

APPLICATION OF OXO REACTION TO TWO SUGAR EPOXIDES

by

RAJINDER MOHAN KALRA

B.Sc.(Hons)., University of Panjab, 1963

M.Sc., University of Panjab, 1964

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

Master of Science

in the Department

of

Chemistry

We accept this thesis as conforming to the
required standard.

June, 1967

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the Head of my Department or by his representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of Chemistry

The University of British Columbia
Vancouver 8, Canada

Date 26/6/67

ABSTRACT

Methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside was allowed to react with carbon monoxide and methanol in the presence of dicobalt octacarbonyl at elevated temperatures and pressures. The resulting product mixture contained unreacted epoxide, methyl 3-O-methyl- α -D-altropyranoside and methyl 4,6-O-benzylidene- α -D-altropyranoside.

Methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside was allowed to react with carbon monoxide (990 p.s.i.) and hydrogen (910 p.s.i.) in the presence of dicobalt octacarbonyl at 140°. The resulting product mixture contained two products. The n.m.r. indicated that the epoxide ring had not been opened. In one product, the benzylidene ring was completely removed and in the other component the benzylidene ring had been partially altered.

When Brigl's anhydride was allowed to react with carbon monoxide (910 p.s.i.) and hydrogen (990 p.s.i.) in the presence of dicobalt octacarbonyl at 106° for 30 minutes, the resulting product mixture contained one major product and two minor products. The minor product was presumed to be a sugar and the major product (75-80%) had been characterized as 2,6-anhydro-D-glycero-D-gulo-heptitol.

CONTENTS

	Page
HISTORICAL INTRODUCTION	
Sugar Epoxides	
(i) Synthesis	1
(ii) The Stereochemistry of Epoxide Formation	4
(iii) Reactions	7
The Oxo Reaction	
(i) Nature of the Catalyst	11
(ii) Mechanism of the Oxo Reaction	13
(iii) Application to Carbohydrate Chemistry	16
(iv) Application to Epoxides	16
DISCUSSION	
A. Hydroformylation Reactions of Methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside	
(i) Synthesis of Methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside	20
(ii) Fractionation and Characterization of Reaction Products	23
B. Hydroformylation of 1,2-anhydro- α -D-glucopyranose triacetate (Brigl's anhydride)	
(i) Synthesis of Brigl's anhydride	29
(ii) Identification and characterization of Products	32

EXPERIMENTAL

General Considerations

36

Experimental Section A

Synthesis of 2,3-Anhydro-4,6-O-benzylidene
methyl- α -D-mannopyranoside

38

Hydroformylation of 2,3-anhydro-4,6-O-
benzylidene methyl- α -D-mannopyranoside
with carbon monoxide and methanol

40

Characterization of Fractions I, II, III,
and IV

42

Synthesis of Methyl 4,6-O-benzylidene- α -D-
altropyranoside

43

Synthesis of Methyl 4,6-O-benzylidene
3-O-methyl- α -D-altropyranoside

45

Summary of work Table I and II

48-49

Hydroformylation of Methyl 2,3-anhydro
4,6-O-benzylidene- α -D-mannopyranoside with
Carbon Monoxide and Hydrogen

50

Preparation of 2,4-Dinitrophenyl hydrazone
derivatives of Oxo Product

51

Gas liquid chromatography of trimethyl
silyl derivatives of the Oxo Product

52

Characterization and Identification of Products

53

Synthesis of Methyl 2,3-anhydro- α -D-
mannopyranoside

54

Experimental Section B

Synthesis of 1,2-anhydro- α -D-glucopyranose
triacetate (Brigl's anhydride)

55

An improved synthesis of Brigl's anhydride

58

	Page
Hydroformylation of Brigl's anhydride	59
Preparation of 2,4-Dinitrophenyl hydrazone derivative of Oxo Product	60
Gas liquid chromatographic separation of the acetylated polyols derived from the Oxo Product	61
Product Determination by Paper Chromatography	62
Characterization of Fractions I, II and III	63
REFERENCES	65
Figure I	68
Figure II	69

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to Professor A. Rosenthal for his encouragement and guidance throughout the investigation. I also wish to thank Dr. L. D. Hall and Mr. J. Manville for their assistance.

Grateful acknowledgement is also made to Dr. J. N. C. Whyte and Mr. H. J. Koch for their advice and assistance. I wish to express my gratitude to Professor C. A. McDowell for his interest and encouragement during my research.

I am indebted to my wife for her co-operation.

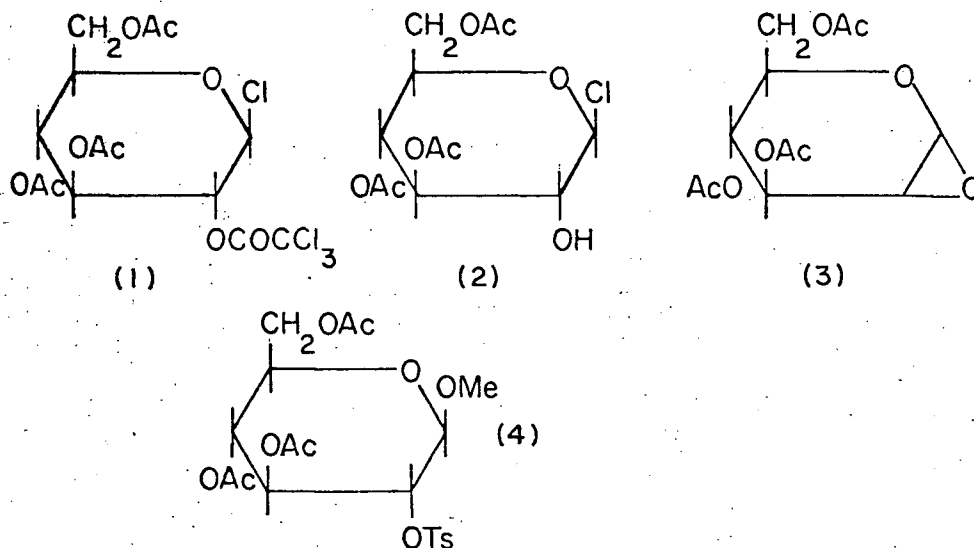
HISTORICAL INTRODUCTION

Synthesis of Sugar Epoxides

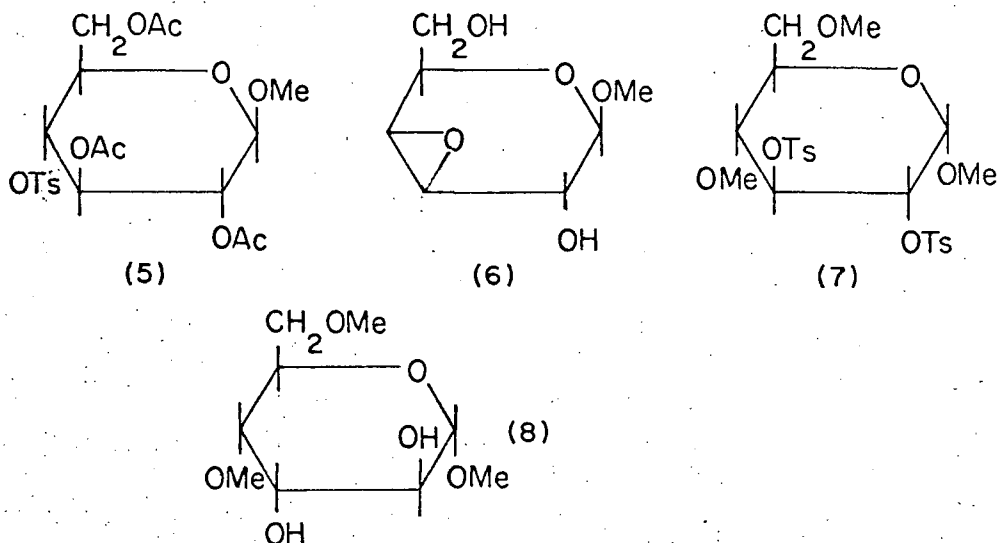
Sugar epoxides encompass a particular group of anhydro sugars in which a linkage of the ethylene oxide type is found.

The earliest reference for the preparation of a sugar epoxide was an intermediate postulated by Fischer¹ in his preparation of methyl epi-glucosaminide (methyl-3-amino-3-deoxy- β -D-altroside). The postulated intermediate was methyl 2,3-anhydro- β -D-mannopyranoside.

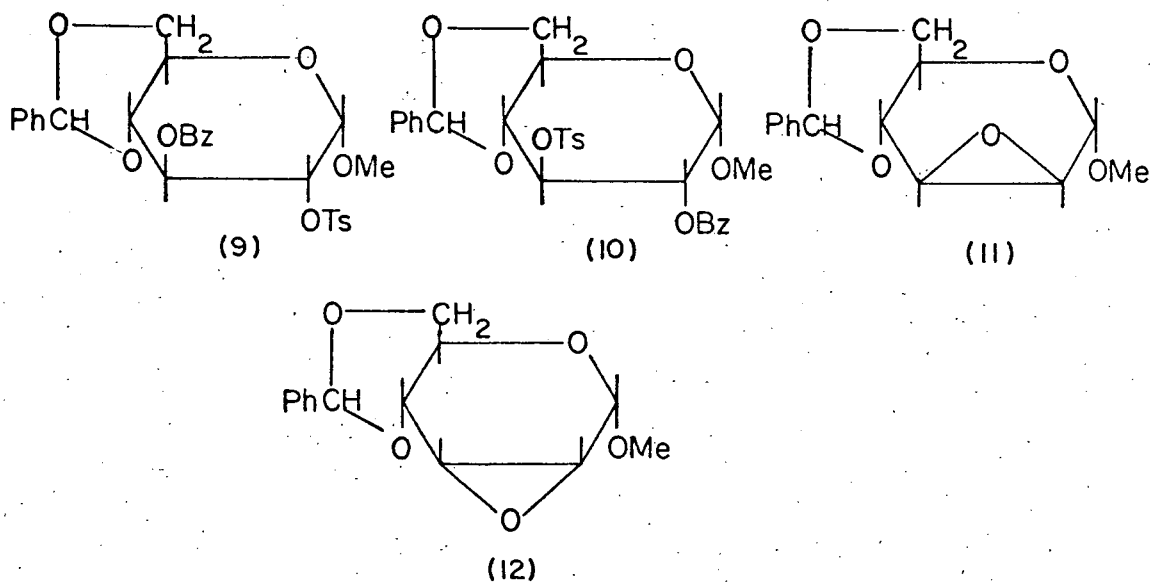
The first example of a sugar epoxide was given by Brigl² in 1921. He found that when tetra-O-acetyl- β -D-glucopyranoside was treated with phosphorus pentachloride 3,4,6-tri-O-acetyl-2-O-trichloroacetyl- β -D-gluco-pyranosyl chloride (1) was formed. Careful treatment of this compound with ammonia removed only the O-trichloroacetyl group forming 3,4,6-tri-O-acetyl- β -D-glucopyranosyl chloride (2) and on further mild treatment with ammonia this was converted into 3,4,6-tri-O-acetyl-1,2-anhydro- α -D-glucopyranose (3). This compound is a valuable synthetic intermediate. It reacts with methanol to give methyl 3,4,6-tri-O-acetyl- β -D-glucopyranoside and the 2-O-tosyl derivative (4) was important in establishing the chemistry of the 2,3-epoxides.



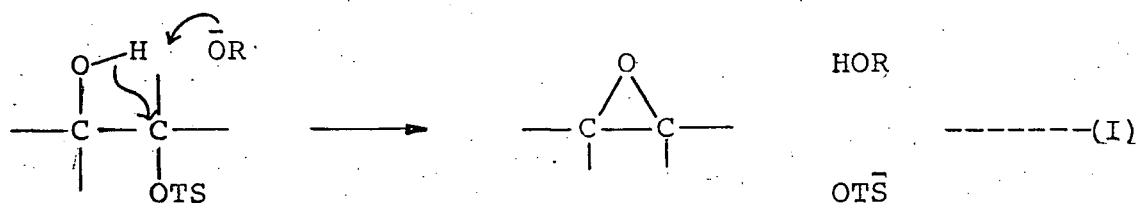
Helferich and Müller³ isolated a crystalline methyl anhydro-β-D-hexoside after treating methyl 2,3,6-tri-O-acetyl-4-O-tosyl-β-D-glucopyranoside (5) with sodium methoxide; this product was shown by Müller to be methyl 3,4-anhydro-β-D-galactoside (6). An anhydro sugar was obtained from methyl 4,6-di-O-methyl-2,3-di-O-tosyl-α-D-glucopyranoside (7) and under the alkaline conditions some methyl 4,6-di-O-methyl-α-D-altroside (8) was also produced.



The manner in which these reactions were proceeding was now becoming apparent and Robertson and Griffith⁴ showed that the products obtained from methyl 3-O-benzoyl-4,6-O benzylidene-2-O-tosyl- α -D-glucopyranoside (9) and methyl 2-O-benzoyl-4,6-O-benzylidene-3-O-tosyl- α -D-glucopyranoside (10) by treatment with sodium methoxide were methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside (11) and α -D-allopyranoside (12) respectively.



In all these reactions the formation of an anhydro ring has been accompanied by inversion of configuration at the carbon atom to which the sulfonyl group was attached. In the alkaline medium the anion of the vicinal trans-hydroxyl group can displace the p-toluenesulfonyl group to form the epoxide.



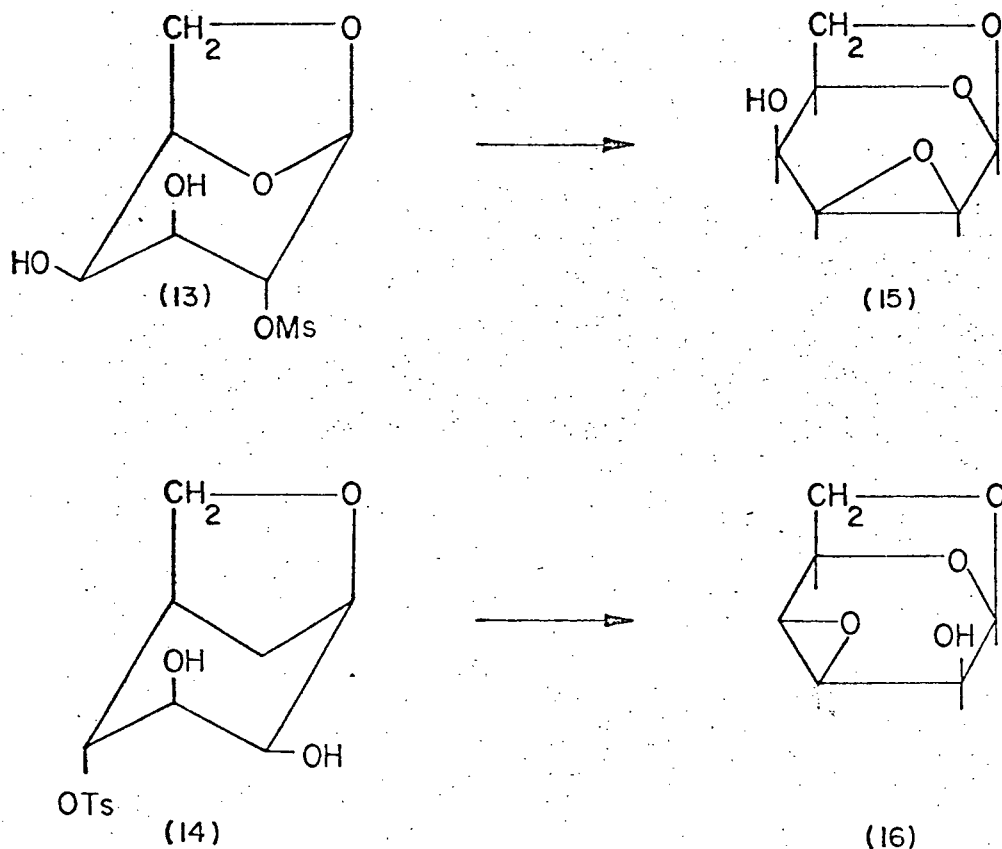
The Stereochemistry of Epoxide Formation

The Haworth ring formulae show configurational changes but do not help in finding the steric cause of different reactivities or the reason why a reaction follows a particular course. It was not until the introduction of conformational analysis that intra-molecular interactions became apparent and an explanation could be given for such behaviour.

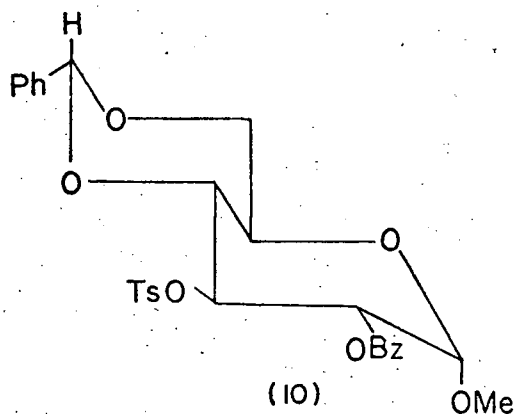
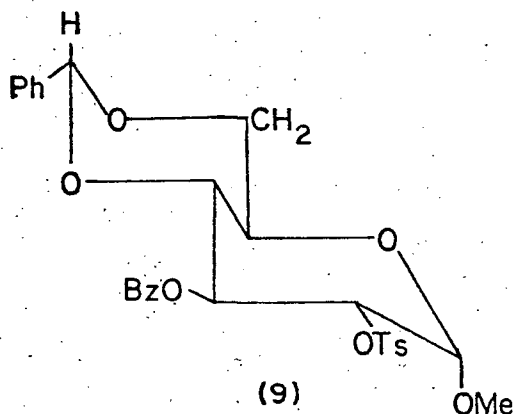
In the base catalysed formation of an epoxide from a trans 1,2-diol mono-O-p-toluenesulfonate, the intra-molecular SN_2 type process in a six membered ring requires the two groups to be in the diaxial position. The entering and departing anion and the carbon atoms to which they are attached are then believed to be co-planar and this permits maximum participation.

This condition is found in 1,6-anhydro-2-O-methane sulfonyl- β -D-galactose (13) and 1,6-anhydro-4-O-tosyl- β -D-

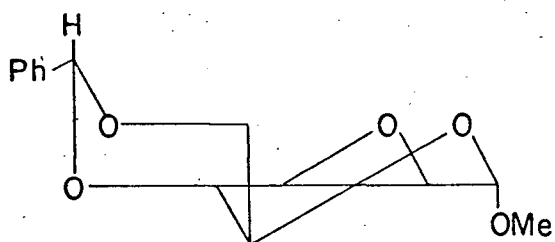
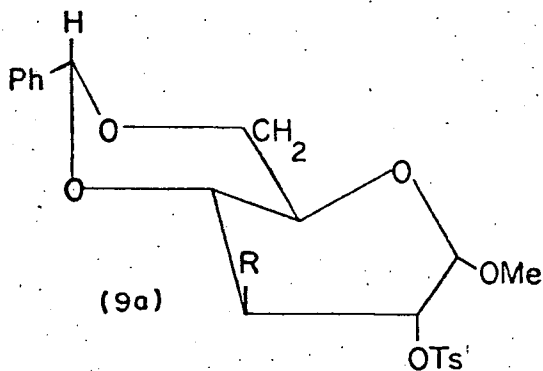
mannose (14) and they are easily converted into 2,3⁵ (15) and the 3,4⁶ -taloepoxide (16) by mild alkali.



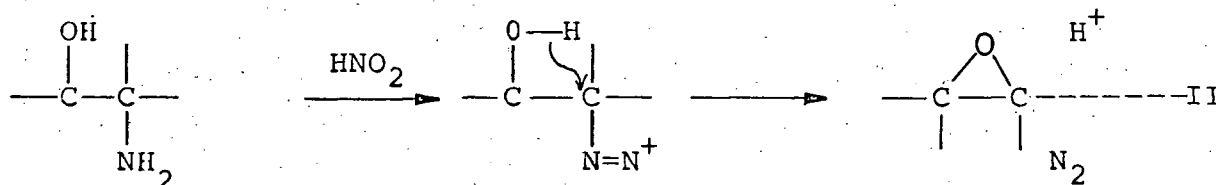
The majority of p-toluene sulfonyl groups vicinal to a trans hydroxyl group are, however, in di-equatorial position, as for example in the 2-(9) and the 3-O-tosyl derivatives (10) which are smoothly converted into the manno (11) and allo-epoxides (12). The ease with which these compounds react suggests structural modification before epoxide formation.



In a monocyclic system the di-equatorial groups can pass into the diaxial position by a change in conformation of the ring from 4C_1 to 1C_4 but in the bicyclic compounds (9) and (10), the trans fused bicyclic system containing 4,6-O-benzylidene group shows rigidity in the chair form of the sugar ring. Carbon -2 on the other hand, can move to give the boat form (9a) without disturbing the point of ring fission and the two groups at C-2 and C-3 are now co-planar and in a position to react⁷.



Another method of sugar epoxide preparation is the deamination by nitrous acid of an amino deoxy group with vicinal trans hydroxyl group.



Reactions of Sugar Epoxides

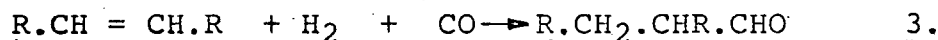
Anhydrosugars of the ethylene oxide type are widely utilized in the synthetic chemistry of sugars. The ethylene oxide ring is very reactive and is split by a number of alkaline and acid reagents with the formation of the most varied derivatives.

Sugar epoxides undergo addition by an acid. The epoxide oxygen remains on one carbon atom and the attacking species on the other.

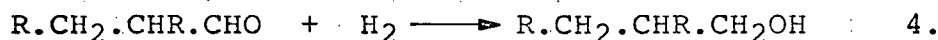
Mills^{7a} first suggested the applicability to sugar epoxides of Furst and Plattner's rule that steroid epoxides break to give predominantly the axial isomer. This in fact can be demonstrated only with rigid systems since flexible systems might intraconvert.

Peat⁸ has described the stereochemistry ring opening by nucleophilic reagents. It is only necessary

The stoichiometry of aldehyde formation is as shown in equation 3.



This reaction is often referred to as hydroformylation⁹ being formally equivalent to the addition of hydrogen and a formyl group at either end of the double bond. Alcohol formation in the oxo reaction (equation 4) results from the further reduction of aldehyde formed by the hydroformylation reaction.



Historically, the oxo reaction developed from the well known process for hydrocarbon synthesis discovered by Fischer and Tropsch¹⁰ in which hydrogen and carbon monoxide at moderate pressure was passed over an iron catalyst. It was observed that small amounts of oxygen containing products were often formed and in 1929 Smith, Hawk and Golden¹¹ obtained an increased yield of oxygenated material when ethylene was added to carbon monoxide-hydrogen mixture before passing it over a cobalt catalyst under Fischer-Tropsch conditions. Credit for the development of the oxo reaction as a commercial process goes largely to Roelen and coworkers of Ruhrchemie A.G. in Germany before

and during World War II¹². By changing the conditions of the Fischer-Tropsch synthesis using a higher pressure and a lower temperature the reaction of ethylene with water gas (equal volumes of carbon monoxide and hydrogen) was made to yield a product consisting of propionaldehyde together with some diethyl ketone, no hydrocarbon being formed. Following World War II the oxo synthesis attracted wide interest, in particular because of its wide range of applicability in the conversion of olefins to aldehydes and alcohols. In general, temperatures between 75° and 200° and pressures of synthesis gas from 100 to 300 atmospheres are employed, higher temperatures being used when alcohols rather than aldehydes are the desired products.

In step with the commercial development of the oxo process, much fundamental work has been carried out on this and related reactions catalysed by the metal carbonyls, and their chemistry has been well reviewed from time to time^{13, 14}. Despite the accumulation of a considerable amount of knowledge of these reactions, many of the finer points of the complex mechanisms are still not known with certainty.

A brief survey will be made of current views regarding the nature of the catalyst and the probable role which it plays in the conversion of olefins to aldehydes, and aldehydes to alcohols.

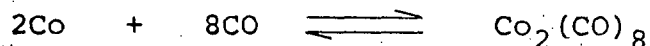
Nature of the Catalyst

In the early stages of development of the Oxo Synthesis in Germany the catalyst used was the conventional Fischer-Tropsch catalyst, consisting of a mixture of metallic cobalt and kieselgur, together with small amounts of thorium and manganese oxides. It became evident to Roelen and coworkers that all the components of the Fischer-Tropsch catalyst, with the exception of cobalt were superfluous, and that the active catalyst was probably a soluble carbonyl of cobalt formed by the in situ reaction of the metal with syntheses gas. This was confirmed by subsequent investigations of the reaction on a laboratory scale. Adkins and Kresk¹⁵ who introduced the use of preformed dicobalt octacarbonyl as catalyst, demonstrated that the hydroformylation reaction was insensitive to sulfur poisoning. The fact that the oxo reaction is catalysed by a cobalt carbonyl contributes to the commercial importance of the process since the form in which cobalt is added is not important, as would be the case with a conventional solid phase catalyst. In practice crude organic salts such as the octanoate or naphthenate are often used.

The divalent cobaltous ion is first reduced to the metal by hydrogen

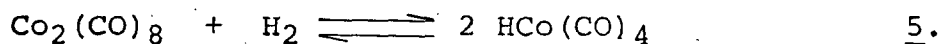


and the metal then reacts with carbon monoxide to form dicobalt octacarbonyl



Hence the presence of both carbon monoxide and hydrogen are required to convert cobalt salts to the carbonyl.

A considerable amount of evidence has accumulated which indicates that the cobalt hydrotetracarbonyl, $\text{HCo}(\text{CO})_4$ rather than dicobalt octacarbonyl, is effective in initiating the oxo reaction. The hydrotetracarbonyl is formed by the reaction of hydrogen with dicobalt octacarbonyl.



This step is thus of fundamental importance in that it involves the activation of molecular hydrogen which is transferred from the gas to the liquid phase. Orchin and coworkers¹⁶ have shown that the hydrotetracarbonyl is present under oxo conditions in the absence of olefin, but when olefin is present no cobalt hydrotetracarbonyl is detectable (as the cobalt tetracarbonyl anion $(\text{Co}(\text{CO})_4)^-$) until hydroformylation of the olefin is complete, when an appreciable amount of the hydrotetracarbonyl again appears in the reaction mixture.

Mechanism of the Oxo Reaction

Evidence for the mechanism of the oxo reaction as carried out under conditions of high temperature and pressure is largely speculative and is based on the results on reactions between olefins and cobalt hydrotetracarbonyl at atmospheric pressure and temperature. Early mechanistic theories ^{17, 18} did not take into account the now well proven intermediacy of cobalt hydrotetracarbonyl and no longer appear to be relevant. An early finding of importance was that the rate of hydroformylation varied inversely with increase in partial pressure of carbon monoxide at constant hydrogen pressure.

The stoichiometry of the reaction of olefins with cobalt hydrotetracarbonyl and carbon monoxide at room temperature was investigated by Orchin and coworkers ^{19, 20} and with a moderate excess of olefin (1-pentene) under 1 atmosphere of carbon monoxide was found to be

$$2 \text{HCo}(\text{CO})_4 + \text{CO} + \text{olefin} \longrightarrow \text{Co}_2(\text{CO})_8 + \text{aldehyde} \quad \underline{6}.$$

The reaction of olefins with cobalt hydrotetracarbonyl at room temperature and below was further explored by Heck and Breslow ^{21, 22}, on whose work current views regarding the mechanisms of the oxo reaction, separately discussed below for hydroformylation and hydrogenations are largely based.

(a) Hydroformylation

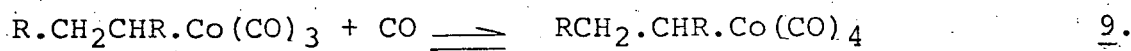
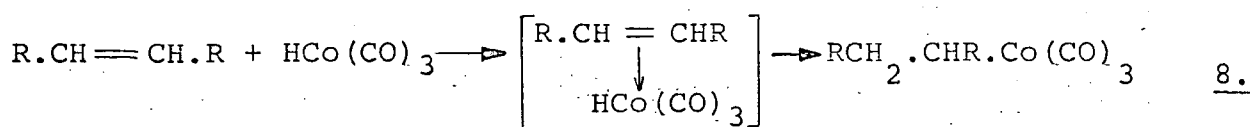
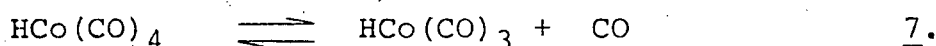
Subsequent to the generation of cobalt hydro-tetracarbonyl by the hydrogenolysis of dicobalt octacarbonyl (equation 5) the conversion of olefins to aldehydes is regarded as proceeding in three distinct stages:

1. Formation of a π -complex between olefin and cobalt hydrocarbonyl, which rearranges so that a carbon-metal sigma bond is formed.

2. Insertion of carbon monoxide between metal and carbon, and

3. Hydrogenolysis of the resulting complex to give an aldehyde.

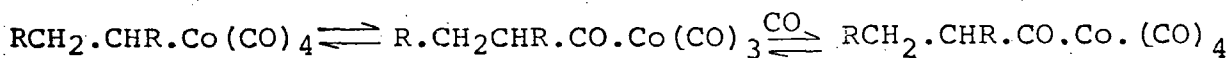
1. Heck and Breslow²¹ consider that this first stage involves at least three distinct steps as follows:



Their view that cobalt hydrotricarbonyl, rather than the hydrotetracarbonyl, is the reactive species is based on the evidence that the formation of alkyl cobalt tetracarbonyls is inhibited by carbon monoxide, more fundamentally initial

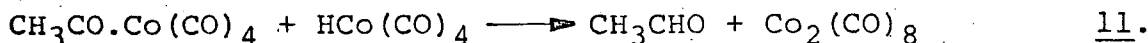
complexing with olefin would presumably require the participation of a co-ordinately unsaturated carbonyl.

2. Heck and Breslow²² found that methyl cobalt tetracarbonyl absorbed exactly one mole of carbon monoxide to give a product with a strong bond in the infrared at 1728 cm⁻¹ assigned to the acylcobalt linkage R.CO.Co.



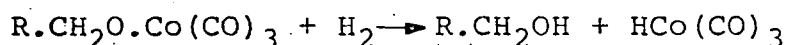
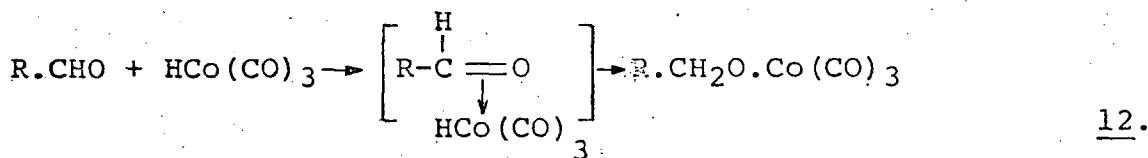
10.

3. The reaction of acetyl cobalt tetracarbonyl with cobalt hydrotetracarbonyl under room temperature conditions afforded acetaldehyde and dicobalt octacarbonyl in good yield.



(b) Hydrogenation

A scheme which is analogous to that described above for hydroformylation has been proposed by Marko²³ for subsequent hydrogenation of aldehydes to alcohol under oxo conditions (equation 4). Co-ordinately unsaturated carbonyls are considered to be the reactive intermediates



Application to Carbohydrate Chemistry

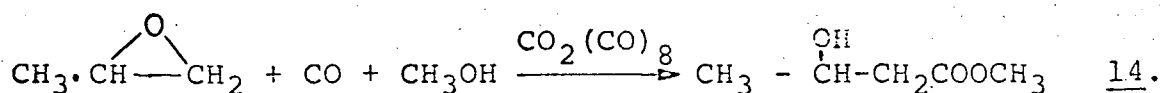
The oxo reaction was first applied to unsaturated carbohydrates by Rosenthal and Read²⁴ who synthesised a seven carbon sugar alcohol by the hydroformylation of 3,4,6-tri-O-acetyl-D-galactal.

Rosenthal and Abson^{25,26} have also shown 3,4-di-O-acetyl-D-xylal to react in a similar manner and also to form the aldehydo-anhydro-xylohexose and lyxohexose as well as hexitols if reaction conditions are carefully controlled.

Rosenthal and Koch²⁷ have also prepared anhydro hexitols from the hydroformylation of 3,4-di-O-acetyl-D-arabinal.

Applications of Oxo Reaction to Epoxides

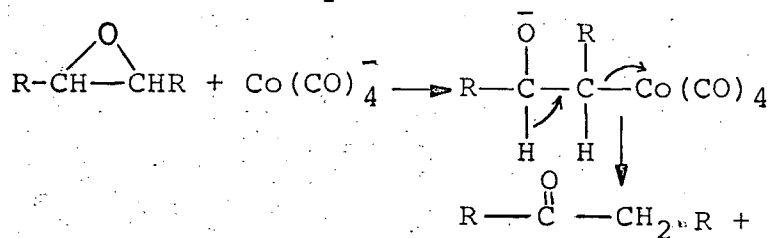
Eisenmann²⁸ and coworkers have studied the effect of modified oxo reactions on propylene oxide. They have found that propylene oxide reacts with carbon monoxide and methanol in a temperature range from 110° to 190° C. and a pressure range from 800 to 1,000 p.s.i. with dicobalt octacarbonyl as catalyst methyl β-hydroxy-butyrate in yields varying from 20% to 40% with minor yields of the 1-methoxy and 2-methoxy propanols.



They have further found that in the absence of carbon monoxide in methanol solution, cobalt octacarbonyl catalytically rearranges epoxides to ketones.

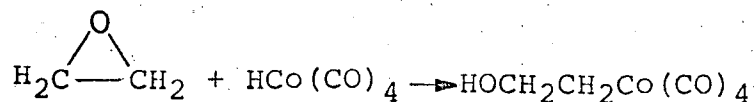
Thus propylene oxide reacts at room temperature to give a 70% yield of acetone.

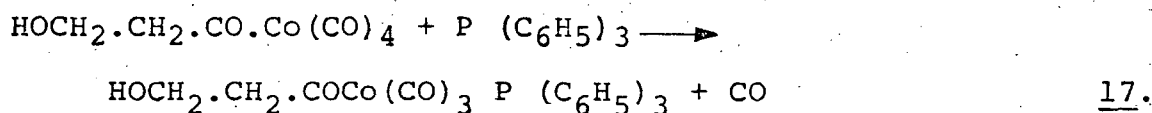
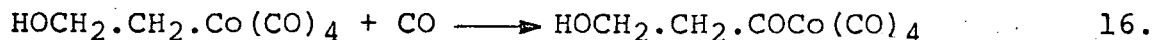
Presumably cobalt carbonyl $\text{Co}(\text{Co}(\text{CO})_4)_2$ formed by the disproportionation of $\text{Co}_2(\text{CO})_8$ is reacting with epoxide to form the anion of 2-hydroxy ethyl cobalt carbonyl and then a hydride shift forms the ketone with elimination of cobalt carbonyl anion.



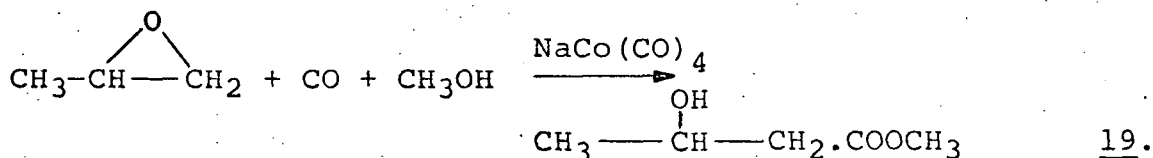
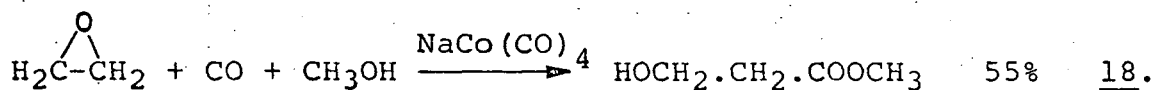
Lenel ²⁹ has noted that unsymmetrical epoxides undergo the oxo reaction with dicobalt octacarbonyl to give mixtures of hydroformylated products at 100° and at 100 atmospheres pressure.

Heck ³⁰ has been able to isolate β -hydroxy-acyl cobalt tetracarbonyls as their (triphenyl phosphine) derivatives from the reactions of carbon monoxide and cobalt hydrocarbonyl with ethylene, propylene and cyclohexene oxides at 0° C.





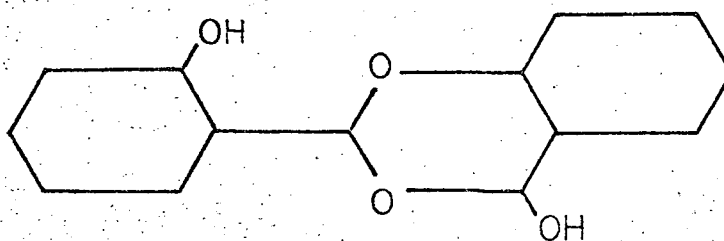
He has been able to demonstrate that esters are formed by the reactions of epoxides with carbon monoxide and alcohol using sodium cobalt carbonyl as the catalyst.



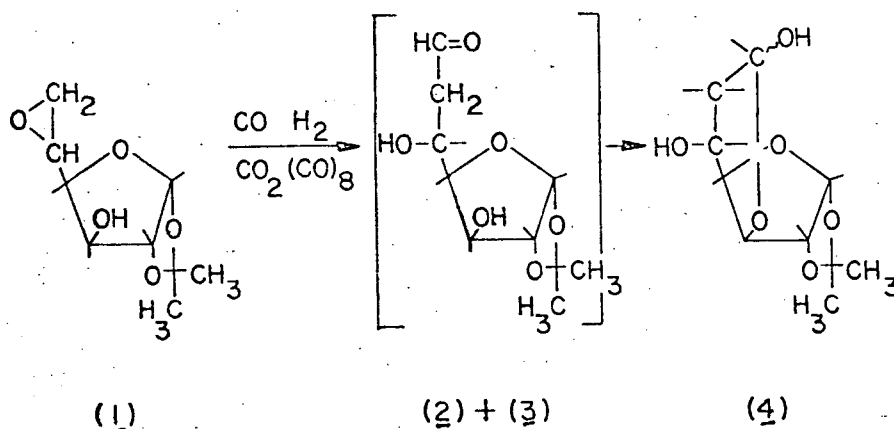
Yokokawa, Watanbe and Tagegami have applied the classical oxo reaction to ethylene and propylene oxides using dicobalt octacarbonyl in toluene with reaction temperatures of 80° C. and 150-160 atmospheres of carbon monoxide and hydrogen. They have isolated β -hydroxy-propionaldehyde and β -hydroxy butyraldehyde, respectively.

Further work on acceleration and inhibition of the hydroformylation of epoxides has been performed by these workers^{31,32}. The compounds ethyl alcohol, n-butylalcohol, ethylene, chlorohydrin, acetone, promote the carbonylation of epoxide.

Orchin ³³ and coworkers have reported that the major product resulting from the stoichiometric hydroformylation of cyclohexene oxide is not the expected 2-hydro-cyclohexane carboxaldehyde but its dimer. The implications of the above work for the mechanism of the hydroformylation reaction are under study.



Recently Rosenthal and Kan ³⁴ have applied a modified oxo reaction to 5,6-anhydro-1,2-O-isopropylidene- α -D-glucofuranose (1) to yield 6-deoxy-1,2-O-isopropylidene- α -D-glucopyranose-3,7-pyranose (4).



sugar molecule were first blocked by the benzylidene group.

In the second step, the benzylidene-derivative (I) was converted into 2-O-tosyl derivative (II) by preferential tosylation using equimolar mixture of p-toluene-sulfonyl chloride and substrate in pyridine at 0°.

In the last step of the synthesis the 2-O-tosyl derivative (II) was treated with sodium methoxide in methanol to afford methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside (III). The epoxide ring is readily formed through the displacement of a tosyl ester function by a neighbouring trans hydroxyl group under the influence of sodium methoxide in methanol solution. If the conditions of treatment with alkali are made somewhat more drastic, the epoxide is attacked in turn by the methoxide ion. Nucleophilic-displacement occurs with ring opening to give methyl 4,6-O-benzylidene-3-O-methyl- α -D-altropyranoside.

Reaction of Methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside with Carbon Monoxide and Methanol in the presence of Dicobalt Octacarbonyl.

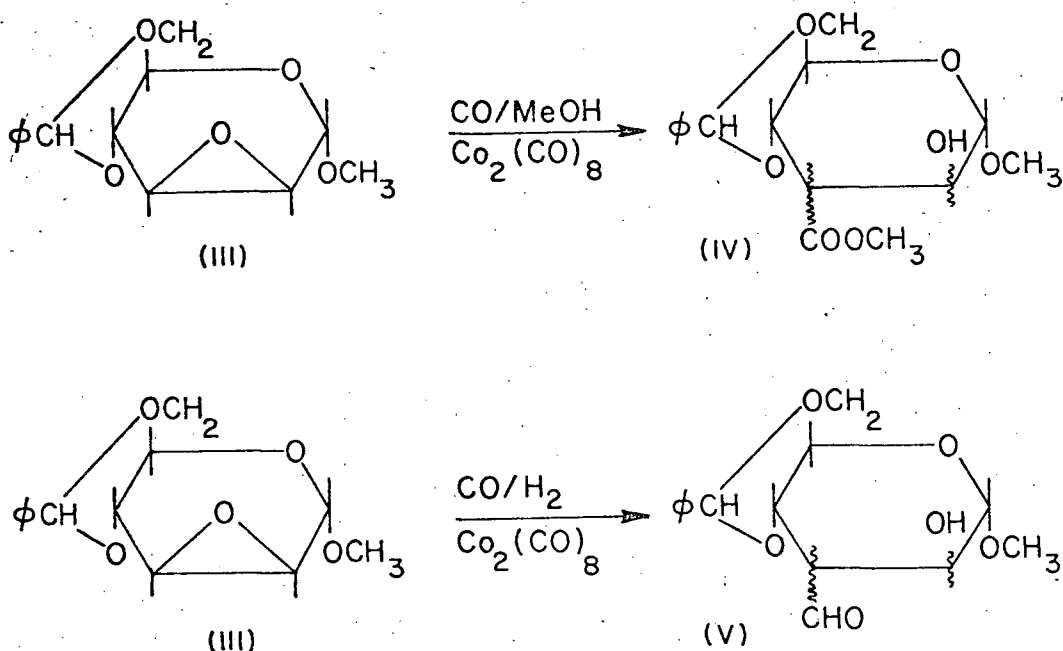
The objective of the first part of the investigation was to apply a modified oxo reaction to methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside (III).

In the first set of experiments the substrate

was reacted with carbon monoxide and methanol as shown below.

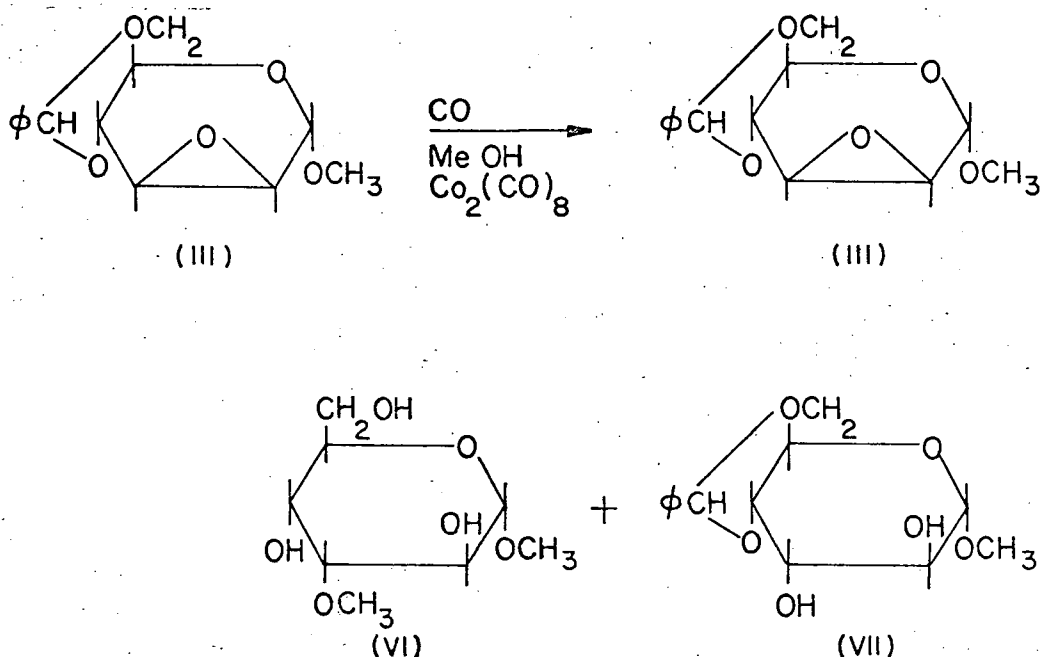
In the second set of conditions (to be discussed subsequently) carbon monoxide and hydrogen were used.

In both cases dicobalt octacarbonyl was used as catalyst. It was hoped to produce a branched-chain ester (IV) or branched-chain sugar (V) as illustrated below.



When methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside was reacted with 1920 p.s.i. carbon monoxide (measured at room temperature) and methanol for two hours, a mixture of three major components (shown below) were obtained which were separated by column chromatography using alumina as absorbent and benzene-isopropanol (96:4)

as developer and were confirmed by T.L.C. as subsequently described.



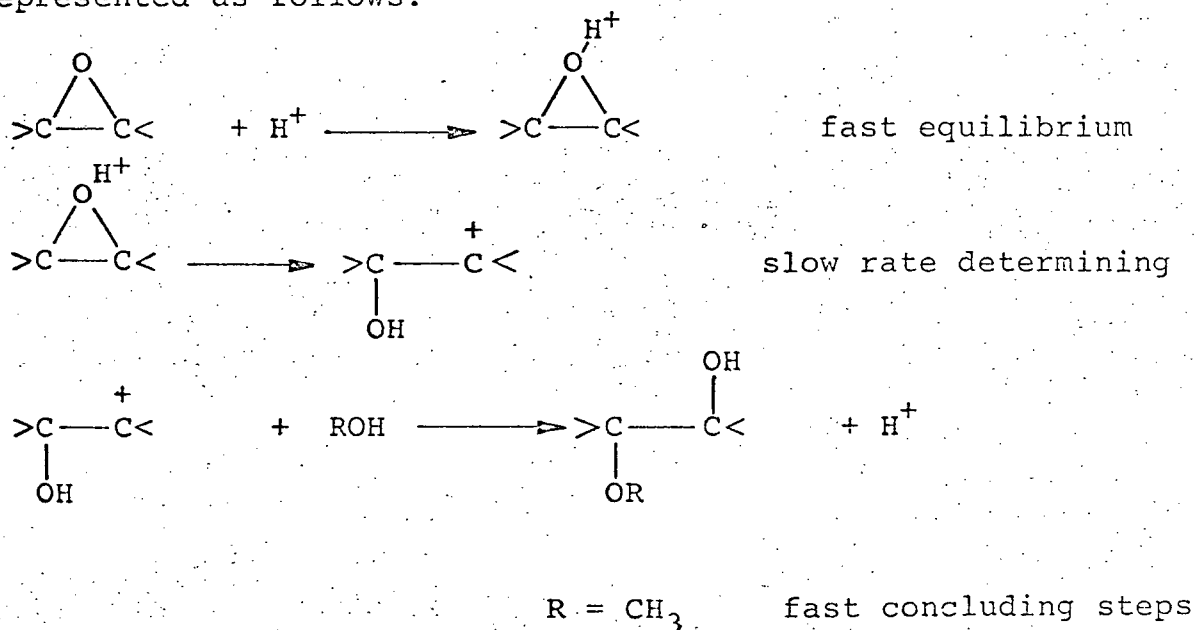
In the first two experiments 15% of the material isolated from the product mixture was characterized as unreacted epoxide (III) by direct comparison with the starting material (m.p., mixed m.p., identical I.R. and n.m.r.).

This demonstrates that the substrate is partially resistant to the reaction conditions. Compound (VI) was characterized as methyl 3-O-methyl- α -D-altropyranoside by direct comparison with an authentic sample of methyl 3-O-methyl- α -D-altropyranoside⁴ prepared according to the

procedure of Robertson and Griffith⁴ (same $[\alpha]_D$ and n.m.r. and I.R.).

The presence of compound (VI) indicates that there has been acid catalyzed methanolysis of the substrate. Presumably the catalyst, dicobaltoctacarbonyl or H.Co(CO)_4 , (which could be produced in situ during the reaction) was the reagent which promoted methanolysis of the substrate. In order to test this hypothesis, the substrate was allowed to react with carbon monoxide and methanol in the absence of catalyst under the same conditions of temperature and pressure as used in the first experiment. No methanolysis took place as evidenced by the fact that the starting material was recovered quantitatively.

Acid catalysed hydrolysis of epoxides presumably follows S_N^1 — carbonium ion mechanism³⁶ and may be represented as follows:



The cleaving of the benzylidene group to form substance (VI) might be due to the abstraction of the proton by the catalyst from the solvent (methanol) and this cleavage might be accounted for by catalytic hydrogenolysis.

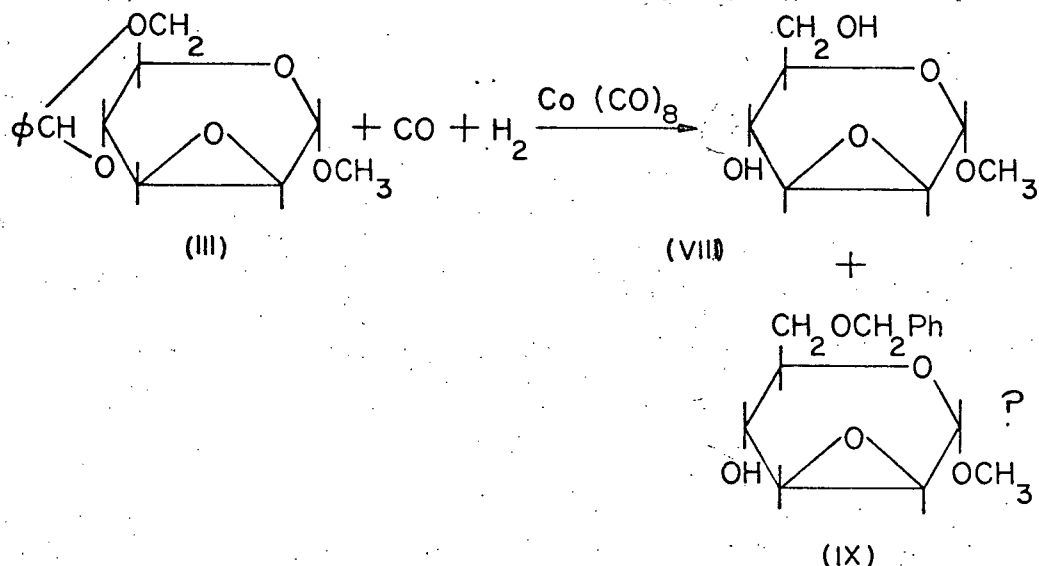
Compound (VII) was characterized as methyl 4,6-O-benzylidene- α -D-altropyranoside by direct comparison (m.p., mixed m.p., identical n.m.r. and identical I.R.) with an authentic sample³⁷. The presence of component (VII) indicated that there seemed to be some hydrolysis which opened the epoxide with Walden inversion at C-2.

In experiment (4) (Table I) the same substrate was again reacted with carbon monoxide and methanol at a higher temperature (210°) and pressure (3,000 p.s.i.) for a period of 8 hours. Under these drastic conditions no starting material remained after the reaction and the product consisted of intractable material which could not be separated by T.L.C.

Reaction of Methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside with Carbon Monoxide and Hydrogen.

When methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside was allowed to react with 990 p.s.i. of carbon monoxide and 910 p.s.i. of hydrogen (measured at room temperature) at a temperature of 140° for 5 hours in

the presence of preformed dicobalt octacarbonyl as catalyst only two components which were separated by G.L.C. were obtained as shown below:



Compound (VIII) was characterized as methyl 2,3-anhydro- α -D-mannopyranoside by direct comparison with an authentic sample³⁸ (m.p., mixed m.p. and identical n.m.r.).

This demonstrates that the epoxide ring had not been opened but there had been catalytic hydrogenation of the benzylidene group or hydrolysis of the blocking group.

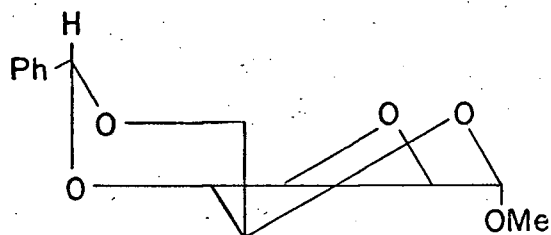
An attempt was made to characterize compound (IX). N.M.R. indicated that the epoxide hydrogens ($\text{H}_{(2)}$ and $\text{H}_{(3)}$) were still intact and thus the epoxide ring had not been opened. There had been partial reduction of benzylidene ring as indicated by a singlet 2.7 τ equal to 5 protons and assigned to phenyl group.

An attempt was made to characterize (IX) by comparing its R_F on T.L.C. with R_F 's of a mixture of the

mono-O-benzyl ethers obtained by the mono benzylation of compound (VII). Compound (IX) had the same R_F as one of the components of the latter mixture.

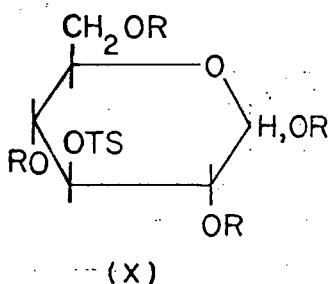
This demonstrates that epoxide ring had not been opened and benzylidene group has been partially reduced.

The fact that hydroformylation did not take place in the above experiment may be accounted for by an examination of the stereochemistry of methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside



If we examine the model of the substrate we see that in order to have a Walden inversion at C-3 the $\text{Co}(\text{CO})_4^-$ anion should attack opposite to the oxygen to have a transdiaxial ring opening. From the model we can visualize more clearly that α - OCH_3 which rotates must hinder the attack at the "reactive position" (temperature 190°). Since the α -methyl group protects C-3 the chances of having a hydroformylation is small.

Hughes and Speakman³⁹ have studied the benzoate displacement reaction of two 1,2,4,6-tetra-O-benzoyl-3-O-toluene p-sulfonyl α - and β -D-glucopyranoses (X).

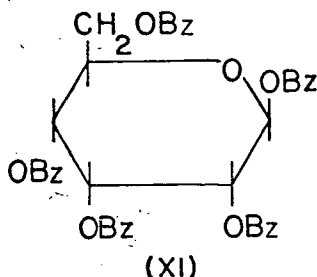


R = PhCO

a = α anomer

b = β anomer

Reaction of the β -anomer with sodium benzoate in dimethyl formamide gave a single crystalline product, namely, 1,2,3,4,6-penta-O-benzoyl- α -D-allopyranose.



On de-benzoylation the pentabenzoate (XI) gave D-allose identified by comparison with an authentic sample.

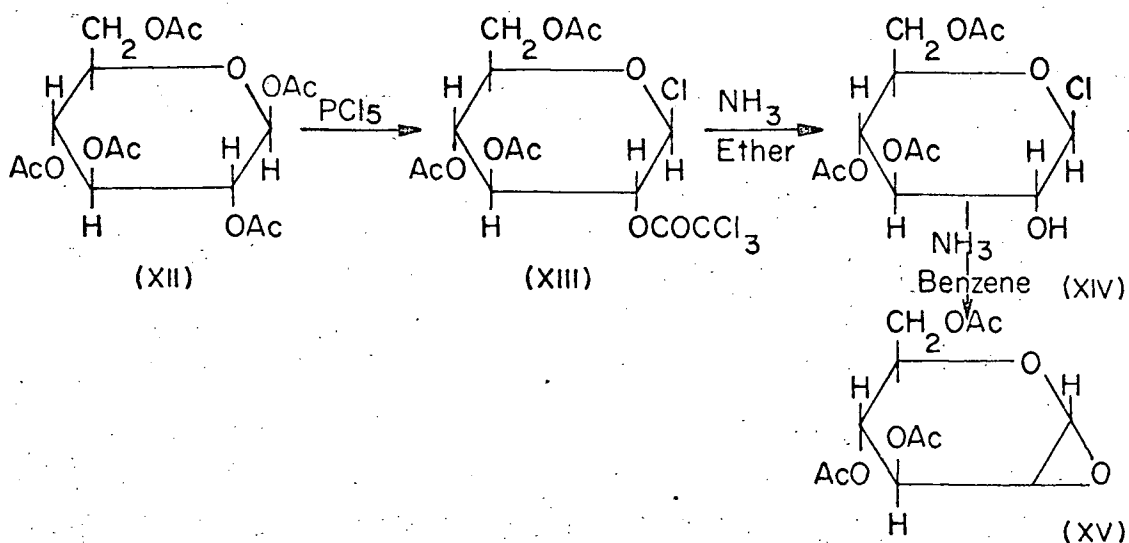
The isolation of a single penta benzoate suggests a straight forward SN^2 displacement without neighbouring group assistance with the Walden inversion at 3 position.

By contrast the α -anomer failed to undergo the displacement reaction. The axial benzoate group at position 1 in the α -anomer probably hinders the approach of benzoate ion to position 3. A similar reason may account for the lack of reactivity of methyl 2,3-anhydro-4,6-O-benzylidene α -D-mannopyranoside.

Reaction of 1,2-anhydro- α -D-glucopyranose triacetate (Brigl's anhydride) with carbon monoxide and hydrogen in the presence of Dicobalt Octacarbonyl.

(i) Synthesis of 1,2-anhydro- α -D-glucopyranose triacetate (Brigl's anhydride)^{40, 41}.

A very important substance in the chemistry of sugar synthesis is 1,2-anhydro-3,4,6-tri-O-acetyl- α -D-glucopyranose first prepared by Brigl by a sequence of reactions from penta-O-acetyl- β -D-glucopyranose (XII). The action of phosphorus pentachloride upon (XII) gave rise to 2-O-trichloroacetyl-3,4,6-tri-O-acetyl- β -D-glucopyranosyl chloride (XIII) which on ammonolysis in ether at 0° C gave 3,4,6-tri-O-acetyl- β -D-glucopyranosyl chloride (XIV). Further treatment with ammonia in benzene converted this derivative into 1,2-anhydro-3,4,6-tri-O-acetyl- α -D-glucopyranose (XV) (Brigl's anhydride).



3,4,6-tri-O-acetyl-2-O-trichloroacetyl- β -D-glucopyranosyl chloride (XIII) was obtained from β -D-glucopyranose penta-acetate (XII) by the action of phosphorus pentachloride.

The conversion of compound (XII) into (XIII) presents two striking points:

(i) Phosphorus pentachloride appears to react by two different mechanisms.

First replacement of the 1-acetyl group by chlorine yielded phosphorus oxychloride and acetylchloride as by-products. Secondly, only the 2-O-acetyl group appears to be attacked. The latter fact may be related to the configuration at C₍₂₎.

The halogen in position 1 may also favour substitution by its -I effect, although this involves the assumption that the reaction at the 1-position precedes chlorination.

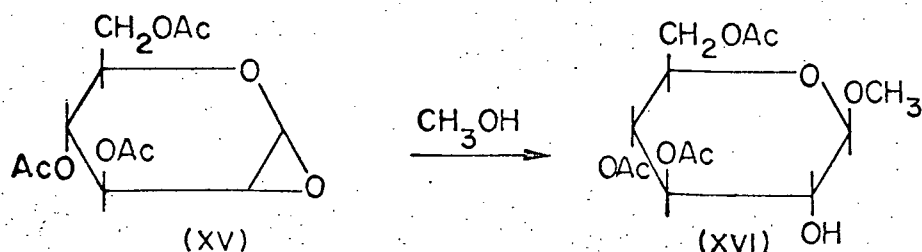
Chlorination by phosphorus pentachloride should lead to phosphorus trichloride as another product and this was isolated in good yield from the reaction mixture. The phosphorus pentachloride as such has no chlorinating action, this presumably arises by dissociation $\text{PCl}_5 \rightleftharpoons \text{PCl}_3 + \text{Cl}_2$ which according to Smith and Lombard occurs to appreciable extent under the reaction conditions used in the present work. The action of chlorine on the acetoxy

group is catalysed by acid chlorides. The isolation of phosphorus trichloride favours this hypothesis and it has been found that β -D-glucopyranose penta-acetate is unaffected by the trichloride. The properties of 3,4,6-tri-O-acetyl-2-O-trichloroacetyl- β -D-glucopyranosyl chloride (XIII) are extraordinarily advantageous for synthesis.

The chlorine atom at C-1 of (XIII) is not very reactive whereas the more reactive trichloroacetyl group at C-2 can be removed rapidly by the careful action of ammonia in an etherial solution affording compound (XIV). It is important to follow carefully Brigl's detailed experimental procedure for the conversion of (XIII) into (XIV) outlined in his original paper rather than the method outlined in reference⁴¹ if pure compound (XIV) is to be obtained from compound (XIII).

By further ammonolysis of compound (XIV), it is converted into 3,4,6-tri-O-acetyl-1,2-anhydro- α -D-glucopyranose (XV).

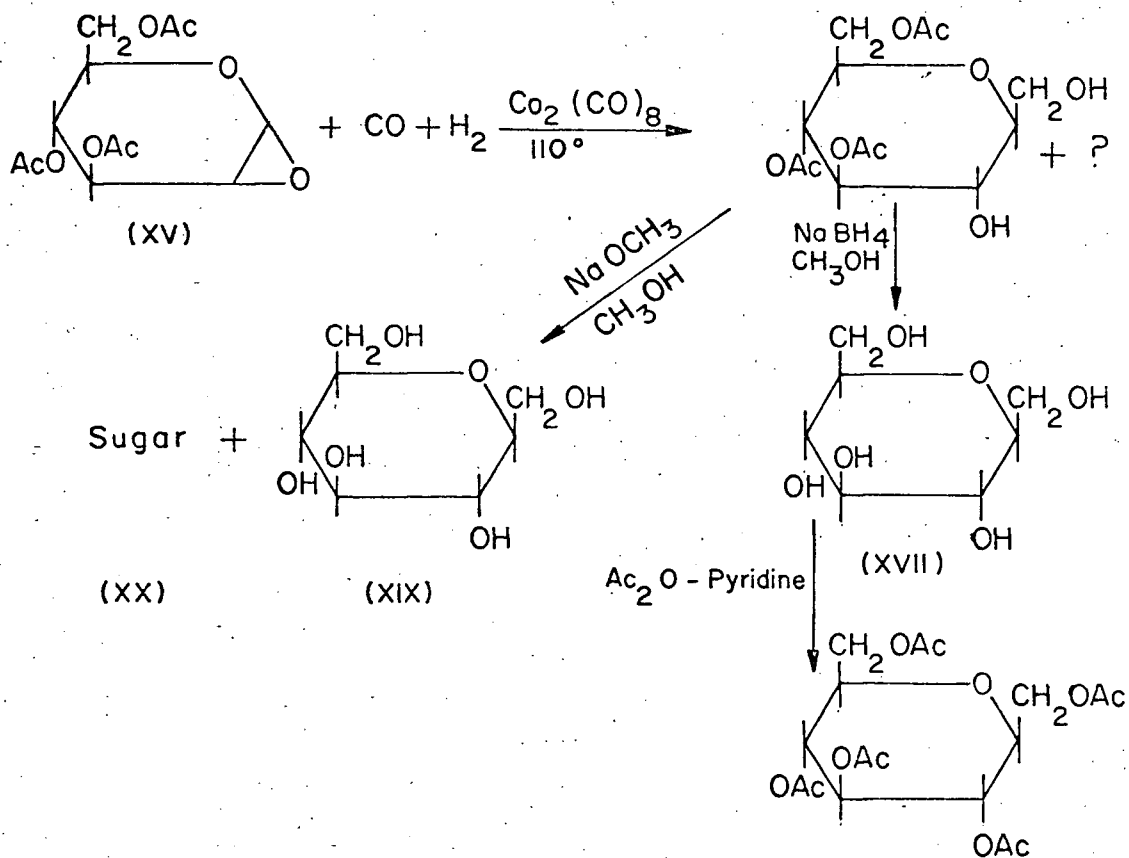
The ethylene oxide ring in Brigl's anhydride is readily cleaved as exemplified by the immediate reaction of (XV) with water at room temperature to afford 3,4,6-tri-O-acetyl- α -D-glucopyranose. Substance (XV) also reacts readily with methanol to form a methyl glycoside with simultaneous Walden inversion at C-1 as shown below.



Hydroformylation of 1,2-anhydro-3,4,6-tri-O-acetyl- α -D-glucopyranose.

Brigl's anhydride (XV) was allowed to react with carbon monoxide (900 p.s.i.) and hydrogen (990 p.s.i.) in the presence of dicobalt-octacarbonyl at 100-110° for 30 minutes. The product consisted of two main components as evidenced by T.L.C. using silica gel as absorbent and benzene-acetone (9:1) as developer. Sodium borohydride reduction of the product mixture gave essentially one product (XVII) (paper chromatography using water-saturated butanol containing 5% ethanol as developer). Reacetylation of the reduced product (XVII) gave essentially one substance (XVIII) (T.L.C. and V.P.C.).

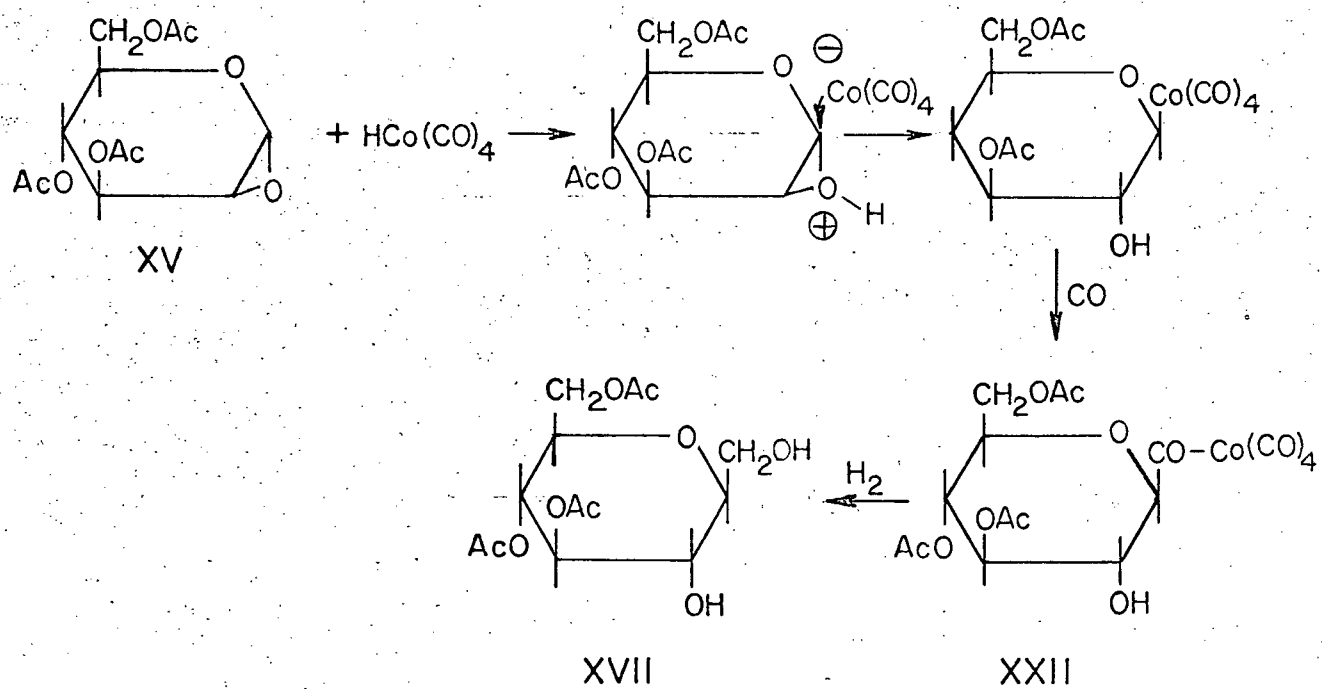
Direct comparison of compound (XVIII) with an authentic sample of 1,3,4,5,7-penta-O-acetyl-2,6-anhydro-D-glycero-D-gulo-heptitol⁴² showed both compounds to be the same (identical n.m.r. and no depression in mixed m.p.).



De-O-acetylation of the product mixture with sodium methoxide in methanol afforded a mixture of compounds. Preparative paper chromatographic separation of this mixture (using water-saturated 1-butanol plus 5% ethanol as developer) gave one slow moving zone (positive test with 2,4-dinitrophenyl-hydrazine) in 17% yield and one diffuse zone which was sectioned into two zones. The middle zone (XIX) isolated in 50% yield was directly compared with an authentic sample of 2,6-anhydro-D-glycero-D-gulo-heptitol⁴² and shown to be the same (similar n.m.r.,

m.p. and identical R_F 's). The faster moving segment of the diffuse zone also had a similar n.m.r. to that of compound (XIX) but was not crystalline. Paper chromatographic separation of the latter using ethyl acetate-acetic acid-water-formic acid as developer showed that this segment contained about 5% of a third component but was mainly (XIX). Substance (XX) appeared to be a sugar precursor of the heptitol as evidenced by the fact that sodium borohydride reduction of substance (XX) gave a compound with the same R_F as substance (XIX).

A possible mechanism for the formation of compound (XVII), is as follows. In the first step it is suggested that protonation of the epoxide takes place followed by cobalt tetracarbonyl anion attack on C-1 to afford the intermediate (XXI). Carbon monoxide insertion between carbon -1 and cobalt might then be envisaged to afford the acyl derivative (XXII). Reduction with hydrogen cobalt tetracarbonyl might then be expected to afford the anhydro heptitol (XVII).



EXPERIMENTAL

GENERAL CONSIDERATIONS

Hydroformylation apparatus

The high pressure hydroformylation and hydroxymethylation reactions using carbon monoxide and hydrogen were carried out in an Amino Micro Series autoclave (2-9/16" outside diameter) made of manganese steel. This reactor is sold by the American Instrument Company Inc., Silver Spring, Maryland, U.S.A.

Infrared Spectra

All infrared spectras were measured on Perkins Elmer Model 21 and Model 137 (sodium chloride) spectrophotometers.

Proton Magnetic Resonance Spectra

Nuclear Magnetic resonance spectra were determined at 60×10^6 Hz on a varian A 60 spectrometer and at 100×10^6 Hz on a varian HA-100 spectrometer.

Gas Liquid Partition Chromatography

Gas liquid partition chromatography separations were effected on Aerograph, Model A-700 and Model A-1520 instruments sold by Varian Associates, Palo Alto, California, U.S.A. Detectors were of the thermal conductivity type and the carrier gas was helium.

Paper Chromatography

All paper chromatography was descending. The

solvent system was 1-butanol saturated with water at 0° or water saturated (room temperature) 1-butanol containing 5% ethanol. The addition of ethanol prevents separation of water from the solvent mixture in case the chromatogram is run at a temperature lower than that used for the preparation of the solvent. Reported R_F values are with reference to this solvent system unless otherwise indicated. Polyols were detected with a sodium periodate schiff reagent⁴⁴.

Thin Layer Chromatography

Thin layer chromatography was on plates of silica gel G and alumina (according to Stahl) containing 13% calcium sulfate as a binder. Zones were located by spraying with concentrated sulfuric acid, containing 5% concentrated nitric acid followed by heating to 130° C.

Catalyst

Dicobalt octacarbonyl was obtained from Alpha Inorganics Inc., Beverly, Mass., U.S.A.

Melting Points

All melting points were uncorrected and were taken on the Microscope Heating Stage, manufactured by Leitz A.G., Wetzlar, Germany.

Elemental Analysis

Elemental analyses were performed in the Micro-analytical Laboratory, Department of Chemistry, University of British Columbia, Vancouver, Canada.

Preparation of Methyl 4,6-O-benzylidene- α -D-glucopyranoside³⁵

Methyl 4,6-O-benzylidene- α -D-glucopyranoside was prepared using a modification of the procedure described by Richtmyer³⁷.

A mixture of 120 g of methyl- α -D-glucopyranoside, 90 g of freshly fused and powdered zinc chloride (anhydrous) and 300 ml of benzaldehyde (reagent grade) was shaken in a glass bottle for 16 hours.

The mixture was poured slowly with stirring into 2.5 litres of cold water. The material was inoculated with seed crystals and the mixture was refrigerated overnight. Petroleum ether was then stirred 5 hours with the mixture to aid in removing excess benzaldehyde and the product was separated on a Buchner funnel, washed twice with 20 ml of cold water, twice with 200 ml of petroleum ether (35-60°), and again with 200 ml of cold water. The product was dried overnight in the air and then in a vacuum oven at 70°; yield of the crude benzylidene compound satisfactory for the next step 128 g (70%) m.p. 161-163°.

Methyl-4,6-O-benzylidene- α -D-glucopyranoside was purified by recrystallization from chloroform-petroleum ether (30-60°) needles m.p. 162-164°; literature m.p. 162-164°.

Preparation of Methyl 4,6-O-benzylidene-2-O-p-tolylsulfonyl α -D-glucopyranoside.

Methyl 4-6-O-benzylidene- α -D-glucopyranoside was

dissolved in dry pyridine and the mixture was cooled in an ice bath and rapidly stirred while a solution of p-toluene-sulfonyl chloride (25 g) also dissolved in dry pyridine (80 ml) was added over a period of 30 minutes. The solution was allowed to stand 24 hours at room temperature and was then shaken with a mixture of 200 ml of water and 200 ml of benzene. The benzene layer was removed and the aqueous layer was extracted again with a further 50 ml of benzene.

The extracts were combined and washed with 5% hydrochloric acid, with sodium-hydrogen carbonate solution and finally with water. The benzene extract was dried over magnesium sulfate and evaporated to dryness. The residue was dissolved in hot ethanol and from this solution, methyl-4,6-O-benzylidene-2-O-p-tolylsulfonyl- α -D-glucopyranoside separated; yield 21 g, m.p. 153-154; literature m.p. 152-153.

Preparation of Methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside⁴⁵

Methyl 4,6-O-benzylidene 2-O-tolylsulfonyl- α -D-glucopyranoside (5 g) was dissolved in methanol (0°C, 125 ml) containing sodium (2.9 g) and the solution was then refluxed for 30 minutes. After cooling and dilution with water, long needles (2.25 g) m.p. 147-150° separated recrystallization from aqueous methanol raised the m.p. to 149-151°.

The above compound was verified by mixed melting point with an authentic sample obtained from Dr. L. D. Hall, (Department of Chemistry, U.B.C.) which gave no melting point depression and also verified by an n.m.r. spectrum.

Four separate oxo runs were performed on the above sugar epoxide, using dicobalt octacarbonyl as a catalyst.

The procedure for carrying out the oxo run was based on the work of Rosenthal²⁴ and Adkins⁴⁶. The whole work is described in Tables I and II.

Reaction of Methyl 2,3-anhydro 4,6-O-benzylidene- α -D-mannopyranoside with Carbon monoxide and Methanol in the presence of Dicobalt Octacarbonyl.

To a mixture of methyl 2,3-anhydro 4,6-O-benzylidene- α -D-mannopyranoside (3 g) in dry, purified benzene (14 ml), anhydrous methanol (9.5 ml) contained in a 300 ml shaker bomb was added dicobalt octacarbonyl (0.5 g). After flushing the bomb with carbon monoxide, carbon monoxide (1920 p.s.i.) was added and the reactants heated with rocking at 190° for 2 hours. An observed pressure drop of 40 p.s.i. at 26° was noted. The bomb was then cooled overnight and the gases were vented.

The reaction product consisted of a dark brown solution.

Half the product mixture was heated at 80° for 20 minutes to decompose the catalyst. The oxo product was evaporated on the flash evaporator. The residue was dissolved in chloroform. The product was decolorized by treatment with Darco Active charcoal and was evaporated. The hydroformylation mixture of the first half gave a total weight of 1.10 g.

In all subsequent discussions unless otherwise specified all thin layer chromatography work was performed on silica and alumina (0.10 cm) plates (2½" x 7½") which were run in benzene-isopropanol (96:4) and were developed using sulfuric acid - nitric acid spray and heat.

A T.L.C. plate (silica) was prepared by spotting side by side

- (i) The initial epoxide sugar
- (ii) Oxo product soluble in chloroform

1

2

Very Heavy Spot

Three Major Spots

$R_F = .92$

- (i) Heavy Spot $R_F = .92$
- (ii) Heavy Spot $R_F = .64$
- (iii) Very Heavy Spot
 $R_F = .26$

The oxo product was separated into slightly impure fractions by column chromatography. Oxo product (0.8 g) was added to the top of alumina column (17.5 x 3.4 cm. diameter) by dissolving it in a mixture of 4 ml

of isopropanol and chloroform (1:1). The following mixture (200 ml) of benzene-isopropanol (96:4) was added and the fractions were collected.

Characterization of Fraction I (Methyl 2,3-anhydro 4,6-O-benzylidene- α -D-mannopyranoside).

Fraction I (0.80 g)

- (i) $R_F = .92$
- (ii) Crystalline, m.p. = 145-147°
- (iii) Mixed m.p. with Methyl 2,3-anhydro 4,6-O-benzylidene- α -D-mannopyranoside = 146-147°
- (iv) same I.R. as the authentic sample
- (v) N.M.R.

H ₁	H ₂	H ₃	H ₄	H ₅	H ₆	Methine	OCH ₃	Benzylidene
5.14	6.56	6.88	5.77	6.25	6.36	4.51	6.60	4.51
J1,2=0	J2,3=4.0	J3,4=0	J4,5=5					

The compound had an identical n.m.r. spectrum to that of authentic sample of methyl 2,3-anhydro 4,6-O-benzylidene- α -D-mannopyranoside.

Fraction II (.154 g) (Methyl 3-O-methyl- α -D-altropyranoside)

- (i) $R_F = .26$
- (ii) Syrup
- (iii) (α)_D²⁰ + 142 in chloroform (C = 2.45)

Literature (α)_D¹⁵ + 140.3 (C = 2.45)

The compound had an identical n.m.r. to that of authentic sample of methyl 3-O-methyl- α -D-altropyranoside.⁴

Fraction III (.183 g)

Two spots R_F = .26

On T.L.C. (Silica) = .56

Developer isopropanol and benzene (4:96)

Mixture - no conclusion could be drawn.

Fraction IV (.160 g)

(Methyl 4,6-O-benzylidene- α -D-altropyranoside)

(i) R_F = .64

(ii) M.P = 166-169°

Mixed m.p. with authentic sample = 167-169°

R_F (authentic sample) = .64

The compound had an identical n.m.r. to that of authentic sample of methyl 4,6-O-benzylidene- α -D-altropyranoside.³⁷

Synthesis of Methyl 4,6-O-benzylidene- α -D-altropyranoside³⁷

A solution of 1.30 g of potassium hydroxide in 35 ml of water was boiled with 1 g of methyl 2,3-anhydro-4,6-O-benzylidene- α -D-allopyranoside for 48 hours. The solution was cooled and filtered to remove any undissolved starting material and then partially neutralized with 3 ml of 6N sulfuric acid.

The aqueous solution was extracted successively with 5 ml, 2.5 ml, 1.5 ml and 1.5 ml of dichloroethane and

the combined extracts were washed with 5 ml of water. The layers were separated carefully. The dichloroethane layer was dried with granular calcium chloride, while the aqueous layer was returned to the main aqueous solution. This aqueous solution was extracted 8 times with 1.5 ml portions of dichloroethane, the combined extracts were washed with 2 ml of water and the layers were separated carefully.

The dichloroethane extract was dried over calcium chloride and the water layer was returned to the main aqueous solution. The process was repeated. Finally the main aqueous solution was extracted 15 times with 4 ml portions of dichloroethane and the dichloroethane extracts were combined and saved, without being washed to be used in making the first extract of a succeeding run.

The dried dichloroethane extracts were treated with a small amount of decolorizing carbon, filtered and concentrated under reduced pressure to a thin syrup. Ether and petroleum ether were added and the product (1 g) was separated in crystalline form. The material was recrystallized from methanol yield (.8 g) m.p. 168-170°; the literature m.p. of methyl 4,6-O-benzylidene- α -D-altropyranoside is 169-170°.

Synthesis of Methyl 4,6-O-benzylidene 3-O-methyl- α -D-altropyranoside⁴

Methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside (1 g), m.p. 146-147°, was heated in a sealed tube with methyl alcohol (20 ml) containing sodium (1 g) for 24 hours at 100°.

After cooling and dilution with water, the mixture was extracted four times with chloroform. The combined extract was dried over sodium sulfate and evaporated to dryness. A clean yellow glass (0.7 g) which crystallized spontaneously was obtained. It was crystallized from aqueous ethyl alcohol (yield 70%), m.p. 129-130°, literature m.p. 130-131°.

Partial Hydrolysis of methyl 4,6-O-benzylidene-3-O-methyl- α -D-altropyranoside

Methyl 4,6-O-benzylidene 3-O-methyl- α -D-altroside (1 g), m.p. 133°, was dissolved in a mixture of acetone (66 ml), water (29 ml) and N- hydrochloric acid (5 ml) and the solution was boiled until of constant rotation (2 hours) (α)_D^{20°} = + 149°.

After neutralization with barium carbonate and filtration the acetone was evaporated. The aqueous solution was extracted with chloroform to remove benzaldehyde and evaporated to dryness. The residue was extracted three times with boiling acetone. The combined extracts were

evaporated to dryness. The product methyl 3-O-methyl- α -D-altropyranoside was obtained as a syrup which could not be crystallized.

Product Determination by Thin Layer Chromatography

Three preparative silica containing 1% phosphor (0.25 cm thickness) plates (7½" x 7½") were prepared and the product (0.070 g) in methanol solution was lined equally on each plate. The plates were run in standard benzene-isopropanol (75:25). Bands on the plates were identified under U.V.

The bands containing the major products were identified and carefully scraped from the plates. The silica was washed several times with chloroform and the product was isolated by evaporation of the chloroform solvent.

The first zone (Z1) (.010 g) was crystalline, m.p. 145-147°, R_F = .92. This zone was confirmed as starting material (methyl 4,6-O-benzylidene-2,3-anhydro- α -D-mannopyranoside) by mixed melting point (145-146°). The compound had an identical n.m.r. and I.R. as that of starting material.

Characterization of Zone II

The Zone II (.017 g) was characterized as methyl 4,6-O-benzylidene- α -D-altropyranoside.

m.p. = 169-170°

mixed m.p. with authentic sample = 168-170°

The compound had an identical n.m.r. and I.R. to that of authentic sample.

Characterization of Zone III (.027 g)

(Methyl 3-O-methyl- α -D-altropyranoside).

This compound was confirmed by the direct comparison with the authentic sample.

(i) $R_F = .26$

(ii) R_F (authentic sample) = .26

(iii) $(\alpha)_D^{20} = 140^\circ$ in chloroform (C = 2.45)

(iv) $(\alpha)_D^{20} = 142^\circ$ in chloroform (C = 2.45)

It had exactly similar n.m.r. to that of authentic sample.

Two more modified oxo reactions were carried out on different conditions as shown in Table I and were followed exactly the same procedure as previously.

TABLE I

Reaction of Methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside* with carbon monoxide and methanol

Experi- ment No.	Initial CO Pressure in p.s.i.	Methanol vol in ml	Temp. OC	Time in Hours	CO ₂ (CO) g wt in g	Product	Yield
1	1920	9.5	190	2	0.5	Unreacted epoxide	14%
						Methyl 3-O- methyl- α -D- altropyranoside	30%
						Methyl 4,6-O- benzylidene- α - D-altropyrano- side	26%
2	2960	20	190	3	0.5	same	
3	3000	0.6	210	8	0.6	no major product. Product decomposed.	

* 3 g of substrate used in each experiment.

TABLE II

Reaction of Methyl 2,3-anhydro 4,6-O-benzylidene- α -D-mannopyranoside with carbon monoxide and hydrogen.

Experi- ment No.	Initial CO Pressure in p.s.i.	Initial H ₂ Pressure in p.s.i.	Time in Hours	CO ₂ (CO) ₈	Product	Yield
4	990	140	4	0.5 g.	Methyl 2,3-anhydro- α -D-mannopyranoside	40%
					Methyl 2,3-anhydro 6-O-benzyl- α -D-mannopyranoside	45% (?)

Reaction of Methyl 2,3-anhydro 4,6-O-benzylidene- α -D-mannopyranoside with Carbon monoxide and Hydrogen in the presence of Dicobalt Octacarbonyl.

To a mixture of methyl 2,3-anhydro 4,6-O-benzylidene- α -D-mannopyranoside (3.35 g) in dry purified benzene (15 ml) contained in a 300 ml shaker bomb was added dicobalt octacarbonyl (.5 g). After flushing the bomb with carbon monoxide, carbon monoxide (990 p.s.i.) and hydrogen (910 p.s.i.) were added and the reactants heated with rocking at 140° for 5 hours. The bomb was then cooled overnight (pressure drop of 180 p.s.i.) and the gases were vented. The reaction mixture consisted of a dark brown solution.

Half the product mixture was heated at 80° for 20 minutes to decompose catalyst. The solvent from the oxo product was evaporated on a flash evaporator. The residue was dissolved in chloroform. The product was decolorized by treatment with Darco Active Charcoal and the solvent was evaporated. The hydroformylation mixture of the first half gave a total weight of 1.5 g.

An n.m.r. spectrum was obtained on a smear of the oxo product.

Thin layer chromatography work was performed on silica and alumina (0.10 cm) plates (2½" x 7½") which were run in benzene-isopropanol (82:18) and were developed using

sulfuric acid-nitric acid spray and heat.

A T.L.C. plate was prepared by spotting side by side

- (i) the initial sugar epoxide
- (ii) methanol soluble oxo product

1

2

Very Heavy Spot

Two Heavy Spots

$R_F = .92$

$R_F = .28$

$R_F = .72$

Preparation of 2,4-Dinitrophenylhydrazone derivatives of Oxo Product.

An amount of 100 mg of the oxo product was dissolved in 2 ml of ethanol containing 1 drop of acetic acid and the solution was heated to the boiling point on a steam bath. To this was added portionwise a hot saturated solution of 2,4-dinitrophenylhydrazine in ethanol until the orange colour imparted to the solution no longer faded to yellow. On diluting with water to turbidity and standing in the refrigerator, a yellow solid separated which was collected by filtration m.p. $235-237^{\circ}$. The m.p. of authentic 2,4-dinitrophenylhydrazone derivative of pure benzaldehyde by the same procedure as above was $235-238^{\circ}$, mixed m.p.; $238-240^{\circ}$.

T.L.C. was performed on silica (.10 cm) plates (2½" x 7½") in chloroform. Both 2,4 dinitrophenylhydrazone derivatives gave identical $R_F = .43$.

Gas-Liquid Chromatography of Trimethyl Silyl Derivatives (TMS) of the Oxo Product⁴⁷

The formation of the TMS derivative in pyridine containing hexamethyldisilazane and trimethylchlorosilane took place very rapidly at room temperature.

100 mg of oxo product was treated with 10 ml of anhydrous pyridine (kept over KOH pellets), 2 ml of hexamethyldisilazane and 1 ml of trimethylchlorosilane. The reaction was carried out in a plastic stoppered flask. The mixture was shaken vigorously for about 30 seconds and was then allowed to stand for 5 minutes or longer at room temperature prior to chromatography.

The accurately measured aliquot drawn into a Hamilton syringe, was injected into the chromatograph. Each injection consisted of about 1 ml of solution. The column which was made up of copper tube (12' x 3/8") was packed with chromosorb W (manufactured by F and M) carrying 10% (wt) silicon gum rubber SE-52 (manufactured by F and M Scientific, Avondale, Penn., U.S.A.) and operated at 250°. The carrier gas was helium, detector temperature 310°, injected temperature 260°, filament current 150 mA.

The gas chromatograph was an Aerograph A-700 instrument using thermal conductivity detectors. Two major zones were isolated. In both cases the loss due to aerosol formation was considerable.

Zone A (Methyl 2,3-anhydro- α -D-mannopyranoside)

Retention time = 39 minutes

Amount = 20 mg

This zone was collected as a light yellow syrup which crystallized overnight, m.p. 77-79°, mixed m.p. of Zone A with an authentic sample, 78-79°.

It had an identical n.m.r. to that of an authentic sample of methyl 2,3-anhydro- α -D-mannopyranoside.

Zone B

Retention time = 19 minutes.

It was obtained as a syrup which could not be crystallized.

An attempt was made to characterize by comparing its R_F on T.L.C. with the R_F 's of a mixture of mono-O-benzyl ethers obtained by the monobenzylation of the zone A. Zone B had the same R_F as that of one of the components of the latter mixture. In order to study the effect of oxo reaction on benzylidene group, the oxo product aliquot (10 ml) was injected into chromatograph. Each injection consisted of about 1 ml of solution. Three zones were obtained and were characterized as benzene, benzaldehyde and toluene. The zones were confirmed by comparing the retention times with authentic samples.

Synthesis of Methyl 2,3-anhydro- α -D-mannopyranoside³⁸

Methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside (5.0 g) was heated with methanol (30 ml) and .01N sulfuric acid (100 ml) under reflux until all the solid had dissolved (one-half hour). Methanol was removed by distillation and the remaining solution extracted with benzene. The aqueous layer was neutralized with barium carbonate and the filtrate evaporated to dryness. The syrup was dissolved in ethanol and ethyl acetate (100 ml of each) and filtered through neutral alumina (20 g) which was washed with 200 ml of the same solvent. The combined filtrates were evaporated to a syrup, which crystallized from chloroform, light petroleum, to give the methyl 2,3-anhydro- α -D-mannopyranoside (2.90 g, 87% yield) m.p. 81-82°.

EXPERIMENTAL SECTION B

Synthesis of 1,2-anhydro- α -D-glucopyranose triacetate

(Brigl's anhydride)^{40, 41}

Preparation of β -D-glucopyranose penta-acetate

A suspension of 50 g of anhydrous sodium acetate in 70 ml of acetic anhydride in a 2 liter, round bottomed flask was heated over a flame to the boiling point in an efficient fume hood. About 3 g of anhydrous α -D-glucopyranose from a 100 g supply was added and the flask without shaking was heated carefully at the point nearest the sugar laying on the bottom. Initiation of the reaction was indicated by continued boiling after removal of the flame, the flask was placed on a cork ring and the flame was extinguished. The remainder of the sugar was then added in small portions at a rate which maintained the boiling temperature of the mixture. The flask was gently shaken.

After the addition of all the sugar and after the reaction had subsided, the solution was brought to a full boil. It was then cooled and poured with stirring onto 2 liters of cracked ice. After standing 3 hours with occasional stirring, the crystalline material was filtered with suction and washed with cold water. Yield 169 g (74%).

Purification was effected by recrystallization from 1 liter of hot 95% ethanol followed by filtration with decolorizing carbon. The product was filtered as soon as

the temperature of the crystallizing material was cooled to room temperature. Further recrystallization in the same manner produced pure β -D-glucopyranose penta-acetate m.p. 130-132°.

Preparation of 3,4,6-tri-O-acetyl-2-O-trichloro acetyl- β -D-glucopyranosyl chloride

Pure finely powdered, dry β -D-glucopyranose penta-acetate (78 g) was mixed thoroughly with 177 g of powdered phosphorus pentachloride in a 500 ml round bottomed flask equipped with a reflux condenser.

Forty ml. of carbontetrachloride was added and the reaction mixture was protected from atmospheric moisture with a tube containing calcium chloride. The mixture was heated in a fume hood on a steam bath for about 30 minutes, the mixture became partially liquid and volatile components began to reflux with the evolution of hydrogen chloride. At the end of the reaction period, a clear yellowish solution was obtained. The solution was evaporated under reduced pressure (water aspirator) until the bath temperature had risen to about 85°. The thick syrup was dissolved in 160 ml of dry ether and cooled overnight at -10°. The crystalline precipitate was collected on a Büchner funnel, pressed to a firm cake and washed first with 20 ml of cold methanol and then with 20 ml of cold

dry ether yield, 36 g (38%) of crude product m.p. 131-138°. The compound was sufficiently pure after two recrystallization from ether to be used in the following preparation; m.p. 140-142°.

Preparation of 3,4,6-Tri-O-acetyl- β -D-glucopyranosyl chloride.

Anhydrous ether (200 ml) contained in a 500 ml erlenmeyer flask was saturated with dry ammonia at room temperature. The solution was cooled to 0°C and 10 g of finely powdered, dry 3,4,6-tri-O-acetyl-2-O-trichloro-acetyl- β -D-glucopyranosyl chloride was added. The mixture was shaken vigorously to bring about solution as rapidly as possible. Almost immediately after solution was complete, the product began to crystallize. The solution was cooled to 0° for 5 minutes before collecting the precipitate which was washed with ether.

3,4,6-tri-O-acetyl- β -D-glucopyranosyl chloride is dried under reduced pressure over phosphorus pentaoxide and potassium hydroxide; yield, 6.0 g (93%) m.p. 156-158°
[α]_D²⁰ + 28 (C1 chloroform)

Preparation of 1,2-anhydro- α -D-glucopyranose triacetate

Dry and finely powdered 3,4,6-tri-O-acetyl- β -D-glucopyranosyl chloride (10 g) was added to 50 ml of dry benzene contained in a 3-necked 150 ml flask equipped with a stirrer (sealed shaft) a gas inlet tube which extended

to near the bottom of the flask and a drying tube which was filled with crushed potassium hydroxide pellets. A stream of dry ammonia was passed through the stirred solution for 3 hours at room temperature. The precipitated ammonium chloride was removed by filtration and the filtrate was evaporated to about 20 ml. The solution was passed rapidly through a bed of dry silicic acid which was prepared by pouring a slurry of 5 g of dry silicic acid in about 10 ml of benzene into a 2 cm (approximate diameter) chromatographic tube. The bed was washed with 50 ml of dry benzene and the total eluate was evaporated under reduced pressure to a thick oil. Dry petroleum ether (20 ml) was added and on rubbing with a glass rod, the product was soon crystallized. Yield 6.5-7.0 g of 1,2-anhydro- α -D-glucopyranose triacetate m.p. 49-54°. Material which melted at 55-56° could be obtained by recrystallization from three parts of ethers and one part of low boiling petroleum ether.

An improved synthesis of 3,4,6-tri-O-acetyl-1,2-anhydro- α -D-glucopyranose (Brigl's anhydride)⁴⁸

Crude 3,4,6-tri-O-acetyl- β -D-glucopyranosyl chloride, (7.4 g), m.p. 130-133°, was suspended in 60 ml of dry benzene and 2 ml of diethylamine by shaking for a half hour. The solution was filtered through a bed of 5 g of dry silicic acid and the filtrate was evaporated to a

syrup, 1.43 g. The syrup rapidly crystallized from ether Skelly solve B and 1.3 g of "Brigl's Anhydride", m.p.-56.5-57° was obtained. The precipitate on the silicic acid bed was collected and reacted further in 60 ml of benzene and 5 ml of diethylamine for one hour. As above, 4.49 g of the syrup was obtained which deposited 3.22 g of crystals, m.p. 55-56° from ether Skelly solve B. The total yield of "Brigl's Anhydride" was 70%.

Reaction of 1,2-anhydro- α -D-glucopyranose triacetate (Brigl's anhydride) with Carbon monoxide and Hydrogen in the presence of Dicobalt Octacarbonyl.

To a mixture of 1,2-anhydro- α -D-glucopyranose (1.20 g) in dry purified benzene (10 ml) contained in a 300 ml shaker bomb was added dicobalt octacarbonyl (.5 g). After flushing the bomb with carbon monoxide, carbon monoxide (910 p.s.i.) and hydrogen (990 p.s.i.) were added and the reactants heated with rocking at 106° for a half hour. The bomb was then cooled and the gases were vented. The reaction mixture consisted of a dark brown solution.

Approximately half the product mixture was removed from the bomb and then placed on a florisil continuous flow chromatography column (17.5 x 3.4 cm diam). The catalyst was eluted with petroleum ether (30-60°). When the eluate was no longer coloured the hydroformylation

products were eluted using a benzene-methanol (98:2) mixture. The colourless eluate was collected in tared flask (100 ml) and the solvent was removed by evaporation.

The product was a syrupy material (.447 g) which was soluble in methanol.

A thin layer chromatography work was performed on silica (0.10 cm) plates (2½" x 7½") using benzene-acetone (91:9) as developer and sulfuric acid-nitric acid spray and heat as detector.

There were three zones having R_F 's of .30, .36, .38 on T.L.C. one of which was major and other two minor.

An amount of 0.70 g of the oxo product was acetylated with acetic anhydride and pyridine as usual. T.L.C. of the acetylated oxo product gave one spot R_F = .64. It had an n.m.r. which was almost similar to that of an authentic sample⁴² of 1,3,4,5,7-penta-O-acetyl-2,6-anhydro-D-glycero-D-gulo-heptitol.

Preparation of 2,4-Dinitrophenyl hydrazone derivative of oxo product.⁴⁹

An amount of .015 g of the oxo product was dissolved in 2 ml methanol containing one drop of acetic acid and the solution was heated to boiling point on a steam bath. To this was added portionwise a hot saturated solution of 2,4-dinitrophenyl hydrazine in ethanol until the orange colour imparted to the solution no longer faded

to yellow. On dilution with water and standing in the refrigerator deposited a yellow solid which was accidentally lost.

Gas Liquid Partition Chromatographic separation of the acetylated polyols derived from the oxo product.

The oxo product (200 mg) was reduced with sodium borohydride (200 mg) in methanol (20 ml). After two hours the reaction mixture was filtered, diluted with water (20 ml) and deionized with amberlite IR 120H ion exchange resin. Evaporation of the solvent yielded a crystalline mass from which methanol (20 ml) was evaporated five times to removed borate esters. Removal of the solvent gave a light brown syrup (40 mg) which was acetylated with acetic anhydride (1 ml) and pyridine (1 ml) as usual. To the syrup acetate mixture was added anhydrous ether. Crystals (40 mg) were isolated, m.p. 90-92°.

The compound was compared with authentic sample of 1,3,4,5,7-penta-O-acetyl-2,6-anhydro-D-glycero-D-gulo-heptitol and was shown to have identical p.m.r., infrared spectra and no depression in mixed melting point (90-92°).

The crystals were dissolved in anhydrous ether and were injected into G.L.C. apparatus as ethyl ether solution. The column which was made up of copper tube (12' x 3/8") was packed with chromosorb W (manufactured by F and M Scientific, Avondale, Penn., U.S.A.) and operated

at 280°. The carrier gas was helium (200 ml/min), detector temperature 315°, injector temperature 290°.

The gas chromatograph was an A-700 instrument using thermal conductivity detectors. One sharp major peak (at least 95%) was observed at retention time 23 minutes and traces of two other substances.

The compound from the main zone was compared with an authentic sample of 1,3,4,5,7-penta-O-acetyl-2,6-anhydro-D-glycero-D-gulo-heptitol and shown to have the same retention time of 23 minutes.

Product Determination by Paper Chromatography

The oxo product (300 mg) was de-O-acetylated by dissolving the oxo product in 10 ml of anhydrous methanol and then adding 1-2 ml of 2N-methanolic sodium methoxide and leaving the mixture at 5° overnight. Carbon dioxide was bubbled through the cold solution for 0.5 hours to destroy the sodium methoxide, methanol and methyl acetate were removed by concentration under reduced pressure and the residual syrup was dissolved in water and deionized by passage through Amberlite IR-120. The solution was concentrated under reduced pressure to a fairly thick syrup (125 mg).

The syrup was dissolved in a small volume of methanol (3 ml), was applied equally to four sheets (57 x 46 cms) of Whatman No. 1 filter paper, prepared for descending

chromatography cabinet saturated with eluent vapours for 6 hours. Developer used was water-saturated butanol with 5% ethanol for 6 hours. After equilibration and development for 60 hours, the three zones were located by spraying tests, strips cut from each sheet, with aqueous sodium periodate-schiff reagent and separately extracted with hot aqueous methanol (1:1 V/V) to afford Fraction I (0.015 g) 17% $R_F = .15$.

Zone II was diffused and was sectioned into two fractions

Fraction II (.038 g) $R_F = .18$

Fraction III (.026 g) $R_F = .20$

Characterization of Fraction II

(2,6-anhydro-D-glycero-D-gulo-heptitol)

The compound was obtained as a syrup which crystallized on standing, m.p. 203-205°. The reported m.p. of 2,6-anhydro-D-glycero-D-gulo-heptitol is 204-205°.

Mixed m.p. of fraction II with authentic 2,6-anhydro-D-glycero-D-gulo-heptitol was 203-205°.

Fraction II had an identical n.m.r. to that of the authentic sample. (Fig. I).

Fraction I (.015 g)

was obtained as a syrup which could not be crystallized.

Reduction of Fraction I with sodium borohydride gave Fraction II which was characterized by paper chromatogram with identical R_F of the component, m.p. 203-204° (Fig. II).

Fraction III was again subjected to paper chromatography using ethyl acetate acetic acid-water-formic acid (18:3:4:1) as developer. It consisted of mainly Fraction (II) and a trace (less than 5%) of a third component which was not characterized. The combined yield of Fraction (II) was 75-80%.

REFERENCES

1. E. Fischer, M. Bergmann and H. Schotte, Ber., 53, 509 (1920).
2. P. Brigl, Z. Physiol. Chem., 116, 1,245 (1921).
3. B. Helferich and A. Muller, Ber., 63, 2,142 (1930).
4. George J. Robertson and Charles F. Griffith, J. Chem. Soc., 1,193 (1935).
5. Sybil P. James, F. Smith, M. Stacey and L. F. Wiggins, J. Chem. Soc., 625 (1946).
6. R. M. Hann and C. S. Hudson, J. Am. Chem. Soc., 64, 925 (1942).
7. F. H. Newth, J. Chem. Soc., 441 (1956).
- 7a. P. Mills cited by Newth and Homer, J. Chem. Soc., 989 (1953).
8. S. Peat, Adv. Carbohydrate Chem., 2, 37 (1946).
9. H. Adkins and G. Krsek, J. Am. Chem. Soc., 70, 383 (1948).
10. F. Fischer and H. Tropsch, Brennstoff Chem., 4, 276 (1923).
11. D. F. Smith, C. O. Hawk and P. L. Golden, J. Am. Chem. Soc., 52, 3221 (1930).
12. O. Roelen, Ger. Patent 103,362 (filed 1938); U.S. Patent 2,327,066 (1943); Chem. Abstracts, 38, 550 (1944).
13. I. Wender, H. W. Sternberg and M. Orchin, "Catalysis" Vol. 5, ed. by P. H. Emmett, New York, Reinhold Publishing Corporation, 1957, p. 73.
14. C. W. Bird, Chem. Rev., 62, 283 (1962).
15. H. Adkins and G. Krsek, J. Am. Chem. Soc., 71, 3051 (1949).
16. M. Orchin, L. Kirch and I. Goldfarb, J. Am. Chem. Soc., 78, 5450 (1956).
17. A. R. Martin, Chem. and Ind., 1536 (1954).

18. G. Natta, R. Ercoli, S. Castellano and P. H. Barbieri, J. Am. Chem. Soc., 76, 4049 (1954).
19. G. L. Karapinka and M. Orchin, J. Org. Chem., 26, 4187 (1961).
20. L. Kirch and M. Orchin, J. Am. Chem. Soc., 80, 4428 (1958).
21. R. F. Heck and D. S. Breslow, J. Am. Chem. Soc., 83, 4023 (1961).
22. D. S. Breslow and R. F. Heck, Chem. & Ind., 467 (1960).
23. L. Marko, Proc. Chem. Soc., 67 (1962).
24. A. Rosenthal and D. Read, Can. J. Chem., 35, 788 (1957).
25. A. Rosenthal and D. Abson, Can. J. Chem., 42, 1911 (1964).
26. A. Rosenthal and D. Abson, J. Am. Chem. Soc., 86, 5356 (1964).
27. A. Rosenthal and H. Koch, Can. J. Chem., 42, 2025 (1964).
28. J. L. Eisenmann, R. L. Yamartino and J. F. Howard, Jr., J. Org. Chem., 26, 2102 (1961).
29. P. O. Lenel, Proc. Chem. Soc., 50 (1958).
30. R. F. Heck, J. Am. Chem. Soc., 85, 1460 (1963).
31. C. Yokakawa, H. Watanabe and Y. Takegami, Bull. Chem. Soc. Japan, 37, 672 (1962).
32. C. Yokakawa, H. Watanabe and Y. Takegami, Bull. Chem. Soc. Japan, 37, 677 (1964).
33. L. Roos, Goetz, M. Orchin, J. Amer. Chem. Soc., 3023 (1965).
34. A. Rosenthal and G. Kan, Tetrahedron Letters, 477 (1967).
35. L. F. Wiggins, Methods in Carbohydrate Chemistry, Vol. II, ed. by R. L. Whistler and M. L. Wolfrom, New York, Academic Press, 1963, p. 189.
36. J. G. Pritchard and F. A. Long, J. Am. Chem. Soc., 6008 (1956).

37. Nelson K. Richtmyer, Methods in Carbohydrate Chemistry, Vol. I, ed. by R. L. Whistler and M. L. Wolfrom, New York, Academic Press, 1962, p. 108.
38. J. G. Buchanan and Schwarz, J. Org. Chem., 4770 (1962)
39. N. A. Hughes and R. H. Speakman, J. Chem. Soc., 2236 (1965).
40. P. Brigl, Z. Physiol Chem., 122, 245 (1922).
41. R. U. Lemieux and J. Howard, Methods in Carbohydrates, Vol. II, ed. by R. L. Whistler and M. L. Wolfrom, New York, Academic Press, 1963, p. 400.
42. A. Rosenthal and D. Abson, Carbohydrate Research, 3, 112 (1966).
43. H. Koch, Ph.D. Thesis, Univ. of British Columbia (1967).
44. J. Baddiley, J. G. Buchanan, J. F. Prescott, J. Chem. Soc., 2818 (1956).
45. J. F. Manville, Bachelor's Thesis, University of British Columbia, Chemistry Dept. (1963).
46. H. Adkins and G. Krsek, J. Am. Chem. Soc., 70, 383 (1940).
47. C. C. Sweeley, R. Bentley, M. Makita and W. W. Wells, J. Am. Chem. Soc., 28, 2497 (1963).
48. A. R. Morgen, Ph.D. Thesis, Univ. of Alberta, 1964, p. 60.
49. D. Abson, Ph.D. Thesis, Univ. of British Columbia, 1964, p. 181.

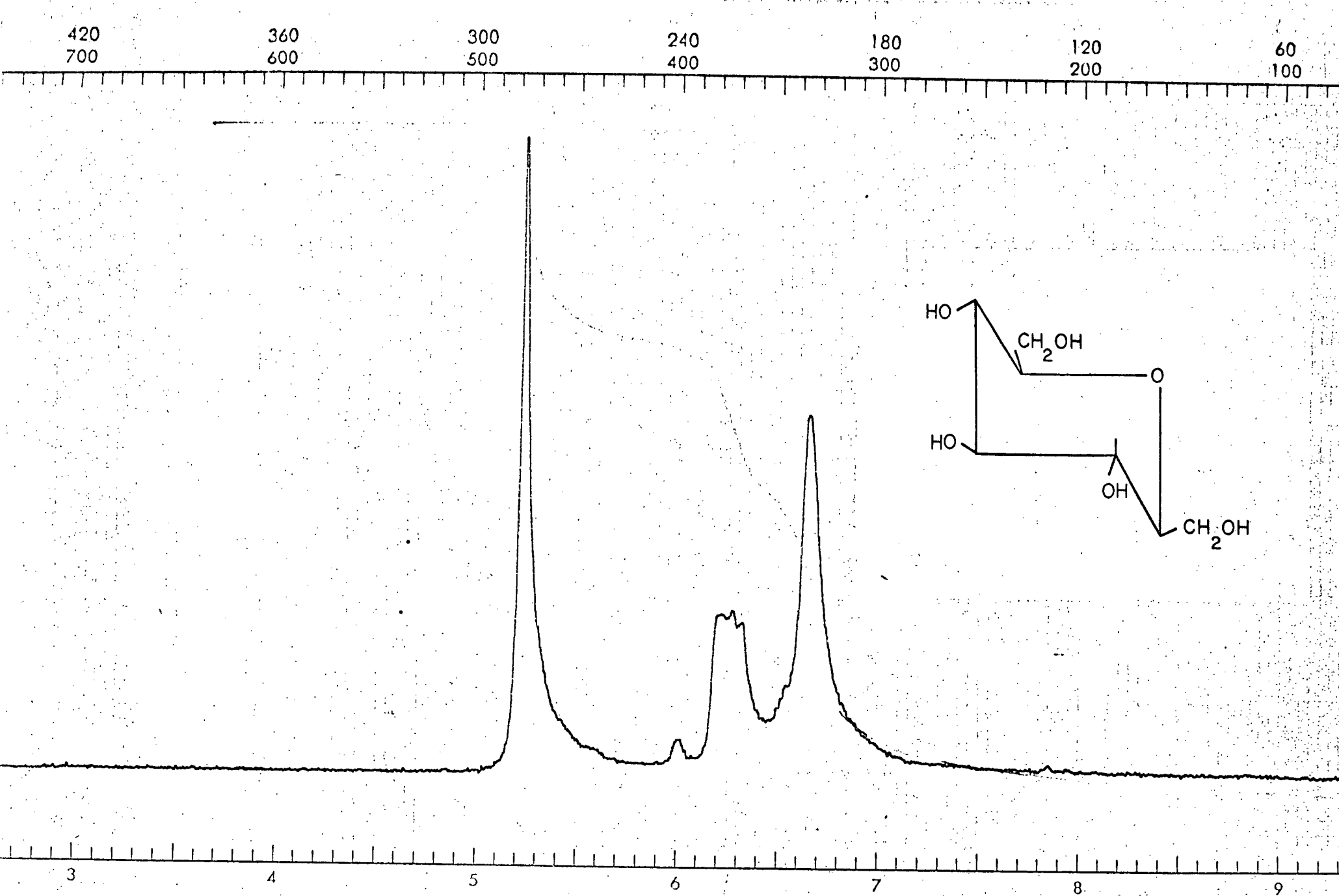


Fig. 1 - Nuclear Magnetic Resonance Spectrum at 60 mc of 2,6-anhydro-D-glycero-D-gulo-heptitol in Deuterium Oxide (Fraction II).

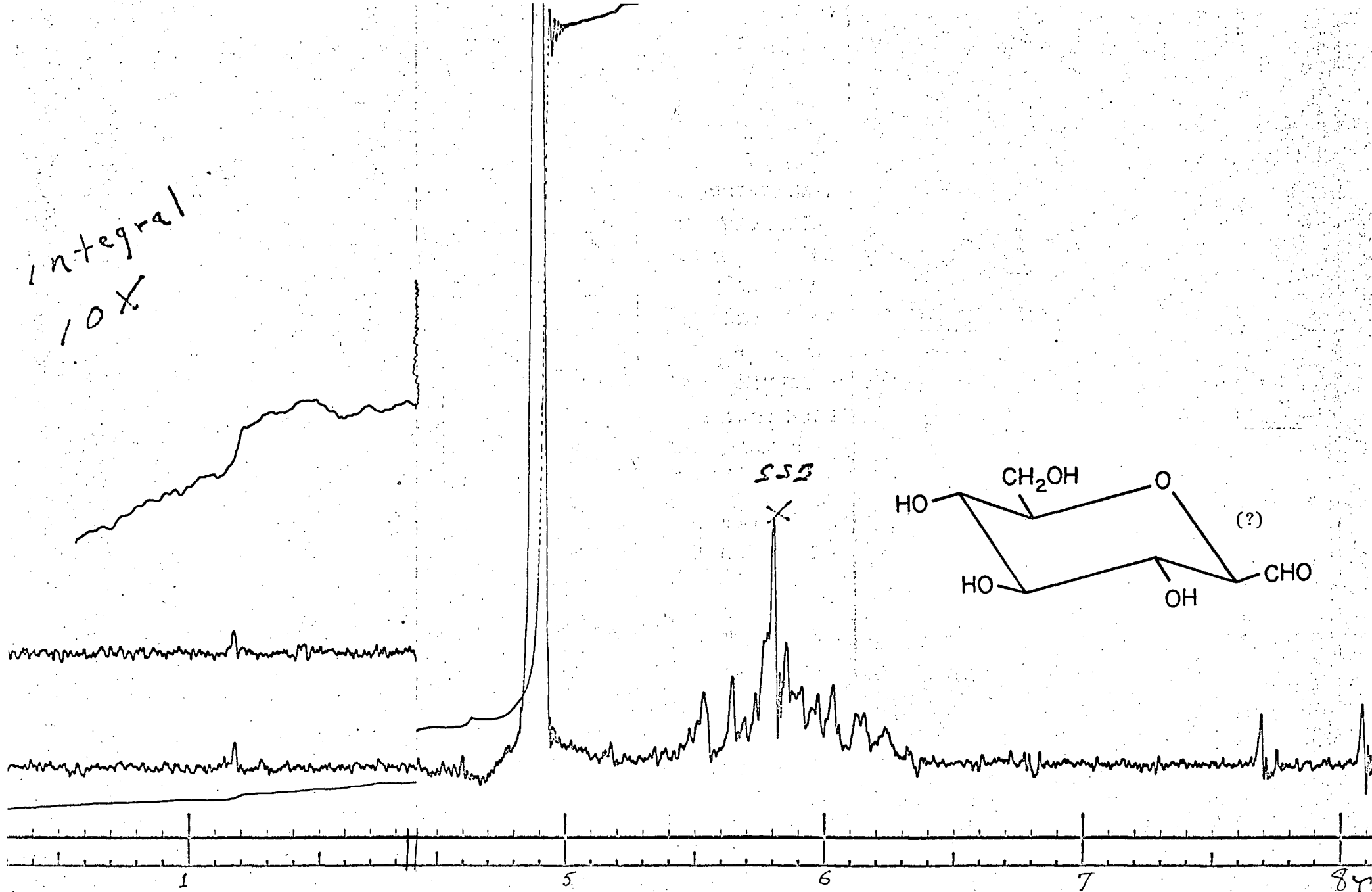


Figure II - NuclearMagnetic Resonance Spectrum at 100 mc of 2,6-anhydro-D-glycero-D-gulo-aldehydo-D-heptose. (Fraction I)