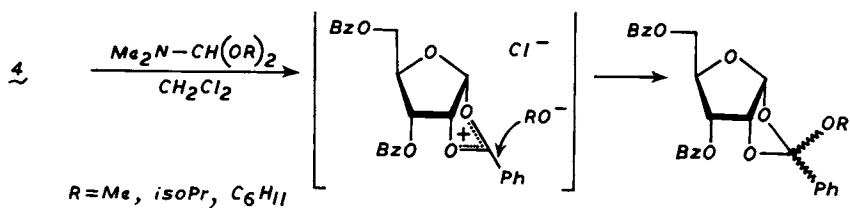


Figure 15

can also be rationalized based on the concept of "hard" and "soft" acids and bases (46), if we consider that the alcohol and the acyloxonium ion are, respectively, a "hard" base and "hard" acid. The synthesis of glycosides from orthoesters is based on an acid catalyzed rearrangement reaction, and the methodology has been considerably improved to allow the synthesis of di-, tri-, and oligosaccharides. In spite of the occurrence of minor side-reactions (47,48), glycosylations by the orthoester method are generally characterized by a high degree of stereocontrol, leading to 1,2-trans-glycosides as the principal products. There are at present several methods in the literature for the preparation of orthoesters (1,19,49) containing a variety of alkoxyl groups, including sugar derivatives. While preparatively useful in many respects, many of these methods are nevertheless, time consuming and in some cases, they are laborious.

Amide acetals have been found to be excellent reagents for the rapid and efficient preparation of carbohydrate 1,2-orthoesters (50). Treatment of 2,3,5-tri-O-acetyl- β -D-ribofuranosyl chloride 4, with various N,N-dimethylformamide dialkylacetals, in the absence of added salts or a proton acceptor, gave high yields of the corresponding orthoesters, Figure 15. The structures of the orthoesters were ascertained from their n.m.r spectra in which the presence of endo/exo mixtures was evident. Treatment of the respective products with aqueous hydrochloric acid in 1,4-dioxane gave, in each case, 2,3,5-tri-O-benzoyl-D-ribofuranose, which was characterized as the crystalline 1-acetate derivative 1.

Interestingly, when 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide 30 was treated with N,N-dimethylformamide dimethylacetal in dichloromethane, no reaction occurred. Again, this reflects the relative reactivities of the glycosyl halide derivatives 4 and 30, and the extent to which 1,2-acyloxonium ion formation is enhanced under the reaction conditions. The favorable 1,2-trans orientation of chlorine atom and benzoate group in 4 most likely plays a role in enhancing the formation of the corresponding acyloxonium ion. An analogous relationship exists between the bromine atom and the lone pair of electrons situated on one of the p orbitals of the ring oxygen atom in 30. Such stereoelectronic assistance however, will initially lead to an oxonium ion (Figure 2), and subsequently to the relatively strained 1,2-acetoxonium ion. In the presence of an equivalent amount of silver trifluoromethanesulfonate and the amide acetal however, 30 was

rapidly transformed into the corresponding 1,2-ortho-ester derivative, Figure 16. In this manner, methoxyl, isopropoxyl, neopentyloxyl and other alkoxyl derivatives were prepared. As expected, the powerful activating effect of the silver salt leads to a rapid release of bromide ion, and the formation of the 1,2-acetoxonium ion which is trapped by the alkoxide ions in solution. This constitutes a convenient and preparatively efficient synthesis of 1,2-orthoester derivatives in this series, (50).

It has also been found that the individual treatment of the orthoesters belonging to the D-ribofuranose series with stannic chloride in dichloromethane solution led to the corresponding β -D-glycosides in high yields. Similarly, methyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside was obtained from the corresponding orthoester. The merits of Lewis acids as catalysts in the rearrangement of orthoesters into 1,2-trans-glycosides are therefore worthy of further exploration. In view of these results, it is not unlikely that the Lewis acid catalyzed glycosylations with sugar peresters initially give the corresponding orthoesters, which undergo spontaneous rearrangement in solution.

Formation of glycosides in the presence of silver trifluoromethanesulfonate

Since the use of silver salts in glycosylation reactions by Koenigs and Knorr (18), many other acid acceptors have been introduced (1) with varying degrees of success. In general, such a "catalyst" should: a. promote the departure of halide ion from the 1-halogeno sugar derivative, b. effectively neutralize the hydrogen halide that is formed in the reaction, c. it should not form water in the reaction mixture, d. it should be neutral and non-nucleophilic in order to minimize competing attack at the anomeric center. Several such catalysts exist and they have been extensively used (1).

Silver trifluoromethanesulfonate (triflate) has proved to be an efficient catalyst for the formation of simple glycosides (51,52). Silver-assisted halide abstraction from glycosyl halide derivatives are rapid and occur at room temperature or lower. This is exemplified by the facile synthesis of the crystalline disaccharide derivative 31 in 50% yield from 30 and 1,2:3,4-di-O-isopropylidene- α -D-galactopyranose in the presence of this salt (50), Figure 17. It should be noted that the very strong acid, trifluoromethanesulfonic acid, is released in silver triflate-catalyzed

glycosylations and that aglycons or reaction products possessing acid-sensitive groups may undergo partial or total hydrolysis, particularly if the reaction conditions are not rigorously anhydrous.

Silver triflate has been found to be an efficient catalyst for the synthesis of several 1,2-trans-linked disaccharides, particularly in conjunction with N,N-tetramethylurea as a proton acceptor. This very weak base is capable of considerably diminishing the acidity of the powerful acid that is formed in the reaction. In addition, it is freely soluble in water, thus facilitating the isolation of the disaccharide derivatives. Using this combination of catalyst and acid acceptor, systematic glycosylations were carried out with the glycosyl bromide derivative 30, among other related compounds, at the hydroxyl groups situated individually on C-2, C-3 and C-4 of suitably protected methyl α -D-hexopyranosides. The respective 1,2-trans-disaccharide derivatives thus formed were isolated in good yields and individually characterized. Figure 17 illustrates the synthesis of the well known crystalline disaccharide derivative 32. The disaccharide derivatives 32, 33, 34 and 35 were obtained from the respective aglycons by a similar procedure, in yields over 70%. The position of linkage was established by conversions, wherever possible, into known derivatives. For example reductive desulfonylation of 33 with sodium amalgam, followed by acetylation gave the known (53) crystalline 36.

It is noteworthy that facile glycosylation was effected in the case of methyl 2,3,6-tri-O-benzoyl- α -D-galactopyranoside, to give the disaccharide derivative 35 in 70% yield. The structure and position of linkage was established by chemical degradation and mass spectrometry. The glycosylation procedure using silver triflate alone, or in combination with N,N-tetramethylurea appears to be of general applicability. Hopefully it will continue to be useful in the synthesis of other di-, tri-, and oligosaccharides and of glycosides containing complex aglycons. Indeed the stereocontrolled synthesis of glycosides related to the antitumor agent adriamycin, has been accomplished by this method (54). Finally, silver triflate and collidine have been recently used in the synthesis of 1,2-trans-glycosides in the amino sugar series (55).

Experimental Procedures

The following are selected experimental procedures for the preparation of some representative disaccharide

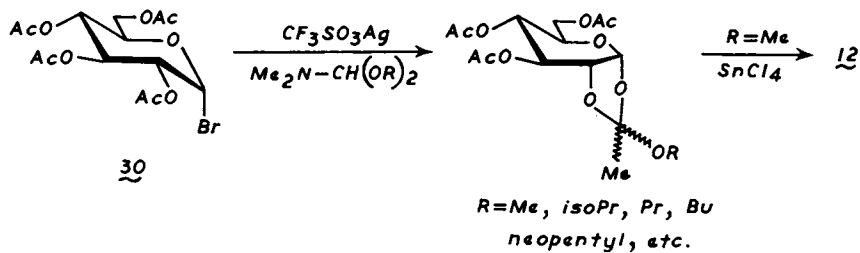


Figure 16

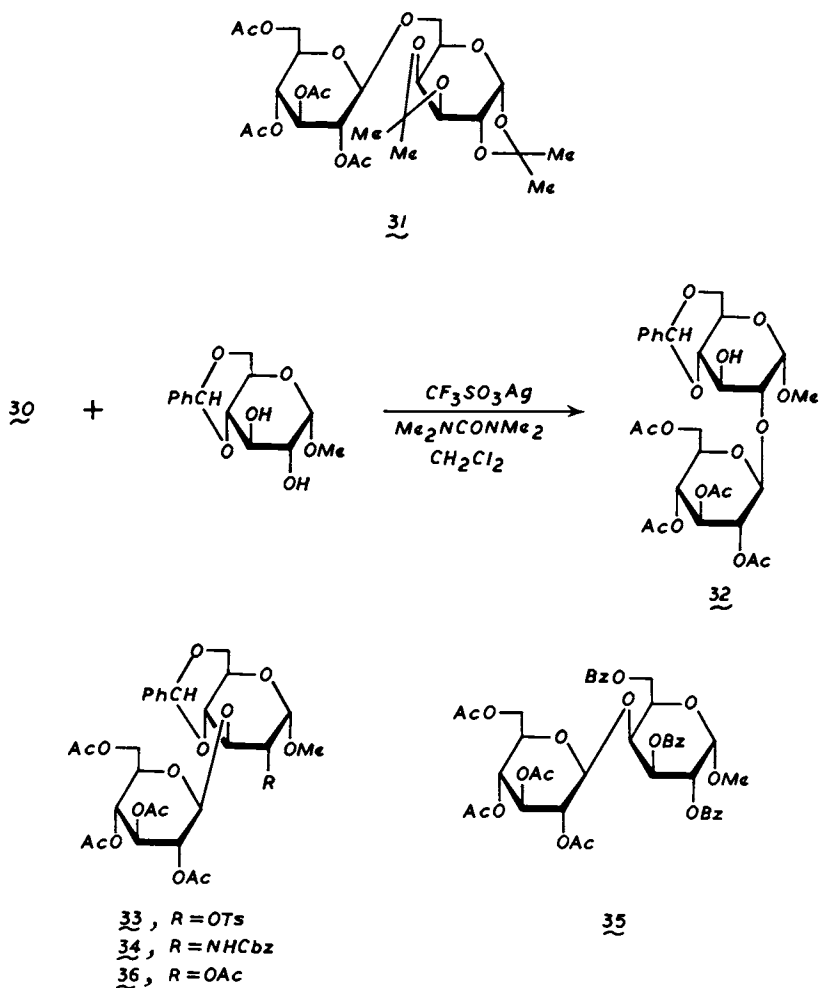


Figure 17

derivatives. The preparations of 1,2-orthoesters and their rearrangement (50), alkyl glycosides via amide acetals (31, 33), and other glycosides (56) have been previously communicated. In view of the extreme sensitivity of the acyloxonium ion intermediates and of silver triflate to moisture, it is of utmost importance to use solvents, reagents and starting materials, that have been rigorously dried, by azeotropic distillation of traces of water, or by other suitable methods.

Preparation of disaccharides with cyclic amide acetals (33).— A solution containing methyl 2-O-methanesulfonyl- β -D-arabinopyranoside 20 (1 mmole) and N,N-dimethylformamide dimethylacetal (1 mmole) in dichloromethane was stirred for 4h, then the solvent was removed by evaporation. The resulting syrupy acetal 21 was held at 0.1 torr for 1 h, dissolved in the minimum volume of dichloromethane, and added to a solution containing 1-O-acetyl-2,3,5-tri-O-benzoyl- β -D-ribofuranose 1 (1 mmole) and stannic chloride (1.1 mmole) in 10 ml of dichloromethane. After stirring 18 h at 25°, t.l.c indicated the absence of starting material and the presence of a strongly U.V absorbing polar substance. Usual workup (aq. sodium bicarbonate, extraction, drying, etc) gave a syrup that consisted of a major product. Purification on silica gel gave crystalline methyl 4-O-formyl-2-O-methanesulfonyl-3-O-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)- β -D-arabinopyranoside 22 (70%), m.p. 164–165°; $[\alpha]_D^{25}$ -43.16° (CHCl₃). Treatment of this product with methanol (reflux 4 h) gave the corresponding de-formylated disaccharide derivative as an amorphous solid; $[\alpha]_D$ -33.1° (CHCl₃).

Preparation of disaccharides in the presence of stannic chloride.— A solution containing 1 (1 mmole), stannic chloride (1 mmole) in 10 ml of dichloromethane was treated with 1,2:3,4-di-O-isopropylidene- α -D-galactopyranose (1 mmole). After stirring at 0° for 4 h, the solution was poured into aqueous sodium bicarbonate, and the organic layer was processed as usual. Chromatography gave 1,2:3,4-di-O-isopropylidene-6-O-(2,3,6-tri-O-benzoyl- β -D-ribofuranosyl)- α -D-galactopyranose, as a syrup (83%), which crystallized from ethanol, m.p. 201–203°.

Debenzoylation, followed by acetylation, gave the corresponding acetylated disaccharide derivative as a syrup; $[\alpha]_D$ -19° (CHCl₃); m/e 503 (M-15), etc.

Preparation of disaccharides using silver triflate.
a. 6-O-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)1:2,

3:4-di-O-isopropylidene- α -D-galactopyranose (31) — A suspension containing 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide 30 (1.3 mmoles), silver triflate (1.4 mmole) and N,N-tetramethylurea (3 mmoles) in 10 ml of dichloromethane was treated with 1,2:3,4-di-O-isopropylidene- α -D-galactopyranose (1.1 mmole). After 4 h at 25°, the mixture was filtered through Celite, the filtrate was neutralized with aqueous sodium bicarbonate and the organic layer was processed as usual to give a syrup. Chromatography, on silica (1:4 EtOAc-benzene) gave the title compound (70%), m.p. 140-141°; $[\alpha]_D^{25}$ -50° (CHCl₃) (57). The corresponding β -D-galactopyranosyl analog was similarly prepared.

b. Methyl 4,6-O-benzylidene-2-O-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)- α -D-glucopyranoside (33) — Essentially, the same procedure was followed as described above, except that the aglycon and catalyst were used in a two fold excess. The title compound was obtained as a chromatographically homogeneous syrup (47%) after chromatography on silica gel (1:9 EtOAc benzene). Crystallization from methanol gave the crystalline disaccharide derivative (41%), m.p. 226-227°; $[\alpha]_D$ +40.1° (CHCl₃) (58). The corresponding β -D-galactopyranosyl analog was similarly obtained.

Acknowledgments

Financial assistance from the National Research Council of Canada is gratefully acknowledged.

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Some Aspects of Organic Synthesis on Modified C-Nucleosides, Oxaprostaglandines, and Aminoglycoside Antibiotics

S. D. GERO, J. CLEOPHAX, D. MERCIER, and A. OLESKER

Institute de Chimie des Substances Naturelles, CNRS, 91190 Gif sur Yvette, France

For several years quite a few C-Nucleosides antibiotics have been found to display interesting antiviral and antitumoral activities (1-3). In these natural occurring antibiotics (Figure 1) the two heterocyclic systems are separated by a solid carbon-carbon bond. These linkages are not subject of either hydrolytic or enzymatic cleavage. The synthesis of such molecules is a difficult task in organic chemistry, but the preparation of such molecules has been described by several laboratories (4-7). However, there are very few data dealing with the preparation of modified C-Nucleosides antibiotics (8-10).

Considerable efforts (11-12) have also been made in the last years to replace the oxygen hetero-atom with another hetero-atom or to replace (18-20) the hydroxy-methylene or methylene groups with another hetero-atom. In the artisteromycin 1, the oxygen atom of the adenosine has been substituted (13-14) with a methylene group, the oxygen atom of D-glucose has been replaced in the 5-thio-D-glucose 2, and in the nojirimycine 3, with a sulfur (15-16) and with a nitrogen (17) hetero-atom, respectively. Oxa- and thia-prostaglandines 4 and 5 have been described in the literature (18-20).

Along this line, we have been interested in recent years in our laboratory in creating synthon intermediates which can be transformed to modified C-Nucleosides and 11-oxaprostaglandines.

Our approaches for these problems are outlined in Figure 2. We thought if the two functionalized epoxydes 6 and 8 could be synthesized, then they can be transformed to a modified C-Nucleoside antibiotics 7 and to the tetrahydrofuranoide system 9, and the latter then can be transformed to 11-oxaprostaglandines.

These two epoxydes were unknown in the literature and we synthesized them from the readily available D-Xylose. D-Xylose was transformed to the 2,5-anhydro-di-isobutyl-dithioacetal-D-Xylose 10, prepared by Zinner (1959) (21) and this is converted by well-established methods to the highly functionalized 11. The latter was treated with 2.5 molar of methanolic sodium methoxide and a mixture of the desired epoxydes 13 and 14 were obtained in a 70%

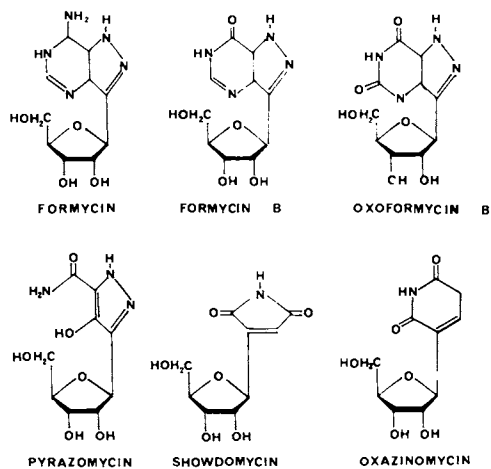
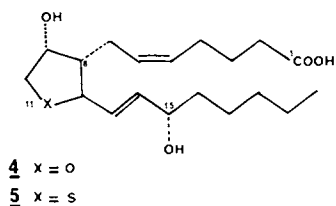
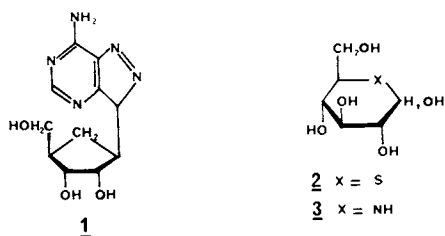


Figure 1



Structures 1-5

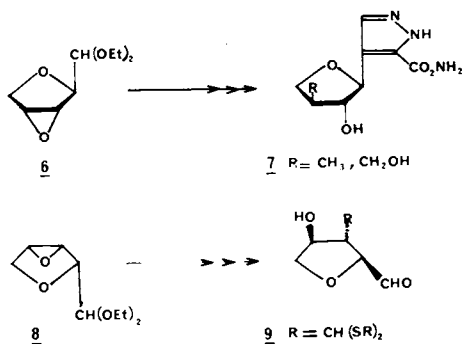
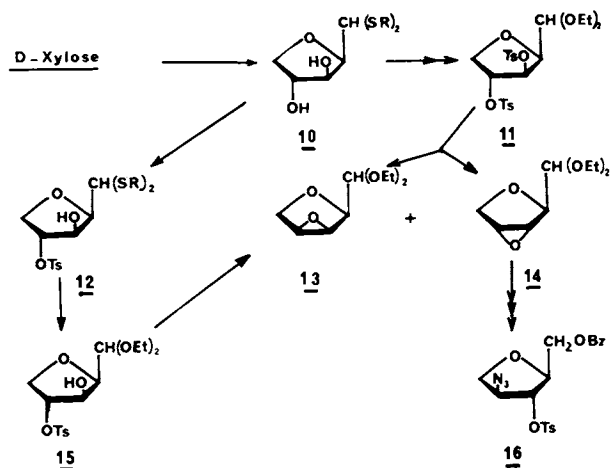
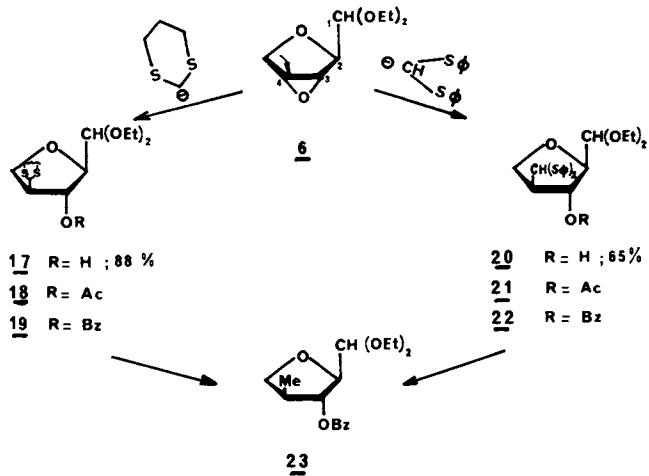


Figure 2



Structures 10–16



Structures 17–23

yield. The ratio of the epoxydes is 35% to 65%. The structure of these epoxydes has been confirmed by physical methods and by chemical correlation. The major epoxyde 14 was transformed by a series of reactions to 16 which was described by us in 1968 (22). The 14 was chosen for the synthesis of modified C-Nucleosides and the epoxyde 13 for the preparation of the synthon 9. Alternatively, the minor epoxyde 13 could also be synthesized by treating 10 with 1.2 molar of tosyl chloride followed by the transformation on treatment with methanolic sodium methoxide to the epoxyde 13 obtained previously from 11. This series of reactions can be realized without the isolation of the intermediates.

The modified C-Nucleosides have been prepared from the major epoxyde 6. The latter, on treatment with carbanions derived from dithiane or diphenyl dithioacetal of formaldehyde, gave in a regio-specific fashion 17 and 20 in a yield of 88% and 68%, respectively. The structure of these derivatives has been confirmed by physical methods, especially with ^{13}C NMR spectroscopy of their O-acetates 18 and 21 and of their O-benzoates 19 and 22. Both 19 and 22 have been desulphurized with Raney Nickel to the derivative of C-methyl 23. Both reagents opened the epoxyde 6 at the position 4. We were unable to detect the second possible isomer even in trace amounts. 23 was smoothly hydrolyzed to the C-formyl 24, which on treatment with carboethoxy methylenetriphenylphosphorane gave 25, which on further treatment with dizomethane followed by chlorination and dehydrochlorination furnished via 26 the carboethoxy C-Nucleoside 27, which was converted on treatment with ammoniac to 28. Using the same approach, a variety of other C-Nucleosides can also be prepared. (Figure 2)

The synthon 9 (Figure 2) for the preparation of 11-oxaprostaglandines have been synthesized from the epoxyde 13. The epoxyde on treatment with the carbonion derived from the diphenyl dithioacetal of formaldehyde gave two products, 29 and 31, in a yield of 79% and in a ration of 63% and 37%, respectively. The structure of these products, 29 and 31, was confirmed by NMR spectroscopy of their O-acetates 30 and 32. The minor opening product 31 has an absolute configuration which corresponds to the absolute configuration of the naturally occurring prostaglandines. In the major product 29 the two functionalized side chains are also *trans* but in a *meta* position 1, 3. The minor product 32 was hydrolysed to the aldehyde 33, and the latter on treatment with dimethyl (2-oxoheptyl) phosphonate furnished the unsaturated ketone 34, which was selected for further transformation to a variety of 11-oxaprostaglandines.

If we are using epoxyde 13 derived from either L-Xylose or D-Xylose (Figure 3), we can prepare the two enantiomeric 35 and 36, which corresponds at positions 8 and 12 to the absolute configuration of the natural and enantiomeric prostaglandines. The O-Acetate in 35 and 36 can be epimerized with well-established methods.

MUTATIONAL BIOSYNTHESIS OF AMINOGLYCOSIDE ANTIBIOTICS

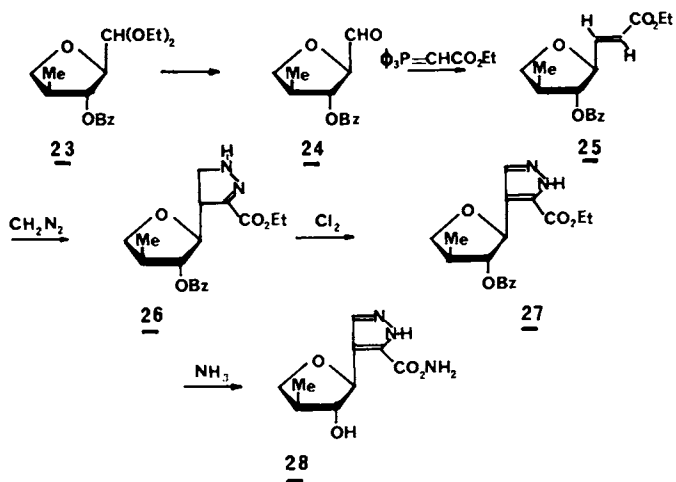
Recent isolation of a variety of aminoglycoside antibiotics, with clinical and molecular biological importance, has provided challenging problems to organic chemists and biochemists (23-26). In these antibiotics, outlined in Figure 4, the central moiety 2-deoxy-streptamine is glycosylated at positions 4 and 5 for the neomycin type and at positions 4 and 6 for the kanamycin type antibiotics with a large variety of carbohydrate derivatives.

Due to their extensive clinical use, R-factor mediated enzymes were developed (24, 26, 27) which inactivate these antibiotics by O-phosphorylation, O-adenylation and N-acetylation at the different positions shown by the arrows (Figure 4). Undoubtedly, the inactivation of these antibiotics against different bacterial strains provided an impetus for an intensive chemical and biological research.

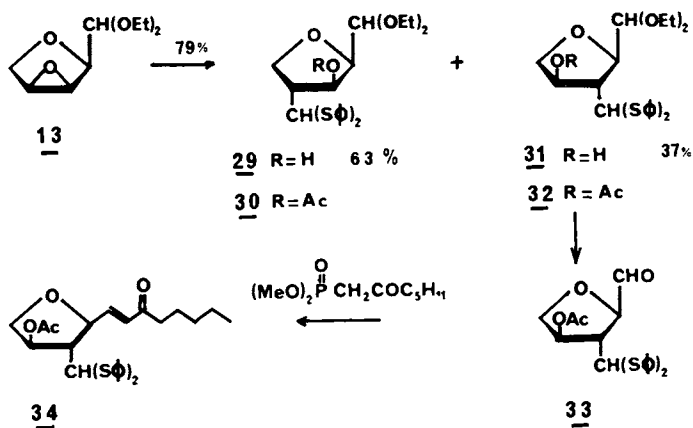
In the ribostamycin 37, (Figure 5), the fourth subunit of neomycin is absent, and in the butirosin B 38 the 1-amino group of ribostamycin is acylated with L(-)- γ -amino- α -hydroxybutyric acid. The presence of this side chain at the C-1 amino group of the 2-deoxystreptamine confers exceptional antibacterial properties (26) on the butirosin B, including its activity against gram negative bacteria-for instance, *Pseudomonas aeruginosa*. Due to this discovery, a large variety of N-acylated derivatives of these type of antibiotics have been synthesized and the amikacin 39 in which the C-1 amino group of kanamycin A is acylated with the same L(-)- γ -amino- α -hydroxybutyric acid has been discovered (28). The latter is an excellent antibiotic against a variety of bacteria which inactivate the parent kanamycin A. In butirosin 38 and in amikacin 39 the central moiety of the 2-deoxystreptamine has been modified, and the fact that active antibiotics have been obtained by modifying the central part of these antibiotics suggest that by modifying this part of the molecule, interesting and new type of antibiotics can be obtained.

It is very interesting to note that in minosaminomycin 40 -a recently discovered (29) antibiotic- the aglykon part of the molecule is a 1-D-1-amino-1-deoxy-myoinositol, and the sugar part, which is located as usual at the position 4, is kasugamine. The C-1 amino group is acylated with a dipeptide. We are dealing in the minosaminomycin from a biosynthetic point of view with a mixed antibiotic of the kasugamycin and 2-deoxystreptamine types. This is the first time that 1-D-1-amino-1-deoxymyoinositol appears as a component of aminoglycoside antibiotics.

The third event on the modification of the 2-deoxystreptamine moiety of these antibiotics has produced, with the isolation of mutant strains by Rinehart and his colleagues (25, 30, 31) from *Streptomyces fradiae*, producing neomycin-type antibiotics. D⁻mutants could not produce neomycin from the normal carbon and nitrogen sources except if amino-cyclitols were added to the fermentation medium. 2-deoxystreptamine, streptamine and epistreptamine were transformed by this mutant to the corresponding antibiotics



Structures 23–28



Structures 29–33

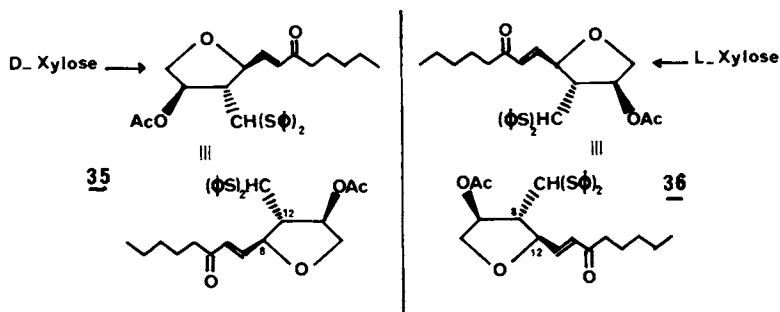


Figure 3

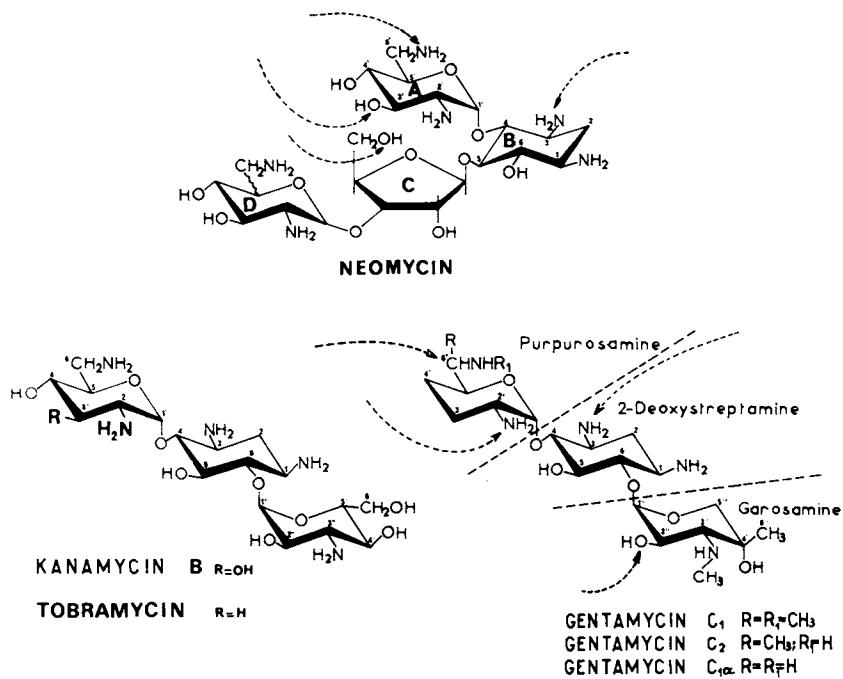


Figure 4

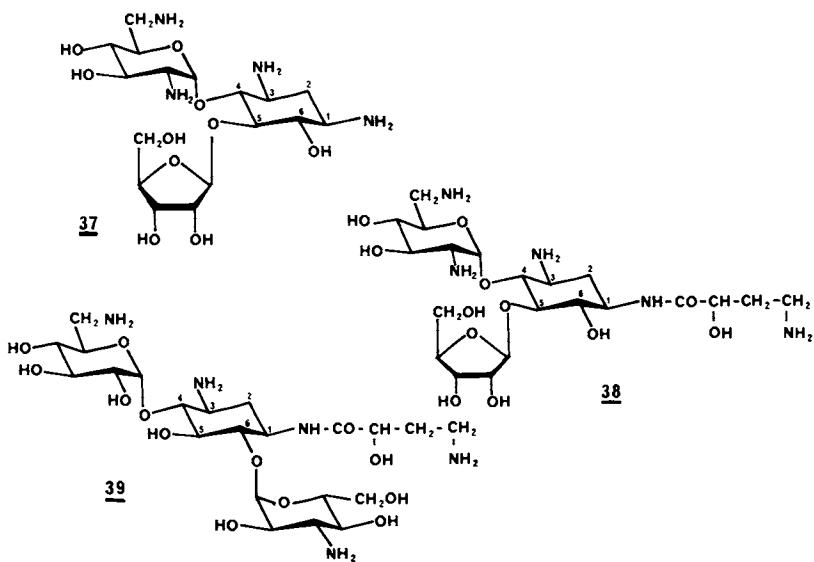


Figure 5

called hybrimycins (Figure 6). These new antibiotics, with a modified amino-cyclitols, retained antibacterial properties (31).

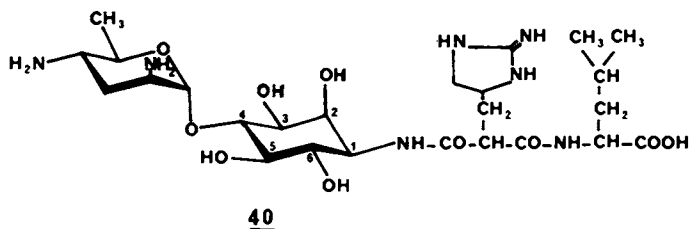
A large variety of D⁻mutants (32-36), using the same approach have been isolated and used for the biosynthesis of new types of antibiotics. Mutants isolated from *Micromonospora inyoensis* (34), the sisomicin-producing organism, which require the addition of 2-deoxy-streptamine to the fermentation broth for sisomicin production. The addition of analogues of 2-deoxystreptamine to this mutant resulted in the formation of new antibiotics called mutamicins. These mutamicins, shown in Figure 6, produced by the addition of 2-deoxystreptamine and 2,5-dideoxystreptamine to the fermentation broth exhibit broad spectrum antibiotics. Most interestingly, mutamicin 2 produced by the addition of 2,5-dideoxystreptamine, exhibits similar broad spectrum activity against gentamicin-sisomicin-acetylating strains.

It was clear to us that an entirely new approach is available in using D⁻mutants for producing antibiotics. To use this type of mutational biosynthesis, we needed the individual components of these antibiotics, and in the past years we have prepared a variety of these substances - for instance: tobrosamine (37), purpurosamine (38,39), lividosamine (40), and a variety of amino-cyclitols related to 2,4-dideoxystreptamine (41). However, I would not like to talk about the synthesis of these substances, which was partially discussed (42) in my lecture at the Philadelphia American Chemical Society meeting in 1975, but I would like to talk about a new biosynthetic methodology, namely, the mutational biosynthesis of these amino-cyclitol glycoside antibiotics, especially the mutational biosynthesis of neomycin (43).

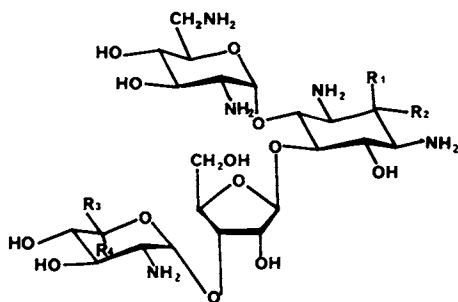
It has been reported recently by Rinehart (25-44) that the subunits A, B, C, D of neomycin derived from D-glucose. The order of the assembly of their subunits, however, never has been disclosed. Rinehart stated (23,31) that a D⁻mutants isolated from *Streptomyces fradiae* could not produce antibiotic neomycin if neamine, which are the A, B subunits of the neomycin, has been added to the fermentation broth. For a couple of years we were engaged in biosynthetic studies in this field and we asked ourselves two questions: (1) what is the exact order of the formation of the 4 subunits - A, B, C, D, - of the neomycin, and (2) when the functionalization occurs.

Rinehart failed to produce neomycin antibiotic, supplementing the medium of D⁻mutants with exogenous neamine, and therefore he considered as a possible biosynthetic intermediate 5-O-D-ribosyl-2-deoxystreptamine. Surprisingly enough, and contrary to his view, neamine, the subunit A and B of the neomycin, was transformed (43), using D⁻mutants to neomycin (Figure 7). Supplementing the medium with a synthetic 5-O-D-ribosyl-2,6-dideoxystreptamine (45), neomycin was not biosynthesized (Figure 7).

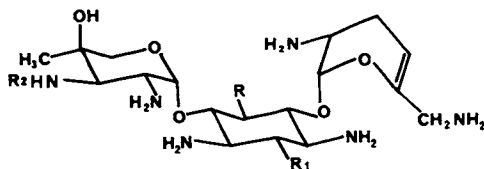
This experience, however, did not provide conclusive evid-



Structure 40



	Aminocyclitol	R ₁	R ₂	R ₃	R ₄
Hybrimycin A ₁	Streptamine	H	OH	H	CH ₂ NH ₂
Hybrimycin A ₂	Streptamine	H	OH	CH ₂ NH ₂	H
Hybrimycin B ₁	Epistreptamine	OH	H	H	CH ₂ NH ₂
Hybrimycin B ₂	Epistreptamine	OH	H	CH ₂ NH ₂	H



Sisomicin	R = OH	R ₁ = H	R ₂ = CH ₃
Mutamicin 1	R = R ₁ = OH		R ₂ = CH ₃
Mutamicin 1a	R = R ₁ = OH		R ₂ = COCH ₃
Mutamicin 1b	R = R ₁ = OH		R ₂ = H
Mutamicin 2	R = R ₁ = H		R ₂ = CH ₃

Figure 6

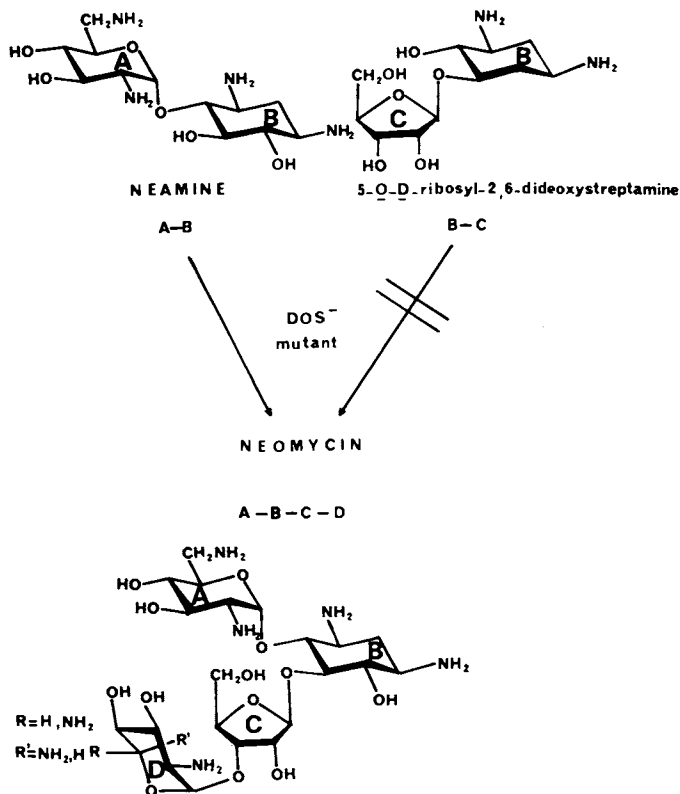


Figure 7

ence whether the exogenous neamine was cleaved by an enzyme present in the medium to the 2-deoxystreptamine and transformed to the neomycin. In order to shed light whether the neamine incorporated into the neomycin without cleavage in an intact fashion, we decided to biosynthesize two types of radioactive neamine (Figure 8): first, labelled at both subunits A, B with ^{14}C ; and secondly, a neamine labelled only at subunit A with tritium. By mixing these two differently labelled neamine the ratio of the tritium and ^{14}C was found to be $^3H/^{14}C=14$. When the mixture of these labelled neamines is given to the D^- mutants of *Streptomyces fradiae*, the neomycin produced had a radioactivity of $^3H/^{14}C=15$. Neamine is transformed without cleavage to the neomycin. If the neamine might have been cleaved enzymatically, and biosynthesized by D^- mutants the ratio of the radioactivity found should have been totally different. This is the first time, as far as we are aware, that we demonstrated univocally that the neamine-pseudo disaccharide had been accepted by D^- mutants and incorporated without clea-

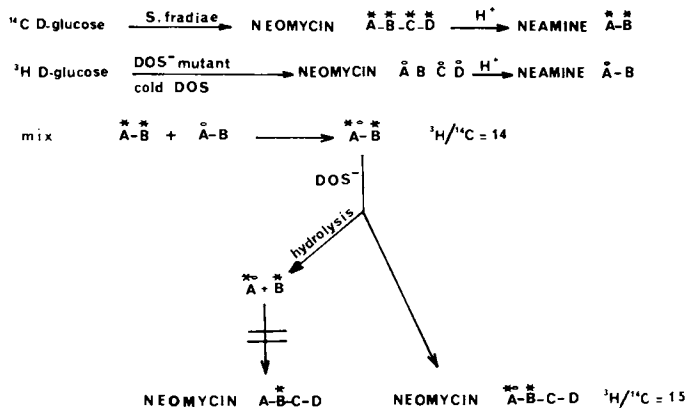


Figure 8

vage to the antibiotic neomycin. Consequently, in the neomycin biosynthesis the neamine must be on the biosynthetic pathway. Most probably, the third subunit C -the D-ribosyl, - and the fourth subunit D, - neosamine B - were attached successively.

Similarly, to our results, pseudo di- and tri- saccharides have also been transformed by D⁻mutants isolated from *Micromonospora inyoensis* or *Micromonospora purpurea* to sisomicin and gentamicin types antibiotics (35, 36).

These studies, which will be continued in our laboratories, should have an important bearing for many academic questions on the detailed biosynthesis of these antibiotics, and also should provide a very powerful new biochemical methodology producing new type of antibiotics.

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Stereochemistry of Nitrogen Heterocycles Containing Sugar: A Generalized Circular Dichroism Rule

HASSAN S. EL KHADEM

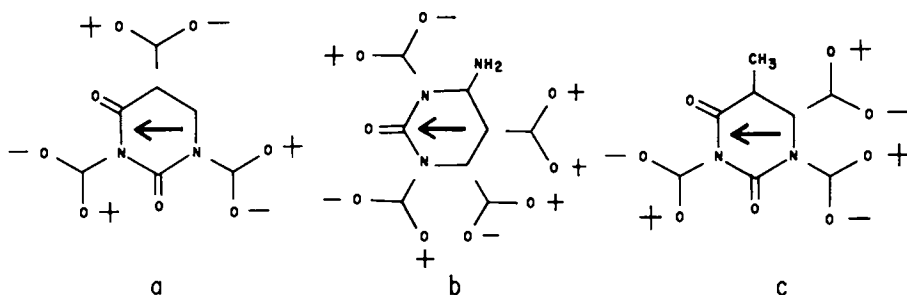
Department of Chemistry and Chemical Engineering, Michigan Technological University, Houghton, Mich. 49931

The circular dichroism (c.d.) of pyrimidine and purine nucleosides has been extensively studied (1-4). It has been shown that dipole-dipole coupling between the near-ultraviolet bands of the chromophore and the far-ultraviolet bands of the sugar produces a coupled-oscillator contribution to the optical activity of the aromatic chromophore. Several rules have been proposed to correlate the sign of the Cotton effect of nucleosides with their conformation and more specifically, the angle between the plane of the heterocyclic ring and the direction of the C-1'→0 bond (1,3,4). Attempts have also been made (4) to compute the magnitude of the Cotton effect by using as variables (a) the unit vector in the direction of the electric dipole moment, \vec{e}_B ; (b) the unit vector in the direction of the principle axis of polarizability of the D-ribosyl group, \vec{e}_S , and (c) the distance vector, \vec{R}_{BS} .

El Khadem, Kreishman, Swartz, and El Khadem (5) have used similar parameters to develop an empirical rule that predicts the sign of the Cotton effect of glycosyl pyrimidines and purines linked to the various positions of these bases. The present work aims at refining the above mentioned rule and generalizing it so as to apply to any heterocycle linked to a cyclic sugar or a hydroxyalkyl chain. The present rule correlates the sign of the Cotton effect of the heterocycle with the following variables: (a) the R and S configuration of the first chiral center attached to the heterocycle; (b) the direction of the principle axis of polarizability of the sugar residue defined by the direction of the C-1'→0 vector relative to the electric dipole moment vector, in the more stable conformer; (c) the position of the glycosyl group relative to the dipole moment vector of the heterocycle.

The rule may be illustrated for pyrimidine nucleosides by placing the pyrimidine ring along the x axis with the negative end of the dipole moment pointing in the negative direction. Since pyrimidine rings do not have planes of symmetry, they must be aligned arbitrarily in the x, y plane in such a way as to give

the correct sign of Cotton effect for known nucleosides (6-11). The figure shows the proper alignment for uracil (a), cytosine (b), and thymine (c). The orientation of the glycosyl group with respect to the base is depicted by the C-1'→O bonds in the syn and anti orientations, and the sign of the Cotton effect given for each conformer. A study of the data for the known compounds has led to the generalizations given below which may be used to predict the sign of the Cotton effect of as-yet-unknown glycosyl-pyrimidines.



1. For a nucleoside having C-1' of the glycosyl group in the R configuration, such as a β -D-ribofuranosyl group, and having \vec{R}_{BS} negative in the y direction, i.e. the glycosyl group lying below the base, the sign of the Cotton effect will be negative if the x components of \vec{e}_S (roughly represented by the C-1'→O bond) and the dipole moment vector of the base and \vec{e}_B point in the same direction. The sign of the Cotton effect will be positive if these two vectors point in opposite directions.

2. If the \vec{R}_{BS} vector is positive in the y direction, the glycosyl group lying above the base, the sign of the Cotton effect will be positive when the x components of \vec{e}_S and \vec{e}_B are in the same direction, and it will be negative if the x components are in opposite directions.

The inversion of the sign above and below the x axis in rules 1 and 2 is to be expected, as a rotation of 180° of the base inverts the sense of the ring in the x, y plane, and changes \vec{e}_B to $-\vec{e}_B$, owing to the contributions of the transitional, bond-order term (1) to \vec{e}_B as follows:

$$\vec{e}_B \times \vec{e}_S \cdot \vec{R}_{BS} = - \left[-\vec{e}_B \times \vec{e}_{SR} \cdot \vec{R}_{BSR} \right]$$

where \vec{e}_{SR} and \vec{R}_{BSR} are the \vec{e}_S and \vec{R}_{BS} vectors, respectively, rotated about the x axis by 180° . It may also be shown that a rotation of 180° around the y and x axes will not cause an inversion of the sign of the Cotton effect.

3. If \vec{R}_{BS} is essentially aligned with \vec{e}_B , the glycosyl bond being aligned with the dipole moment vector, as in 5-glycosylcytosines, the sign of the Cotton effect is independent

of rotation about the glycosylic bond. This is to be expected, since under these circumstances, rotation of the base with respect to the glycosyl group does not change the angle between \vec{e}_B and \vec{e}_S . In such cases, if the \vec{R}_{BS} vector is in the same direction as the \vec{e}_B vector, the sign of the Cotton effect is negative; it is positive if the two vectors oppose each other.

For glycosyl groups having the S configuration of C-1', the sign of the Cotton effect is the reverse of that described for the R configuration.

The foregoing rule may be applied to predict the sign of the Cotton effect of nucleoside analogs if three requirements are met: (1) The base itself is not modified in any way which would significantly change its dipole moment. Accordingly, 6-azacytidine is excluded; (2) The sugar is not significantly modified by derivatization. Thus, for example, 4'-thiouridine and *p*-toluene-sulfonic esters of nucleosides are excluded; (3) The base is not strained by ring formation. Thus, 2,2'- and 2,5'-anhydrouridine are excluded. Requirements 1 and 2 are necessary, as the relative orientation of the dipole moment of the base and the axis of polarizability of the glycosyl group is paramount in determining the sign of the Cotton effect. Requirement 3 is necessary because, as pointed out by Miles et al (4), the strained conformation markedly alters the electronic spectra of anhydronucleosides, and hence their Cotton effects.

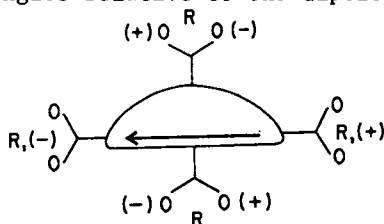
The rule allows the replacement of a cyclic glycosyl group by a hydroxyalkyl chain having the same configuration at C-1', because the latter also exists in favored conformations (12,13) and the sign of rotation is governed (14) by the configuration of C-1' and by the orientation with respect to the heterocyclic ring.

Application of the CD Rule to Other Heterocycles

The above mentioned rules could be generalized so as to apply to other heterocycles attached to hydroxyalkyl chains or cyclic sugars.

1. Heterocycles having no plane of symmetry along the dipole moment vector:

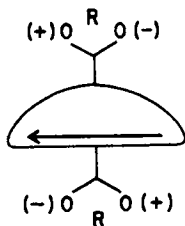
The figure below depicts an idealized heterocycle having the dipole moment vector pointing towards the negative direction of the x axis and shows the predicted sign of Cotton effects for a hydroxyalkyl chain or a cyclic sugar attached to the heterocycle at various angles relative to the dipole moment vector.



The idealized heterocycle does not possess a plane of symmetry in the direction of the dipole moment vector and must be properly oriented along the x axis to define its upper and lower halves before one can predict the Cotton effect of hydroxyalkyl chains or cyclic sugars attached to one of the two halves of the ring. This is, however, not necessary if the bond linking the heterocycle to the saccharide residue is aligned with the dipole moment vector. Thus, in the heterocycle shown below where the bond linking the heterocycle to an R chiral center is pointing in an opposite direction to the dipole moment vector, the sign of the Cotton effect will be positive, and conversely, it will be negative if both these vectors are aligned and pointing in the same direction.



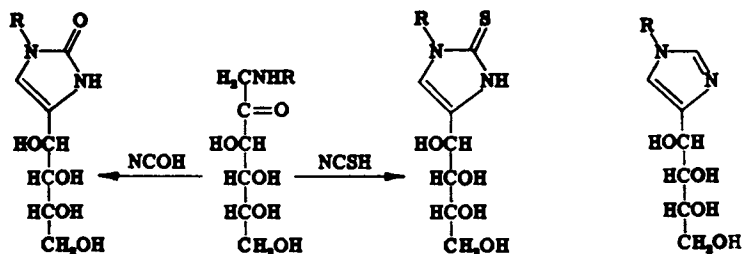
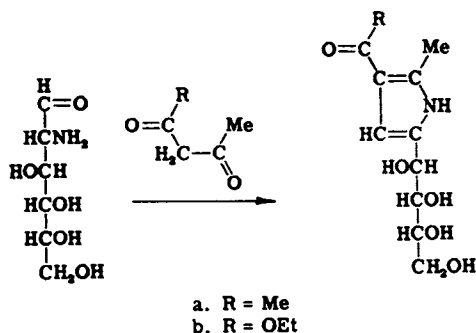
This seems to be a general rule applicable to compounds having hydroxyalkyl groups attached to heterocycles or chromophores by bonds aligned with the dipole moment of the heterocyclic ring or chromophore. Such molecules can exist in a multitude of enantiomeric pairs of conformers which will cancel one another's effect on the circular dichroism. The conformation of the first chiral center next to the heterocycle will, therefore, have no effect on the sign of the Cotton effect, and the latter will be solely determined by the configuration of this first chiral center.

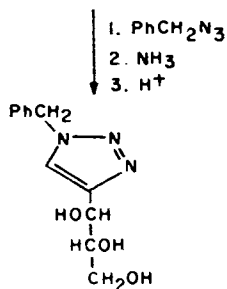
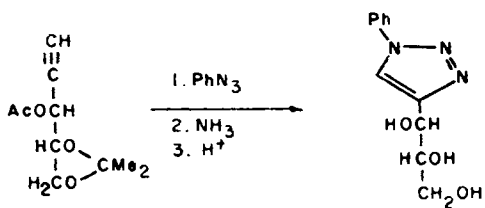
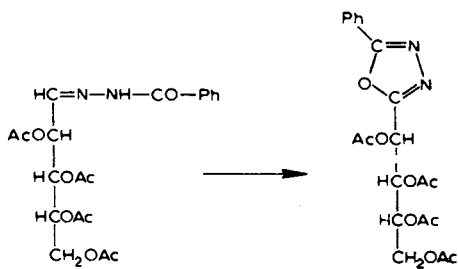
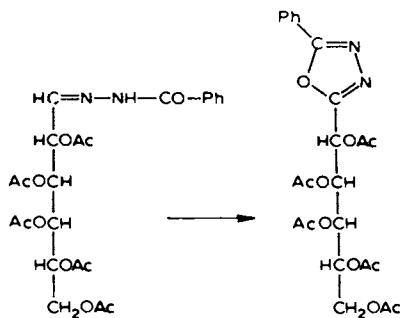


As mentioned earlier, if the saccharide ring or hydroxyalkyl chain in the heterocycle shown above is perpendicular to the dipole moment vector of the heterocycle or has a component in the direction of the y axis, it will be necessary first to establish the position of the sugar residue relative to the dipole moment vector and define whether it is attached to the lower half or the upper half of the heterocyclic ring in order to predict the sign of the Cotton effect of the stable conformer.

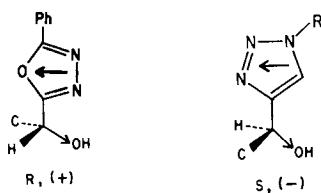
This is because exchanging the position of the sugar in these semicircles will result in an inversion of the sign of the Cotton effect (see rule 2, p. 2). The means of determining the exact orientation of the heterocycle around the x axis presents the main difficulty in the present rule. The proper alignment of the ring in the case of pyrimidine was arbitrarily determined by studying a large number of substituted pyrimidines whose CD curves were measured and whose conformation had been established. Similar studies were needed for other heterocycles which, unfortunately, were not as exhaustively studied and whose stable conformation could only be guessed.

A review of the literature reveals several examples of heterocyclic rings attached to hydroxyalkyl chains or to glycosyl rings that obey the above generalized rule for CD. These include the hydroxyalkylpyrroles, the hydroxyalkylimidazoles and thioimidazoles discussed in this volume by Garcia-Gonzalez and the hydroxyalkyloxadiazoles prepared by H. El Khadem and coworkers (15) and the hydroxyalkyl 1,2,3-triazoles prepared by El Khadem, Horton and others (16) which are shown in the following:

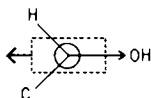




All the previous compounds will obey rules 1, 2, and 3, discussed on page 2, when the ring is properly aligned. In general, this requires the negative substituent or heteroatom in the ring to be located in the upper half of the ring and the hydroxyalkyl chain at the bottom. Assuming that the stable conformation for the hydroxyalkyl chain is that in which the oxygen of the hydroxyl group of the chiral center attached to the heterocycle will tend to move away from the negative end of the dipole, then the sign of the Cotton effect will be determined by the configuration of the first chiral center attached to the ring. If the configuration is R, the Cotton effect is positive and is negative when it is S, as exemplified by the R oxadiazole and the S triazole shown below:



This rule may also be illustrated by the Newman projections represented in the following page which shows a heterocyclic ring drawn behind the plane paper and perpendicular to it, and the first chiral center attached to it protruding towards the observer. If, as expected, the stable conformer will tend to have the OH away from the negative end of the dipole moment vector, the compound will follow the generalized rotation rule by El Khadem and El Shafei (17) which states that the rotation of a hydroxyalkyl heterocycle is determined by the configuration of the first chiral center. When this has an R configuration, the rotation is (+) and vice versa.

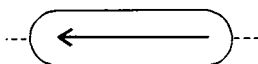


If the stable conformer in all of these compounds does tend to have the OH group which is the most negative part of the first chiral center away from the negative end of the dipole moment of the ring, then according to rule 1, the R form of these compounds will be dextrorotatory or have a positive Cotton effect and vice versa.

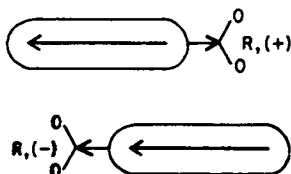
2. Heterocycles having a plane of symmetry along the dipole moment vector:

Another class of heterocycles of interest are the hydroxy-alkyl derivatives of heterocycles having a plane of symmetry

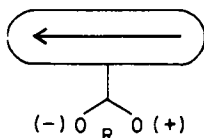
along the dipole moment axis. The upper half of these heterocycles is a mirror image of the lower half represented below:



As with the heterocycles discussed in the previous section, if the bond linking the hydroxyalkyl chain and the heterocycle is aligned with the dipole moment vector, then the sign of the Cotton effect will depend only on the configuration of the first chiral center. It will be positive for the R compound irrespective of conformation if the bond linking the heterocycle to the sugar is residue pointing in the direction opposite of that of the dipole moment vector and vice versa.

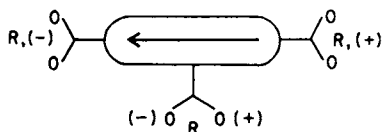


If the bond linking the heterocycle to the saccharide residue is perpendicular to the dipole moment vector or has a component in that direction, then again the same relationship discussed for the group of heterocycles lacking a plane of symmetry along the x axis will hold true. The only difference being that the upper and lower halves of the molecule are mirror images and the molecule does not require a proper orientation by rotation around the x axis. By convention, the hydroxyalkyl residue or the saccharide ring will be put below the ring as shown in the following:

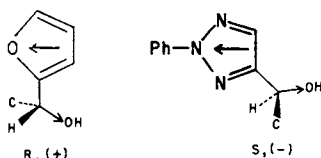


The stable conformer will tend to have the OH away from the negative end of the dipole moment vector in most compounds. For an R configuration with an OH pointing away from the dipole moment vector of the ring, the Cotton effect will be positive and it will be negative if the OH is pointing towards it. This would explain why the generalized rotation rule by El Khadem and El Shafei (17) holds true for this group of compounds.

The predicted sign of Cotton effect of hydroxyalkyl groups having an R configuration attached to the various positions of a heterocycle of this type is shown below:



A review of the literature reveals several examples of heterocyclic rings attached to hydroxyalkyl chains or to glycosyl rings, which possess a plane of symmetry along their dipole moment vectors. These include the hydroxy alkyl furans described by Horton and co-workers (18) and the 2-aryl-4-hydroxyalkyl-1,2,3-triazoles (19) depicted below:

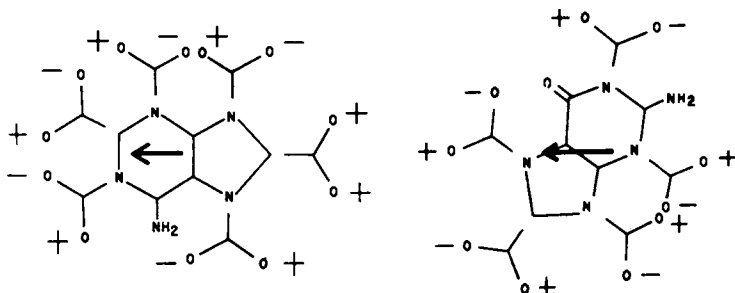


All the previous compounds will obey rules 1,2, and 3 discussed on p. 2. Assuming that the stable conformation for the hydroxyalkyl chain is that in which the oxygen of the hydroxyl group of the chiral center attached to the heterocycle will tend to move away from the negative end of the dipole, then the sign of the Cotton effect will be determined by the configuration of the first chiral center attached to the ring. If the conformation is R, the Cotton effect is positive and is negative when it is S. Here and throughout this work it is assumed that the priority of the groups attached to the first chiral center are $\text{OH} > \text{heterocyclic ring} > \text{the rest of the hydroxyalkyl chain} > \text{H}$.

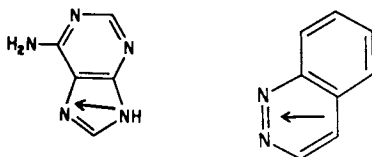
3. Fused ring systems:

The application of the present rule to fused ring systems presents certain problems. One approach applied to purines by El Khadem, Kreishman, Swartz, and El Khadem (5) was to treat the fused ring system as one entity and to establish the dipole moment of the whole system. The fused ring was then aligned along the x axis in such a way that the known nucleosides in the favored conformation gave the expected sign of the Cotton effect

when rules 1,2, and 3, p. 2, were applied. The adenine and guanine nucleoside analogs represented in the proper orientation are depicted below:

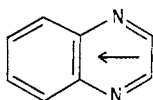


Another approach to fused ring systems is to consider only the ring to which the saccharide residue is attached and to disregard the other ring. One would determine its dipole moment and predict the sign of the Cotton effect. For a glycosyl purine linked to positions 7, 8, or 9, one would only consider the dipole moment of the imidazole ring, the R and S configuration of the first chiral center and its orientation relative to the dipole moment of the base in the most stable conformer. One difficulty which may arise is how to establish accurately the direction of the dipole moment vector of one of the rings in a fused ring system since experimentally, the dipole moment measurements are made on the whole purine molecule. However, one can calculate this and usually the dipole moments are only shifted slightly from the dipole moment vectors of the monocyclic system. The following is a rough representation of the dipole moment vector of the imidazole ring of a purine and the pyridazine ring of a cinnoline oriented in the proper way to predict the Cotton effect using rules 1, 2 and 3, p. 2.



The treatment of the quinoxaline system may present a problem since the diazine ring is symmetric and has no dipole moment. However, one may argue that a saccharide residue linked in position 3 of a quinoxaline ring will be located at the positive end of a dipole moment vector pointing in the direction of the benzene ring, and that the C-1→O bond of the stable conformer

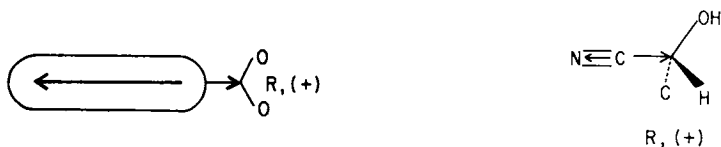
will tend to move away from the negative end of the dipole moment in its vicinity.



4. Acyclic chromophores

A closer look at acyclic compounds which have the dipole moment vector of their chromophore aligned with the bond linking the chromophore to the hydroxyalkyl chain or glycosyl ring reveals that these compounds have no preferred conformation for the first chiral center relative to the chromophore. They should, therefore, follow rule 3, p. 2, that governs the sign of the Cotton effect of heterocycles having their dipole moment vector aligned with the bond linking the heterocyclic ring to the first chiral center.

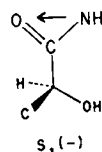
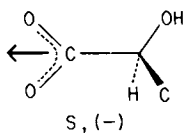
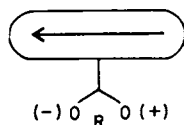
Thus, for example, hydroxyalkyl nitriles have the bond linking the first chiral center to the sp hybridized orbital of the nitrile group in direct alignment. Accordingly, one would not expect any C-1 rotamer to be favored and to predominate. The sign of the Cotton effect will, therefore, depend mainly on the configuration of the first chiral center. If rule 3, p. 2, is applicable to acyclic chromophores, then one would expect that when the direction of the vector going from the chromophore towards the first chiral center is opposite to that of the dipole moment vector of the chromophore, the rotation is positive for an R chiral center. This would explain why the rotation of nitriles depends on the first chiral center attached to the CN group and is positive when the first chiral center has a \underline{D} -configuration (20).



Other examples of acyclic compounds having the bond linking the chromophore to the first chiral center aligned with the dipole moment vector of the chromophore are the alkali metal salts of aldonic acid. These compounds exist in the ionic carboxylate form and their dipole moment is aligned with the bond linking the carboxylate group to the first chiral center. Unlike the carboxylic acid whose rotation is not predictable by the present rules, the rotation of the alkali metal salts of sugar acids depends solely on the configuration of the first chiral center.

Since the direction of the bond going from the carboxylate group to the first chiral bond opposes the dipole moment vector of the carboxylate group, the rotation should be positive for R compounds and negative for S compounds. A rotation rule described in the literature (21) confirms this expectation.

It is interesting to note that certain acyclic compounds having the dipole moment of their chromophore perpendicular to the bond linking their first chiral center to the chromophore seem to obey the rules applicable to heterocyclic rings. Thus, for example, the rotation of sugar acid amides and hydrazides depends solely on the configuration of the first chiral center, positive for R compounds and negative for S (22).



It should be noted that the above rotation rule is not applicable to all acyclic compounds because of hydrogen bonding. Thus, hydroxyalkyl carboxylic acids do not obey the rule, probably because they exist as equilibrium mixtures with the various lactones.

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6

Synthesis of 2-Amino-2-deoxy- β -D-glycopyranosides

Properties and Use of 2-Deoxy-2-phthalimidoglycosyl Halides.

R. U. LEMIEUX, T. TAKEDA, and B. Y. CHUNG

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

The importance of achieving a reliable method for the preparation of 2-amino-2-deoxy- β -glycopyranosides has been commented on in several recent publications (1,2). The importance derives mainly from the natural occurrence of numerous oligo- and polysaccharides which possess this linkage and the chemical synthesis of segments of these structures is of interest to a number of immunochemical and enzymological studies.

It is not possible to present in this paper, a critical review of the many approaches developed to meet the challenge of establishing the above-mentioned linkage. However, the most employed reactions have involved either reactions of a protected glycosyl halide with alcohol under Koenigs-Knorr or Helferich conditions which employ heavy metal salts such as silver carbonate and mercuric cyanide as promoters (3-6) or a strong-acid promoted reaction of a 1,2-oxazoline derivative of the aminosugar with the alcohol (7-9). Although these approaches have made available a large number of desired structures, the stereochemical control and yields achieved have been highly variable and, in general, rather unsatisfactory. The present research was undertaken in the hope of ameliorating this situation.

In principle, a most attractive means for the establishment of a 1,2-*trans*-glycosidic linkage would be to form a cationic species from a derivative of the sugar with participation of the 2-substituent but with the latter substituent so chosen that its engagement does not lead to products other than the desired 1,2-*trans*- β -glycoside. The choice of an imide derivative of the aminosugar appeared promising in this regard since it could be anticipated from the work of Akiya and Osawa (10) that engagement of the imide grouping in charge delocalization at the anomeric center would

lead only to reactive intermediates.

Baker and coworkers (11) prepared 1,3,4,6-tetra-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranose in 1954 and observed that treatment of this compound with hydrogen bromide in acetic acid gave 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranosyl bromide (5) and, indeed, Akiya and Osawa (10) prepared β -glycosides of simple alcohols from the latter compound in high yield using Koenigs-Knorr conditions.

At the start of this investigation, it was established that reaction of either 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranosyl or β -D-galactopyranosyl bromides with the simple alcohol, 2-propanol, under Helferich conditions (12) provided the β -glycosides in excellent yield. However, when 2,2,2-trichloroethanol was used, the main product of the reaction of 5 was the glycosyl cyanide, a well known by-product of glycosidation reactions using mercuric cyanide as promoter. This result could be attributed to the weak nucleophilicity of the alcohol which also has a hindered hydroxyl group. For this reason, the promotion of the reaction by the soluble 1:1 complex (13,14) of silver trifluoromethanesulfonate (silver triflate) and 2,4,6-trimethylpyridine (collidine) was examined.

In the first effort to utilize the silver triflate-collidine complex to promote the reaction of the β -bromide (5) with 2,2,2-trichloroethanol, the yield was 60%. However, when greater precaution was taken to exclude water, the yield rose to 89%. Thus it was apparent that, indeed, the use of the phthalimido protecting group augured well for the development of a generally useful preparation of 2-amino-2-deoxy- β -D-glucopyranosides. In order to test this hypothesis, it was decided to attempt the syntheses of three previously reported disaccharides, namely, β -D-glcNac $\xrightarrow{1,3}$ D-glcNac (4,1 β), β -D-glcNac $\xrightarrow{1,4}$ D-glcNac (1,5), and β -D-glcNac $\xrightarrow{1,4}$ D-gal (6,7). Thus, a comparison of the utility of the method with other methods could be achieved under a variety of circumstances. The purpose of this communication is to present the results obtained and, also, an examination of the chemical properties of the anomeric 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-D-glucopyranosyl halides.

Akiya and Osawa (10) demonstrated that replacement reactions at the anomeric center of 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-D-glucopyranosyl halides provide mainly the β -anomers. Furthermore, reaction of the 1,2-*trans*- β -bromide was shown not to yield an orthoester under conditions wherein 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl halides do. The marked ob-

struction to formation of 1,2-*cis*- α -anomers was assigned to a steric hindrance arising from the phthalimido group. These phenomena appeared worthy of further investigation.

It proved readily possible to obtain pure samples of both the anomeric forms for 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-D-glucopyranosyl chloride, bromide and iodide from the known 1,3,4,6-tetra-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranose using basically standard conditions. All were crystalline except the α -bromide which was obtained as a chromatographically pure syrup. This unique availability of both the anomeric forms for a glycosyl halide with the halogen as either chlorine, bromine or iodine prompted a brief kinetic investigation of the reactions with tetraethylammonium halides. Good pseudo first-order kinetics for the anomerization reactions were obtained starting with the α -anomers. However, the polarimetric rates were not cleanly first-order starting with the β -anomers and examination of products isolated after various intervals of time, showed this to result from partial hydrolysis of the β -halide by traces of water which are inevitably present in the reaction mixtures, a situation reminiscent of the experience with the anomeric tetra-O-acetyl-D-glucopyranosyl chlorides (15). Thus, it was apparent that the phthalimido group can participate in the overall reaction and thereby lead to a cationic intermediate which has a strong affinity for water but which, as indicated by the results of Akiya and Osawa (10) and supported by our experience, does not yield a stable orthoester. That some kind of participation occurs was also indicated by the different routes of the reactions displayed by the α - and β -bromides (5 and 6) when reacted with tetraethylammonium chloride (0.02 M) in acetonitrile. Whereas the reaction of the α -anomer (6) produced an essentially quantitative yield (>90%) of the β -chloride (3) the reaction of the β -bromide (5) proceeded with extensive (near 50%) retention of configuration. At a higher chloride ion concentration (0.3 M), the yield of the α -chloride (4) was 80%.

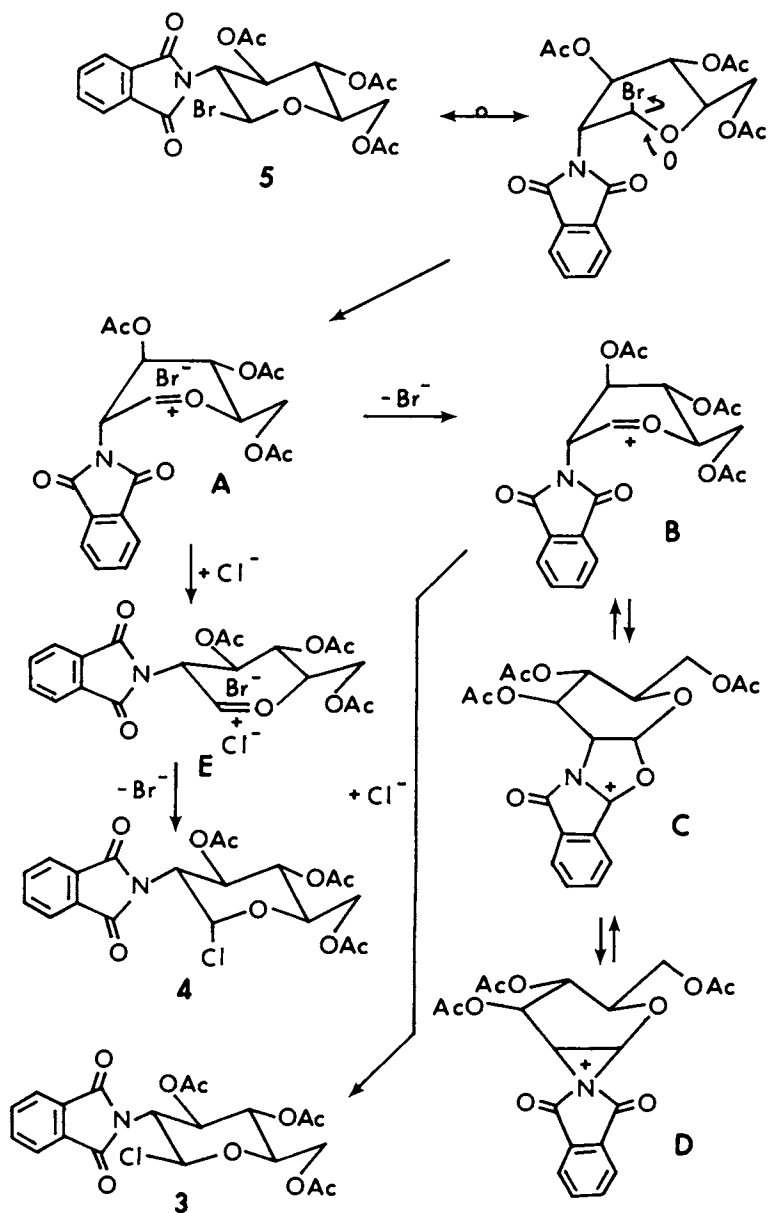
The participation of a 2-acyloxy group in a reaction at an anomeric center is considered to provide anchimeric assistance by providing a solvation-like influence on the formation of an ion-pair and is manifested by the collapse of the intermediate ion-pair to the more stable 1,2-acyloxonium salt (15).

The experimental basis for this opinion is the demonstration by Lemieux and Hayami (15) that whereas the chloride-ion catalyzed anomerization of 1,2-*cis*-

tetra-O-acetyl- α -D-glucopyranosyl chloride proceeded at the same rate as exchange of chloride ion with the environment, the rate of incorporation of radioactive chloride ions from the environment by the 1,2-*trans*- β -chloride was much greater than the rate of $\beta \rightarrow \alpha$ anomerization. These results seem best interpreted on the basis of an attack by chloride ion on an intimate ion-pair resulting from spontaneous dissociation of the C-Cl bond with participation of the ring oxygen atom for effective charge delocalization in the transition state. In the case of the β -chloride, attack at the anomeric center of the ion-pair by chloride ion was in competition with the nucleophilic attack by the 2-acetoxy group with the former reaction leading to the ion-triplet intermediate necessary for the anomerization and the latter course of reaction leading to the 1,2-acetoxonium ion. On this basis, the above-mentioned retention of configuration obtained on reaction of the β -bromide (5) with chloride ion may be rationalized as is displayed in Scheme 1. The most stable form of the intermediate cation which arises from the β -bromide cannot be predicted but presumably is either B, C or D. If C, the ion could, in the presence of alcohol, provide an orthoamide product. However, like Akiya and Osawa (10), we did not detect such compounds in the course of this work. It is expected, as indicated in Scheme 1, that the solvolysis of the β -bromide proceeds by way of a boat conformation so as to better orient a *p*-orbital of the ring oxygen relative to the C-Br bond (16).

As mentioned above, it was not possible to obtain the same velocity constants ($k_{\alpha} + k_{\beta}$) for anomerization starting with the β -anomers as k_{β} were obtained for α -anomers and the difference (about 20%) is attributed to capture of traces of water by the intermediate cation (B, C or D in Scheme 1) formed by solvolysis of the β -anomer. The values obtained starting with the α -anomers are considered reliable and are reported under one set of conditions in Table I. As expected, the rates of anomerization were directly proportional to the halide ion concentration (15). These results are considered of interest with regard to halide-ion catalyzed glycosidation reactions (16) since these show a much greater reactivity of the bromides than the chlorides (700 times greater) but little difference (about a factor of two) between the bromides and iodides. These differences are even more remarkable when it is considered that the order of nucleophilicity is $\text{Cl}^- > \text{Br}^- > \text{I}^-$ under the aprotic conditions used. Indeed, the α -iodide (8) was attacked about two times faster by

Scheme 1



tetraethylammonium chloride than by tetraethylammonium bromide.

TABLE I

Reactions of 3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido-D-glucopyranosyl Halides

	K_e	k^α, hr^{-1}	$t_{1/2}, \text{hr}$	$k_{\text{rel.}}$
<u>Anomerization</u> ^a				
X = X' = Cl	3.25	1.4×10^{-4}	4950	1
X = X' = Br	1.22	0.10	6.9	700
X = X' = I	3.05	0.22	3.15	1600
X = X' = OAc	4.5			
<u>Reaction</u>				
X = I, X' = Cl	—	3.3	0.21	15
X = I, X' = Br	—	2.0	0.34	9.3

^a For 0.02M solutions at 25°C of the glycosyl halide in acetonitrile and made 0.02M in tetraethylammonium halide. An average value for the 1-acetates anomerized in 1:1 acetic acid-acetic anhydride, 0.1M in perchloric acid (17).

The ¹H-NMR spectra of compounds 1 to 8 required ⁴C₁ conformation for both the anomeric pairs. The doublets for the anomeric hydrogens of the α -anomers had spacings in the range 3.5-4.0 Hz and those for the β -forms near 9.0 Hz. For both forms, the spacings found in the signals for H-3 and H-4 were in the range 9-11 Hz. In line with this conformation, H-3 for an α -form was strongly deshielded (18) by the *syn*-axial halogen as compared to H-3 of the β -anomer (see Table II). In all cases, one of the acetyl groups produced

TABLE II

^1H and ^{13}C Nuclear Magnetic Resonance Parameters for
3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido-D-glucopyranosyl Compounds

Compound	Chemical Shifts (CDCl_3 , TMS internal)		
	H-1	H-3	C-1
β -Acetate (1)	<u>6.48</u>	<u>5.86</u>	<u>89.9</u>
α -Acetate (2)	6.28	6.56	90.6
β -Chloride (3)	6.20	5.79	85.7
α -Chloride (4)	6.43	6.83	91.4
β -Bromide (5)	6.43	5.80	78.4
α -Bromide (6)	6.62	6.67	87.3
β -Iodide (7)	6.71	5.73	78.2
α -Iodide (8)	6.97	6.52	75.1

its signal to exceptionally high field (1.8-1.9 ppm). Indeed, the plane of the phthalimido group would be expected to be near perpendicular to the mean plane of the pyranose ring and therefore have a specific shielding influence on the C-3 acetoxy group. In this orientation, the carbonyl of the phthalimido group which is on the α -side of the pyranose ring can exert a strong non-bonded interaction with an axial substituent at C-1. That such an interaction does in fact exist is evident from the relative chemical shifts of the anomeric hydrogens of tetraacetates 1 and 2. As seen from Table II, the signal for the β -anomer is actually 0.2 ppm to lower field in contrast, for example, to the situation for the glucopyranose pentaacetates where the signal for H-1 of the β -form is 0.58 ppm to higher field than that of the α -form (18). For the anomeric 2-acetamido-1,3,4,6-tetra-O-acetyl-2-deoxy-D-glucopyranoses, the signal for H-1 of the β -form is 0.45 ppm to higher field than that of the α -form (19). Strong electrostatic specific deshielding of the anomeric hydrogen of β -acetate (1) is therefore indicated. Clearly, the substitution of this axial hydrogen by a more bulky atom must lead to strong non-bonded interaction that would destabilize the molecule and in the case of anomers tend to favor the β -form. Indeed, as seen in

Table I, the interaction is powerful enough to counter the anomeric effect (20) and lead to anomerization equilibria which favor the β-form. Thus, there can be no doubt that the phthalimido group is well oriented to well shelter the α-side of the pyranose ring and, indeed, provide a participation in reactions at the anomeric center.

The ¹³C-chemical shifts for C-1 of compounds 1 to 8 are listed in Table II. It is seen that except for the anomeric iodides, the signal for C-1 of the α-anomer is to lower field than that of the β-form (21).

Reaction of near 1:1 mixture of the α- and β-bromides (6 and 5) with 2,2,2-trichloroethanol in the presence of the silver triflate-collidine complex gave only a slightly lower yield of the β-glycoside than when pure β-bromide was used. It was apparent that the α-bromide may be slightly more prone to dehydrobromination. Nevertheless, there appears little advantage in using pure β-bromide instead of a mixture with its α-anomer in these glycosidation reactions. Also, the reaction with the β-chloride (3) gave the same yield as the β-bromide (5). Indeed, although the glycosidation reactions reported herein utilized the β-bromide, it likely will prove advantageous to use the β-chloride in such reactions in view of its greater stability on storage. Also, in the preparations to be reported, the initial reaction temperature is -30°. This was mainly as a precautionary measure since virtually the same yields were obtained at ambient temperatures for the glycosidation of 2,2,2-trichloroethanol.

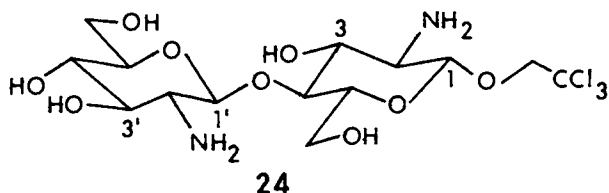
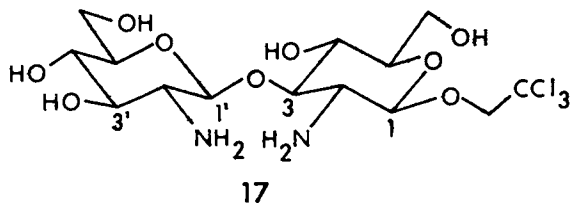
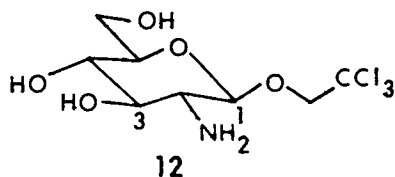
The reaction of a halide with silver triflate-collidine (1:1) is extremely rapid as indicated by the appearance of precipitated silver halide. However, this rapid initial reaction may lead, even in the presence of an alcohol, to glycosyl triflate which in turn provides the glycoside since near the same yield of the 2,2,2-trichloroethyl glycoside was obtained, using the β-bromide as reagent, when the alcohol was added 10 minutes after the addition of the silver triflate-collidine complex and the formation of silver bromide was complete as when the alcohol and the promoter were added at the same time. Reaction of the β-bromide (5) with 2,2,2-trichloroethanol in nitromethane and using only collidine to neutralize the liberated acid gave mainly (~70%) the product of dehydrobromination (9). Thus, the success of the method appears to rely on the liberation over the course of the reaction of a cationic intermediate (B, C or D of

Scheme 1) which has a pronounced tendency to form the β -glycoside while avoiding elimination of a proton or forming either an orthoamide or an orthoacetate. Thus, a highly promising method for establishing β -glycosam-inide linkages seemed at hand and this promise was well substantiated by the following syntheses.

2,2,2-Trichloroethyl 4,6-O-benzylidene-2-deoxy-2-phthalimido- β -D-glucopyranoside (14) was condensed with the β -bromide (5) in nitromethane using the silver triflate-collidine complex to form compound 15 in 82% yield. Although care was taken to exclude water from the reaction mixture, a main by-product appeared to be that from the hydrolysis of 5 (tlc). A small amount of the glycoseen (9) was also formed. The yield obtained is to be contrasted to the 25% yield reported by Heyns and coworkers (4) in a similar condensation but using mercuric cyanide to promote the glycosidation reaction. Using the oxazoline method, Zurabyan and coworkers (8) realized an 81% yield in forming benzyl 3-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy- β -D-glucopyranosyl)-2-acetamido-4,6-O-benzylidene-2-deoxy- β -D-glucopyranoside. Acid hydrolyses to remove the benzylidene and acetyl groups of 15 provided the diphtalimido glycoside (16) which was treated with hydrazine to form the 2,2,2-trichloroethyl 3-O-(2-amino-2-deoxy- β -D-glucopyranosyl)-2-amino-2-deoxy- β -D-glucopyranoside (17). The effect of pH on the ^{13}C -NMR spectrum of 17 is reported in Table III.

2,2,2-Trichloroethyl 3,6-di-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranoside (21) was prepared from 14 by way of the intermediates 19 and 20. Reaction of 21 with a slight excess of 5 under usual conditions provided a 51% yield of the desired β -linked disaccharide derivative 22. The yield was raised to 68% when additional mole equivalents of 5 and the promoter were added after the initial reaction had subsided. It is apparent therefore that the hydroxyl group of 21 is indeed quite unreactive (1). In previous syntheses of the disaccharide (chitobiose) (1,5), very special derivatives of D-glucosamine were prepared in order to make the 4-hydroxyl more readily available to the glycosidation reaction. In spite of this precaution, the yields achieved in the glycosidation reaction were 10% (~35% of the α -linkage) (5) and 36% (8% of the α -linkage) (1) using Helferich-type condensations. Thus, the present method is capable of providing far superior yields even when using a type of alcohol which is notorious for its unreactivity. Although some α -glycoside must form in our present method none has been detected in any of the reactions so far studied.

The chitobiose derivative (22) was deacetylated under acid conditions to provide the diphtalimido glycoside (23) which was then converted using hydrazine to 2,2,2-trichloroethyl chitobioside (24).



A comparison of the ^{13}C -NMR titration curves (22) for the compounds 17 and 24 appears of interest to the subject of conformational preferences about glycosidic linkages (20). As seen in Table III, the shielding of C-1 of compounds 12, 17 and 24 on protonation of the geminal 2-amino group was 4.7-5.2 ppm, normal β -shifts (22) for this transformation. Normal β -shifts (~4.4 ppm) were also observed in the C-3' atoms of 17 and 24. These signals could be reliably assigned

from the spectrum for the simple glycoside 12. However, although the β -shift for C-3 of the chitobiose derivative 24 was normal, that for C-3 of the 1' \rightarrow 3 linked disaccharide 17 was remarkably high, namely, 8.6 ppm. That is, for 17, the β -shifts observed for both C-1' and C-3' of the terminal unit and C-1 were normal but that of the aglyconic C-3 atom of the non-terminal unit was abnormally high. The two amino groups of the chitobiose derivative 24 are expected to be well separated as displayed in the conformational formula for 24 presented above. Thus, it is not surprising that the β -shifts observed on protonation of 24 were normal, little if any conformational change occurring on passing from the free base to the salt form. However, considerations based on the *exo*-anomeric effect and non-bonded interactions (20) would require that the 1' \rightarrow 3 linked disaccharide 17, in the free base form, has the two amino groups in very close proximity. Thus, protonation of the amino groups would be expected to produce a repulsion between groups both as the result of electrostatic repulsion between the charged groups and an increase of the effective volumes of the two groups because of strong hydrogen bonding with the water. Thus, an adjustment of the conformation of 17 would be expected, on its passing from the free base to the salt form, that would allow a greater separation between the two amino groups. The abnormal β -shift observed for the aglyconic C-3 atom may be considered a manifestation of this conformational change. If so, the fact that the β -shifts were normal for the other three carbons which are β to an amino group in 17 would infer that the conformational change which occurred on protonation of 17 was largely restricted to a rotation about the aglyconic C-3 to oxygen bond, [change in the ψ torsion angle (20)]. This conclusion would be in line with the expectation based on the *exo*-anomeric effect that the ϕ torsion angle tends to remain constant (*exo*-anomeric effect) (20) and the main adjustment to establish the most stable conformation about a glycosidic linkage is by change of the ψ angle.

The 2-acetamido-2-deoxy- β -D-galactopyranosyl group occurs at the 4-position of a D-galactopyranosyl group in certain gangliosides (6,23). Thus, it was of interest to examine the effectiveness of the method for the glycosidation of the readily available methyl 2,3,6-tri-O-benzoyl- α -D-galactopyranoside (24). Indeed, reaction with 5 produced the desired compound (26) in excellent yield (79%) and it is planned to use the method in the course of an effort to synthesize gang-

lioside related structures. The ^{13}C -NMR spectrum substantiated the structure of the derived methyl 4-O-(2-amino-2-deoxy- β -D-glucopyranosyl)- α -D-galactopyranoside (27).

TABLE III
 ^{13}C -NMR Parameters To Display β -Shifts

Compound	Base			Salt		
	a	17	24	a	17	24
C-1'	104.3	103.6	103.3	99.4	98.9	98.1
C-2'	57.0	57.0	57.0	56.1	55.2	56.3
C-3'	76.5	76.6	76.5	72.2	72.1	72.1
C-4'	70.2	69.9	70.0	70.1	69.5	70.4
C-5'	76.0	76.1	75.3	76.9	76.4	75.2
C-6'	61.3	61.0	61.0	60.7	60.4	60.7
C-1	-	103.6	103.9	-	98.9	99.1
C-2	-	55.9	56.6	-	55.2	55.9
C-3	-	85.7	74.4	-	77.1	70.1
C-4	-	68.2	78.9	-	67.2	77.1
C-5	-	76.1	76.0	-	76.4	76.3
C-6	-	61.0	60.6	-	60.4	60.5

a

C-1 is denoted C-1' for convenience of presentation.

Experimental

All solvent extracts were dried over anhydrous sodium sulfate prior to solvent removal using a rotary evaporator under the vacuum of a water aspirator. The ^1H -NMR spectra were measured at 100 MHz (Varian HA-100) and ^{13}C -NMR spectra at 22.6 MHz (Bruker HFX-90). Unless otherwise stated, deuteriochloroform was used as a solvent and internal TMS as a standard. Thin layer chromatograms (TLC) were developed on a silica gel G (E. Merck A.G., Darmstadt) using ethyl acetate-Skellysolve B or ethyl acetate-benzene and visualized by spraying with 5% sulfuric acid in ethanol followed by heating at 100°. Column chromatography was performed on silica gel (CAMAG) or on Woelm Alumina (neutral, Activity I). The glycosidation reactions were performed under a dry nitrogen atmosphere. The nitromethane, 2,2,2-trichloroethanol and 2,4,6-trimethylpyridine (collidine) were dried and freshly distilled prior to use. All solid reactants for glycosidation were dried overnight over phosphorus pentoxide under high vacuum prior to use.

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranose (1). D-glucosamine hydrochloride (21.6 g, 100 mmol) was added to a sodium methoxide solution (prepared from 2.3 g of sodium in 100 ml of methanol). After shaking for 10 min, the separated sodium chloride (50 ml). The combined filtrates were treated with finely ground phthalic anhydride (7.4 g, 50 mmol) and shaken for 10 min. Triethylamine (10.1 g, 100 mmol) was then added and the clear solution was treated with phthalic anhydride (8.1 g, 55 mmol). After shaking for 10 min, a crystalline solid started to precipitate. The mixture was then brought to 50° and stirred for 20 min. After being kept at 0° for 1 hr, the solid (20.5 g) was collected by filtration and dried. ^1H -NMR indicated the solid to be the triethylammonium salt of 2-(2'-carboxybenzamido)-2-deoxy-D-glucopyranose (25,26). Drying overnight in air resulted in the loss of the triethylamine. Evaporation of the filtrate gave a yellow solid which was suspended in diethyl ether (200 ml) and collected by filtration. The ^1H -NMR spectrum in D_2O showed this fraction to be contaminated with a trace of the unreacted glucosamine.

The products were combined (46.5 g) and treated with pyridine (200 ml) and acetic anhydride (100 ml), at room temperature for 16 hr. The solution was poured into ice-water and the aqueous mixture subsequently extracted with chloroform (3 x 100 ml). The combined ex-

tracts were washed successively with cold water, 3% hydrochloric acid, saturated sodium bicarbonate solution and water. Solvent removal left a yellow foam which was dissolved in diethyl ether (500 ml) and treated with charcoal. Concentration to a volume of 150 ml and storage overnight at 0° gave a colorless solid (39.1 g, 82% yield). The $^1\text{H-NMR}$ spectrum of the product showed it to be a 2:1 mixture of β - and α -anomers. A 3:1 mixture of the β - and α -anomers was obtained on reaction of the triethylamine salt with sodium acetate and acetic anhydride at 100° for 1 hr. However, the product was dark red and difficult to decolorize. The pure β -anomer (15-20 g) can be obtained by crystallization from ethanol and recrystallization from ethyl acetate, mp 90-94° [lit. 199-200° (11), 91-94° (19)], $[\alpha]_{\text{D}}^{22} + 65.5^\circ$ (*c*, 1 in chloroform). The $^1\text{H-NMR}$ spectrum was in general accord with that reported by Horton and coworkers (19).

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-phthalimido- α -D-glucopyranose (2). A sample (6.6 g) of 2-(2'-carboxybenzamido)-2-deoxy- α -D-glucopyranose which had the same physical constants as reported in the literature was obtained by fractional crystallization of a preparation of the β -anomer following the procedure reported by Hirano (25). Acetylation of the material as described by Hirano (25) provided a 51% crude yield of a product with mp 116-116.5° and $[\alpha]_{\text{D}}^{22} + 114^\circ$ (chloroform). After two recrystallizations from methanol, the mp was 126-127° and $[\alpha]_{\text{D}}^{22} + 119.2^\circ$ (*c* 1, in chloroform). Hirano (25) has reported mp 131°, $[\alpha]_{\text{D}}^{16} + 98^\circ$ whereas Akiya and Osawa (10) reported mp 124-126°, $[\alpha]_{\text{D}}^{25} + 116.1^\circ$. The NMR spectra (see Table II) were in agreement with the assigned structure.

3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido- α -D-glucopyranosyl Chloride (4). This compound was prepared from the β -bromide (5, to be described below) under kinetic conditions using the procedure of Lemieux and Hayami (15).

Compound 5 (1.03 g) was dissolved in dry acetonitrile (10 ml) which contained tetraethylammonium chloride (0.50 g). After 5 hr at room temperature, the product was isolated in the usual manner and was recrystallized from diethyl ether-Skellysolve B to afford an 80% yield (0.72 g) of material, mp 174-175°, $[\alpha]_{\text{D}}^{25} + 122.2^\circ$ (*c*, 0.88 in acetonitrile) (see Table II).

Anal. Calcd. for $\text{C}_{20}\text{H}_{20}\text{NO}_9\text{Cl}$: C, 52.93; H, 4.44; N, 3.09; Cl, 7.80. Found: C, 53.13; H, 4.59; N, 3.39; Cl, 7.78.

The β -anomer (3) (see Table II) was prepared from β -tetraacetate (1) using aluminum chloride as described

by Akiya and Osawa (10) and the physical constants agreed.

3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranosyl Bromide (5). A solution of the β -acetate 3 (9.54 g, 20 mmol) and acetic anhydride (5 ml) in a saturated hydrogen bromide solution of glacial acetic acid (30 ml) was kept at room temperature for 24 hr. After dilution with chloroform (200 ml) and chilling with ice, the solution was washed with cold water (3 times) and saturated sodium bicarbonate solution. Solvent removal after drying left a foamy solid which was crystallized from diethyl ether (7.77 g, 78% yield of a colorless solid, see Table II), mp 122-123°, $[\alpha]_D^{24} + 57.3^\circ$ (c, 1 in chloroform). Lit. mp 120-121° (11).

3,4,5-Tri-O-acetyl-2-deoxy-2-phthalimido- α -D-glucopyranosyl Bromide (6). The mother liquors from the above preparation of compound 5 were evaporated to dryness and the residue applied to a silica gel column for chromatography using benzene-diethyl ether (1:1) as developing phase. Four fractions were separated. The second fraction to be eluted was the β -form 5. The third fraction resisted crystallization but NMR spectra required a high state of purity.

$^{13}\text{C-NMR}$: 169.0, 169.9, 170.4 (3 acetyl carbonyls), 167.3 (2 phthaloyl carbonyls), 134.5, 131.4 and 123.9 (aromatic), 87.3 (C-1), 72.6, 69.1, 67.8 (C-3, C-4, C-5), 61.1 (C-6), 56.4 (C-2), 20.6 (3 acetyl methyls).

$^1\text{H-NMR}$: δ 7.80 (m, 4, phthalimido), 6.97 (d, 4 Hz, H-1); 6.52 (q, 9, 11 Hz, H-3); 5.18 (q, 9, 10 Hz, H-4); 4.35 (q, 4, 11 Hz, H-2); 4.2 (m, H-5, H-6 and H-6'); 2.10, 2.08, 1.88 (s, O-acetyl).

3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranosyl Iodide (7). A solution of hydrogen iodide in acetic acid was prepared by addition of acetic anhydride (14 ml) to 47% hydroiodic acid (3 ml) at 0° in a nitrogen atmosphere. Compound 1 (15.0 g) was added, the solution was stirred for 1 hr at room temperature and then poured into ice-water. The chloroform extract was first neutralized with saturated aqueous sodium bicarbonate and then with aqueous sodium thiosulfate prior to drying over sodium sulfate. The chloroform solution was evaporated to an oily residue which crystallized from diethyl ether.

The yield was 50%, mp 91-92°. Recrystallization from ether raised the melting point to 94-94.5° (dec.), $[\alpha]_D^{25} + 38.2^\circ$ (c, 1 in chloroform).

$^1\text{H-NMR}$: δ 7.83 (m, 4, phthalimido), 6.71 (d, 10 Hz, H-1); 5.73 (q, 9, 10 Hz, H-3); 5.26 (t, 10 Hz, H-4); 4.68 (t, 10 Hz, H-2); 4.24 (m, H-6 and H-6'); 3.94

(m, H-5); 2.12, 2.04, 1.86 (s, O-acetyl).

3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido- α -D-glucopyranosyl Iodide (8). The mother liquor from the crystallization of 7 was left at room temperature. After two days, a compound, mp 89.5-90°, $[\alpha]_D^{25} +131.3^\circ$ (c, 0.58 in acetonitrile) crystallized. The yield was 15% (2.6 g). Since the NMR spectra (see Table II) indicated high purity and, like 7, the product was quite unstable, no further purification was attempted.

$^1\text{H-NMR}$: δ 7.80 (m, 4, phthalimido); 6.97 (d, 4 Hz, H-1); 6.52 (q, 10, 8 Hz, H-3); 5.18 (t, 8 Hz, H-4); 4.35 (q, 4, 10 Hz, H-2); 4.60-4.10 (m, 3, H-5, H-6 and H-6'); 2.10, 2.08, 1.88 (s, O-acetyl).

3,4,6-Tri-O-acetyl-1,2-dideoxy-2-phthalimido-D-arabino-hex-1-enopyranose (9). A solution of the bromide 5 (996 mg, 2 mmol), 2,2,2-trichloroethanol (330 mg, 2 mmol) and 2,4,6-trimethylpyridine (254 mg, 2.1 mmol) in nitromethane (20 ml) was stirred at 90° for 48 hr. The solution was diluted with chloroform (50 ml) and washed with cold water and cold 10% hydrochloric acid. Evaporation of the solvent gave a syrup which was passed through a short alumina column using ethyl acetate-diethyl ether (1:1). Treatment of the eluent with charcoal, evaporation and crystallization from diethyl ether gave a colorless solid (585 mg, 70% yield), mp 117-118°, $[\alpha]_D^{24} - 34.2^\circ$ (c, 0.5 in chloroform).

$^1\text{H-NMR}$: δ 7.98-7.68 (m, 4, phthalimido); 6.78 (s, H-1); 5.61 (d, 4 Hz, H-3); 5.32 (t, 4 Hz, H-4); 4.66-4.25 (m, 3, H-5 and H-6); 2.16, 2.13, 1.94 (s, O-acetyl).

Anal. Calcd. for $\text{C}_{20}\text{H}_{19}\text{NO}_9$: C, 57.55; H, 4.59; N, 3.36. Found: C, 57.52; H, 4.57; N, 3.29.

2,2,2-Trichloroethyl 3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranoside (10). A solution of the β -bromide 5 (9.96 g, 20 mmol) in nitromethane (20 ml) was added dropwise to a cooled (-30°) solution of 2,2,2-trichloroethanol (3.30 g, 22 mmol), silver triflate (5.66 g, 22 mmol) and collidine (2.66 g, 22 mmol) in nitromethane (20 ml). After stirring at -30° for 2 hr and dilution with chloroform (100 ml), the solid was removed by filtration and washed with chloroform (20 ml). The combined filtrates were washed with cold water, 3% hydrochloric acid and water and dried. Solvent removal left a yellow foam which was passed through a short alumina column using diethyl ether-ethyl acetate (1:1). Treatment with charcoal, solvent removal and crystallization from diethyl ether gave a colorless solid (9.74 g, 86% based on 5), mp 176-177°, $[\alpha]_D^{23} + 4.4^\circ$ (c, 0.5 in chloroform).

$^1\text{H-NMR}$: δ 7.95-7.65 (m, 4, phthalimido); 5.92 (t, 10 Hz, H-3); 5.60 (d, 8 Hz, H-1); 5.19 (t, 10 Hz, H-4); 2.12, 2.04, 1.88 (s, O-acetyl); 4.52-3.82 (m, 6 remaining protons).

Anal. Calcd. for $\text{C}_{22}\text{H}_{22}\text{NO}_{10}\text{Cl}_3$: C, 46.62; H, 3.91; N, 2.47; Cl, 18.77. Found: C, 46.68; H, 3.97; N, 2.34; Cl, 18.84.

2,2,2-Trichloroethyl 2-Deoxy-2-phthalimido- β -D-glucopyranoside (11). A solution of the triacetate 10 (7.93 g, 15 mmol) in acetone (200 ml), water (100 ml) and conc. hydrochloric acid (40 ml) was stirred at 70° for 3 hr. Removal of acetone left a white suspension which was extracted with ethyl acetate (3 x 100 ml). The combined extracts were washed with cold water, saturated sodium bicarbonate solution and water and dried. Solvent removal and recrystallization from benzene-ethyl acetate (20:1) gave a colorless solid (6.0 g, 91% yield), mp 224-225°, $[\alpha]_{\text{D}}^{20}$ - 37.6° (c, 0.5 in acetone).

$^1\text{H-NMR}$ (acetone- d_6): δ 7.86 (s, 4, phthalimido); 5.46 (d, 8 Hz, H-1); 4.31 (d, 5 Hz, 2, CH_2CCl_3); 4.72 (d, 5 Hz, 1, OH, D_2O exchangeable); 2.80 (d, 3 Hz, 2, OH, D_2O exchangeable); 4.80-3.45 (m, 6 remaining protons).

$^{13}\text{C-NMR}$ (acetone- d_6): 99.9 (C-1), 97.4 (CCl_3), 81.1 (CH_2), 77.9 (C-5), 72.4 (C-3), 71.8 (C-4), 62.5 (C-6), 57.7 (C-2).

Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{NO}_7\text{Cl}_3$: C, 43.61; H, 3.66; N, 3.18; Cl, 24.14. Found: C, 43.70; H, 3.65; N, 2.93; Cl, 24.00.

2,2,2-Trichloroethyl 2-Amino-2-deoxy- β -D-glucopyranoside (12). A solution of the phthalimido compound 11 (2.20 g, 5 mmol) and 87% hydrazine hydrate (1.0 g) in 95% ethanol (50 ml) was refluxed for 4 hr. The precipitate was removed by filtration and washed with ethanol (10 ml). Solvent removal left a pale yellow solid which was applied to an ion-exchange resin (Dowex 1x, hydroxide form) column and eluted with water. Freeze-drying left a colorless solid which was dried over P_2O_5 under high vacuum (1.35 g, 87% yield), mp 167-168°, $[\alpha]_{\text{D}}^{20}$ - 44.2° (c, 0.5 in water).

$^1\text{H-NMR}$ (D_2O): δ 5.12 (d, 8 Hz, H-1); 4.88 (d, 5 Hz, 2, CH_2CCl_3); 4.46-3.04 (m, 6 remaining protons).

The $^{13}\text{C-NMR}$ is reported in Table III.

Anal. Calcd. for $\text{C}_8\text{H}_{14}\text{NO}_5\text{Cl}_3$: C, 30.94; H, 4.54; N, 4.51; Cl, 34.25. Found: C, 31.18; H, 4.54; N, 4.33; Cl, 34.07.

2,2,2-Trichloroethyl 2-Acetamido-2-deoxy- β -D-glucopyranoside (13). A solution of the amino compound 12 (1.25 g) and acetic anhydride (6 ml) in 50% aqueous methanol (20 ml) was stirred at room temperature for 2

hr. Solvent removal and drying over P₂O₅ gave a colorless solid which was recrystallized from benzene-acetone (2:1) (1.34 g, 96% yield), mp 171-172°, $[\alpha]_D^{20}$ -35.7° (c, 0.6 in water), (lit.(27) 170-171°).

¹H-NMR (D₂O): δ 5.24 (d, 8 Hz, H-1); 4.83 (d, 5 Hz, CH₂CCl₃); 2.45 (s, N-acetyl), 4.45-3.80 (m, 6 remaining protons).

¹³C-NMR (D₂O): 102.9 (C-1), 96.5 (CCl₃), 80.9 (CH₂), 76.4 (C-5), 73.7 (C-3), 70.3 (C-4), 61.2 (C-6), 55.8 (C-2).

Anal. Calcd. for C₁₀H₁₆NO₆Cl₃: C, 34.05; H, 4.57; N, 3.97; Cl, 30.16. Found: C, 34.46; H, 4.65; N, 4.21; Cl, 29.77.

2,2,2-Trichloroethyl 4,6-O-Benzylidene-2-deoxy-2-phthalimido- β -D-glucopyranoside (14). A solution of the hydroxy compound 11 (6.61 g, 15 mmol), α,α -dimethoxytoluene (9.10 g, 60 mmol) and *p*-toluenesulfonic acid (100 mg) in freshly distilled acetonitrile (200 ml) was stirred at room temperature for 12 hr. Treatment with triethylamine (1 ml) and solvent removal left a sticky solid which was dissolved in chloroform (100 ml) and washed with cold water and saturated sodium bicarbonate solution. Solvent removal after drying, and crystallization from ethyl acetate-Skellysolve B gave a colorless solid which was recrystallized from 2-propanol (7.37 g, 93% yield), mp 196-197°, $[\alpha]_D^{20}$ -47.2° (c, 0.5 in chloroform).

¹H-NMR: δ 7.89-7.24 (m, 9, benzyl and phthalimido); 5.58 (s, 1, benzylidene); 5.50 (d, 8 Hz, H-1); 4.72-4.50 (m, 1, H-2); 2.98 (d, 3 Hz, OH, D₂O exchangeable); 4.44-3.50 (m, 7 remaining protons).

Anal. Calcd. for C₂₃H₂₀NO₇Cl₃: C, 52.24; H, 3.81; N, 2.65; Cl, 20.11. Found: C, 52.33; H, 3.85; N, 2.38; Cl, 20.25.

2,2,2-Trichloroethyl 3-O-(3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranosyl)-4,6-O-benzylidene-2-deoxy-2-phthalimido- β -D-glucopyranoside (15). A solution of the β -bromide 5 (800 mg, 1.5 mmol) in nitromethane (5 ml) was added to a cooled (-30°) solution of the 3-hydroxy compound 14 (670 mg, 1.27 mmol), silver triflate (385 mg, 1.5 mmol) and collidine (182 mg, 1.5 mmol) in nitromethane (10 ml). After stirring at -30° for 3 hr, then at room temperature for 1 hr, the mixture was diluted with chloroform (50 ml). The solid was removed by filtration and washed with chloroform (20 ml). The combined filtrates were washed successively with cold water, 3% hydrochloric acid and water. Solvent removal left a yellow foam which was applied to a silica gel column and eluted with ethyl acetate-Skellysolve B (1:1). Solvent removal and crystallization from diethyl ether gave a colorless solid (980

mg, 82% yield based on 14), mp 167-168°, $[\alpha]_D^{20} - 0.6^\circ$ (*c*, 0.5 in chloroform).

$^1\text{H-NMR}$: δ 7.76-7.28 (m, 13, benzyl and 2 phthalimido); 5.60 (s, 1, benzylidene); 5.52 (t, 10 Hz, H-3'); 5.49 (d, 8 Hz, H-1); 5.24 (d, 8 Hz, H-1'); 5.07 (t, 10 Hz, H-4'); 4.96 (q, 9 Hz, H-3); 2.02, 1.92, 1.71 (s, O-acetyl); 4.45-3.50 (m, 11 remaining protons).

Anal. Calcd. for $\text{C}_{43}\text{H}_{39}\text{N}_2\text{O}_{16}\text{Cl}_3$: C, 54.59; H, 4.15; N, 2.96; Cl, 11.24. Found: C, 53.99; H, 4.06; N, 2.88; Cl, 11.11.

2,2,2-Trichloroethyl 3-O-(2-Deoxy-2-phthalimido- β -D-glucopyranosyl)-2-deoxy-2-phthalimido- β -D-glucopyranoside (16). A solution of compound 15 (550 mg, 0.58 mmol) in 10% trifluoroacetic acid (90%) in dichloromethane (10 ml) was stirred for 10 min at room temperature. Solvent removal left an oil which was dissolved in a mixture of acetone (20 ml), water (10 ml) and conc. hydrochloric acid (4 ml). The solution was stirred at 70° for 3 hr. Evaporation of acetone gave a suspension which was collected by filtration and washed with cold water. Recrystallization from acetone-ethyl acetate gave a colorless solid (400 mg, 94% yield), mp, 263.5-264°, $[\alpha]_D^{23} - 0.86^\circ$ (*c*, 0.35 in acetone).

$^1\text{H-NMR}$ (acetone- d_6): δ 8.0-7.10 (m, 8, phthalimido); 5.23, 5.21 (d, 8 Hz, H-1 and H-1'); 4.72-4.38 (m, H-2 and H-2').

$^{13}\text{C-NMR}$ (acetone- d_6): 99.4 (C-1, C-1'), 97.1 (CCl₃), 82.3 (CH₂), 80.5 (C-3), 78.3, 77.9 (C-5, C-5'), 72.1 (C-3'), 71.4 (C-4'), 70.7 (C-4), 62.0 (C-6, C-6'), 57.9 (C-2), 55.6 (C-2').

Anal. Calcd. for $\text{C}_{30}\text{H}_{29}\text{N}_2\text{O}_{13}\text{Cl}_3$: C, 49.23; H, 3.99; N, 3.83. Found: C, 49.48; H, 4.02; N, 3.75.

2,2,2-Trichloroethyl 2-Amino-2-deoxy-3-O-(2-amino-2-deoxy- β -D-glucopyranosyl)- β -D-glucopyranoside (17). A solution of the phthalimido compound 16 (366 mg), and 85% hydrazine hydrate (2 ml) in 95% ethanol (20 ml) was refluxed for 2 hr and the solution cooled to 0°. The solid was removed by filtration and washed with cold ethanol (5 ml). The combined filtrates were evaporated to a foam which was dissolved in water (10 ml) and applied to a column of Dowex 1x8 resin (hydroxide form). Freeze-drying of the eluent gave a colorless solid (208 mg, 88% yield), mp 202-204° (dec.), $[\alpha]_D^{25} - 33.6^\circ$ (*c*, 0.25 in water).

$^1\text{H-NMR}$ (D_2O): δ 5.22, 5.19 (d, 8 Hz, H-1 and H-1').

The $^{13}\text{C-NMR}$ is reported in Table III.

Anal. Calcd. for $\text{C}_{14}\text{H}_{25}\text{N}_2\text{O}_9\text{Cl}_3$: C, 35.65; H, 5.34; N, 5.94. Found: C, 35.82; H, 5.23; N, 5.78.

2,2,2-Trichloroethyl 2-Acetamido-2-deoxy-3-O-(2-acetamido-2-deoxy- β -D-glucopyranosyl)- β -D-glucopyranoside (18). A solution of the amino compound 17 (161 mg,

0.34 mmol) in 50% aqueous methanol (10 ml) was treated with acetic anhydride (1.0 ml) and the solution was stirred for 2 hr at room temperature. Solvent removal left a foam which was dissolved in water (10 ml) and treated with Ion Retardation Resin, AG 11A8 (50-100 mesh, Bio-Rad). Filtration and freeze-drying of the filtrate gave a solid (170 mg, 90% yield), mp 222-224° (dec.), $[\alpha]_D^{25} - 26.6^\circ$ (c, 0.5 in water).

$^1\text{H-NMR}$ (D_2O): δ 5.12 (d, 8 Hz, H-1); 4.92 (d, 8 Hz, H-1'); 2.33, 2.39 (s, *N*-acetyl).

$^{13}\text{C-NMR}$ (D_2O): 103.9 (C-1), 101.3 (C-1'), 81.5 (C-3), 75.8, 75.5 (C-5, C-5'), 73.3 (C-3'), 69.9 (C-4), 68.6 (C-4'), 60.7 (C-6, C-6'), 55.7, 54.3 (C-2, C-2').

Anal. Calcd. for $\text{C}_{18}\text{H}_{29}\text{N}_2\text{O}_{11}\text{Cl}_3$: C, 38.90; H, 5.26; N, 5.04. Found: C, 38.54; H, 5.26; N, 5.23.

2,2,2-Trichloroethyl 3-O-Acetyl-4,6-O-benzylidene-2-deoxy-2-phthalimido- β -D-glucopyranoside (19). Acetic anhydride (8 ml) was added to a cooled solution of the 3-hydroxy compound 14 (3.70 g) in dry pyridine (16 ml). The solution was kept overnight at room temperature and poured into crushed ice. Collection of the separated solid by filtration and recrystallization from ethyl acetate-ethanol (1:4) gave a colorless solid (3.58 g, 90% yield), mp 208°, $[\alpha]_D^{20} - 29.8^\circ$ (c, 0.5 in chloroform).

$^1\text{H-NMR}$: δ 7.90-7.22 (m, 9, benzyl and phthalimido); 6.00 (t, 9 Hz, H-3); 5.64 (d, 8 Hz, H-1); 5.53 (s, 1, benzylidene); 1.90 (s, O-acetyl); 4.52-3.64 (m, 7 remaining protons).

Anal. Calcd. for $\text{C}_{25}\text{H}_{22}\text{NO}_8\text{Cl}_3$: C, 52.60; H, 3.88; N, 2.45; Cl, 18.63. Found: C, 52.89; H, 3.97; N, 2.31; Cl, 18.72.

2,2,2-Trichloroethyl 3-O-Acetyl-2-deoxy-2-phthalimido- β -D-glucopyranoside (20). A solution of the above benzylidene compound 19 (2.85 g) in 60% aqueous acetic acid (150 ml) was stirred at 100° for 30 min. Solvent removal left a yellow solid which was slightly contaminated by the starting compound. The crude mixture was applied to a silica-gel column and eluted with ethyl acetate-benzene. Solvent removal of the second fraction gave a colorless solid (2.15 g, 89% yield), mp 190-191°, $[\alpha]_D^{20} - 29.2^\circ$ (c, 1 in acetone).

$^1\text{H-NMR}$ (acetone- d_6): δ 7.86 (s, 4, phthalimido); 5.70 (t, 10 Hz, H-3); 5.67 (d, 8 Hz, H-1); 4.88 (d, 5 Hz, 1, OH, D_2O exchangeable); 4.36 (d, 4 Hz, 2, CH_2CCl_3); 2.91 (s, 1, OH, D_2O exchangeable); 1.86 (s, O-acetyl); 4.50-3.55 (m, 5 remaining protons).

Anal. Calcd. for $\text{C}_{18}\text{H}_{18}\text{NO}_8\text{Cl}_3$: C, 44.79; H, 3.74; N, 2.90; Cl, 22.03. Found: C, 44.93; H, 3.82; N, 2.81; Cl, 22.06.

2,2,2-Trichloroethyl 3,6-Di-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranoside (21). Acetic anhydride (0.306 g, 3 mmol) was added to a cooled solution of compound 20 (1.466 g, 3 mmol) in dry pyridine (4 ml). After stirring at room temperature for 2 hr, the solution was cooled to 0° and treated with methanol (5 ml). Solvent removal left a foamy solid which was shown to be a mixture of 10, 20, and 21 by TLC. The crude mixture was applied to a silica gel column and eluted with benzene-ethyl acetate (4:1). Solvent removal of the second fraction gave a colorless solid (0.86 g, 54.5% yield), mp 139-140° [α]_D²⁴ -36.7° (c, 0.9 in chloroform). ¹H-NMR: δ 7.95-7.68 (m, 4, phthalimido); 5.82 (q, 9 Hz, H-3); 5.62 (d, 8 Hz, H-1); 3.33 (d, 5 Hz, OH, D₂O exchangeable); 2.16, 1.96 (s, O-acetyl); 4.55-3.60 (m, 7 remaining protons).

Anal. Calcd. for C₂₀H₂₀NO₉Cl₃: C, 45.78; H, 3.84; N, 2.67; Cl, 20.27. Found: C, 45.83; H, 3.94; N, 2.70; Cl, 20.11.

2,2,2-Trichloroethyl 4-O-(3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranosyl)-3,6-di-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranoside (22). A solution of the β -bromide 5 (1.10 g, 22 mmol) in nitromethane (15 ml) was added to a cooled (-30°) solution of the 4-hydroxy compound 21 (1.05 g, 2.0 mmol) and collidine (266 mg, 2.2 mmol) in nitromethane (15 ml). After stirring at -30° for 4 hr, 1 mmol each of 5, the silver salt and collidine were added. The mixture was stirred for an additional 2 hr at -30° and then left overnight at room temperature. Chloroform (50 ml) was added and the solids were removed by filtration and washed with chloroform (20 ml). The combined filtrates were washed with cold water, 3% hydrochloric acid and water and dried. Solvent removal left a yellow foam which was applied to a silica gel column and eluted with benzene-ethyl acetate (4:1). Removal of the solvent from the second fraction and crystallization from diethyl ether gave a colorless solid (1.28 g, 68% yield based on 21), mp 133-134°, [α]_D²⁴ +1.6° (c, 0.5 in chloroform).

¹H-NMR: δ 8.0-7.62 (m, 8, 2 phthalimido); 5.87 (q, 9 Hz, H-3); 5.74 (t, 10 Hz, H-3'); 5.51 (d, 8 Hz, H-1); 5.48 (d, 8 Hz, H-1'); 5.15 (t, 10 Hz, H-4'); 2.11, 2.01, 1.99, 1.94, 1.84 (s, O-acetyl); 4.60-3.62 (m, 11 remaining protons).

Anal. Calcd. for C₄₀H₃₉N₂O₁₈Cl₃: C, 51.00; H, 4.17; N, 2.97; Cl, 11.29. Found: C, 50.85; H, 4.27; N, 3.10; Cl, 11.36.

2,2,2-Trichloroethyl 2-Deoxy-2-phthalimido-4-O-(2-deoxy-2-phthalimido- β -D-glucopyranosyl)- β -D-glucopyranoside (23). A solution of the compound 22 (346 mg, 0.5 mmol) in a mixture of acetone (20 ml), water (10 ml) and conc. hydrochloric acid (4 ml) was stirred at 70° for 6 hr. Evaporation of acetone left a white suspension which was collected by filtration and washed with water. Recrystallization from ethyl acetate-benzene gave a colorless solid (220 mg, 82% yield), mp 221-223° (dec.), $[\alpha]_D^{25}$ -20.8° (c, 0.25 in acetone).

$^1\text{H-NMR}$ (acetone- d_6): δ 7.88, 7.86 (m, 8, 2 phthalimido); 5.38, 5.36 (d, 8 Hz, H-1, H-1'); 5.86-2.80 (m, remaining 19 protons).

$^{13}\text{C-NMR}$ (acetone- d_6): 100.6, 100.4 (C-1, C-1'), 81.5 (C-4), 78.4 (C-5'), 76.6 (C-5), 72.8, 72.5 (C-3, C-3'), 70.7 (C-4'), 62.8, 61.7 (C-6, C-6'), 58.5, 57.1 (C-2, C-2').

Anal. Calcd. for $\text{C}_{30}\text{H}_{29}\text{N}_2\text{O}_{13}\text{Cl}_3$: C, 49.23; H, 3.99; N, 3.83. Found: C, 49.84; H, 4.12; N, 3.54.

2,2,2-Trichloroethyl 2-Amino-2-deoxy-4-O-(2-amino-2-deoxy- β -D-glucopyranosyl)- β -D-glucopyranoside (24). Compound 24, mp 160-162° (dec.), $[\alpha]_D^{24}$ -7.8° (c, 2 in water), was obtained in 87% yield from compound 23 by the method used for the preparation of the compound 17.

$^1\text{H-NMR}$ (D_2O): δ 5.26 (d, 8 Hz, H-1); 5.02 (d, 8 Hz, H-1'); 4.69 (d, 3.5 Hz, 2, CH_2CCl_3).

The $^{13}\text{C-NMR}$ is reported in Table III.

Anal. Calcd. for $\text{C}_{14}\text{H}_{25}\text{N}_2\text{O}_9\text{Cl}_3$: C, 35.65; H, 5.34; N, 5.94. Found: C, 35.63; H, 5.17; N, 5.99.

2,2,2-Trichloroethyl 2-Acetamido-2-deoxy-4-O-(2-acetamido-2-deoxy- β -D-glucopyranosyl)- β -D-glucopyranoside (25). Compound 25, mp 218-219° (dec.), $[\alpha]_D^{23}$ -22.4° (c, 0.25 in water), was prepared in 80% yield from compound 24 by the method used for the preparation of the compound 18.

$^1\text{H-NMR}$ (D_2O): δ 4.98 (d, 8 Hz, H-1); 4.74 (d, 8 Hz, H-1'); 2.22, 2.18 (s, N-acetyl).

$^{13}\text{C-NMR}$ (D_2O): 102.8, 102.0 (C-1, C-1'), 79.8 (C-4), 76.3 (C-5'), 75.0 (C-5), 74.2, 73.8 (C-3, C-3'), 72.4 (C-4'), 61.0, 60.6 (C-6, C-6'), 56.0, 55.1 (C-2, C-2').

Anal. Calcd. for $\text{C}_{18}\text{H}_{29}\text{N}_2\text{O}_{11}\text{Cl}_3$: C, 38.90; H, 5.26; N, 5.04. Found: C, 38.35; H, 5.20; N, 5.12.

Methyl 4-O-(3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranosyl)-2,3,6-tri-O-benzoyl- α -D-galactopyranoside (26). A solution of the β -bromide 5 (1.99 g, 4 mmol) in nitromethane (10 ml) was added to a cooled (-30°) solution of methyl 2,3,6-tri-O-benzoyl- α -D-galactopyranoside (24), mp 135.5°, $[\alpha]_D^{22}$ -120° (c, 1 in chloroform), (1.52 g, 3 mmol), silver triflate

(1.03 g, 4 mmol), and collidine (0.48 g, 4 mmol) in nitromethane (20 ml). After stirring at -30° for 3 hr and at room temperature for 1 hr, the mixture was diluted with chloroform (70 ml). The solid was removed by filtration and washed with chloroform (20 ml). The combined filtrates were washed with cold water, 3% hydrochloric acid and water. Concentration left a yellow foam which was passed through a short alumina column using diethyl ether-ethyl acetate. Solvent removal and crystallization from diethyl ether gave a solid, mp $153-154^{\circ}$, $[\alpha]_D^{22} +110^{\circ}$ (*c*, 1 in chloroform), 2.19 g (79% yield based on the galactopyranoside).

$^1\text{H-NMR}$: δ 8.12-7.12 (m, 19, 3 benzoyl and 1 phthalimido); 5.80 (q, 9 Hz, H-3'); 5.52 (d, 8 Hz, H-1'); 5.47 (q, 12 Hz, H-2); 5.19 (d, 4 Hz, H-3); 4.97 (t, 4 Hz, H-4); 4.73 (d, 2 Hz, H-1); 3.31 (s, 3, OCH₃); 2.03, 1.93, 1.80 (s, 0-acetyl); 4.67-3.50 (m, 7 remaining protons).

Anal. Calcd. for C₄₈H₄₅NO₁₈: C, 62.40; H, 4.91; N, 1.52. Found: C, 62.61; H, 5.02; N, 1.58.

Methyl 4-O-(2-Amino-2-deoxy- β -D-glucopyranosyl)- α -D-galactopyranoside (27). A solution of the disaccharide 26 (1.02 g, 1.1 mmol) in a mixture of acetone (40 ml), water (20 ml) and conc. hydrochloric acid (8 ml) was stirred at 70° for 3 hr. After the removal of acetone, the sticky residue was extracted with ethyl acetate (2 x 50 ml) and the combined extracts were washed with cold water and cold saturated sodium bicarbonate solution. Solvent removal left a solid (890 mg) which appeared to be a deacetylated compound. A solution of this benzoyl group containing product and 85% hydrazine hydrate (3.0 ml) in 95% ethanol (10 ml) was refluxed for 3 hr and cooled to 0° . The solid was removed by filtration and the filtrate was evaporated to a syrup which was applied to a column of Dowex 1x8 resin (hydroxide form) using water. Freeze-drying of the eluent gave a foam which was crystallized from 98% ethanol (302 mg, 77% yield), mp $210-212^{\circ}$ (dec.), $[\alpha]_D^{24} +102^{\circ}$ (*c*, 0.5 in water).

$^1\text{H-NMR}$ (D₂O): δ 5.15 (d, 2 Hz, H-1); 4.86 (d, 8 Hz, H-1'); 3.70 (s, 3, OCH₃); 2.96 (t, 8 Hz, H-2'); 4.60-3.56 (m, 11 remaining protons).

$^{13}\text{C-NMR}$ (D₂O, pH 9.5 and 5.0 respectively): 100.0, 99.9 (C-1), 69.2, 68.9 (C-2), 70.4, 69.7 (C-3), 78.9, 79.1 (C-4), 70.6, 70.1 (C-5), 61.5, 60.9 (C-6), 105.0, 100.1 (C-1'), 57.5, 56.9 (C-2'), 76.5, 72.6 (C-3'), 70.4, 70.1 (C-4'), 76.5, 76.4 (C-5'), 61.5, 61.5 (C-6').

Anal. Calcd. for C₁₃H₂₅NO₁₀: C, 43.94; H, 7.09; N, 3.94. Found: C, 43.32; H, 6.96; N, 3.90.

Methyl 4-O-(2-Acetamido-2-deoxy- β -D-glucopyranosyl)- α -D-galactopyranoside (28). The compound, mp 160-162° (dec.), $[\alpha]_D^{25} +83.3$ (c, 0.5 in water), was obtained in 94% yield from compound 27 by the method used for the preparation of the compound 18.

$^1\text{H-NMR}$ (D_2O): δ 5.12 (d, 2.5 Hz, H-1); 4.94 (d, 8 Hz, H-1'); 3.72 (s, OCH_3); 2.38 (s, N-acetyl).

$^{13}\text{C-NMR}$ (D_2O): 102.2 (C-1'), 99.5 (C-1), 77.2 (C-4), 75.6 (C-5'), 73.9 (C-3'), 70.9 (C-5), 70.2 (C-3), 69.4 (C-2), 68.5 (C-4'), 61.0 (C-6, C-6'), 55.8 (C-2').

Anal. Calcd. for $\text{C}_{15}\text{H}_{27}\text{NO}_{11}$: C, 45.34; H, 6.85; N, 3.53. Found: C, 44.98; H, 6.80; N, 4.02.

Acknowledgements

The authors are indebted to the National Research Council of Canada for grants-in-aid of this research to R. U. Lemieux (A-172). The NMR and microanalyses were provided by the service laboratories of this Department.

Abstract

The chemical properties of the anomeric tri-O-acetyl-2-deoxy-2-phthalimido-D-glucopyranosyl halides were examined. With the halogen Cl, Br and I, the anomerization equilibrium constants are 3.2, 1.2 and 3.0, respectively, in accord with earlier evidence (S. Akiya and T. Osawa, 1960) for destabilization of the α -forms by the phthalimido group. The α -anomers undergo replacement of the halogen with inversion whereas extensive retention of configuration occurs using the β -forms and therefore a cationic intermediate is indicated. Reaction of the β -halides with 2-propanol in nitromethane containing mercuric cyanide provided the β -glycosides in high yield. However, with 2,2,2-trichloroethanol, glycosyl cyanide formation was extensive. Using silver triflate-collidine (1:1) as the halogen acceptor, 2,2,2-trichloroethyl tri-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranoside was formed in 86% yield. Under these conditions, the tri-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranosyl derivatives of 2,2,2-trichloroethyl 4,6-O-benzylidene-2-deoxy-2-phthalimido- β -D-glucopyranoside, 2,2,2-trichloroethyl 3,6-di-O-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranoside and methyl 2,3,6-tri-O-benzoyl- α -D-galactopyranoside were synthesized in 82, 68 and 79% yields, respectively.

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Some Aspects of the Chemistry of D-Glucal

I. D. BLACKBURNE, A. I. R. BURFITT, P. F. FREDERICKS, and R. D. GUTHRIE
 School of Science, Griffith University, Nathan, Q.4111, Australia

D-Glucal (Fig. 1) is a well known unsaturated sugar (1) - in the words of Fraser-Reid (2) "venerable". There has been much study of the chemistry of this compound, and of its stereoisomers, D-galactal etc., as witnessed by work described in the excellent reviews in *Advances in Carbohydrate Chemistry* by Ferrier (3,4) and its continuing mention in the Specialist Periodical Reports on Carbohydrate Chemistry. Not unexpectedly much of the research on D-glucal has involved addition of a wide variety of molecules to the 1,2-double bond (3,4). Little work has been done to exploit the other feature of D-glucal, namely that it has three different types of hydroxyl group, primary, secondary, and allylic. (Fig. 1) Those few derivatives at the 3,4 or 6 position that have been made have been prepared from the appropriate D-glucose compound then finally putting the 1,2-double bond in place. No studies have been made, as far as we are aware, of the selectivity of reaction amongst the three hydroxyl groups.

This exploitation of D-glucal chemistry has "relevance" as all our work is nowadays supposed to have. Amino-glycoside antibiotics (5) are now important chemotherapeutic substances. The nitrosyl chloride based synthesis devised by Lemieux (Fig. 2) is of particular interest here as it utilises glucals in the synthesis of α -linked glycosides with an amino or an hydroxyl group at C-2.

Thus one could envisage a semi-synthetic route to modified kanamycins. (Figs. 3 and 4) These suppose that D-glucal derivatives with required modification at C-3 or C-6 (Fig. 5) are available: such compounds are our targets. We decided first to investigate the synthesis of 6-deoxy-6-fluoro derivatives.

3,4-Di-O-benzoyl-6-O-tosyl-D-glucal (Fig. 6) is probably the most readily available (7) potential starting material. Reaction with fluoride ion in protic solvents such as ethylene glycol led to products that were difficult to separate. Caesium fluoride in DMF, in contrast gave a beautifully crystalline compound, (92%) which was identified as the novel

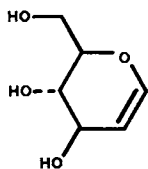


Figure 1. D-Glucal, showing, from top to bottom, a primary, secondary, and an allylic hydroxyl group

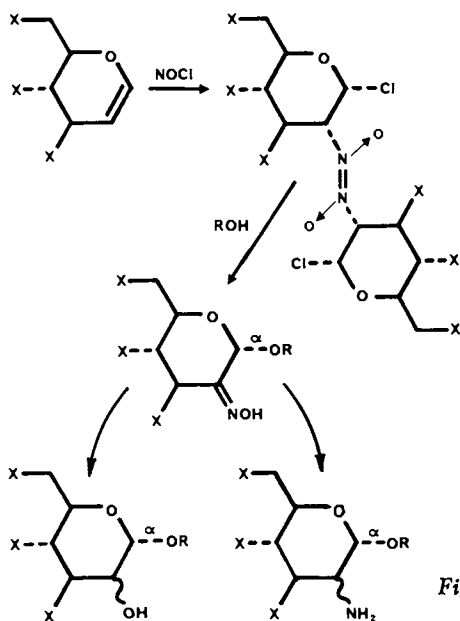


Figure 2. Synthesis of modified kanamycins

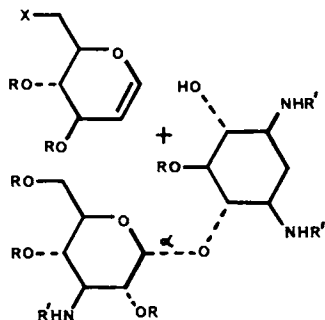


Figure 3. Synthesis of modified kanamycin A

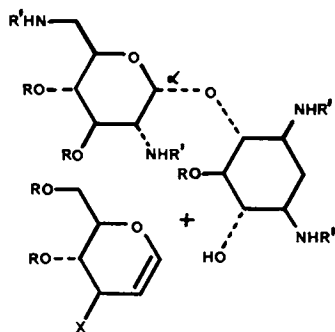


Figure 4

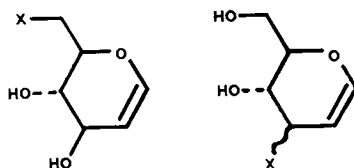
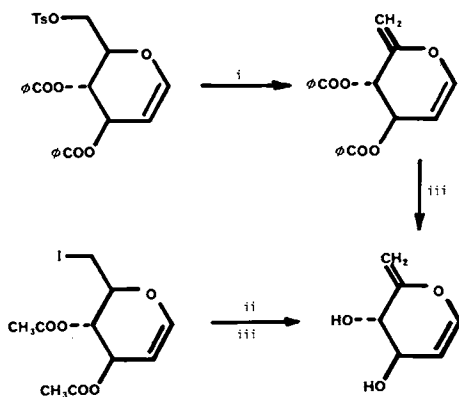


Figure 5



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Figure 6. Reagents: (i) CsF , DMF ; (ii) AgF , pyr ; (iii) MeONa , MeOH (Kiss, Carbohydr. Res. (1969) 11, 579)

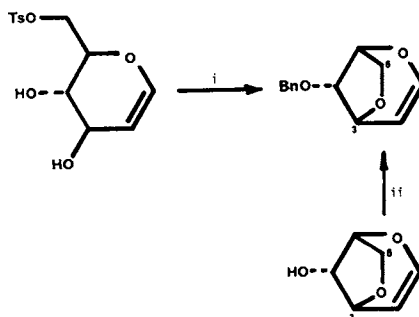


Figure 7. Reagents: (i) PhCH_2Br , BaO , $\text{Ba}(\text{OH})_2$; (ii) NaH , PhCH_2Br

diene dibenzoate by comparison with a compound prepared by Kiss (8).

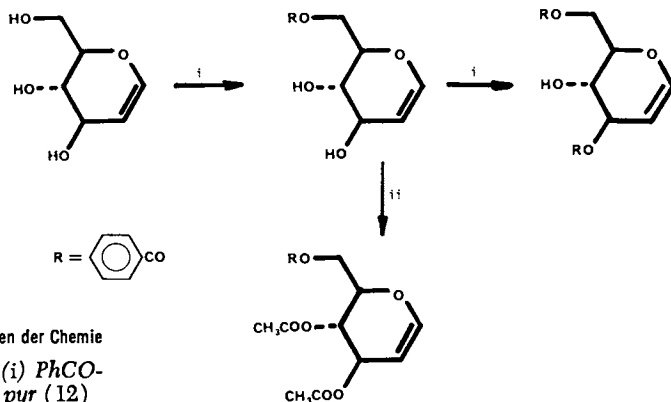
The basic nature of the fluoride ion (9) suggested that a more stable blocking group was needed for the C-3 and C-4 hydroxyl groups than benzoyl, for example, benzyl ether groups. Furthermore, an unprotected hydroxyl group is undesirable at C-3 because of the known (10) possibility of formation of a 3,6-anhydro compound. Efforts were then directed towards the synthesis of 3,4-di-O-benzyl-6-O-tosyl-D-glucal.

Using the benzylation of benzyl 2-acetamido-2-deoxy-6-O-mesyl- α -D-glucopyranoside as a model (11), 6-O-tosyl-D-glucal was treated as shown (Fig. 7). The major product had only one benzyl group and was readily shown to be the 3,6-anhydro derivative, by benzylation of authentic (7) 3,6-anhydro-D-glucal. No 3,6-anhydro-sugar formation was reported by Shulman and Khorlin (11) and the ease of our reaction presumably reflects the ease with which 6-O-tosyl-D-glucal can attain the required conformation.

Attention was next turned to the selective benzylation of D-glucal, in the hope that some blocking group sequence might be developed and also out of pure academic interest on the relative reactivity of the three different types of hydroxyl groups. Reaction with one equivalent of benzoyl chloride gave a complex mixture that after chromatography and crystallisation gave, as the major product (30%) 6-O-benzoyl-D-glucal (Fig. 8), identified by conversion to the known 3,4-diacetate, prepared by Brigl by an indirect route (12). Treatment of D-glucal with two equivalents of benzoyl chloride gave the dibenzoate (65%), identified by nmr analysis (Fig. 9) as the 3,6-derivative. Of note is that irradiation at δ 5.60 (H-C-COPh) removed the long-range coupling to H-1 and the coupling to H-2.

The lack of success with the above reactions in terms of yields led us to turn to other possible routes for blocking the C-3 hydroxyl group. Fraser-Reid (13) has described the synthesis of 4,6-O-isopropylidene-D-glucal *en route* to the 3-ketone, but did not characterise the intermediate (Fig. 10). It was, however isolable, as a syrup, either by chromatography, or by benzylation of the crude product to give a crystalline 3-benzoate, followed by de-benzylation. Treatment of 4,6-O-isopropylidene-D-glucal with sodium hydride and benzyl chloride gave the 3-O-benzyl ether (Fig. 11). This was de-acetalated with *p*-toluenesulphonic acid to give crystalline 3-O-benzyl-D-glucal (40%). The low yield presumably results from the side reactions of the acid-sensitive vinyl ether function. The structure of the 3-ether was proved by comparison with a compound prepared from a 3-O-benzyl-D-glucose derivative (14).

Concurrently with the above another approach was studied, namely placing a temporary blocking group at O-6, putting blocking groups such as benzyl ether at O-3 and O-4, removing the O-6 group and replacing it with tosyl or mesyl. Obviously the

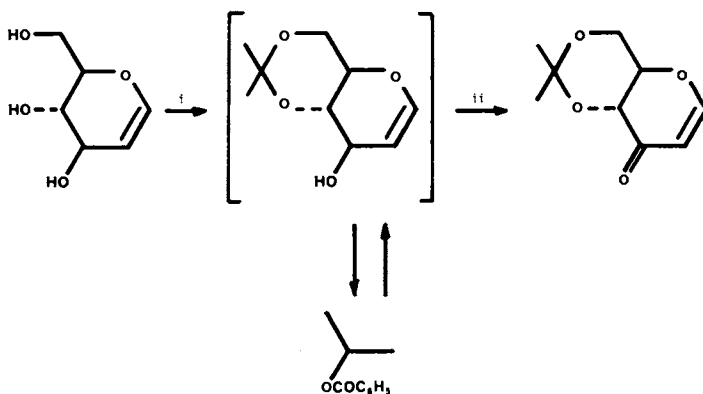
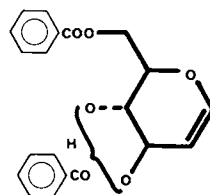


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Figure 8. Reagents: (i) $\text{PhCO-Cl}(x1)$, pyr; (ii) Ac_2O , pyr (12)

Figure 9

δ	Assignment	J Values (Hz)
6.51 d of d	H-1	$J_{1,2}$ 6.5; $J_{1,3}$ 1.4
4.89 d of d	H-2	$J_{1,2}$ 6.5; $J_{2,3}$ 2.8
5.60 m	H-3 or H-4	
	Irradiate at 5.60: H-1	d, $J_{1,2}$ 6.5
	H-2	d, $J_{1,2}$ 6.5
	Irradiate at 4.89: H-1	bs
	H-3	bd $J_{3,4}$ 6.3
	H-4	



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Figure 10. Reagents: (i) $(\text{CH}_3)_2\text{C}(\text{OCH}_3)_2$, TsOH , DMF ; (ii) MnO_2 , CHCl_3 (Fraser-Reid et al., *Canad. J. Chem.* (1973) 51, 3950)

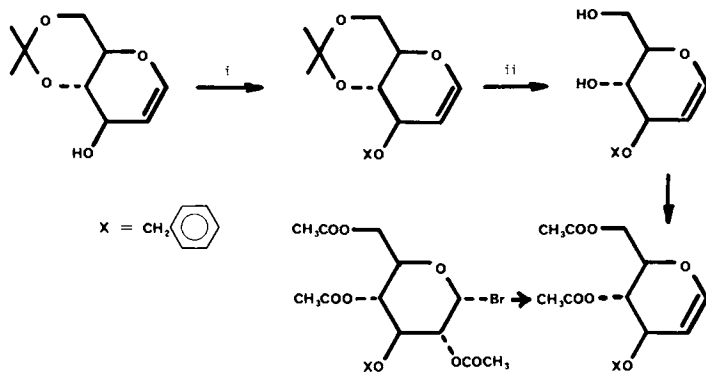
temporary 0-6 blocking group ideally had to be removed using conditions that were neither acidic, nor by hydrogenation. Recent papers have described the use of the t-butyl-dimethylsilyl (BDMS) ether function (15-20), which fits the above requirements. The BDMS chloride reacts preferentially with primary hydroxyl groups (18,21) and the formed Si-O bond is particularly susceptible to attack by fluoride ion to regenerate the parent hydroxyl function. We have shown that use of pyridine as catalyst (21) rather than imidazole (15,20) confers greater selectivity on the reagent.

Treatment of D-glucal with one equivalent of BDMS chloride gave a mono-derivative, assigned the 0-6 structure (Fig. 12) (and see later). Benzylolation by the sodium hydride method gave 3,4,6-tri-O-benzyl-D-glucal; use of the barium hydroxide, barium oxide, benzyl bromide method gave a di- and mono-O-benzyl ether. Desilylation gave a mixture of D-glucal di- and mono-benzyl ethers (Fig. 13). The D-glucal mono-benzyl ether was shown to be different from the 3-O-benzyl ether and was converted to 3,6-anhydro-4-O-benzyl-D-glucal, thus the secondary rather than the allylic hydroxyl was preferentially benzylated.

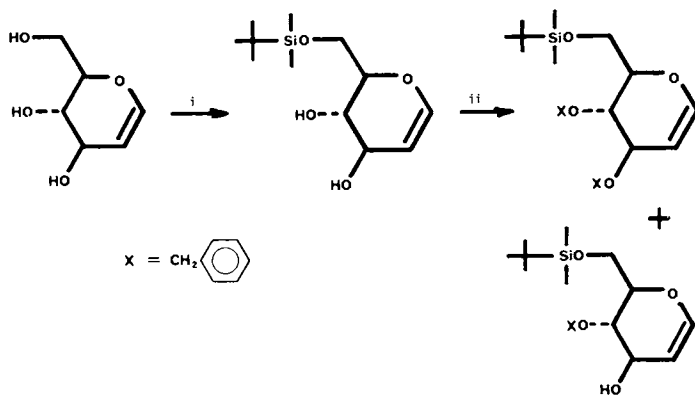
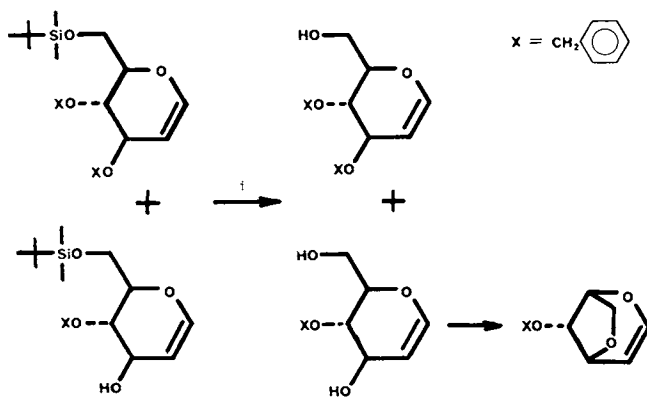
3,4-Di-O-benzyl-D-glucal was then tosylated (Fig. 14) and the product treated with tetrabutylammonium fluoride in DMF to give the 6-fluoro derivative (75%). It is interesting to compare this reaction with that described by Pacak et al (22). Treatment of the dibenzyl-tosyl-glucal with caesium fluoride in ethylene glycol gave two products, one of which was the 2'-hydroxyethyl derivative (Fig. 15).

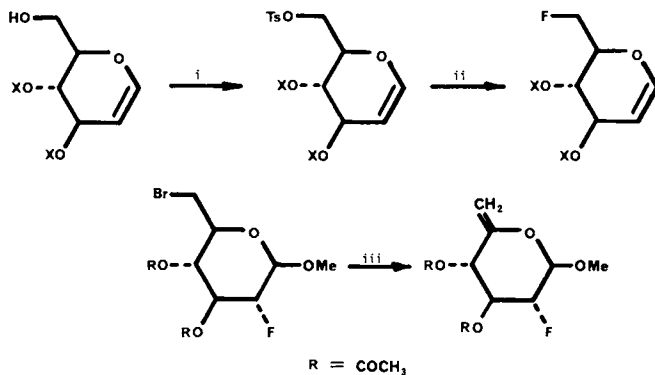
The ^1H n.m.r. spectrum of the deoxy-fluoro product showed the presence of vinyl ether (δ 6.39, 1H) and two benzyl ether (δ 7.30, 10H) functions. The ^{19}F spectrum at 94 MHz was a triplet of doublets (J 47.2 and 24.6 Hz) due to coupling of the fluorine substituent with the two C6 and one C5 protons, establishing firmly that the BDMS group was previously at C-6. The successful application of the t-butyl-dimethylsilyl protecting group in the present synthesis follows its recently described (15-19) utility in the nucleoside field and emphasizes its suitability as an alternative to the trityl protecting group, particularly in acid-sensitive systems.

In similar fashion, 3-deoxy-D-glucal (23) and ethyl 2,3-dideoxy- α -D-erythro-hex-2-enopyranoside (24) were converted via the BDMS ethers to the 4-O-benzyl ethers. Conversion into the tosylates in the usual way and treatment with caesium fluoride in ethylene glycol gave the 6-deoxy-6-fluoro derivatives (Fig. 16) along with small amounts in each case of lower- R_f components. The by-product from the latter reaction was isolated by p.l.c.; n.m.r. and high resolution mass spectrometry indicated the 6-O-(2'-hydroxyethyl) structure. Compounds in the 3-deoxy-D-glucal series, including the 6-deoxy-6-fluoride were in general found to decompose particularly readily.



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Figure 11. Reagents: (i) NaH , PhCH_2Cl ; (ii) MeOH , TsOH (14)Figure 12. Reagents: (i) BDMS-Cl , pyr ; (ii) PhCH_2Br , BaO , Ba(OH)_2 Figure 13. Reagents: (i) Bu_4NF , DMF



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Figure 14. Reagents: (i) TsCl , *pyr*; (ii) Bu_4NF , *DMF*; (iii) Bu_4NF , *MeCN* (22)

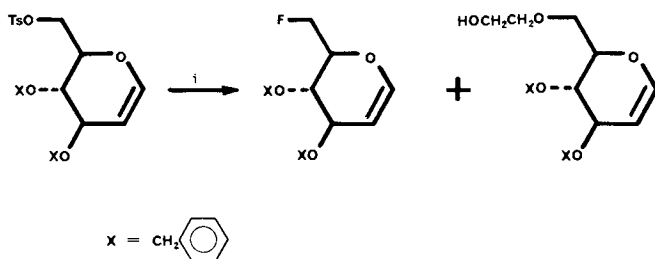


Figure 15. Reagent: (i) CsF , $(\text{CH}_2\text{OH})_2$

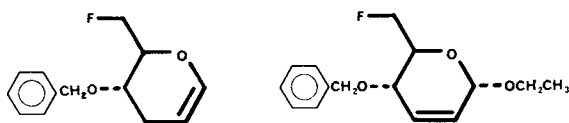
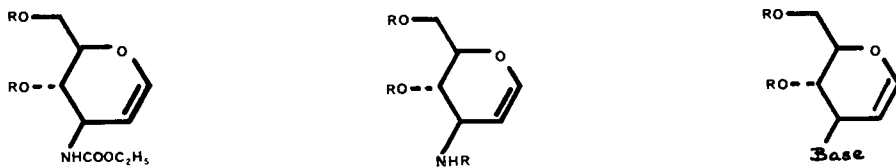


Figure 16



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Figure 17. The structures are, from left to right, from a reaction of a hex-2-ene and $\text{OCN-SO}_2\text{Cl}$ (Hall, Jordaan & Laurens, *J. Chem. Soc. (Perkin I)* 1973, 38), from a *D*-glucose derivative (Umezawa *et al.*, *J. Am. Chem. Soc.* (1972) 94, 4353), and from *D*-glucal

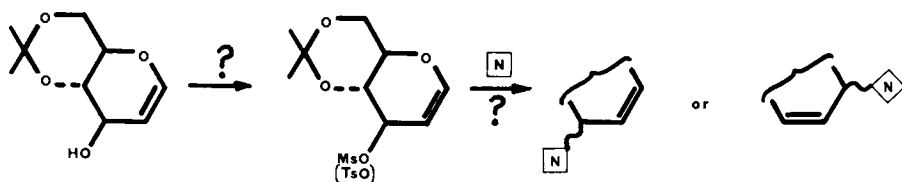
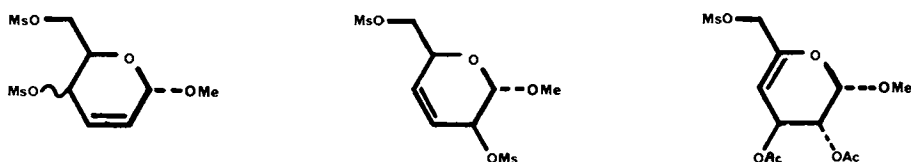


Figure 18



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Figure 19. These compounds have the allylic mesyloxy group displaced by an S_N2 process (Overend *et al.*, *J. Chem. Soc.*, 1950, 738, Brimacombe *et al.*, *J. Chem. Soc. (Perkin I)* 1975, 979, and Guthrie *et al.*, unpublished work, respectively)

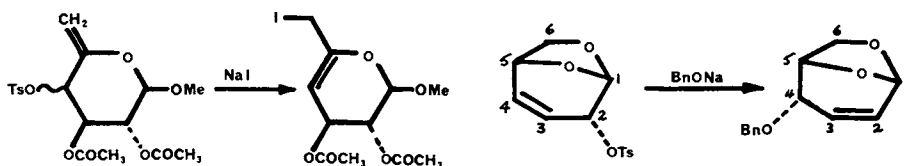
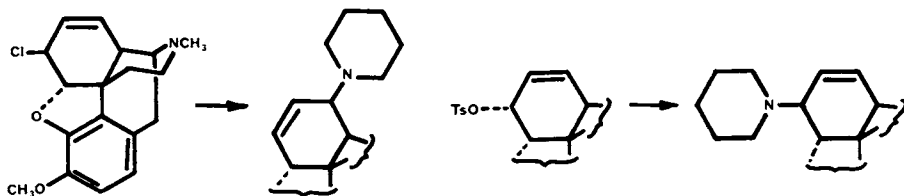
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Figure 20. Two allylic sulphonates proceed via S_N2' processes (Brockhaus & Lehmann, *Justus Liebigs Ann. Chem.*, 1974, 1675 and Pecka, Stanek & Cerny, *Coll. Czech. Chem. Commun.* (1974) 39, 1192, respectively)



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Figure 21. (Stork & White, *J. Am. Chem. Soc.* (1956) 78, 4626)

Attention was then turned to the 3-position of D-glucal. Some D-glucal compounds at the 3-position are known as shown in Fig. 17 (and references therein). The approach planned, and it was hoped also that it would be applicable to the epimeric D-allal, was to place a leaving group at C-3, such as a sulphonate ester.

The question then arises: how will a nucleophile attack this allylic system - by S_N1 or S_N2 attack to give a 3-substituted glucal or allal derivative (Fig. 18), or by an S_N2' process to yield a 1-substituted 2,3-unsaturated sugar.

It is interesting to look at the pathways for displacements on known allylic sugar sulphonates. Fig. 19 (and references therein) show the systems that have been reported as proceeding via S_N2 processes. Fig. 20 (and references therein) shows those allylic sulphonates shown to proceed via S_N2' processes. The first is explicable in that the double bond in a six-membered ring generally prefers to move to an endocyclic position if possible. The second case was argued on the grounds that the benzyloxy anion would have a much lower energy approach path to C-4 than to C-2 because of the two ring oxygens. On this argument it is difficult to see why the 2-O-mesy-3-ene compound of Brimacombe (Fig. 19) does not undergo S_N2' displacement at C-4.

Fig. 21 shows displacements on the codeine type skeleton. S_N2 approach to the chloro group by piperidine (in benzene) is hindered and so an S_N2' pathway is followed; the epimeric tosylate is displaced in an S_N2 fashion by same reagent, presumably because of lack of hindrance to the pathway. There seem few examples of allylic sulphonate displacements recorded in the literature other than simple systems.

The system (A) (Fig. 22) is not just a simple allylic system, but one which as far as we can see has not been studied elsewhere - it is an extended allylic system - extended by the ring oxygen atom. In this way it differs from all of the other allylic systems studied, and this should affect its activity markedly.

The first unexpected finding was that we could not tosylate the molecule (Fig. 22). This is a result that is difficult to believe, but we have repeated the experiment many times. It was interesting that we could not tosylate 4,6-O-benzylidene-D-allal either. (However, it will be recalled that a benzoate ester and a benzyl ether of 4,6-O-isopropylidene-D-glucal can be prepared.) Mesylation gave in the majority of cases material of low R_f that could not be identified, but under one set of conditions gave a major and minor product, readily identified by ^{13}C n.m.r. spectroscopy as novel products, but in no way what we wanted.

Fig. 23 shows the ^{13}C n.m.r. spectrum of 4,6-O-isopropylidene-D-glucal and Fig. 24 the ^{13}C spectrum of the major product. Instantly it is obvious that there are too many carbon

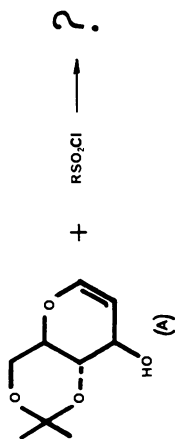
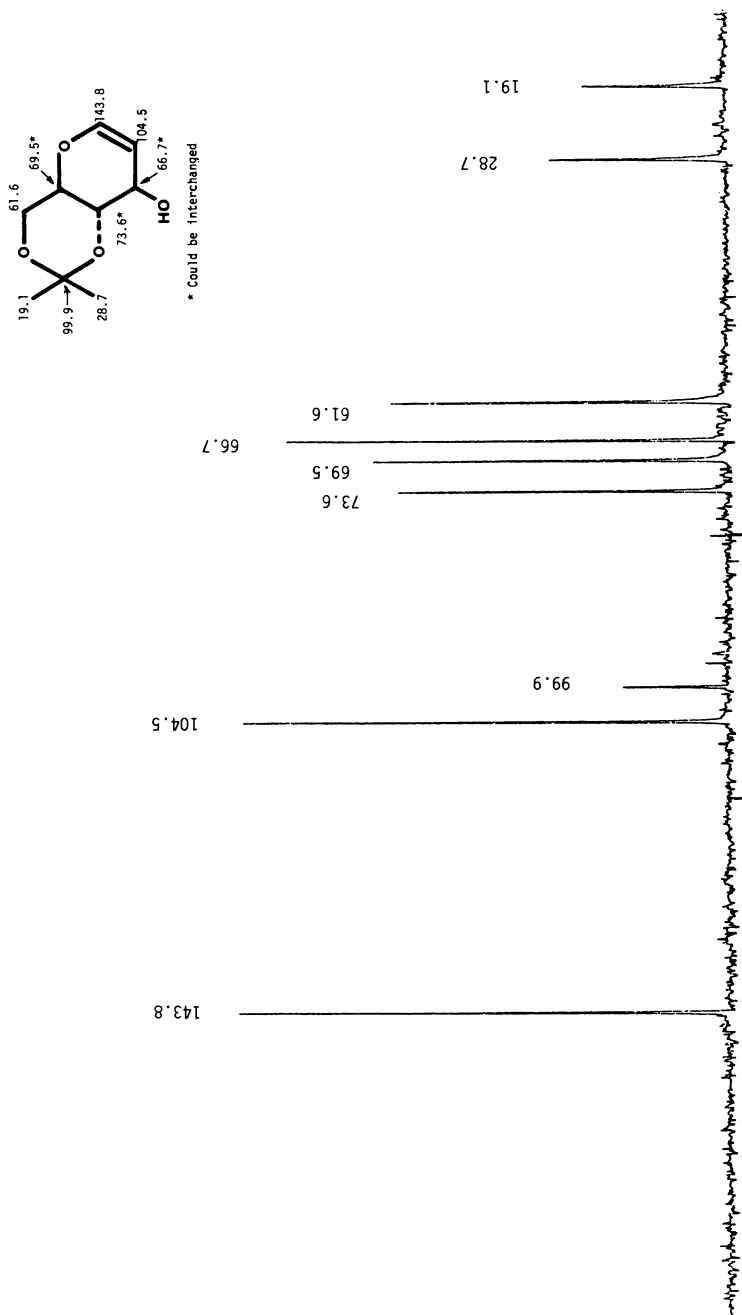


Figure 22

RSO_2Cl (equiv.)	Base (equiv.)	Solvent	Temp.	Time	Products
TsCl (1.2)	Et_3N (1.2)	CHCl_3	0°	4d	A
TsCl (1.2)	pyr (1.2)	CHCl_3	$0 \rightarrow 20^\circ$	5d	A
TsCl (1.2)	pyr (92)	(pyr)	$-10 \rightarrow 30^\circ$	23d	A
MsCl (2.0)	pyr (46)	(pyr)	$-20 \rightarrow 8^\circ$	1d	$R_f < 0.1$
MsCl (1.0)	Et_3N (1.2)	CH_2Cl_2	$-50 \rightarrow -16^\circ$	2.5d	$R_f < 0.1$
MsCl (1.0)	Et_3N (1.0)	C_6H_6	$-10 \rightarrow 5^\circ$	1.5h	$R_f \sim 0.5$

Figure 23. ^{13}C nmr spectrum of 4,6-O-isopropylidene-D-glucal

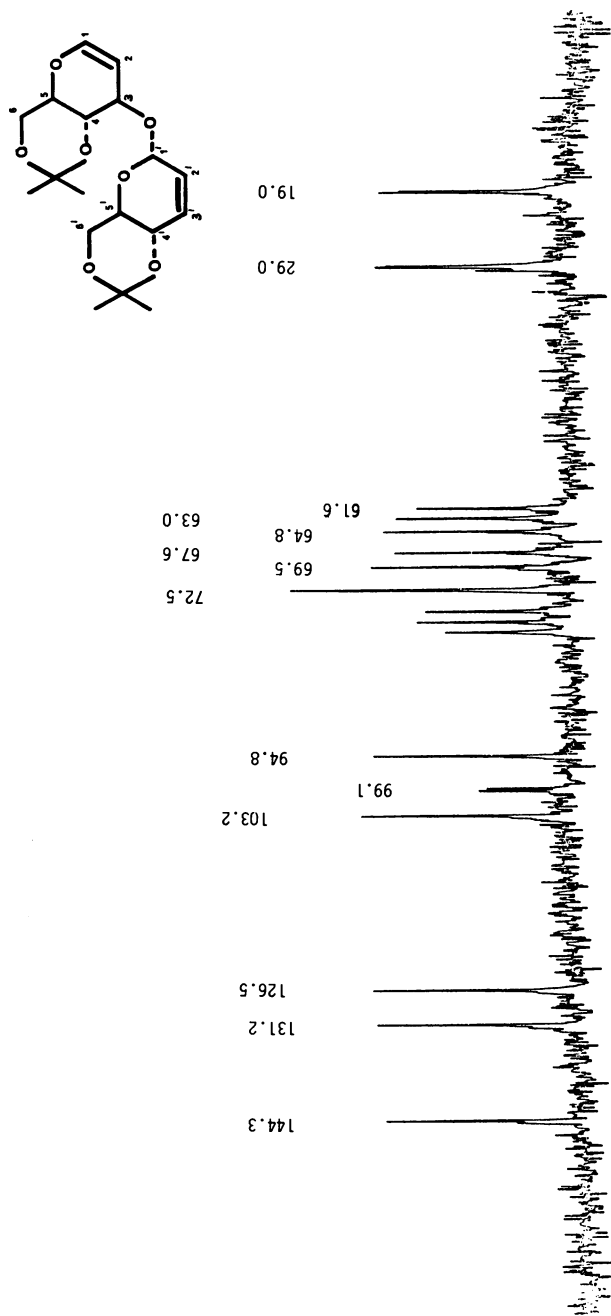


Figure 24. ^{13}C nmr spectrum of the major product of the mesylation of A in figure 22. It is consistent with the doubly unsaturated disaccharide shown above.

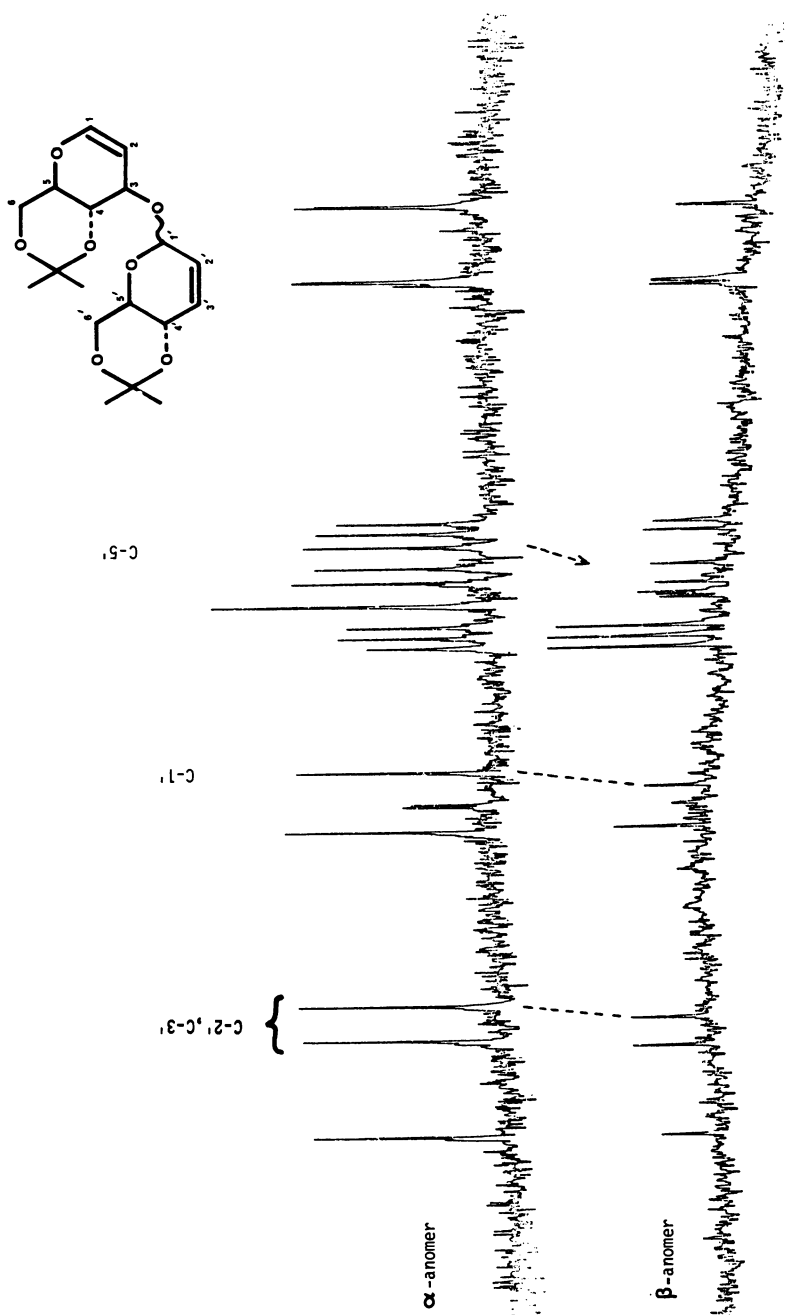


Figure 25. ^{13}C nmr spectra of major and minor products

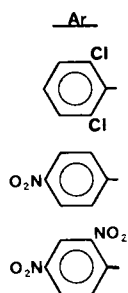
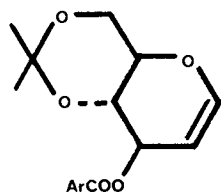


Figure 26

atoms, twice too many in fact, and the spectrum is consistent with the doubly unsaturated disaccharide shown. The assignments fit well with ^{13}C spectra of model 2,3-unsaturated sugars (25). The spectrum is consistent with the α -anomer. The dimeric structure was further supported by a low resolution mass spectrum which showed the expected molecular ion and a strong (M-15) ion, typical of molecules bearing an isopropylidene group. The ^{13}C n.m.r. spectra of both major and minor products are shown in Fig. 25. The spectra are consistent with an anomeric pair: note particularly the shift of the signals due to C-1', the C-2', C-3' pair, and in the region where C-5' would be expected to be.

One might expect the anion of the 3-hydroxyl compound to be destabilised by the glucal system (Fig. 26) and this may account for the 4-benzyl ether rather than the 3-benzyl ether being formed in Fig. 12. That the 3-anion is not too stable to exist is demonstrated by its intermediacy in the synthesis of the benzyl ether of 4,6-O-isopropylidene-D-glucal (Fig. 11).

It would be expected that the mesylate of 4,6-O-isopropylidene-D-glucal would be exceptionally reactive and in the majority of reactions with mesyl chloride it is presumably formed and reacts further. Tosyl chloride is less reactive than mesyl chloride and it may be that a balance of effects is found here. Furthermore, carboxylic acid chlorides are more reactive than sulphonic acid chlorides and perhaps tosyl chloride is sufficiently inactive towards this particular alcohol.

Further studies with other sulphonyl chlorides of reactivity between that of tosyl and mesyl chlorides are necessary. The whole study throws up an interesting basic problem of the chemistry of the oxa-allylic system " $\text{RO-CH}=\text{CH-C-H-X}$ " and systems simpler than carbohydrates will need to be studied to throw light on these intriguing problems.

In view of the ability to prepare carboxylic esters of 4,6-O-isopropylidene-D-glucal, a number of such esters were prepared that might be expected to provide good leaving groups on the oxa-allyl system (Fig. 26): none of the esters was affected by sodium azide in DMF.

Acknowledgements

We thank the Science Research Council for a studentship to P.M. Fredericks, and the Schering Corporation for financial assistance.

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Methods for Introducing Atoms Other than Oxygen into Sugar Rings

ROY L. WHISTLER and ABUL K. M. ANISUZZAMAN

Department of Biochemistry, Purdue University, Lafayette, Ind. 47907

Introduction

In the last fifteen years some attention has been directed toward the production of modified sugars wherein the normal ring oxygen atom is replaced by another heteroatom. In some instances syntheses have been induced with the desire to create analogs which might possess interesting and even potentially useful properties and in some instances synthesis has reflected simply a basic interest in chemical structures and reaction chemistry.

Our laboratory originally became interested in sugar analogs with sulfur replacing the ring oxygen because we anticipated that such analogs, but especially the analog of D-glucose, might possess new and useful biochemical effects. Our first sulfur analog was methyl 5-thio- α -D-xylopyranoside where the sulfur was locked into the ring by glycoside formation (1). Although we thought we were the first to introduce sulfur into a sugar ring and so commented at the time of writing, two other groups (2,3) reported 5-thio-D-xylose with the suggestion of sulfur as the ring heteroatom in November 1961 while our methyl D-xyloside analog manuscript was received by the Journal of the American Chemical Society on December 2, 1961. Since that initial period many sugars with ring atoms of sulfur and some with nitrogen, selenium and phosphorus have been prepared. Those with the greatest biochemical interest and hence with the greatest potential medical value have, so far, continued to be the sulfur analogs.

This review will report a short description of methods for introducing heteroatoms that may become part of the sugar ring system.

Introduction of potential ring heteroatoms may be accomplished rather easily, in general, by simple nucleophilic displacement of a good leaving group such as the *p*-tolylsulfonyloxy or methylsulfonyloxy. This technique works well for primary positions and usually well at chiral secondary positions where the

enantiomorphous form is obtained by inversion of carbon. Naturally, a number of other introductory procedures have been applied and some of these will be discussed.

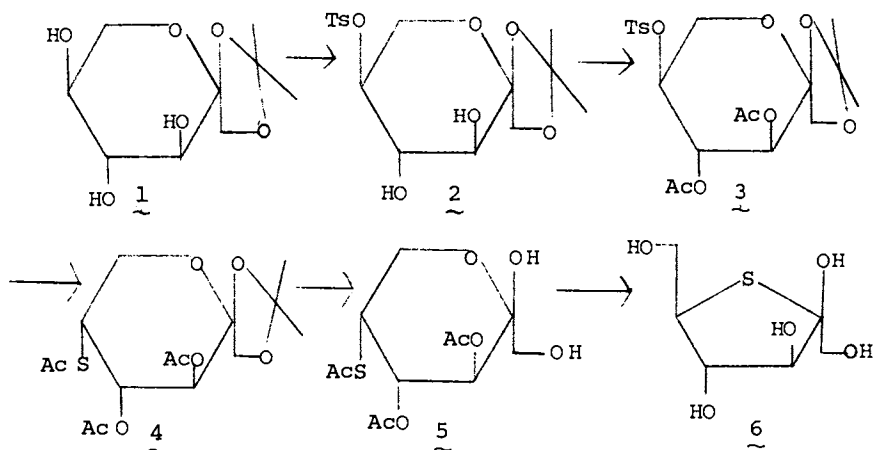
The heteroatom to become a part of the monosaccharide ring is normally placed on carbon C-4, or carbon C-5 of an aldose sugar or carbon C-5 or C-6 of a ketose sugar so that it will be capable of nucleophilic attack on the carbonyl carbon to produce a hemiacetal or hemiketal in a moderately stable pyranose or furanose ring. The ring stability will depend on the size and electronic characteristics of the heteroatom. While in normal monosaccharides the oxygen on the delta or epsilon carbon to the carbonyl group can nucleophilically attack the carbonyl carbon to form a hemiacetal or hemiketal, the ring may open and close giving various portions of acyclic and of five and six membered ring forms and, on occasion, a proper hydroxyl may react to give a minute portion of a seven membered ring. The various isomers in equilibrium will exist in proportion to their relative stabilities. When heteroatoms more nucleophilic than oxygen are in position to react with the carbonyl group the rings will have higher stability and less ring opening will occur. This will give rise to a higher population of isomers with the sugar ring involving the particular nucleophile. The order of nucleophilicity of reactive substituents is $-\text{SeH} > -\text{SH} > -\text{PH}_2 > -\text{NH}_2 > -\text{OH} > \text{NHCOR}$. Experimental results show that in 5-thio-D-glucose solutions only a negligible portion of furanose forms are present while in 4-thio-D-glucose (4) the furanoid is the prevalent form. Normal oxygen ketoses have always shown a proclivity to form a family of isomers in solution with a fair amount of acyclic form present. 5-Thio-D-fructose (5) also appears inclined toward a mixture of isomers with β -D-fructofuranose predominating but in the presence of Lewis acid catalyst under acetylating conditions the main product is the acyclic 5-thio-keto-D-fructose pentaacetate.

Of all the sugar analogs containing a heteroatom other than oxygen, by far the most interesting biochemically is 5-thio-D-glucose. This monosaccharide analog, its glycolytic pathway analogs and its nucleotide analogs such as uridine 5'-(5-thio- α -D-glucopyranosyl)pyrophosphate (UDPTG) have shown unusually usefulness in enzyme controlled reactions. Most significantly 5-thio-D-glucose alone acts as a reversible control of male fertility. It is the first agent controlling male fertility that is not a hormone nor a toxic substance (6). This sugar analog is being continuously examined with anticipated demand for large amounts. Since its present synthesis involves a number of steps, a new simplified synthesis of 5-thio-D-glucose is highly desirable. A unique feature of UDPTG is that, in small amounts, it increases the activity of glycogen synthetase some 500 percent (7).

Sugar Rings Containing Sulfur

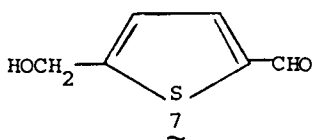
1. Nucleophilic Displacement of Sulfonyloxy Groups.

Nucleophilic displacement of a *p*-tolylsulfonyloxy (tosyloxy) or methylsulfonyloxy (mesyloxy) group by a sulfur nucleophile is most widely used for replacing a monosaccharide ester oxygen with a thioalkyl or thiolacyl group. Commonly a thiolacyl such as thiolacetyl is used because, in a properly blocked monosaccharide derivative, acetylation will deblock the sugar allowed by the introduced sulfur to attack the carbonyl carbon, following acetylation of the stable ring form containing sulfur. Among other sulfur containing displacing agents used are benzylthioide, thiocyanate or thiosulfate anions but these groups require reduction to form the thiol. Thiobenzyl derivatives are usually reduced (1) with sodium in liquid ammonia to remove the benzyl group as toluene and 1,2-diphenylethane. Thiocyanate and thiosulfate are cleaved by reduction with lithium in ammonia (8) or sodium borohydride (2). Thiocyanate and thiosulfate give poor yields and require rather long reduction times in displacements on secondary carbons. Hence these nucleophiles have been most satisfactorily applied in displacements at primary carbons. All displacements at secondary positions are more difficult than at primary, as may be expected. Best conditions require the use of a good aprotic solvent such as *N,N*-dimethylformamide (DMF). *p*-Tolylsulfonyloxy groups have been displaced with thiobenzyl, thiolacetyl or thiolbenzoyl anions in the synthesis of 5-thio-*D*-xylopyranose (1-3), 5-thio-*D*-ribofuranose (9,10), 6-deoxy-4-thio-*D*-glucofuranose (11), 5-thio-*D*-glucose (12), 4-thio-*L*- and *D*-ribofuranose (13,14), 4-thio-*D*-xylose (15), and 6-thio-*D*-galactoseptanose (16) structures. The method was recently used (5) to prepare 5-thio-*D*-fructofuranose, 6. While several preparative sequences were used the following illustrates the reaction and is easy to conduct.



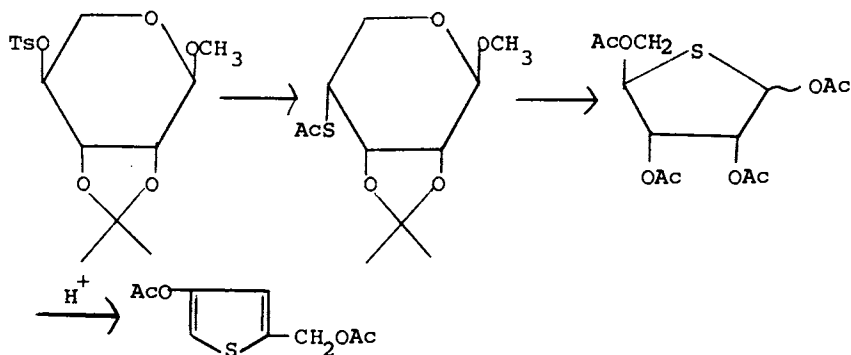
Here 1,2-O-isopropylidene-L-sorbofuranose, 1, is tosylated (40%) with an equimolar quantity of p-toluenesulfonyl chloride at 0° to produce the tosyl derivative, 2, which on acetylation yields the di-O-acetate, 3. Compound 3 is converted to the thioacetyl derivative, 4 by reaction with potassium thioacetate in N,N-dimethylformamide at 80°. Hydrolysis of 4 with aqueous trifluoroacetic acid yields 3,4-di-O-acetyl-5-S-acetyl-5-thio-β-D-fructopyranose, 5, which on deacetylation, in methanol containing sodium methoxide, produces 5-thio-D-fructofuranose, 6. Alternatively methyl 1,3-O-benzylidene-L-sorbofuranoside may be selectively tosylated in high yield at C-5 and the reactions continued as indicated above, but the number of synthetic steps is increased.

5-Thio-β-D-fructofuranose, 6 is the major anomer but the α-D is also obtained. Use of strong acids or high temperatures produces the thiophene derivative, 7. There is indication that sugar derivatives of the thiofuranose form undergo easy desaturation to thiophene derivatives. The reaction is similar to the

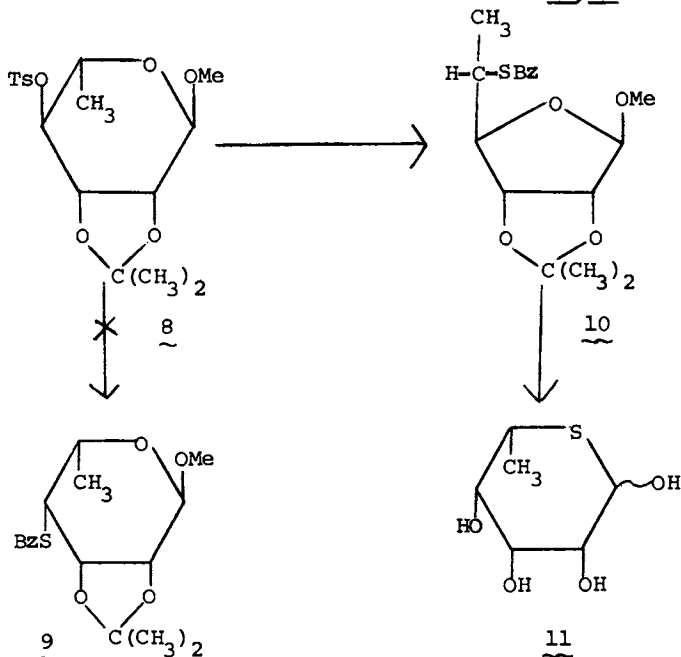


mineral acid induced formation of furan compounds from mono- and polysaccharides (17) where ketoses decompose more readily than aldoses (18). The possibility of obtaining thiophene, stabilized by higher resonance energy, makes the degradation of 5-thio-D-fructose very easy. Mineral acids also convert 4-thioaldoses to thiophene but to somewhat less degree than in the 5-thioketose reaction (19).

Another excellent example of p-tolylsulfonyloxy displacement by a compound containing a sulfur nucleophile is the preparation 4-thio-D-ribofuranose (20). The starting material is methyl L-lyxopyranoside which easily forms the 2,3-di-O-isopropylidene derivative that can be tosylated at O-4. Displacement of the 4-O-p-toluenesulfonyloxy groups by thioacetate introduces sulfur and subsequent hydrolysis of blocking groups gives the 4-thio-D-ribofuranose which is stable in the cold but undergoes slow degradation at room temperatures and readily dehydrates to thiophene in acid or base. It can be directly acetylated by acetic anhydride in pyridine; the acetate being stable. Further it can be converted to the acetochloro sugar using normal reactions and further converted to glycosides or nucleosides (13, 21, 22).

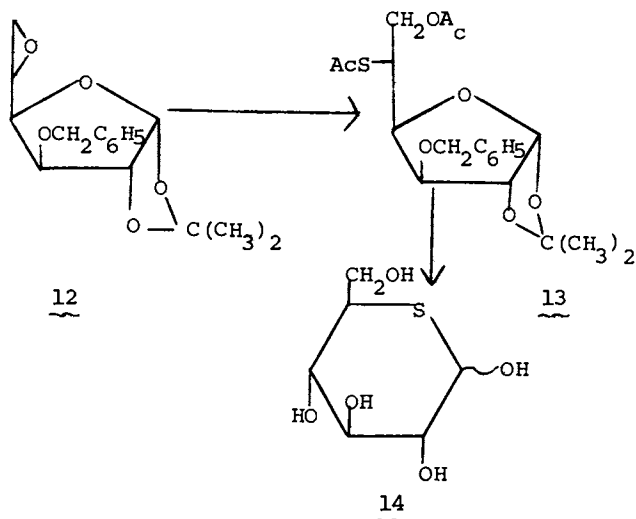


Although displacement of the sulfonyloxy group by the \ominus SR ion normally proceeds with inversion of configuration, simultaneous rearrangement and inversion can also occur. Thus, the reaction of methyl 2,3-O-isopropylidene-4-O-p-tolylsulfonyl- α -L-rhamnopyranoside, **8** with potassium thiobenzoate gives not the expected 6-deoxy-4-thio-L-talose derivative, **9** but methyl 5-S-benzoyl-6-deoxy-2,3-O-isopropylidene-5-thio- α -L-talofuranoside, **10** (23). Reaction of **10** with sodium methoxide followed by acetolysis and deacetylation gives crystalline 6-deoxy-5-thio-L-talopyranose, **11**. In general L-rhamnose tends to undergo ring size contraction under a number of conditions (24, 25).

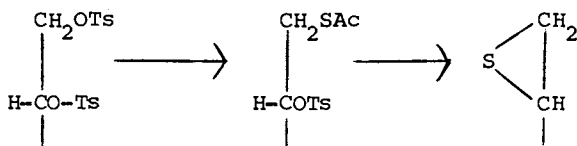


Reaction of Oxirane Rings

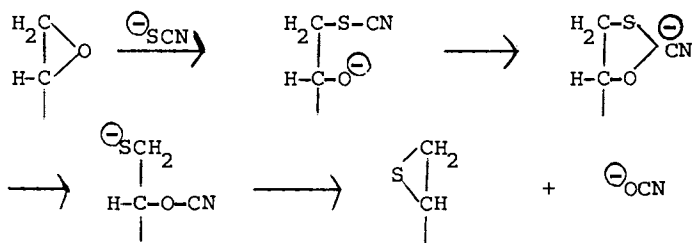
Terminal oxirane rings are easily produced, especially in hexoses, and are convertible in good yield to thirane rings by reaction with thiourea. A good example of the use of this method for sulfur introduction is that used in one route for the synthesis of 5-thio-D-glucose (26). Here 3-O-benzyl-1,2-O-isopropylidene-D-glucofuranose is benzoylated in the cold to produce the C-6 ester and then tosylated to form the C-5 ester. Alkali saponifies the benzoyl group at the primary position allowing the O-6 oxygen to displace the tosyl group with formation of the terminal epoxide, 12. This on treatment with thiourea produces the expected thirane ring with inversion of C-5. Acetoxy attack preferential at C-6 gives rise under acetylating conditions to 13 which with sodium in liquid ammonia and hydrolysis produces 5-thio-D-glucose, 14, easily crystallized in the α -D form.



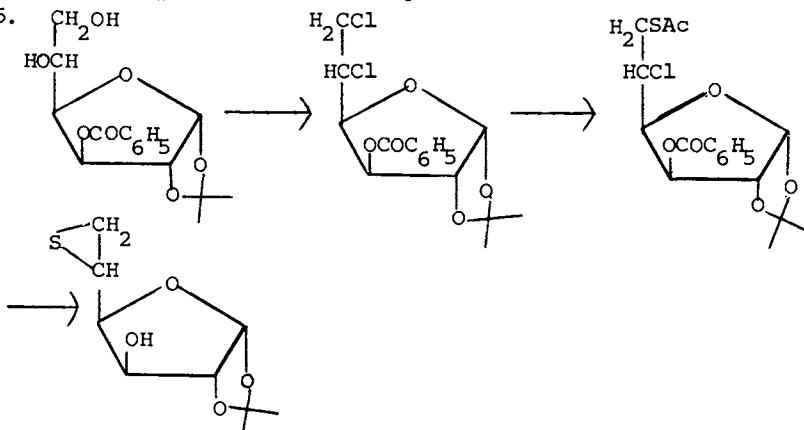
The oxirane structure can be obtained also from an appropriate 5,6-di-O-p-tolylsulfonyl derivative by the action of potassium thioacetate to produce the 6-S-acetyl-6-thio-5-O-p-tolylsulfonate derivative that on treatment with cold sodium methoxide forms a 5,6-episulfide ring (27). Further opening of the thirane ring can proceed in the normal ways.



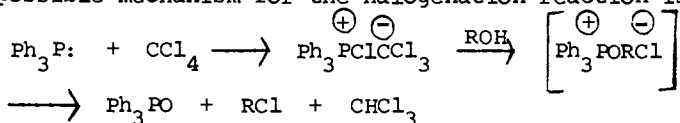
Another way of forming thirane rings from terminal oxirane rings is by treatment with thiocyanate anion (28).



Still another route to an appropriate terminal thirane ring is from the 5,6-dideoxy-5,6-dichloro sugar derivative produced, for example, from 3-0-benzoyl-1,2-0-isopropylidene- α -D-glucofuranose by reaction with a mixture of carbon tetrachloride and triphenylphosphine (29). Thiolaacetate easily displaces the primary chlorine anion and subsequent treatment with potassium hydroxide causes the S-6 sulfur to displace the secondary chlorine to form the expected thirane ring with normal inversion at carbon C-5.

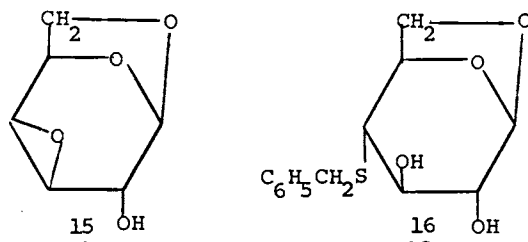


A possible mechanism for the halogenation reaction is shown.



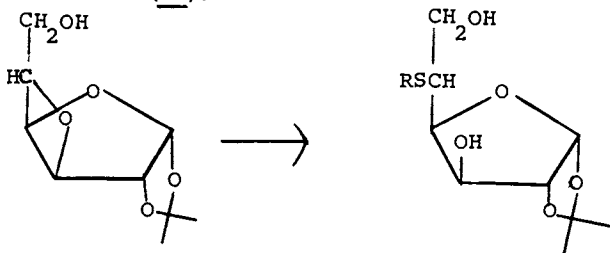
Direct opening of an oxirane ring by a nucleophilic sulfur compound may also be easily effected. Thus 5,6-anhydro-1,2-0-isopropylidene- α -D-glucofuranose on treatment with sodium α -toluene thioxide produces the 6-S-benzyl-6-thio compound (16). Treatment of 1,6:3,4-dianhydro- β -D-galactopyranose, 15 (4) with α -toluene thioxide produces preferential attack at C-4 with formation of the D-glucose derivative, 16. The 1,6-anhydro ring is not

opened under the conditions because of its great stability. Reductive removal of the benzyl group followed by hydrolysis or acetolysis gives 4-thio-D-glucofuranose or its acetate. Since the underivatized sugar analog is in equilibrium with other isomeric forms in solution, principally the 4-thio-D-glucofuranose forms, acetylation produces a 7:3 ratio of furanose to pyranose acetates indicating the comparative greater stability of the sulfur ring forms.



Oxetane Ring Opening

Oxetane rings can be opened by nucleophilic reagents in much the same way as are oxirane rings. The only example of oxetane ring use in carbohydrates for introduction of sulfur and also of nitrogen is with the 3,5-anhydro rings in 1,2-O-isopropylidene- α -D-xylopyranose and in 1,2-O-isopropylidene- β -L-idofuranose. The latter compound is made from 3-O-acetyl-1,2-O-isopropylidene-5-O-p-tolylsulfonyl- α -D-glucofuranose with or without a 6-O-triphenylmethyl group. Treatment in methanol with sodium methoxide removes the acetyl group and allows nucleophilic attack on C-5 by the O-3 oxygen to produce the oxetane ring by the ensuing displacement of the p-tolylsulfonyloxy group. Opening of the ring to insert sulfur at C-5 and reestablish the D-gluco configuration occurs on treatment with sodium α -toluenethiooxide in N,N-dimethylformamide at 150°. Due to steric hindrance at C-3 the major displacement of the oxetane oxygen occurs at C-5 (30). A similar displacement occurs with the azido group to give the 5-azido derivative (31).



Alteration of Existing Sulfur Containing Structure

It is sometimes difficult to find good methods for inserting sulfur at an appropriate position in a monosaccharide that it may participate in the intended sugar ring. Therefore the expedient is often sought to insert the sulfur into a sugar which can then be isomerized or caused to undergo chain lengthening or shortening reactions to produce the structure desired. Two examples are the preparation of 4-thio-D-arabinose and 2-deoxy-4-thio-D-ribose (C-4-thio-D-deoxyribose) structures.

In the preparation of methyl 4-thio-D-arabinoside (12) a possible intermediate in the synthesis of 5-thio-D-glucose may serve as starting material. Thus, 5-S-acetyl-3,6-di-O-benzyl-1,2-O-isopropylidene-5-thio-D-glucopyranose is hydrolyzed to remove the isopropylidene group and then periodate oxidized to excise carbon one. The product is then converted to a glycoside and the benzyl groups reductively removed by sodium in liquid ammonia to produce the free D-arabinofuranoside.

Methyl 2-deoxy-4-thio-D-riboside (32) is prepared in good yield by a rather long route starting with 1,2:5,6-di-O-isopropylidene- α -D-glucopyranose. This is tosylated at O-3, the tosyloxy group displaced by thiolacetate and the sugar desulfurized by Raney nickel to 3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-glucopyranose. This is converted to the 3-deoxy-1,2-O-isopropylidene- α -D-glucopyranose. The product is benzoylated in the cold to introduce a 6-O-benzoyl group and then tosylated. This is then alkali treated to produce the 5,6-epoxide, which is opened with benzyl anion to obtain the 6-O-benzyl derivative. This product is tosylated and the tosyloxy group displaced with thiolacetate anion and the isopropylidene removed by hydrolysis. This product is oxidized with periodate to excise carbon one of the sugar. Since the sulfur is less negative by attachment of the acetyl group the sulfur is not oxidized to the oxide but remains unaffected. Under acidic conditions in methanol the methyl 5-O-benzyl-2-deoxy-4-thio-D-erythropentofuranoside is formed and the benzyl group reductively removed by sodium in liquid ammonia.

One of the most interesting transformations of one sugar, containing sulfur, into another is the formation of 6-thio- β -D-fructopyranose from 6-thio-D-glucose. When the later compound is treated with isomerase it is isomerized to the D-fructose derivative with sulfur becoming a part of the pyranose ring (33). However, while 6-thio-D-glucose is a substrate for isomerase 6-thio-D-fructose is not and hence essentially no equilibrium is established but rather the conversion is nearly quantitative with major loss being in disulfide formation from the 6-thio-D-glucose and from general work up loss. Nicely crystalline 6-thio- β -D-fructopyranose can easily be isolated. The lack of significant reversion is probably due to the high stability of the 6-thio-D-fructopyranose ring and its limited tendency to open to provide

the acyclic form necessary for enzyme binding and isomerization. It is especially interesting to note that 6-thio- β -D-fructopyranose is the sweetest sugar known being some 30% sweeter than D-fructose.

Selenium in the Sugar Ring

There is only one example of a sugar analog containing selenium as the ring heteroatom (34). The compound is prepared by routes similar to those for making the sulfur sugar analog. Preparation proceeds from 1,2-O-isopropylidene-5-O-p-tolylsulfonyl- α -D-xylofuranose which is reacted with the sodium salt of α -tolueneselenol to give 5-Se-benzyl-1,2-O-isopropylidene-5-seleno- α -D-xylofuranose. Removal of the benzyl group by reduction with sodium in liquid ammonia and subsequent reaction with methanolic hydrogen chloride gives a mixture of bis(methyl 5-deoxy- α -D-xylofuranosid-5-yl)-5,5'-diselenide and two C-2 diastereomers of D-threo-3,4-dihydroxy-2,3,4,5-tetrahydroselenophene-2-dimethyl acetal, the structure of which is established from nmr and mass spectroscopic information.

Nitrogen in the Sugar Ring

An amino group properly positioned in a monosaccharide structure participates in a ring compound due to nucleophilic joining with the carbonyl carbon of the sugar. Consequently all syntheses start with reactions designed to locate a useful nitrogen containing group at a desired location along a monosaccharide chain. Introduction of nitrogen most often occurs by displacement reactions although reduction of Schiff bases in the form of oximes or hydrazones are often employed.

Displacement of a tosyloxy group by ammonia was an early method. Thus, Jones and Szarek (35) reacted 1,2-O-isopropylidene-5-O-p-toluenesulfoyl- α -D-xylofuranose with ammonia in methanol and acetylated the amino group before hydrolytic removing the isopropylidene group. The resulting sugar cyclizes to produce 5-acetamido-5-deoxy-D-xylopyranose and the 5-acetamido-5-deoxy-D-xylofuranose in a ratio of 4:1. When either form is heated in water solution, it equilibrates with the other form. Treatment in methanolic hydrogen chloride produces the two ring forms as methyl D-xylosides.

In the above compounds the equilibrium between pyranose and furanose forms can be altered in favor of the larger and nitrogen containing ring by an increase in the nucleophilicity of the N-acyl group. Thus if the acetamido group is replaced by the (benzyloxycarbonyl) amino group, the equilibrium is shifted in favor of the pyranose form. Thus 5-[(benzyloxycarbonyl)amino]-5-deoxy-1,2-O-isopropylidene- α -D-xylofuranose gives, on hydrolysis of the isopropylidene, almost exclusively the crystalline 5-[(benzyloxycarbonyl)amino]-5-deoxy- α -D-xylopyranose (36) and

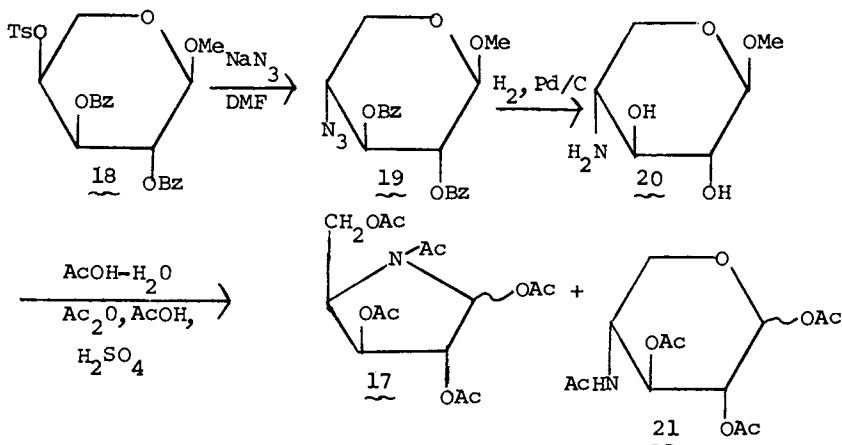
the six-membered ring structure follows from the absence of an Amide II band in the ir spectrum.

For 5-benzamido-5-deoxy-D-xylose, the equilibrium proportion of the pyranose form is likewise increased, as compared with 5-acetamido-5-deoxy-D-xylose. Hydrolysis of 5-benzamido-5-deoxy-1,2-O-isopropylidene- α -D-xylofuranose with an acid ion-exchange resin yields crystalline 5-benzamido-5-deoxy-D-xylopyranose and syrupy 5-benzamido-5-deoxy-D-xylofuranose in the ratio of 3:1 (37).

For 5-acetamido-5-deoxy-(D or L)-arabinose, the equilibrium is displaced in favor of the furanose form. Thus, 1,2-O-isopropylidene-5-O-tolylsulfonyl- β -L-arabinofuranose, on treatment with ammonia and subsequent acetylation, yields 5-acetamido-5-deoxy-1,2-O-isopropylidene- β -L-arabinofuranose (38). Hydrolysis of this compound with acid gives a mixture of crystalline 5-acetamido-5-deoxy-L-arabinopyranose and syrupy 5-acetamido-5-deoxy-L-arabinofuranose.

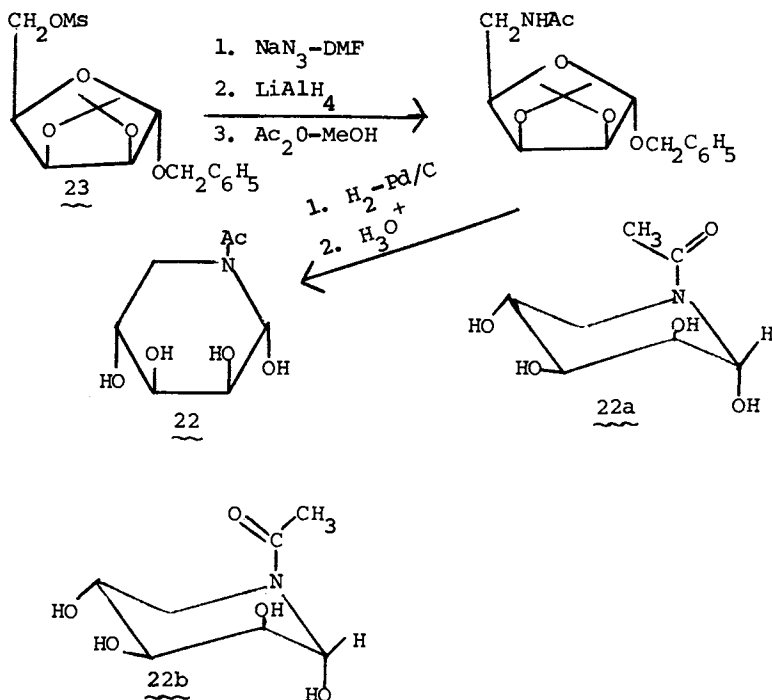
A similar reaction is found to proceed with L-arabinose (39).

Azido is a good nucleophile that readily displaces a leaving group such as p-toluenesulfonyloxy, and the reaction has had wide application. An example is found in the preparation 4-acetamido-1,2,3,5-tetra-O-acetyl-4-deoxy-D-xylofuranose, 17. Reaction of 2,3-di-O-benzoyl-4-(p-tolylsulfonyl)- β -L-arabinopyranoside, 18 with sodium azide gives methyl 4-azido-4-deoxy- α -D-xylopyranoside, 19 which on catalytic hydrogenation produces methyl 4-amino-4-deoxy- α -D-xylopyranoside, 20. N-acetylation of 19 followed by acetolysis yields 17 and possibly a small amount of its pyranose form, 21 (40).



The ir spectra of 17 shows absorption due to OAc and NAc but there is no evidence for NH absorption at 3.0μ or amide II absorption at 6.5μ . These and the nmr spectra of 17 are comparable with the furanose structure.

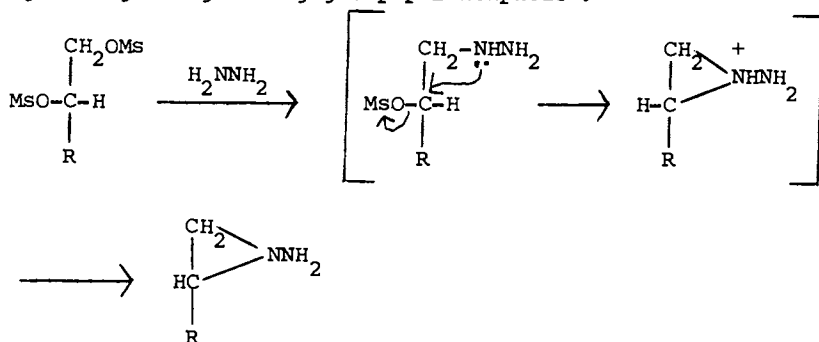
Another example of the use of azide displacement reaction for the preparation of sugars containing nitrogen as the ring heteroatom is the preparation of the crystalline 5-acetamido-5-deoxy- α -D-lyxopyranose 22 from benzyl 2,3-O-isopropylidene-5-O-methylsulfonyl- α -D-lyxofuranoside 23 (41). In the nmr spectrum of 22 the 1-H signals appear as doublets ($J_{1,2} = 2.5$ Hz) centered at τ 4.09 and 4.52. This indicates that 22 is the α anomer and is a mixture of its rotamers 22a and 22b. The origin of rotational isomerism is due to restriction of rotation around the C-N bond resulting from resonance of the type

$$\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{N}=\end{array} \longleftrightarrow \begin{array}{c} \text{O} \\ \parallel \\ -\text{C}=\text{N}^+ \end{array}$$


Azide displacement has been also used for the preparation of 5-acetamido-5-deoxy-D-xylopyranose (39), 5-benzamido-5-deoxy-D-xylopyranose (37), 5-acetamido-5-deoxy-D-ribofuranose (39), 5-acetamido-5-deoxy-L-arabinopyranose (39), 4-acetamido-4,5-dideoxy-D-xylofuranose (42,43), 4-acetamido-4-deoxy-D (and L)-arabinofuranose (44), 4-acetamido-4-deoxy-L-xylofuranose

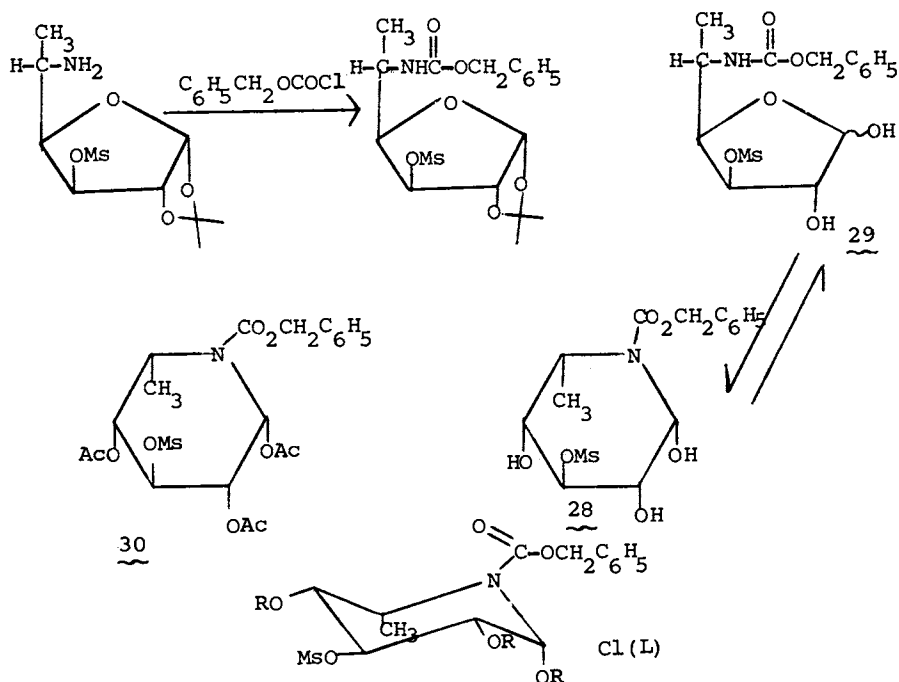
Acid hydrolysis of 25 gives a mixture of crystalline 5-acetamide 5-deoxy- α -D-lyxopyranose, 26 and syrupy 5-acetamido-5-deoxy-lyxofuranose, 27 in the ratio 1:1.

Hydrazine is also useful as a displacing agent for introduction of nitrogen into sugars. A convenient method (48) for the preparation of an N-aminoaziridine compound of hexoses is the reaction of a 5,6-di-O-(methylsulfonyl)aldohexose with hydrazine. The first step involves nucleophilic substitution of the primary methylsulfonyloxy group by hydrazine to form the 6-hydrazino-5-O-(methylsulfonyl) compound which converts to a three-membered ring through neighboring group participation.



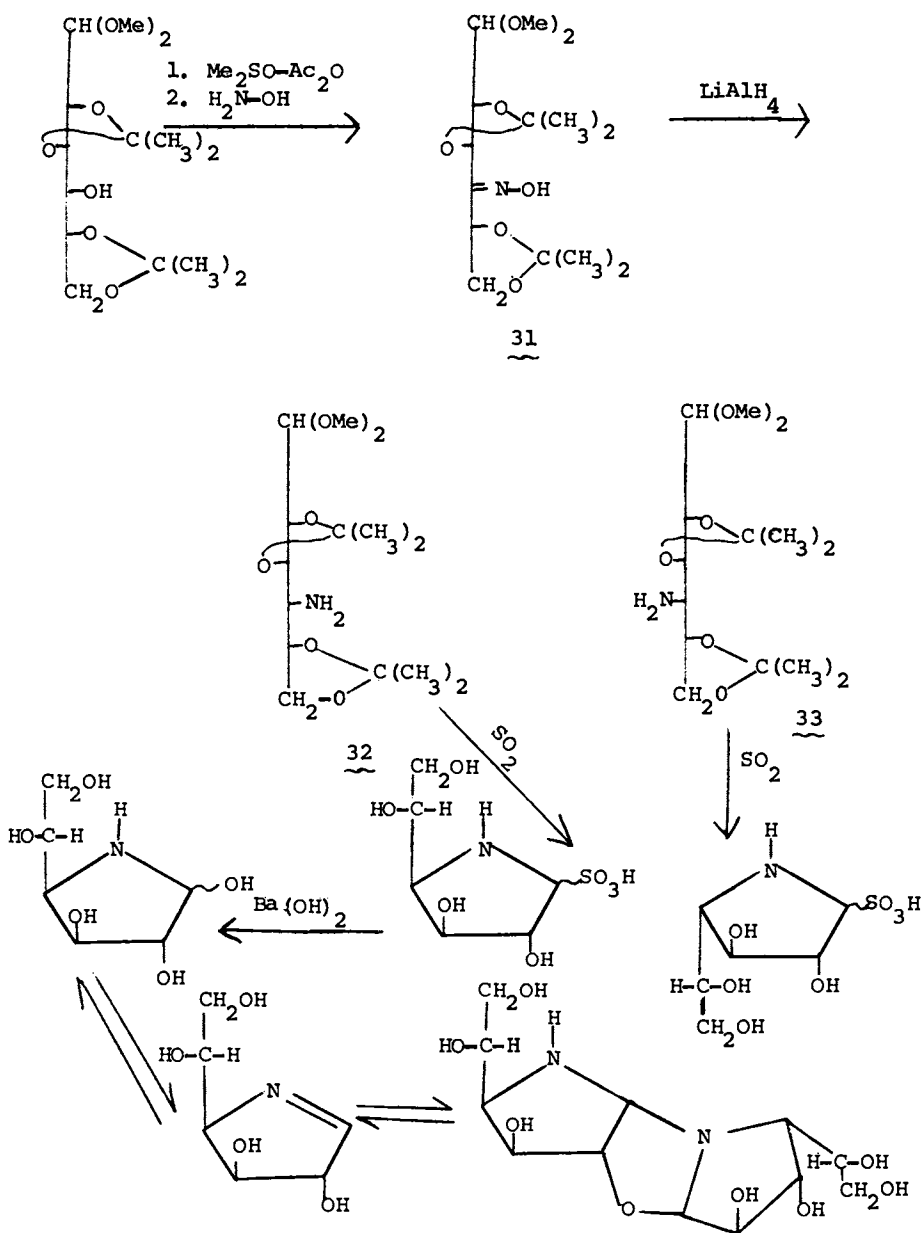
Reduction with hydrazine in presence of nickel gives 5-amino-5,6-dideoxy derivatives which can be cyclized to an amino-pyranose derivative (49). Thus, 5-amino-1,2-O-isopropylidene-3-O-(methylsulfonyl)-5,6-dideoxy- β -L-idofuranose prepared from 1,2-O-isopropylidene-3,5,6-tri-O-(methylsulfonyl)- α -D-glucofuranose on reaction with benzyloxyformyl chloride followed by hydrolysis of the isopropylidene group gives 5-(benzyloxycarbonylamino)-5,6-dideoxy- β -L-idopyranose, 28. This exists in equilibrium with furanose form 29 in the ratio of 4:1. The compound 28 is separated by chromatography and it reacts with acetic anhydride and pyridine to yield its tri-O-acetyl derivative, 30. The nmr spectra of 28 and 30 indicate that both these compounds prefer the C1(L) conformation with substituents at C-1 and C-5 being in axial position.

Reduction of oximes (50) can also be used to produce amino groups at specific location in sugar molecules. Thus the keto-oxime derivative, 31 obtained from 2,3:5,6-di-O-isopropylidene-D-glucose dimethyl acetal by oxidation with dimethyl sulfoxide and subsequent reaction with hydroxyl amine, is reduced with lithium aluminium hydride to a 1:1 mixture of a 4-amino-4-deoxy-D-glucose derivative, 32 and a 4-amino-4-deoxy-D-galactose derivative, 33. Hydrolysis of these with sulfur dioxide gives bisulfite adducts from which free sugars are obtained by reaction with barium hydroxide. The nmr spectra of the free sugars indicate that these exist in equilibrium with the pyrroline form and a dimeric form.

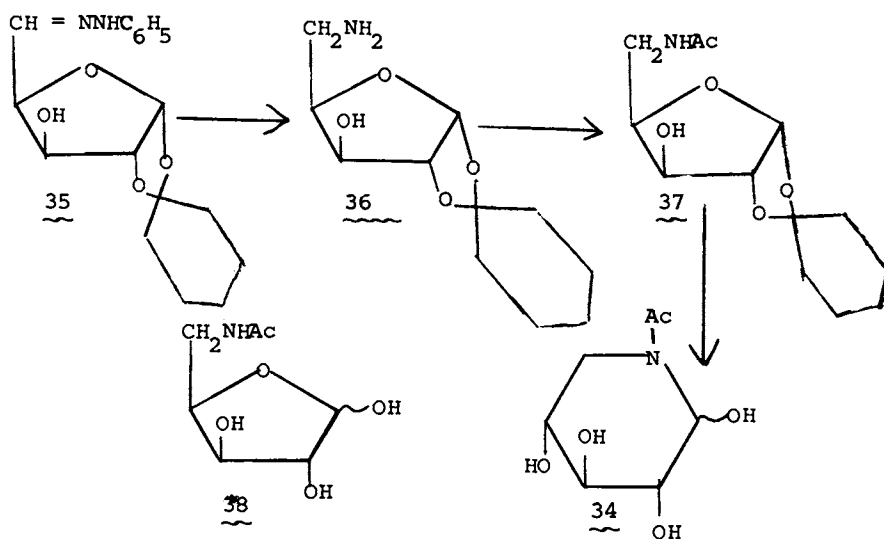


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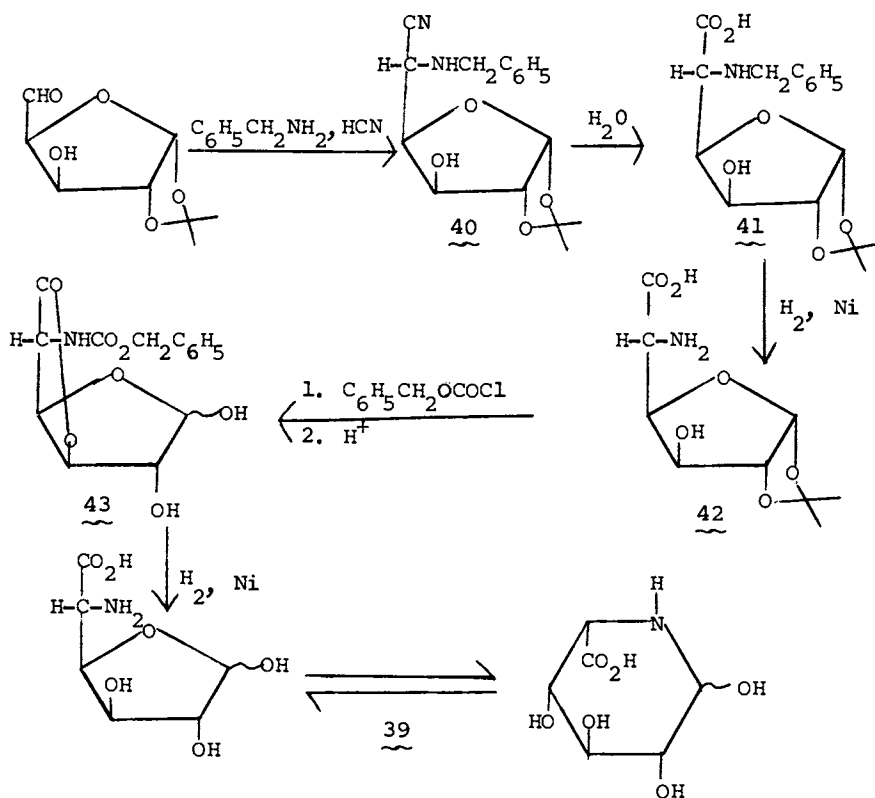
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An example of the use of a hydrazone derivative to introduce nitrogen in the sugar ring is the preparation 5-acetamido-5-deoxy-D-xylopyranose, 34 from 1,2-cyclohexylidene- α -D-xylopentodialdo-1,4-furanose phenyl hydrazone, 35 (51). Hydrogenation of 35 affords the amino compound, 36 which on N-acetylation gives 5-acetamido 1,2-O-cyclohexylidene-5-deoxy-D-xylofuranose, 37. A 2:1 mixture of 34 and its furanose isomer 38 is obtained by the acid hydrolysis of 37. Both 34 and 38 are stable in neutral solution but readily equilibrate in acid at 70°. A benzyl glycoside of 34 consumes two moles of sodium periodate with the liberation of a mole of formic acid and this result is compatible with a pyranose structure.

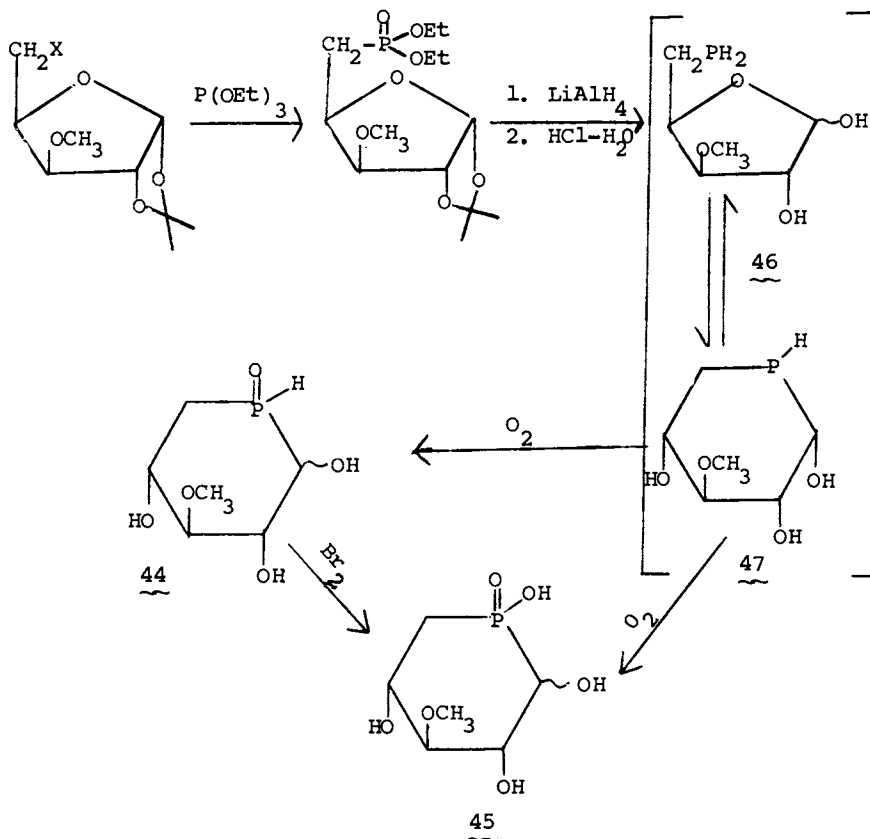


5-Amino-5-deoxy-L-iduronic 39 acid related to the carbohydrate component of polyoxins has been synthesized recently (52). The reaction of 1,2-O-isopropylidene-5-aldopentodialdo-furanose with benzyl amine and hydrogen cyanide gives 5-benzylamino-5-deoxy-1,2-O-isopropylidene- β -L-idofuranonitrile, 40, which on hydrolysis with water yields 5-benzylamino-5-deoxy-1,2-O-isopropylidene-L-iduronic acid, 41. Hydrogenolysis of 41 leads to the formation of 5-amino-5-deoxy compound, 42 from which the free 5-amino-5-deoxy-L-iduronic acid 39 is prepared by way of the benzyl oxy carbonyl compound, 43. The free acid 39 exists in an equilibrium of the furanose form and piperidine form and the latter six membered form predominates.

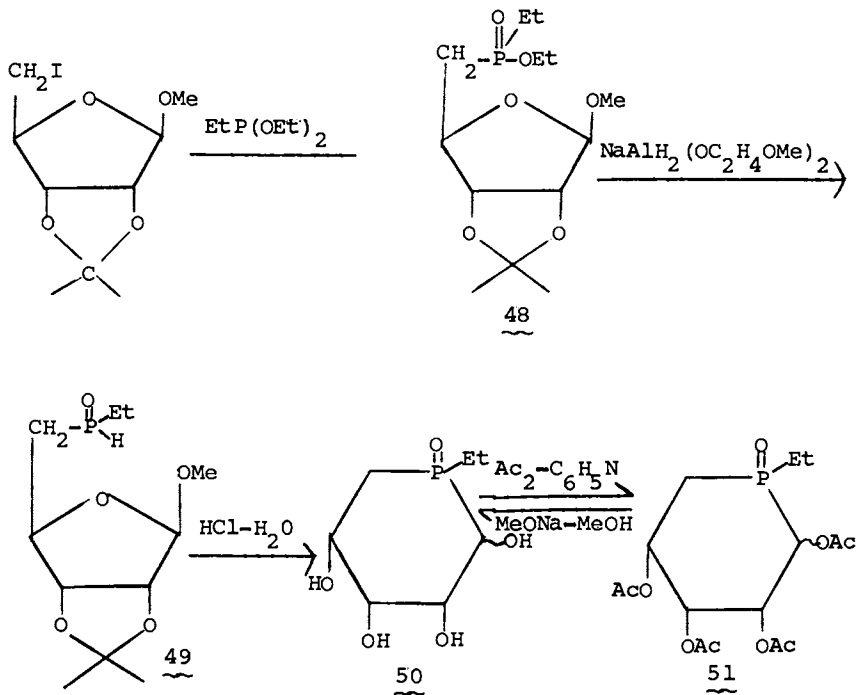


Phosphorus in the Sugar Ring

As an exercise in chemistry and to show the further generality of producing sugar rings containing various heteroatoms we undertook the replacement of oxygen by phosphorus in the six member D-xylose ring (53). In this sequence, 1,2-0-isopropylidene-3-0-methyl-5-0-(p-toluenesulfonyl) α -D-xylofuranose or 5-bromo-5-deoxy-1,2-0-isopropylidene-3-0-methyl- α -D-xylofuranose is reacted with triethylphosphite to produce the 5-deoxy-5-(diethylphosphinyl) derivative. Reduction with lithium aluminium hydride followed by hydrolytic removal of the isopropylidene group produces in the one case 5-deoxy-3-0-methyl-5-phosphinyl-D-xylopyranose, **44** and 5-deoxy-3-0-methyl-5-(phosphinic acid)-D-xylopyranose, **45**. Formation of **44** and **45** presumably proceed through intermediates **46** and **47**. Compound **44** does not mutarotate and is stable toward air oxidation. However, with bromine it is oxidized to the phosphinic acid **45**. The ir spectrum of **44** shows absorption due to the P-H group.



Inokawa and associates recently synthesized a D-ribose derivative containing phosphorus in the ring (54). They undertake nucleophilic displacement of the iodo group in methyl 5-deoxy-5-iodo-2,3-O-isopropylidene- β -D-ribofuranoside with ethyldiethoxyphosphine to produce methyl 5-deoxy-5-(ethoxyethylphosphinyl)-2,3-O-isopropylidene- β -D-ribofuranoside 48. Reduction of 48 with sodium dihydro-bis(2-methoxyethoxy)aluminum in THF gives methyl 5-deoxy-(ethylphosphinyl)-2,3-O-isopropylidene- β -D-ribofuranoside 49, acid hydrolysis of which yields 5-deoxy-5-(ethylphosphinyl)-D-ribofuranose 50. Evidence for the pyranose structure of 50 is derived from the absence of characteristic PH peaks in its nmr and ir spectra. The reaction of 50 with a mixture of acetic anhydride and pyridine gives its 1,2,3,4-tetra-O-acetyl derivative, 51 which reverts to 50 on deacetylation with sodium methoxide in methanol. By using reactions similar to those described above, 5-(alkylphosphinyl)-5-deoxy-3-O-methyl-(and benzyl)-D-xylopyranoses were also prepared (55,56).



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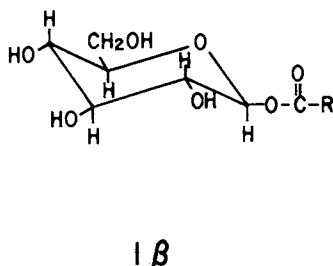
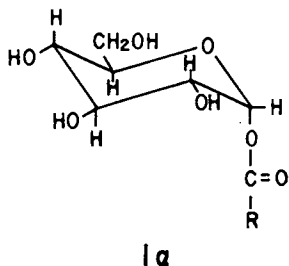
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Stereoselective Synthesis and Properties of 1-*O*-Acyl-D-Glucopyranoses

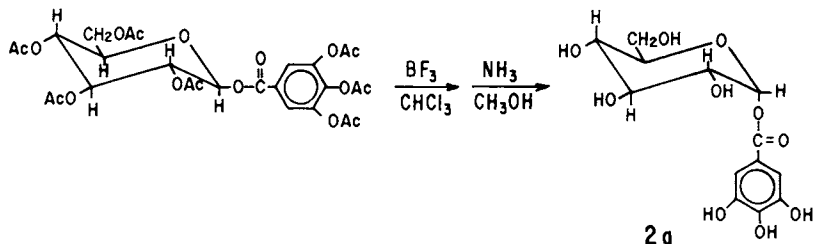
PHILIP E. PFEFFER, GORDON G. MOORE, PETER D. HOAGLAND,
and EDWARD S. ROTHMAN

Eastern Regional Research Center, Agricultural Research Service,
U.S. Department of Agriculture, Philadelphia, Pa. 19118

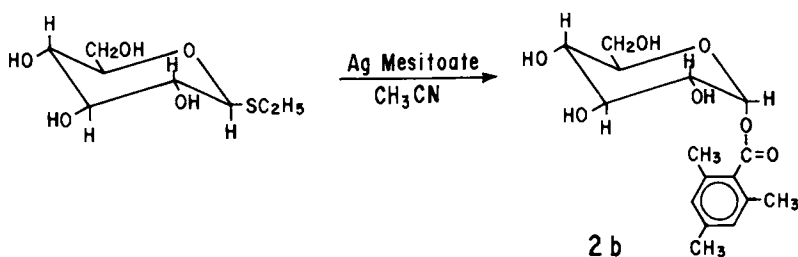
In general, 1-*O*-acylaldoses, and in particular the derivatives with a cis hydroxyl group at C-2, are difficultly accessible substances. A few 1-*O*-acyl-D-glucoses have been found in nature, e.g., 1-*O*-benzoyl- β -D-glucopyranose (periplanetin) in insects (1), stevioside in *Stevia Rebaudiana* Bertoni (2), asiaticoside from *Cantella asiatica* (3) and 1-*O*-galloyl- β -D-glucopyranose in Chinese rhubarb (4). Over the years there have been numerous attempts at preparing anomERICALLY pure



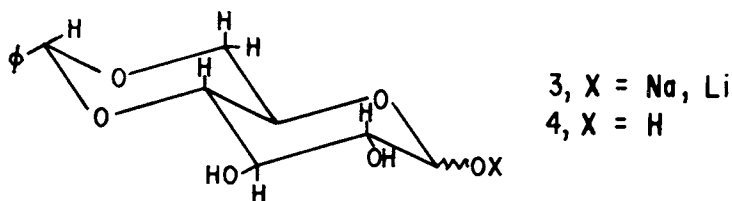
1- α and β -D-glucopyranose esters 1 α and 1 β using various reactions aimed at controlling the anomerism of the C-1 acylation site. Schmidt (5) prepared the sterically hindered 1-*O*-galloyl- α -D-glucopyranose 2a in 5% yield through a lengthy five-step synthesis.



The key steps in this scheme involved a BF_3 isomerization for five days of the more accessible 2,3,4,6-tetra-O-acetyl-1-O-(triacetyl-galloyl)- β -D-glucopyranose followed by preferential deacylation of the more labile acetyl protecting groups. This work represented the first reported preparation of a 1-O-acyl- α -D-glucopyranose 1 α . In later studies Fletcher (6) questioned the positional assignment of the ester grouping of Schmidt's compound 2a and took another approach to solve the problem. In his attempt using a silver benzoate displacement reaction on D-glucose diethyl dithioacetal, Fletcher prepared in very low conversions 2-O-benzoyl- β -D-glucose, which was isolated as its tetraacetate. A similar treatment of ethyl-1-thio- β -D-glucopyranoside gave after acetylation both 1,3,4,6-tetra-O-acetyl-2-O-benzoyl- β -D-glucopyranose and 2,3,4,6-tetra-O-acetyl-1-O-benzoyl- β -D-glucopyranose (6). Although, the 1- α -D-glucosyl ester was apparently an initially formed product, ester migration to the 2-position evidently took place upon isolation. Successful preparation of a stable 1-O- α -D-glucosyl ester, which did not undergo migration, was finally realized in the synthesis of the hindered mesitoate derivative 2b in 17% yield (6).



Although 2b was stable to neutral conditions, it could be induced to undergo C_1 to C_2 ester migration under basic conditions (7). It was concluded (6)² that 2b would be "the only example of a cis-1-O-acylaldose that could be prepared and isolated" without rapid rearrangement. Preparation of the 1-O-acyl- β -D-glucopyranoses 1 β is less complex because of the inability of the trans

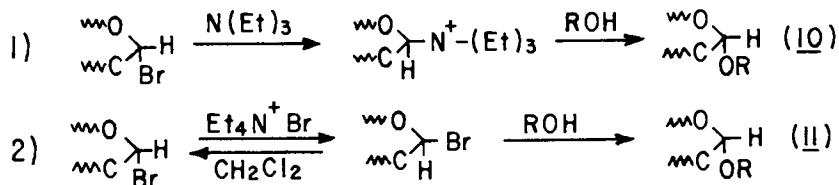


oriented 1-O-acylaldehyde to undergo analogous ester shifting. Acylation of partially protected 4,6-O-benzylidene-1-O-sodio-D-glucopyranose 3 yielded 1b after deblocking (8). Nevertheless, overall conversions of the anomerically pure product ester 1b based on glucose were only 30-40% due to the low and variable results obtained for the isolation and purification of 4,6-O-benzylidene-D-glucopyranose 4 and its corresponding salt 3.

In this report we will describe some new synthetic approaches to the preparation of glucosyl esters 1a and 1b, and examine their spectral properties and chemical reactivity including acyl migration. We will also discuss the mechanistic implications which are important in explaining the stereochemical control achieved in the key acylation reaction.

Stereoselective Acylation of 2,3,4,6-tetra-O-benzyl-1-O-lithio-D-glucopyranose (TBG⁻Li⁺) (9)

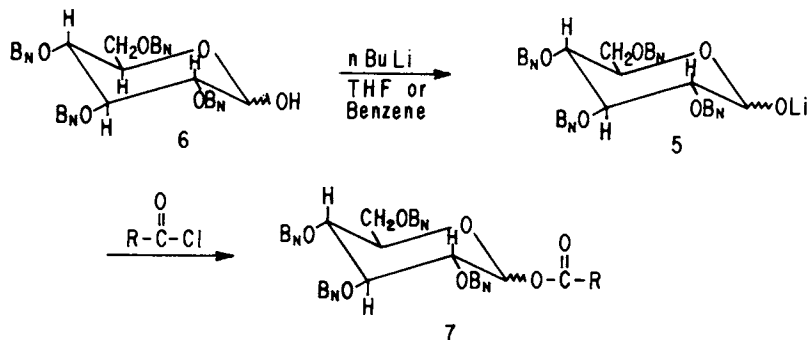
One of the most elegant methods for achieving stereoselective glycosidation has recently been demonstrated by Schuerch (10), equation 1, and Lemieux (11), equation 2. Utilizing 2,3,4,6-tetra-O-benzyl-1-bromo- α -D-glucopyranose (TBGB), these workers carried out double inversion displacement reactions in which the final glycoside linkage had the desired configuration. Equation 1



depicts stereochemical control through the agency of the "reverse anomeric" effect exhibited by the equatorial preference of ammonium salt intermediate (10), while equation 2 demonstrates the approach through equilibration effected by solubilized bromide ion. In each case a high selectivity for α -glycoside linkage formation was shown. However, in the early stages of the latter reaction (equation 2) a preference for the β -anomer could be realized, but overall conversion to this species was low. For the study of the acylation of the anomeric OH of glucose, we examined the reactions of 2,3,4,6-tetra-O-benzyl-1-O-lithio-D-glucopyranose 5 (TBG⁻Li⁺) because of its nonparticipating group at the C₂ position. Furthermore, if stereoselective acylation could be carried out directly on 5, it would obviate the need to prepare the unstable bromide derivative TBGB (11) for an indirect displacement reaction.

Metalation of 2,3,4,6-tetra-O-benzyl-D-glucopyranose (TBC) 6 (10 mmol) in 125 ml of tetrahydrofuran (THF) at -30 to -40° with

1.1 equivalents of *n*-butyl lithium (1.6 M in hexane) followed by acylation with 1.1 equivalents of acyl halides, (20 minutes) produced a mixture of 2,3,4,6-tetra-*O*-benzyl-1-*O*-acyl-D-glucopyranose esters (TBG esters) 7 α and β in 90-95% yield with a



decided preference for the α -configuration 7 α . Often the isolated products were oils which could not be crystallized; however, the anomeric composition was easily determined by evaluation of the proton nmr spectrum of the characteristic anomeric hydrogens. Table I lists the physical properties of esters prepared by this procedure. For each member in this series, the anomeric composition of the isolated product esters was always at least 90% α and 10% β by nmr analysis. However, selectivity for the α -anomer diminished (70% α , 30% β) with acylation temperature elevation to 60°. Metalation of 6 in benzene at 0-5°C followed by acylation at this temperature produced a mixture of esters 7 α and 7 β , containing equal amounts of both α - and β -anomeric forms. At higher temperatures, \sim 60°, we observed unexpectedly high selectivity for the production of the β -anomeric ester 7 β . In all cases studied at \sim 60° we obtained products with a β/α ratio of 9/1, a complete reversal of the selectivity shown in THF at -30°. Table II contains physical properties of ester products obtained from acylation of 5 in benzene at 60°. This stereoselectivity is much greater than previously reported. For example, the direct acylation of 6 in methylene chloride-pyridine over a wide range of temperatures gives only slight selectivity for formation of the α -anomer (60-70% α , 30-40% β) (12) as does the dehydration-acylation reaction with the *N*-acylamino acid facilitated by dicyclohexylcarbodiimide (13).

To establish the mechanism responsible for the stereoselective control of this reaction we studied the products as a function of solvents and temperature using a single acylating agent. Table III shows the results obtained through acylation of 5 with hexadecanoyl chloride in benzene and in THF at temperatures from -40° to +62°C. As previously noted in the THF, the α -glycosyl ester 7 α is the predominant product over the temperature range of -40° to +60°. However, selectivity for the α -anomer decreased (70% α , 30% β) when the reaction temperature was raised to 25°, and

Table I. Acylation Products of TBG⁻Li⁺ in THF at -30 to -40°C^a

R	ir, C=O, cm ⁻¹	δ (ppm) C-1 α-anomer	C-H, J (Hz) β-anomer	[α] _D ²⁵ (CH ₂ Cl ₂ , 1c)
C ₁₇ H ₃₅ ^b	1745 ^c	6.65(d, 2.6)	5.85(d, 6.8)	+39.2
C ₁₅ H ₃₁ ^b	1745 ^c	6.65(d, 2.6)	5.85(d, 6.8)	+45.9
<u>cis</u> -9, C ₁₇ H ₃₃ ^b	1750 ^c	6.65(d, 2.6)	5.85(d, 6.8)	+42.8
phenyl ^d	1740 ^e	6.70(d, 3.3)	5.90(m) ^f	+73.5
p-nitrophenyl ^g	1737 ^e	6.60(d, 3.3)	5.90(m) ^f	+72.0
2,4,6-trimethylphenyl	1740 ^e	6.66(d, 2.7)	5.90(m) ^f	+73.7

^aAll products are 90% α-anomer, 10% β except where otherwise indicated, rotations are for pure α-anomers when recrystallization was possible.

^bNoncrystallizable glasses.

^cNeat films.

^dmp of recrystallized product 84-85 (EtOH).

^eChloroform solution.

^fABX multiplet.

^gmp of recrystallized product 124.2-125.0 (EtOH).

Table II. Acylation Products of TBC-LI⁺ in Benzene at 60°^a

R	ir, C=O, cm ⁻¹	δ, (ppm) C ₁ -H, J (Hz)	[α] _D ²⁵ (CH ₂ Cl ₂ , 1c)
		α-anomer	β-anomer
C ₁₇ H ₃₅ ^b	1750	6.65(d, 2.6)	5.85(d, 6.8)
C ₁₅ H ₃₁ ^c	1750	6.65(d, 2.6)	5.85(d, 6.8)
phenyl ^d	1735	6.70(d, 3.3)	5.90(m) ^e
2,4,6-trimethylphenyl ^f	1740	6.66(d, 2.8)	5.90(m) ^d
p-nitrophenyl ^g	1737	6.60(d, 3.3)	5.90(m) ^d

^aAll products were 90% β, 10% α, rotations are for pure β-anomers when recrystallization was possible.

^bNoncrystallizable glass.

^cmp of recrystallized product 52-53 (EtOH).

^dmp of recrystallized product 96.0-97.2 (cyclohexane).

^eABX multiplet.

^fmp of recrystallized product 131.0-1.5 (EtOH).

^gmp of recrystallized product 96-98, see reference 12.

^h(Dioxane, 6 c) reference 12.

Table III. Stereochemical Distribution of Anomeric 1-O-Hexadecanoyl-D-TBG as a Function of Temperature and Solvent

Solvent	Anomeric Distribution		Temperature	$[\alpha]_D^{25}$ (CH ₂ Cl ₂ , 1c)
	α	β		
THF	90%	10% (via pmr) ^a	-30 to -40°	+45.9
"	70	30	25°	+39.2
"	70	30	45°	-
"	70	30	60°	+36.0
Benzene	50	50	0 to 5°	+27.8
"	26	74	40 to 45°	+20.6
"	11	89	62°	+14.9
" + 4% HMPA	70	30	62°	+35.0

^aDerived from the integration of the anomeric protons.

seemed to remain constant above this temperature. Overall conversions tend to drop from 95% to 85% with prolonged heating. In benzene, acylation selectivity exhibits more sensitivity to temperature change. The high selectivity for 7β formation at elevated temperature (62°), decreases with decreasing temperature (limiting temperature is the freezing point of benzene). Addition of 4% of a highly polar aprotic solvent, hexamethyl phosphoramide (HMPA), reversed the product distribution in benzene at 62°C to give the same product distribution observed in THF at 25° . Figure 1 depicts the rotation of 1-O-hexadecanoyl-D-TBG esters as a function of the α/β ratio. Although we have been unable to isolate the 1-O-hexadecanoyl- α -D-TBG in high purity owing to the noncrystalline nature of the reaction product, by extrapolation of the data of Figure 1 we obtain a rotation value of $+51.0$ for the pure α material.

Concerning the Structure of TBG, TBG^-Li^+ , and the Mechanism of Acylation

That TBG 6 mp $152\text{--}153^\circ$ exists in the α -configuration is well documented (11, 12, 14, 15). However, this fact is inconsistent with the observations that the stereochemistry of its acylation products vary so widely. For this reason our first task was to reexamine the stereochemistry of TBG. In studying the proton spectrum of TBG, earlier workers (14) had failed to observe that the α -anomeric proton resonance does not account for a single proton relative to the other protons in the molecule. We observed that the measured intensity of this resonance relative to all other proton resonances in TBG reflects only a fraction of the anomeric composition. This mixed anomeric composition may also be verified by measurement of the anomeric OH resonance in a slow OH exchanging ether solvent such as THF- d_8 . Examination of TBG in various aprotic solvents by 220 MHz proton nmr spectroscopy confirmed that TBG is an anomeric mixture. Table IV lists the anomeric composition of TBG in four aprotic solvents. In each solvent except for chloroform, the anomeric composition appeared to be very similar. This is also borne out by the rotational data (Table IV). These data support the idea that crystalline TBG apparently exists as a eutectic mixture or solid solution of α and β forms, since instantaneous mutarotation in aprotic media would be highly unlikely. In addition, the equilibrium concentrations of TBG found in THF and benzene do not reflect the acylated product distributions of 7α and 7β in these respective solvents. An a priori explanation for the acylation product distribution might be based on a solvent dependent equilibration between the anomeric metalated species 5α and 5β . Thus, we might expect a predominance of anomer 5α in THF and a predominance of 5β in benzene in accord with the observed acylation product distribution. However this does not turn out to be the case. To examine this

Table IV. Anomeric Composition of TBG by 220 MHz H'NMR and Rotational Measurements

Solvent	α -anomer		β -anomer		fraction ^b % α
	a [α] _D ²⁵	δ C ₁ -H ppm, J(Hz)	δ C ₁ -H ppm, J(Hz)	δ C ₁ -H ppm, J(Hz)	
pyridine d ₅	+55.0	5.89 d, 3.0	5.45 d, 11.0	5.45 d, 11.0	52
THF d ₈	+46.8	5.20 brs	5.0	d, 10.5	50 ^c ; 67 ^d
Benzene d ₆	+53.6	5.23 d, 3.0	- ^e	- ^e	59 ^d ; 67 ^f
Chloroform d ₁	+19.1	5.12 d, 3.0	- ^e	- ^e	65 ^f

^a0.100 g/10 ml of solvent.

^bSpectra taken at 17° except where indicated otherwise.

^cComposition was confirmed by comparison of the α and β -OH resonances observed at 5.9 δ and 5.38 δ , respectively.

^dMeasurement made at 55°.

^eCould not be observed.

^fFraction estimated from comparison of the area of the anomeric proton resonance with the area of the remaining protons in molecules.

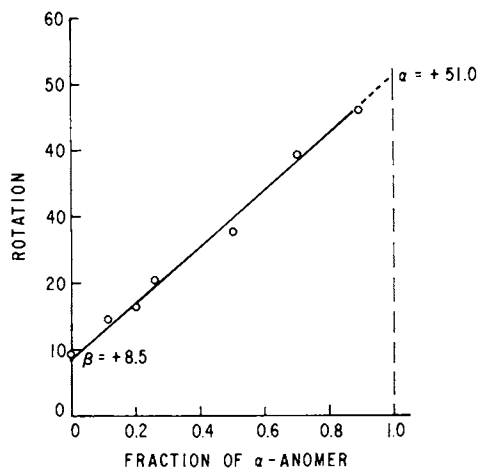


Figure 1. Plot of the α,β composition of 1-O-hexadecanoyl-D-TBG against observed rotation $[\alpha]_D^{25}$ (CH_2Cl_2 , 1c)

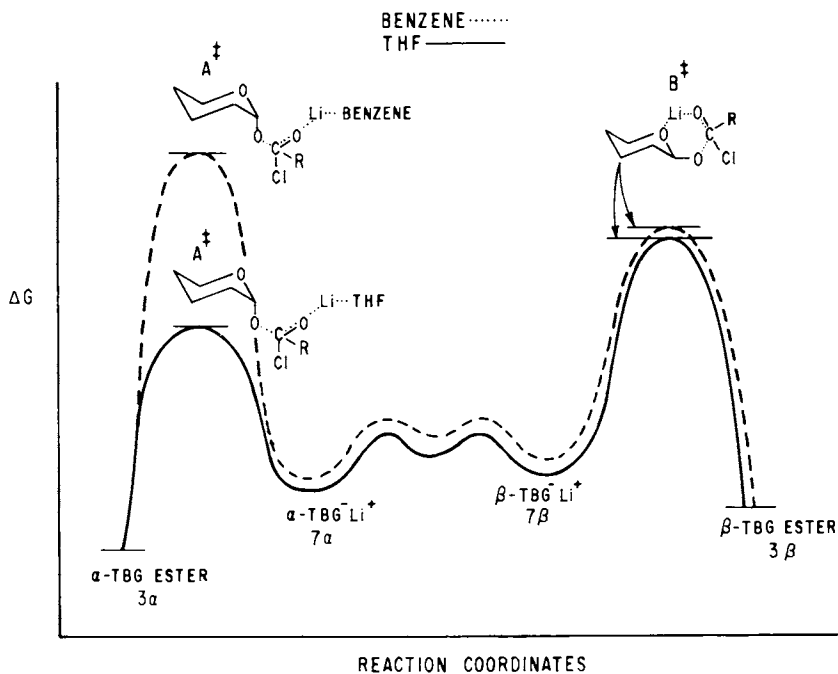
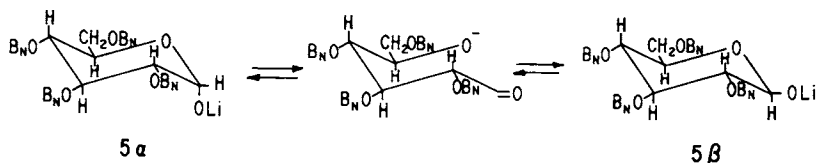


Figure 2. Pathway for the reaction of α - and β -TBG Li $^+$ with acid chlorides in benzene and THF

hypothesis we measured the equilibrium concentrations of 5α and 5β in the two reaction solvents.



An attempt to evaluate the composition of **5** in both THF- d_8 and benzene- d_6 by proton nmr met with failure due to inordinately broad resonances. However, examination of the low frequency ^{13}C spectrum showed narrow lines which were readily assignable to the respective anomeric carbons. Samples were prepared by the addition of one equivalent of *n*-butyl lithium in hexane to a dried degassed solution (2 ml), containing 150 mg of **6** in a 10 mm nmr tube. The spectra were recorded at 22.63 MHz on a ^{13}C FT spectrometer. Ten second delay times were utilized between scans to allow for differences in T_1 relaxation times and to assure quantitation resonance absorption responses, (relaxation times (T_1) have been observed to be never more than 1.5 seconds) (16). Table V gives the ^{13}C chemical shifts and intensities of the anomeric carbons for **6** and **5** in benzene- d_6 and THF- d_8 . The C_1 carbon of the β -anomer 6β is observed at lower field than the C_1 of the α -anomer 6α (17). The α/β ratio agreed well with the data obtained by proton nmr (see Table IV). Upon metalation each of the respective C_1 carbons underwent a 3 ppm upfield shift due to the shielding effect of the negative charge on oxygen (18). Only a small change in the anomer distribution was observed, i.e., the α anomer contribution decreased from 61% and 67% in benzene and THF, respectively, to 50% and 52% in the metalated forms. Apparently there are no significant differences in the equilibrium concentrations of either anomeric forms of TBG Li^+ , 5α or 5β , in either reaction solvent. The stereochemical selectivity of this reaction must, therefore, be controlled by the relative velocity with which either of these two species 5α and 5β are acylated. Figure 2 shows postulated relative energies of the various solvated activated complexes that might account for the observed

Table V. Anomeric Composition and ^{13}C Chemical Shifts

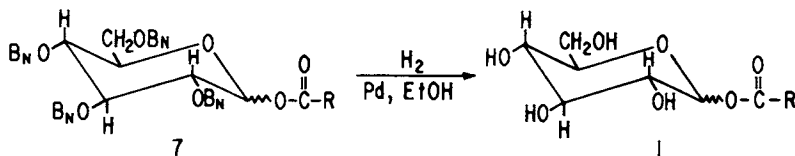
	δ Benzene		δ THF		% α Benzene	% α THF
	α	β	α	β		
TBG	91.3	98.2	91.6	98.6	61	67
TBG Li^+	89.1	95.9	88.8	96.1	50	52

product outcome. In THF solution, the lower energy pathway provided by solvent-solvated A^\ddagger relative to the higher energy pathway given by internally solvated B^\ddagger leads to a predominance of product 7α . Conversely, in benzene intramolecular coordination of B^\ddagger is favored since it offers greater stabilization relative to the stabilization imparted to A^\ddagger by the relatively nonpolar, poorly solvating benzene. Therefore, in benzene, product 7β predominates. Increase in the polarity of the benzene solution with as little as 4% v/v HMPA, (Table III) permits the formation of a low energy HMPA intermolecularly solvated transition state A^\ddagger leading to product 7α .

In the absence of kinetic data we can only speculate on the effect of temperature on product distribution. However, we can see that in both solvents, increased temperature is associated with an increase in the reaction through pathway B^\ddagger to produce more 7β . This temperature effect appears consistent if we assume a high ΔS^\ddagger for transition state B^\ddagger relative to A^\ddagger due to the latter's ordering of solvent molecule. Thus, as the temperature is increased in both solvent systems, the $T\Delta S^\ddagger$ term could become dominant (more positive), effectively lowering even further the ΔG^\ddagger for the pathway through transition state B^\ddagger relative to pathway through A^\ddagger .

1-O-Acyl-D-Glucopyranoses 1α and 1β

Both products 7α and 7β from acylation in THF and benzene, respectively, underwent final purification by elution from a column of Florisil with methylene chloride-petroleum ether. (Reference to brand or firm name does not constitute endorsement by the U.S. Department of Agriculture over others of a similar nature not mentioned.) Each was then hydrogenated (40 psi) in



ethanol with palladium black for eight hours. In most cases we found prior chromatographic purification essential for successful deblocking. On some occasions, addition of a few drops of acetic acid was necessary to catalyze the hydrogenolysis. Although the protected esters 7α and 7β were 90:10 anomeric mixtures which in most cases were not separable, the deblocked esters 1α and 1β could easily be recrystallized to produce both pure α - and β -forms in 70-85% yield. In contrast to the finding of previous reports (6, 7), we observed the 1- α -D-glucosyl esters 1α to be

Table VI. Physical Properties of 1-Glucosyl Esters α , 1 β

R	Configu- ration	mp	ir, (CHCl ₃) C=O, cm ⁻¹	δ C ₁ -H ppm ^a , J(Hz)	$[\alpha]_D^{25}$
C ₁₆ H ₃₁	α	98-108 ^b	1742	6.48 d, 3.0	66.9 (MeOH, 0.9c)
C ₁₆ H ₃₁	β	108, 170-5 ^b	1725	5.65 d, 6.8	-1.17 (MeOH, 1.2c)
C ₁₈ H ₃₅	α	112-121 ^b	1742	6.48 d, 3.0	+72.9 (MeOH, 1c)
C ₆ H ₅	α	c	1720	6.55 d, 3.0	+85.2 (H ₂ O, 0.36c)
C ₆ H ₅	β	192-3 ^d	1712	5.90 m	-27 (HO, 0.45c)
CH ₃	α	c	1740	6.27 d, 3.0	-
2,4,6-trimethylphenyl	α	166-9 ^d	1725	6.40 d, 3.0	+102 (H ₂ O, 0.50c)
2,4,6-trimethylphenyl	β	153-9 ^d	1729	5.75 m	-
<u>cis</u> -9, C ₁₇ H ₃₃	β	c	1725	e	+59.0 (MeOH 0.9c)
<u>cis</u> , <u>cis</u> -9, 11 C ₁₇ H ₃₁	β	c	1725	e	+51.0 (MeOH, 0.9c)

^aSpectra obtained at 60 MHz in CD₃OD (sealed tubes at 76°) because of the insolubility of the derivatives.

^bRecrystallized from chloroform-hexane.

^cUnable to crystallize these derivatives.

^dRecrystallized from EtOH.

^eAnomeric proton resonance coincided with the double bond proton resonances.

relatively stable, giving rise to rearrangement only after prolonged heating. Further details of this acyl migration will be elaborated on in the last section. Table VI lists the physical properties of the isolated 1α and 1β esters.

The configuration of each of these materials was established by both ^1H and ^{13}C nmr except for the unsaturated esters where ^{13}C could only be used because of overlapping resonance signals in the proton spectra. Figures 3A and 3B illustrate typical ^{13}C spectra of 1α and 1β derived from long chain saturated carboxylic acids. As is observed for the parent glucose molecule, the α -anomeric carbon C_1 absorbs at a higher field than the β - C_1 carbon (17), yet the difference in chemical shift between α - C_1 and β - C_1 is only 2 ppm compared to the 4 ppm noted for glucose (17). The smaller difference in field positions is likely due to induced upfield shielding of the β - C_1 relative to the α - C_1 by the ester carbonyl. Shielding of 2.2 ppm is also evident in the C_2 resonance of 1α , presumably because of orientation with respect to the carbonyl whereas C_2 of 1β is deshielded by 1.6 ppm. A comparison of the hexose ring ^{13}C shifts for 1α and 1β and glucose is given in Table VII. The anomeric purity of each compound was verified by glc analysis of the corresponding trimethylsilyl derivatives on a 6' 1/4" O.D. glass column packed with 3% SP2100 and programmed from 180-250° at 6°/minute. Under these conditions each of the isomeric α - and β -pairs could be readily separated, the β -anomer having the longer retention time. Typical retention times for the α - and β -hexadecanoate esters were 12.0 and 12.5 minutes, the α - and β -mesitoates, 8 and 8.2 minutes, respectively.

Table VII. Hexose Ring ^{13}C Shifts for α and β -D-Glucose and Corresponding 1-Hexadecanoyl Esters

	Carbon Shifts (ppm) ^a					
	C_1	C_2	C_3	C_4	C_5	C_6
δ -D-Glucose ^b	92.8	72.3	73.6	70.4	72.3	61.6
β -D-Glucose ^b	96.7	74.9	76.7	70.4	76.5	61.6
1- α -D-Glucosylhexadecanoate ^c	92.2	73.9	74.2	69.7	71.0	61.4
1- β -D-Glucosylhexadecanoate ^c	94.3	72.7	76.8	69.9	76.8	61.7

^aAll shifts relative to TMS as internal standard.

^bSpectra taken in D_2O .

^cSpectra taken in 50/50 v/v CDCl_3 , CD_3OD .

Alternate Routes to 1-O-Acyl-D-glucofuranoses Derived from Unsaturated Carboxylic Acids

To prepare 1-D-glucofuranosyl esters derived from unsaturated carboxylic acids, a second pathway was needed since the method mentioned above required a final reductive step to remove all

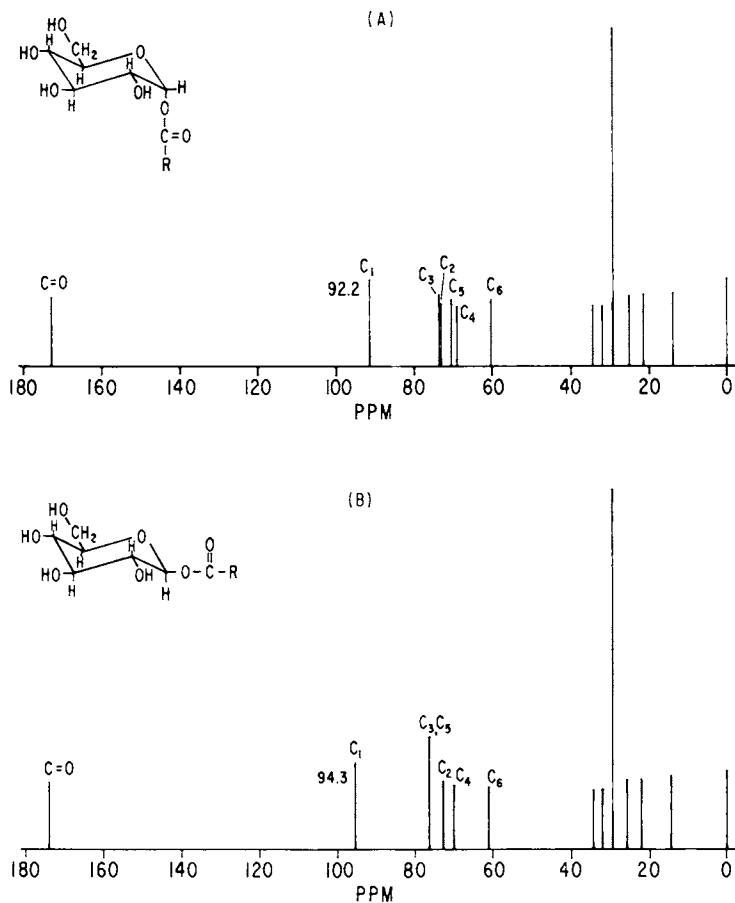
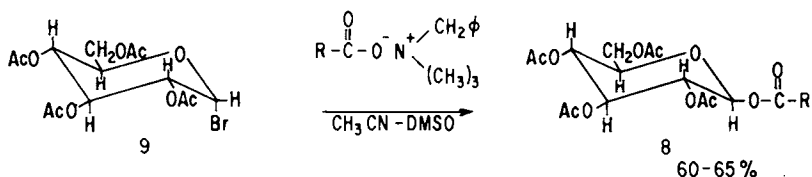


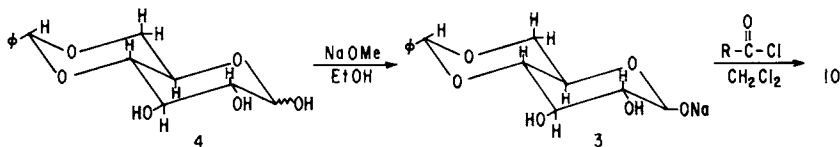
Figure 3. ^{13}C spectra of (A) 1- α -D-glucosyl hexadecanoate and (B) 1- β -D-glucosyl hexadecanoate were taken at 22.63 Hz using 150 mg of sample in 2 ml of 50/50 v/v $\text{CD}_3\text{OD}-\text{CDCl}_3$ at 50°C . The spectra were obtained on a Fourier Transform nmr spectrometer after 700 transients with a 5 sec delay time. All shifts are relative to internal TMS.

blocking groups. Our first approach at solving this problem was the preparation of 2,3,4,6-tetra-O-acetyl-1-O-acyl- β -D-glucopyranose **8** through displacement of the corresponding bromide **9** (**19**). This was easily accomplished by reaction of **9** with the benzyl-trimethyl ammonium salt of either octadecanoic or *cis*-9-octadecenoic acid in 65:35 DMSO- CH_2Cl_2 at 50° for 24 hours.



After workup and chromatographic purification of the reaction mixture through a Florisil column with CH_2Cl_2 -petroleum ether, we obtained 60-65% of pure ester **8** with the β -configuration. Nmr in CDCl_3 showed the characteristic anomeric proton resonance at 6.0 δ d, $J = 6.5$ Hz, ir, $\text{C}=\text{O}$ 1750 cm^{-1} , rotation -1.5 (MeOH), 1 C). The melting point of the octadecanoate was $69-70^\circ$, (lit. mp 77° (**20**)), whereas the octadecenoate was a viscous oil. Both compounds provided the correct elemental analyses. Attempted deacetylation of these compounds with either barium hydroxide (**21**) or sodium hydroxide in methanol at temperatures as low as -40° failed to show preferential removal of acetate over the long chain acyl group. Even the ammonia in methanol deacetylation described by Robert (**22**) for the preparation 1- β -D-glucosyl anthranilate resulted in unselective deacetylation. The latter procedure appears to be applicable to the removal of acetate only in the presence of less reactive aromatic esters.

The pathway selected for the preparation of the unsaturated glucosyl esters **1** employs 4,6-O-benzylidene-D-glucose **4** (**23**). Preparation and isolation of the dried sodium salt of 4,6-O-benzylidene-D-glucose **3** from ethanol solution followed by



acylation in CH_2Cl_2 , (heterogeneous mixture) led to 4,6-O-benzylidene-1-O-acyl-D-glucopyranose 10 in 40-50% isolated yield based on 4 (8) (overall yields based on glucose were more variable because the yields in preparing 4 ranged from 20-80%).

The stereochemistry of these derivatives was studied by both ^1H and ^{13}C nmr. Figure 4 shows how the anomeric proton resonance which coincides with the chemical shift of the benzyl hydrogen in 10 is shifted downfield with the incremental additions of $\text{Eu}(\text{fod})_3$ pseudocontact shift reagent. Judging from the initial chemical shift of the anomeric proton (5.8 δ) and coupling constant, 7.5 Hz, the hexadecanoate ester has the β -configuration. In studying this acylation reaction, we observed that as the acylation reagent became more unsaturated the reaction became less stereoselective, e.g., acylation of 3 with hexadecanoyl chloride or octadecanoyl chloride gave effectively 100% of the β -isomer while cis-9-octadecenoyl chloride gave 90% β ; cis,cis-9,12-octadecadienoyl chloride, 85% β ; and the cis,cis,cis-9,12,15-octadecatrienoyl chloride, 60% β (Table VIII).¹³ Measurement of the isomer ratio was routinely performed by ^{13}C nmr because of the difficulty in directly observing the β -anomeric proton in the absence of shift reagent as mentioned above. Comparison of the C_1 anomeric carbon resonances at 92.2 δ (α) and 94.1 δ (β) provided a direct analysis of the stereoselectivity of the reaction. The isomer ratios were also confirmed by glc analyses of the corresponding TMS derivatives.

Table VIII. Stereoselectivity of Acylation of 1-O-Sodio-4,6-O-Benzylidene Glucose as a Function of the Degree of Unsaturation in the Acylating Agent

R	mp ^a	anomeric % α	composition ^b % β
$\text{C}_{17}\text{H}_{35}$	132-3	0	100
$\text{C}_{15}\text{H}_{31}$	131-131.8	0	100
<u>cis</u> -9,10 $\text{C}_{17}\text{H}_{33}$	- ^c	10	90
<u>cis,cis</u> -9,12, $\text{C}_{17}\text{H}_{31}$	- ^c	15	85
<u>cis,cis,cis</u> -9,12,14, $\text{C}_{17}\text{H}_{29}$	- ^c	40	60

^aAll esters had $\text{C}=\text{O}$ absorption at 1755 cm^{-1} (CHCl_3).

^bAll compositions determined by ^{13}C nmr comparison of the anomeric carbon resonances prior to recrystallization.

^cViscous glass.

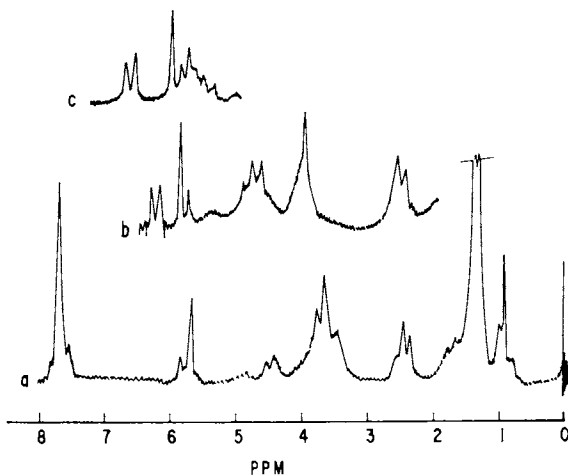


Figure 4. Low field 60 MHz proton spectrum of 1-O-hexadecanoyl-4,6-O-benzylidene- β -D-glucopyranose (0.04 g in 0.400 ml of CDCl_3). (a) Spectrum in the absence of $\text{Eu}(\text{fod})_3$ solution; (b) after addition of 15 ml of 0.30 M $\text{Eu}(\text{fod})_3$ solution in CCl_4 ; (c) after addition of 20 ml of 0.30 M $\text{Eu}(\text{fod})_3$ solution in CCl_4 .

The ^{13}C spectrum of the isomeric mixture of 1-O-cis,cis-9,12-octadecadienoyl-4,6-O-benzylidene-D-glucopyranose is shown in Figure 5a. Assignments at all ring carbons could not be readily made owing to the unpredictable changes in chemical shifts imposed by the acetal bridging. Nevertheless the α/β ratio at the anomeric center as well as the cis/trans ratio was easily determined. Because of the alkalinity of the reaction medium, we observed as much as 5-7% trans product at acylation temperatures of -30 to -40° . Comparison of the C_8 and C_{14} resonances, (external allylic carbons associated with an adjacent cis double bond) at 27.3 δ with the C_8 and C_{14} resonances at 32.6 δ , associated with the trans double bonds, yielded the cis/trans ratio directly.

At present we cannot explain why an increase in the degree of unsaturation of the acid chloride caused a decrease in stereoselectivity. However, one possible cause may be solubility changes taking place in the heterogeneous acylation reaction mixture due to structural differences in the various polyunsaturated acid chlorides used. Acylation of both sodium and lithium salts 3 generated in situ homogeneously from either sodium or *n*-butyl lithium in THF at -30° gave varying product distributions, i.e., ester mixtures composed of 50-60% 9b, 20-25% 9a, and 15-20% acyl migrated compounds 12. Presumably, 3 when isolated in crystalline form, assumes the β -configuration 3 β which when acylated in a nonsolubilized form yields 10 β . However, as the solubility of 3 is increased, either by solubilizing agents, i.e., polyunsaturated acid chlorides or by generation in soluble form in situ, equilibration of the anomeric salts 3 α and 3 β can occur. Unlike TBG Li^+ 5, no change in the distribution of isomeric acylation products is noticed when benzene is substituted for THF. This difference in behavior is probably a reflection of participation by free $\text{C}_2\text{-OH}$ which is made unavailable in TBG through ether protection.

β -Glucosyl esters 1b derived from unsaturated carboxylic acids were readily generated from 9b by hydrolysis in 75% acetic acid-water at 60° for one hour (24). Yields of isolated and purified (silica gel chromatographed) esters 9 β were in the range of 40-50% based on glucose. The ^{13}C spectrum of 1-O-cis,cis-9,11-octadecadienoyl-D-glucopyranose (85% α , 15% β) is seen in Figure 5b. Other physical properties of the unsaturated esters are given in Table VI.

Stability of 1-O-Acyl- α -D-Glucopyranose Derivatives

In several attempts to prepare 1-O-acyl- α -D-glucopyranose 1 α , it has been reported that isolation could not be accomplished (6, 7). Only when the ester was highly hindered, e.g., the mesitoate derivative 2a, could the compound be isolated in the unmigrated state. The previous attempts to generate 1 α and 1 β (through deblocking precursor compounds containing acyl protecting groups) were carried out in basic solution. This caused acyl

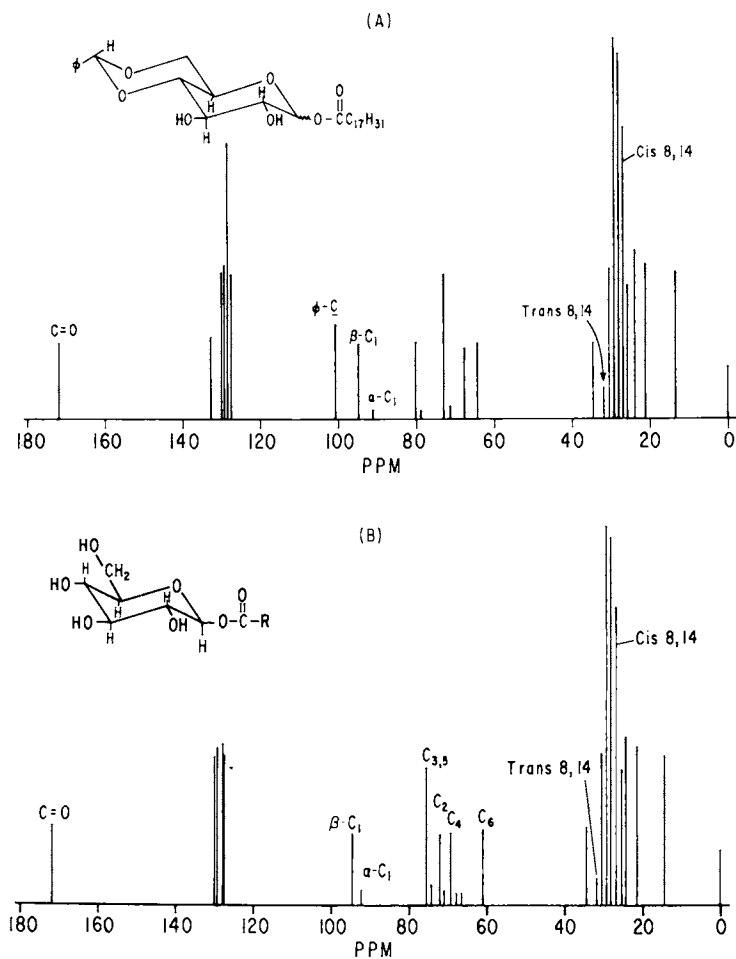
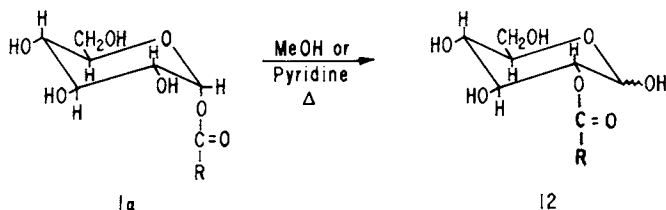


Figure 5. (A) ^{13}C spectrum of 0.150 g of cis,cis-9,12-octadecadienyl- α,β -4,6-O-benzylidene glucose in CDCl_3 . Chemical shifts relative to internal TMS. (B) ^{13}C spectrum of 0.150 g of cis,cis-9,12-octadecadienyl-D-glucopyranose (85% β , 15% α).

migration and saponification. We have successfully deblocked 7 α by hydrogenolysis in neutral or slightly acid medium. This has permitted us to isolate pure, unrearranged 1 α . Although 1-O-acyl- α -D-glucopyranoses 1 α are stable in the crystalline state, they



slowly rearrange upon prolonged heating in neutral solution or upon melting on a glass surface. Rearrangement of 1 α was studied in methanol and pyridine by proton nmr. The progress of acyl migration of the hexadecanoate derivative in CD₃OD at 76° is illustrated in the spectrum shown in Figure 6. Appearance of the anomeric proton resonances at the high positions of 5.5 δ and 4.7 δ is indicative of the formation of the isomeric mixture of free C₁-OH glucopyranoses 12 α and 12 β esterified at C₂. The detailed 220 MHz proton spectrum of 12 α and 12 β in pyridine-d₅, (Figure 7) identifies the migration products as the C₂-OH esterified product by its characteristic H-C-O-acyl shift pattern and field position

Table IX. Migration Rates of 1-O-Acyl- α -D-glucopyranoses and Rotations of the Product 2-O-Acyl-D-glucopyranoses

R	Methanol $k_{76}^a \times 10^2 \text{ min}^{-1}$	Pyridine $k_{76}^a \times 10^2 \text{ min}^{-1}$	$[\alpha]_D^{25}$
$\text{C}_{15}\text{H}_{31}\overset{\text{O}}{\parallel}{\text{C}}$	2.8	1.0	+34.6 (MeOH, 0.6c)
$\text{C}_6\text{H}_5\overset{\text{O}}{\parallel}{\text{C}}$	3.0	-	+41.5 (H ₂ O, 0.96c)
	No reaction	No reaction	+44.5 ^b (H ₂ O, 0.4c)

^a Measured by following the disappearance of the anomeric proton of the 1-O-acyl- α -D-glucopyranose and the appearance of the α and β anomeric protons of 2-O-acyl-D-glucopyranose products.

^b Reference 7.

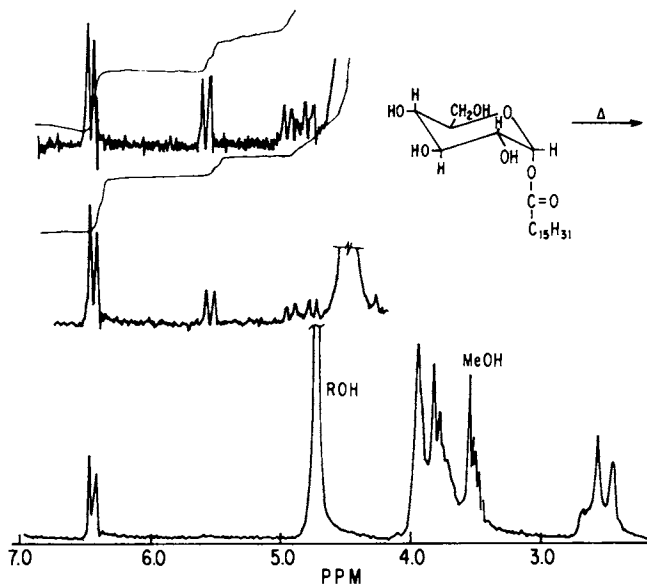


Figure 6. 60-MHz nmr spectrum of 1-O-hexadecanoyl- α -D-glucopyranose in CD_3OD during acyl migration at $76^\circ C$. All shifts are relative to internal TMS.

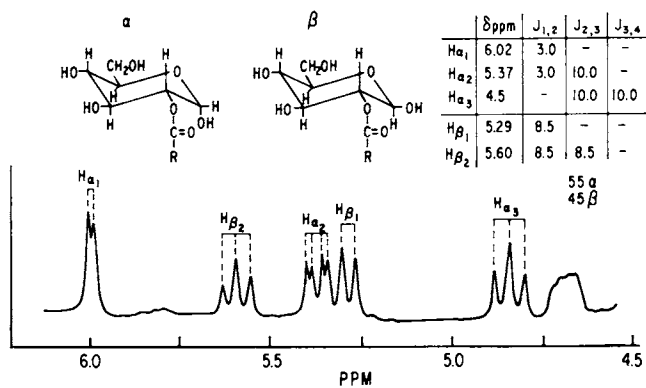


Figure 7. 220-MHz nmr spectrum of 2-O-hexadecanoyl-D-glucopyranose (region from 4.5–6.2 δ) in $pyridine-d_5$. All shifts are relative to internal TMS.

(25). Integration of the α and β anomeric protons shows this mixture to be 55% 1α and 45% 1β . Rearrangement rates at 76° , given in Table IX, are first order in ester 1α in methanol and pyridine, the rate in the former being somewhat faster. Both aliphatic and unsubstituted aromatic esters migrate at the same rate. The mesitoate derivative is stable under these conditions. Significantly, although migration readily occurred at 76° in methanol and pyridine, no acyl migration was observed in the presence of 8.0 mole % acetic acid at 76° after 24 hours. Reaction rates in both teflon as well as quartz nmr tubes were the same as those observed in pyrex, indicating that active sites in the glass were not responsible for catalyzing this process.

Summary

The stereoselectivity of acylation of TBG^-Li^+ is effectively controlled by altering the solvent medium and temperature. The blocking benzyl ether groups were removed by hydrogenolysis to produce both stable $1-\alpha$ and $1-\beta$ glucosyl esters derived from saturated carboxylic acids. TBG and its salt TBG^-Li^+ were found by nmr to be an equilibrium mixture of both α and β -anomeric forms. A mechanism concerning the stereochemical control of TBG^-Li^+ acylation is discussed in terms of inter and intramolecularly solvated transition states. Glucosyl esters of unsaturated carboxylic acids were prepared through the acylation of 4,6-O-benzylidene-1-O-sodio glucopyranose. Stereoselectivity of acylation dropped off with an increase in the degree of unsaturation in the acylating agent. Acylation of both 1-O-lithium and sodium salts of 4,6-O-benzylidene glucose generated in homogeneous solution yielded mixtures of $1-\alpha$ - and β -glucosyl esters and acyl migration products. The stability, kinetics, and products of acyl migration of $1-\alpha$ -glucosyl esters were examined.

Acknowledgment

We thank J. J. Unruh for his able assistance. 220 MHz nmr spectra were taken at the Middle Atlantic Regional NMR facility which is supported by NIH grant RR542 at the University of Pennsylvania.

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Preparation and Characterization of 1,6-Anhydro-3,4-dideoxy- β -D-glycero-hex-3-enopyranos-2-ulose

FRED SHAFIZADEH and PETER P. S. CHIN

Wood Chemistry Laboratory, University of Montana, Missoula, Mont. 59801

Pyrolysis of carbohydrates results in transglycosylation (1,2), dehydration (3) and subsequent decomposition and charring reactions (4). These reactions offer some interesting products which can be used as intermediates for synthesis of carbohydrate derivatives.

1,6-Anhydro-3,4-dideoxy- β -D-glycero-hex-3-enopyranos-2-ulose (levoglucosenone) has recently been detected in several laboratories (5-8) from the pyrolysis of cellulose containing an acidic catalyst and has been assigned the structures, namely 1,5-anhydro-2,3-deoxy- β -D-pent-2-eno-furanose (a) and cis-4,5-epoxy-2-pentenal (b) as well as the levoglucosenone structure (c) shown in Figure 1. The correct structure of this compound was confirmed in our laboratory by making crystalline derivatives (8), and by investigating the reaction of the isolated compound.

These investigations revealed that levoglucosenone can be produced in comparable yields from the pyrolysis of various materials, such as acid-treated starch and waste papers, in addition to pure cellulose (Table I). These yields were determined by pyrolysis gas chromatography of small samples, using a pyrolysis temperature of 350°. The crude pyrolyzate contained, in addition to levoglucosenone, 2-furaldehyde as the major impurity. It was also found that levoglucosenone is unstable at high temperatures and could further pyrolyze, especially in the presence of zinc chloride (8).

In previous studies, levoglucosenone was purified by preparative gas chromatography, which was a time consuming method only suitable for small-scale preparation. In the current investigation, the following procedure was developed for a larger scale preparation. Waste Kraft paper bags were shredded, treated with dilute phosphoric acid and dried. Eight-gram batches of the treated paper containing 5% phosphoric acid were pyrolyzed under nitrogen in a tube furnace. To minimize the excessive decomposition of the products on the hot furnace tube, a reduced temperature of 275° was used. After 208 g of the raw material was pyrolyzed, the accumulated pyrolyzate was extracted

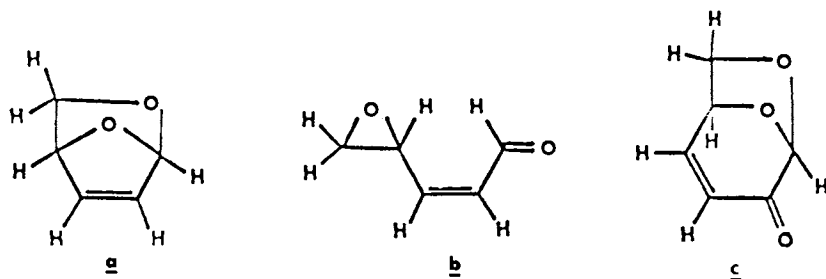


Figure 1. Structures of (a) 1,5-anhydro-2,3-deoxy- β -D-pent-2-enofuranose; (b) cis-4,5-epoxy-2-pentalenal; and (c) 1,6-anhydro-3,4-dideoxy- β -D-glycero-hex-3-enopyranos-2-ulose (levoglucosenone)

TABLE I. YIELDS OF LEVOGLUCOSENONE FROM THE PYROLYSIS OF DIFFERENT MATERIALS AT 350°^a.

Material	Neat (%)	5% H ₃ PO ₄ -treated (%)
Cellulose	1.2	11.1
Starch	0.3	9.0
News-print with ink	T ^b	9.1
Kraft shopping bags	T	10.2

^aDetermined by pyrolyzing 5 mg samples and directly analyzing the volatiles by GLC.

^bT = trace amount.

with chloroform and the chloroform solution was dried, filtered and evaporated. The gas-liquid chromatography (GLC) analysis of this mixture gave chromatogram A in Figure 2, showing the levoglucosenone and 2-furaldehyde as the major components with the ratio of 4:1, respectively.

2-Furaldehyde and other aldehydo impurities were removed from the pyrolyzate by reaction with 5,5-dimethyl-1,3-cyclohexane-dione (dimethone) in 50% aqueous ethanol solution at 100°. Upon cooling, the bismethone derivatives of aldehydo compounds precipitated from the solution and were removed by filtration. Ethanol was removed from the filtrate under vacuum and the remaining aqueous solution was again extracted with chloroform, dried, filtered, and evaporated. The resulting mixture gave chromatogram B in Figure 2, which shows the complete removal of 2-furaldehyde along with other aldehydo impurities. This aldehyde-free pyrolyzate was then vacuum distilled at 1.5 mm Hg. The fraction collected between 55-60° as shown in chromatogram C in Figure 2, contained 96% levoglucosenone, pure enough for synthetic purposes. The yield of purified product weighed 6.8 g, amounting to an overall yield of 3.3% based on the weight of waste paper.

The product was a light-yellow colored liquid with $[\alpha]_D^{26} - 458^\circ$, compared with the -460° reported before (7). This product was further characterized as the crystalline 2,4-dinitrophenylhydrazone (DNPH) reported before (8) and semicarbazone which is a new derivative.

Levoglucosenone possesses an interesting α,β -unsaturated keto structure, which can be used to synthesize branched-chain, keto and amino sugar derivatives. In this study, we have explored some of these possibilities. Table II shows some of the derivatives prepared by modifying the functional groups of this compound.

Selective reduction of the keto group by lithium aluminum hydride in ether gave a mixture containing 84% of 1,6-anhydro-3,4-dideoxy- β -D-erythro-hex-3-enopyranose (d) and 8% of its C-2 epimer. The major product formed in 75% yield, and was characterized by its 3,5-dinitrobenzoate derivative. The nuclear magnetic resonance (NMR) spectrum of this compound showed that there was no spin-spin coupling between the C1 and C2 protons, confirming the assigned configuration.

The second derivative was prepared by hydrogenation of the double bond using Pd/BaSO₄ as a catalyst. This gave 1,6-anhydro-3,4-dideoxy- β -D-glycero-hexopyranos-2-ulose (e) as an oil in 85% yield. This compound was characterized by its DNPH derivative.

The reduction of both keto and double bond functional groups gave 1,6-anhydro-3,4-dideoxy- β -D-erythro-hexopyranose (f) as an oil, that was characterized by its 3,5-dinitrobenzoate derivative. The same product, 3,5-dinitrobenzoate derivative, was obtained by both hydrogenation of d or reduction of e; indicating that the saturation of the double bond on the sugar ring did not change

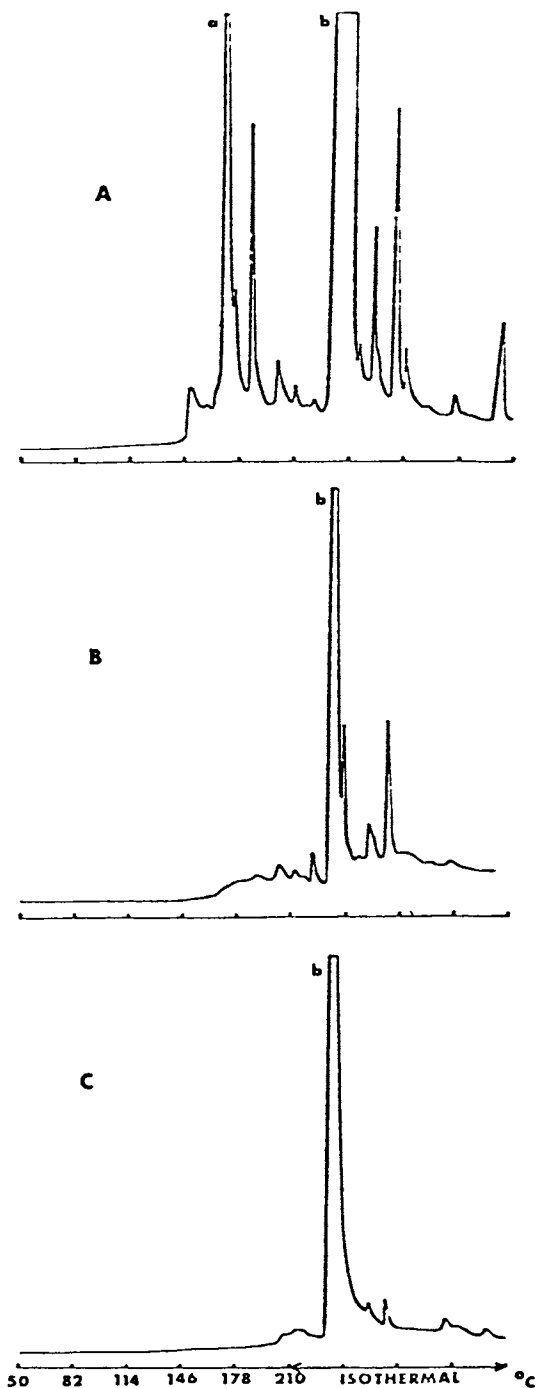


Figure 2. Gas-liquid chromatograms of (A) crude prolyzate; (B) crude pyrolyzate after removing aldehyde impurities; and (C) final product. Peak a is 2-furaldehyde and peak b is levoglucosenone.

TABLE II. DERIVATIVES OF LEVOGLUCOSENONE PREPARED BY MODIFYING ITS FUNCTIONAL GROUPS.

Reaction & Product	Yield (%)	Characterized by	Note
 <chem>O=C1C=CC2OC1C2</chem> (c) $\xrightarrow[\text{Ether}]{\text{LiAlH}_4}$ <chem>OCC1C(O)CC2OC1C2</chem> (d)	75	3,5-DNB derivative	$J_{1,2} = 0$ cps
 <chem>O=C1C=CC2OC1C2</chem> (c) $\xrightarrow[\text{Pd/BaSO}_4]{\text{H}_2}$ <chem>O=C1COC2CC1OC2</chem> (e)	85	DNPH derivative	
 <chem>OCC1C(O)CC2OC1C2</chem> (d) $\xrightarrow[\text{Pd/BaSO}_4]{\text{H}_2}$ <chem>OCC1C(O)CC2OC1C2</chem> (f)	84	3,5-DNB derivative	
 <chem>O=C1C=CC2OC1C2</chem> (e) $\xrightarrow[\text{Ether}]{\text{LiAlH}_4}$ <chem>OCC1C(O)CC2OC1C2</chem> (f)	70	3,5-DNB derivative	

the stereospecific nature of the lithium aluminum hydride reaction and also confirming the assigned configuration. The former reaction gave 84% yield and the latter reaction gave 70% yield of the major product and 7% of the corresponding isomer.

In addition to modifying the functional groups of levoglucosenone, different branched-chain sugar derivatives could also be prepared by the reaction of levoglucosenone with Grignard reagent under controlled conditions as shown in Table III.

At room temperature, levoglucosenone reacted with methylmagnesium iodide to give mainly the 1,2 addition product, 1,6-anhydro-3,4-dideoxy-2-*c*-methyl- β -D-*erythro*-hex-3-enopyranose (g) in 56% yield. The reaction mixture also contained 6% of the C-2 epimer and 6% of the 1,4-addition product. The major product was separated by column chromatography (CC), reduced by hydrogenation to 1,6-anhydro-3,4-dideoxy-2-*c*-methyl- β -D-*erythro*-hexopyranose (h), and characterized as the 3,5-dinitrobenzoate derivative.

At -78° and in the presence of tetrakis [iodo (tri-*n*-butyl)phosphine] copper (I)], however, the reaction of levoglucosenone with methylmagnesium iodide gave mainly the 1,4-addition product, 1,6-anhydro-3,4-dideoxy-4-*c*-methyl- β -D-*erythro*-hexopyranos-2-*u*lose, (i) in 64% yield. This compound was characterized as the DNPH derivative. The configuration of compound i was assigned by NMR spectroscopy which showed that there was no spin-spin coupling between the C4 and C5 protons.

The reaction of g with methylmagnesium iodide at room temperature was not stereospecific. It gave nearly equal amounts of compound h and 1,6-anhydro-3,4-dideoxy-2-*c*-methyl- β -D-*threo*-hexopyranose (j) as an oil which could not be clearly separated by CC. However, these two compounds were characterized by their 3,5-dinitrobenzoate derivatives from the early and late fractions.

The configurations of compounds g, h and j were determined by NMR spectroscopy with the aid of europium III [Eu (fod)₃] shift reagent. The NMR of the product mixture containing h and j in CDCl₃ shown in spectrum A in Figure 3, contains two equal sized hydroxyl signals at 2.5 and 2.8 ppm due to the equal concentrations of the two compounds. There was only one sharp signal at 5 ppm for the anomeric protons. In order to increase the concentration of one of the two isomers, compound g was hydrogenated to h and added to the solution. This increased the size of the hydroxyl signal at 2.5 ppm as shown in spectrum B in Figure 3. Upon gradual addition of Eu (fod)₃, as shown in spectra C and D, the larger hydroxyl signal at 2.5 ppm shifted significantly to a lower field while the other one remained relatively unchanged. Also, the common signal for the anomeric protons at 5 ppm was gradually separated into two peaks. The peak which shifted to a lower field was larger in size than the one remaining relatively unchanged. Therefore, the isomer prepared by hydrogenation of compound g should have the structure h that contains the more accessible hydroxyl group.

TABLE III. DERIVATIVES OF LEVOGLUCOSENONE PREPARED BY GRIGNARD REACTIONS UNDER DIFFERENT CONDITIONS.

Reaction & Product	Yield (%)		Characterized by	Note
	GLC Analysis	Isolated		
 (g)	56	51	 (h)	
 (i)	64	44	 (h)	DNPH derivative $J_{4,5} = 0$ cps
 (h)	31			3,5-DNB derivative
 (j)	31			3,5-DNB derivative

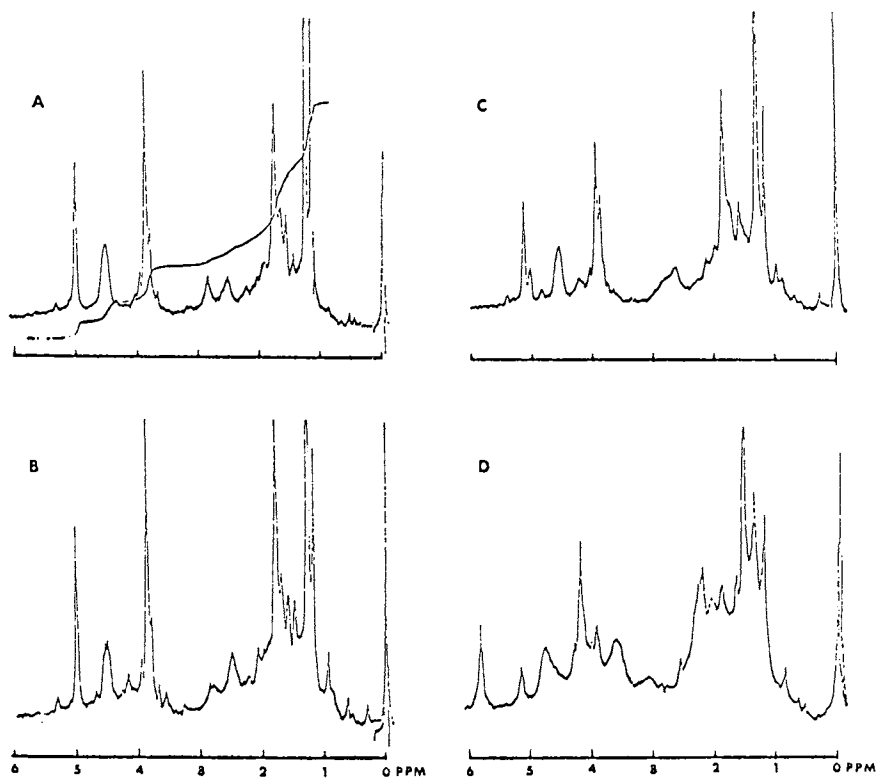


Figure 3. Gradual change in nmr spectra; (A) Grignard reaction products of compound e; (B) after adding the hydrogenation product of compound g; (C) after adding $\text{Eu}(\text{fod})_3$; and (D) at the end of the addition of $\text{Eu}(\text{fod})_3$.

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Formation and Conversion of Phenylhydrazones and Osazones of Carbohydrates

HELMUT SIMON and ADOLF KRAUS

Technische Universität München, Organisch-Chemisches Institut,
D-8000 Munich, West Germany

Since their discovery by E. Fischer (1,2) sugar phenylhydrazones and sugar osazones have interested carbohydrate chemists for different reasons (3-7):

a) At first, the hydrazones and osazones were used for the identification and to some extent, the estimation and separation of saccharides.

b) Then, chemists were interested in the mechanism of osazone formation and the structure of phenylhydrazones and osazones.

c) Later, chemists wanted to know why the reaction between phenylhydrazine and sugars usually stopped at the bishydrazone stage, and why disubstituted hydrazines such as N-methyl-N-phenylhydrazine could "oxidize" sugars beyond the bishydrazone level as shown by Chapman et al. (8,9). It was also interesting to know why the formation of osazones from different monosaccharides proceeded in such widely varied yields and rates.

d) Sugar osazones have been used as starting materials for numerous interesting heterocycles (10-13).

We have carried out some work in area "b", especially on the mechanism of osazone formation and in areas "c" and "d".

For a long time efforts to solve problems "b" and "c" did not lead to decisive results for two reasons. Chemists have often tried to get information about the structure of phenylosazones or phenylhydrazones from their reaction products and it was not realized that certain isomers present only in small concentrations in the equilibrium mixture could be the reacting species. Although the structures of some hydrazones and osazones in the crystalline state are well known (4), the structures of most of the species present in solution are not. This means that many of the kinetically controlled intermediates and the products of the reactions of aldoses and ketoses with phenylhydrazine are not known. Further, our knowledge of the reaction mechanism was hampered by our not knowing for certain what all the reactions taking place are. This does not mean that we do not know what the predominant forms are, but rather that the starting materials for certain reactions could be present in concentrations not detect-

able by the physicochemical methods available. Further, the occurrence of a given reaction does not prove the presence of only one structure. For more details see a review by Mester *et al.* (14) and a paper by Blair *et al.* (15) on the structure of phenylhydrazones of different hexoses.

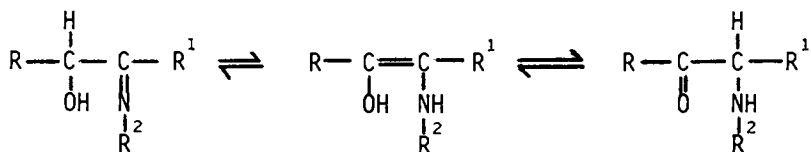
The structure of osazones has been discussed in detail. A careful analysis of all the available information suggests that the structure originally proposed by Fieser and Fieser (16) is still valid (17,18). It explains reasonably well why the two phenylhydrazone groups of osazones behave differently in most of their reactions. These structures, however, do not explain satisfactorily why the reaction of saccharides with phenylhydrazines stops at the second carbon atom.

We (7,19) and others (20,21) studied a series of model compounds and reactions of phenylhydrazones of α -hydroxyaldehydes, α -hydroxyketones and monoses as well as reactions of osazones under the influence of acid or base catalysis in order to gain more insight into the behaviour of sugar phenylhydrazones and osazones under the conditions of their formation.

Phenylhydrazones

The problems of formation of peroxides and the equilibrium between different isomers are of current interest. The mutarotation of 3,4,5,6-tetra-O-benzoyl-D-glucose phenylhydrazone previously attributed (22) to a phenylhydrazone \rightleftharpoons phenylazo tautomerism has been shown to be due to the formation of a phenylazohydroperoxide equilibrium (23). Further, phenylhydrazones under the influence of acids and bases exist in equilibrium with different isomers (24) and may react in different ways, as can be seen in Figure 1. For simplicity the equilibria between the different cyclic and acyclic isomers which may exist for sugar derivatives were omitted (for a discussion of these forms see ref. 25). Usually form 1 is by far the most predominant form but there are examples such as that of D-xylo-4,5,6-trihydroxy-2-oxo-1,3-bis(phenylhydrazono)-cyclohexane where both forms 1 and 4 are known (26).

In such cases where X = OH 6 is an intermediate in a rather general reaction which in the field of carbohydrates has been first described by Amadori (27). It may be summarized by the following tautomerizations:



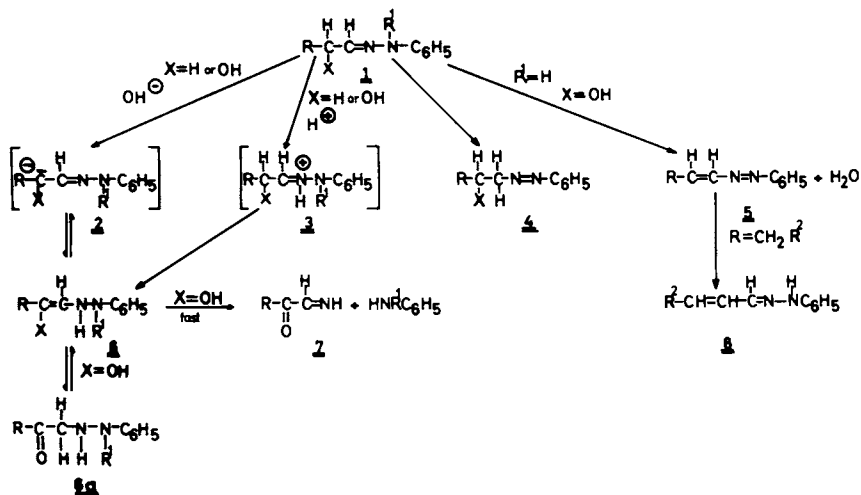


Figure 1

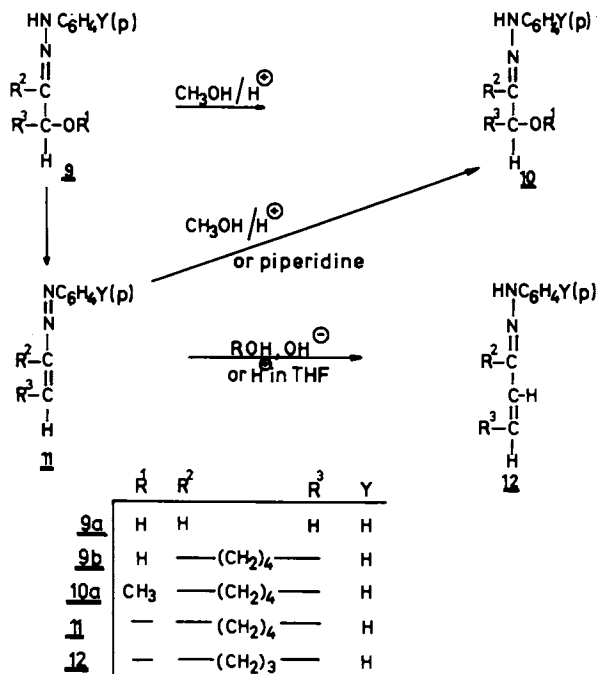


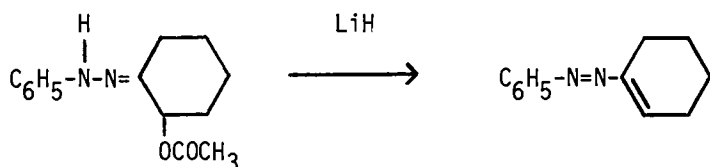
Figure 2

Usually the equilibrium in this reaction is shifted towards the side of the α -amino carbonyl compound. Like many other reactions in the field of carbohydrate chemistry this rearrangement can be catalyzed by acids, bases, by compounds containing activated methylene groups such as ethyl malonate and by the addition compounds of amines with Lewis acids (28). In the case of hydrazino derivatives a form such as 6a has not been isolated yet. The reason may be that this form is in equilibrium with form 6 which is able to react irreversibly to give the α -ketoimine 7. An analogous elimination will be discussed later. We have studied the exchange of carbon-bound hydrogen atoms of the phenylhydrazones of aldehydes and ketones in ethanol-potassium hydroxide as well as in dilute mineral acid solutions under a strictly oxygen free atmosphere (24,29,30). Our results can be summarized as follows:

Reactions of Hydrazones in Dilute Alkaline Solution. Based on the positions of hydrogen exchange determined in the reisolated phenylhydrazones we could conclude that structures 1,4 and 6 are formed reversibly in cases where $X = R^1 = H$. The hydrazone-azo hydrazone-tautomerism behaves differently when $R^1 = \text{CH}_3$ or $X = \text{OH}$. When $X = \text{OH}$ two elimination reactions (1 \rightarrow 5 and 1 \rightarrow 6 \rightarrow 7) take place. When $R^1 = \text{CH}_3$ the azo form 4 cannot be formed and consequently no hydrogen exchange can be observed (24). With the phenylhydrazones of glycolaldehyde 9a and 2-hydroxy-cyclohexanone 9b (Figure 2) as model compounds and the phenylhydrazones of mannose and glucose in 0.12 M KOH in ethanol labeled with tritium in the OH-group the following was observed (30): Within 15 min at 80° 10.3 % of the hydrogen atom attached to C-1 of glycolaldehyde phenylhydrazone was exchanged with protons of the medium. This can be explained by an equilibrium between 1 \rightleftharpoons 4. Acetaldehyde phenylhydrazone shows hydrogen exchange at C-1 and C-2 in a ratio of 1.0 : 1.7 (30). This probably occurs via 1 \rightleftharpoons 2 \rightleftharpoons 6 and 1 \rightleftharpoons 4 respectively. In contrast to acetaldehyde phenylhydrazone and other aldehyde phenylhydrazones with no OH-group in the 2-position there is no exchange at C-2 of the phenylhydrazones of glycolaldehyde (9a), mannose and 2-hydroxy-cyclohexanone (9b). That means that the hydroxy group at C-2 prevents the equilibrium 1 \rightleftharpoons 6. The reason is very probably the fast consecutive reaction 6 \rightarrow 7. In agreement with this conclusion, we observed that aniline was eliminated during the reaction. The ratio of exchange rates at C-1 of the phenylhydrazones of acetaldehyde, glycolaldehyde and mannose were found to be 1.0 : 3.5 : 7.0. 2-Hydroxy-cyclohexanone phenylhydrazone exchanged in 120 min 22.5 % of its hydrogen atoms presumably at C-6, and was finally transformed to phenylhydrazono-cyclohexene 12a via 9b \rightarrow 11a \rightarrow 12. This corresponds to 1 \rightarrow 5 \rightarrow 8 in the general Figure I. Glycolaldehyde phenylhydrazone however eliminated some aniline presumably via 1 \rightarrow 2 \rightarrow 6 \rightarrow 7.

Aldose phenylhydrazones 13 show some additional reactions and yield other products, such as N-phenyl-pyrazole 16 which is

formed under strictly identical conditions in yields of 35 % from mannose phenylhydrazone and in 20 % from glucose phenylhydrazone. The reaction sequence may be represented according to Figure 3. Intermediate 14 which corresponds to compound 5 in Figure 1 is 1-phenylazo-D-arabino-3,4,5,6-tetraacetoxyhexene-(1) which is formed from 13 in pyridine-acetic anhydride according to Wolfrom *et al.* (31,32). The formation of such alkene-azoaryl structures has been also observed by Caglioti *et al.* (33). They described the formation of 1-phenylazo-cyclohexene-(1) 11 from 2-acetoxycyclohexanone phenylhydrazone by treating this 11 with lithium-hydride in benzene and the 1.4-addition of phenylhydrazine to the alkene-azoaryl system discussed later.

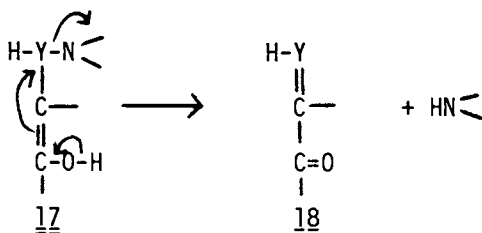


Reactions of Hydrazones in Dilute Acid Solutions. The elimination of aniline is an important reaction of α -hydroxyaldehydes in acetic acid-methanol as can be seen from Table I.

Table I Aniline Elimination from Phenylhydrazones and Formation of Bis(phenylhydrazones) During 6 h Heating in $\text{CH}_3\text{OH-CH}_3\text{COOH}$ (1:1) at 40°

Starting Material	Aniline/Mole	Bisphenylhydrazone/ Mole
Glycolaldehyde-phenylhydrazone	0.42	0.23
Glucosephenylhydrazone	0.23	0.07
Mannosephenylhydrazone	0.18	0.03
2-Deoxy-2-phenylhydrazino-glycolaldehyde phenylhydrazone	0.63	0.44

Besides aniline, bis(phenylhydrazones) are formed. However, there is no stoichiometric relationship between aniline and osazone formation. This aniline elimination is comparable to the amine elimination which occurs during the formation of nitrogen containing reductones from N-glycosides (34,35).



When $Y = N$ we have an amine elimination from the 1-amino-3-hydroxy-azaallyl system and when $Y = CH$ we observe the amine elimination from the 1-amino-3-hydroxy-allyl system. Erythrose reacts with an amine such as *N*-methyl-benzylamine to give the *N*-containing reductone 23 in 45 % yield (Figure 4). [^{14}C]Erythrose forms this reductone with 97 % of the carbon-14 in the methyl group and 3 % in the amino methylene group (34). A reasonable explanation of this would be that the Schiff base rearranges to the Amadori product 20 which enolizes to 21. This can eliminate in two directions. If the amine is eliminated C-1 of the erythrose becomes the methyl group in 22. If the OH-group is eliminated C-4 of the erythrose becomes the methyl group in 24. The ratio is about 30 : 1 in favor of the amine elimination. The fast elimination of a structure such as 21 with $Y = N$ can also be seen from the fact that [$3\text{-}^3\text{H}$]-1-deoxy-1-benzylamino-D-fructose does not lose ^3H even when 50 % of the starting material has reacted via amine elimination (34). That means that the step corresponding to $\text{20} \rightarrow \text{21}$ is irreversible since it is followed by a fast elimination.

Another important reaction is the formation of alkene-azoaryl systems such as 5 which can lead to addition products. Heating hydrazone 9b with 0.02 *n* hydrochloric acid in methanol for a few minutes leads quantitatively to phenylhydrazone 10a as shown in Figure 2 (30). Very probably 11 is the intermediate since 10a is formed from 11 about three times faster than from 9b under identical conditions. We studied this phenomenon with several model compounds (36-38) but also with carbohydrate derivatives (19,39). The isomerization $\text{9b} \rightarrow \text{12a}$ occurs in acid as well as in basic solutions. In acidic and basic media a competition exists also between the addition of nucleophiles of the type HX and the isomerization to a Δ^2 -enphenyl-hydrazone such as 12a. In acidic media the isomerization $\text{9b} \rightarrow \text{12a}$ with different substituents Y in the para position of the phenylhydrazine residue shows a strong dependence on Y . The reaction rate constants ($\text{sec}^{-1} \times 10^{-5}$) for the conversion $\text{11} \rightarrow \text{12a}$ are shown for different Y groups in Figure 2. In 0.55 *n* HCl tetrahydrofuran at 25° the rates are as follows (37): $-\text{NO}_2 = 1.7$; $-\text{CO}_2\text{C}_2\text{H}_5 = 22$; $\text{H} = 507$; $\text{CH}_3 = 1810$; $\text{OCH}_3 = 2860$. The latter value was calculated by using the Hammett equation. In acidic media the group Y has only little influence on the rate of addition of compounds such as methanol. Besides alcohols the alkene-azoaryl system adds sodium

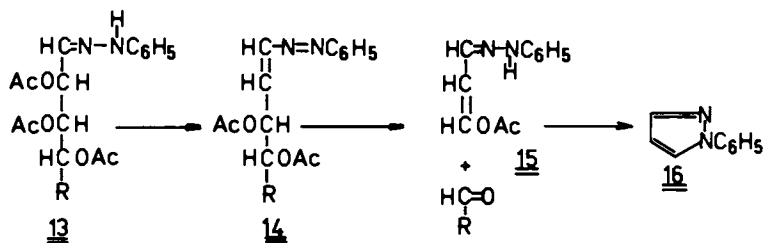


Figure 3

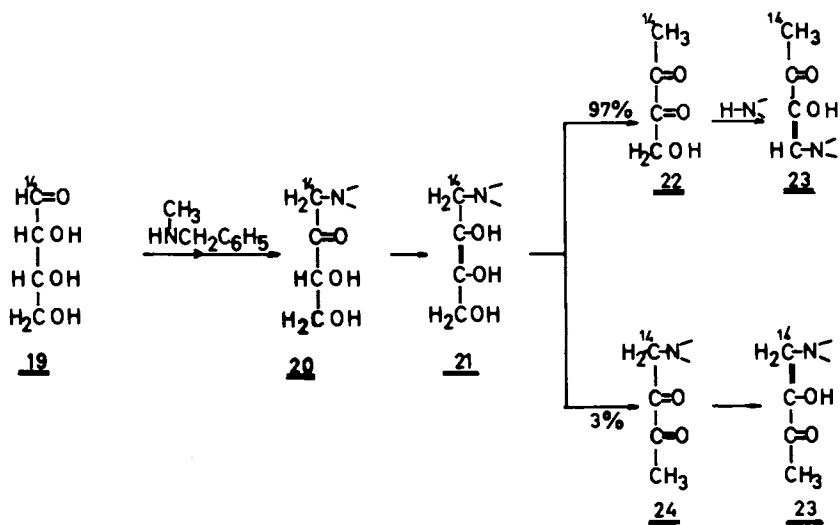


Figure 4

hydrogen sulfite, acetic acid and compounds with activated C-H bonds. Examples are diethyl malonate, malonodinitril, 2-acetamino-diethyl malonate, ethyl cyanoacetate etc. (38). Overend *et al.* (40-42) have used arylazo-glycosides for preparative work in the carbohydrate field taking advantage of the 1,4-additions that occurred in a highly stereoselective fashion. We found that 1-phenylazo-3,4,5,6-tetra-O-acetyl-D-arabino-transhexene-(1) adds methanol, acetic acid or 2,4-dinitrothiophenol. Only in the latter case was it possible to isolate the expected glucose and mannose derivative (39).

Phenylosazones

Some of the reactions which are observed with the phenylhydrazones of sugars occur also with the bis(phenylhydrazones). However, the presence of two phenylhydrazone groups in the latter compounds causes osazones to behave differently from hydrazones in most of their reactions.

Reactions of Bis(hydrazones) in Dilute Alkaline Solution. In slightly alkaline media the hydrogen atoms bound to carbon exchange with protons of the medium to varying degrees (Figure 5) (29). In the case of glucose phenylosazone this exchange occurs mainly at C-1 and to a small extent at C-3 as can be seen in Table II.

Table II Hydrogen Exchange^{a)} of Osazones (29).

Substance	30 min.	60 min.	90 min.
Glucose phenylosazone	45.0 ^{b)}	51.8 ^{b)}	60.4 ^{b)}
2-Phenyl-1,2,3-triazole-(4)-carboxylic acid ^{c)}	41.0	48.4	55.5
Glyoxal bis(phenylhydrazone)	-	-	56.7 ^{d)}
Methylglyoxal bis(phenylhydrazone)	-	-	28.0
Glucose methylphenylosazone	-	-	1.0
Glyoxal bis(methylphenylhydrazone)	-	-	1.0

a) Conditions: 0.1 m KOH in ethanol, 80° under nitrogen. The molar radioactivity of C₂H₅O³H corresponds to 100 %.

b) Measured in form of the phenylosotriazole.

c) Obtained from the phenylosotriazole by periodate treatment. The difference of the molar specific radioactivity of phenylosotriazole and 2-phenyl-1,2,3-triazole-(4)-carboxylic acid

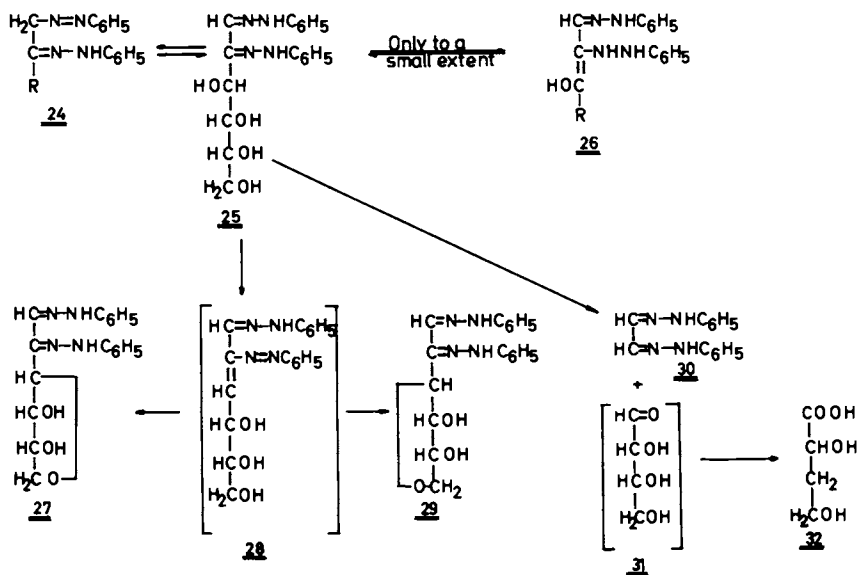


Figure 5

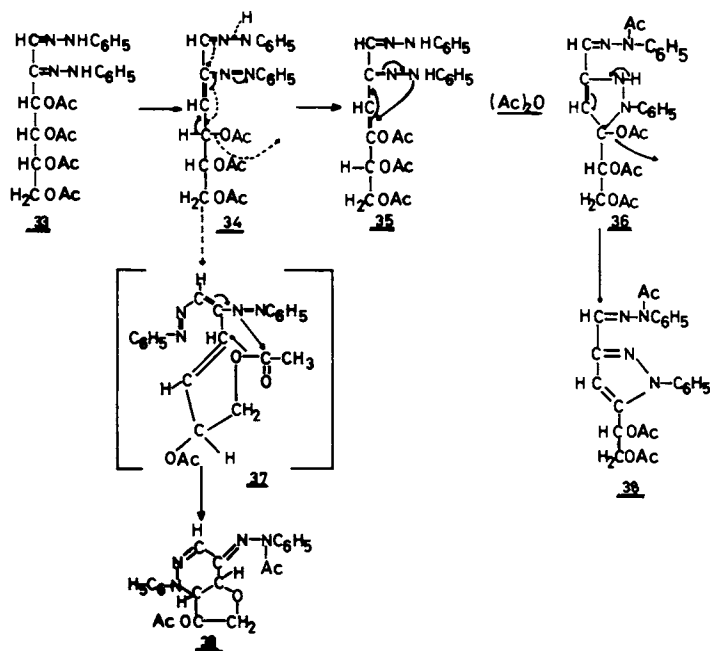


Figure 6

gives the tritium content at C-3 of the glucose phenylosazone.

- d) In order to compare this value with the other compounds it has to be divided by two.

This reaction corresponds to a similar tautomerism observed with α -hydroxy-phenylhydrazones. Methylphenylosazones show no exchange since the step $1 \rightarrow 4$ and $25 \rightarrow 24$ (See Figures 1 and 5) cannot occur (29). After treatment of glucosazone in 0.1 n KOH-ethanol at 80° four products (27, 29, 30, 32) could be identified (See Figure 5). Besides glyoxal bis(phenylhydrazone) and 2,4-dihydroxybutyric acid, 3,6-anhydro-D-ribo-hexulose phenylosazone was formed with a yield of about 5%. This product was often called "Diels' anhydro-osazone" (43) until, finally it was shown to be 3,6-anhydro-D-ribo-hexulose phenylosazone by El Khadem et al. (44). The fourth product was chromatographically very similarly to 27 and was tentatively identified as 3,6-anhydro-glucosazone. The splitting of the osazones to glyoxal bis(phenylhydrazone) has already been described by Diels et al. (43). Under identical conditions the ratio of glyoxal bis(phenylhydrazone) formation from the osazones of glucose, arabinose and xylose was 6.6 : 1.0 : 1.2.

Also the formation of Percival's dianhydro-osazone 39 and the dianhydro-osazones containing pyrazole rings such as 38 can be explained by the general formulation $5 \rightarrow 8$ or $11 \rightarrow 12a$. Compound 39 was obtained by deacetylation of osazone acetates with sodium hydroxide in dilute acetone (45). The correct structure was suggested by Henseke et al. (46) and confirmed by El Kahdem et al. (47). The pyrazole derivative 38 was discovered by El Kahdem et al. (48,49) by acetylating glucosazone with acetic anhydride. We obtained the analogue of 38 from 3,4,5-tri-O-acetyl arabinose or xylose osazone by heating them with pyridine in ethanol (19). We propose for their formation the mechanism shown in Figure 6. Like the key intermediates 5 or 8, the dianhydro-osazones are formed in acid as well as in basic solution. They are formed because the O-acetyl group is a good leaving group and will readily lead to an alkene-azophenyl system.

Reactions of Osazones in Acidic Solution. In contrast to the bis(phenylhydrazones) derived from α -hydroxy-carbonyl compounds such as glycolaldehyde or 2-hydroxycyclohexanone, the bis(phenylhydrazones) of sugars are not end products under the conditions of their formation. Furthermore several side reactions occur during their formation. The relative rates of the different side reactions and of the consecutive reactions after the osazones are formed depend heavily on such conditions as acid concentration, solvent, the presence of aromatic amines, the temperature and to a great extent on the hydrazine derivative used. Examples of such reactions are given in Figure 7 and 8 as well as in Table II. The latter gives also some information about the question why alkylphenylhydrazines, and not phenylhydrazines react with carbohydrates to give polyhydrazones. Mesoxalaldehyde-1,3-bis(phenyl-

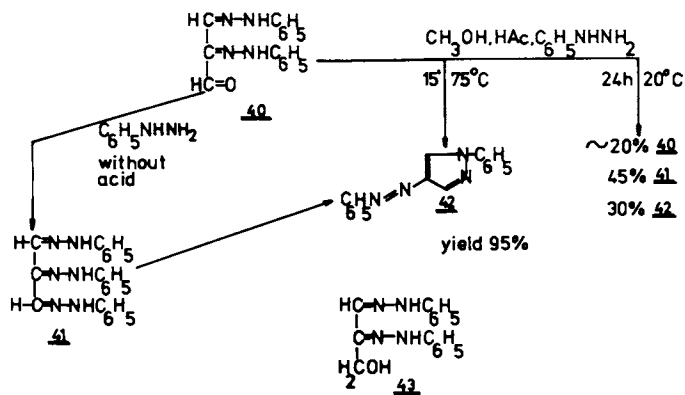


Figure 7

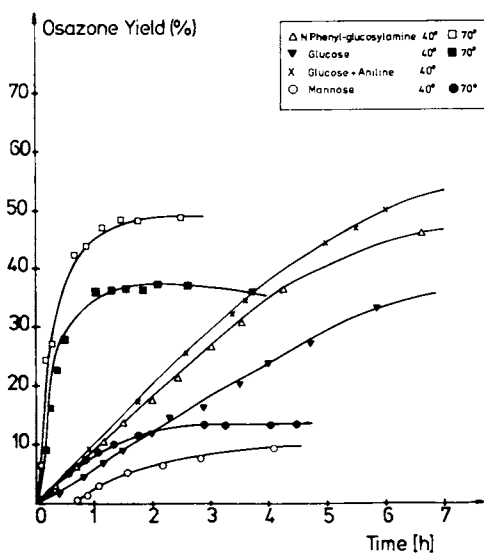


Figure 8. Rate and yield of osazone formation under different conditions

hydrazone) 40 could be used to form a tris(phenylhydrazone) of a triose (43). However, bis(hydrazone) 40 reacts at elevated temperatures under conditions of osazone formation very fast to give the pyrazole 42 (50). After 24 h at 20° the tris(phenylhydrazone) 41 is obtained from 40 together with 30 % of the pyrazole 42. On the other hand under these conditions the unchanged triose osazone (43) is still present to the extent of 30 % even after 32 days reaction. It takes 120 h at 50° in methanol/acetic acid for the triose osazone 43 to disappear completely. During this time 0.9 mole of aniline is formed per mole osazone. That means that the consecutive reactions leading from 40 or 41 to other products are much faster than the formation of 40 or 41. On the other hand dihydroxy acetone reacts rapidly with methylphenylhydrazine at room temperature according to Chapman et al. (8,9) to give the tris(methylphenylhydrazone) an analogue of 41.

Under the conditions of their formation (methanol or ethanol as solvent, acetic acid and phenylhydrazine) phenylosazones of sugars may undergo at least four different consecutive reactions (50). These are shown in Figure 9.

a) In the case of tetrose or pentose osazones via the elimination 44 → 45 the solvent alcohol may be added to 45 to give products corresponding to 46 and 47. However, hexose osazones perform an intramolecular addition reaction to anhydro-osazones 27 + 29.

b) The carbon chain may undergo a dealdolization between C-3 and C-4 to give 48 and 49 (44 → 48 + 49) or

c) a splitting between C-2 and C-3 (44 → 50 → 30 + 49) could occur and give glyoxal bis(phenylhydrazone) (30).

d) Aniline is eliminated (44 → 51 → 52).

Only reaction d leads to an intermediate which would be able to react further with phenylhydrazine to give a tris(phenylhydrazone) and reactions a and c should not be possible with bis(methylphenylhydrazones).

Addition of alcohols to the intermediate alkene-azoaryl compound 45 is very probable because [3-³H]phenylglucosazone is converted to 27 and 29 without any loss of tritium. That means that enolizations between C-2 and C-3 can be excluded (19). This mechanism explains also the observation of Diels et al. (43) that alkylphenylosazones of glucose can not be converted to anhydro-osazones. The anhydro-osazones 27 and 29 are obtained from glucose phenylosazone in a ratio 3 : 2. This ratio corresponds to the thermodynamic equilibrium. Under the conditions of its formation pure 27 is converted again to a 3 : 2 mixture of 27 and 29. This result contradicts the rule that in anhydro-osazones the carbon atom in position three always seeks to acquire the configuration of the subsequent carbon not involved in ring formation (51). Consequently starting with 8 hexose phenylosazones there could be 8 anhydro-osazones of the Diels type and not only 4 as predicted (51). In the case of pentose-phenylosazones, 46a and 47a

are formed. Heating D-arabinosephenylosazone in a solution of ethanol or isopropanol with a trace of sulfuric acid leads to mixtures corresponding to 46a and 47a with a yield of about 80 %. The mixtures can be separated by thin layer or column chromatography. These products are identical with those erroneously described by Diels et al (43) as anhydro-osazones containing crystal alcohol. If also these compounds are formed via an elimination-addition mechanism one could expect again a reversible conversion from 46a to 47a under the conditions of their formation. That is the case. The configuration of 46a was determined by preparing its osotriazole and comparing the fully O-methylated product with that of the osotriazole of D-arabinose phenylosazone after O-methylation (19). Unlike the anhydro-osazone formation which yields two isomers with glucose phenylosazone we could detect only one dehydroosazone. This product was first described by Diels et al. (52) who obtained it by oxidation of glucosazone in alkaline solution with air. According to Mester (4, 53) it is a dehydro-allose osazone 57. We have evidence that alkene-azophenyl intermediates play an important role in its formation and transformations (19,39). We were interested to see how the inversion at C-3 occurs. We found that [3-³H]glucose phenylosazone lost no tritium during its conversion to 57 (19). This means that no enolization took place during the inversion of the configuration at C-3. Therefore, we suggest again an elimination-addition mechanism via a bis(phenylhydrazone) of structure 53 which would give an alkene-azophenyl intermediate 55 which is converted to 56. The latter is in equilibrium with 57 (Figure 10). If this is correct it should be possible to get other elimination-addition products as well. We could show that heating of 57 in 0.03 n H₂SO₄/methanol leads to an O-methyl-product which probably is best described by structure 58. Chromatographic runs in 7 different solvent systems always showed only one reaction product.

We measured CD spectra from 18 different phenylhydrazones, phenylosazones and their derivatives which were obtained during these studies. In every case the sign of the Cotton effect depended upon the configuration of that carbon atom which follows the chromophore (19). Mester et al. (51) observed a positive Cotton effect in the region of 230-300 nm or 340 nm for osazones and osotriazoles respectively in those derivatives having the OH-group or the linkage to a cyclic ether on the right in the Fischer projection. This rule can now be expanded to 3-O methyl-derivatives of phenylosazones and osotriazoles.

The Key Reaction of the Osazone Formation and the Differences Between Phenylhydrazine and Methylphenylhydrazine.

Phenylhydrazones of α -hydroxy carbonyl compounds eliminate aniline under conditions of osazone formation at a rate comparable with that observed during osazone formation (35). Therefore, it is reasonable to assume that the elimination (1 \rightarrow 6 \rightarrow 7) is

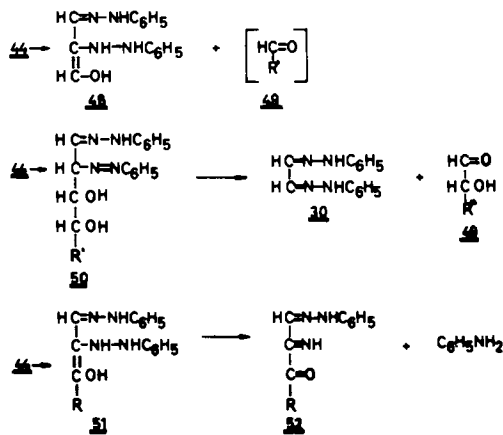
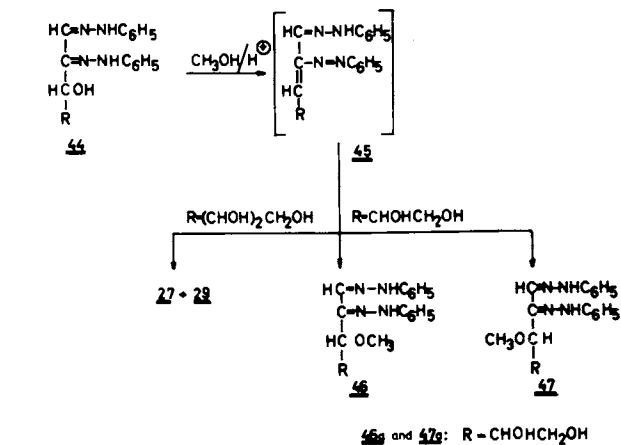


Figure 9

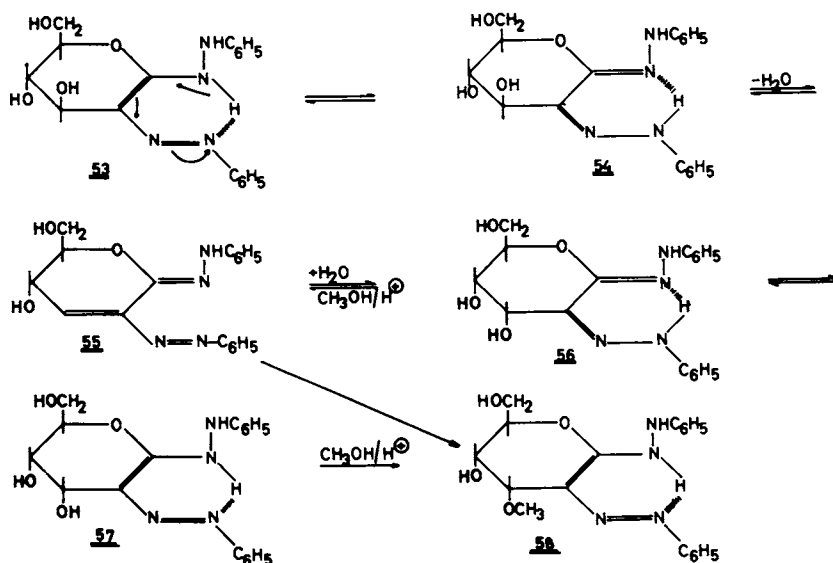
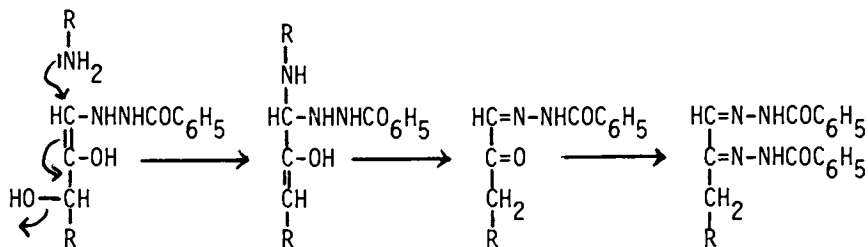


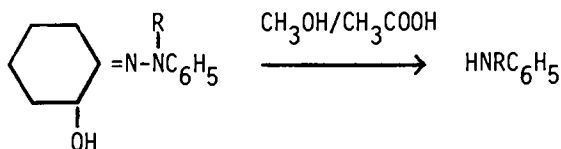
Figure 10

usually the key reaction in osazone formation. Unlike other suggested mechanisms, this elimination reaction can be proved and measured. The formation of an intermediate $\underline{6}$ with a side equilibrium to $\underline{6a}$ can be made detected by the incorporating hydrogen isotopes from the medium when the osazone formation is conducted in labeled water/alcohol (54). But since $\underline{6a}$ is the product of a side equilibrium the amount of proton exchange at C-1 of glucose during osazone formation varies widely with the conditions (55). Hydrogen exchange via $\underline{1} \rightleftharpoons \underline{4}$ cannot be excluded, but it should be rather low in solutions with weak acids. In special cases another elimination may occur. Osazone formation of 2-methoxycyclohexanone runs slower than that of 2-hydroxycyclohexanone. Presumably an elimination $\underline{10} \rightarrow \underline{11}$ takes place followed by addition of phenylhydrazine according to Caglioti et al. (33). This addition product can then eliminate aniline. Another elimination takes place during the formation of 3-deoxy-bis-(benzoylhydrazones) in the presence of p-toluidine. This reaction was described by El Khadem et al. (56). In this special case two moles of benzoylhydrazine should be sufficient to transform the sugar to the osazone according to the following mechanism:



In any case one should no longer talk about oxidation with respect to osazone formation, since there is no oxidising agent.

What is now the difference between phenylosazones and methylphenylosazones? The main difference is not the stability of the former due to chelation. There are two other significant differences: 1) As shown above there are at least two consecutive reactions which can prevent osazone formation from continuing and involving the third and subsequent carbon atoms. 2) The N-N bond of a α -hydroxymethylphenylhydrazone is broken much faster than that of a α -hydroxyphenylhydrazone and the same is true for the two different kinds of osazones. We studied aniline and N-methyl aniline elimination from the corresponding hydrazones of α -hydroxycyclohexanone.



In the case of $R = CH_3$ the amine elimination was about 100 times faster than with $R = H$. A factor of about 10 was found for the elimination of N-methylaniline compared to that of aniline from glucose methylphenylosazone and glucose phenylosazone (57).

Many details of the osazone formation remain unexplained. For instance, what are the reasons for the significant differences in the rate of osazone formation from glucose and mannose? Figure 8 shows this and other observations which cannot be readily interpreted. We find that the rate of osazone formation from glucose at 40° is at least one order of magnitude higher than that of mannose. Glucosazone formation conducted at 70° stops after about 1 h with a yield of about 35 %. There is no doubt that there is no glucose left at this point. The reaction at 40° continues even after 6 h and the yield surpasses that obtained in the reaction conducted at 70°. The importance of steric details can be seen from our studies with (1R)[1-³H]D-fructose and (1S)[1-³H]D-fructose (58). The enantiotopically labeled fructoses were converted into the phenylosazones under a variety of conditions. The ratio of the radioactivities in the osazones produced from the two forms was always about 3:2. That means the pro R and pro S hydrogen atom at C-1 of the fructose are different in this reaction. This discrimination between the two hydrogen atoms can be best interpreted if either a furanose or a pyranose derivative of the phenylhydrazone is first formed and that this undergoes elimination. Furthermore, a primary kinetic isotope effect has been observed proving that the C-H bond splitting is rate determining.

Acknowledgment

We thank Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie for the financial support of this work and the N.S.F. for stipend to cover travel expenses.

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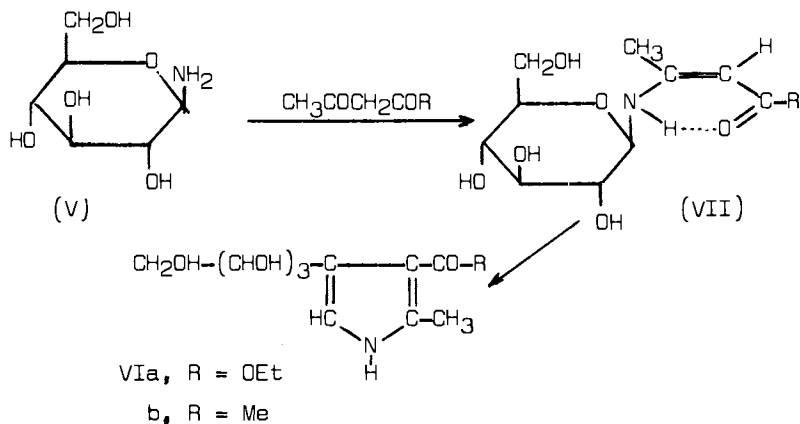
compound the radicals introduced in the furan where as follows: $R_1 = H, n\text{-Bu}, \text{CH}_2\text{COOEt}, \text{CH}_2\text{C}_6\text{H}_5, p\text{-CH}_3\text{C}_6\text{H}_4, p\text{-CH}_3\text{OC}_6\text{H}_4$ or $p\text{-C}_2\text{H}_5\text{OC}_6\text{H}_4$; $R_2 = \text{Me}, H$ or CH_2COOEt and $R_3 = \text{OEt}, \text{SEt}, \text{C}_6\text{H}_5$ or Me (26, 28, 36, 39).

More recently the synthesis of polyhydroxyalkyl pyrroles has been extended to trihydroxypropyl and pentahydroxypentyl pyrroles. The 2-methyl-3-ethoxycarbonyl-5-(D-erythrotrihydroxypropyl)pyrrole (III, $R_1 = H, R_2 = \text{Me}, R_3 = \text{OEt}, n = 2$) has been prepared by reacting the epimeric pair of 2-amino-2-deoxy-D-arabinose and 2-amino-2-deoxy-D-ribose with ethyl acetoacetate (40).

The 1-benzyl-2-methyl-3-ethoxycarbonyl-4-L-erythrotrihydroxypropyl and the 1-n-propyl(1-n-butyl, 1-benzyl)-2-methyl-3-ethoxycarbonyl-4-D-threotrihydroxypropylpyrroles have been obtained by reacting the corresponding 1-alkylamino-1-deoxypentuloses with ethyl acetoacetate (40). The 2-methyl-3-ethoxycarbonyl-5-D-galacto(D-gluco, D-manno)-pentahydroxypentyl-pyrroles are obtained by reacting the 2-amino-2-deoxy-D-glycero-L-manno-heptose, 2-amino-2-deoxy-D-glycero-D-gulo-heptose or 2-amino-2-deoxy-D-glycero-D-talo-heptose with ethyl acetoacetate (41).

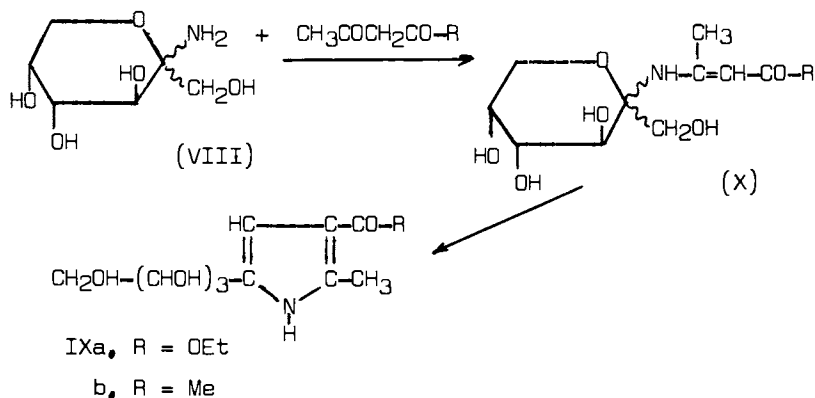
The structure of all these polyhydroxyalkyl pyrroles have been established by oxidative degradation with sodium metaperiodate and oxidation of the corresponding pyrrole aldehydes, as well as by polarimetry and UV and IR spectroscopy.

Polyhydroxyalkylpyrroles have been also obtained by reaction of glycosylamines with β -dicarbonyl compounds. Thus β -D-Glucopyranosylamine (V), N-n-butyl-D-glucosylamine and several N-aryl-D-glucosylamines were found to react with ethyl acetoacetate and 2,4-pentanedione in methanol containing catalytic amounts of piperidine giving ethyl 2-methyl-4-(D-arabinotetrahydroxybutyl) pyrrole-3-carboxylate (VIa), 3-acetyl-2-methyl-4-(D-arabinotetrahydroxybutyl) pyrrole (VIb) and N-substituted pyrroles (27 36).



In a similar way, D-fructosylamine (VIII), N-ethyl-D-fructosylamine and N-benzyl-D-fructosylamine reacted with ethyl acetoace-

tate and 2,4-pentanedione giving ethyl 2-methyl-5-(D-arabinotetrahydroxybutyl)pyrrole-3-carboxylate (IXa), 3-acetyl-2-methyl-5-(D-arabinotetrahydroxybutyl)pyrrole (IXb) and the corresponding N-substituted pyrroles (27,36).



The yields of pyrrole compounds produced in these reactions was found to depend on the glycosylamine used, and varied from 3-5% for D-glucosylamine and its N-alkyl derivatives, to 10-30% for the N-alkyl-D-fructosylamines. The yields reflect the ability of the glycosylamines to undergo the Amadori rearrangement (20) and support the prediction (27) that an Amadori rearrangement is involved in these reactions. When the reaction of glycosylamines with β -dicarbonyl compounds is carried out under milder conditions the N-glycosyl derivatives of β -amino- α,β -unsaturated esters or ketones (VII) may be isolated. Ethyl 3-(β -glycopyranosylamino)crotonates have been obtained (42) by allowing the glycosylamines of the common aldohexoses (D-glucose, D-galactose, D-mannose and L-rhamnose) to react with ethyl acetoacetate for several days.

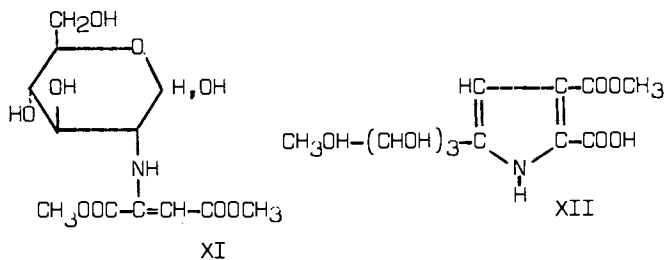
The structure of these compounds was determined by chemical and spectroscopic (UV, IR and PMR) methods. The amino and ethoxycarbonyl groups of the enamine portion were found to be in *cis* configuration and intramolecularly bonded. The pyranose ring sizes and anomeric configuration (β -L for the rhamnose derivative and β -D for the remaining compounds) were assigned for the D-acetyl derivatives on the basis of the chemical shifts and the observed coupling constants. The same pyranose structures and anomeric configurations have been proposed for the parent compounds after considering the chemical shifts and coupling constants of the anomeric protons (42,43).

Other intermediate products of the reaction of glycosylamines with β -dicarbonyl compounds are the N-glycosyl derivatives of β -amino- α,β -unsaturated ketones obtained by reaction of aldo-

sylamines with 2,4-pentanedione, 1-phenyl-1,3-butanedione and benzoylacetaldehyde (45).

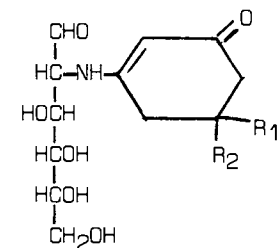
The reaction of ketohexosylamines with ethyl acetoacetate and 2,4-pentanedione proceeds (42,44) readily to yield the corresponding 5-tetrahydroxybutylpyrroles instead of the *N*-ketohexosyl derivatives of type X.

In the reaction of 2-amino-2-deoxy-D-glucose with 2,4-pentanedione an intermediate, 2-deoxy-2-[2-(4-oxo-2-pentenyl)amino]-D-glucose has been isolated (32). The yield was high when the reaction was performed in anhydro basic media. This enamine cyclized readily into the 5-arabinotetrahydroxybutylpyrrole when it was kept in aqueous solution at room temperature for several days. The 2-amino-2-deoxy-D-glucose also reacted (34) with benzoylacetaldehyde and 1-phenyl-1,3-butanedione in methanol in the presence of triethylamine yielding 2-deoxy-2-[1-(3-oxo-3-phenyl-1-propenyl)amino]-D-glucose and 2-deoxy-2-[1-methyl-1(3-oxo-3-phenyl-1-propenyl)amino]-D-glucose. The former compound could be obtained in high yield by merely treating an aqueous solution of the amino sugar with benzoylacetaldehyde at room temperature. The structure of these compounds has been established by studying their chemical and spectroscopic properties (45). Heating of these enamines in aqueous ethanol, or a mixture of triethylamine and methanol, resulted in cyclisation to the tetrahydroxybutylpyrroles (45). Another enamine, 2-deoxy-2-[(1,2-dimethoxycarbonylvinyl)amino]-D-glucose (XI) has been obtained (46) in almost quantitative yield by reaction of 2-amino-2-deoxy-β-D-glucopyranose with the dimethyl acetylenedicarboxylate. Heating the adduct (XI) with water, or slightly basic solution, afforded 3-methoxycarbonyl-5-(D-arabinotetrahydroxybutyl)-2-pyrrole carboxylic acid (XII).

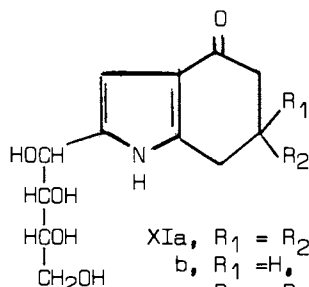


Polyhydroxyalkyl-1,5,6,7-tetrahydroindol-4-ones.

The reaction of amino-sugars with β-dicarbonyl compounds has also extended to cyclohexane-1,3-diones (47,48). The primary products of the reaction of 2-amino-2-deoxy-β-D-glucopyranose with cyclohexane-1,3-diones in aqueous solution at room temperature are enamine (XIII), which cyclize spontaneously to give 1,5,6,7-tetrahydro-2-(D-arabino-tetrahydroxybutyl)indol-4-ones (XIV). Both products are obtained as mixtures that can be separated by fractional crystallization or by chromatography on a cellulose column (yields 25-40%).

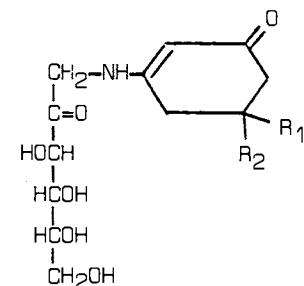


XIIIa, $R_1 = R_2 = H$
 b, $R_1 = H, R_2 = Me$

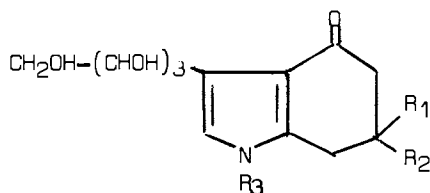


XIa, $R_1 = R_2 = H$
 b, $R_1 = H, R_2 = Me$
 c, $R_1 = R_2 = Me$

Similarly, the 1-amino-1-deoxy-D-fructose reacts (48) with cyclohexane-1,3-diones to give enamines XV and tetrahydroxybutyl-tetrahydroindolones XVI. Ketose enamines XV are more stable than the isomeric aldose derivatives XIII and are obtained in higher yields (ca. 70%). In addition, enamines XIIIa and XVa are more stable than their homologous compounds XIIIb and XVb. Apparently the introduction of a methyl group into the enamine system increases the susceptibility to cyclization. The failure to obtain enamines similar to XIII and XV derived from dimedone may be attributed to this fact. Also, the reaction of 1-benzylamino-1-deoxy-D-fructose with cyclohexane-1,3-dione gave only compound XVIc, and no intermediate could be isolated or detected chromatographically.



XVa, $R_1 = R_2 = H$
 b, $R_1 = H, R_2 = Me$



XVIa, $R_1 = R_2 = R_3 = H$
 b, $R_1 = R_3 = H, R_2 = Me$
 c, $R_1 = R_2 = Me, R_3 = H$
 d, $R_1 = R_2 = H, R_3 = CH_2Ph$

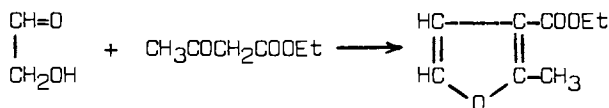
Enamines XIII and XV cyclize to tetrahydroxybutylindol-4-ones XIV and XVI in high yields by heating in water. In the case of the 2-amino-2-deoxy-D-glucose derivative small amounts (ca. 9%) of 1,5,6,7-tetrahydroindol-4-ones which lacked the polyol chain were also obtained at a neutral pH. If the reaction was performed at pH 9-10 the yield of these secondary products increased up to 30%. The other enamines XV cyclized without losing the tetrahydroxybutyl chain. All structures have been established by degradative oxidations and UV, IR and NMR spectroscopy.

Reaction mechanisms:

During the reaction of β -dicarbonyl compounds with aldoses and with 2-amino-(2-alkylamino or 2-arylamino)-2-deoxyaldoses two molecules of water are eliminated and a heteroaromatic pentacycle, furan or pyrrole, is formed. Although this analogy may lead one to suggest a similar reaction mechanism for both reactions, it must be kept in mind that replacing an amino group by a hydroxyl group may produce enough change in reactivity to lead to a different reaction route. In agreement with this is the fact that in the case of 2-amino-(or 2-alkylamino)-2-deoxyaldoses, it has been possible to isolate the intermediate 2-enamines, which can be transformed into the polyhydroxyalkyl-pyrroles (45,46), but in the case of aldose derivatives no similar intermediates have been detected.

The formation of polyhydroxyalkylfurans. No systematic investigation of reaction mechanism has been carried out for the condensation of aldoses and β -dicarbonyl compounds. One difficulty is the deep structural change that is involved in the reaction which affects a multitude of bonds. This suggests that the reaction does not proceed by a concerted process and that several reaction intermediates are formed which have not been detected at present. The complexity of the problem can be seen if we realize that the two reactants can exist in several interconvertible forms. Thus the sugar may exist in aldehydic (even solvated), anomeric and enediolic forms, and the dicarbonyl compound in the keto- and enol-forms. The participation of enediolic forms can certainly be discarded since the reaction of D-glucose with β -dicarbonyl compounds yields 5-polyhydroxyalkylfurans I while D-fructose yields the isomer with the polyhydroxyalkylated substituent in position-4, II, XVII (17).

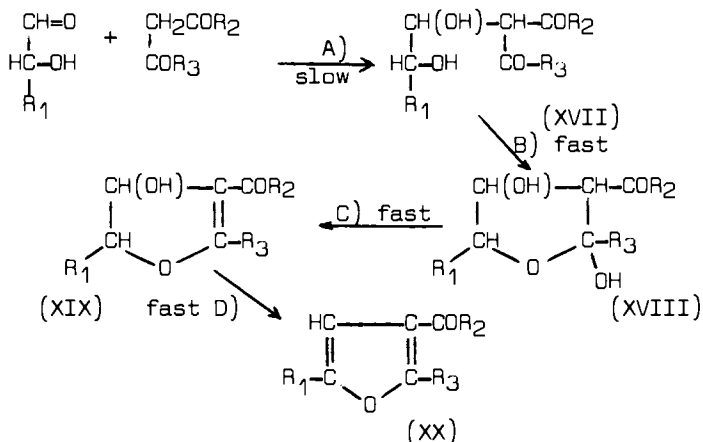
The reaction is possible, not only with aldohexoses and aldopentoses, which can exist as pyranoses or furanoses, but also with D-glyceraldehyde in which the hemiacetal forms are less stable (15). In addition, the reaction has been carried out with simple α -hydroxyaldehydes or α -hydroxyketones (15)(17).



In the case of hydroxyketones the participation of a cyclic form is not very probable owing to the higher stability of the ketonic carbonyl group.

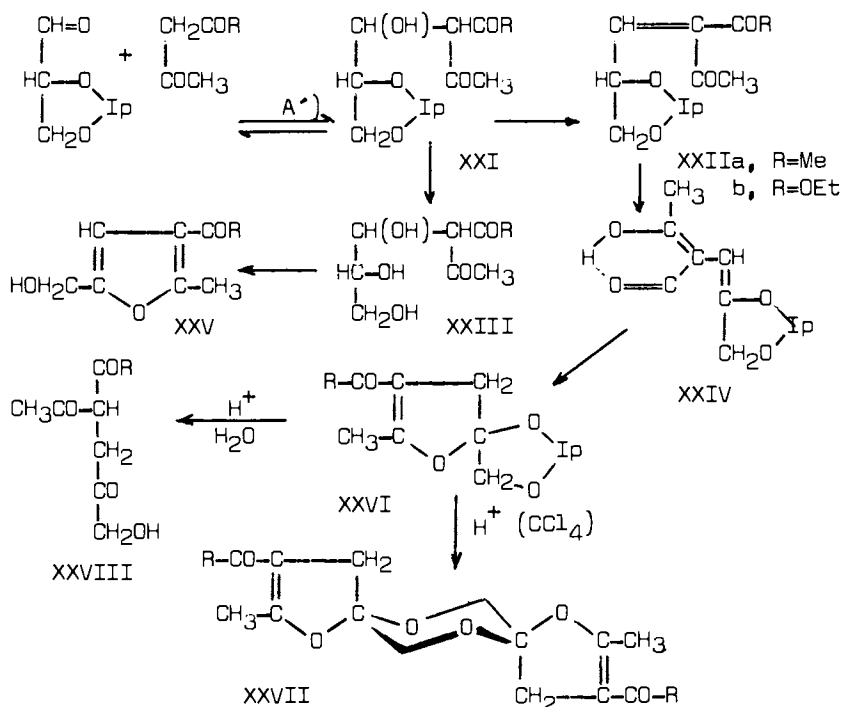
It is therefore reasonable to suppose that the free aldehydic form of the aldose is taking part in the reaction. It may be supposed that this form, in the presence of an active methylene

group, can undergo an aldolic type addition as the first step A) in the reaction:



Step A) is similar to other nucleophilic attacks on the carbonyl form of monosaccharides and resembles closely the first step in Knoevenagel type reactions of aldehydes with active methylene groups. It is probably reversible and slower than the subsequent steps: B) formation of the hemiacetal; C): formation of the conjugated system $\text{O}-\text{C}=\text{C}-\text{C}=\text{O}$, and D): aromatization. None the intermedias in this hypothetical scheme has been detected. Nevertheless, a similar reaction with a previous blocked hydroxyl in C-2 has been studied (49), to eliminate step B and subsequent steps. O-Isopropylidene-D-glyceraldehyde was reacted with ethyl acetoacetate (or with 2,4-pentanedione) yielding the unsaturated products XXIIa and XXIIb. With ethyl acetoacetate the aldol type product XXI could be isolated, which corresponds to intermediate XVII in the reaction of the unprotected D-Glyceraldehyde.

When the protecting group was removed in XXI by acid hydrolysis, the furan derivative XXV was readily formed. This result demonstrates the great tendency of the aldol type product XXIII to cyclize to a furan by a double dehydration. The hydrolysis of the isopropylidene group appears to be much slower than the cyclation. The gradual fading of the PMR signals corresponding to product XXI can be observed (50) at the time, several new signals appear belonging to acetone and to the furan compound XXV. No other signals were observed that could be ascribed to the hypothetical intermedia XVIII and XIX. When the hydrolysis was carried out in the presence of periodate ions two molecules of oxidant were consumed and one mole of formic acid was formed, as expected from an intermediate such as XXIII (50). The addition A' without the use of any catalyst can be observed by PMR. It appears to be a reversible process. In our early experiments (49) we found that on acid hydrolysis compound XXII do not give furan derivatives.



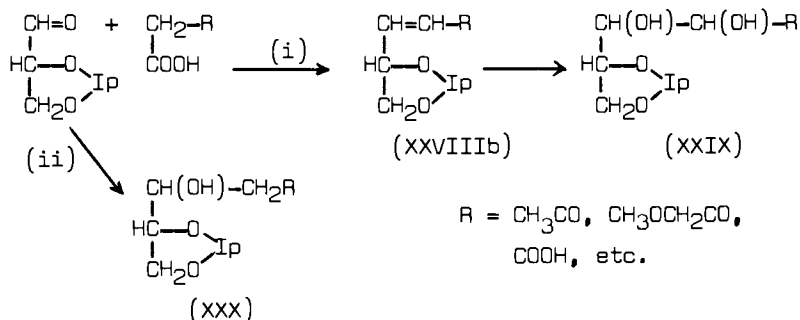
However by using PMR technique it is possible to observe that structures XXII are sensitive to acids in the absence of water (51). The α , β -double bond migrates to the β , δ -position at the same time that optical activity disappears and the enol XXIV can be observed. In acidic conditions XXIV readily cyclizes to give the spiro dihydrofuran XXVI, without losing its isopropylidene group. With longer reaction time or with stronger acids, such as trifluoroacetic, the dioxolane group is broken producing the dioxan derivative XXVII which seems to be very stable (50, 51).

By removing the isopropylidene group in aqueous media the tricarbonyl compound XXVIII is formed (50). The structure of this last type of compound has been proved in the case of $\text{R} = \text{OMe}$, by degradation to levulinic acid by periodic oxidation and hydrolysis.

Aldol type addition and Knoevenagel condensation. The use of aldehyde-sugar derivatives and β -dicarbonyl compounds to carry out addition and Knoevenagel type condensation has been investigated by several investigators. As mentioned above, Knoevenagel type compounds have been isolated with O -isopropylidene- D -glyceraldehyde and aldehyde sugars (49, 50, 52, 53). Di- O -isopropylidene-pentoses have been also used.

When a free carboxyl group is present in the methylene active compound the reaction can take the form of a Varley-Doebner pro-

cess (i) or even that of a single decarboxylation without elimination of water (ii) as in the following example:



The trans isomers of the unsaturated compounds XXVIII are generally isolated. Only in the case R = CN both, the cis and trans isomers separated.

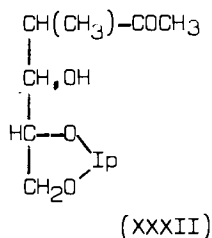
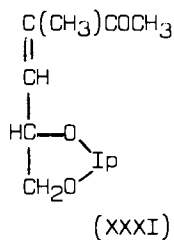
The unsaturated derivatives type XXVIII can be hydroxylated by OsO₄ to XXIX. If the R group is a carboxyl group (obtained by using malonic acid) its reduction by H₄BNA allows the synthesis of aldoses (55). Similarly, the hydroxylation in a compound of type XXIX having R = COCH₃, can be used to synthesise 5,6-Q-isopropylidene-1-deoxy-D-fructose and 5,6-Q-isopropylidene-1-deoxy-D-sorbose.

A similar set of reactions has been performed with trans-5,6-Q-isopropylidene-1-methyl-3,4-dideoxy-D-glycerohex-3-enulose (XXVIIIb, R = CH₃OCH₂CO) obtained from Q-isopropylidene-D-glyceraldehyde and γ -methoxy-acetoacetic acid. 1-Methoxy-D-fructose and 1-methoxy-D-sorbose were prepared, as well as their corresponding 5,6-Q-isopropylidene derivatives (56).

The relative yield of reaction (i) and (ii) depends on the catalyst used. Pyridine/piperidine favors the second process more than diethylamine in toluene.

The hydroxylation of XXVIII seems to be stereoselective.

The use of α -methyl-acetoacetic acid, in a similar form, produces the two expected products XXXI and XXXII corresponding to XXVIII and XXX with a methyl group in the position 3 (57).

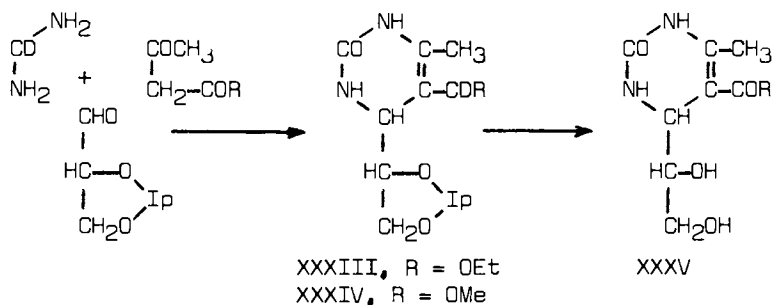


In reaction (ii) a pair of diastereomers is formed in the

case of XXX (R = CH₃OCH₂CO) these are: 5,6-O-isopropylidene-1-O-methyl-3-deoxy-D-erythrohexenulose and its isomer having the threo configuration. When R = CH₃CO only the erythro isomer was isolated. In compounds of type XXXII the stereochemistry at C-3 and C-4 of both diastereomers has not yet been studied.

Polyhydroxyalkylpyrimidines.

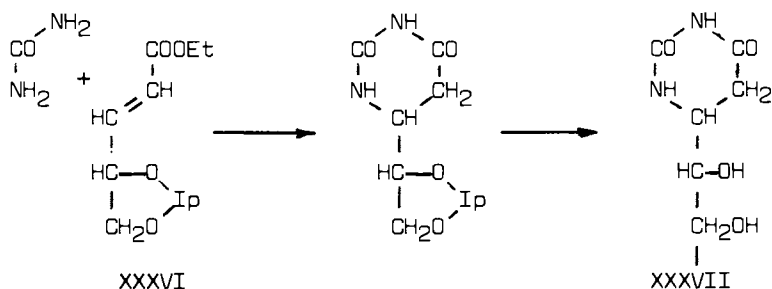
The synthesis of C-polyhydroxyalkylpyrimidine derivatives can have some value in the synthesis of pseudonucleosides. Different types of reactions have been carried out with this objective in mind, though up to the present it has been limited to a dihydroxy ethyl substituent. O-isopropylidene-D-glyceraldehyde reacts with urea and β -dicarbonyl compounds under the conditions of the Biginelli reaction. With methyl- or ethyl-acetoacetate the reaction is carried out without acid catalysis, to avoid possible hydrolysis of the isopropylidene group. The O-isopropylidene derivatives of 2-hydroxy-4-(D-1,2-dihydroxyethyl)-5-ethoxycarbonyl (or methoxycarbonyl)-6-methyl-3,4-dihydropyrimidine XXXIII or XXXIV have been isolated (50).



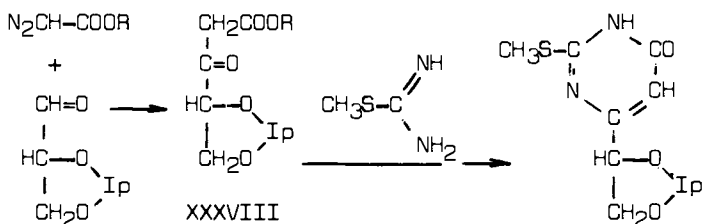
With 2,4-pentanedione it was necessary to add a few drops of concentrated hydrochloric acid as a catalyst. 2-Hydroxy-4-(D-1,2-dihydroxyethyl)-5-methyl-6-acetyl-3,4-dihydropyrimidine XXXV was isolated. The isopropylidene group having been hydrolysed in the acidic medium.

In the second type of synthesis ethyl trans-4,5-O-isopropylidene-4,5-dihydroxy-D-pent-2-enoate XXXVI, described above, and urea were used. The reaction product isolated was 4-(O-isopropylidene-D-1,2-dihydroxyethyl)-5,6-dihydro uracil. Acid hydrolysis afforded the pyrimidine derivative XXXVII with the free hydroxyls groups.

The O-isopropylidene derivative XXXVIII having a β -ketoester group and a polyhydroxyalkyl chain was obtained by the reaction of O-isopropylidene-D-glyceraldehyde with methyl diazoacetate. It forms a copper salt and its basic hydrolysis followed by decarboxylation produced O-isopropylidene-3,4-dihydroxybutan-2-one. These β -keto-ester XXXVIII has been used in the third



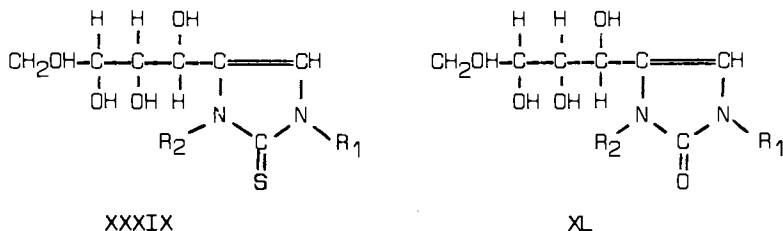
method of synthesis following the scheme: (58)



Up to the present no other investigation has been made using derivatives of higher aldoses according to this line.

Polyhydroxyalkylimidazolines and polyhydroxyalkylimidazoles.

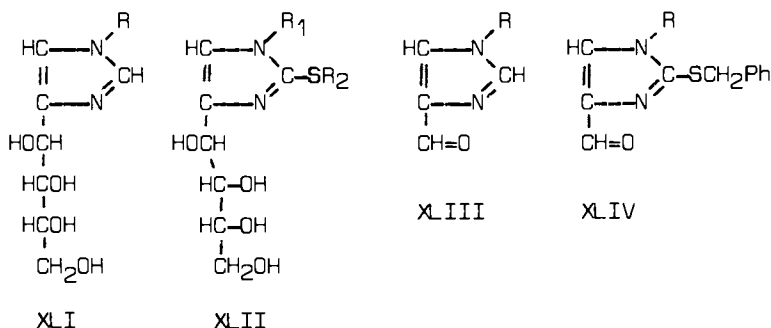
The study of polyhydroxyalkylimidazoles was initiated by Neuberg and Wolff (59) and Steudel (60), who proposed structure XXXIX ($R_1 = \text{CH}_2 - \text{CH} = \text{CH}_2$, Ph; $R_2 = \text{H}$) and XL ($R_1 = \text{Ph}$; $R_2 = \text{H}$) for the compounds obtained by reacting 2-amino-2-deoxy-D-glucose (D-glucosamine) hydrochloride with allyl (phenyl) isothiocyanates and phenylisocyanate, respectively.



Pauly and Ludwig (19) and Ishifuku (61) assigned a 2-thiol-4(5)-tetrahydroxybutylimidazole (XXXIX, $R_1 = R_2 = \text{H}$) for the condensation product of D-glucosamine hydrochloride with potassium thiocyanate. In a similar way, they proposed (19) structure XL ($R_1 = R_2 = \text{H}$) for the compound obtained by reacting this

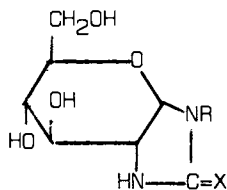
aminosugar with silver cyanate.

Later, García González, Fernández-Bolaños and coworkers undertook the study of these compounds (62). They proved structure XXXIX ($R_1 = R_2 = H$) for the condensation product of D-glucosamine hydrochloride with potassium thiocyanate. The thiol group was removed by the use of Raney nickel (63,64) giving 4(5)-D-arabino-tetrahydroxybutylimidazole (XL, $R = H$). They also protected the thiol group by alkylation with monochloroacetic acid (63) and with benzylchloride (65,66) and obtained 2-carboxymethylthio-4(5)-D-arabino-tetrahydroxybutylimidazole (XLII, $R_1 = H, R_2 = CH_2COOH$) and 2-benzylthio-4(5)-D-arabino-tetrahydroxybutylimidazole (XLII, $R_1 = H; R_2 = PhCH_2$).

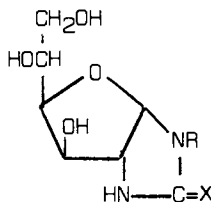


Periodate oxidation yielded the 5-formylimidazole (XLIII, $R = H$) (64) and 2-benzylthio-5-formylimidazole (XLIV, $R = H$) (66,67)

The elucidation of the structure of the condensation products of D-glucosamine with alkyl (aryl) isothiocyanates was undertaken by similar method. When the compound obtained by reacting D-glucosamine with phenylisothiocyanate was desulphurized with Raney nickel and then oxidized with periodic acid (68) the consumption of oxidant suggested that only two adjacent hydroxyl groups were present and not four, as expected for a tetrahydroxybutyl chain. This result was explained by a bicyclic pyranoimidazolidine formula (XLV, $X = S, R = \text{alkyl, aryl}$) (68-72)



XLV



XLVI

$X = O, S$

Similarly, the condensation product of D-glucosamine with phenylisocyanate was formulated (73) as 1-phenyl-4,5-(1,2-D-glucopyrano)imidazolidin-2-one (XLV, R = Ph; X = O). The synthesis of similar compounds (XLV, R = aryl, X = O, S) starting from 1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy- β -D-glucopyranose has been achieved (74). The latter was converted into the 2-aryluureido or 2-arylthioureido derivatives, and then deacetylated with ammonia in methanol and cyclized.

Later, however, a furanoid structure (XLVI, R = aryl) for the sugar moiety of these compound has been established by PMR and periodate oxidation (75) and also by oxidation with lead tetraacetate (76,77).

Recently, the structure of 1-alkyl(aryl)-4,5-(1,2-D-glucofuran)-imidazolidine-2-thiones (XLVI, R = Me, CH₂ = CH - CH₂, Ph, 4-ClC₆H₄, 4-BrC₆H₄; X = S) has been confirmed by X-ray crystallographic methods. (78-82).

Compounds with the bicycle glucofuranimidazoline-2-thione structure (XLVI, R = Me, Et, CH₃(CH₂)₂, CH₃(CH₂)₃, (CH₃)₂CH, CH₂ = CH - CH₂, Ph, 4-CH₃C₆H₄, 4-CH₃OC₆H₄, 4-C₂H₅OC₆H₄, C₁₀H₇) can be isomerized (72,83,84) to acyclic imidazolinethione XXXIX by heating with acetic acid. Some of these compounds have been obtained by reacting D-glucosamine with the corresponding alkyl isothiocyanate in ethanol and acetic acid (72).

The imidazoline derivatives XXXIX have been also obtained by reacting 1-alkyl(aryl)amino-1-deoxy-fructoses with ammonium(potassium)thiocyanate in the presence of acids. (71,85). Similarly, the synthesis of 1-alkyl(aryl)-4-D-arabinotetrahydroxybutylimidazoline-2-ones (XL, R = alkyl, aryl) by reaction of 1-alkyl(aryl) amino-1-deoxy-D-fructoses with isocyanic acid has been reported (85,87).

3-Alkyl(aryl)-4-D-arabinotetrahydroxybutylimidazoline-2-thiones (XXXIX, R₁ = H; R₂ = H, Me, Ph, 4-Br-C₆H₄) have been obtained by reaction of 1-amino-1-deoxy-D-fructose with alkyl(aryl) isothiocyanates. The compound having R₁ = H and R₂ = Me has been also prepared by reacting 2-deoxy-2-methylamino-D-glucose hydrochloride with potassium thiocyanate (88).

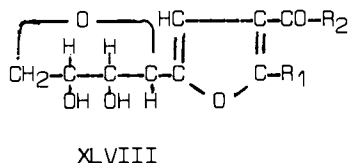
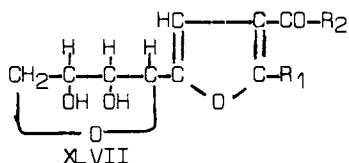
The synthesis of 1-aryl-3-alkyl(aryl)-4-D-arabinotetrahydroxybutylimidazoline-2-thiones (XXXIX, R₁ = aryl; R₂ = alkyl(aryl)) by reaction of 1-arylamino-1-deoxy-D-fructose with alkyl(aryl) isothiocyanates have been reported (89). The thione group was removed by reductive desulphuration or protected by alkylation with benzyl chloride giving the corresponding 1(3)-alkyl(aryl)-4-D-arabinotetrahydroxybutylimidazoles (90,91) and 2-benzylthio derivatives (71,83,88). Oxidative degradation of the polyol chain (92) afforded formyl imidazol derivatives (93,94).

Anhydro-polyhydroxyalkylheterocycles.

One of the most characteristic chemical properties of the polyhydroxyalkylheterocycles is that they can be easily dehydra-

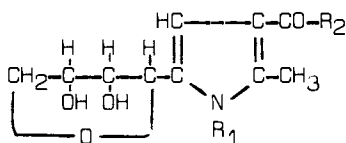
ted giving C-glycosides of heterocycles.

A study about this reaction was undertaken by García González and coworkers (1,95,96) who established the structure of 2-(1,4-anhydro-tetrahydroxybutyl)furans for the dehydration products of 2-(D-arabinotetrahydroxybutyl)furans (I, $R_1 = \text{CH}_2\text{COOH}$, Me; $R_2 = \text{OMe, OEt, OH or Me}$).



Later, Gómez Sánchez and Rodríguez have demonstrated the configuration at C-1'. An acid catalyzed dehydration of 2-(D-arabino tetrahydroxybutyl)furans is a reversible process (97-99) which proceeds preferentially with inversion of the configuration at C-1' yielding the thermodynamically more stable 2-(1,4-anhydro-D-ribo-tetrahydroxybutyl)furans XLVII and, to a much smaller extent the D-arabino isomer XLVIII. An unequivocal proof that supports this structure is the synthesis of XLVIII by reaction of 3,6-anhydro-D-glucose with acetoacetic esters (98). Oxidation of these anhydro compounds with periodic acid gave dialdehydes which crystallized as monohydrates and were formulated as hemialdals (99-101).

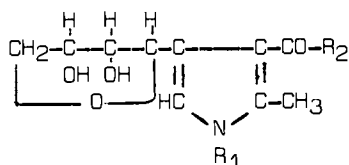
In a similar way, 2-(D-arabinotetrahydroxybutyl)pyrroles (III, $R_1 = \text{H, } R_2 = \text{Me, } R_3 = \text{Me}$; $R_1 = \text{H, } R_2 = \text{Me, } R_3 = \text{OEt}$; $R_1 = \text{Et, } R_2 = \text{n-C}_4\text{H}_9, R_3 = \text{Me, } R_3 = \text{Me}$) and 3-(D-arabinotetrahydroxybutyl)pyrroles (IV, $R_1 = \text{n-C}_4\text{H}_9, R_2 = \text{Me, } R_3 = \text{OEt}$) lose a molecule of water giving the corresponding 1',4'-anhydro derivatives IL and L (102, 103, 32).



b, $R_1 = \text{H, } R_2 = \text{OEt}$

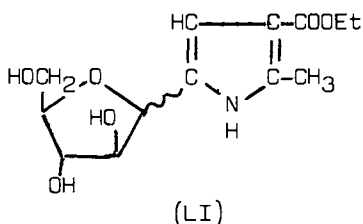
c, $R_1 = \text{Et, } R_2 = \text{Me}$

d, $R_1 = \text{n-C}_4\text{H}_9, R_2 = \text{Me}$

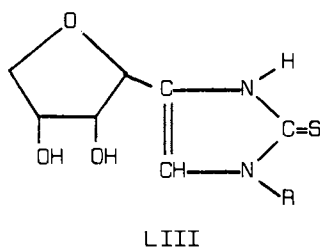
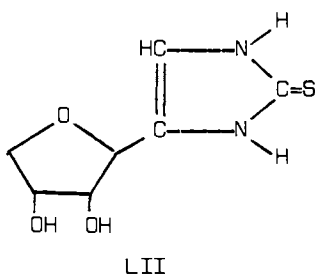


An anhydropentahydroxypentylpyrrole has recently been isolated from the reaction of the 2-amino-2-deoxy-D-glycero-D-guloheptose with ethyl acetoacetate, that has been formulated as 2-methyl-3-ethoxycarbonyl-5-(α - or β -D-arabinofuranosyl)pyrrole

The structure of these compounds are supported by oxidation with sodium metaperiodate, polarimetric measurements, UV and IR spectroscopy.



The 4-D-arabinotetrahydroxybutyl-imidazoline-2-thione can be easily dehydrated by heating its aqueous solution (1%) for six hours under pressure ($\sim 2 \text{ Kg/cm}^2$) giving the 4-(β -D-erythro-furanosyl)imidazoline-2-thione (104) LII.



Recently, the synthesis of 1-halogenophenyl-4-(α -D-erythro-furanosyl)imidazoline-2-thiones LIII ($R = 4\text{-ClC}_6\text{H}_4$, $4\text{-BrC}_6\text{H}_4$, or $3,4\text{-Cl}_2\text{C}_6\text{H}_3$) by treatment of the 1-halogenophenyl-4,5-(cis-1,2-D-glucofuranosyl)imidazolidine-2-thiones XLVI, ($X = S$) with trifluoroacetic acid has been also reported (105).

The structures of these compounds have been established by preparation of derivatives, oxidative estimation with periodate, UV spectroscopy and X-ray crystallographic methods (106, 107).

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Synthesis of Chiral Hydrocarbons from Carbohydrates

G. LOUIS, G. KNAUEL, F. MICHEEL, and M. PESENACKER

Organisch-Chemisches Institut der Universität, D 44 Munster,
Orléans-Ring 23, West Germany

It was shown in previous communications (1-10), that hexoses and pentoses form chiral alicyclic aromatic hydrocarbons when treated with aromatic hydrocarbons in liquid hydrogen fluoride. The course of the reaction was found to depend largely upon the nature of the aromatic hydrocarbon and on the ratio of the sugar to the aromatic hydrocarbon. Thus, mononuclear aromatic hydrocarbons in the ratio of 1 sugar to 10 aromatic hydrocarbon yield monomeric products whereas sugars and polynuclear aromatic hydrocarbons in equal ratios yield highly polymeric compounds which are insoluble in all solvents.

Mononuclear aromatic compounds such as benzene, toluene and anisole were found to react with D-glucose, to give first, 2,5-anhydro- α - and β -1-aryl-D-sorbitol. The anomeric designations, α - and β - were based on rotatory power assigned in an analogous manner to glycosides and have not been confirmed. The second step in this reaction involves the formation 1-deoxy-1,1-diaryl-D-sorbitol as shown for the reaction with toluene in figure 1.

The similar reaction of biphenyl with D-glucose, produced a polymer which was soluble enough in pyridine to enable acetylation to the peracetylated polymer of molecular weight of 2.5×10^6 shown in figure 2.

As the reaction of sugars with mononuclear aromatic hydrocarbons progresses, a stepwise elimination of oxygen was found to take place, leading to a large number of alicyclic aromatic hydrocarbons. These may contain 1, 2, 4, or 6 carbon atoms from the parent hexose or pentose, as determined from experiments with ^{14}C and ^3H labeled sugars. The determination of the structure of these compounds was carried out by chemical methods as well as by spectroscopic methods that included i.r., p.m.r., ^{13}C n.m.r., and mass spectroscopy.

The mechanism of formation of triarylmethane, 1,1-diaryl-

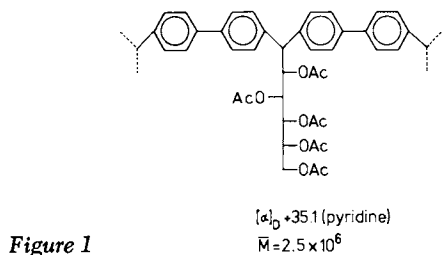


Figure 1

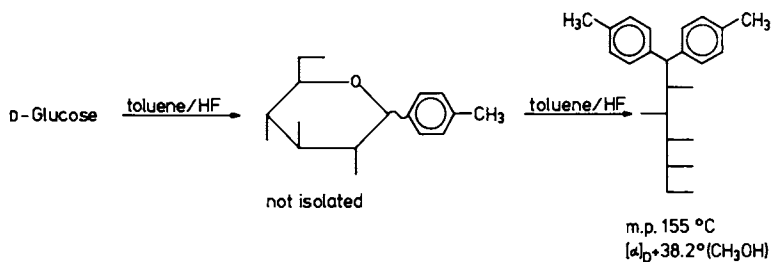


Figure 2

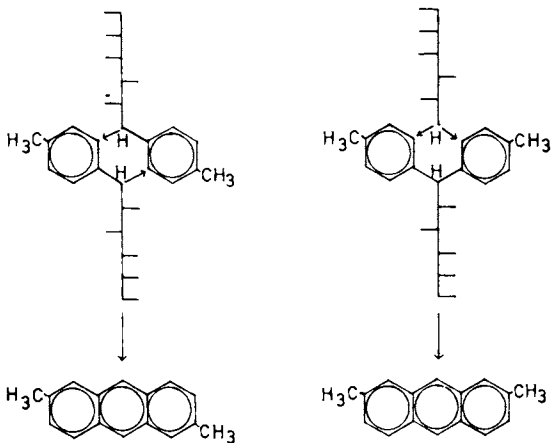


Figure 3

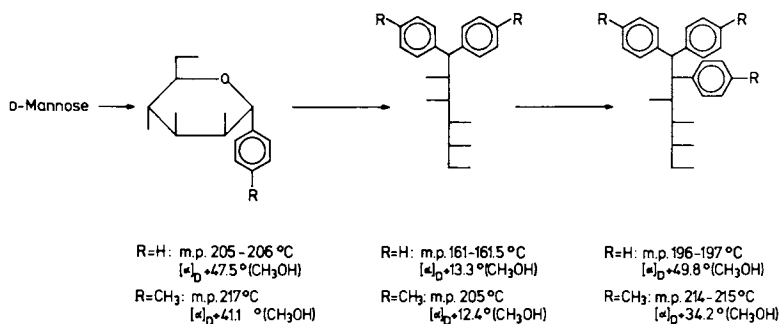


Figure 4

ethane and 1,2,2-triarylethane having in their molecule one and two carbon atoms originating from the sugar chain will not be treated here. Instead, the formation of the anthracene derivatives shown in figure 3 will be discussed briefly. It was possible by using ^{14}C -1-D-glucose to show that C-1 of this sugar becomes C-9 or C-10 of anthracene. It should be noted, however, that 25% of the carbon atoms in these two positions originated from the non-radioactive carbon atoms of the degraded sugar chain. The fate of carbon atom 2-6 of the sugar chain is not clear at this time.

By far, the most interesting products of the reactions of sugar with aromatic hydrocarbons are the many chiral hydrocarbons that are formed after 5 to 30 minutes of reaction time. Isolation of the intermediates of these hydrocarbons and the elucidation of their structures enabled us to determine their mode of formation. Thus, 1,2-dideoxy-1,2,2-triarylhexitol shown in figure 4 was found to originate from 1-deoxy-1,2-diaryl hexitol by migration by one of the aryl residues through a phenonium ion and the introduction of a third aryl residue at C-1 (using C_6H_5 - ^{14}C H_3).

This migration causes inversion of configuration at C-2 and glucose was found to yield a mannitol derivative and mannose to afford a sorbitol derivative as shown for the formation of the mannitol derivative (figure 5).

The next step in this reaction sequence is the ring closure between C-3 of the hexitol residue and one of the aryl residue on C-1 to give an indane derivative. The latter was found to have the three residues attached to the five membered ring in the trans-configuration shown in figure 6.

The next reaction step is the splitting of the trihydroxy side chain to a 2,3-diaryl hydrindane derivative shown in figure 7 by a mechanism which has not been explained.

After long studies we could show that this reaction does not proceed through a splitting by hydrogen fluoride or water because no fluorine containing product or glycerol were produced. A 1-fluoro-D-glycerol would produce D-glyceraldehyde which forms with mononuclear aromatic hydrocarbons in liquid hydrogen fluoride isochromane derivatives such as the one shown in figure 8, and which are not produced during the formation of the hydrindane derivative. We have, therefore, assumed that hydrogenation and dehydrogenation play an important role in the formation of these hydrocarbons.

D-fructose behaves in an unexpected manner, and after a short reaction period one obtains both the α - and β -2,5-anhydro-2-

deoxy-2-tolyl-sorbitol (figure 9).

The β -form was investigated more closely and was found to form on further treatment with toluene in liquid hydrogen fluoride a 1,2-ditolyl derivative which was shown by proton magnetic resonance to have the tolyl residue in a trans di-axial configuration shown in figure 10, together with the proposed mechanism for its formation.

We have suggested in figure 11 the mechanisms for the formation of the same ditolyl derivative from D-mannose.

Table I shows the principle hydrocarbons obtained by the action of mononuclear aromatic hydrocarbons on sugars in the presence of hydrogen fluoride. The chiral cyclic hydrocarbons obtained from hexoses may contain 3, 4 or 6 carbon atoms that originate from the sugar molecules, whereas those obtained from the pentose arabinose contain 5 such carbon atoms. The atoms originating from the sugar molecule are designated in the formula by heavy points.

In addition to hydrindane the hydrocarbons isolated include dihydroazulenes, tetralines, acenaphthenes and combinations of these ring systems. It seems that the tetraline derivatives are formed either directly or through the isomerization of dihydroazulene derivatives.

A particularly interesting compound isolated, was a deep red hydrocarbon $C_{27}H_{20}$, which we have named purpuricene. This compound was identified as 2,6,12-fluoreno-[9a, 1-a, 9, 9a-b]-benzo[e]-azulene (see figure 18).

The following generalizations may be made concerning the hydrocarbons obtained from sugars:

Azulene derivatives are obtained from D-mannose and D-fructose but not from D-glucose.

The main intermediate in the reaction, when toluene is used as the aromatic hydrocarbon, is 1,5-anhydro-1,2-ditolyl-D-sorbitol which may be converted according to the scheme shown in figure 12 to an azulene derivative. Although unconfirmed, our mechanism shows a course of reaction that will lead to the conversion of 1,2-ditolyl to 1,2,3-tritolyl azulene by a ring expansion involving C-1 of the sugar chain. It shows also how the sorbitol configuration can allow the formation of the tropylium ring (figure 13).

The mass spectra of the azulene derivatives isolated show a characteristic fragmentation pattern exemplified by that of the azulene derivative shown in figure 14.

In addition to the triaryl azulene derivatives discussed earlier, we have obtained 1,2-diarylazulene. Both types of

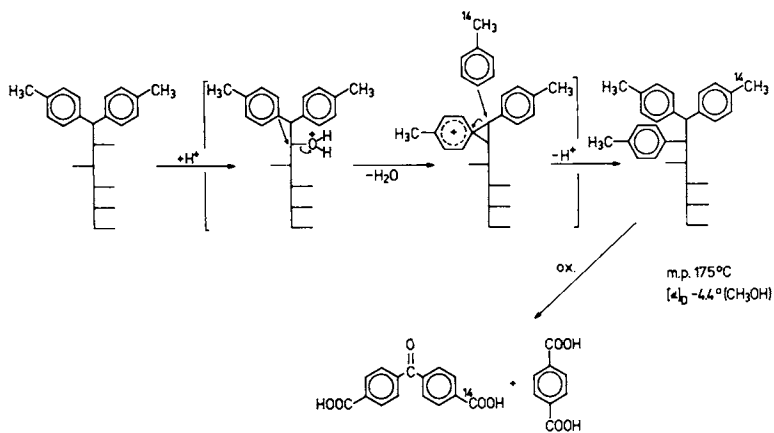


Figure 5

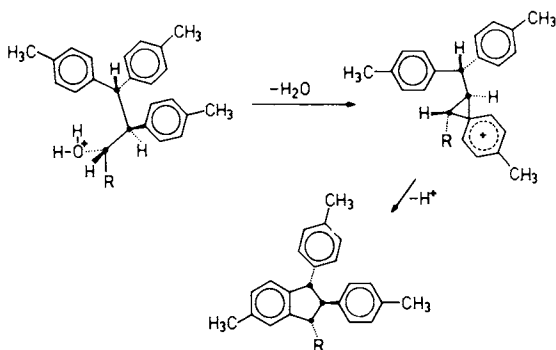

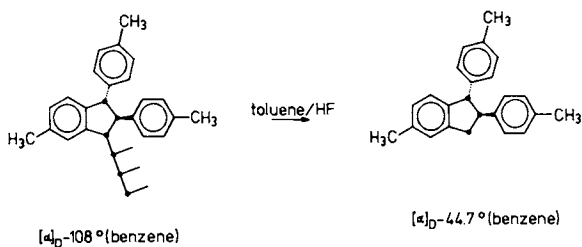
-R =  Figure 6

Figure 7

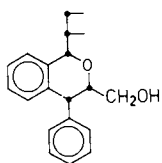


Figure 8

azulene derivatives are readily converted upon dissolution and slight warming into tetraline derivatives as seen in figures 15 and 16 and on the top of next page.

By using proton magnetic spectroscopy it is possible to determine the position of the constituents in the saturated ring of 2,3-diaryl and 1,2,3-triaryl tetraline derivatives and from these we could establish the configuration of the azulene precursors.

In the pentose series, D- and L-arabinose have been selected for our investigation. It is evident that ring systems in which the six carbon atoms of hexoses become part of the hydrocarbon ring cannot be formed with pentoses. A hydrindane derivative possessing a glyceryl side chain attached to its five-membered ring in the case of hexoses would have a dihydroxyethyl group attached to it in the case of arabinose. The latter side-chain can upon ring closure by elimination of water give a hydroxytetraline derivative which can lose water and form a double bond, probably conjugated with the aromatic ring. This intermediate would then add another aromatic ring on the carbon atom adjacent to the ring as shown in figure 17.

This is evident from the NMR spectrum which shows the methylene protons shifted to higher field, unlike a benzyl group that would be expected if the addition took place on the double bond (figure 18).

The dehydrogenation of the previous product with DDQ in benzene-methanol or ethanol proceeds in an interesting way. The saturated ring of the tetraline system is dehydrogenated, the proton on C-1 of the five membered ring is replaced through an ionic type reaction with a methoxy or ethoxy group and racemization occurs. An analogous reaction was observed by D. Walker and J. D. Hiebert (11), during the dehydration of 2,3-dimethylhydrindane, where 2,3-dichloro-4,5-dicyano-1,4-dihydrobenzene product was found to react with the dehydration product as shown in figure 19.

As mentioned earlier, one of the most interesting compounds isolated was the deep red hydrocarbon $C_{27}H_{20}$ purpuricene to which we assigned the helicene structure shown in figure 20. This compound was obtained by the reaction of toluene in hydrogen fluoride on D-mannose, D-glucose and D-fructose but probably not with D-galactose. Its proton magnetic resonance spectrum showed only the $3 \times 3 = 9$ methyl protons of the tolyl residues and the aromatic protons. The very high specific rotation (-1260° in benzene and more than -3000° in nitro benzene) is characteristic of halocenes. The molecule is in the formed helix in which the

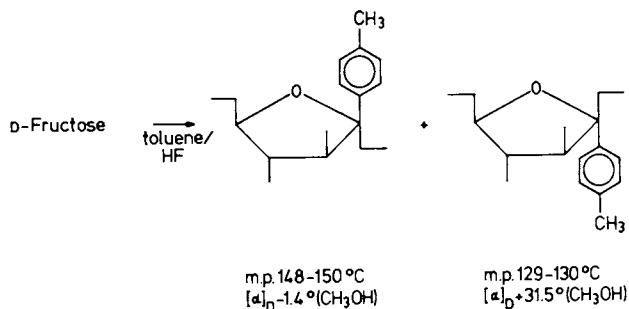


Figure 9

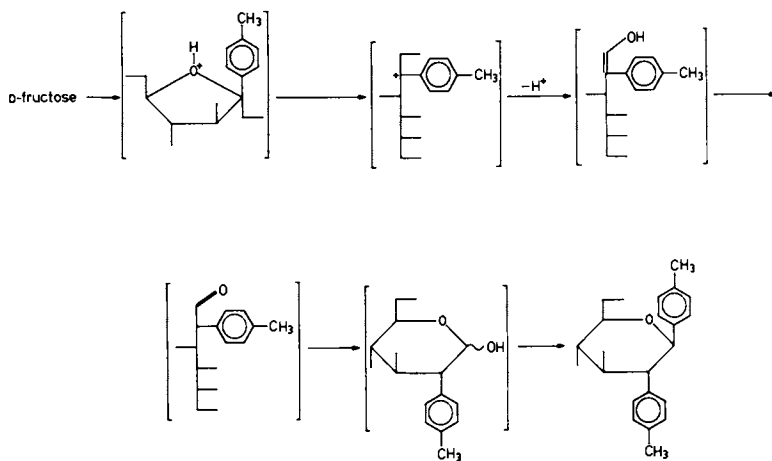


Figure 10

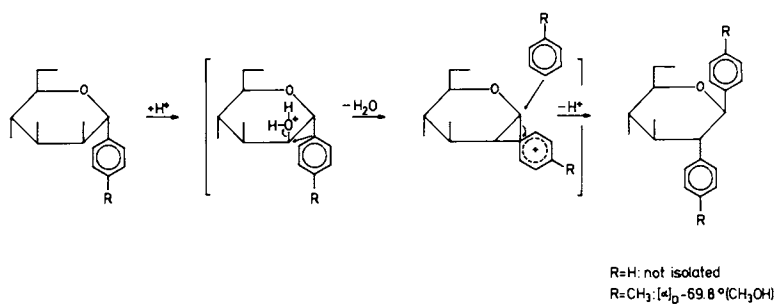







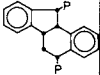


Figure 11

	C-atoms of sugar	$[\alpha]_D$	ara:ali:H	mol- weight	yield (%)	
	D-glucose toluene	3	-44.0		3.6	
	D-mannose toluene	4	+70	12:14	326	76
	R ¹ =P, R ² =H; D-mannose benzene	4	-21	19:5	360	2.0
	R ¹ =T, R ² =CH ₃ ; D-mannose toluene	4	+18.0	15:17	416	16.3
	D-mannose toluene	4	+29.1	11:15	326	
	R ¹ =P, R ² =H; D-mannose benzene	4	-158.1	19:5	360	3.5
	R ¹ =T, R ² =CH ₃ ; D-mannose toluene	4	-37.0 +18.9	15:17	416	4.5
	D-glucose o-xylene	6	-41.0	10:20	390	0.2
	D-mannose benzene	6	+129.5	23:7	462	1.2
C ₂₇ H ₂₀	D-mannose toluene	6	-126.0	11:9	344	1.5
	D-arabinose benzene	5	-84.0	18:6	372	3.5


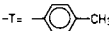
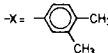




Figure 12

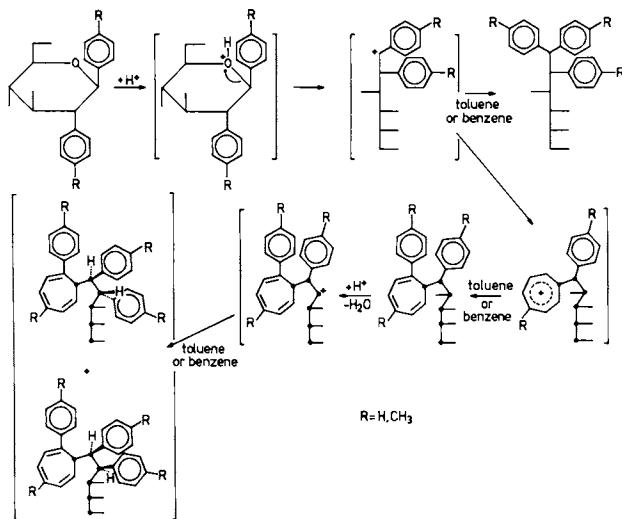


Figure 13

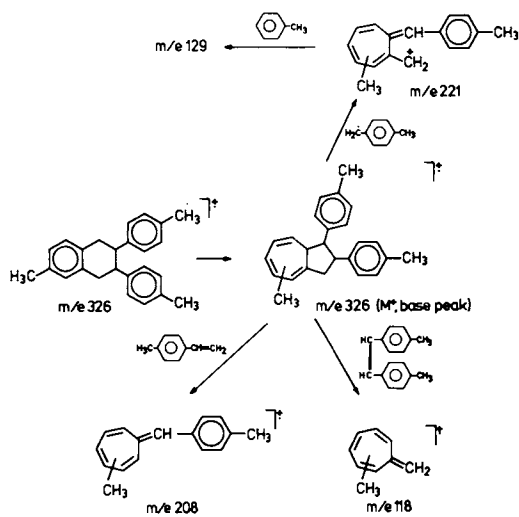


Figure 14

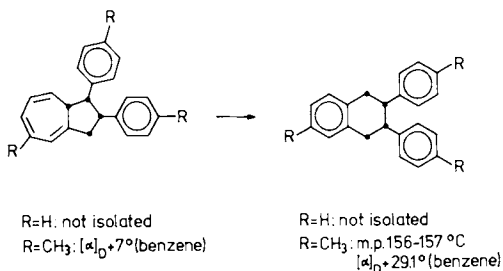


Figure 15

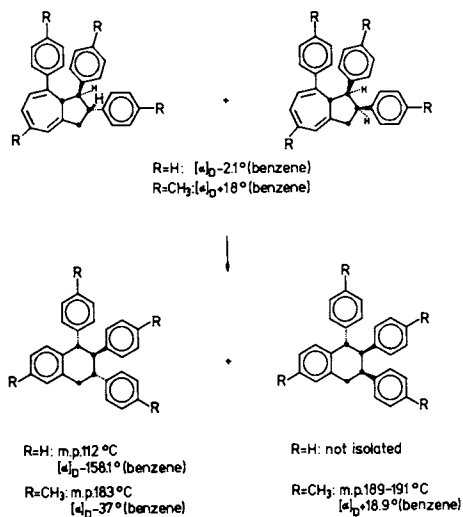


Figure 16

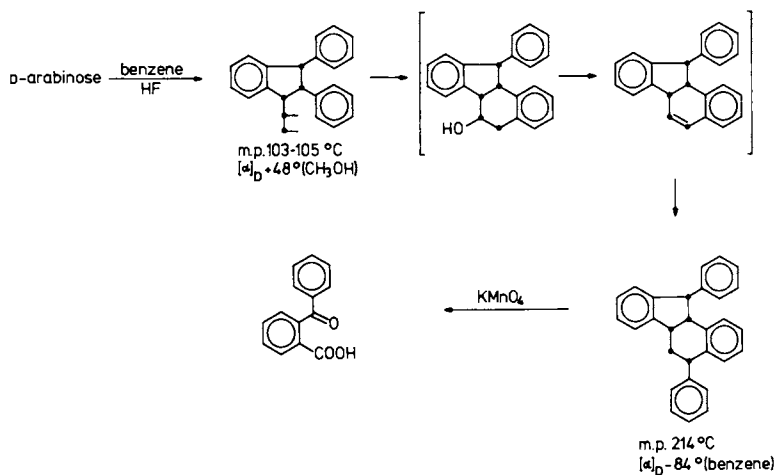


Figure 17

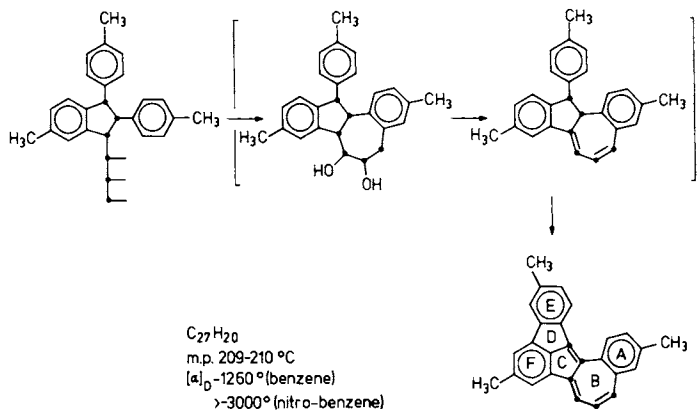


Figure 18

protons of ring A and ring E cannot be accommodated in one plane. The intense coloration of purpuricene is probably due to azulene system present in the molecule.

Upon heating in nitrobenzene to 140° purpuricene is racemized. However, it was not possible to follow the racemization to its ultimate completion because of the extreme dark coloration of the solution. The azulene system contains three reactive double bonds. Thus, it can form 3 epoxy groups with 3-chloroperbenzoic acid. Upon catalytic hydrogenation, it yields first a colorless dihydro derivative, $C_{27}H_{22}$ which may be separated by column chromatography, from the tetra- and hexahydro products. The dihydro product can be converted into purpuricene by dehydrogenation with DDQ. The product obtained is, however, racemic. This was attributed to the fact that the disappearance of the double bond in the five-membered ring C eliminated the steric hindrance that freed the molecule to assume a helical chiral form.

The formation of purpuricene seems to involve a series of dehydrogenation reactions, probably similar to those occurring during the splitting of 1,2-dihydroxyethyl and 1,2,3-trihydroxypropyl side chain mentioned earlier. The hydrogen atoms needed for the hydrogenation step are generated by the dehydrogenations occurring during the formation of ring C in purpuricene. Ring closure between ring E and F occurs also with a loss of two hydrogen atoms each.

Dihydropurpuricene loses two hydrogen atoms upon keeping a benzene solution in an inert atmosphere, to form purpuricene and other unidentified compounds. It should be noted further that

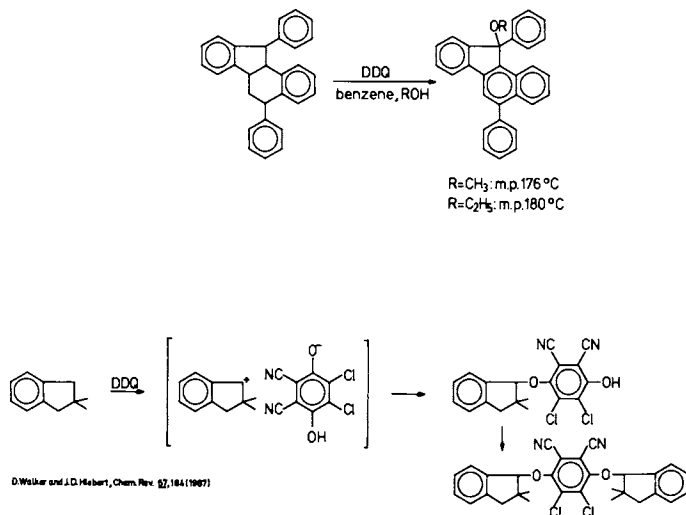


Figure 19

purpuricene possesses an acidic proton, thus reacts with potassium *t*-butylate in dimethylsulfoxide giving a dark green salt. This is accompanied by an increase in the specific rotation from -460° to -640° , and upon acidification, purpuricene is obtained unchanged (figure 21).

The chiral alicyclic aromatic hydrocarbons described here have not been isolated from natural sources, like their alicyclic analogs, the terpenes and steroid which are widely distributed in nature. Although the mode of formation of alicyclic aromatic hydrocarbons bears no relation to the biosynthesis of terpenes and steroids, it might bear some relation to the processes involved in the formation of coal from the components of wood (cellulose, mannans, xylans and lignin). The presently accepted view, is that coal is formed from lignin and that the polysaccharide components of wood mysteriously disappear. We believe that our studies have shown that the carbohydrates of wood may play an important role in the coalification. The conditions of coal formation are somewhat similar to the condition we described for the interaction of carbohydrates and aromatic systems. The medium in both is acidic, although in coal formation it is weaker than in the hydrogen fluoride use. However, the temperature is much higher and the reaction time is considerably longer.

Lignin is a macromolecule composed of mononuclear aromatic residues linked through three atomic aliphatic residue. Hydroxyl, methoxyl, and ether linkages are abundant. We have treated

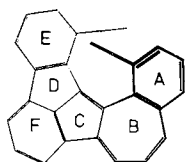


Figure 20

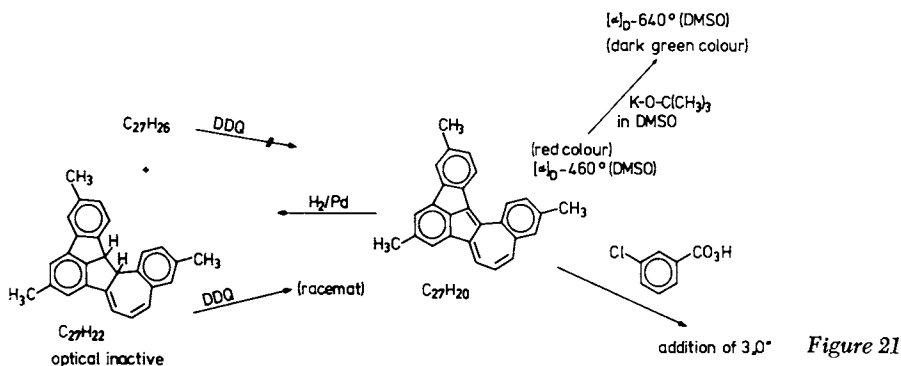


Figure 21

glucose with lignin obtained from woods, under the conditions described earlier for ^{13}C -labelled D-glucose, and obtained lignin derivative containing 6-17% of the radioactivity calculated as a D-glucose. The D-glucose residue or their fragments were found in the form of the carbon-carbon bound lignins. It is certainly possible that the aldoses liberated from polysaccharides would link to lignins in an analogous manner. We believe, therefore, that our discovery may have a great significance in understanding the processes involved in coal coalification.

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Synthesis of New Sugar Derivatives of Biogenic Amines

LASZLO MESTER and MADELEINE MESTER

Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, 91190 Gif sur Yvette, France

Many specific roles have been proposed for the biogenic amines in physiological processes. Serotonin (1) is a powerful agent for platelet aggregation, a neurotransmitter and its role in the introduction of sleep is well established. Catecholamines (2,3) are important regulators for many basic biological processes and involved in diseases, such as manic depressive psychosis, Parkinsonism and essential hypertension. The polyamines (4) spermine, spermidine and putrescine have a role in the bacterial cell division and in the growth of animal cells.

Sugar Derivatives of Serotonin and of Catecholamines

In spite of the impressive number of studies on serotonin in the last two decades, our knowledge on the mode of action of this biogenic amine is highly speculative (5).

In 1971 we have reported (6) the enzymically catalysed incorporation of ^{14}C labelled N-acetylneuraminic acid into the platelet membrane (Figure 1). The higher sialic acid content increased the serotonin induced aggregation of blood platelet (7). The incorporation of N-acetylneuraminic acid accelerated the uptake of serotonin by the platelets (8) and also the serotonin catalysed transport of potassium ions through the platelet membrane (9). These effects suggest that sialic acid is a component of the primary receptor for serotonin on the platelet membrane.

However, serotonin can react in other biological processes in a different way. Alivisatos and coworkers (10) suggested a Schiff-base type interaction to explain the mode of action of serotonin in the central nervous system (Figure 2). The presence of a Schiff-base structure has been demonstrated by chemical methods.

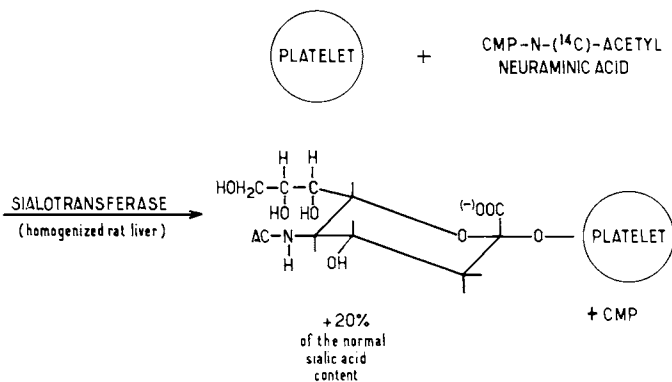
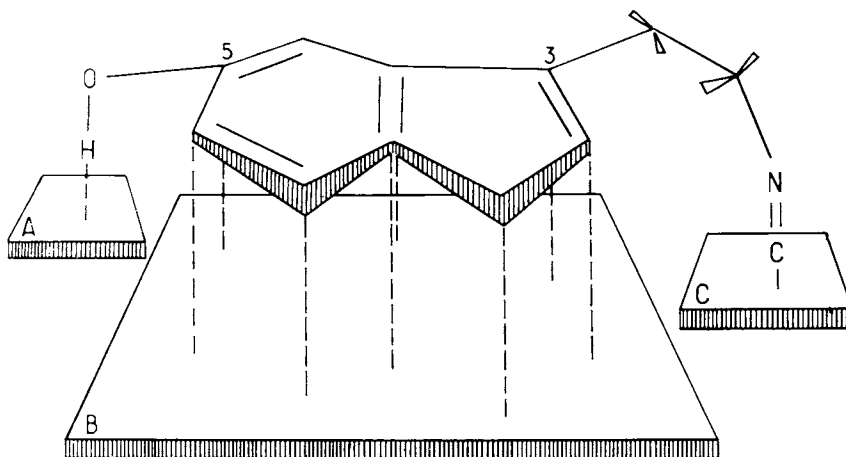


Figure 1. Incorporation of ^{14}C -labeled sialic acid into the platelet membrane using CMP-N- ^{14}C -acetyl neuraminic acid and rat liver sialyltransferase



Science

Figure 2. Mode of action of serotonin in the central nervous system (10)

The Schiff-base structure advanced by Alivisatos to explain the mode of action of this biogenic amine, incited us to investigate the interaction of reducing sugars with the primary amino group of serotonin (11) (Figure 3).

Between a large number of substituted serotonin derivatives, prepared in order to understand the role of 5-HT in health and disease (12), only two sugar derivatives of serotonin (13,14) have so far been reported. However, the presence of hydrophilic groups may have a decisive effect on the transport and metabolism of the amine. One of these sugar derivatives is the O(β -D-glycopyranosyl)-serotonin (1) showing an increased hydrosolubility, but having properties very close to the well studied group of O-ethers of serotonin. The second one is the N-glucoside (2), which is of limited interest because of its easy hydrolysis into 5-HT and D-glucose in aqueous solution even at room temperature. Thus, the preparation of a stable N-substituted sugar derivative of serotonin is of biologic interest.

Only very few attempts have been made to prepare (15,16) 1-desoxy-1-amino-D-fructose derivatives (Amadori compounds) (17) arising from substituted phenylethylamine. The preparation of this type of compounds from 5-HT is rendered even more difficult because of the formation of tetrahydro-norharman (3) derivatives (18). To overcome these difficulties, the oxalate salt of serotonin was used for the reaction with sugar, to obtain the corresponding Amadori compound, the 1-desoxy-1-(5-hydroxy-tryptamino)-D-fructose (4). Oxalic acid is often used to isolate Amadori compounds after the reaction between the sugar and the amine. Starting with the oxalate salt of serotonin, the 1-desoxy-1-amino-D-fructose derivative is stabilized in situ, preventing serotonin from undergoing other reactions.

The resulting product is a pale yellow microcrystalline powder, easily soluble in water, slowly in ethanol, insoluble in ethyl acetic ester, ethyl ether or acetone. The oxalate salt of 1-desoxy-1-(5-hydroxy-tryptamino)-D-fructose is stable in aqueous solution and does not show mutarotation. As for all Amadori compounds prepared from D-glucose, the optical rotatory power is negative (19). NMR spectrum in D₂O clearly shows that the 5-hydroxy-indole fragment of the molecule, characterized by four typical proton signals in the region from 6.5 to 7.5 ppm, is unchanged and no trace of any other condensed system could be detected. Carbon-13 NMR spectroscopy shows the Amadori compound to exist in D₂O mainly as the β -pyranose structure in the Reeves 1C conformation (20). The signal of C-2 is located at

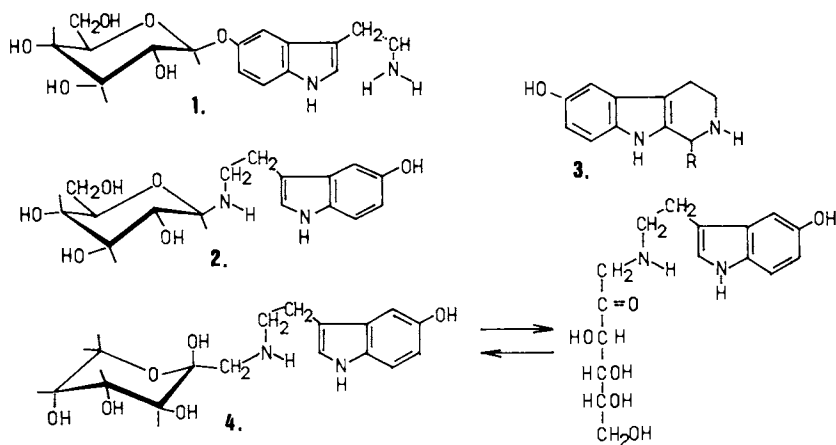


Figure 3. Sugar derivatives of serotonin

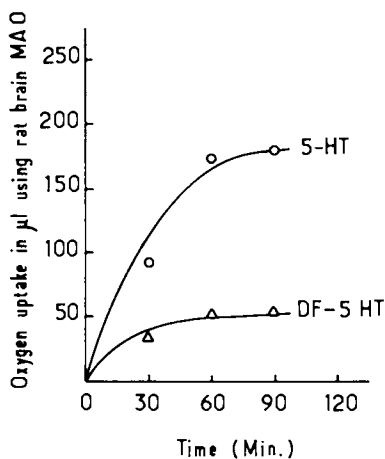


Figure 4. Metabolism of serotonin (5-HT) and desoxy-fructo-serotonin (DF-5-HT) by rat brain MAO expressed by the rate of oxygen uptake in conventional Warburg manometric technique

TABLE I.
 CARBON-13 N.M.R. DATA OF AMADORI TYPE SUGAR DERIVATIVES OF TRYPTAMINE IN D_2O

COMPOUND	SUGAR CARBONS					
	C ₁	C ₂	C ₃	C ₄	C ₅	C ₆
1-Desoxy-1-(5-hydroxy-tryptamino)-D-fructose	53.8 ^c	96.3 ^a	70.9 ^b	70.4 ^b	69.9 ^b	64.8 ^c
1-Desoxy-1-(5-methoxy-tryptamino)-D-fructose	53.8	96.3	70.9	70.4	69.9	64.9

a= quaternary carbon

b= tertiary carbon

c= secondary carbon

confirmed by
 off resonance
 decoupling

96.3 ppm, the C-3, C-4 and C-5 signals appear as three peaks at 70.9, 70.4 and 69.9 ppm. The signals at 64.8 and 53.8 ppm correspond to the C-6 and C-1 carbons respectively (ppm relative to TMS=0). (Table I). In 0.1 N NaOH solution at pH = 11, 24°C, 1-desoxy-1-(5-hydroxy-tryptamino)-D-fructose reduced 1.5 moles of Tillmans reagent (21).

1-Desoxy-1-(5-methoxy-tryptamino)-D-fructose has been prepared in a similar way and carbon-13 NMR spectroscopy shows a very similar structure.

Due to their strong reducing power and high stability, these new sugar derivatives of serotonin show interesting biological properties.

At a final concentration of 1×10^{-4} mol, 1-Desoxy-1-(5-hydroxy-tryptamino)-D-fructose induced an aggregation of human platelets in citrated PRP (plasma rich in platelet), which was similar to the aggregation induced by serotonin itself (22), but the incorporation of the ^{14}C labeled (spec.act. 0.1 mC/mM) sugar derivative into the platelets during 1 hour of incubation (23) was very limited.

Tested on rat uterus, the minus logarithmic dose response for serotonin (5-HT) was higher than for 1-desoxy-1(5-hydroxy-tryptamino)-D-fructose (DF-5-HT). However, both are inhibited by Methylsergide, showing both activities to be of the same nature (24).

Serotonin is rapidly metabolised, while 1-desoxy-1(5-hydroxy-tryptamino) - D-fructose is only slowly oxidized by monoamine oxidase (MAO). This was demonstrated by the rate of uptake of oxygen at various intervals as an index of metabolism of rat brain mitochondrial MAO, using serotonin and its sugar derivative as substrates in conventional Warburg manometric technique (25) (Figure 4).

Using various concentrations of DF-5HT and 5-HT, the substrate activity curves show that desoxyfructo-serotonine has much less substrate affinity towards MAO than serotonin itself. When Lineweaver-Burk plots were drawn, the Michaelis constant for desoxyfructo-serotonine was found to be two and half time higher than for serotonin (Figures 5 and 6).

An other field, where the synthesis of Amadori type sugar derivatives is of great biological interest, is given by the catecholamines. A new type of bis-(catecholamines) became available through the synthesis, elaborated by Barton and his coworkers (26) for the alkaloids, and could be transformed in sugar derivatives (Figure 7).

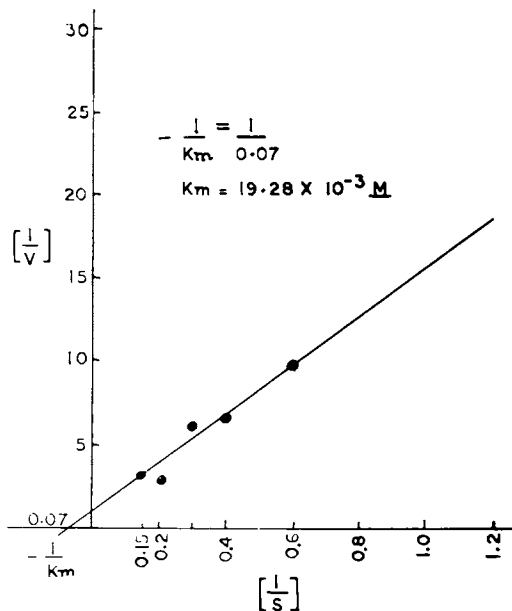


Figure 5. Substrate activity of desoxy-fructo-serotonin with rat brain MAO

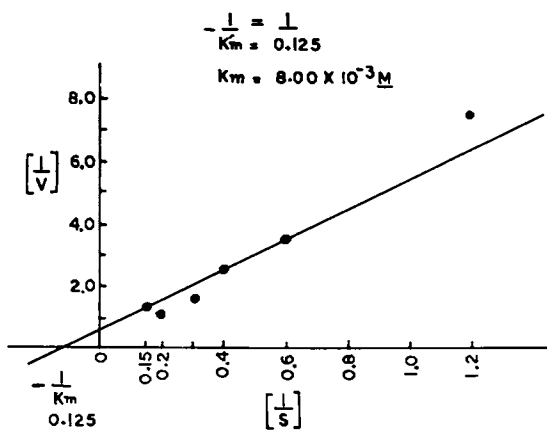
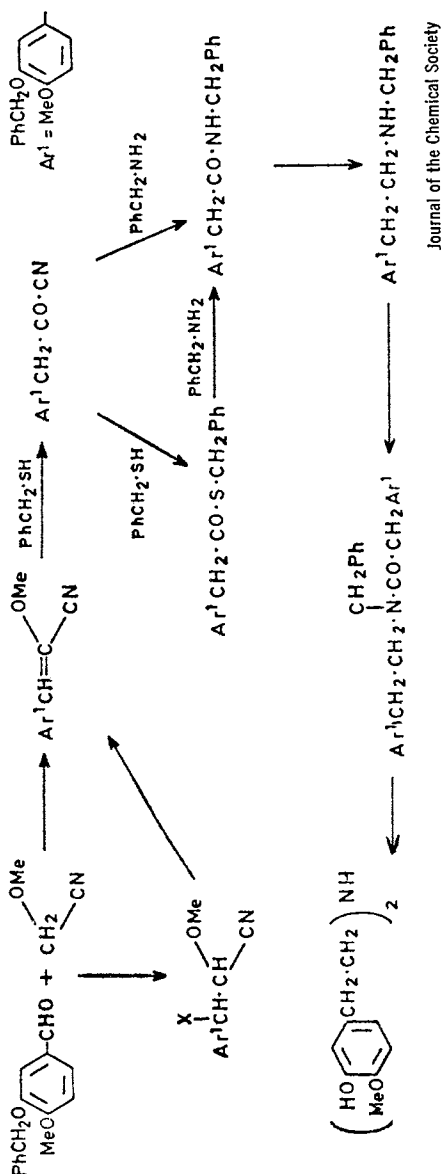


Figure 6. Substrate activity of serotonin with rat brain MAO



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Figure 7. Synthesis of bis-(2-arylethyl) amines (26)

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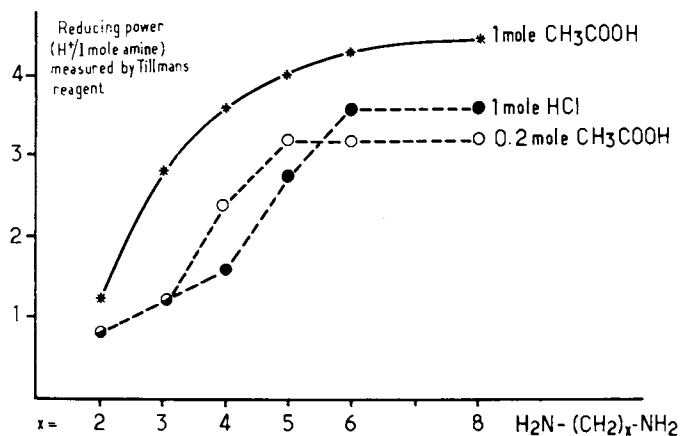


Figure 8. Formation of Amadori type sugar derivatives of diamines expressed in reducing power: 1 mol diamine and 2 mol of D-glucose boiled for 2 hr in methanol with different concentrations of acid

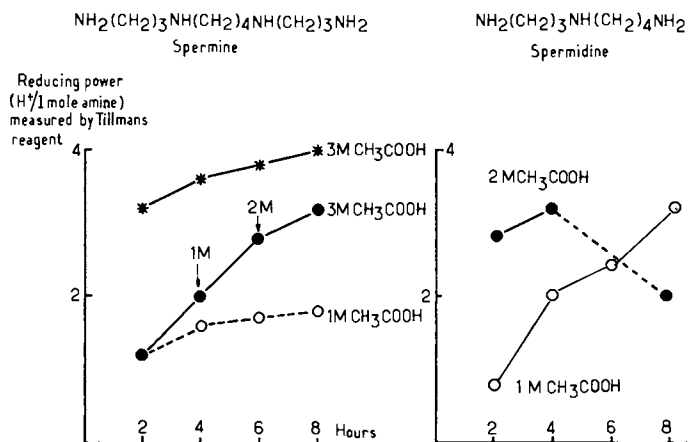


Figure 9. Formation of Amadori type sugar derivatives from spermine and spermidine expressed in reducing power: 1 mol of polyamine and 2 mol of D-glucose heated in methanol with different concentrations of acid and for different times

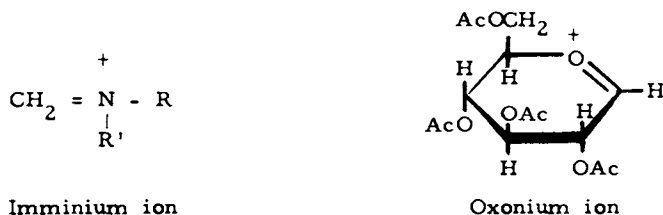


Figure 10. Typical ions in the mass spectra of acetylated Amadori type or N-glycosidic sugar derivatives

Sugar Derivatives of Di- and Polyamines

Special attention has been devoted to the formation of Amadori type sugar derivatives from di- and polyamines, because some antipolyamine antibodies show cytolytic activity (27). The optimal conditions for the synthesis of these new sugar derivatives are shown on Figure 8. Di-amines with a long carbon-chain form easier Amadori type compounds than di-amines with a short carbon-chain. Strongly reducing Amadori type sugar derivatives were obtained also from the polyamines spermine and spermidine (Figure 9).

Investigation by Mass Spectrometry

A rapid mass spectrometric method has been elaborated (28) for investigation of Amadori type sugar derivatives. Mostly a simple acetylation is sufficient to prepare the samples for analysis. Simple Amadori compounds are giving an imminium ion, while the corresponding N-glycosides gave a typical oxonium ion (e/m 331) (Figure 10).

Some typical examples are given in the Table II.

Conclusion

The preparation of Amadori type sugar derivatives is now possible even from complex biogenic amines. Due to their great stability, high reducing power and increased hydrosolubility, these sugar derivatives are of great biological interest.

Acknowledgement

Carbon-13 N.M.R. spectra were measured by M. Guy Berenger on Bruker Physik A.G. HX90E Type spectrometer with F.T.

TABLE II.
 TYPICAL IONS IN THE MASS SPECTRA OF ACETYLATED AMADORI TYPE OR
 N-GLYCOSIDIC SUGAR DERIVATIVES OF AMINES

<u>AMADORI COMPOUNDS</u>		<u>N-GLUCOSIDES</u>	
Amines	Imminium ions	Amines	Oxonium ions
p-Toluidine	m/e 120	Aniline	m/e 331
N-Methyl-aniline	m/e 120	n-Butylamine	m/e 331
n-Butylamine	m/e 86	Piperidine	m/e 331
Piperidine	m/e 98	Ethylene-diamine	m/e 331
Dibenzylamine	m/e 210	o-Phenylene-diamine	m/e 331

Abstract

Amadori type sugar derivatives of serotonin, 5-methoxytryptamine and catecholamines were prepared through reaction of the biogenic amines with aldoses. The method of D.H.R. Barton (J.Chem.Soc., 1975, 579) for synthesis of bis-(2-arylethyl)amines has been used in the preparation of sugar derivatives of di-catecholamines. The optimal conditions for the formation of N-glycosides and Amadori type sugar derivatives from the biogenic polyamines : putresceine, cadaverine, spermine and spermidine were investigated. Carbon-13 N.M.R. spectroscopy shows the Amadori compounds to exist in D₂O mainly as a β -pyranoside in the Reeves 1C conformation. A mass spectrometric method was elaborated for rapid detection of Amadori compounds.

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Studies on the Synthesis of Serologically Active Glycolipids

ROY GIGG

Laboratory of Lipid and General Chemistry, National Institute for Medical Research, Mill Hill, London NW7 1AA.

Many of the glycolipids present in mammalian tissues and in microorganisms are "foreign" to the human and are thus capable of inducing the formation of antibodies i.e. they are antigenic. The immunochemical activity of the glycolipids resides in the oligosaccharide portion and most of this activity (as in other antigenic oligosaccharides) is exhibited by the terminal two or three sugars of the molecule(1).

As isolated 'homogenous' molecules, these relatively low molecular weight compounds exhibit low antigenic activity whereas they are highly active as components of the tissues to which they belong. The glycolipids exist in the native state as components of the membranes (2) of cells i.e. as part of a macromolecular aggregate, and this macromolecular form is required for the exhibition of immunochemical activity in glycolipids(3).

The presence of an antigen in guinea pig organs which would induce an antibody capable of lysing sheep erythrocytes was demonstrated by Forssman (4) in 1911 and subsequently it was shown that similar antigens ("Forssman antigens") were present in the lipid fractions of many other mammalian tissues although it was not until 1971 (5, 6) that the structure of the Forssman antigen (1) was established and the antigenic activity was associated with the terminal α -NAcgal(1 \rightarrow 3) β -NAcgal(1 \rightarrow 3)Gal-portion of the molecule.

(1) α -NAcgal(1 \rightarrow 3) β -NAcgal(1 \rightarrow 3) α -Gal(1 \rightarrow 4) β -Gal(1 \rightarrow 4)Gluc-Ceramide

(II) α -L-Fuc(1 \rightarrow 2)
 α -Gal(1 \rightarrow 3) } β -Gal(1 \rightarrow 4)NAcgluc Ceramide

(III) α -L-Fuc(1 \rightarrow 2) β -Gal(1 \rightarrow 4)NAcgluc Ceramide

(IV) α -L-Fuc(1 \rightarrow 2)
 α -NAcgal(1 \rightarrow 3) } β -Gal(1 \rightarrow 4)NAcgluc Ceramide

Ceramide = N-acylsphingosine

(V) α -Gal(1 \rightarrow 6) α -Gal(1 \rightarrow 6) β -Gal(1 \rightarrow 3)1,2-Di-o-acyl-L-glycerol

$(VI)\alpha\text{-Gluc}(1\rightarrow2)\alpha\text{-Gluc}(1\rightarrow2)\alpha\text{-Gluc}(1\rightarrow3)1,2\text{-Di-o-acyl-L-glycerol}$

The blood group substances of human erythrocytes are glycolipids with perhaps a small contribution from glycoproteins (7,8). The classical work (9,10) on the structure of the immunologically active portions of the blood group substances was carried out on glycoprotein blood group active substances which were readily isolated and purified from body fluids. However the glycolipid type blood group substances present in the erythrocytes (e.g. II, III & IV) have been shown (8) to possess identical terminal oligosaccharide portions to those of the glycoproteins and some of these terminal di- and trisaccharides have been synthesised (11).

The structures of several glycolipids from microorganisms have been established (12-14) and the serological activities of some of these have been demonstrated. The realisation of the variety of structural (and therefore antigenic) information that can be incorporated into a trisaccharide unit and of the tendency of glycolipids to associate with other membranous structures led the author (15) to formulate a hypothesis, relating the glycolipids of microorganisms with possible immunopathological phenomena, which may be stated briefly as follows.

Glycolipids originating from microorganisms invading the host may become inserted into the cellular membranes of host tissues. Antibodies, raised against these "foreign" glycolipids present in the macromolecular environment of the microorganism, may then attack the host tissue containing the "foreign" glycolipid leading (in the presence of complement) to "immune lysis" (16) of the host cells i.e. to a type of autoimmune attack on the host tissues.

One of the microorganisms for which the presence of serologically active glycolipids has been established (17-20) is Mycoplasma pneumoniae, the causative agent of primary atypical pneumonia. The structures of the active glycolipids have been tentatively related (19) by serological reactions to the galactosyl diglycerides of plant lipids the structures (e.g. V) of which have been established (21-25). The structures (e.g. VI) of glycolipids isolated from Streptococci have been fully determined (26-28) and the serological activities of these have been established (29,30). With some of these glycolipid structures established we considered it pertinent to attempt their synthesis, firstly to prove that these structures were in fact the active components and secondly to make the materials more readily available for testing our hypothesis.

At the outset it was realised that the synthetic methods to prepare the types of glycosidic linkages present in these molecules were not fully established. In particular routes to 1,2-cis-linked neutral and 2-amino sugars were not available with any degree of certainty (although the methods for the preparation of 1,2-trans-linked neutral and 2-amino-2-deoxy sugars were well

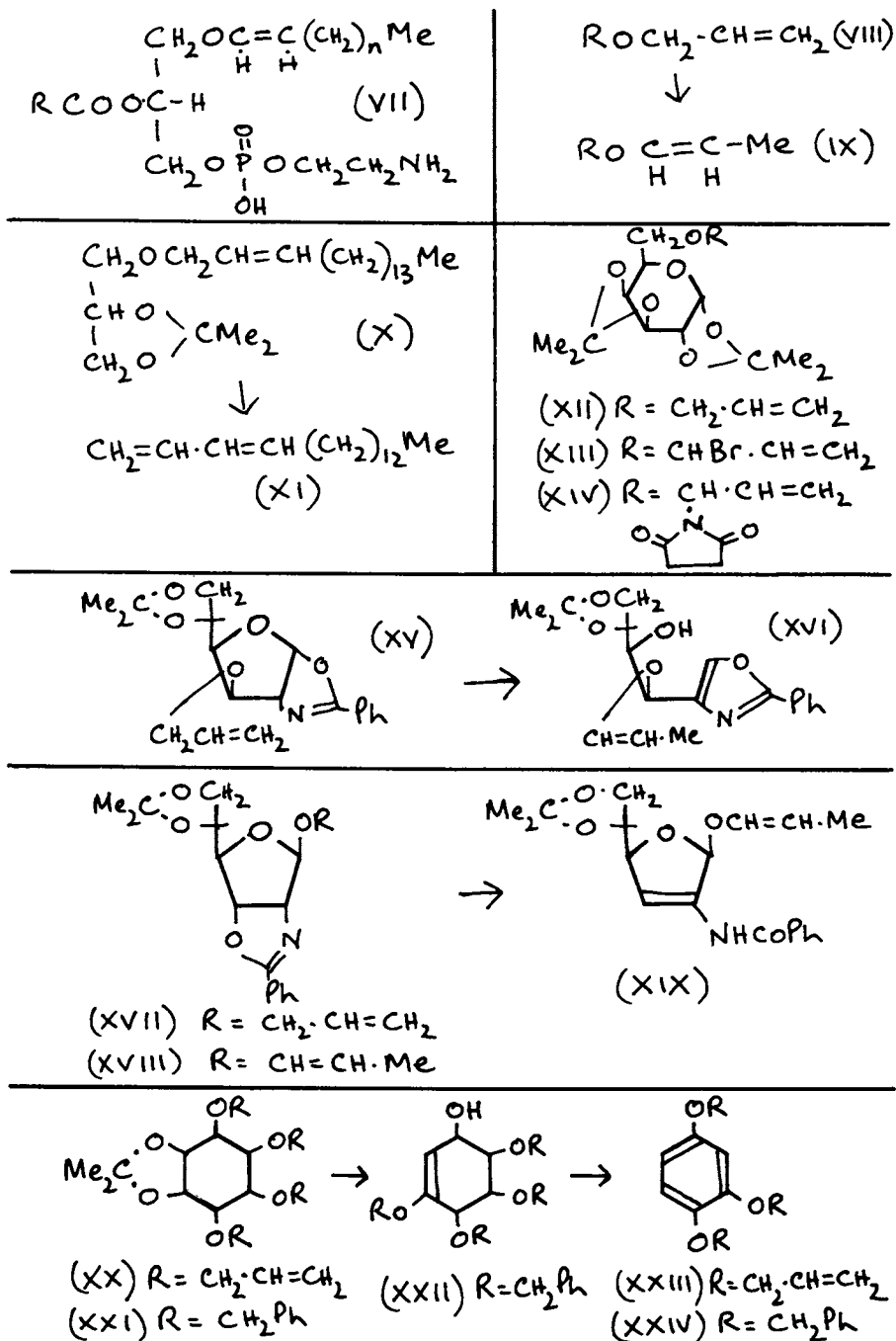
documented) and moreover the problem of the protection of hydroxyl groups had also to be considered.

We had previously introduced (31-35) the allyl ether protecting group into carbohydrate chemistry and had shown its particular value in the preparation of benzyl ethers of carbohydrates. Awareness of earlier work (36-38) on the prevalence of 1,2-*cis*-glycoside formation when non-participating groups were present on the 2-hydroxyl group, led us to consider (39) a general type of oligosaccharide synthesis using benzyl ethers for 'persistent' protection and allyl ethers for 'temporary' protection of hydroxyl groups. It is therefore relevant at this stage to review our development of the allyl ethers as protecting groups.

Allyl Ethers as Protecting Groups

In the course of studies on the chemical synthesis (40-42) of the phospholipids known as the plasmalogens (e.g. VII) it was necessary to investigate new methods for the synthesis of vinyl ethers. Prior to this work, two papers (43,44) had appeared describing the rearrangement of allyl ethers (VIII) to *cis*-prop-1-enyl ethers (IX) under basic conditions and the rearrangement was shown (44) to be particularly rapid and quantitative with potassium *t*-butoxide in dimethyl sulphoxide. For our work on the plasmalogens we attempted a similar rearrangement with a γ -substituted allyl ether and as a model compound we chose the heptadec-2-enyl ether (X). We found however, that with potassium *t*-butoxide in dimethyl sulphoxide, this compound was rapidly degraded to heptadecadiene (XI) and its isomers. At this time we were also interested in the syntheses of the phospholipid known as phosphatidyl inositol (45) and of the long-chain sphingolipid bases, phytosphingosine (46,47) and sphingosine (48,49) from carbohydrate precursors and this work required the extensive use of carbohydrate protecting groups. It occurred to us that the ready elimination of dienes from γ -substituted allyl ethers could form the basis of a new protecting group and we found (33) for example, that the readily prepared but-2-enyl ether of 1,2:5,6-di-*o*-isopropylidene-D-glucofuranose was rapidly converted into 1,2:5,6-di-*o*-isopropylidene-D-glucofuranose by potassium *t*-butoxide in dimethyl sulphoxide at room temperature. At the same time we realised that the allyl ether itself was perhaps a potentially more useful protecting group in the carbohydrate series than the but-2-enyl group.

The allyl group was stable to aqueous acid and base and was rapidly isomerised to the prop-1-enyl group with potassium *t*-butoxide in dimethyl sulphoxide without affecting other conventional base-stable protecting groups. The prop-1-enyl group was stable to base but was very acid labile and could also be removed by oxidation with alkaline permanganate, by ozonolysis



followed by alkaline hydrolysis (31,32) or by the action of mercuric chloride (33). Thus, both the allyl and prop-1-enyl groups could be used under the appropriate conditions as protecting groups.

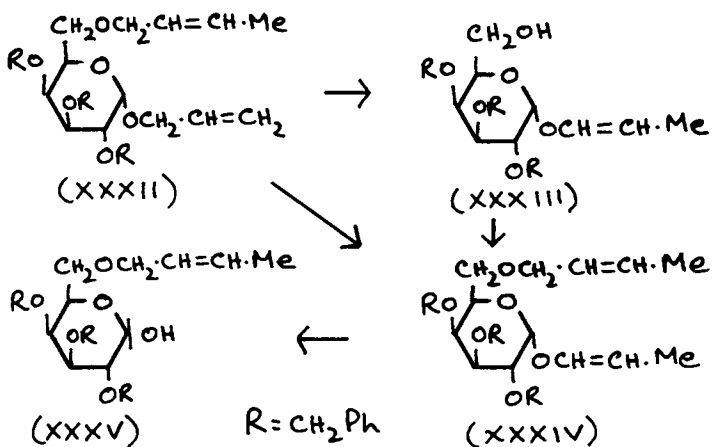
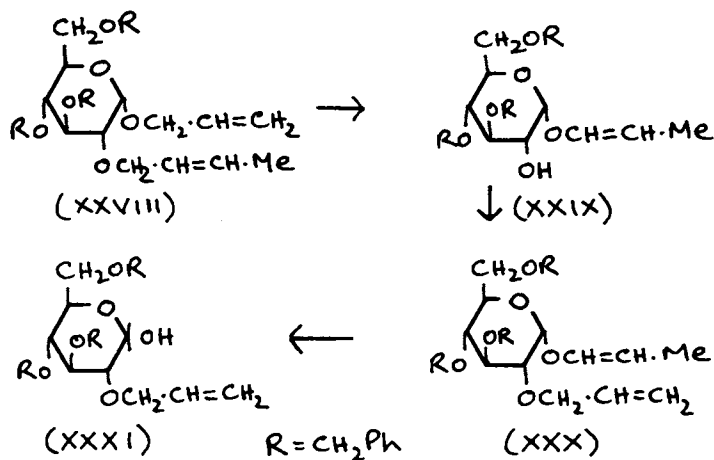
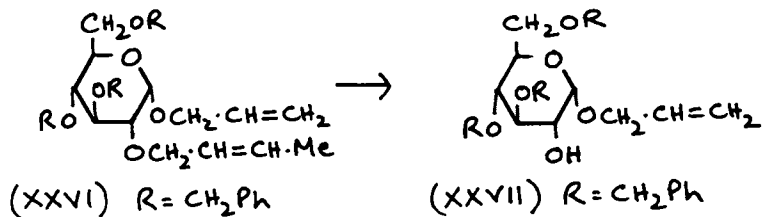
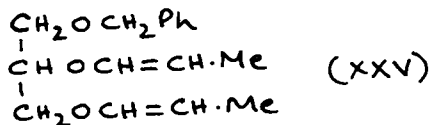
The instantaneous hydrolysis of the prop-1-enyl group by mercuric chloride (33) was particularly useful since by the addition of mercuric oxide to the reaction mixture the hydrolysis could be carried out under neutral conditions thus preserving other acid-labile protecting groups in the molecule. Moreover mercuric chloride was found to react only very slowly with allyl ethers and thus prop-1-enyl groups could be removed in the presence of allyl groups by this method. Amido groups were also stable (33) to the action of potassium *t*-butoxide in dimethyl sulphoxide and thus the allyl ethers could be used for the protection of 2-acylamino sugars.

Mono prop-1-enyl ethers of vicinal glycols are also converted into propylidene acetals (33) by acid catalysts and thus the allyl ethers could be used for the preparation of this type of protecting group.

Subsequent work by other groups has shown that allyl ethers can be removed by oxidation with selenium dioxide (50) and that the allyl group can be isomerised to the prop-1-enyl group by trisphenylphosphine rhodium chloride under conditions sufficiently mild to preserve alkali-labile groups such as esters (51). Also in the presence of diethyl diazodicarboxylate the allyl ether gives an addition product which is a vinyl ether and is thus readily hydrolysed (52, 53). We have also shown (54) that the action of *N*-bromosuccinimide on allyl ethers (e.g. XII) gives a mixture of the bromo ether (XIII) and the succinimide derivative (XIV) both of which can be hydrolysed by aqueous base resulting in the removal of the allyl group.

Thus various other methods for the removal of the allyl group are available for use in circumstances where the very basic conditions of potassium *t*-butoxide in dimethyl sulphoxide are not acceptable. Some of these other methods for the removal of the allyl group suffer from disadvantages e.g. the rhodium catalyst is expensive, has to be separated from the product and does not effect complete isomerisation of the allyl group.

We have found only a few cases where the strongly basic conditions of potassium *t*-butoxide in dimethyl sulphoxide cause other rearrangements in the carbohydrate molecule. The reaction with the phenyloxazoline (XV) led rapidly (33) to the formation of the oxazole (XVI) although the phenyloxazoline group in compound (XVII) was considerably more stable to these conditions and compound (XVII) was readily converted (49) into the prop-1-enyl glycoside (XVIII) under mild conditions although it was degraded to other products (e.g. XIX) under more vigorous conditions (55). The oxazoline group is however stable in the



presence of the rhodium catalyst (56).

The allyl derivative (XX) of 1,2-0-isopropylidene-myo-inositol was also degraded by the action of potassium t-butoxide in dimethyl sulphoxide to give the hydroxyhydroquinone derivative (XXIII). This behaviour was also shown by the benzyl ether (XXI). Compound (XXII) was isolated as an intermediate in the conversion of the benzyl ether (XXI) into the aromatic ether (XXIV) (57). Isopropylidene groups in pyranosides and furanosides are however, stable to these conditions.

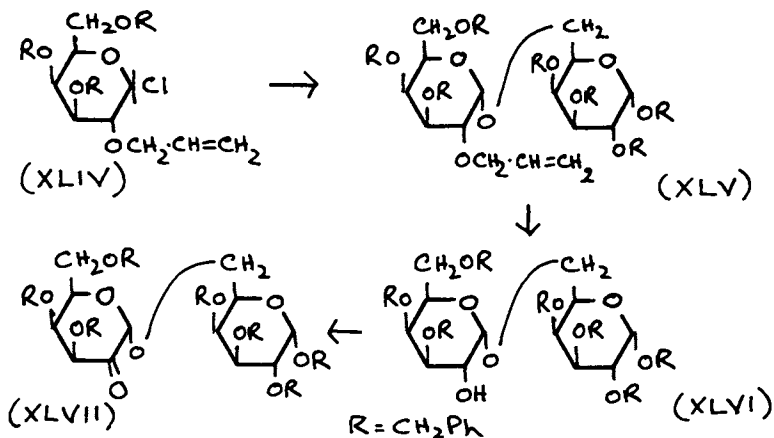
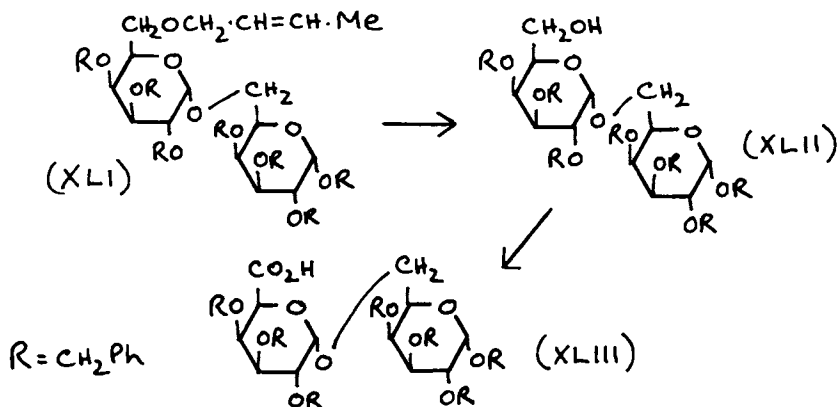
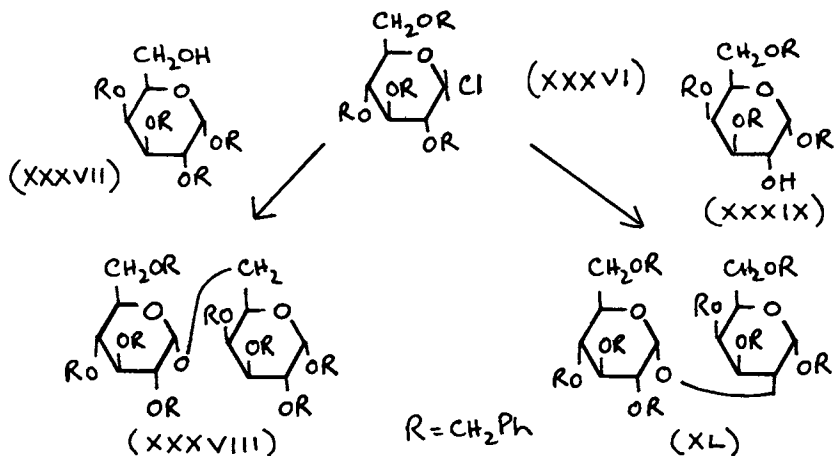
We have recently (58) observed that the vicinal bis prop-1-enyl ether (XXV) is further degraded by the action of potassium t-butoxide in dimethyl sulphoxide and the nature of the products is being investigated.

Having thus established the allyl and prop-1-enyl groups as useful protecting groups in the carbohydrate series, we then investigated (34) the potential of the but-2-enyl group. It is removed much more rapidly than the allyl group is isomerised and it is therefore possible to remove a but-2-enyl group with only partial isomerisation of an allyl group when both are present in the same molecule (34). Thus the allyl ether (XXVII) was obtained (59) from the but-2-enyl ether (XXVI) in about 40% yield by this procedure.

One of the main uses that we have found for the but-2-enyl group is as a temporary protecting group during the preparation of other allyl ethers. Thus the allyl glycoside (XXVIII) gave (59) the prop-1-enyl glycoside (XXIX) on treatment with potassium t-butoxide in dimethyl sulphoxide. Allylation of compound (XXIX) to give (XXX) and subsequent hydrolysis of the prop-1-enyl group gave 2-0-allyl-3,4,6-tri-0-benzyl-D-glucopyranose (XXXI).

A further extension of the use of allyl ethers came when we investigated the comparative rates of isomerisation of other methyl substituted allyl ethers. Both 1-methyl-(34) and 2-methylallyl (33,35) ethers were isomerised at a considerably lower rate than the allyl ethers by potassium t-butoxide in dimethyl sulphoxide and the 2-methylallyl ethers (35) which are readily prepared are convenient protecting groups in the presence of but-2-enyl groups since the latter can be removed completely (35) without isomerisation of 2-methylallyl group.

We also showed that the but-2-enyl group is isomerised much more slowly than the allyl group by the rhodium catalyst and this allowed (56, 60) the removal of the allyl group in the presence of the but-2-enyl group. Thus the allyl galactopyranoside derivative (XXXII) gave predominantly the prop-1-enyl glycoside (XXXIV) on treatment with the rhodium catalyst and compound (XXXIV) was then hydrolysed to the free sugar (XXXV) (60). This transformation of compound (XXXII) into the prop-1-enyl glycoside (XXXIV) was however accomplished in higher yield and with fewer byproducts by first treating compound (XXXII) with



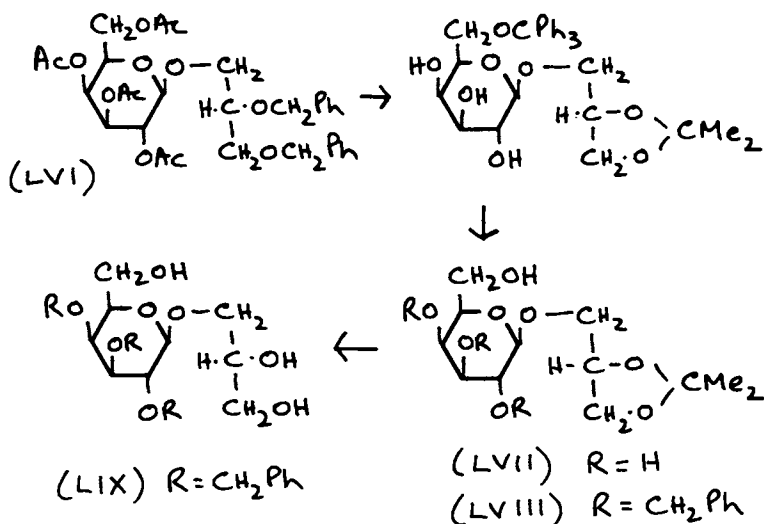
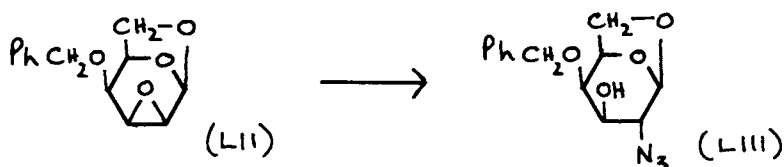
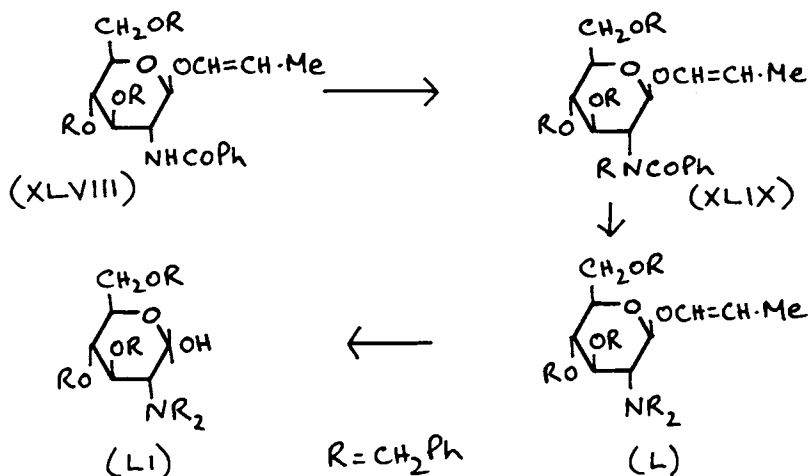
butoxide, to isomerise the allyl group and remove the but-2-enyl group, giving the prop-1-enyl glycoside (XXXIII) which was then treated with 'crotyl bromide' and sodium hydride to give the but-2-enyl ether (XXXIV) (61).

In all of our early work on the use of potassium *t*-butoxide in dimethyl sulphoxide for the rearrangement of allyl ethers we used laboratory prepared potassium *t*-butoxide. Recently this material has become commercially available in the U.K. and the commercial material is considerably more active than our own preparation. Allyl ethers are rapidly isomerised at 20° by the commercial material whereas we routinely used higher temperatures in our early work. Many other groups (62-75) have found the allyl ethers useful as protecting groups in the preparation of carbohydrate derivatives and other compounds.

1,2-Cis-Glycoside Synthesis

The long standing problem of 1,2-*cis*-glycoside synthesis has been fully reviewed (36-38) and at the outset of our work on the synthesis of the glycolipids this was our major concern since many of these compounds contained this glycosidic linkage. When considering our projected general oligosaccharide synthesis using benzyl ethers for 'persistent' protection and allyl ethers for 'temporary' protection we were encouraged by earlier work which showed higher yields of 1,2-*cis*-glycosides when non-participating groups were present on the 2-position (36-38) and by the work of Ishikawa and Fletcher (76) on the relative rates of reaction of fully benzylated α - and β -glycosyl halides. We adopted these ideas in our initial work and developed (39) simultaneously, a similar route to 1,2-*cis*-glycosides as that used by Lemieux and his co-workers (11,77,78) and termed by him "halide catalysed glycosidation reactions". However, since we intended to use allyl ethers as protecting groups in the glycosyl halides, we decided to avoid using the glycosyl bromides since their preparation could lead to problems with the unsaturated centres of the allyl groups and we therefore concentrated on the reactions of the glycosyl chlorides.

Our other concern at this stage was the feasibility of using perbenzylated intermediates; the degree of steric hindrance that might result from their use and also the physical properties of the products. Our initial experiments (39) were carried out with fully benzylated glucosyl chlorides and some of the tri-*O*-benzyl ethers of benzyl α -D-galactopyranoside. Using dichloromethane as a solvent, tetraethylammonium chloride as a chloride source and triethylamine as a base, to remove the hydrogen chloride liberated, we showed that the fully benzylated glucosyl chloride (XXXVI) gave high yields of glycosides when condensed with benzyl 2,3,4-tri-*O*-benzyl- α -D-galactopyranoside (XXXVII) and the product was moreover crystalline. N.m.r. spectroscopy of the crude disaccharide derivative also showed a high proportion of the



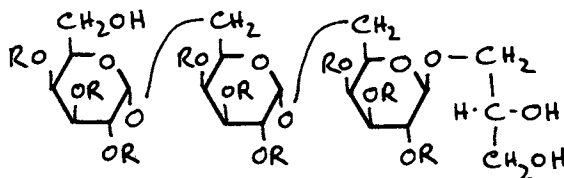
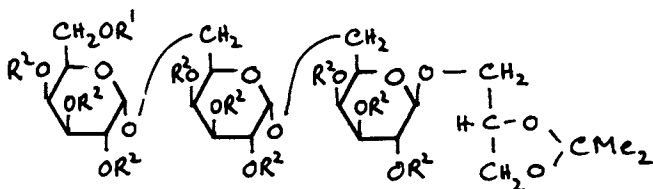
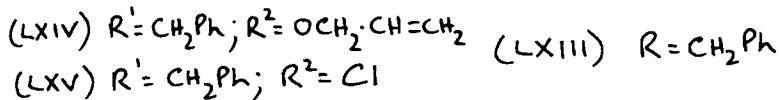
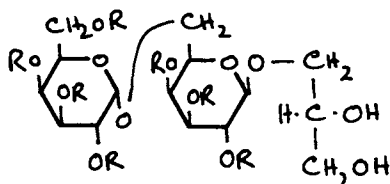
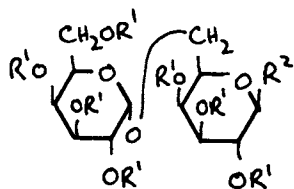
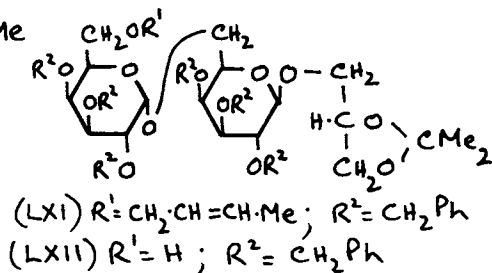
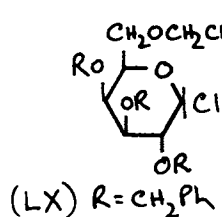
1,2-*cis*-glycoside (XXXVIII) (ca 90%). Using benzyl 3,4,6-tri-*O*-benzyl- α -D-galactopyranoside (XXXIX) as the aglycone (i.e. reaction with a secondary hydroxyl group) lower yields (39) of the disaccharide were obtained but the 1,2-*cis*-glycoside (XL) was present in the same high proportion and the product was again crystalline and therefore could be readily separated from the small amount of 1,2-*trans*-glycoside present.

The reactions were conducted at ca. 80° to achieve a reasonable rate and with dichloromethane as a solvent the reaction had to be carried out in a sealed tube. We subsequently (79) showed that 1,2-dichloroethane was a suitable solvent and thus the reaction could be carried out in an open flask and more readily followed by t.l.c.

The glycosyl chlorides are less reactive than the bromides in this reaction and we have considered (79) using tetraethylammonium bromide in place of tetraethylammonium chloride in the reaction mixture so that the β -glycosyl bromide can be formed directly from the α -glycosyl chloride in the reaction mixture, thus avoiding any problems associated with the formation of glycosyl bromides by conventional procedures. Igarishi and his co-workers (80) have also described a procedure for 1,2-*cis*-glycoside synthesis under mild conditions using glycosylchlorides and silver perchlorate. We have shown (81) that the condensation of 2,3,4,6-tetra-*O*-benzyl-D-glucosyl chloride (XXXVI) with benzyl 2,3,4-tri-*O*-benzyl- α -D-galactopyranoside (XXXVII) under their conditions gives a similar yield of the mixture of the 1,2-*cis*-glycoside (XXXVIII) (ca. 90%) and 1,2-*trans*-glycoside as we obtained by the method described above.

With a successful outcome to our initial experiments on the use of the glycosyl chlorides in the synthesis of 1,2-*cis*-glycosides and the demonstration of the suitability of the perbenzylated derivatives as intermediates, we extended the method by incorporating an allyl group into the glycosyl chloride. When the chloride derived from 2,3,4-tri-*O*-benzyl-6-*O*-(but-2-enyl)-D-galactopyranose (XXXV) was condensed with the galactopyranoside (XXXVII) similar yields of the crystalline 1,2-*cis*-glycoside (XLI) were obtained (60) thus demonstrating that the allyl ethers were suitable protecting groups under these conditions. The action of potassium *t*-butoxide in dimethyl sulphoxide on the disaccharide derivative (XLI) gave the crystalline alcohol (XLII) which was suitably protected for further glycosidation reactions or for oxidation by methods described previously (82, 83), for use in the presence of benzyl ethers, to give the corresponding uronic acid derivative (XLIII). Several uronic acid containing bacterial glycolipids have been described (12-14).

Many of the glycolipids in which we were interested contained 1,2-*cis*-linked 2-amino sugars (particularly 2-amino-2-deoxy-D-galactose) and we envisaged a route to these compounds by using the 2-*O*-allyl group as a non-participant in an otherwise fully



benzylated glycosyl halide. 2-O-Allyl-3,4,6-tri-O-benzyl-D-galactopyranose was prepared, as described above for the corresponding glucose derivative (XXXI), and was converted into the chloride (XLIV) which was condensed with the galactoside (XXXVII) to give the crystalline 1,2-cis-linked disaccharide derivative (XLV). Removal of the allyl group by potassium t-butoxide in dimethyl sulphoxide gave the crystalline alcohol (XLVI) (84). Oxidation of the free hydroxyl group of compound (XLVI) with acetic anhydride-dimethyl sulphoxide gave the crystalline ketone (XLVII) (15).

2-Keto sugars (in the form of their oximes) have previously been converted into amines by Lemieux and his co-workers (85, 86) during their work on the nitrosyl chloride route to 1,2-cis-glycoside synthesis. In some cases the conversion into the amine was fairly stereospecific (e.g. the preparation of 1,2-cis-linked 2-amino-2-deoxy-D-glucose derivatives) but in other cases (particularly with 2-amino-2-deoxy-D-galactose derivatives) the conversion was far less stereospecific (85, 86).

A further route to 1,2-cis-linked 2-amino-2-deoxy-sugar glycosides was envisaged by using the N,N-dibenzylamino derivative as a non-participating group. Thus the fully benzylated derivative (LI) of 2-amino-2-deoxy-D-glucose was prepared (39) from the prop-1-enyl glycoside (XLVIII). Benzylation of compound (XLVIII) with benzyl chloride and sodium hydride in tetrahydrofuran gave the N-benzyl benzamido derivative (XLIX). Benzylation under different conditions (15) (particularly with benzyl chloride and sodium hydride in N,N-dimethylformamide) leads to considerable O-benzylation of the benzamido group. Compound (XLIX) was readily reduced with lithium aluminium hydride to give the N,N-dibenzyl derivative (L) which on acid hydrolysis gave the free sugar (LI).

Recently, Paulsen and Stenzel (87) have shown that the 2-azido group is a suitable non-participant for the synthesis of 1,2-cis-linked 2-amino-2-deoxy-D-glucose derivatives and we have prepared (54) the crystalline p-nitrobenzoate of the azide (LIII) from the epoxide (LII) for investigating the preparation of 1,2-cis-linked 2-amino-2-deoxy-D-galactosides by this method.

For the synthesis of 1,2-trans-glycoside linkages, which occur in the glycolipids, both the Koenigs-Knorr and the ortho-ester methods have been well developed (36-38) and the latter method has been used successfully with fully benzylated ortho-esters (88). The oxazoline method for the synthesis of 1,2-trans-glycosides of 2-acetamido-2-deoxy sugars has also been well established (36-38). These methods of 1,2-trans-glycoside synthesis should be applicable in the presence of allyl and benzyl ether protecting groups.

With a general route to oligosaccharide synthesis thus established in outline, we were in a position to use the methods for the synthesis of some of the glycolipids.

Synthesis of Galactosyl Diglycerides

Mono-(LIV) and digalactosyl diglycerides (LV) were first isolated from wheat flour lipids (21-23) and were subsequently shown to be present in human brain (89), many plant tissues (13, 14) and various microorganisms (12-14). Subsequently tri- (V) (24,25) and tetra-galactosyl diglycerides (90) were also isolated from plants.

(LIV) β -D-Gal(1 \rightarrow 3) 1,2-Di-O-acyl-L-glycerol

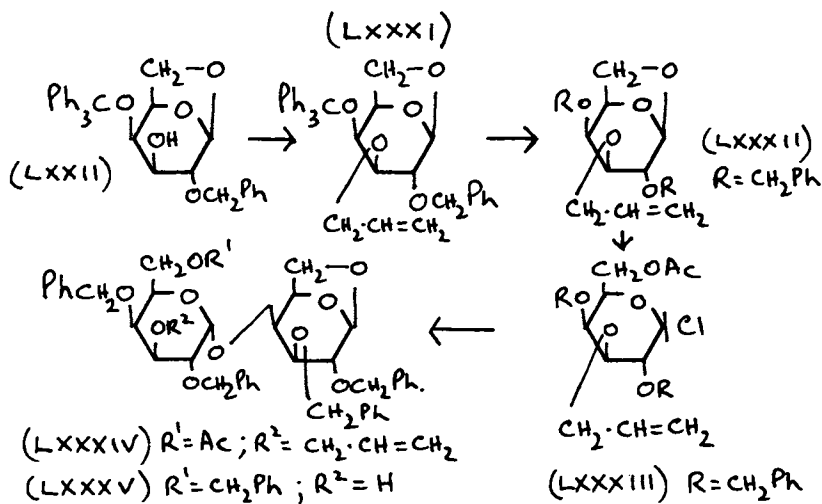
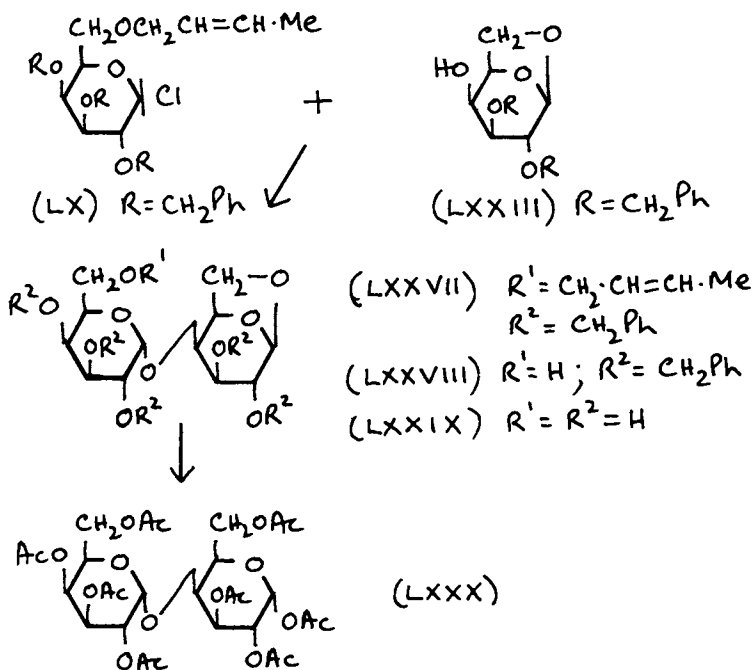
(LV) α -D-Gal(1 \rightarrow 6) β -D-Gal(1 \rightarrow 3) 1,2-Di-O-acyl-L-glycerol

Our main interest in this series of glycolipids was to try to confirm, by synthesis, that the serologically active glycolipids of *Mycoplasma pneumoniae* (17-20) (which are not readily available by isolation (19)) had the same structures as the plant glycolipids since the trigalactosyl diglyceride fraction from spinach had been shown (19) to have similar serological activity.

The route to the trigalactosyl diglyceride using our general method of oligosaccharide synthesis required the preparation of a protected derivative of 3-O-(β -D-galactopyranosyl)-L-glycerol. It has been shown previously (91-92) that chiral isopropylidene glycerol is not a suitable intermediate for the preparation of 1,2-trans-glycosides by the Koenigs-Knorr procedure because of the migration of the isopropylidene group and racemisation. We therefore carried out the Koenigs-Knorr reaction with 1,2-di-O-benzyl-L-glycerol and 2,3,4,6-tetra-O-acetyl-D-galactopyranosyl bromide and the product (LVI) was converted into the isopropylidene derivative (LVIII) which was purified by reversible conversion into the crystalline 3-O-(2,3,4-tri-O-benzyl- β -galactopyranosyl)-L-glycerol (LIX) (61). Compound (LVIII) was readily converted (61) into a mono-galactosyl diglyceride (LIV) and into a 3-O-(6-O-acyl- β -D-galactopyranosyl)-1,2-di-O-acyl-L-glycerol; a compound which is formed by enzymic transacylation during the isolation of mono-galactosyl diglycerides (93, 94).

It has been shown (95) that, in the presence of racemic isopropylidene glycerol, enzymic transfer of galactose from lactose to 1,2-O-isopropylidene-L-glycerol can occur to give the 3-O-(β -D-galactopyranosyl)-1,2-O-isopropylidene-L-glycerol (LVII) and this enzymic reaction might well provide a simpler route to the derivative (LVIII).

Condensation of the chloride (LX) derived from the galactopyranose derivative (XXXV), with the isopropylidene derivative (LVIII) under the conditions which we have established for 1,2-cis-glycoside synthesis gave the crystalline digalactosyl glycerol derivative (LXI) which on treatment with potassium t-butoxide in dimethyl sulphoxide gave (79) the crystalline alcohol (LXII) which was thus suitably substituted for a further



glycosidic condensation. Compound (LXII) was also converted (79) into a digalactosyl diglyceride (LV) and can also be converted readily into the benzylated digalactosyl glycerol derivative (LXIII).

Vicinal sulphonates are readily eliminated on treatment with zinc and sodium iodide in refluxing acetone and thus glycerol moieties can be converted into allyl groups (61). Conversion of compound (LXIII) into the allyl glycoside (LXIV) by this method and subsequent removal of the allyl group by the methods described above should give a free sugar suitable for conversion (via the *p*-nitrobenzoate) into the chloride (LXV) which could be used for the addition of a disaccharide moiety in 1,2-*cis*-linkage. Thus the condensation of the chloride (LXV) with the crystalline intermediate (LXII) should give a derivative suitable for the preparation of tetragalactosyl diglycerides.

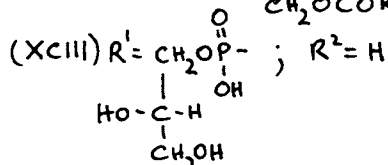
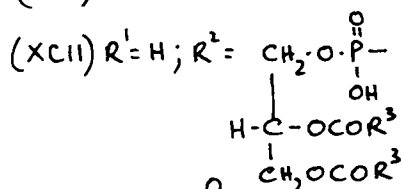
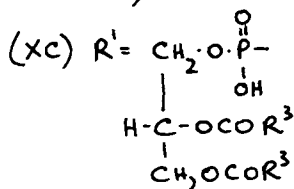
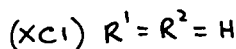
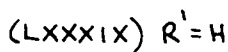
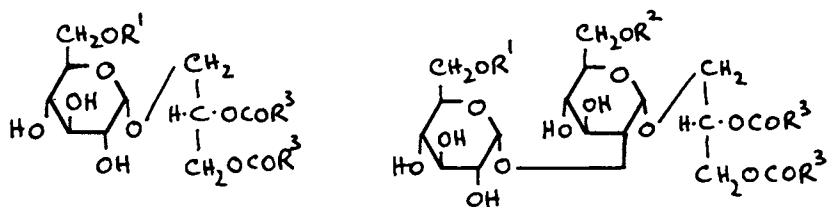
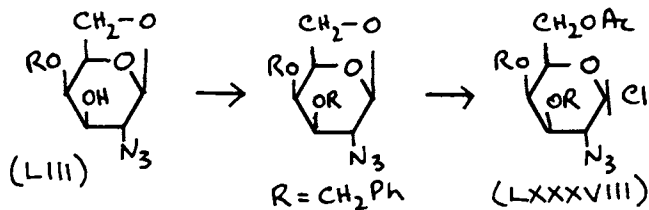
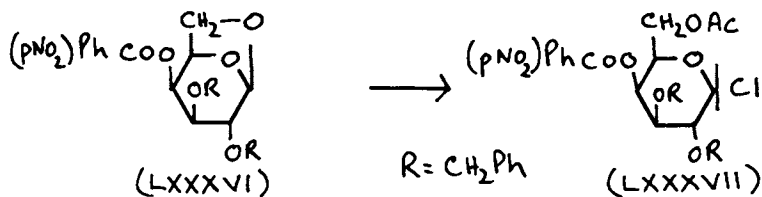
A further condensation of the chloride (LX) with the protected digalactosyl glycerol (LXII) gave the crude trigalactosyl glycerol derivative (LXVI) which was converted into the alcohol (LXVII). Compound (LXVII) was purified by reversible conversion into the crystalline tris-*p*-nitrobenzoate of the triol (LXVIII) (96). Compound (LXVIII) was readily converted (96) into the trigalactosyl diglyceride (V) but this compound showed (97) "no antigenic activity against either human or rabbit antiserum as compared to similar material extracted from spinach", indicating that the serologically active glycolipids of *Mycoplasma pneumoniae* do not have this structure in the oligosaccharide portion. Glucose and galactose containing glycosyl diglycerides have also been detected in plant lipids (98, 99) and in *Mycoplasma pneumoniae* (17) and it is possible that the serological cross-reactivity observed (19) between the trigalactosyl diglyceride fraction of spinach and *Mycoplasma pneumoniae* glycolipids may be due to these species of glycolipids.

Intermediates for the Synthesis of the Forssman and P¹-Antigens

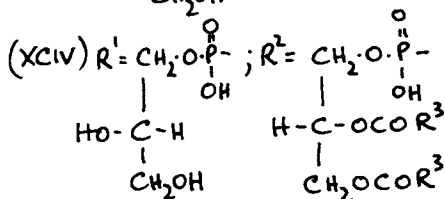
Recently (100) the P¹-antigen of human erythrocytes has been isolated and characterised. This compound (LXIX) has a terminal α -D-gal (1 \rightarrow 4) D-gal linkage and this disaccharide unit is also present in the Forssman antigen (1) and in several other mammalian glycolipids (14).

α -Gal(1 \rightarrow 4) β -Gal(1 \rightarrow 4) β -NAcgluc(1 \rightarrow 3) β -Gal(1 \rightarrow 4)Gluc-Ceramide (LXIX)

The axial 4-hydroxyl group of galactopyranose derivatives in the ⁴C₁ conformation is very unreactive in glycoside forming reactions and thus derivatives of 1,6-anhydro- β -D-galactopyranose, where the 4-hydroxyl group of the ¹C₄ conformation is equatorial, have been used (101, 102) for glycosidation reactions at this position. The 2,3-di-O-acetyl derivative has been used (101, 102) in these reactions but the ease (103) of acetyl migration in this compound, which would probably be enhanced under the basic



$\text{R}^3 =$ long chain
alkyl radical

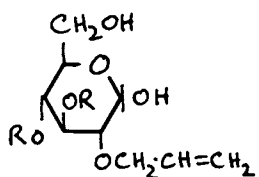
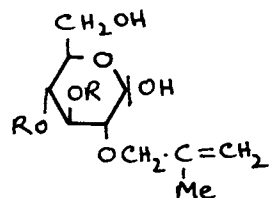
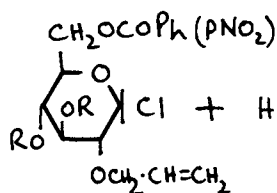
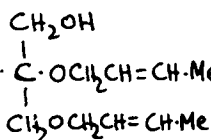


conditions of our 1,2-*cis*-glycoside synthesis, led us to consider the synthesis and use of the 1,6-anhydro-2,3-di-0-benzyl- β -D-galactopyranose (LXXIII). Compound (LXXIII) was prepared (54) by four different methods, mainly by using allyl ethers as protecting groups, and was isolated and characterised as the crystalline p-nitrobenzoate. The most convenient method involved allylation of the epoxide (LXXVI) (104, 105). The product was hydrolysed with base to give the diol (LXXV) which was benzylated and the allyl group was subsequently removed to give the required dibenzyl ether (LXXIII). A further route involving both allyl and but-2-enyl ethers was the conversion of compound (LXX) into the prop-1-enyl ether (LXXI) by the action of potassium t-butoxide in dimethyl sulphoxide. The addition of benzyl chloride to the reaction medium then gave the dibenzyl ether of compound (LXXI) directly and subsequent hydrolysis of the prop-1-enyl group gave the required dibenzyl ether (LXXIII). Tritylation of 1,6-anhydro-2-0-benzyl- β -D-galactopyranose (LXXIV) gave the trityl ether (LXXII) which was also converted into the dibenzyl ether (LXXIII).

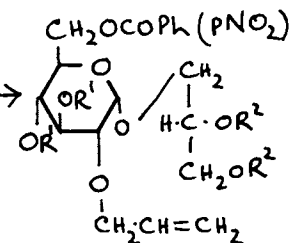
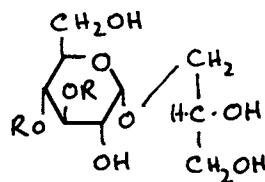
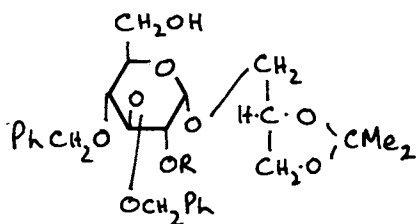
Condensation (54) of the chloride (LX) with 1,6-anhydro-2,3-di-0-benzyl- β -D-galactopyranose (LXXIII) under the conditions which we have developed for 1,2-*cis*-glycoside synthesis gave the crude glycoside (LXXVII) which was converted into the alcohol (LXXVIII) by the action of potassium t-butoxide in dimethyl sulphoxide. Hydrogenolysis gave the crude 1,6-anhydro-4-0-(α -D-galactopyranosyl)- β -D-galactopyranose (LXXIX). Acetylation of compound (LXXIX) and subsequent acetylation gave directly (54) the crystalline octaacetate (LXXX) which has been prepared previously (102) by a Koenigs-Knorr condensation which gave a mixture of the α - and β - linked disaccharides in a ratio of 4:3. Compound (LXXX) is suitably substituted for conversion into a glycosyl halide and for addition in 1,2-*trans*-glycoside linkage to a protected derivative of N-acetyl-D-glucosamine to give the terminal trisaccharide unit of the P¹-antigen (LXIX).

In the Forssman antigen (I) the α -D-gal (1 \rightarrow 4) D-gal unit is substituted at the 3-position of the non-reducing end by an N-acetyl-galactosamine residue and we required a suitably substituted derivative to achieve a glycosidation reaction at this position. Thus a route to the derivative (LXXXV) has been planned. Allylation of the trityl derivative (LXXII) gave (54) the crystalline allyl derivative (LXXXI) which was converted into 3-0-allyl-1,6-anhydro-2,4-di-0-benzyl- β -D-galactopyranose (LXXXII). Conversion of compound (LXXXII) into (LXXXIII) and condensation with compound (LXXIII) should give the 1,2-*cis*-linked disaccharide (LXXXIV) which could be converted into the required derivative (LXXXV).

In considering the conversion of 1,6-anhydro- β -D-galactopyranose derivatives [e.g. (LXXXII)] into galactopyranosyl chlorides [e.g. (LXXXIII)] we recalled our work on the conversion

(XCV) $R = \text{CH}_2\text{Ph}$ (XCVI) $R = \text{CH}_2\text{Ph}$ (XCVII) $R = \text{CH}_2\text{Ph}$ 

(XCVIII)

(XCIX) $R^1 = \text{CH}_2\text{Ph};$
 $R^2 = \text{CH}_2\text{CH}=\text{CH}\cdot\text{Me}$ (C) $R = \text{CH}_2\text{Ph}$ (C1) $R = \text{H}$ (C11) $R = \text{CH}_2\text{-C}(\text{Me})=\text{CH}_2$

of aliphatic acetals into chloro-ethers by the action of acetyl chloride, which we had used in the synthesis (41,42) of the plasmalogens. When the crystalline *p*-nitrobenzoate (LXXXVI) was treated with acetyl chloride at 20° for four days it was converted (54) into the chloride (LXXXVII) which was characterised by conversion into a known methyl galactopyranoside. This reaction which we have termed (54) "chloracetolysis" should be useful in this series of compounds and we found subsequently that a similar reaction catalysed by titanium tetrachloride, had previously been reported (106). The conversion of the azide (LIII) into the chloride (LXXXVIII), by this method, is under investigation since the latter compound should be a suitable intermediate for the synthesis of the α -NAc gal (1 \rightarrow 3) NAc gal residue present in the Forssman antigen, in view of the work reported by Paulsen and Stenzel (87).

The Serologically Active Glycolipids of Streptococci.

Mono-(LXXXIX), di-(XCI) and triglucosyl diglycerides (VI) have been isolated from various Streptococci (12-14,26-28). More recently phosphorylated derivatives (XC, XCII, XCIII, XCIV) of these glycolipids were isolated and characterised (107-111) and the immunochemical activities of these compounds have been investigated (29, 30).

For synthetic studies in this series of glycolipids we aimed for an intermediate which would be potentially useful for the synthesis of all of these neutral and phosphorylated glycolipids. 2-O-Allyl-3,4-di-O-benzyl-D-glucopyranose (XCV) was therefore prepared (59) and converted by way of the bis *p*-nitrobenzoate into the glucosyl chloride (XCVII) (58). Condensation of compound (XCVII) with 1,2-di-O-(but-2-enyl)-L-glycerol (XCVIII) (58) under the conditions which we have described for 1,2-cis-glycoside synthesis gave the crude glucosyl glycerol derivative (XCIX) which, after removal of the acyl, allyl and but-2-enyl groups by the standard procedure, gave the crude 3-O-(3,4-di-O-benzyl- α -D-glucopyranosyl)-L-glycerol (C). Compound (C) was converted (58) into the crystalline isopropylidene derivative (CI) which has also been converted (15) into the crystalline monoglucosyl diglyceride (LXXXIX) containing octadecanoyl groups on the glycerol moiety.

Our desire to obtain a crystalline derivative after the 1,2-cis-glycosidation reaction (to allow us to remove the small amount of 1,2-trans-glycoside which is formed) has, in this case, resulted in the loss of the built in differential protection which was used on the 2- and 6-positions of the glucose molecule. However the 2- and 6-positions of compound (CI) can be readily differentiated and present work is aimed at converting compound (CI) into the neutral and phosphorylated oligoglucosyl diglycerides.

The direct glycosidation of 1,2-O-isopropylidene-L-glycerol is also being investigated in this case but we have suspected previously (61) that migration of the isopropylidene group occurs under the conditions of our 1,2-cis-glycosidation reaction as it does during the Koenigs-Knorr reaction (91,92). The use of the 2-methylallyl derivative (XCVI) is also being investigated since this should result in the direct synthesis of the glucosyl glycerol derivative (CII) because we have shown (35) that the but-2-enyl group can be removed by the action of potassium t-butoxide in dimethyl sulphoxide, without effecting the isomerisation of the 2-methylallyl group.

Conclusion

The preparations which we have carried out so far along the lines of our proposed general oligosaccharide synthesis using benzyl ethers for 'persistent' protection and allyl ethers for 'temporary' protection have been successful and thus give us considerable encouragement for future work. In particular the use of this method in the preparation of 1,2-cis-linked glycosides has led, in most cases, to crystalline derivatives thus allowing the purification of the product from the small amount of 1,2-trans-isomer formed. The method also shows potential for the synthesis of amino-sugar and uronic acid containing oligosaccharides such as occur in many of the glycolipids. The preparation of benzyl ethers is readily accomplished (112) and we have experienced no difficulty in their removal by hydrogenolysis.

Acknowledgements

I should like to thank my co-workers Drs. Jill Gigg (née Cunningham), Patricia A. Gent, Christopher D. Warren and latterly Anna A.E. Penglis together with Mr. Robert Conant for their dedicated efforts which have led to the results described in this article.

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