NUCLEOPHILIC REACTIONS OF SOME ANHYDRO-SUGARS

A Thesis submitted for the degree of

Master of Philosophy in the

Faculty of Science of the

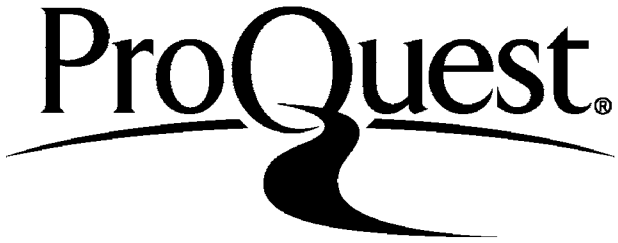
University of London

by

ROSEMARY ANN GRIFFITH

Bedford College, London

December 1984



TO THE LATE FATHER THEO CUNNINGHAM-BURLEY

WITH LOVE AND GRATITUDE

ACKNOWLEDGEMENTS

I would like to express my sincere appreciation to Dr. D. Murphy for his considerable help and encouragement.

I would also like to thank Professor G.H. Williams for letting me work in his department, Miss M. Easton for microanalyses, and my husband and sons for their support and tolerance.

ABSTRACT

The vast majority of the work done so far on the synthesis and reactions of monosaccharide epoxides has been on the aldoses. Some ketoses have therefore been studied.

The work falls into 3 parts:-

a) The known compound 1,2-O-isopropylidene-3,4-anhydro-β-D-psicopyranose has been made from fructose.

Synthesis of methyl 1,3-O-benzylidene-4,5-anhydro-α-L-psicoside and methyl 1,3-O-benzylidene-4,5-anhydro-β-D-fructoside from L-sorbose was attempted. Conformational factors prevented the formation of either of these 4,5-anhydro-compounds.

The following new compounds were made:-

4-O-tosyl-
4,5-di-O-tosyl-
4-O-benzoyl-
4,5-di-O-benzoyl-
4-O-benzoyl-5-O-tosyl-
4-O-tosyl-5-O-benzoyl-
4-O-tosyl-5-O-acetyl-

} methyl 1,3-O-benzylidene-α-L-sorboside

b) In the absence of any entirely satisfactory method of cyanating sugars, an attempt has been made to develop one.

Two methods were used:-

i) Potassium cyanide in acetonitrile, with 18-crown-6 as phase transfer catalyst.

ii) Tetra-n-butylammonium cyanide in a variety of dipolar aprotic solvents.

Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannoside and 1,2-O-isopropylidene-3,4-anhydro-β-D-psicose were the starting materials.

The crown ether was found to be ineffective as a phase transfer catalyst.

No cyano-sugars were obtained using the second method, but some reactions produced lactones.

Tetra-n-butylammonium cyanide was unstable even at temperatures as low as 100°C.

c) Ring-opening of 1,2-O-isopropylidene-3,4-anhydro-5-O-benzoyl-β-D-psicose was carried out with sodium azide to give the 4-azido-sorboside.

Reduction of the mesyl derivative of this with Raney nickel gave the amine. Treatment with sodium methoxide gave a benzamido- compound. Some oxazoline may also have been formed.

Reduction of the 3-mesyl-4-azido-sorboside with lithium aluminium hydride gave a mixture of the amine and an unknown substance which gave, after acetylation, 1,2-O-isopropylidene-3-dideoxy-4-deoxy-4-acetamido-5-O-acetyl-β-D-sorbopyranose. Thin layer chromatography suggested the presence of a little of the 3-acetamido- compound.

In both cases there are conformational reasons for failure to produce an epimine.

In previous reports of synthesis of epimines from azides, the intermediate amine has not been isolated. Apart from the epoxide used as starting material, none of the other compounds has been reported in the literature before.

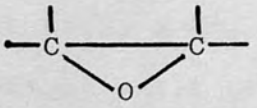
CONTENTS

INTRODUCTION

Anhydro-sugars are ethers in which two ring carbons are joined together by an oxygen, with the elimination of a molecule of water. They fall into two types :-

a) Epoxides

Two adjacent carbons are linked, with the formation of a three-membered ring.



Hexoses can form 1,2-, 2,3-, 3,4-, 4,5- and 5,6-epoxides.

b) The carbons which are linked together are not adjacent, and the resulting ring is 4-, 5- or 6-membered.

Only monosaccharide epoxides will be considered in this work.

PREPARATION OF SUGAR EPOXIDES

The first recorded example of a sugar epoxide was made by Brigl in 1921, when he converted tetra-O-acetyl-β-D-glucose to 3,4,6-tri-O-acetyl-1,2-anhydro-α-D-glucose by a three-stage process.[1] Then in 1928 Freudenberg *et al* heated 6-bromo-[1,2]-O-isopropylidene-α-D-glucose and sodium ethoxide together in a sealed tube to give 5,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose.[2] But although this was an improvement, in being a one-stage process, it would clearly be more convenient still if a method could be found to carry out such reactions at atmospheric pressure, and the following year Ohle and Vargha[3] made use of a relatively new group of compounds, sugar tosylates, which had first been made by Freudenberg and Ivers in 1922.[4] The method was simple; alkaline hydrolysis of 6-O-tosyl-1,2-O-isopropylidene-glucose was achieved by treating it with sodium methoxide for 10-15 minutes in an ice-bath.

This, then, became the standard method of making epoxides, and was applied to a variety of sugar tosylates over a range of temperatures, and with varying degrees of success.[5,6,7] In this way 2,3- and 3,4-anhydro- derivatives of allose,[8,9] galactose,[5,10] psicose,[11] mannose,[8,12] altrose,[10] talose[13] and tagatose[14] were made. The method works whether the hydroxyl group adjacent to the tosyl group is unsubstituted or acetylated, benzoylated or sulphonylated, and both mesyl and tosyl esters have been used, although the latter is more usual.[15]

In 1935 Robertson and Griffith found that by having the tosyl group in different positions, different epoxides could be made.[8] Thus methyl 2-O-benzoyl-3-O-tosyl-4,6-O-benzylidene-α-D-glucoside and the 2-O-tosyl-3-O-benzoyl-compound yielded the 2,3-epoxides of allose and mannose respectively, and this provided a valuable method of converting one sugar into another. The success of this depended, of course, on being able to carry out selective monotosylation.

The significance of the sulphonates is that, unlike other esters, they react by alkyl-oxygen fission, rather than by sulphur-oxygen fission, and consequently make excellent leaving groups.

A more recent modification of this method was employed by Stanek *et al* in 1975[16] when they obtained methyl 2,3-anhydro-6-deoxy-β-D-mannopyranoside, methyl 2,3-anhydro-4-O-acetyl-6-deoxy-β-D-allopyranoside, methyl 3,4-anhydro-6-deoxy-β-D-galactopyranoside and methyl 3,4-anhydro-2-O-acetyl-6-deoxy-β-D-allopyranoside by shaking the six mono- and di-tosyl- derivatives of methyl 6-deoxy-β-D-glucopyranoside with Amberlite IRA-400 resin (OH^- form) in methanol for 3 hours.

Sugar epoxides have also been made by hydrolysis of sugar derivatives containing halogen groups, but this, and other, routes will not be considered here.

SELECTIVE MONOTOSYLATION

The ring hydroxyl groups in the sugar molecule have different reactivities, and the hydroxyl group which is tosylated first will be the one which is most reactive. If tosylation at a different position is required, use must be made of protecting groups. Further tosylation will lead to the di-tosyl derivative.

In general, a primary hydroxyl group is esterified in preference to a secondary one,[17] particularly when the more bulky tosyl group is employed, and an equatorial to an axial one (for steric reasons),[18] but no pattern has been found to the relative reactivities of the ring hydroxyl groups in carbohydrates.

The only conclusion that can be drawn is that, for pyranoses, the mesyl, tosyl and benzoyl chlorides usually show similar substitution patterns,[17] with the acid anhydrides showing a different pattern.[18]

Relative reactivities of the ring hydroxyl groups also vary for different solvents,[19] and use can be made of this when aiming for a particular mono-ester. Phase transfer catalysis has proved to be a useful method for the synthesis of monotosylates[20] and monobenzoates,[21,22] since the mono-derivative has a lower partition coefficient than does the diol between the aqueous and organic phases. Good yields are obtained.

MECHANISM OF EPOXIDE FORMATION

Lack of success in some of their reactions led Ohle and Schultz[14] to conclude that removal of a sulphonate group, together with the proton of an adjacent hydroxyl group, to give an ethylene oxide ring, would only occur when the two groups concerned were *trans* to one another, since the carbon atom to which the sulphonyl group was attached had to undergo a Walden inversion.[23]

The mechanism of epoxide formation has been reviewed by Newth.[24] Under the conditions of alkaline hydrolysis, the hydroxyl group vicinal to the sulphonyl group would lose a proton and the resulting anion would displace the sulphonyloxy anion by an intramolecular S_N2 process, Walden inversion occurring because the participating hydroxyl group is on the opposite side of the pyranoside ring to the sulphonyl group. It is clearly necessary for the two groups to be *trans* in order that they and the carbon atoms to which they are attached should be coplanar.

This was not the only reason for failure, though, and the 2-*O*-tosyl and 3,4-di-*O*-tosyl derivatives of 1,6-anhydro-β-D-altrose resisted conversion into epoxides in spite of having the correct configurations.[24,25] This was because of steric factors preventing the molecule from passing from the "resting" chair conformation to the boat form, in which the reaction would take place.

It appears that, for a satisfactory yield of epoxide, the conditions needed will depend on the ease with which the required conformation can be attained, together with the influence of polar effects that alter the amount of energy required to reach the transition state.[15] It would therefore appear necessary that there should be a free hydroxyl group in the sugar molecule.

Moreover, since proton removal is required, this reaction will only take place in an alkaline medium. There is no known example of epoxide formation from a sulphonate precursor accomplished by an acidic reagent.

But it is, in fact, possible to obtain an epoxide from a ditosyl precursor, provided that one of the ester groups can be removed without difficulty. Angyal and Gilham[26] considered that the removal of the first sulphonyl group (which will be the more accessible of the two) would be facilitated by the inductive effect of the second sulphonyloxy group.

SCISSION OF THE EPOXIDE RING

The ethylene oxide ring of a sugar epoxide can be broken fairly easily by nucleophiles such as OH^-,[9,12,27,28,29,30] OMe^-,[10,11,13,14,27,29,30,31,32] N_3^-,[15,33] CN^-,[15,34,35] and by acids such as hydrochloric acid,[9,10,28,30,36,37] sulphuric acid,[15,36,38,39] acetic acid[10,15,30,39,40] *etc*.

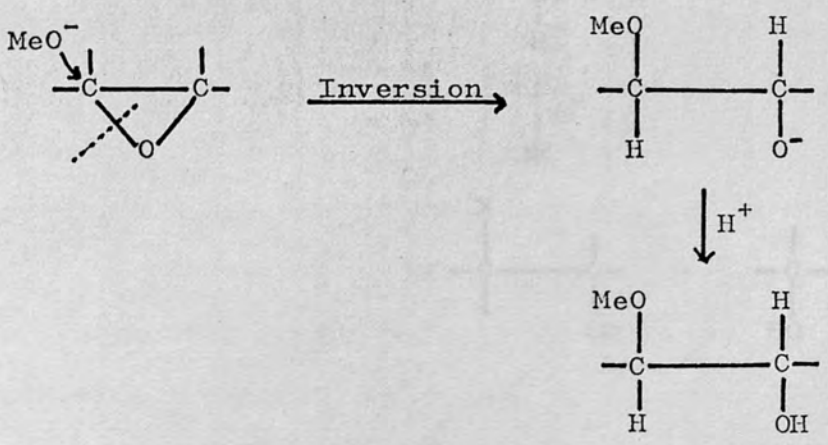
Like ring closure, the reaction is an intramolecular S_N2 one, cleavage with acids and nucleophiles having basically the same mechanism, except that the former reaction is faster, on account of initial protonation.[41]

The nucleophile (or conjugate anion) can attack either of the two carbon atoms in the epoxide ring, to give two possible products. Walden inversion occurs to give a product with a configuration either of the original sugar, or of a different sugar, according to which carbon atom is attacked.

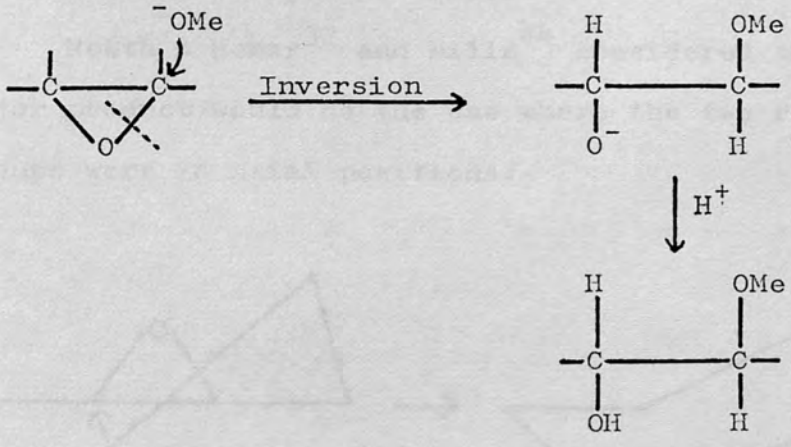
Ohle and Schultz[14] investigated the effect of sodium methoxide on 3,4-anhydro-1,2-*O*-isopropylidene-β-D-psicopyranose and found that inversion occurred at C-4 to give 1,2-*O*-isopropylidene-4-*O*-methyl-β-D-sorbopyranose, but that a small quantity of 1,2-*O*-isopropylidene-β-D-fructopyranose was formed (as a result of the presence of moisture), which indicated that inversion was also occurring at C-3.

Tipson[42] summed up current (1953) thinking on the mechanism of ring opening with methoxide ions.

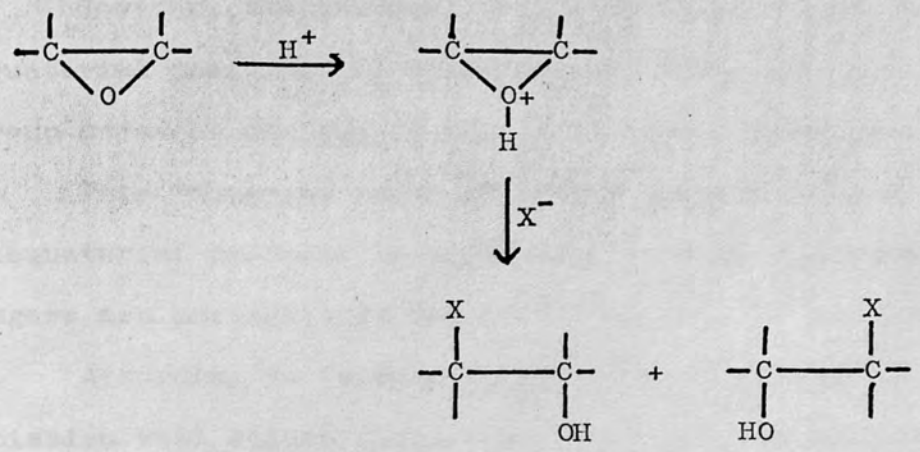
The methoxide ion can attack either of the two carbons:-



OR

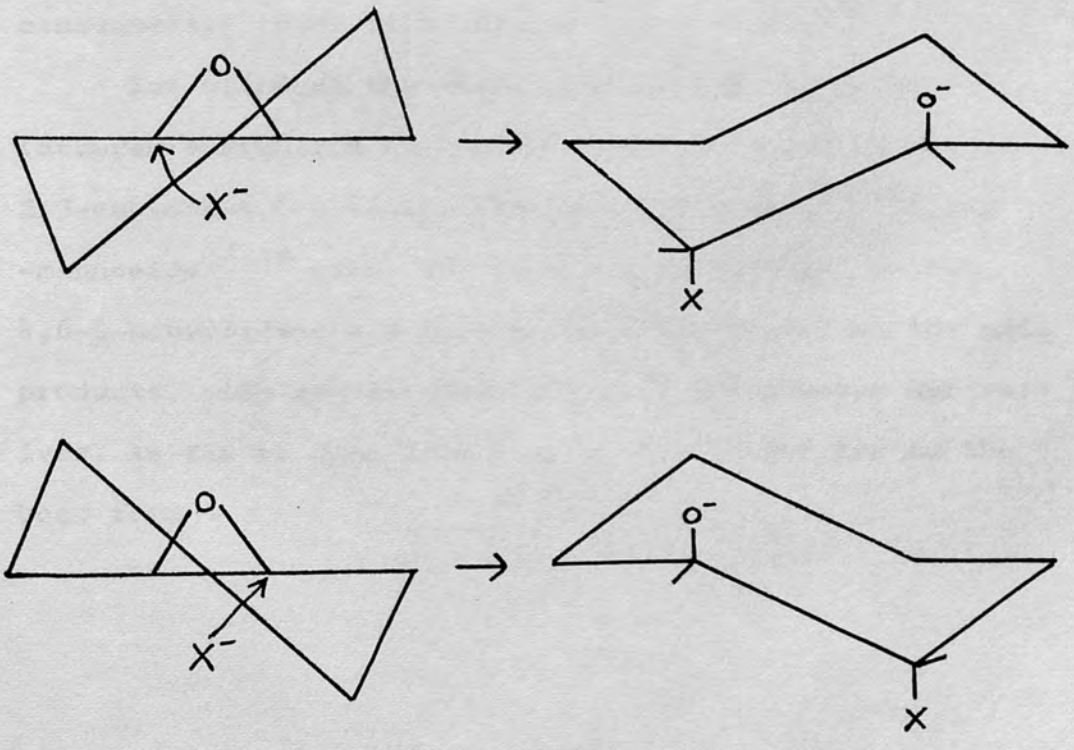


The essential difference between ring cleavage by bases and by acids is that, under neutral or basic conditions, an oxide anion is generated, which is subsequently protonated, whereas under acidic conditions, proton addition to the oxygen atom occurs first, to generate an oxonium ion, followed by nucleophilic attack at the carbon atom.[15]



Sugar epoxides, however, do not seem to show any regularity in the direction of scission, although attempts have been made to predict this.[43]

Newth & Homer[37] and Mills[44] considered that the major product would be the one where the two resulting groups were in axial positions:-



However, the incoming groups would be forced into equatorial positions if there were a sufficiently bulky group adjacent and *cis* to one of the axial positions.[30]

This "abnormal opening" of the epoxide ring to give diequatorial products is something to which 3,4-anhydro-sugars are particularly prone.[15,45]

According to Cookson *et al*,[46] the direction of scission will depend largely on the preferred conformation of the epoxide, which may be deduced.

In general, the chair form will be preferred and all known pyranosides in the boat form are stabilised by the presence of another ring which makes the chair form structurally impossible.[47]

When the epoxide is of rigid conformation (as in 1,6-anhydro- compounds or fused-ring systems), the ring should only be able to open in one direction and consequently there will only be one product.[48]

But although the chair form is the one more favoured energetically, anhydro-ring scission of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-alloside[12,15,27] and -mannoside[12,15] gives the 2- and 3-substituted methyl 4,6-*O*-benzylidene-α-D-altrosides respectively as the main products, with smaller quantities of the glucose derivatives. As can be seen from models, the latter are in the boat form :-

2,3-anhydro-α-D-allosíde

2-substituted α-D-altroside

+

3-substituted α-D-glucoside

Similarly with the alkaline scission of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-taloside and -guloside.[15,29,30]

Epoxides of monocyclic pyranoses [illegible], on the other hand, are more flexible, and will normally exist as an equilibrium mixture of the two half-chair conformations which are possible for a six-membered ring. Thus, even when ring-opening is always diaxial, a mixture of two different products is likely.[40,49]

But, whichever way the ring opens, the initial product will have two axial groups, although it may well change to a more stable conformation with equatorial groups, for steric reasons.

The product seems to adopt the conformation in which non-bonded interactions are at a minimum. This may, or may not be, the same chair form as in the initial epoxide.[30]

In general, conformational effects operate in determining the product of ring scission in acid media, while steric and polar effects are more important in alkaline media.[39]

Of particular interest are the nitrogen-containing nucleophiles, such as azide and cyanide.

Little work has been done on the opening of epoxide rings with azide, but Guthrie & Murphy found predominantly diaxial opening of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-alloside and -mannoside.[50]

The cyanide ion is especially interesting, because the cyano-alcohol which should result from ring-opening can either be reduced to an amino-sugar, or the cyano-

group can be converted into one of a number of other functional groups such as CHO, CH_3, COOH *etc*. Thus, opening of epoxide rings with cyanide provides a route to branched-chain sugars.

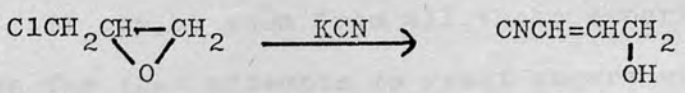
There are many possible medical applications here, as amino-sugars (from epoxide ring-opening with azide) are thought to possess anti-cancer[51,52] or antibiotic[53] properties. Several antibiotics contain branched-chain residues.[52,54,55] For example, L-streptose (5-deoxy-3-*C*-formyl-L-lyxose) is a component of Streptomycin.[56]

Nucleosides with branched sugars can also exhibit cytostatic or virostatic activity, the function of the sugar being to complex with DNA in the micro-organism concerned.[52,57]

Several amino-sugars have also been found to show marked insulin-like activity.[58]

EPOXIDE RING OPENING WITH CYANIDE

In spite of their toxicity, hydrogen cyanide and the alkali metal cyanides have been used in organic chemistry research for over a hundred years, since Pazsche treated epichlorhydrin with potassium cyanide to give an unsaturated cyano-compound which he called "epicyanohydrin".[59]



However, various cyanohydrins were made in the 1870s and 1880s from hydrogen cyanide and ethylene oxide,[60,61] invert sugar,[62] sucrose,[62] glucose[62] and fructose.[61] Cyanohydrins were similarly obtained around the turn of the century from epichlorhydrin.[63,64] It was found that the cyanohydrin could be isolated if the alkali produced by the reaction was continuously neutralised. If not, the reaction would proceed to the unsaturated product obtained by Pazsche.[65]

But it was not until 1913 that alkali metal cyanides were used on sugars, when the addition of aqueous potassium cyanide to glucose solution gave potassium glucoheptonate.[66]

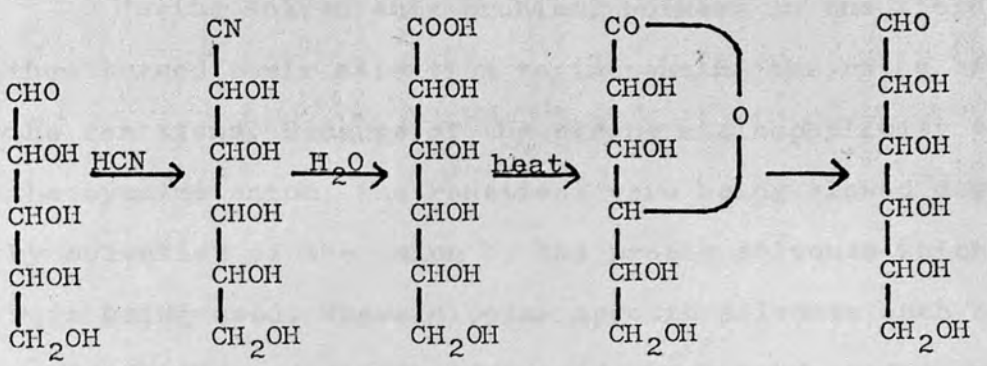
Barium cyanide has also been used as a reagent,[67] and was found to be slightly less prone to form tarry products. Rupp and Hölzlé reacted fructose, mannose, galactose, lactose, maltose and glucose with KCN and

$Ba(CN)_2$ in turn. The two disaccharides, lactose and maltose, gave only tars, whether the reagent was KCN or $Ba(CN)_2$. Fructose, mannose and galactose all gave products (cyanohydrins), with no tars formed, with either cyanide. Glucose, however, gave α-glucoheptoic anhydride, whichever cyanide was used as a reagent; dark-coloured by-products were formed with potassium cyanide, although not with barium cyanide.

It can be seen from all these experiments mentioned so far that attempts to react sugars with cyanides give, not cyano-sugars as might have been expected, but open-chain products.

The explanation for this is that nucleophilic reagents, such as cyanides, attack the carbonyl groups of aldehydes and ketones to give addition products, and they react similarly with sugars. Although sugars are generally thought to exist mainly in cyclic forms in solution, the lack of reactivity of glycosides towards nucleophiles has led to the suggestion that these additions occur <u>via</u> the carbonyl forms of the sugars, rather than <u>via</u> the cyclic forms.[68]

The Kiliani reaction[69] is an illustration of the reaction of cyanide ions with aldehydes and ketones:-



sugar — cyano-hydrin — lactonic acid — lactone — sugar

The cyanohydrins are not usually isolated, as they are hydrolysed directly to the aldonic acids by aqueous base (in the case of KCN) or acid (in the case of HCN). Indeed, of the various sugars whose reactions with KCN or HCN were investigated, only the cyanohydrin of fructose was isolated.[69]

The mechanism of the Kiliani Reaction has been studied in detail by Varma & French (1972)[70] and Serianni et al (1979).[71]

The first natural products to react with cyanides without undue destruction were the steroids.[72] At last the epoxide rings were being opened to give the expected cyano-alcohols, without the basic structure of the molecule being changed. The problem had been that the reaction mixture had become too basic, and hydrolysis and base-catalysed condensation had occurred. The problem was solved by the addition of ammonium chloride, which was converted to ammonium hydroxide, ammonia being liberated on heating.[73]

Having solved this problem, workers in the field then turned their attention to increasing the rates of the reactions. Because of the strong nucleophilicity of the cyanide anion, the reactions were being slowed down by solvation of the anion by the protic solvents which were being used. Where dipolar aprotic solvents such as acetonitrile and dimethylformamide were used, rates and yields were found to increase considerably. This now posed a solubility problem. Tetraalkylammonium salts seemed to be the most soluble in dipolar aprotic solvents, and thus the best source of nucleophiles.[74,75] The method certainly worked for the opening of 3,4-anhydro-1,2-O-isopropylidene-β-D-psicopyranose with tetrabutylammonium fluoride in acetonitrile.[76]

The first tetraalkylammonium cyanide to be made was reported by Webster et al in 1962,[77] when tetraethylammonium cyanide was made from the corresponding chloride by dropwise addition of sodium cyanide in anhydrous methanol under an atmosphere of nitrogen. By 1965, tetrabutylammonium cyanide had been made.[78]

At about the same time, a method was developed for making aryl cyanides by means of ion-exchange resins.[79,80] This was quick and simple and involved merely stirring up the appropriate halide with Amberlite IRA-400 or other suitable resin in the cyanide form. Solodar extended this to tetraalkylammonium cyanides some years later,[81] and the cyanides which he obtained were found to give improved yields when used instead of sodium cyanide in the benzoin

condensation.[82]

The first work on the opening of sugar epoxide rings with cyanide was reported by Austin *et al* in 1965,[83] but since the reagent used was aqueous potassium cyanide, the expected cyanohydrins were hydrolysed, and the products from methyl 2,3-anhydro-α-D-ribofuranoside and -β-D-ribofuranoside were a lactone and a 3,5-anhydride respectively. The problem was alkalinity again, and when methyl 2,3-anhydro-β-D-ribopyranoside was treated with aqueous sodium cyanide, buffered at pH 8.0-8.5, two isomeric cyano-deoxy sugars were successfully obtained, albeit not the ones expected.[34]

One of the methods used successfully to open steroid epoxides was the aluminium di- or tri-ethyl and hydrogen cyanide in tetrahydrofuran system,[84,85,86] and Davison *et al* applied this satisfactorily to sugar epoxides, having first tried potassium cyanide in dimethylformamide, which caused extensive decomposition, with no recognisable products isolable.[35]

However, the alkyl aluminium cyanide reagents are pyrophoric and require extremely careful handling[87] and, perhaps not surprisingly, it was not a method generally adopted, although in 1980 some Japanese workers carried out a hydrogenation where the starting material, an unsaturated deoxy-nitro- sugar, was treated with a solution prepared by passing an aqueous solution of potassium cyanide through a column of cation exchange resin.[88] A

modification of Davison's method, using diethyl aluminium cyanide, was in use in 1982.[89]

The main drawback with the tetraalkylammonium cyanides is their thermal instability and their need to be handled and weighed under completely anhydrous conditions, to avoid hydrolysis to hydrogen cyanide.

Another approach was to try to dissolve potassium cyanide in dipolar aprotic solvents by means of a phase transfer catalyst. Tetraalkylammonium salts had been found to work quite well as phase transfer catalysts[90,91,92] and attention was turned to the cyclic polyethers or crown ethers. They had already been used successfully to dissolve metal salts in aromatic hydrocarbons, the best known example being potassium permanganate in benzene ("purple benzene").[93] Instead of tight ion pairing, the ions in the metal salt are separated by the molecules of ether, the resulting "naked" anion being considerably more effective as a nucleophile.[94] Crown ethers appear to have a greater effect in dipolar aprotic solvents than in other solvents,[95] because solvation is less in the former.

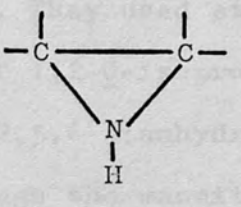
"Naked" cyanide has been prepared by a number of workers[87,93,96,97,98] with varying degrees of success, but in general this system was found to compare favourably with both dipolar aprotic solvents and other phase transfer catalyst systems in reaction time, yield, lower reaction temperature and simplicity of work-up.[96] Sasaki

et al found crown ethers to be more effective phase transfer catalysts than were quaternary ammonium salts.[98] Some reactions of nucleosides with potassium cyanide would not take place at all without the presence of a crown ether.[99] Also, small amounts of water did not appear to affect the reactions adversely.[100] The most generally used cyanide in preparative organic chemistry is the potassium salt (it is more soluble than the sodium salt), and the optimum crown ether for complexation of the potassium ion was found to be 18-crown-6.[97] Unfortunately, its thermal stability is low (it degrades above 120°C)[97] and it has also been found to complex with acetonitrile.[101] An advantage of crown ethers over quaternary ammonium salts is that they can quite easily be recovered and re-used after the reaction is over.[100]

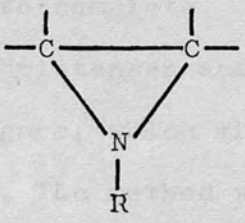
However, in spite of their many advantages, they had not been used in carbohydrate research until this work was started. They are also of unknown toxicity. Even quaternary ammonium salts have been used very little in sugar chemistry.[76] Suitable quaternary ammonium cyanides are hygroscopic, difficult to handle and decompose very easily in the presence of water, to give hydrogen cyanide.[75] The reactions are therefore very sensitive to moisture, and only solvents which are reasonably easy to obtain in an anhydrous condition are used.

EPIMINO-SUGARS

The epimino-sugars, or aziridines, are analogous to the epoxides. They contain a three-membered ring in which a nitrogen atom bridges two adjacent carbons.



They may be N-substituted.



SYNTHESIS OF EPIMINO-SUGARS

The interest in epimino-sugars only began in the late 1950s, when Vargha *et al*[102] began a series of syntheses of new sugar derivatives with potential anti-tumour activity. They used ethyleneimine to open the epoxide rings of 1,2-*O*-isopropylidene-5,6-anhydro-gluco-furanose and 1,2,5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol. Although the mannitol derivative was formed easily and was found to be strongly cytotoxic, the glucose derivative was only slightly so, and the reaction took four days to complete.

In 1960 Christensen and Goodman[103] made the first true epimino-sugars, which they saw as potential anti-radiation drugs. The method was the same as that used for making epoxides, the dithiocarbamate derivative of an altroside mesylate being treated with sodium methoxide to give a thioacylated ethyleneimine, which was then reduced with sodium borohydride to give methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-epimino-α-D-alloside. This compound was found to exist in two crystalline forms with different melting points.

Aziridines are alkylating agents (as are epoxides) and more recently it has been found that many compounds capable of alkylating proteins and nucleic acids are carcinogenic.[104]

Meanwhile, there was some interest in making amino-

sugars, in the hope of developing new antibiotics, it having been realised that several antibiotics in use contained amino-sugar structures.[53] Various amines were reacted with 5,6-anhydro-1,2-O-isopropylidene-D-gluco-furanose[53] and some of the resulting amino-sugars did, in fact, appear to possess antibiotic properties.

So easier methods of making amino-sugars were sought, and soon Guthrie & Murphy reported the first application of the opening of the epoxide rings of sugars with sodium azide.[33] VanderWerf *et al* had described the opening of epoxides by azide ion some eight years previously, but had used non-carbohydrate epoxides such as propylene oxide, 2,3-epoxybutane and cyclohexene oxide.[105]

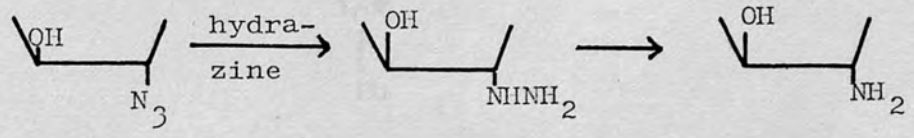
The azido-sugar products were then reduced with Adams' Catalyst to the corresponding amino-sugars.[33] Reist *et al*[51] obtained similar results by sulphonate displacement with azide, followed by H_2/Pd reduction to the amino-sugar, and Ali obtained excellent yields of amines with sodium borohydride.[106]

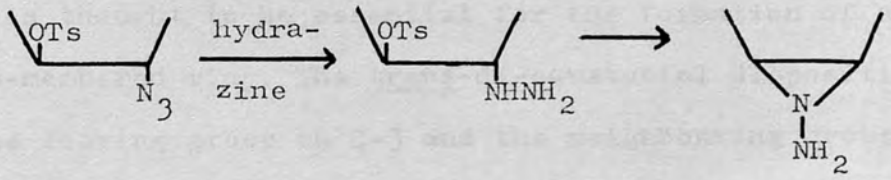
Other methods, not now in general use, have also been used to reduce azides to amines.[107,108,109]

A recent application of the Staudinger reaction[110a] to azido-sugars has been found to be a convenient means of reducing them to amino-sugars. The azide is treated with triphenyl phosphine, and the resulting phosphin-imine, which crystallises out, is readily hydrolysed in basic medium to the amine.[110b]

Treatment of the resulting amines with alkali led to the formation of aziridines.

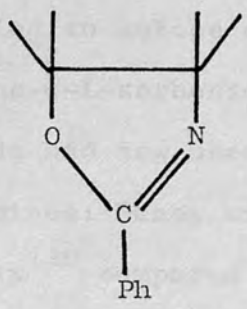
Guthrie & Murphy[111] found that treatment of the azide with dilute methanolic hydrazine hydrate in the presence of Raney nickel produced the epimine in one step. The reaction also worked for steroids.[112] The intermediate amine was not isolated at this time, although it was later found that if there was no suitable leaving group in a trans-diaxial position, the amine would be obtained, since the reaction could not go on to give the aziridine.[113]





Further reduction of the epimine with Raney nickel gave, on acetylation, the acetamido- derivative.[114] Methyl 4,6-O-benzylidene-2,3-dideoxy-2,3-epimino-α-D-mannopyranoside gave a mixture of the two products in crystalline form, whereas the alloside gave a syrup.

Another route to epimino-sugars is *via* reduction of the corresponding benzamido- compound with lithium aluminium hydride,[111,115] a method originally used to reduce aliphatic and aromatic azides to their amines.[116] The resulting epimines were found, unlike epoxides, to be resistant to ring-opening by alkali,[50] although this could be achieved by azide.[115] In this method, a five-membered oxazoline ring is formed as a by-product.



As in epoxide synthesis, a *trans*-diaxial relationship is thought to be essential for the formation of a three-membered ring. The *trans*-di-equatorial disposition of the leaving group on C-3 and the neighbouring group on C-2 of methyl 2-deoxy-2-benzamido-3-*O*-mesyl-4,6-*O*-benzylidene-α-D-glucopyranoside would be expected to favour oxazoline formation. However, Gibbs *et al*[117] obtained methyl 2,3-dideoxy-2,3-epimino-4,6-*O*-benzylidene-α-D-allopyranoside on reduction with lithium aluminium hydride in tetrahydrofuran, but obtained the amine if they used sodium ethoxide for the reaction, together with a small

amount of methyl 2-benzamido-4,6-O-benzylidene-α-D-glucopyranoside.

In the steroid field, Ponsold and Klemm[118] were successful in converting azide to epimine in one stage with lithium aluminium hydride. Again, the intermediate amine could not be isolated.

So far, nearly all the work on amino-sugars had been done on aldoses, and it was not until 1967 that previously used methods for the synthesis of amino-sugars was applied to ketose derivatives, such as methyl 1,3-O-benzylidene-α-L-sorboside and -β-D-fructoside.[119]

Two methods had now been found to convert azides directly to epimines: Raney nickel and lithium aluminium hydride. Cleophax[120] compared the two reagents by reducing methyl 3,5-diazido-3,4-dideoxy-2-O-tosyl-β-D-ribofuranoside and benzoylating the product. Raney nickel gave a dibenzamido- compound and lithium aluminium hydride gave an epimine, reduction of which with Raney nickel gave the dibenzamido- compound. It was concluded that, in the first reaction, the expected epimine had been hydrogenolysed during the reaction. Lithium aluminium hydride therefore became the method of choice because apart from the problem of over-reduction, Raney nickel often gave low or variable yields.[120,121,122]

Failure to produce an epimine, then, is caused either by ring-opening of the epimine to give an amide,[122] over-reduction to the amine,[123] or by failure to react, due either to failure to achieve a trans-diaxial arrange-

ment or to inadequate nucleophilicity of the nitrogen, as when this is contained in an acylamido- or sulphonamido- group.[124]

Since the present work was started, Guthrie and Murphy's synthesis of an epimine from an epoxide by azidolysis, followed by cyclisation with lithium aluminium hydride, has been successfully employed by Banaszek and Zamojski.[125]

Other recent cyclisations have been carried out by Japanese workers with tributyltin hydride[123] and with various organo-silicon and organo-phosphorus compounds,[126] some of the latter having been found to have anti-bacterial properties.

A variety of non-toxic members of the family therefore needs to be made.

EXPERIMENTAL

EXPERIMENTAL DETAILS

Unless otherwise stated, extraction of product was with chloroform, the extracts being dried over magnesium sulphate and the solvent removed under reduced pressure. Thin-layer chromatography was performed on Merck pre-coated silica gel 60 plates (F_{254}). The solvent was 1:1 benzene/ether and the plates were examined under ultra-violet light and iodine vapour.

Reaction mixtures were stirred with a magnetic stirrer.

Pyridine was dried over potassium hydroxide pellets.

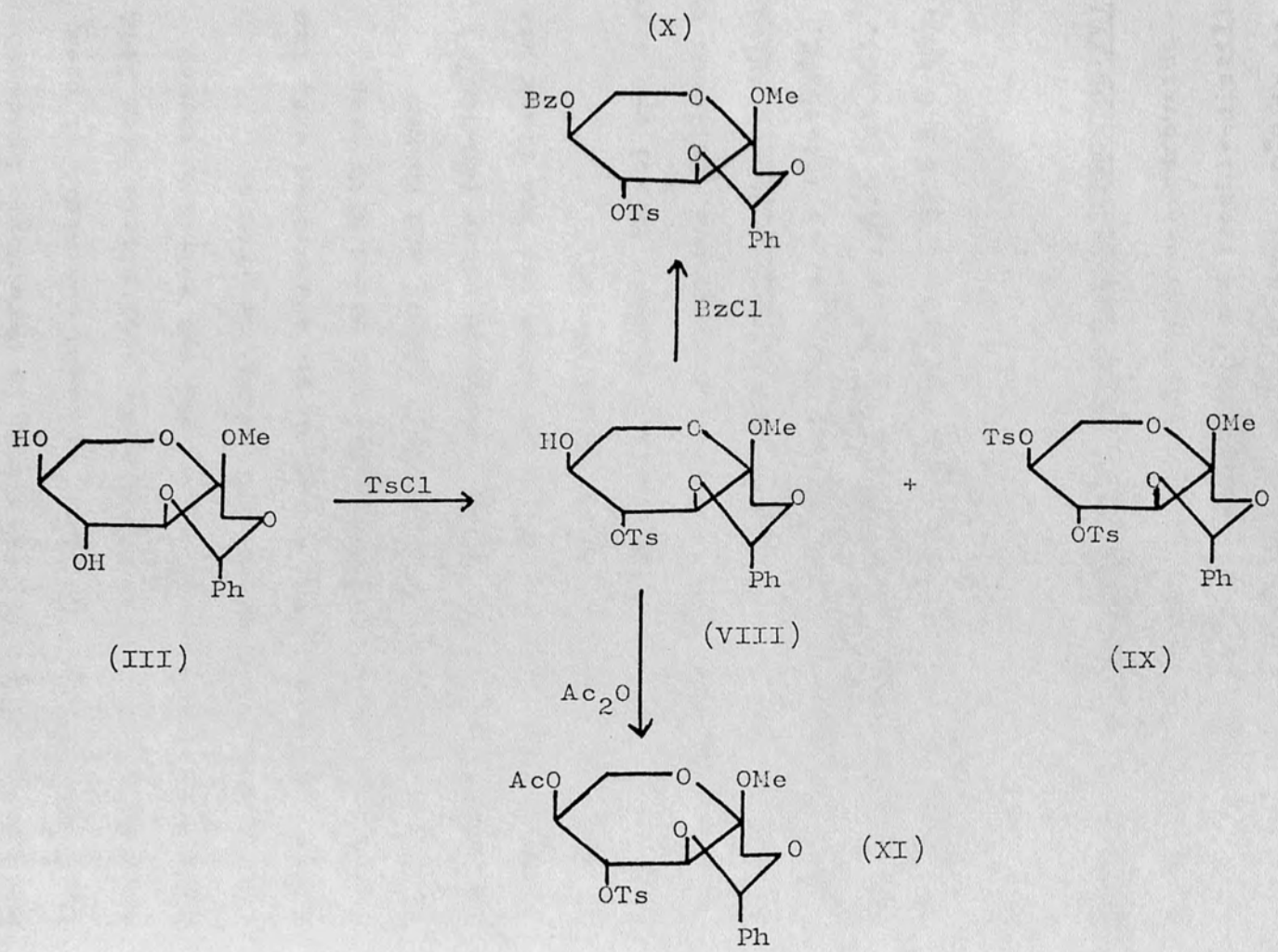
Chloroform was dried over 3A molecular sieve for 1 hour.

Dichloromethane was purified by shaking with 5% sodium carbonate solution, then with water, and dried over calcium chloride. It was distilled and the fraction boiling between 40-41°C was collected.[127]

Tetrahydrofuran was dried by refluxing over 5A molecular sieve for $2\frac{1}{2}$ hours, and stored over sieves.

(III)
(II)
(I)
Ph
OMe
OH
HO
CH2OH

(III)
HO
OH
O
OMe
Ph
O
BzCl
(IV)
HO
OBz
O
OMe
Ph
O
+
(V)
BzO
OBz
O
OMe
Ph
O
TsCl
(VI)
TsO
OBz
O
OMe
Ph
O
(VII)
TsO
OH
O
OMe
Ph
O


(X)
BzO
OMe
OTs
Ph
BzCl
HO
OMe
OH
Ph
TsCl
HO
OMe
OTs
Ph
+
TsO
OMe
OTs
Ph
(III)
(VIII)
(IX)
Ac2O
AcO
OMe
OTs
Ph
(XI)

METHYL 1,3-O-BENZYLIDENE-α-L-SORBOSIDE (III)

Sorbose(I) (30g) was dissolved in methanolic hydrogen chloride (1200ml) and left to stand overnight at room temperature.[128] The mixture was neutralised with lead carbonate. At the end-point, the red solution turned yellow and was found to be neutral to litmus.
After filtration, the methanol was evaporated off. The resulting methyl sorboside(II) was mixed with zinc chloride (10g) and benzaldehyde (28ml) and shaken mechanically for 25 hours. Petroleum ether (80-100°C) (100ml) and water (100ml) were added and the flask was shaken until no further crystals formed.
The crystals were filtered on a Buchner funnel and dried in air. Recrystallisation from isopropanol, followed by drying in an oven at 100°C, gave methyl 1,3-O-benzylidene-α-L-sorboside(III) (25.4g, 54%), m.p.= 181-182°C, (literature m.p.= 183-184°C),[119] $[\alpha]_D$= -54.6 (c1.06).[119] (Found C 59.5 H 6.4. $C_{14}H_{18}O_6$ requires C 59.6 H 6.4%).

METHYL 1,3-O-BENZYLIDENE-4-O-BENZOYL-α-L-SORBOSIDE(IV)

A solution of methyl 1,3-O-benzylidene-α-L-sorboside (III) (10g) in dry pyridine (40ml) and freshly-distilled dichloromethane (73.5ml) was cooled to -10°C in an ice/salt bath. A solution of benzoyl chloride (4.4ml) in dichloromethane (67.7ml) was added, with constant stirring, over a period of 1½ hours and left at -10°C

overnight. The reaction mixture was then left to stand at room temperature for 2 days, when it was diluted with dichloromethane (113ml). The solution was washed twice with dilute sulphuric acid (300ml), followed by saturated sodium bicarbonate solution (235ml) and water (235ml) (3 times). It was found to be neutral to litmus. Drying and evaporation of the solvent gave a pale yellow syrup, which formed a white solid on cooling. The mixture was dissolved in boiling benzene (100ml) and the solution allowed to stand overnight. Since there was no unreacted diol, the solution was evaporated to dryness.

Recrystallisation from isopropanol, followed by drying in a vacuum desiccator over calcium chloride, and then in a drying pistol, gave crystals of methyl 1,3-O-benzylidene-4-O-benzoyl-α-L-sorboside(IV) (11.6g, 85%), m.p.= 128-130°C, $[\alpha]_D = -77.2°$. (Found C 64.9, H 5.7. $C_{21}H_{22}O_7$ requires C 65.3, H 5.7%).

Infra-red spectroscopy showed the presence of only one OH, showing that this is the monobenzoate.

Thin-layer chromatography (chloroform as solvent) indicated the presence of small quantities of the other monobenzoate and of the di-benzoate.

METHYL 1,3-O-BENZYLIDENE-4,5-DI-O-BENZOYL-α-L-SORBOSIDE(V)

A repeat of the above preparation of the 4-benzoate, but with the benzoyl chloride solution added over a period of 2 hours, and the product worked up immediately after an overnight stand at -10°C, yielded 15.2% of unreacted diol

and 52.1% of methyl 1,3-O-benzylidene-4,5-di-O-benzoyl-α-L-sorboside(V), m.p.=158-159°C, $[\alpha]_D$= -20.7°. (Found C 68.4 H 5.3. $C_{28}H_{26}O_8$ requires C 68.6 H 5.3%). Infra-red spectroscopy confirms that the product is the dibenzoate, by the absence of any OH groups.

METHYL 1,3-O-BENZYLIDENE-4-O-BENZOYL-5-O-TOSYL-α-L-SORBOSIDE (VI)

A solution of the monobenzoate (IV) in pyridine was tosylated by the usual method. After pouring into water the reaction mixture was diluted with dichloromethane (341ml) and washed as described in the preparation of the benzoates. The solid remaining after drying and evaporation of the dichloromethane extract was treated with boiling benzene (500ml) and left to stand overnight. Filtration and drying at 100-105°C, followed by recrystallisation from acetone/isopropanol (5:1) gave crystals of methyl 1,3-O-benzylidene-4-O-benzoyl-5-O-tosyl-α-L-sorboside(VI) (19.0g, 33%), m.p.= 157.5°C(d), $[\alpha]_D$= -68.0° (c0.2), (Found C 62.0 H 5.1 S 5.98. $C_{28}H_{28}O_9S$ requires C 62.2 H 5.2 S 5.93).

METHYL 1,3-O-BENZYLIDENE-4-O-TOSYL-α-L-SORBOSIDE(VIII)

A solution of methyl 1,3-O-benzylidene-α-L-sorboside(III) (27.4g) in pyridine (274ml) was cooled in an ice/salt bath and treated with tosyl chloride (19.2g) with stirring. The mixture was left at -10°C overnight and poured into

ice-water (2 litres). The product was a pale flesh-coloured solid which, after working up as usual, gave methyl 1,3-O-benzylidene-4-O-tosyl-α-L-sorboside (VIII) (25.1g, 60%), m.p.= 116°C(d), $[\alpha]_D$= -54.8°(c.0.8). (Found C 57.5 H 5.4. $C_{21}H_{24}O_8S$ requires C 57.8 H 5.6%).

METHYL 1,3-O-BENZYLIDENE-4-O-TOSYL-5-O-BENZOYL-α-L-SORBOSIDE (X)

A solution of the 4-O-tosyl derivative (VIII) (20g) in pyridine (300ml) was allowed to stand in ice for 1½ hours. Benzoyl chloride (8.8ml) was added, slowly and with stirring, with the flask still standing in ice. The mixture was left at room temperature over the week-end. The product was worked up as usual and oven-dried at 100°C for 2½ hours.

Recrystallisation from acetone/isopropanol (5:1) gave methyl 1,3-O-benzylidene-4-O-tosyl-5-O-benzoyl-α-L-sorboside (X) (23.9g, 96%), m.p.= 140-141°C(d), $[\alpha]_D$= -51.8°(c.0.26). (Found C 62.1 H 5.2 S 5.99. $C_{28}H_{28}O_9S$ requires C 62.2 H 5.2 S 5.93%).

METHYL 1,3-O-BENZYLIDENE-4-O-TOSYL-5-O-ACETYL-α-L-SORBOSIDE(XI)

The 4-O-tosyl derivative (VIII)(5.9g) was dissolved in pyridine and excess acetic anhydride was added. The product was worked up as usual and dried in a vacuum

desiccator at 30°C to give methyl 1,3-O-benzylidene-4-O-tosyl-5-O-acetyl-α-L-sorboside (XI) (5.6g, 87%), m.p.= 141°C(d), $[\alpha]_D$= -65.2° (Found C 58.1 H 5.7 $C_{23}H_{26}O_9S$ requires C 57.7 H 5.4%).

ATTEMPTED EPOXIDATION OF METHYL 1,3-O-BENZYLIDENE-4-O-TOSYL-5-O-ACETYL-α-L-SORBOSIDE(XI)

a) Attempted epoxidation of (XI) by the method of Ohle & Just[11] yielded only a compound (6%) with m.p.= 119-120°C, and an infra-red spectrum and analysis which were consistent with its being the 4-O-tosyl compound (VIII).

b) Treatment of (XI) with sodium methoxide gave a mixture of methyl 1,3-O-benzylidene-α-L-sorboside (III) and a compound, m.p.= 127-129°C, $[\alpha]_D$= -71.1°, and analysis and infra-red spectrum consistent with its being methyl 1,3-O-benzylidene-4,5-di-O-tosyl-α-L-sorboside (IX). (Found C 56.9 H 5.1 $C_{28}H_{30}O_{10}S_2$ requires C 56.9 H 5.1%).

ATTEMPTED EPOXIDATION OF METHYL 1,3-O-BENZYLIDENE-4-O-TOSYL-5-O-BENZOYL-α-L-SORBOSIDE(X)

Attempted epoxidation of the above compound by the method of Ohle & Just[11] gave only starting material (32%).

ATTEMPTED EPOXIDATION OF METHYL 1,3-O-BENZYLIDENE-4-O-BENZOYL-5-O-TOSYL-α-L-SORBOSIDE(VI)

A solution of the above compound (VI) (3g) in dry chloroform (150ml) was refluxed with sodium methoxide solution (3ml 25% solution, diluted with dried methanol (50ml)) for 12 hours, made slightly acid with ice-cold dilute hydrochloric acid and neutralised with sodium carbonate. The solution was washed with water, dried, filtered and evaporated to give a white solid. Recrystallisation from acetone/isopropanol (5:1) gave starting material (40%), but the white solid (60%), extracted from the filtrate and recrystallised from isopropanol, proved to be a monotosylate, methyl 1,3-O-benzylidene-5-O-tosyl-α-L-sorboside (VII), m.p.= 132-133°C, $[\alpha]_D$= -46.3° (Found C 58.1 H 5.6 $C_{21}H_{24}O_8S$ requires C 57.8 H 5.6%).

(literature values:- m.p.= 135-6°C, $[\alpha]_D$= -45.4° (c1.0))[129]

This compound was formed by removal of the 4-O-benzoyl group.

REACTIONS OF METHYL 2,3-ANHYDRO-4,6-O-BENZYLIDENE-α-D-MANNOSIDE[8] WITH TETRA-n-BUTYLAMMONIUM CYANIDE

PREPARATION OF TETRA-n-BUTYLAMMONIUM CYANIDE

Preparation was by the method of Solodar,[81] except that tetra-n-butylammonium iodide was used instead of the bromide.

Methanol was dried by adding magnesium turnings and resublimed iodine and distilling off the absolute methanol.[130]

Elution continued until tests with silver nitrate for iodide ions in the eluent were negative.

The product was a white hygroscopic solid. This was cleaned up by washing it with ethyl acetate (which had been dried over calcium chloride). It was stored over phosphorus pentoxide in a vacuum desiccator.

a) REACTION IN ACETONITRILE

The mannoside (0.5g) was dissolved in acetonitrile (20-25 ml) which had been dried over 3A molecular sieve . Tetra-n-butylammonium cyanide (1.5g) was added and the solution refluxed for 12 hours. The reaction mixture was poured into water and extracted with ether.

Recrystallisation from isopropanol gave starting material (m.p.= 145°C). The filtrate was evaporated down to give a dark brown, tarry-looking syrup, which was extracted with ether and acetone.

Samples taken during the reaction showed only starting material when examined by thin-layer chromatography.

Infra-red spectroscopy of the syrup showed the presence of contaminated starting material, plus some degradation products.

b) REACTION IN DIMETHYLFORMAMIDE

The reaction took place as above, but with the reaction mixture being heated at about 100°C for 18 hours.

Removal of solvent in vacuo was followed by co-distillation with xylene and attempted recrystallisation from isopropanol. This was unsuccessful because the DMF proved impossible to remove.

Infra-red spectroscopy showed the presence of cyanide in the product, but thin-layer chromatography showed only starting material (R_f = 0.82).

REACTIONS IN MIXTURES OF DMF AND ACETONITRILE

c) REACTION USING 6% DMF IN ACETONITRILE AS SOLVENT

The reaction took place as in the acetonitrile reaction. The reaction mixture was refluxed for 6 hours. Working up as usual gave white crystals (0.2g, 40%), m.p.= 145-146°C. Both thin-layer chromatography and infra-red spectroscopy showed only starting material to be present, with no cyanide product.

d) REACTION USING 20% DMF IN ACETONITRILE AS SOLVENT

The reaction took place as in the acetonitrile reaction. The reaction mixture was refluxed for 6 hours. On pouring into water, 0.37g of a black solid was obtained.
Chloroform extraction of the filtrate gave 0.01g of starting material.
Thin-layer chromatography of the reaction mixture after heating showed two spots at R_f 0.64 and R_f 0.73, suggesting that the mannoside had reacted with the cyanide.
Recrystallisation of the black solid, from aqueous methanol, gave 0.085g of starting material (m.p.= 145°C).
Evaporation of the filtrate gave a solid, the infra-red spectrum of which showed it to contain cyanide. This was acetylated, and recrystallisation of the product, from aqueous methanol, attempted. The filtrate was evaporated down.
Infra-red spectroscopy of the resulting solid showed an

absence of cyanide, and suggested that the product of acetylation was mainly inorganic material, although all traces of DMF had been finally removed only with great difficulty.

e) REACTION USING 50% DMF IN ACETONITRILE AS SOLVENT

The reaction took place as for acetonitrile. The reaction mixture was heated at 110°C for 6 hours. Thin-layer chromatography showed the presence of two compounds with R_f 0.62 and R_f 0.75.

The product was extracted with chloroform and recrystallised from aqueous methanol. The resulting solid (0.14g, m.p.= 138°C) was acetylated and recrystallisation from isopropanol attempted.

Infra-red spectroscopy showed no evidence of cyanide and the compound (m.p.= 138°C) was not characterised.

REACTIONS IN OTHER DIPOLAR APROTIC SOLVENTS

f) REACTION USING PROPYLENE GLYCOL AS SOLVENT

The reaction took place as for acetonitrile. The reaction mixture was heated at 90-95°C for 16 hours. Thin-layer chromatography indicated a new product (R_f 0.54) as well as starting material.

Extraction and recrystallisation gave only starting material (m.p.= 144°C), but a strong smell of benzaldehyde in the filtrate suggested that the benzylidene group had been removed. The filtrate was evaporated down.

Infra-red spectroscopy of the resulting solid showed an absence of cyanide.

g) REACTION USING HEXAMETHYLPHOSPHORITRIAMIDE AS SOLVENT

The reaction took place as for acetonitrile. The reaction mixture was heated at 110°C for 18 hours. The tarry solid which appeared on extraction was acetylated, but no solid was formed on pouring into water.

Thin-layer chromatography showed two spots of very low R_f value.

Infra-red spectroscopy showed the presence of cyanide in the chloroform layer, and also indicated the presence of starting material, tetra-n-butylammonium cyanide, HMPT and some impurities.

h) REACTION USING TETRAHYDROFURAN AS SOLVENT

The mannoside (1g) was dissolved in tetrahydrofuran (50ml) and refluxed with excess tetra-n-butylammonium cyanide for 15 hours. The product was extracted and dried. Evaporation of the chloroform gave a solid which was dried in a vacuum desiccator and recrystallised from isopropanol. Thin-layer chromatography showed two spots, R_f 0.53 (product) and R_f 0.70 (starting material). The latter became fainter as the reaction proceeded.

Infra-red spectroscopy indicated the presence of starting material and degradation of the tetrahydrofuran.

REACTION OF METHYL 2,3-ANHYDRO-4,6-O-BENZYLIDENE-α-D-MANNOSIDE WITH POTASSIUM CYANIDE AND CROWN ETHER

The anhydro-mannoside (12g), 18-crown-6 (1g) and dry acetonitrile (25ml) were heated until all the solid had dissolved. Potassium cyanide (6g) was added, at which point the reaction mixture turned black. The mixture was refluxed for 30 hours, and the product extracted with ether.

Recrystallisation from isopropanol gave the starting material (m.p.= 146°C).

Thin-layer chromatography showed two products, with R_f 0.66 and R_f 0.72.

PREPARATION OF 3,4-ANHYDRO-1,2-O-ISOPROPYLIDENE-β-D-PSICOPYRANOSE(XII)

1,2-O-isopropylidene-3-O-methanesulphonyl-β-D-fructopyranose (made by the method of Ohle & Just)[11] (20g) was dissolved in boiling ethanol. Using phenolphthalein as indicator, alcoholic sodium hydroxide (1M) was added from a burette at such a rate that the purple colour had just disappeared by the time that the next addition of alkali was made, and continued until there was no further colour change. The sugar solution was kept boiling on a hotplate with magnetic stirrer and topped up as necessary with hot ethanol. The solution was evaporated to dryness, the resulting solid dissolved in water, and the epoxide extracted with ether. Evaporation of the ether, followed by recrystallisation from isopropanol, gave 3,4-anhydro-1,2-O-isopropylidene-β-D-psicopyranose (11.7g, 86%), m.p.= 87-92°C. (Literature m.p.= 92°C).[11]

PREPARATION OF 3,4-ANHYDRO-1,2-O-ISOPROPYLIDENE-5-O-BENZOYL-β-D-PSICOPYRANOSE(XV)

Benzoyl chloride (9.2ml) was added to a solution of (XII) (9.2g) dissolved in pyridine (92ml) and left overnight at 0°C. The solid obtained on pouring the solution into iced water (1 litre), with stirring, was filtered, dried in a vacuum desiccator and recrystallised from isopropanol, to give 3,4-anhydro-1,2-O-isopropylidene-5-O-benzoyl-β-D-psicopyranose (13.8g, 99%), m.p.= 111.5-112.5°C, $[\alpha]_D$= +24°, (literature m.p.= 111.5 C).[11]

REACTIONS OF 3,4-ANHYDRO-1,2-O-ISOPROPYLIDENE-β-D-PSICO-PYRANOSE WITH TETRA-n-BUTYLAMMONIUM CYANIDE

i) IN ACETONITRILE

The anhydro-psicose (1g) and excess cyanide were dissolved in acetonitrile (40ml) and refluxed for 18 hours. Chloroform extraction, followed by drying in a vacuum desiccator, gave a glass, infra-red spectroscopy of which showed the presence of cyanide. Thin-layer chromatography showed the presence of a compound with R_f 0.62.
The glass was dissolved in chloroform, boiled with animal charcoal and filtered. Evaporation of the solvent gave a solid, the infra-red spectrum of which was that of the starting material, with some cyanide contamination.

ii) IN TETRAHYDROFURAN

The anhydro-psicose (1g) was dissolved in dry tetrahydrofuran and refluxed with excess cyanide for 15 hours. The product was extracted with chloroform, dried, filtered and evaporated down. After drying in a vacuum desiccator, the product was recrystallised from isopropanol. 12% of the starting material was recovered.
Infra-red spectroscopy of the product before recrystallisation showed cyanide to be present. The carbonyl peak at 1760cm^{-1} suggests the formation of a γ-lactone, possibly from further reaction of the expected cyano-alcohol, or from the tetrahydrofuran.

(XIX) (XV) (XVI) (XVII) (XVIII) (XIII) (XIV)

REACTIONS OF 3,4-ANHYDRO-1,2-O-ISOPROPYLIDENE-β-D-PSICO-PYRANOSE(XII)

RING-OPENING WITH SODIUM AZIDE

A solution of the 3,4-anhydro-psicose (XII)(3g), sodium azide (4.9g) and ammonium chloride (0.8g) in 95% aqueous methoxyethanol (50ml) was refluxed for 4 hours at 110-115°C.[50] The reaction mixture was poured into water, but no solid product was obtained, and the water was evaporated off.

Acetylation by the usual method gave a product (XIV) which, after recrystallisation from isopropanol, gave 1,2-O-isopropylidene-4-deoxy-4-azido-3,5-di-O-acetyl-β-D-sorbo-pyranose(XIV), m.p.= 99-101°C, $[\alpha]_D$= -51.6° (c0.76) (Found C 47.58 H 5.70 N 12.93. $C_{13}H_{19}O_7N_3$ requires C 47.41 H 5.82 N 12.76%).

Thin-layer chromatography showed no evidence of the formation of a second diacetate.

The diacetate (XIV) was oxidised in solution approximately 0.3M with respect to sodium periodate, buffered to pH7. The initial ratio of sugar to periodate was 1:2.0.

TIME(MINS)	IO_4^- UPTAKE(MOLS)	BLANKS
3	0.00003	0.00002
5	0.00002	0.00003
11	0.00005	0.00005
15	0.00007	
40	0.00005	
100	0.00001	
222	0.00004	

Failure to react with periodate proved the diacetate to be 1,2-O-isopropylidene-4-deoxy-4-azido-3,5-di-O-acetyl-β-D-sorbopyranose (XIV), rather than the 3,4-diacetate.

RING-OPENING OF 3,4-ANHYDRO-1,2-O-ISOPROPYLIDENE-5-O-BENZOYL-β-D-PSICOPYRANOSE WITH SODIUM AZIDE

A solution of 3,4-anhydro-1,2-O-isopropylidene-5-O-benzoyl-β-D-psicopyranose (XV) (4.6g) in 2-methoxyethanol was subjected to azidolysis as described for the unbenzoylated 3,4-epoxide (XII). Recrystallisation from isopropanol gave 1,2-O-isopropylidene-4-deoxy-4-azido-5-O-benzoyl-β-D-sorbopyranose(XVI), m.p.= 121-122°C, $[\alpha]_D$= -121°(c1.0). (Found C 55.13 H 5.41 N 12.03, $C_{16}H_{19}O_6N_3$ requires C 55.0 H 5.5 N 12.0%).

Debenzoylation, by refluxing (XVI) with sodium in methanol, gave 1,2-O-isopropylidene-4-deoxy-4-azido-β-D-sorbopyranose (XIII).

Acetylation of this gave, after recrystallisation from isopropanol, white crystals, m.p.=99-101°C, which a mixed melting-point showed to be identical to the 3,5-diacetate (XIV).

1,2-O-ISOPROPYLIDENE-3-O-METHANESULPHONYL-4-DEOXY-4-AZIDO-5-O-BENZOYL-β-D-SORBOPYRANOSE (XVII)

The 4-azido-5-O-benzoyl derivative (XVI) (2g) was dissolved in pyridine (40ml). Methanesulphonyl chloride (2ml) was added, and the solution allowed to stand overnight at 10°C. Addition to iced water (500ml), with stirring, produced a solid which, on recrystallisation from isopropanol, gave white crystals of 1,2-O-isopropylidene-3-O-methanesulphonyl-4-deoxy-4-azido-5-O-benzoyl-β-D-sorbopyranose (XVII), m.p.= 156-157°C, $[\alpha]_D$= -136°. (Found C 47.94 H 5.04 N 9.96, $C_{17}H_{21}O_8N_3S$ requires C 47.77 H 4.95 N 9.83%).

1,2-O-ISOPROPYLIDENE-3-O-METHANESULPHONYL-4-DEOXY-4-AMINO-5-O-BENZOYL-β-D-SORBOPYRANOSE (XVIII)

The 4-azido-5-O-benzoyl derivative (XVII) (2g) was dissolved in methylated spirits. To this solution was added Raney nickel (2g) which had been stored under distilled water at 10°C overnight. The resulting mixture was warmed and 99% w/w hydrazine hydrate (2ml) was added slowly. Heating was continued, with stirring, until effervescence ceased. Filtration and evaporation of the solvent gave a semi-crystalline mass. This was extracted with chloroform/isopropanol (8:1). The extract was dried over sodium sulphate and evaporated to give a clear syrup which crystallised on standing. Recrystallisation from absolute ethanol gave

white crystals of 1,2-O-isopropylidene-3-O-methanesulphonyl-4-deoxy-4-amino-5-O-benzoyl-β-D-sorbopyranose(XVIII) (1.1g, 59%), m.p.= 134-135°C, $[\alpha]_D$= -104°. (Found C 51.12 H 5.83 N 3.53. $C_{17}H_{23}O_8NS$ requires C 50.87 H 5.78 N 3.49%).

ATTEMPTED PREPARATION OF 1,2-O-ISOPROPYLIDENE-3,4-EPIMINO-β-D-TAGATOSIDE

Reduction of 1,2-O-isopropylidene-3-O-methanesulphonyl-4-deoxy-4-azido-5-O-benzoyl-β-D-sorbopyranose (XVII) with lithium aluminium hydride in ether[131] gave a glass, the infra-red spectrum of which was consistent with the formation of a primary amine. Analysis gave figures which were not those of the desired epimine.

Repetition of the reaction using tetrahydrofuran as a solvent gave a syrup, $[\alpha]_D^{21}$= -21.8°

DISCUSSION

The 4-O-benzoyl-5-O-tosyl- and 4-O-tosyl-5-O-benzoyl- derivatives of methyl 1,3-O-benzylidene-α-L-sorboside were required as precursors of the 4,5-epoxides, methyl 1,3-O-benzylidene-4,5-anhydro-α-L-psicoside and methyl 1,3-O-benzylidene-4,5-anhydro-β-D-fructoside.

Benzoylation of methyl 1,3-O-benzylidene-α-L-sorboside (III) with benzoyl chloride under the usual conditions[132] yielded 40% of a monobenzoate (IV), plus a very small quantity of the other monobenzoate and 60% of the dibenzoate (V). That (IV) was the 4-benzoate was demonstrated by thin-layer chromatography[133] and confirmed when tosylation of (IV), followed by removal of the benzoyl group, gave the known compound methyl 1,3-O-benzylidene-5-O-tosyl-α-L-sorboside (VII).[129]

Tosylation of (III) similarly gave 60% of the monotosylate (VIII), shown to be the 4-tosylate by thin-layer chromatography, plus a small amount of the 5-tosylate and 40% of the ditosylate (IX).

Tosylation of (IV) and benzoylation of (VIII) gave the required 4-benzoyl-5-tosyl- and 4-tosyl-5-benzoyl- derivatives (VI) and (X) respectively.

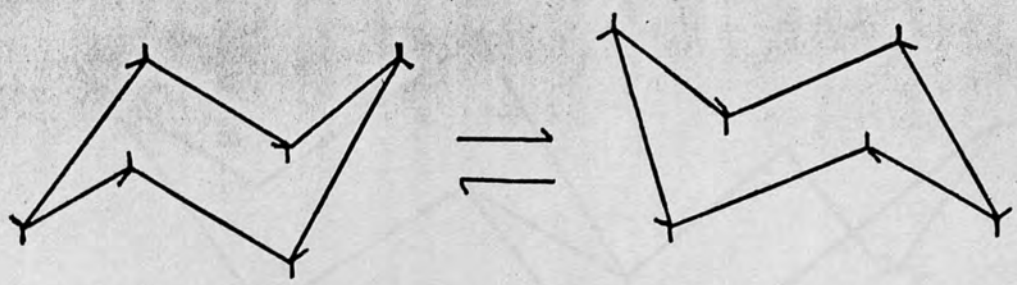
Having obtained the 4-benzoyl-5-tosyl- and 4-tosyl-5-benzoyl- derivatives, it was expected that treatment with alkali would yield the two epoxides.

However, in spite of a number of attempts being made, no trace of epoxide was obtained, and the benzoyl groups were lost to give the 5-tosyl- and 4-tosyl- derivatives respectively. Even when the experiment was repeated, with the 4-tosyl-5-acetyl- derivative being

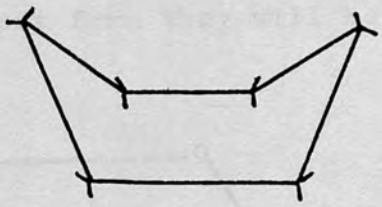
HO
OH
O
OMe
Ph
O
(III)
TsCl
BzCl
TsO
OH
OMe
Ph
BzO
OH
OMe
Ph
BzCl
TsCl
TsO
OBz
OMe
Ph
BzO
OTs
OMe
Ph
OH⁻
OH⁻
OMe
Ph
OMe
Ph

treated with sodium methoxide, only a mixture of the mono- and di-tosylates was obtained (the latter remaining, as an impurity, from the previous step), plus a small quantity of methyl 1,3-O-benzylidene-α-L-sorboside. The possibility was considered of the latter being methyl 1,3-O-benzylidene-β-D-tagatoside from ring-opening of an intermediate epoxide, but conversion to the free sugar gave only sorbose, identified from its p-bromophenylosazone and confirmed by mixed melting points.

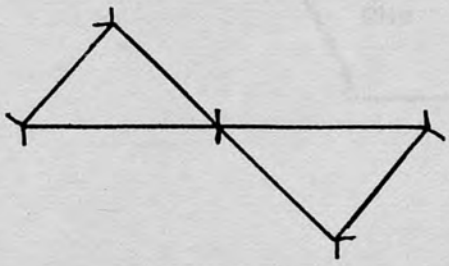
In cyclohexane, the six-membered ring can exist either in the rigid chair form



or in the flexible form, which can take the shape of a boat



or a skew shape

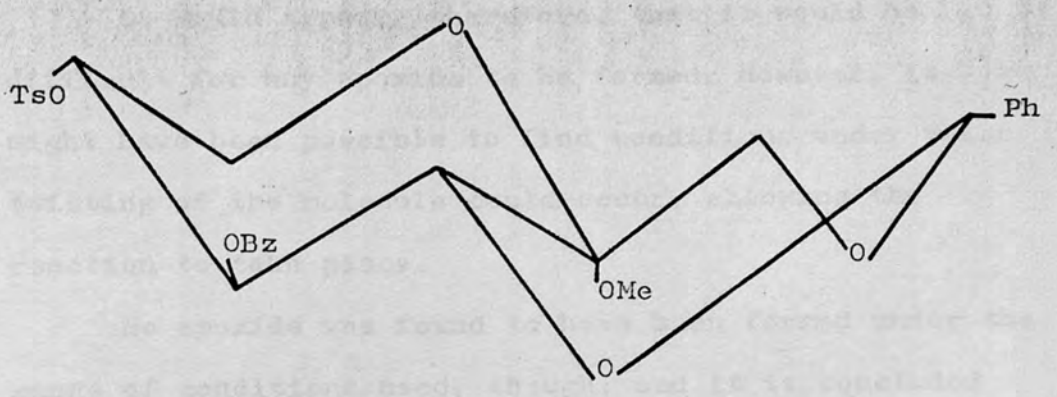


or a variety of irregular forms.

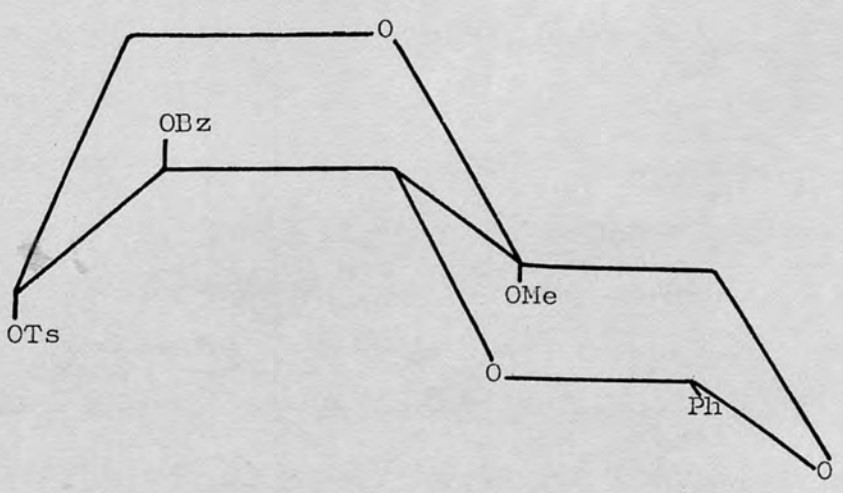
Energetically, the chair is the most favoured, followed by the skew, and then the boat.

In a fused-ring system such as the one being considered here, the chair form will have its bulkier substitu-

ents equatorial,



while in the boat form they will be axial.



But for epoxidation to be successful, the tosyl group and the oxide anion (formed by alkaline hydrolysis of the benzoyl group) are both required to be axial.

However, it is only in the unfavoured boat form that the two reacting groups are <u>trans</u>-diaxial and this arrangement would not be expected to be feasible, on

account of the interaction between the oxygen at C-5 and the anomeric methoxyl group, which is also axial.

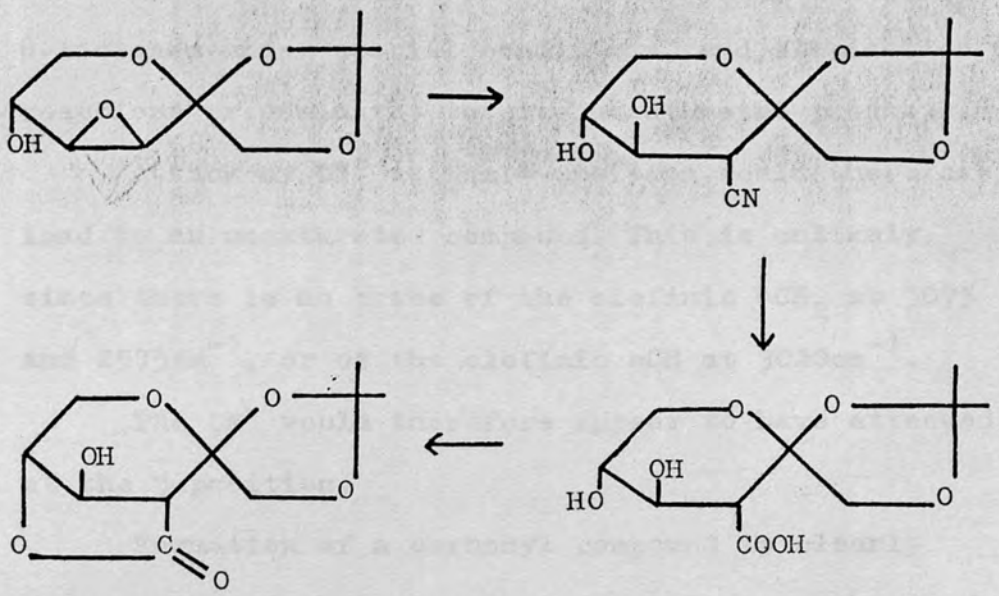
It would appear, therefore, that it would be difficult for any epoxide to be formed. However, it might have been possible to find conditions under which twisting of the molecule could occur, allowing the reaction to take place.

No epoxide was found to have been formed under the range of conditions used, though, and it is concluded that the conformational factors outlined above are the explanation.

A similar reaction scheme was used, successfully, to make 3,4-anhydro-1,2-O-isopropylidene-β-D-psicopyranose, starting from fructose. Its 5-benzoyl derivative was also made.

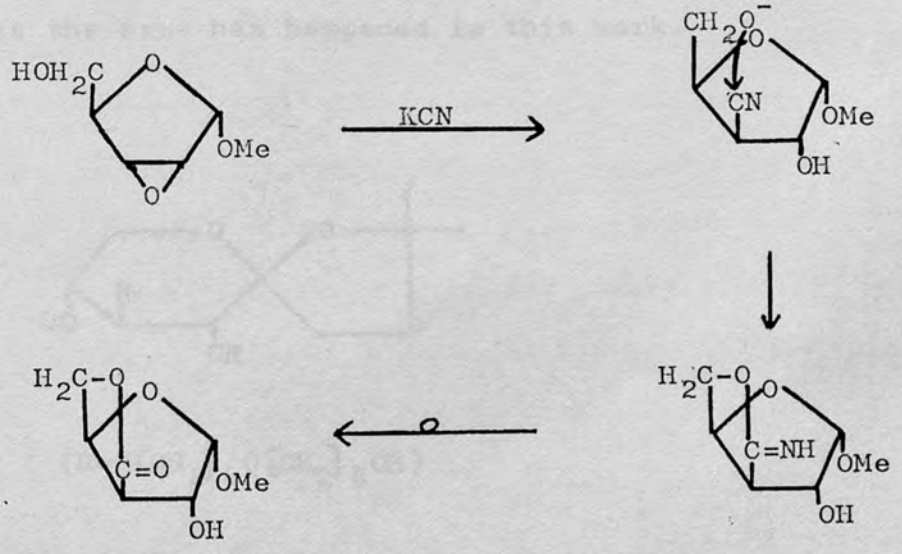
Attempted ring-opening of the psicopyranose with tetra-n-butylammonium cyanide in acetonitrile was unsuccessful, the glassy product being shown by infra-red spectroscopy to be basically starting material with some cyanide contamination.

However, when the same reaction was carried out in tetrahydrofuran, only 12% of the starting material was recovered, and the infra-red spectrum showed the presence of a carbonyl compound. A similar result was reported by Davison & Guthrie when, on attempting hydrocyanation of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside in ether, they obtained (among others) a product whose infra-red spectrum contained cyanide, hydroxyl and carbonyl bands, assumed to be due to further reaction of the expected cyano-deoxy product.[134] The position of the carbonyl band at 1760cm^{-1} suggests the formation of a γ-lactone, presumably from hydrolysis of the cyano-sugar to the corresponding acid, which yields the lactone on heating, as in the Kiliani Reaction:[69]



Lactone

Ring-opening of methyl 2,3-anhydro-α-D-ribofurano-side with KCN also produced a γ-lactone, hydrolysis of the intermediate cyano-compound probably having been catalysed by intramolecular participation of the ionised OH group at C-5.[135]



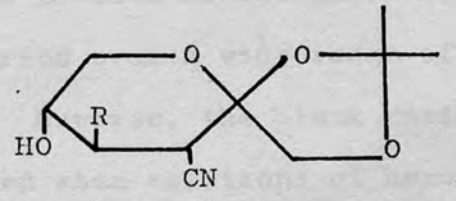
β-Hydroxyacids only form the corresponding β-lactones under special conditions, and elimination reactions predominate, to give unsaturated products.

Attack by CN^- at the 4-position would therefore lead to an unsaturated compound. This is unlikely, since there is no trace of the olefinic $=CH_2$ at 3075 and 2975cm^{-1}, or of the olefinic =CH at 3020cm^{-1}.

The CN^- would therefore appear to have attacked at the 3-position.

Formation of a carbonyl compound is clearly independent of the solvent used, as Davison obtained a carbonyl compound when using ether as a solvent,[134] and methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannoside in acetonitrile gave a carbonyl product in the present work.

The use of tetrahydrofuran has caused problems for several workers in the field[35,89] owing to the incorporation of a tetrahydrofuran dimer into the molecule of the cyano- product, and it would appear that the same has happened in this work.



$(R=O[CH_2]_4O[CH_2]_4OH)$

Similar results were obtained from treatment of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannoside when tetrahydrofuran was used as a solvent. The reaction of the mannoside in acetonitrile also gave a carbonyl compound, and the infra-red spectrum was similar to that of acetone cyanohydrin, but possibly not complex enough at the low wavenumber end to be that of a sugar.

Reactions in hexamethylphosphoramide, dimethylformamide, 50% dimethylformamide in acetonitrile and propylene glycol gave only starting material.

The solvents consisting of different proportions of DMF and acetonitrile gave back varying amounts of starting material. Whereas 40% of the starting material was regained from the reaction in 6% DMF in acetonitrile, only 19% of the mannoside was recovered when the percentage of DMF was increased to 20%, and there was evidence in addition, from the infra-red spectrum of the small quantity of tarry product, that some kind of cyano-compound had been formed, but this was probably some sort of degradation product of the tetra-n-butylammonium cyanide.

Davison *et al* also found DMF unsatisfactory, and could isolate no recognisable products, as decomposition occurred over a wide range of temperatures.[35]

However, the black resinous material which is formed when solutions of hexoses are heated, has been found to be 5-(hydroxymethyl)-2-furaldehyde.[136]

Conductance measurements suggest[137] that anions are naked in many dipolar aprotic solvents, including DMF, so crown ethers are unlikely to improve any of the reactions carried out in these solvents, and this was found to be the case, when attempted ring-opening with KCN in acetonitrile yielded only starting material, although thin-layer chromatography indicated the presence of two products, one of which had a higher R_f value that that of the starting material.

The solvent which seemed to work best was tetrahydrofuran. This was the one with the lowest boiling point (65°C), so it would appear that the quaternary ammonium cyanide is, as has already been suggested, of low thermal stability.[96,138] Failure to produce anything other than starting material when the cyanation reactions were carried out at temperatures as low as 80°C (acetonitrile) and 90-95°C (propylene glycol) suggest that the tetrabutylammonium cyanide decomposes at even lower temperatures than expected. No investigations have been made into the thermal stability of tetrabutylammonium cyanide, but a fair range of other tetra-n-alkylammonium salts decomposes as low as 140°C.[138]

$$R_4NX \longrightarrow RX + R_3N \longrightarrow R_3NH^+X^- + \text{olefin}$$

The production of tars at 100°C (DMF) and 110°C (HMPT) is presumably due to further reaction of the degradation products with the starting material.

SOLVENT	REACTION TEMPERATURE (°C)	PRODUCT
tetrahydrofuran	65	starting material + product
acetonitrile	80	starting material only
propylene glycol	90-95	starting material only
dimethylformamide	100	starting material + tar
HMPT	110	tar only

Another solvent which would be a possibility is diethyl ether (b.p. 35°C). This was found by Davison & Guthrie[134] to be more successful than tetrahydrofuran, since triethylaluminium is more reactive in diethyl ether.

Solvent effects have probably not been very important. Miller & Parker[139] found no apparent correlation between the rates of S_N2 reactions in aprotic solvents and many of the solvent properties which might have been expected to influence the rate (e.g. dipole moment, dielectric constant, viscosity, polarisability and solvent association).

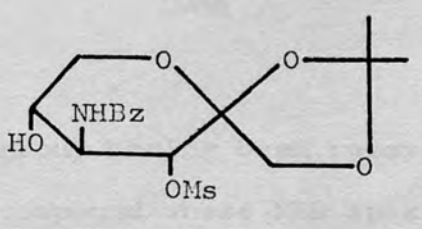
Ring-opening of the previously made 3,4-anhydro-5-O-benzoyl-1,2-O-isopropylidene-β-D-psicopyranose (XV) with azide gave the 4-azido-sorbose derivative (XVI). That it was not the 3-azido- compound was confirmed by periodate oxidation. This is consistent with the results obtained by Rao et al, who found that potassium hydrogen fluoride attacked only at C-4.[140]

Methanesulphonation gave 1,2-O-isopropylidene-3-O-mesyl-4-azido-4-deoxy-5-O-benzoyl-β-D-sorbopyranose (XVII).

Treatment of this with Raney nickel gave the expected amine (XVIII), but reaction of the amine with sodium methoxide gave a syrup A, whose infrared spectrum contained the following bands:-

γ N-H	3300 cm^{-1}
γ C=O of benzoate	1710 cm^{-1}
γ C=O (or γ C=N)	1650 cm^{-1}
δ N-H	1550 cm^{-1}
γ S=O of mesyl	1380 cm^{-1}
γ N-H	760 cm^{-1}

Although the bands at 3300 and 1550 cm^{-1} might seem to indicate the formation of an epimine, the presence of a γC=O at 1650 cm^{-1} is strongly suggestive of a benzamido compound, i.e.



although the presence of some oxazoline would also result in a band at 1650 cm^{-1}.

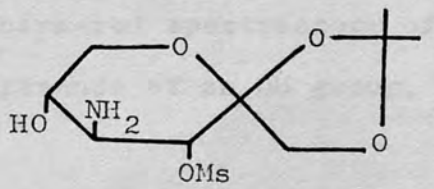
The bands which would be expected from a secondary amide are as follows:-

γN-H		
	Associated	3330-3140 cm^{-1}
γC=O		1680-1630 cm^{-1}
γC-O/δN-H combination		1570-1510 cm^{-1}
γC-N/δN-H combination	(Amide III)	1305-1220 cm^{-1}
N-H out-of-plane δ		770- 620 cm^{-1}

All of these bands can be found in the infra-red spectrum of A, including the Amide III band, which overlaps the benzoate C-Oγ to form a broad band at about 1280-1220 cm^{-1}.

It is concluded that A is a benzamido- compound.

A one-step reduction and cyclisation with lithium aluminium hydride was therefore carried out. A mixture was obtained of an amine, the analysis figures of which suggested it to be

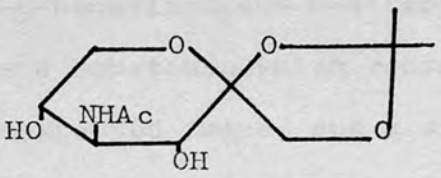


the benzoyl group having been removed during reduction, and another compound whose NMR spectrum indicated the

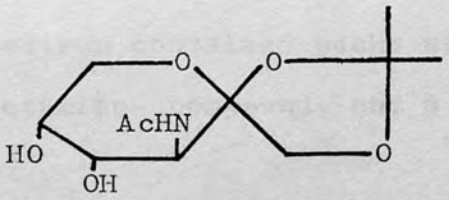
presence of OH, benzoyl, H-N-C=O, and RNH_2 (or ArNHR or CH_3OCOR), but no epimino- groups.

Acetylation of this compound gave a derivative B which had an infra-red spectrum similar to that of A and likewise containing bands at 3300, 1660 and 1570 cm^{-1}.

Removal of the O-acetyl group with sodium methoxide yielded a mixture of two compounds thought to be



and



thin-layer chromatography giving 2 spots of equal intensity. Infra-red spectroscopy of this mixture showed the presence of an OH group, but no benzoyl groups.

This suggests that an epimine has been formed and opened again, but, unlike epoxides, epimines are particularly stable under alkaline conditions, and so this is improbable.[121]

Variation of the reaction conditions gave only a syrup which could not be characterised, the infra-red spectrum of which showed the presence of NH_2, mesyl and benzoyl groups. Treatment of this syrup with sodium methoxide gave another uncharacterisable syrup.

It is interesting that other workers in this field have also obtained puzzling by-products of unknown structure when carrying out similar reactions.

For instance, treatment of methyl 2-amino-2-deoxy-3-O-tosyl-4,6-O-benzylidene-α-D-altroside with sodium methoxide gave a substance which contained a C_3H_6 unit more than the expected imine, and a similar product was obtained on attempting to make the allo-epimine. No structures were proposed, but formation of an N-alkyl-epimine appeared to have taken place.[50]

Guthrie & Liebmann[122] obtained a dimeric substance (whose mass spectrum contained peaks at m/e values of up to 545), an acetamido- compound, and a syrup of unknown composition.

Raney nickel is also known to cause hydrogenolysis of epimines,[114] and acetamido- compounds have been produced on acetylation of the products.

Richardson has pointed out[131] that, although most of the common protecting groups are stable under Raney nickel reduction conditions, O-acyl groups do have a marked tendency to migrate to any amino- group present, and O-benzylidene groups have also been removed by Raney nickel.[141] Lithium aluminium hydride will also remove sulphonate groups.[131]

Raney nickel has also been found to be responsible for the N-alkylation of both primary and secondary amines by alcohols.[142,143] Until very recently, N-alkylation had not been found to occur with methanol, but had been reported for ethanol and isopropanol.[142,143] Wenkert et al have recently (1982) reported methylation of oxindole in methanol to give 3-methyloxindole, accompanied by 3-methyleneoxindole polymer.[144]

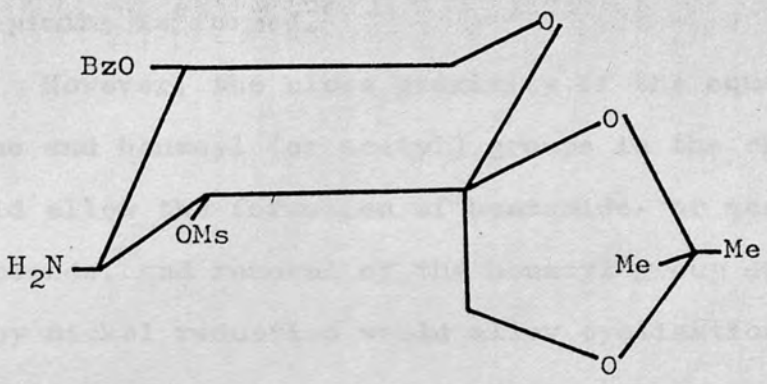
The alcohol is oxidised by the nickel to a carbonyl compound, which then reacts with the amine to give either an intermediate α-hydroxyamine or N-alkylideneamine (Schiff base), which is then hydrogenated to the corresponding N-alkylamine. It is quite likely, therefore, in the case of the Raney nickel reduction, that the benzoyl group from C-5 has attacked to give a benzamido- compound.

In the case of the reduction with lithium aluminium hydride, however, the final product seems to be the acetamido- derivative, the benzoyl group having been completely removed before reduction of the azide. In neither case, apparently, has any epimine been formed, although it is possible that cyclisation could have occurred due to reaction of the benzamido- compound with sodium methoxide, to yield some oxazoline.[145]

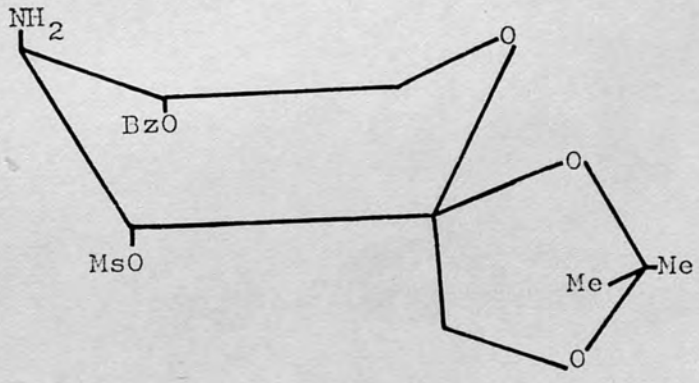
Aziridine ring formation can be considered in the same way in which epoxidation was considered earlier.

The possible conformations which might be adopted are as follows:-

i) The chair



ii) The boat



and a variety of other flexible forms, since the system, although bicyclic, is not a fused-ring one.

Clearly, cyclisation cannot take place if the molecule is in the chair form, since the amino- and mesyl-groups are both equatorial.

The relevant groups are certainly <u>trans</u>-diaxial in

the boat form. However, the interaction between the axial benzoyl (or hydroxyl) and mesyl groups proves to be too strong for this to be a possibility. Therefore no epimine is formed.

However, the close proximity of the equatorial amino and benzoyl (or acetyl) groups in the chair form would allow the formation of benzamido- or acetamido-compounds, and removal of the benzoyl group during Raney nickel reduction would allow cyclisation to the oxazoline.

REFERENCES

REFERENCES

1) P.Brigl, Z.Physiol. Chem., 1921, 116, 245.

2) K.Freudenberg, H.Toepffer & C.C.Andersen, Chem. Ber., 1928, 61, 1750.

3) H.Ohle & L. von Vargha, Chem. Ber., 1929, 62, 2435.

4) K.Freudenberg & O.Ivers, Chem. Ber., 1922, 55, 929.

5) B.Helferich & A.Mueller, Chem. Ber., 1930, 63, 2142.

6) D.S.Mathers & G.J.Robertson, J.Chem.Soc., 1933, 1076.

7) W.N.Haworth, D.L.Hirst & L.Pannizon, J.Chem.Soc., 1934, 154.

8) G.J.Robertson & C.F.Griffith, J.Chem.Soc., 1935, 1193.

9) S.Peat & L.F.Wiggins, J.Chem.Soc., 1938, 1088.

10) S.Peat, Adv. Carbohydr. Chem. Biochem., 1946, 2, 38.

11) H.Ohle & F.Just, Chem. Ber., 1935, 68, 601.

12) G.J.Robertson & W.Whitehead, J.Chem.Soc., 1940, 319.

13) L.F.Wiggins, J.Chem.Soc., 1944, 522.

14) H.Ohle & C.A.Schultz, Chem. Ber., 1938, 71, 2302.

15) N.R.Williams, Adv. Carbohydr. Chem. Biochem., 1970, 25, 109.

16) J.Stanek(Jr), K.Capek & J.Jary, Collect. Czech. Chem. Commun., 1975, 40, 3370.

17) H.B.Sinclair, Carbohydr. Res., 1976, 50, 247.

18) A.H.Haines, Adv. Carbohydr. Chem. Biochem., 1976, 33, 11.

19) J.Stanek & J.Jary, Justus Liebigs Ann. Chem., 1976, 163.

20) P.J.Garegg, T.Iversen & S.Oscarson, Carbohydr. Res.,1977, 53, C5.

21) P.J.Garegg, T.Iversen & S.Oscarson, Carbohyd. Res., 1976, 50, C12.

22) W.Szeja, Synthesis, 1979, 10, 821.

23) A.Mueller, M.Moricz & G.Verner, Chem. Ber., 1939, 72, 745.

24) F.H.Newth, Quarterly Reviews, 1959, 13, 30.

25) F.H.Newth, J.Chem.Soc., 1956, 441.

26) S.J.Angyal & P.T.Gilham, J.Chem.Soc., 1957, 3691.

27) S.Peat & L.F.Wiggins, J.Chem.Soc., 1938, 1810.

28) G.J.Robertson & H.G.Dunlop, J.Chem.Soc., 1938, 472.

29) D.Sorkin & T.Reichstein, Helv. Chim. Acta, 1945, 28, 1.

30) W.G.Overend & G.Vaughan, Chem. Ind. (London), 1955, 995.

31) W.H.G.Lake & S.Peat, J.Chem.Soc., 1939, 1069.

32) G.Charalambous & E.Percival, J.Chem.Soc., 1954, 2443.

33) R.D.Guthrie & D.Murphy, Chem. Ind. (London), 1962, 1473.

34) N.R.Williams, J.Chem.Soc., Chem. Commun., 1967, 1012.

35) B.E.Davison, R.D.Guthrie & A.T.McPhail, J.Chem. Soc., Chem. Commun., 1968, 1273.

36) F.H.Newth, W.G.Overend & L.F.Wiggins, J.Chem.Soc., 1947, 10.

37) F.H.Newth & R.F.Homer, J.Chem.Soc., 1953, 989.

38) J.G.Buchanan, J.Chem.Soc., 1958, 2511.

39) A.Banaszek, Bull. Acad. Pol. Sci.: Ser. Sci. Chim., 1974, 22, 79.

40) R.E.Parker & N.S.Isaacs, Chem. Rev., 1959, 59, 737.

41) F.H.Newth, Chem. Ind. (London), 1953, 1257.

42) R.S.Tipson, Adv. Carbohydr. Chem. Biochem., 1953, 8, 107.

43) A.Fuerst & P.A.Plattner, Abs. Papers, 12th Internat. Congr. Pure and Applied Chem., New York, 1951, p409.

44) J.A.Mills, PhD Thesis, University of Cambridge, 1953.

45) A.K.Bose, D.K.R.Chaudhuri & A.K.Bhattacharyya, Chem. Ind. (London), 1953, 869.

46) R.C.Cookson, D.H.R.Barton, W.Klyne & C.W.Shoppee, Chem. Ind. (London), 1954, 21.

47) R.E.Reeves, J.Am. Chem.Soc., 1950, 72, 1499.

48) S.J.Angyal, Chem. Ind. (London), 1954, 1230.

49) G.Huber & O.Schier, Helv. Chim. Acta, 1960, 43, 129.

50) R.D.Guthrie & D.Murphy, J.Chem.Soc., 1963, 5288.

51) E.J.Reist, R.R.Spencer, B.R.Baker & L.Goodman, Chem. Ind. (London), 1962, 1794.

52) W.A.Remers, 'The Chemistry of Antitumour Antibiotics', Vol. I, Wiley, New York, Chapter 2, p.162.

53) A,Wickstrom & J.K.Wold, Acta Chem. Scand., 1960, 14, 1419.

54) J.S.Burton, W.G.Overend & N.R.Williams, Chem. Ind. (London), 1961, 175.

55) W.A.Szarek, MTP Int. Rev. Sci. Org. Chem. Series 1, 1973, 7, 71.

56) R.J.Ferrier & P.M.Collins, 'Monosaccharide Chemistry', Penguin Books, England, 1972, p.158,228.

57) H.Grisebach & R.Schmid, Angew. Chem. Int. Ed. Engl. 1972, 11, 159.

58) M.M.Ponpipom, R.L.Bugianesi & T.Y.Shen, Carbohydr. Res., 1980, 82, 135.

59) F.O.Pazschke, J.Prakt. Chem., 1870, 1, 82.

60) E.Erlenmeyer, Justus Liebigs Ann. Chem., 1878, 191, 261.

61) J. von Hormann, Chem. Ber., 1879, 12, 23.

62) M.P.Schuetzenberger, Bull. Soc. Chim. Fr., 1881, 36, 144.

63) R.Lespieau, Comptes Rendus, 1898, 127, 965.

64) R.Lespieau, Bull.Soc.Chim.Fr., 1905, 33, 460.

65) C.C.J.Culvenor, W.Davies & F.G.Haley, J.Chem.Soc., 1950, 3123.

66) E.Rupp & A.Holzle, Archiv. Pharm., 1913, 251, 553.

67) E.Rupp & A.Holzle, Archiv. Pharm., 1915, 253, 404.

68) R.J.Ferrier & P.M.Collins, 'Monosaccharide Chemistry', Penguin Books, England, 1972, p.76.

69) H.Kiliani, Chem. Ber., 1885, 18, 3066.

H.Kiliani, Chem. Ber., 1886, 19, 221, 767.

70) R.Varma & D.French, Carbohydr. Res., 1972, 25, 71.

71) A.S.Serianni, H.A.Nunez & R.Barker, J.Org.Chem., 1980, 45, 3329.

72) A.Bowers, M.B.Sanchez, L.M.Sanchez-Hidalgo & H.J. Ringold, J.Am. Chem. Soc., 1959, 81, 5233.

73) W.Nagata, S.Hirai, H.Itazaki & K.Takeda, J.Org. Chem., 1961, 26, 2413.

74) A.J.Parker, J.Chem.Soc., 1961, 1328.

75) D.A.White & M.M.Baizer, J.Chem.Soc., Perkin Trans. 1, 1973, 2230.

76) M.Sarel-Imber & E.D.Bergmann, Carbohydr. Res., 1973, 27, 73.

77) O.W.Webster, W.Mahler & R.E.Benson, J.Am. Chem. Soc., 1962, 84, 3678.

78) R.A.Powers & A.B.Thomas, US Patent 3 223 639 (Cl. 252-62.2), Dec 14/1965 (Appl. July 10/1962).

79) M.Gordon & C.E.Griffin, Chem. Ind. (London), 1962, 1019.

80) M.Gordon, M.L. DePamphilis & C.E.Griffin, J.Org. Chem., 1963, 28, 698.

81) J.Solodar, Synth. React. Inorg. Metal-Org. Chem., 1971, 1, 141.

82) J.Solodar, Tetrahedron Lett., 1971, 287.

83) P.W.Austin, J.G.Buchanan & E.M.Oates, J.Chem.Soc., Chem. Commun., 1965, 374.

84) W.Nagata & M.Yoshioka, Tetrahedron Lett., 1966, 1913.

85) W.Nagata, M.Yoshioka & T.Okumura, Tetrahedron Lett., 1966, 847.

86) W.Nagata, M.Yoshioka & T.Okumura, J.Chem.Soc.(C), 1970, 2365.

87) C.L.Liotta, A.M.Dabdoub & L.H.Zalkow, Tetrahedron Lett., 1977, 1117.

88) T.Sakakibara & R.Sudoh, Carbohydr. Res., 1980, 85, 33.

89) A.Mubarak & B.Fraser-Reid, J.Org.Chem., 1982, 47, 4265.

90) A.Brandstrom, P.Berntsson, S.Carlsson, A.Djurhuus, K.Gustavii, U.Junggren, B.Lamm & B.Samuelsson, Acta Chem. Scand., 1969, 23, 2202.

91) A.W.Herriott & D.Picker, Tetrahedron Lett., 1974, 1511.

92) K.E.Koenig & W.P.Weber, Tetrahedron Lett., 1974, 2275.

93) C.J.Pedersen, J.Am.Chem.Soc., 1967, 89, 7017.

94) F.Del Cima, G.Biggi & F.Pietra, J.Chem.Soc., Perkin Trans. 2, 1973, 55.

95) A.Knoechel & G.Rudolph, Tetrahedron Lett., 1974, 3739.

96) F.L.Cook, C.W.Bowers & C.L.Liotta, J.Org.Chem., 1974, 39, 3416.

97) F.L.Cook, PhD Thesis, Georgia Institute of Technology, 1975.

98) T.Sasaki, S.Eguchi, M.Ohno & F.Nagata, J.Org.Chem., 1976, 41, 2408.

99) W.Meyer, E.Boehnke & H.Follmann, Angew. Chem., 1976, 88, 512.

100) J.W.Kubrick, B.I.Dunbar & H.D.Durst, Tetrahedron Lett., 1975, 71.

101) C.L.Liotta, H.P.Harris, F.L.Cook, G.W.Gokel & D.J.Cram, J.Org.Chem., 1974, 39, 2445.

102) L. von Vargha, L.Toldy, O.Feher & S.Lendvai, J.Chem.Soc., 1957, 805.

103) J.E.Christensen & L.Goodman, J.Am.Chem.Soc., 1960, 82, 4738.

104) U.Bicker & W.Fischer, Nature (London), 1974, 249, 344.

105) C.A.VanderWerf, R.Y.Heisler & W.E.McEwen, J.Am. Chem.Soc., 1954, 76, 1231.

106) Y.Ali & A.C.Richardson, Carbohydr. Res., 1967, 5, 441.

107) S.Hanessian & T.H.Haskell, J.Org.Chem., 1965, 30, 1080.

108) M.O.Forster & F.M. Van Gelderen, J.Chem.Soc., 1911, 99, 239.

109) R.Schroeter, 'Methoden Der Organischen Chemie', Vol. 11/1, 4th Ed., G.Thieme Verlag, Stuttgart, 1957, Chapter 4.

110) a) H.Staudinger & E.Hauser, Helv. Chim. Acta, 1921, 4, 861.

b) J.Kovacs, I.Pinter, F.Szego, J.Toth & A. Messmer, Acta Chim. Acad. Sci. Hung., 1979, 101, 7.

111) R.D.Guthrie, D.Murphy, D.H.Buss, L.Hough & A.C. Richardson, Proceedings Chem. Soc., 1963, 84.

112) K.Ponsold, Chem. Ber., 1964, 97, 3524.

113) L.Mester & H.S.El Khadem, 'The Carbohydrates: Chemistry and Biochemistry', (2nd Ed.), Vol. IB, Academic Press, New York, 1980, p.979-980.

114) D.H.Buss, L.Hough & A.C.Richardson, J.Chem.Soc., 1965, 2736.

115) D.H.Buss, L.Hough & A.C.Richardson, J.Chem.Soc., 1963, 5295.

116) J.H.Boyer, J.Am.Chem.Soc., 1951, 73, 7865.

117) C.F.Gibbs, L.Hough & A.C.Richardson, Carbohydr. Res., 1965, 1, 290.

118) K.Ponsold & D.Klemm, Chem. Ber., 1966, 99, 1502.

119) D.Murphy, J.Chem.Soc.(C), 1967, 1732.

120) J.Cleophax, S.D.Gero & J.Hildesheim, J.Chem.Soc. Chem. Commun., 1968, 94.

121) A.C.Richardson, MTP Int. Rev. Sci. Org. Chem. Ser. 1, 1973, 7, 105.

122) R.D.Guthrie & J.A.Liebmann, J.Chem.Soc., Perkin Trans. 1, 1974, 650.

123) J.Yoshimura, M.Iwakawa & Y.Ogura, Bull. Chem. Soc. Jpn, 1976, 49, 2506.

124) O.C.Dermer & G.E.Ham, 'Ethyleneimine and Other Aziridines', Academic Press, New York, 1969, p.25,27.

125) A.Banaszek & A.Zamojski, Carbohydr. Res., 1976, 51, 276.

126) K.Hiraga, T.Okutani, N.Asako & K.Yoshioko, Japan Kokai 77 83 833(Cl.C07H15/06) 13 Jul/77, Appl. 76/ 1 267, 01 Jan/76 (Chemical Abstracts 88 121 661s).

127) J.H.Mathews, J.Am.Chem.Soc., 1926, 48, 562.

128) G.Arragon, Comptes Rendus, 1934, 119, 1231.

129) A.Armenakian, M.Mahmood & D.Murphy, J.Chem.Soc., Perkin Trans. 1, 1972, 63.

130) A.I.Vogel, 'A Textbook of Practical Organic Chemistry', Longman, London, 1956, p169.

131) A.C.Richardson, Methods Carbohydr. Chem., 1972, 6, 218.

132) G.J.F.Chittenden & J.G.Buchanan, Carbohydr. Res., 1969, 11, 379.

133) H.Jaeger, A.Ramel & O.Schindler, Helv. Chim. Acta 1957, 40, 1310.

134) B.E.Davison & R.D.Guthrie, J.Chem.Soc., Perkin Trans. 1, 1972, 658.

135) P.W.Austin, J.G.Buchanan & R.M.Saunders, J.Chem. Soc.(C), 1967, 372.

136) A.M.Taher & D.M.Cates, Carbohydr. Res.,1974, 34, 249.

137) A.J.Parker, Quarterly Reviews, 1962, 16, 163.

138) J.E.Gordon, J.Org.Chem., 1965, 30, 2760.

139) J.Miller & A.J.Parker, J.Am.Chem.Soc., 1961, 83, 117.

140) G.V.Rao, L.Que, L.D.Hall & T.P.Fondy, Carbohydr. Res., 1975, 40, 311.

141) G.Rembarz, J.Prakt. Chem., 1963, 19, 315.

142) K.Venkataraman, J.Indian Chem. Soc., 1958, 35, 1.

143) R.G.Rice & E.J.Kohn, J.Am.Chem.Soc., 1955, 77, 4052.

B.B.Corson & H.Dressler, J.Org.Chem., 1956, 21, 474.

M.Botta, F. de Angelis & R.Nicoletti, Synthesis, 1977, 722.

144) E.Wenkert, N.V.Bringi & H.E.Choulett, Acta Chem. Scand., Ser. B, 1982, 36, 348.

145) A.D.Barford & A.C.Richardson, Carbohydr. Res., 1967, 4, 408.