

NUCLEOPHILIC DISPLACEMENT REACTIONS
OF SOME CARBOHYDRATE SULPHONATES
IN DIMETHYL SULPHOXIDE

BY

BENNY TILIMUMBALANGA MWAMBA MUYOBELA

B.Sc. University of Zambia

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Signature of author

B. M. M. M.
.....
Department of Chemistry

Certified by

P. S. Speakman
.....
Dissertation Supervisor

Accepted by

M. M. M. M.
.....
Dissertation Chairman

(ii)

This dissertation has been examined by a committee
of the department of chemistry as follows.

Dr. Neil A. Hughes
University of Newcastle Upon Tyne
External Examiner

Professor P. R. H. Speakman
Dissertation Supervisor

PRH Speakman

Professor M. Siamwiza
Dissertation Chairman

Mwindaacefawiz

Chery Lovelace.

Dr. C. Lovelace

(iii)

DECLARATION

I hereby declare that this dissertation or any part of it has not previously been submitted for a degree in this or any other university.

ERRATA

- Page 12, line 9, last word should be "elevated" not "eleveted".
- Page 16, line 3, "toluene sulphonyl" should read "toluenesulphonyl".
- Page 16, fourth and seventh lines, "dimethyl formamide" should read "dimethyl formamide".
- Page 22, line 6, "dimethyl formamide" should read "dimethylformamide".
- Page 23, fourth line from the bottom, compound (32) incorrectly named, delete first methyl.
- Page 24, fig. 23, compound (32) "CH₃-" missing at position five.
- Page 36. One of the first reagents should read "CuSO₄" not "CUSO₄".
- Page 39, line 7, full stop and a new sentence after product (60).
- Page 40, fig.(34), the reagent should read "CH₃SOCH₂" not "CH₃SOCH₃".
- Page 40, fig.(34) compound (59a,b) should not have a double bond between C-5 and C-6.
- Page 43, fig.(A), should read "OCH₃" at C-1.
- Page 55. Paragraph 2, last line should read "R_f 0.35" not "RFO.35".
- Page 57, last line should read "authentic sample (see overleaf). R_f 0.57 and R_f/Ribose = 1.4 in solvent A" not "authentic sample. (see overleaf) R.f.O. RF/Ribose = 1.4 in solvent A".
- Page 58, Acid hydrolysis line 5, the word "compound" is missing after consisted of one.
- Page 60, third line from the bottom should read "Pyridine (8 ml)" not "Pyridine (8.11 ml)".
- Page 60, 2nd line from the bottom should read "toluenesulphonyl" not "toluene sulphonyl".
- Page 63, last sentence, should begin with "The combined ..." not "To combined ...".
- Page 65, third line from bottom, should have "(ethyl acetate)" after double recrystallization.

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ABSTRACT

Several 5-O-toluene-p-sulphonyl and 5-iodo derivatives of α - and β -ribofuranoses and α -xylofuranose have been prepared in order to study their reactions with sodium hydrogen carbonate in dimethyl sulphoxide. Similar reactions are known to convert acyclic primary sulphonates and iodides to aldehydes but the sugar derivatives were observed to yield different products. Detosylation of the sugars to give the corresponding alcohols was the most usual outcome but in two instances the tosyloxy and iodo groups were ejected to give an anhydro sugar and a rearranged product respectively. The mechanisms of these reactions are considered.

Reaction of a ribofuranose primary sulphonate with the anion of dimethyl sulphoxide led to base-induced elimination of toluene-p-sulphonic acid rather than nucleophilic substitution.

The results of the work are presented within the context of possible approaches to converting pentoses into hexoses by way of chain extension reactions at the C-5 carbon atom of pentofuranoses.

I wish to express my indebtedness to Professor P. R. H. Speakman for his painstaking supervision and expert guidance throughout this research and also for countless helpful suggestions both then and during the writing of this dissertation.

I wish to express my sincere appreciation and gratitude to Dr. N. A. Hughes of University of Newcastle Upon Tyne for NMR and many helpful comments and also Mr. P. Kelly of the same university for mass spectrum.

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Finally I wish to express my appreciation to my wife Ngawa, who not only encouraged me in this undertaking but bore with understanding the additional demands upon the research student's time.

M. T. B. MUYOBELA

JULY, 1979.

INTRODUCTION

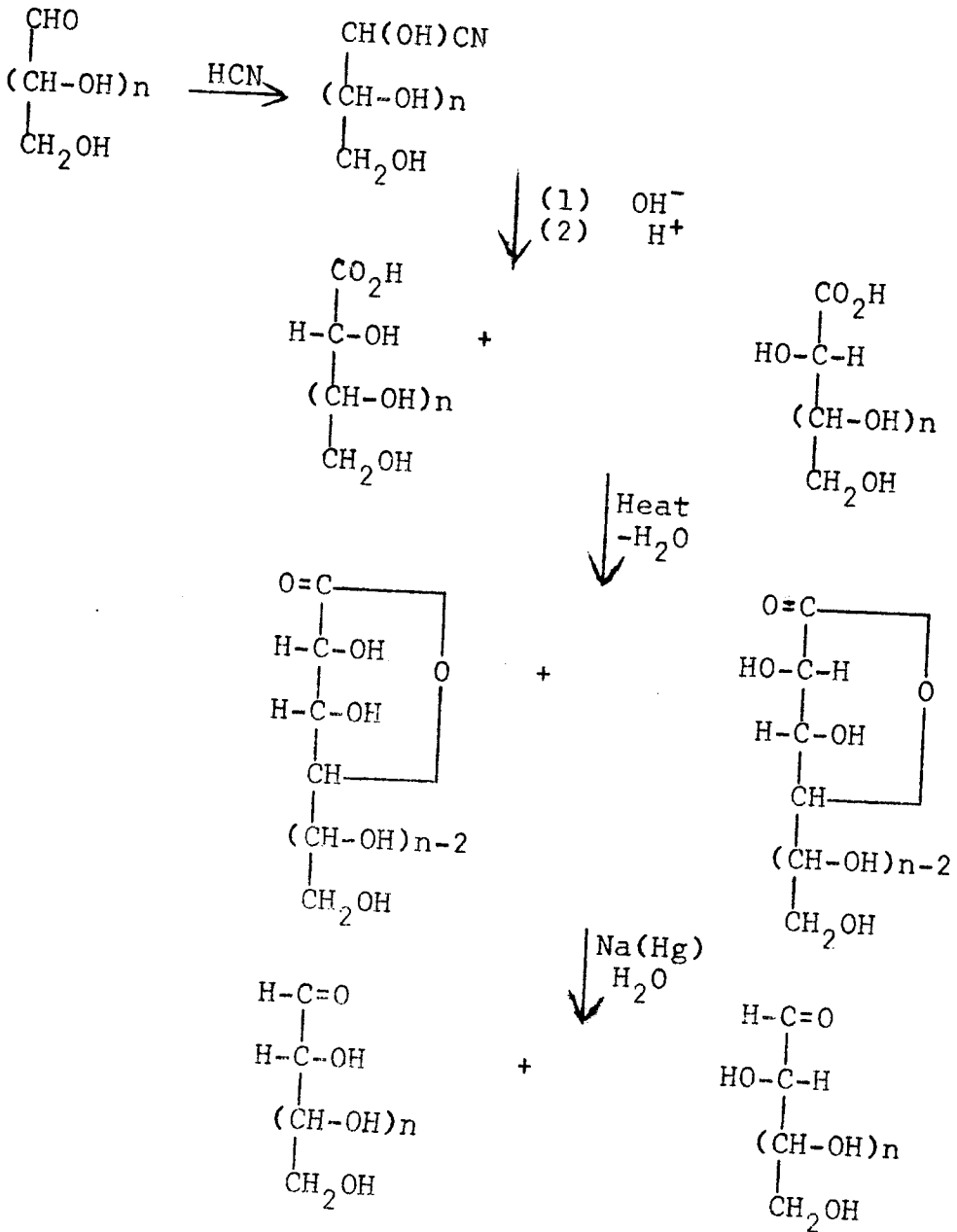
INTRODUCTION

Conversion of pentoses to hexoses is of historical importance in carbohydrate chemistry in that it provided a basis for the elucidation of structures and configurations of hexoses by Fischer who used the chain extension method first investigated by Kiliani.¹

Synthesis of hexoses from pentoses using the Kiliani-Fischer Cyanohydrin method is based on the classical method of extending a carbon chain by the reaction of the aldehyde with hydrocyanic acid. The cyanohydrins are not isolated, but are converted to corresponding lactones which can be reduced to higher aldoses. The reduction of lactones to the corresponding aldoses was first achieved by Fischer² who made use of sodium amalgam in slightly acidic solution. It is also possible to obtain aldoses from lactones by catalytic hydrogenation,³ or by reduction with sodium borohydride.⁴ The general scheme of the reaction is outlined in Fig. (1).

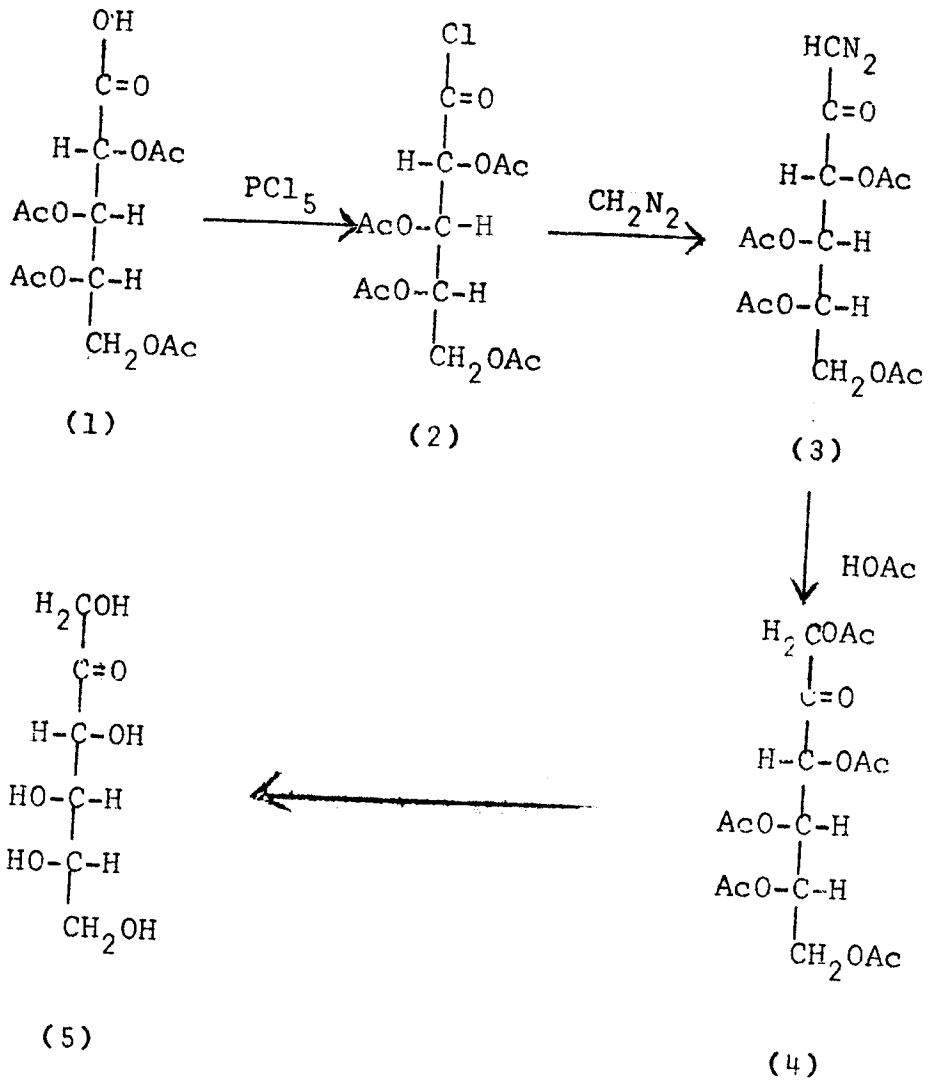
Various hexoses have been prepared from corresponding pentoses by this method. D-Allose^{5,6} and L-Allose^{5,7} have been synthesised from D-ribose and L-ribose respectively. D-Altrose was first prepared in 1910 by Ievne and Jacobs⁸ from D-ribose using a related method.

Fig. (1).



In 1938 another method⁹ for extending the carbon-skeleton was introduced in carbohydrate chemistry. This method is based on the reaction of diazomethane with an acid chloride to give a diazoketone which on hydrolysis (or acetolysis) gives rise to an hydroxy (or acetoxy) methyl ketone. Wolfson and coworkers¹⁰ have widely used this method in the synthesis of ketones. The method is illustrated in the synthesis of β -L-fructose hemihydrate¹¹(5)(Fig. 2). Other examples of diazomethane synthesis include the synthesis of D-sorbose¹² and perseolose (L-galacto-heptulose).¹³

Fig. (2)



More recently nitromethane addition has also been introduced as a method for extending the carbon-chain in the sugar field. This method involves addition of an aldose to nitromethane in absolute methanol solution (or suspension) using sodium methoxide as a catalyst. In favourable cases the solubility relationships lead to precipitation of sodium salts of the deoxynitroalditols which can be separated by filtration. As in the cyanohydrin addition formation of new asymmetric centres results in two unequal epimeric products, which after removal of sodium ions can be separated by fractional crystallization. The reaction therefore involves base-catalysed condensation of primary or secondary nitroparaffins with aldehydes to give nitro alcohols, followed by "the Nef reaction."¹⁴ A typical nitromethane synthesis is illustrated in the preparation¹⁵ of D-glycero-L-manno-heptose (8) and D-glycero-L-gluco-heptose (9) from D-galactose (6) (Fig. 3). L-Gulose¹⁶ has also been prepared from 2,4-O-benzylidene-L-xylose through 2,4-O-benzylidene-6-deoxy-6-nitro-D-glucitol.

An alternative approach to straight-chain hexoses from pentoses is to apply chain extension reactions at C-5 of the pentose. This approach has however received very little attention. Baggett and coworkers¹⁷

oxidised 1,2-O-isopropylidene-3-O-benzyl-D-glucofuranose (7) to an aldehydo-compound (11). Treatment of compound (11) with methylene triphenyl phosphorane gave an olefinic compound (12) (Fig. 4). Baggett and coworker's¹⁷ main objective was to study the Wittig alkene synthesis, and their aldehyde (11) was itself produced from a hexose so that their work did not constitute a pentose to hexose conversion, nevertheless their results demonstrate that such conversions are possible if aldehydes such as (11) can be conveniently prepared from pentoses.

Fig. (3)

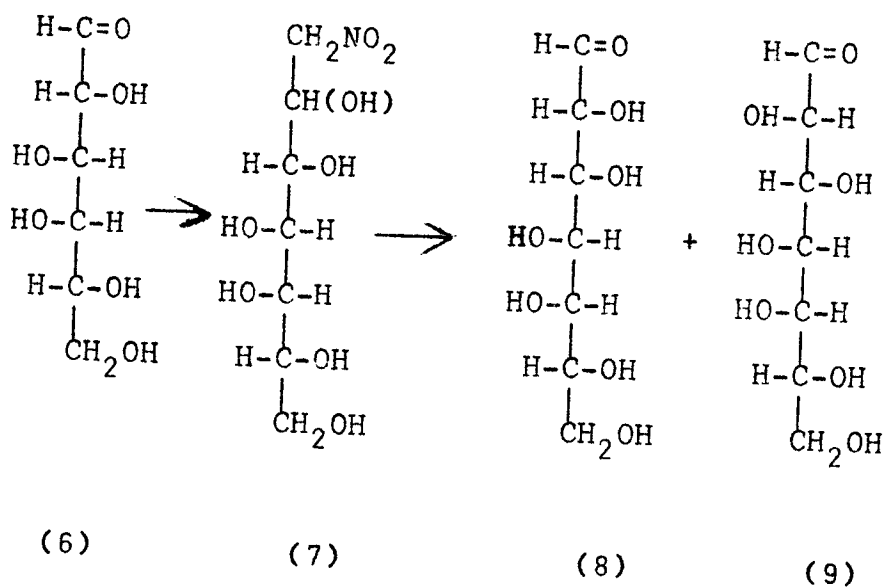
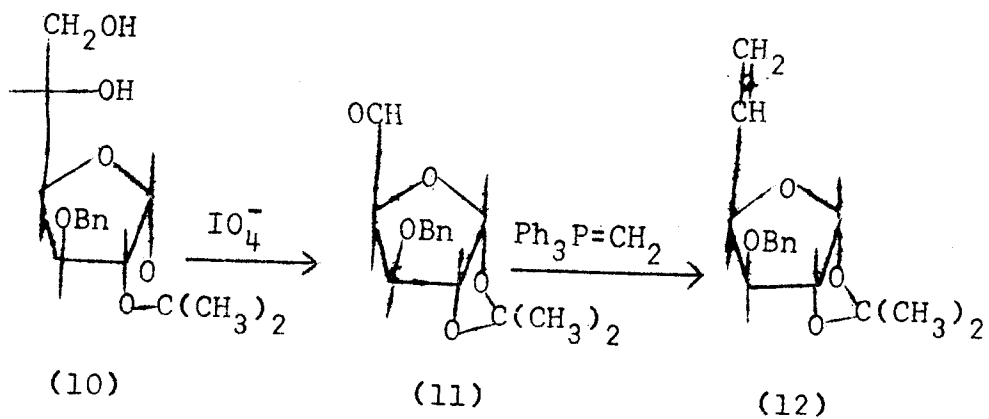


Fig. (4)



Bn = Benzyl

Fig. (5)¹⁸

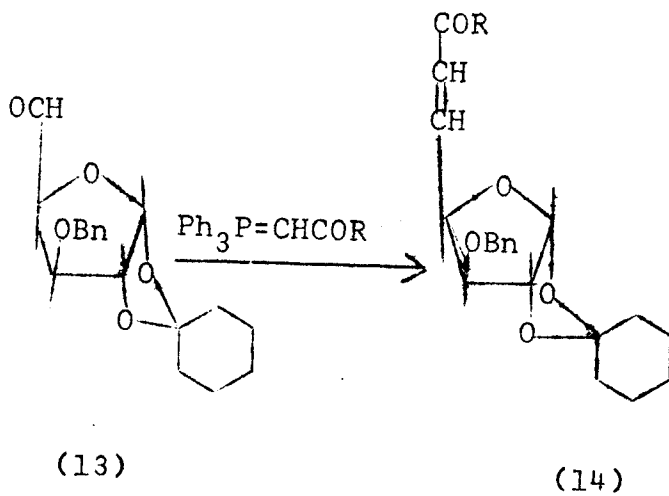
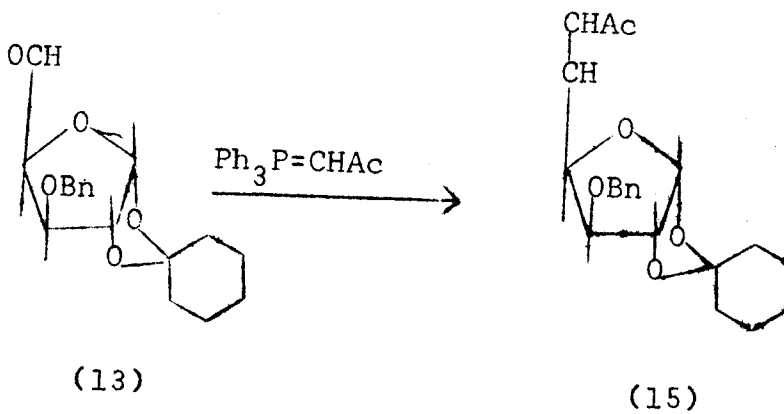


Fig. (6)¹⁹



Several groups of Russian workers have shown^{18,19,20} that a wide variety of chain-extended carbohydrate derivatives could be prepared from aldehydes by using Wittig reagents. Typical examples of these are shown in Figs (5-6). Tronchet and coworkers²¹ used methylthiomethylene triphenyl phosphorane to extend the carbon chains of the aldehyde-compounds (16) and (11) by one carbon. (Fig. 7 and 8) respectively.

Fig. (7)

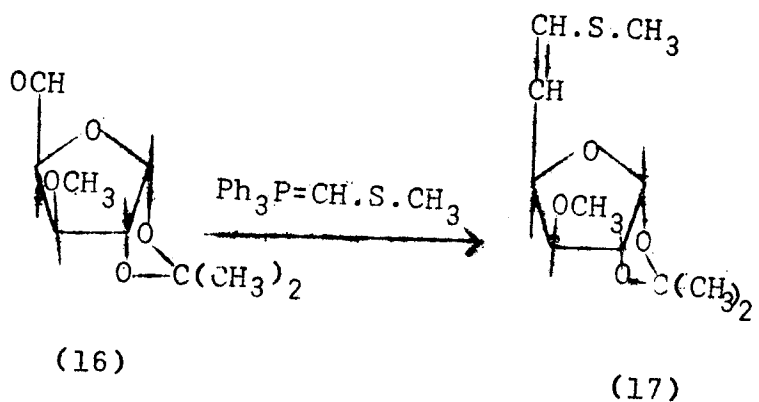
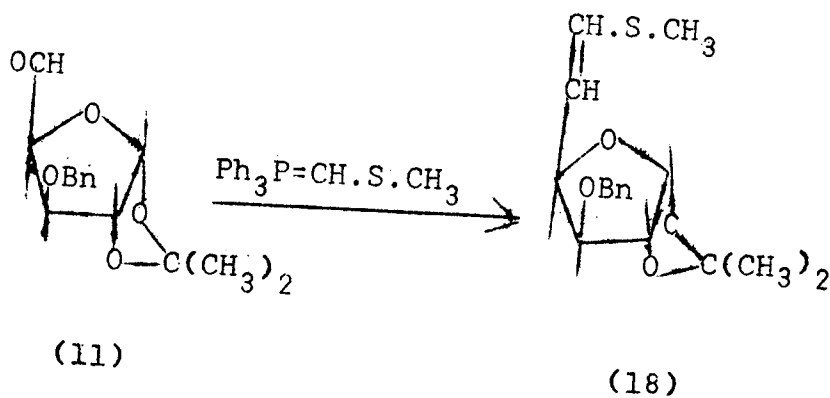


Fig. (8)

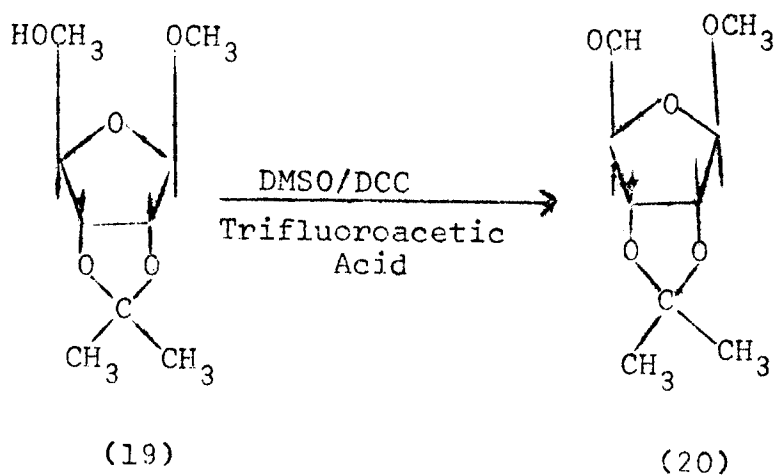


In view of the importance of aldehyde sugars as useful intermediates in chain extension reactions, their synthesis has been undertaken by various workers^{22,23,24,25}. Oxidation of methyl 2,3-O-isopropylidene- β -D-ribofuranoside (19) to methyl 2,3-O-isopropylidene- β -D-ribo-pentodialdofuranoside (20) has been achieved²² with the "Pfitzner-Moffat" reagent (Fig. 9) (dimethyl sulphoxide-dicyclohexyl carbodiimide in the presence of trifluoroacetic acid). Compound (20) has also been prepared from (19) using dimethyl sulphoxide and acetic anhydride²³ and also ruthenium tetroxide,²⁴ but in very low yields. Photolysis of azides has also been shown²⁵ to yield aldehyde sugars. Photolysis of methyl-6-azido-2,3,4-tri-O-acetyl-6-deoxy- α -D-glucopyranoside (21) gave the 6-aldehyde-derivative (22) isolated as its acetylated aldehydrol (23) or its 2,4-dinitrophenyl hydrazone (Fig. 10).

In 1957 Kornblum and coworkers²⁶ reported that a variety of phenacyl halides were oxidised to phenyl glyoxals by simply dissolving the compound in dimethyl sulphoxide in the presence of an acid acceptor such as sodium hydrogen carbonate.

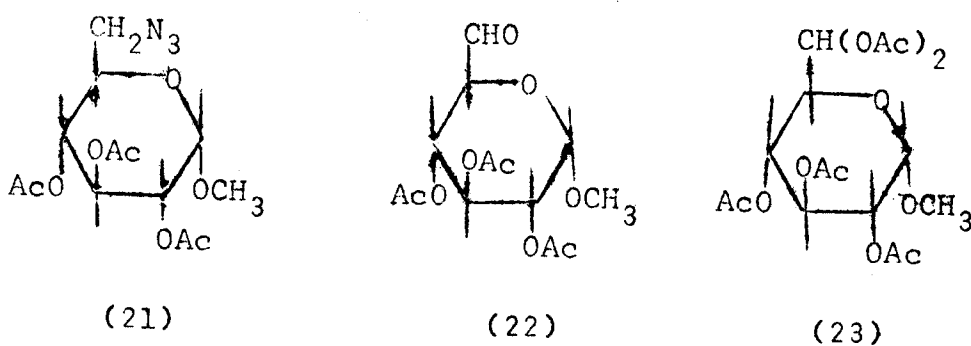
Two years later these authors²⁷ showed that benzyl halides and primary alkyl tosylates could be converted to corresponding aldehydes in good yield (65 - 85%) by heating in dimethyl sulphoxide containing sodium hydrogen carbonate to temperatures of 100 - 105°C for less than 5 minutes.

Fig. (9).



DCC = dicyclohexyl carbodiimide

Fig. (10).



The Kornblum oxidations are important because the overall oxidation of primary alcohols to aldehydes occurs without any over oxidation to give unwanted carboxylic acids.

Typical reactions are listed in Fig. (11a). These oxidations demonstrated the nucleophilicity of the oxygen atom in dimethyl sulphoxide. The oxidation reactions involved the displacement of the tosylate or halide function by dimethyl sulphoxide to form an intermediate alkoxy sulphonium salt, which produces a carbonyl compound and dimethyl sulphide by either an intramolecular²⁸⁻³⁰ or an intermolecular³⁰ route. The pathway depends on the relative acidities of the hydrogen involved (Fig. 11b).

The oxidation reaction can produce other products as well as aldehydes because of alternative transformations of the alkoxy sulphonium salts. The dimethyl sulphonium salts depending on their structures have been shown to undergo four basic types of transformations, namely (1) decomposition to carbonyl compound and dimethyl sulphide (2) nucleophilic displacement on sulphur (3) rearrangement to an α -substituted sulphide (Pummerer rearrangement)(14) oxosulphonium salt formation. All these transformations are shown in Fig. (12).

In the oxidation of halides and tosylates the oxygen atom in dimethyl sulphoxide becomes the carbonyl oxygen in the newly formed aldehyde or ketone. Sodium hydrogen carbonate serves to decompose the alkoxy sulphonium salts to corresponding carbonyl compounds and dimethyl sulphide,

and also to neutralize the acids which are liberated in the displacement reaction. This oxidation method has not been successfully used in the sugar field. Only recently Hanessian and Staub³¹ reported an unsuccessful attempt to oxidise the 5-O-p-toluene sulphonyl derivative of (19) with dimethyl sulphoxide in presence of sodium hydrogen carbonate. This reaction only led to partial desosylation of the starting tosyl compound with no detectable quantity of aldehyde, even at elevated temperatures.

Fig. (11a).

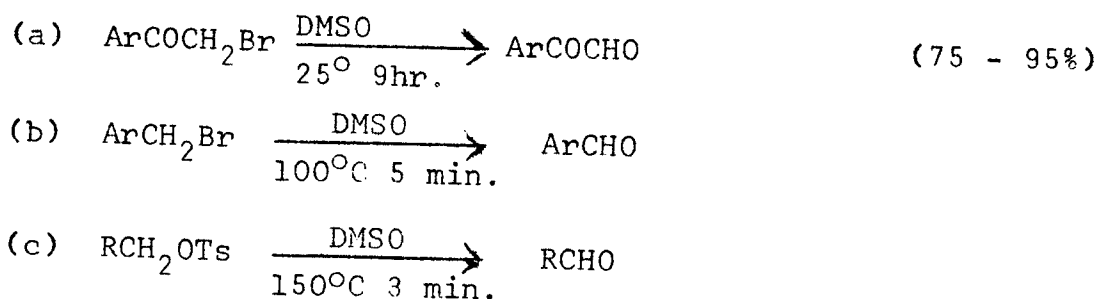


Fig. (11b)

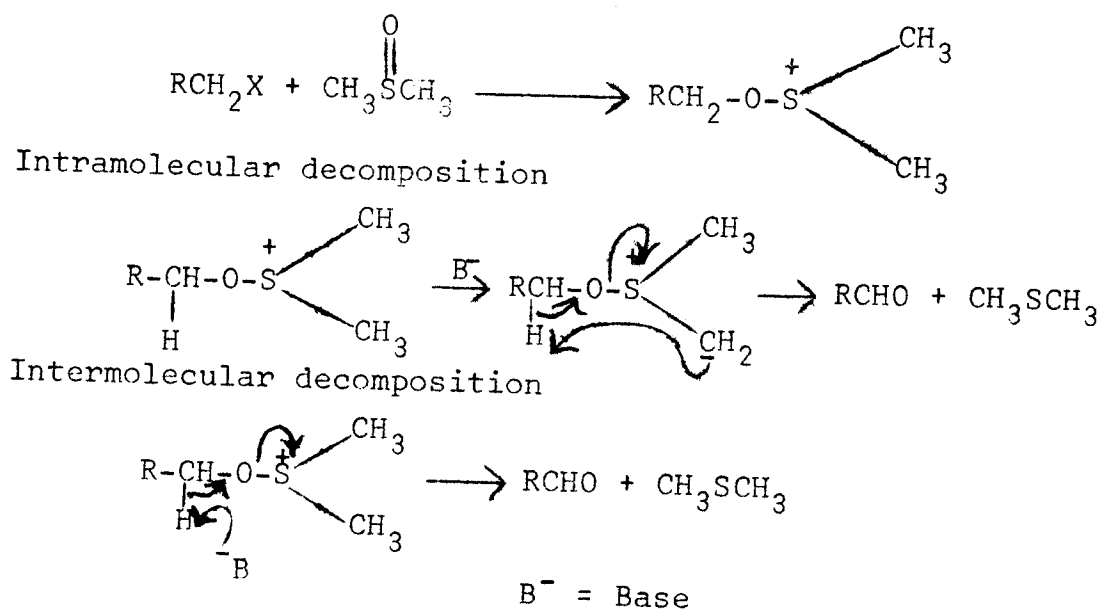
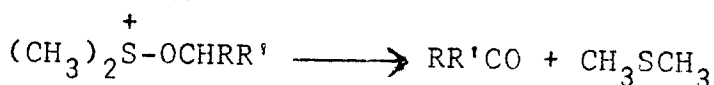
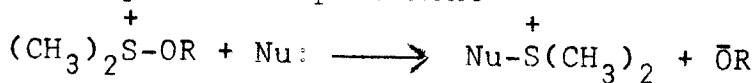


Fig. (12).

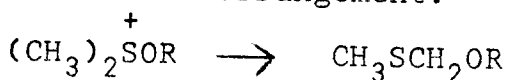
1. Oxidation.



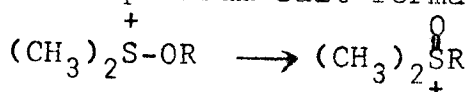
2. Nucleophilic displacement



3. Pummerer rearrangement.



4. Oxosulphonium salt formation.



Another possible chain-extension method is one that involves the reaction of a primary tosylate with the conjugate base of dimethyl sulphoxide (methyl sulphinyl-carbanion)³². The synthesis of methyl sulphinyl carbanion was first achieved by Corey and Chaykovsky^{33,34} who reported that the reaction of dimethyl sulphoxide with finely powdered sodium hydride under nitrogen at 70 - 75°C constituted a convenient and efficient synthesis of sodium methyl sulphinyl carbanion. This finding coupled with the study of some reactions by these authors especially with sulphonium salts,³⁵ aldehydes and ketones^{33,34} has opened a new field in the synthetic applicability of dimethyl sulphoxide.

Methyl sulphinyl carbanion undergoes the reactions expected of a strong nucleophilic base. It reacts with a wide range of reagents to give initially sulphoxides

which can undergo further transformations of synthetic utility. Primary tosylates and halides have been shown³⁶ to undergo substitution with methyl sulphanyl carbanion to give sulphoxide (Fig. 13). This is a chain-extension reaction and in cases where a β -H is present, pyrolysis of the sulphoxide give rise to a terminal olefin.

Pyrolysis of such sulphoxides was first carried out by Kingsbury and Cram³⁷ on 1,2-diphenyl-propylphenyl sulphoxide. Pyrolysis of methyl n-alkyl sulphoxide³⁶ at 180°C afforded terminal olefins in good yields. It was found that pyrolysis of sulphoxides proceeds predominantly by a cyclic intramolecular mechanism which results in stereospecific cis elimination as shown in Fig. (14).

Fig. (13).

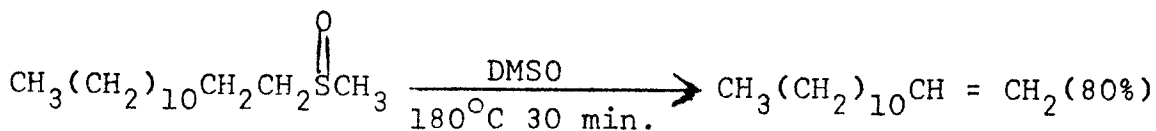
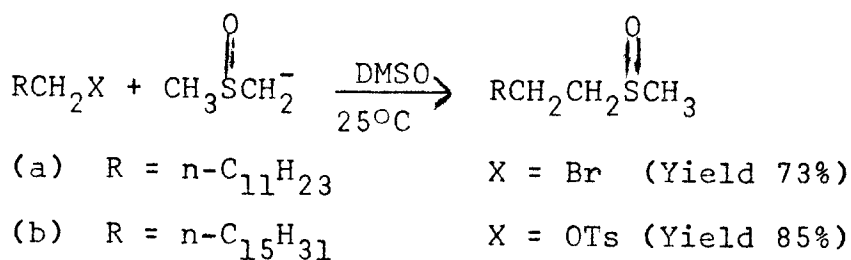
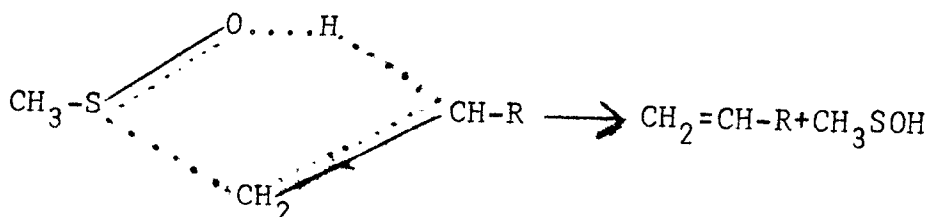


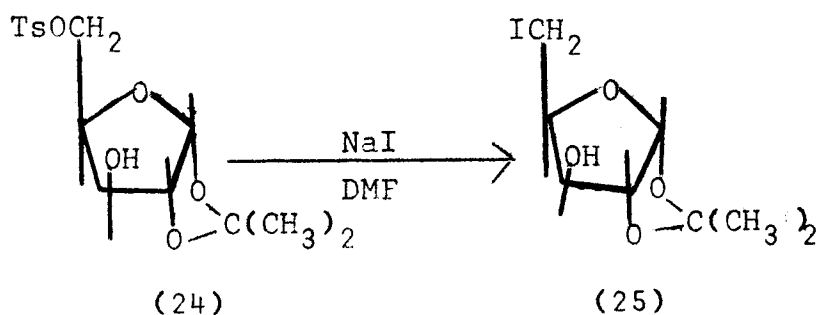
Fig. (14).



Although displacement of a tosyloxy group by methyl sulphanyl carbanion has not been reported in carbohydrate chemistry, it appears to be an attractive possibility because primary tosylate sugars are readily available and reactive towards nucleophiles. Primary sulphonyloxy groups are usually smoothly displaced by heating with appropriate nucleophiles at 100°C.

1,2-O-isopropylidene-5-O-tosyl-D-xylofuranose (24) has been converted to the 5-deoxy-5-iodo compound (25)³⁹ in 98% yield (Fig. 15). Primary tosyloxy groups have also been easily replaced by thioacetate⁴¹ and other sulphur nucleophiles.⁴⁰

Fig. (15).



By the use of potassium acetate in acetic anhydride methyl 2,3,4-O-acetyl-6-O-mesyl- α -D-glucoside was converted into methyl 2,3,4,6-tetra-O-acetyl- α -D-glucoside.⁶³ Similar displacements of primary sulphonates and also the 5-O-sulphonyl group of 5-O-tosyl-D-glucofuranose derivatives have been described by Vargha.⁶⁴

Recently a new route to amino sugars has been obtained via azido sugars. Treatment of 1,2:3,4-di-O-isopropylidene-6-O-p-toluene sulphonyl-D-galactose with sodium azide in N,N-dimethyl formamide at 120°C gave the 6-azide derivative.⁶⁵ A 5,6-di-O-tosyl- α -D-glucofuranose derivative was treated with sodium benzoate in N,N-dimethyl formamide to selectively displace the primary sulphonate.⁶⁶

DISCUSSION

DISCUSSION

Preparation of methyl 2,3-O-isopropylidene- β -D-ribofuranoside (20) which is a potentially useful intermediate in chain extension reactions²² was a desirable first objective in this work. A theoretical route to hexoses, starting from this compound (20) is outlined in Fig. (16). Methyl 2,3-O-isopropylidene- β -D-ribofuranoside (19) is readily obtainable directly from D-ribose in good yields.⁴² D-ribose was treated with anhydrous methanol containing concentrated sulphuric acid for 1 hour and then treated with acetone containing sulphuric acid for a further 1 hour, giving rise to methyl 2,3-O-isopropylidene- β -D-ribofuranoside (19) (Fig. 17).

Treatment of freshly distilled methyl 2,3-O-isopropylidene- β -D-ribofuranoside (19) with the "Pfitzner Moffat" reagent (dimethyl sulphoxide-dicyclohexyl carbodiimide) using the method of Butterworth and Hanessian²² gave a syrup in low yields and contaminated with dicyclohexyl urea (Fig. 9). Thin-layer chromatography revealed that it consisted of two sugar products in relatively equal quantities. Efforts to isolate each of the two products in a pure state were unsuccessful. The infrared spectrum of the crude products showed an appreciable carbonyl absorption around 1730 cm^{-1} indicating that an aldehyde had been formed.

This route was however abandoned because of the low yields and the problem encountered in isolating the products. Because of the unsatisfactory results with the "Pfitzner-Moffat" reaction alternative routes to the aldehyde were investigated.

Fig. (16).

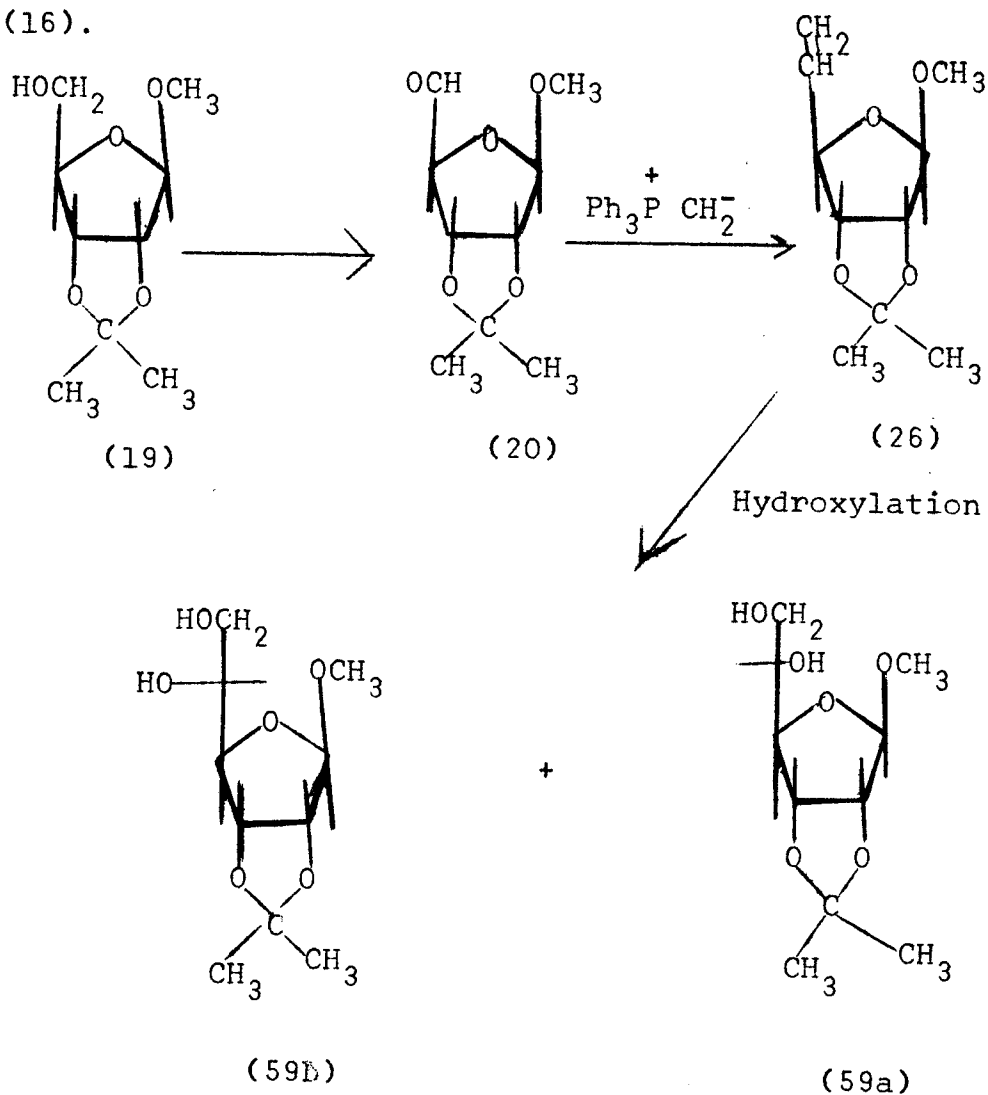


Fig. (17)

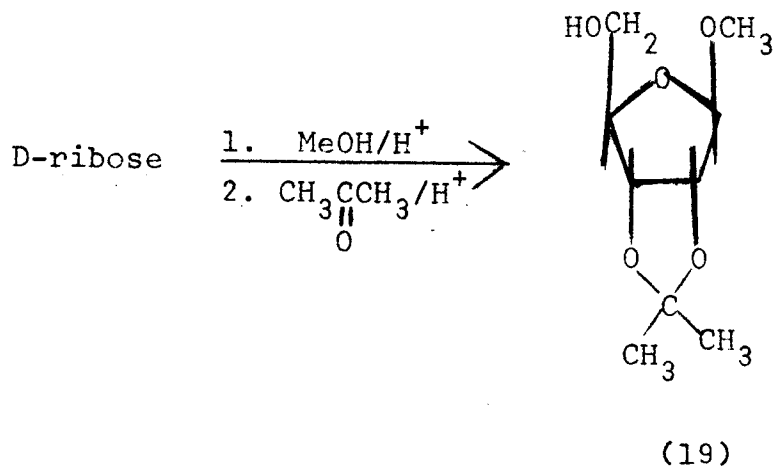
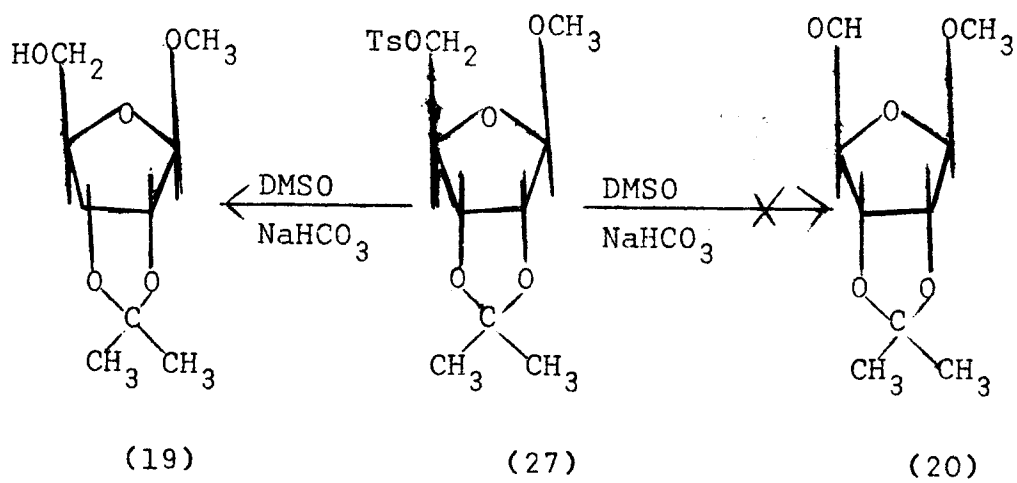


Fig. (18)



Reaction of Methyl-5-O-tosyl-2,3-O-isopropylidene- β -D-ribofuranoside (27) with dimethyl sulphoxide (DMSO).

Crystalline methyl-5-O-tosyl-2,3-O-isopropylidene- β -D-ribofuranoside (27) was prepared from D-ribose by a method communicated by Dr. Neil Hughes.⁴² When (27) was treated with dimethyl sulphoxide in the presence of sodium hydrogen carbonate at 174° - 180°C for 15 minutes, it did not give methyl 2,3-O-isopropylidene- β -D-ribofuranoside (20) (Fig. 18) but a compound with a prominent hydroxyl absorption at 3420 cm⁻¹. This compound had the same infrared spectrum and same thin-layer chromatographic mobility (benzene-ether 1:1) as the authentic methyl 2,3-O-isopropylidene- β -D-ribofuranoside (19). Acid hydrolysis of the product yielded D-ribose (as shown by Paper Chromatography). This confirmed that the reaction product was methyl 2,3-O-isopropylidene- β -D-ribofuranoside (19). Compound (19) could have arisen from a direct nucleophilic attack by dimethyl sulphoxide on the sulphonate group as shown in Fig. (19) or from water attack on the sulphonium salt as shown in Fig. (20). There is also the possibility of it having arisen from an attack by the hydrogen carbonate ion as shown in Fig. (21).

Fig. (19).

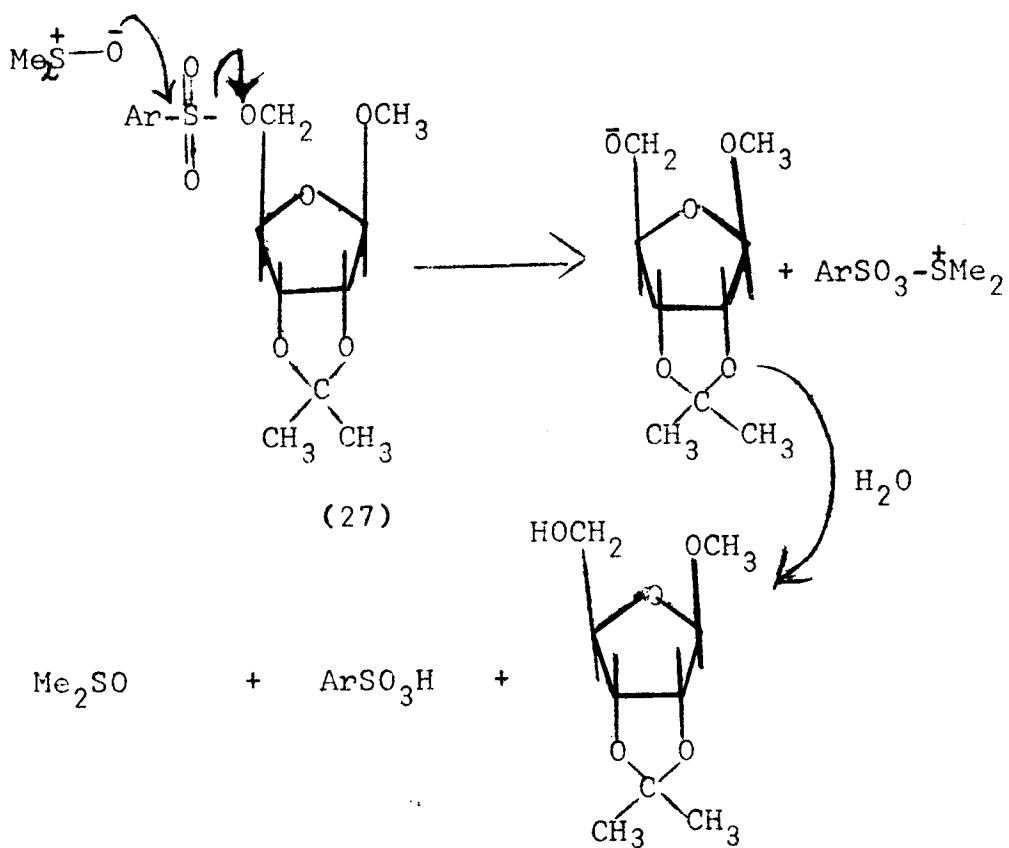
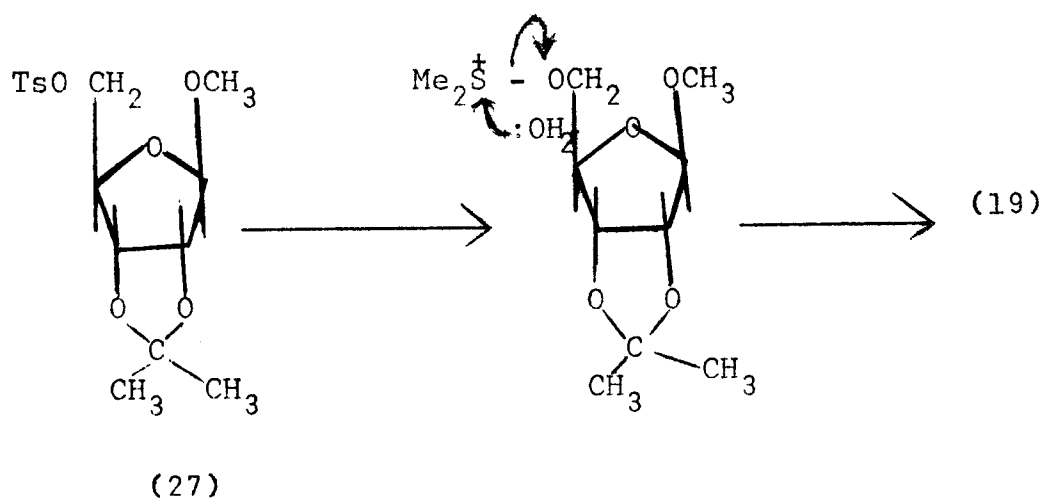


Fig. (20).



Again this compound had the same infrared spectrum and same thin-layer chromatographic mobility (in benzene-ether 1:1) as Methyl 2,3-O-isopropylidene- β -D-ribofuranoside (19). However acid hydrolysis of the product gave two sugars. The higher running sugar was identified as 5-O-methyl-D-ribose and the lower one as D-ribose by comparison with authentic samples; using Paper Chromatography in two different solvent systems) n-Butanol:Acetic acid:water - 80:20:20:- and n-Butanol:acetic acid: water - 40:10:50). The authentic sample of 5-O-methyl-D-ribose was prepared by direct methylation of methyl 2,3-O-isopropylidene- β -D-ribofuranoside (19) using dimethyl sulphate under basic conditions followed by acid hydrolysis of the methylation product as shown in Fig. (22). The 5-O-methyl-D-ribose must have arisen from a particularly favourable case of methoxyl (MeO-5) participation^{43,44} in the ejection of the iodine atom to give a cyclic oxonium ion intermediate (31) which could yield methyl 2,3-O-isopropylidene- β -D-ribofuranoside (19) and methyl 5-O-methyl-2,3-O-isopropylidene-D-ribofuranose (32), depending on whether the ion intermediate is opened by water attack at C-5 or C-1 respectively (Fig. 23).

Fig. (22).

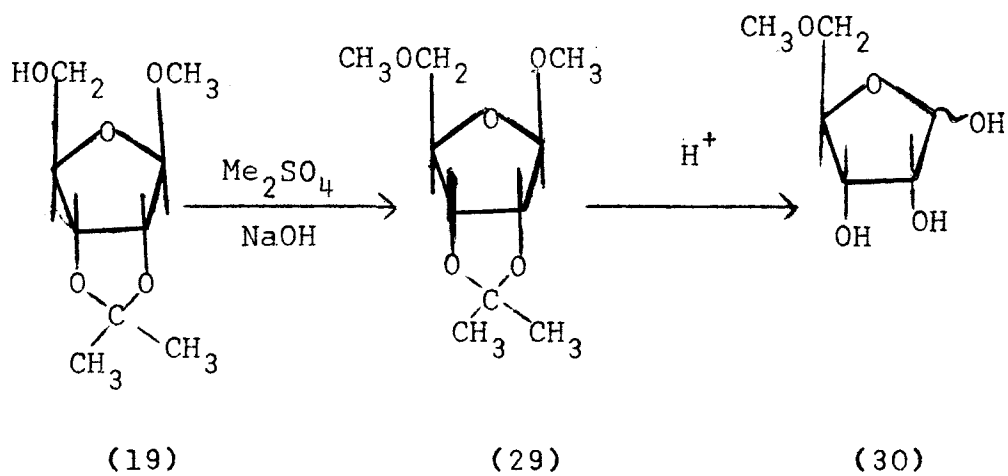
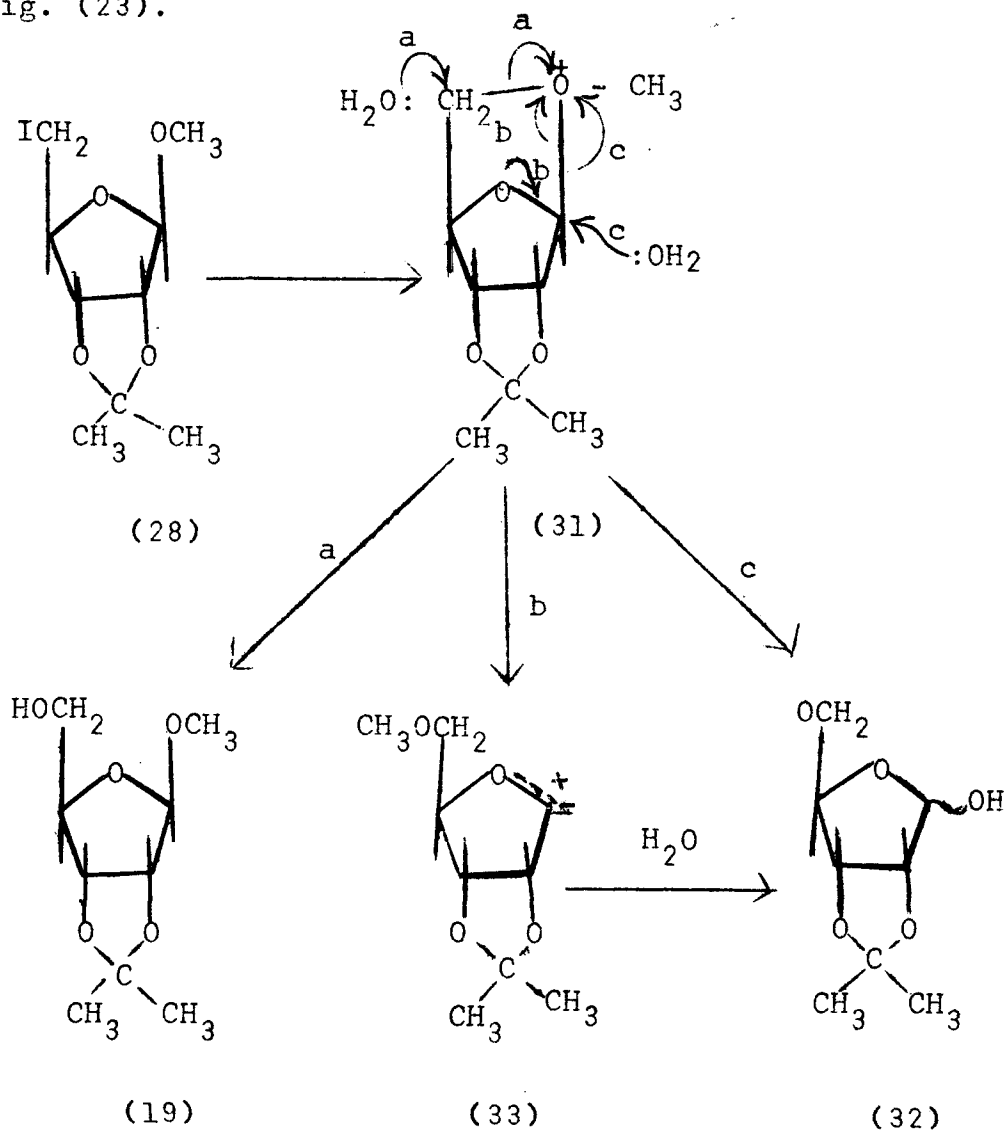


Fig. (23).



Here compound (19) could be formed by methoxy group participation or by any of the mechanisms suggested for the tosylate reaction, particularly those shown in Fig. (20 and 21). On the contrary compound (32) could only come from methoxy group participation. Similar oxonium ion intermediates have been reported.⁴⁵ This mode of ring opening has been ascribed to the mesomeric effect of the ring oxygen atom⁴⁶⁻⁴⁸ and is analogous to that observed with participating methylthio-^{47,48} and benzyloxy-groups.⁴⁵

It is difficult to understand the difference in behaviour of the iodo and tosyl analogues (28) and (27). However, it should be noted that the mechanism shown in Fig. (19) allows for detosylation without neighbouring group participation in the case of tosylate (27) whereas a similar mechanism is not available for the iodo compound (28) which consequently may react by the participation route. This infers that for the tosyl compound (27), the direct attack shown in Fig. (19) is energetically more favourable than a participation route.

Cases of methoxyl migration are rare in carbohydrate chemistry and few previous instances have been reported. A 1,2-methoxy group migration occurred when 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo- α -D-mannopyranoside (34) was subjected to brominolysis in acetic acid containing silver acetate and potassium acetate.⁴⁶ About 20% of the product was 1,3,4,6-tetra-*O*-acetyl-2-*O*-methyl-D-glucopyranoside (37) (Fig. 24). The brominolysis reaction involved cleavage of the axial C-1 bond at position 2 with the participation of the axial methoxyl-group at position 1 to give a 1,2-methoxonium ion (35). It is likely that this is opened up by mesomeric participation of the lactol oxygen to give a new ion (36) (Fig. 24), which is attacked by acetate ion to give the glucopyranoside (37). Direct attack on methoxonium ion (35) is also possible.

A 1,4-methoxy group migration occurred when 2,3,5-tri-*O*-benzyl-4-*O*-toluene-*p*-sulphonyl-D-ribose dimethyl acetal (38) was treated with tetra-*n*-butylammonium benzoate in *N*-methylpyrrolidone.⁴⁸ The product was not the expected 4-*O*-benzoyl compound that would have resulted from direct SN2 displacement, but was 1-*O*-benzoyl-2,3,5-*O*-benzyl-4-*O*-methyl-L-lyxose methyl hemiacetal (41) (Fig. 25).

Fig. (24)

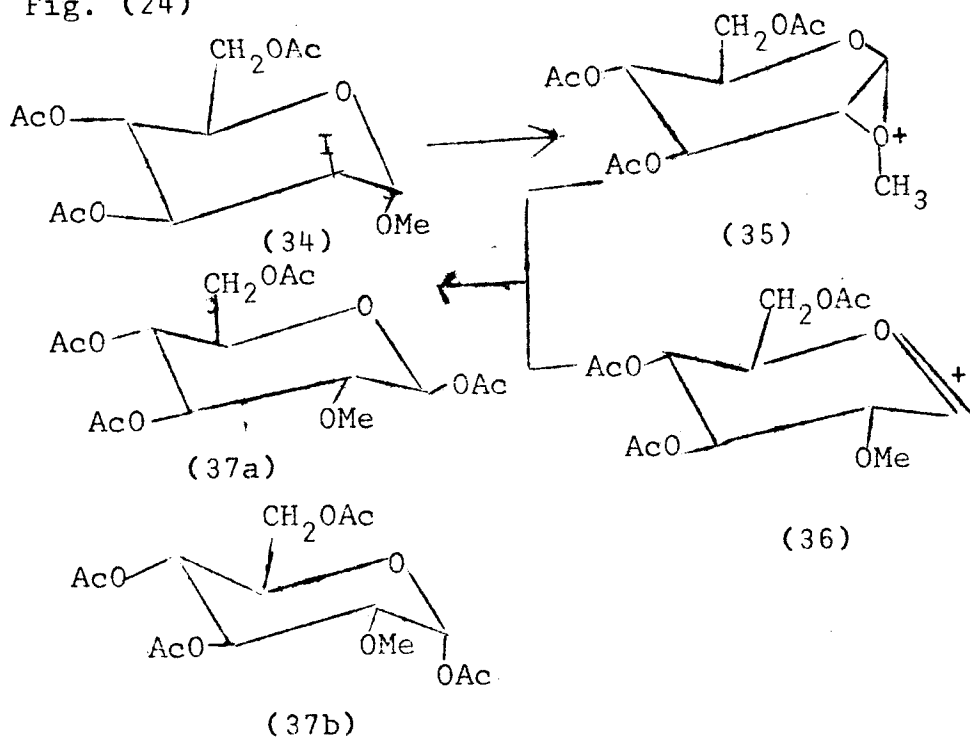
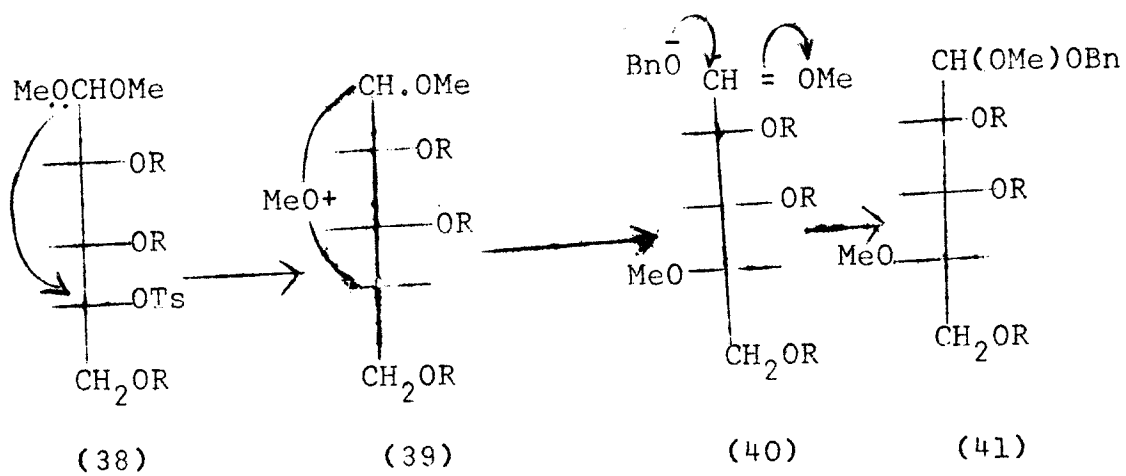


Fig. (25).

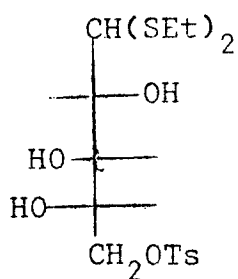


R = CH₂Ph
 BnO = PhCO.O

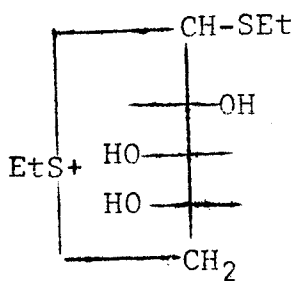
Hughes and Robson⁴⁹ reported that when an aqueous acetone solution of 5-O-toluene-p-sulphonyl-L-arabinose diethyl dithioacetal (42) was heated in the presence of solid barium carbonate anomeric mixtures of ethyl 1,5-dideoxy-ethylthio- α - and β -L-arabinofuranoside (45a and 45b) were obtained⁴⁹ (Fig. 26). These were smoothly converted to 5-deoxy-5-ethylthio-L-arabinose diethyl dithioacetal (46) by acid hydrolysis. This reaction proceeds by an intramolecular displacement leading to the cyclic sulphonium ion (43). As in the analogous oxygen case,⁴⁸ this cyclic ion is opened up by a mesomeric effect from the second ethylthio-group to give a new sulphonium ion (44) which undergoes cyclisation with hydroxyl group favourably placed at position 4.

It was of interest to examine the dimethyl sulphoxide reaction with other 5-tosylates in which there is no possibility of the C-1 substituent either participating in or sterically hindering attack at C-5. The tosylates chosen for the study were methyl 2,3-O-isopropylidene-5-O-tosyl- α -D-ribofuranoside (48) and 1,2-O-isopropylidene-5-O-tosyl- α -D-xylofuranose (24) (Fig. 27).

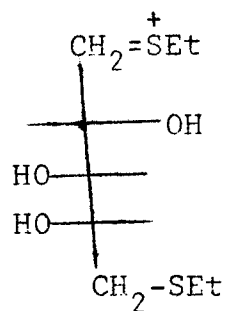
Fig. (26).



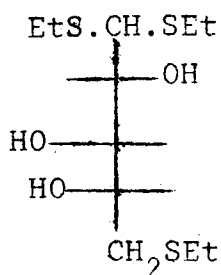
(42)



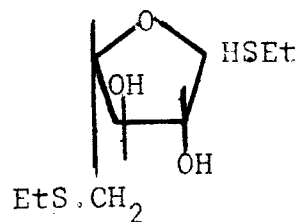
(43)



(44)



(46)

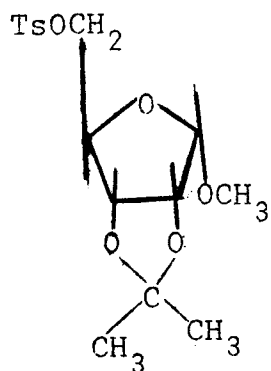


(45a,b)

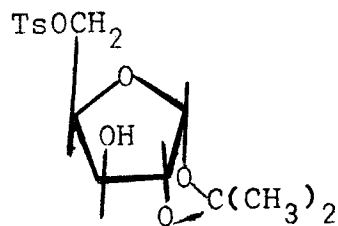
a = α

b = β

Fig. (27).



(48)



(24)

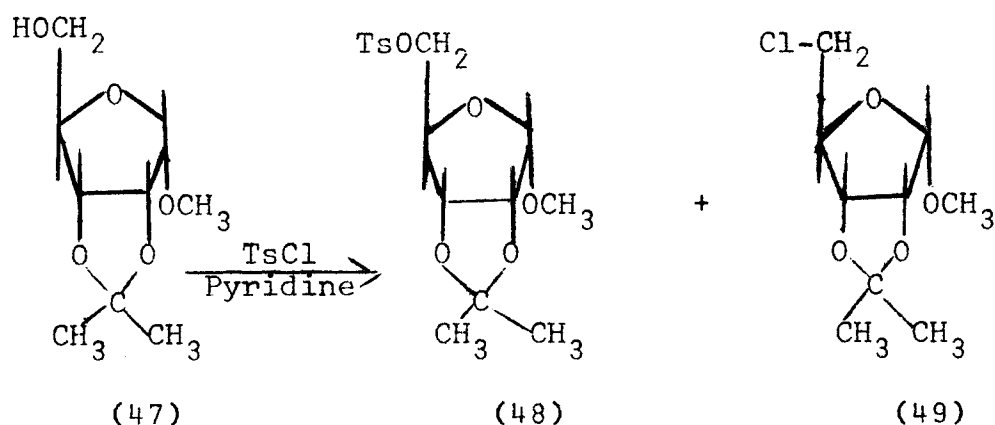
Methyl 2,3-O-isopropylidene-5-O-tosyl- α -D-ribofuranoside (48) which is the α -anomer of compound (27) was prepared by a method communicated by Dr. Neil Hughes.⁴² D-ribose in dry methanol containing a catalytic amount of concentrated sulphuric acid was left at room temperature for one hour, and to this was added dry acetone containing concentrated sulphuric acid to give a mixture of methyl 2,3-O-isopropylidene- β -D-ribofuranoside (19) and methyl 2,3-O-isopropylidene- α -D-ribofuranoside (47). The β -anomer had much higher mobility on thin-layer chromatograms than the α -anomer (47). The higher mobility of the β -anomer (19) could be ascribed to intramolecular hydrogen bonding in this compound which is not possible in the β -anomer (47). As hydrogen bonding with the adsorbent is important in increasing the adsorption affinity, it is to be expected that intramolecular hydrogen bonding will decrease the adsorption affinity. This means that the β -anomer (19) would be less strongly adsorbed and thus more mobile than the α -anomer (47). To isolate the α -anomer (47) from the β -anomer (19) multiple partitioning between chloroform and water was used. This separated them because the α -compound (47) is more water-soluble than compound (19). Again the differences in solubilities are explained in terms

of hydrogen bonding. Because of its lack of intramolecular hydrogen bonding, the α -compound (47) is expected to form intermolecular hydrogen bonds with water thereby showing more water solubility than β -compound (19).

The chromatographically homogeneous α -compound (47) was then converted to methyl 2,3-O-isopropylidene-5-O-tosyl- α -D-ribofuranoside (48) (Fig. 28) by a reaction with p-toluene sulphonyl chloride in pyridine. Thin-layer chromatography showed two sugars. The higher running was not a tosylate (infrared spectrum, tosyl spray) but after column chromatography it was identified as the 5-chloro compound (49) (nmr, mass spectrometry see pages 47 and 48).

Although chlorination is generally more prevalent the higher the temperature at which sulphonylation is performed⁵⁰ some chlorination of sucrose was found when using methanesulphonyl chloride in pyridine at -30°C .⁵¹

Fig. (28).



Treatment of the 5-tosyl compound (48) with dimethyl sulphoxide in the presence of sodium hydrogen carbonate at 100° - 105°C for 3 hours gave a compound of lower mobility on thin-layer chromatograms than the starting tosyl compound (48) (in benzene-ether 1:1), and a strong hydroxyl absorption at 3420 cm^{-1} . This compound had the same infrared spectrum and same chromatographic mobility (benzene-ether 1:1) as the authentic methyl 2,3-O-isopropylidene- α -D-ribofuranoside (47). No neighbouring group participation is possible in this reaction and plausible mechanisms (Fig. 29b-d) parallel those suggested for detosylation of the β -anomer (27).

Fig. (29a).

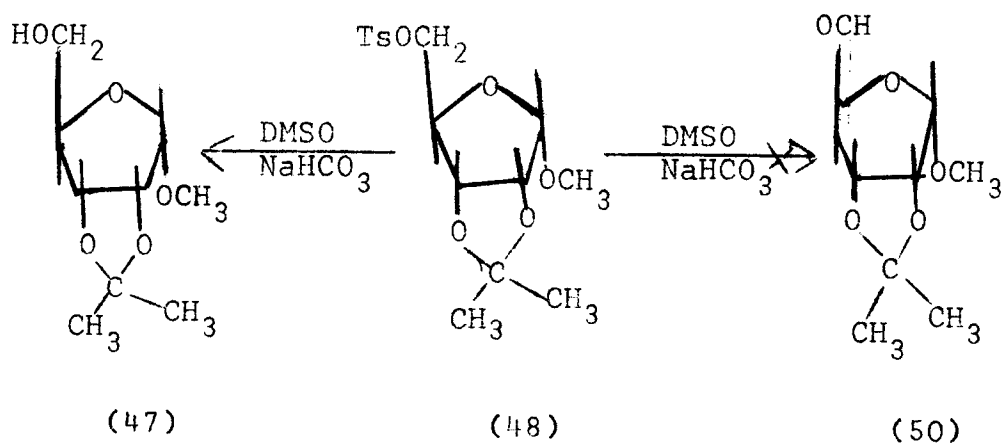


Fig. (29b).

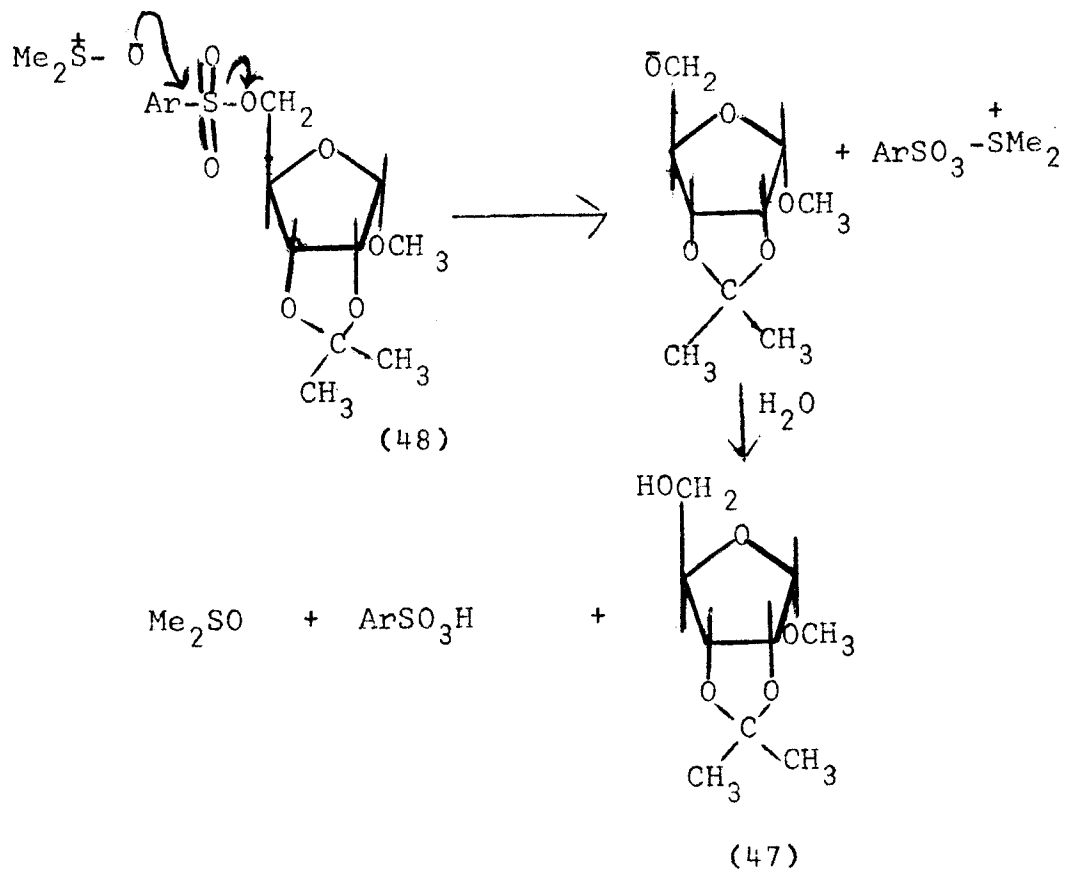


Fig. (29c)

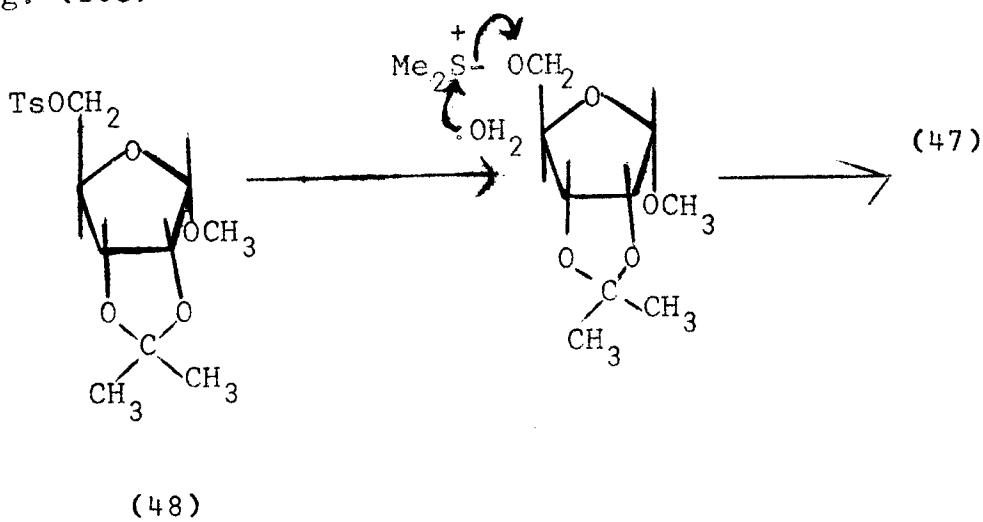
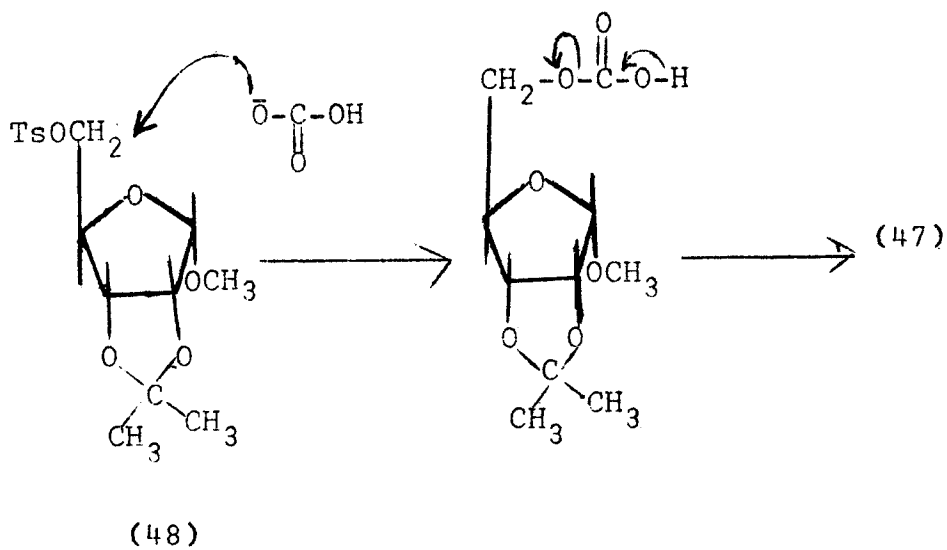


Fig. (29d)



D-XYLOSE DERIVATIVES

1,2-0-isopropylidene- α -D-xylofuranose (52) was prepared from D-xylose as described by Baker and Schaub,⁵² and then sulphonylated using toluene sulphonyl chloride in pyridine to give 1,2-0-isopropylidene-5-0-tosyl- α -D-xylofuranose (24) (Fig. 30).

Treatment of 1,2-0-isopropylidene-5-0-tosyl- α -D-xylofuranose (24) with dimethyl sulphoxide containing sodium hydrogen carbonate for 15 minutes at 174° - 180°C gave a syrup. The infrared spectrum revealed that this compound had no carbonyl absorption and no hydroxyl absorption, thus ruling out the aldehyde structure (53). The syrupy product showed prominent infrared absorption peaks at 1075 - 1020 cm^{-1} and 1225 - 1200 cm^{-1} suggesting the possibility of it being a 3,5-anhydro compound (54). The 3,5 anhydro compound (54) could have arisen from internal displacement of the tosylate group at C-5 by a mechanism shown in Fig. (31). This type of displacement has been reported in carbohydrates bearing hydroxyl groups in such a position as to facilitate backside attack on the tosylate group.^{53,54} In 1933, Levene and Raymond⁵⁵ reported the first synthesis of 3,5-anhydro-1,2-0-isopropylidene- α -D-xylofuranose (54) from 1,2-0-isopropylidene-5-tosyl- α -D-xylofuranose (24) using sodium methoxide in

methanol at room temperature (Fig. 32).

Fig. (30).

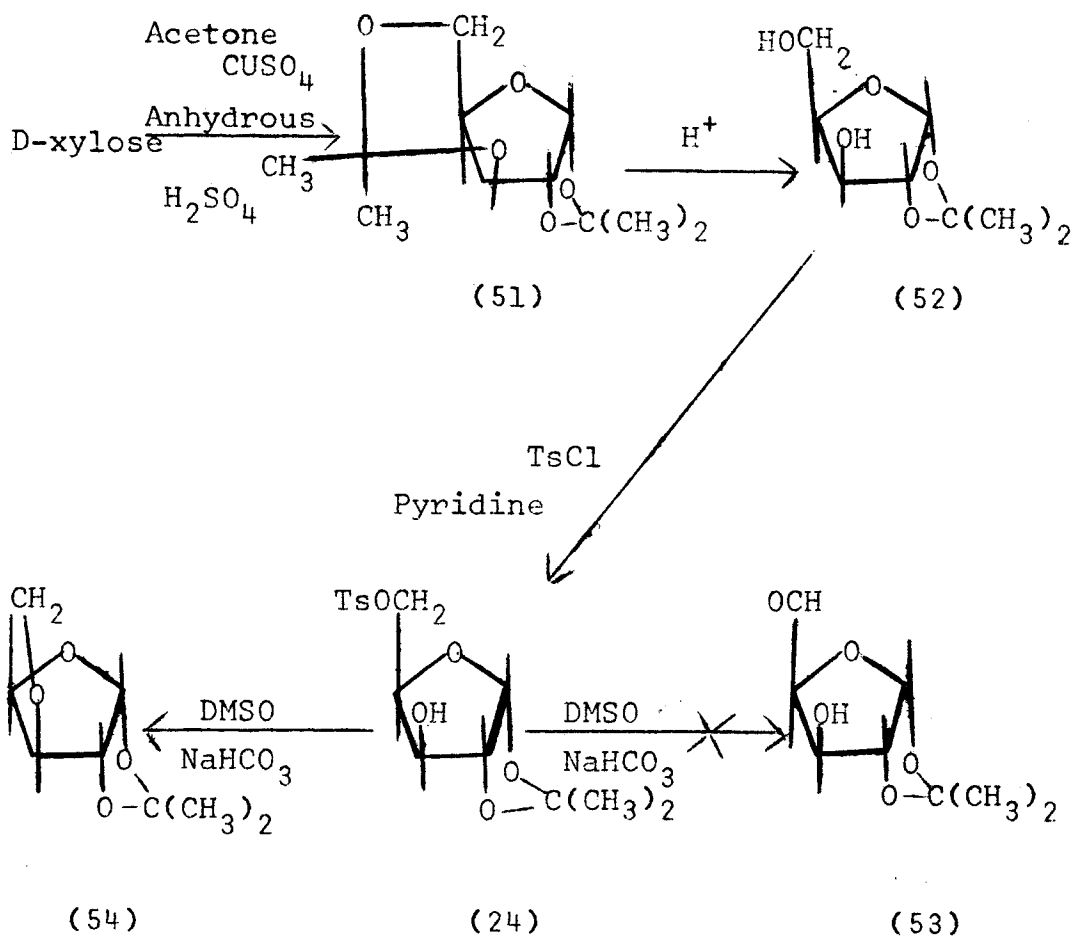


Fig. (31)

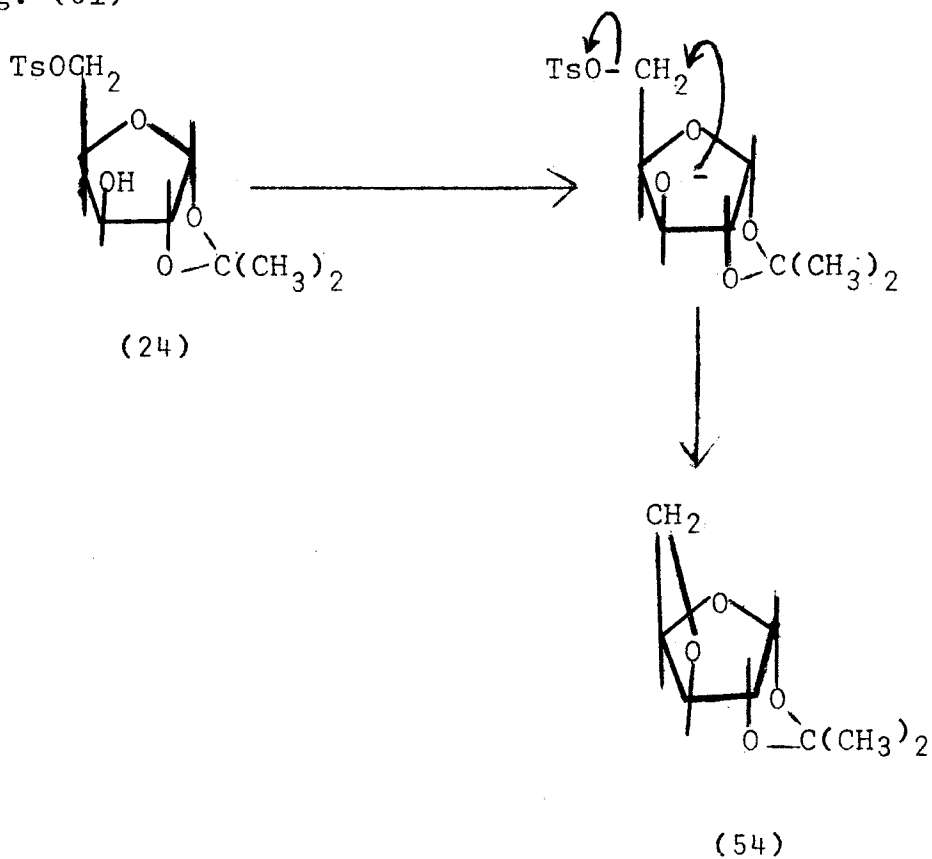
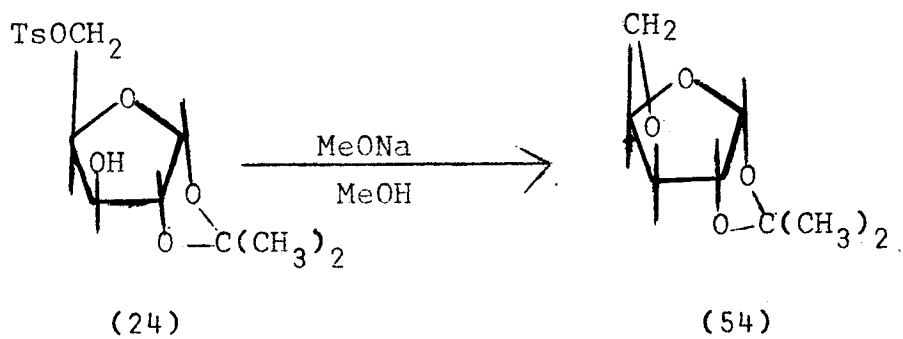


Fig. (32)



Similar reactions in the nucleoside field have led to the synthesis of 1-(3,5-anhydro-2-deoxy- β -D-threopentofuranosyl)thymine (55),⁵⁶ 1-(3,5-anhydro- β -D-xylofuranosyl) uracil (56)⁵⁷ and 1-(3,5-anhydro- β -D-lyxofuranosyl) uracil (57)⁵⁸ (Fig. 33). To confirm the structure (54) an authentic sample of 3,5-anhydro-1,2-O-isopropylidene- α -D-xylofuranose (54) was prepared from 1,2-O-isopropylidene-5-O-tosyl- α -D-xylofuranose (24) using the method of Whistler, Luttenegger and Rowell.⁵⁹ The 3,5-anhydro-1,2-O-isopropylidene- α -D-xylofuranose prepared by this method had identical mobility on thin-layer chromatograms and also identical infrared spectrum with compound (54).

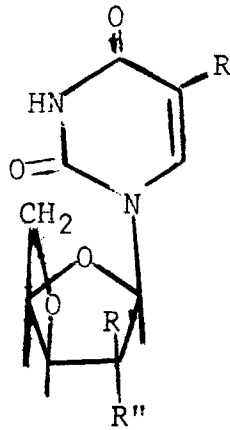
The Reaction of Methyl Sulphinyl Carbanion with Methyl-5-O-tosyl-2,3-O-isopropylidene- β -D-ribofuranoside (27).

The theoretical scheme outlined in Fig. (34) illustrates a potential conversion of a pentose into a hexose and prompted an investigation of the reaction of Methyl Sulphinyl Carbanion with Methyl 5-O-tosyl-2,3-O-isopropylidene- β -D-ribofuranoside (27). However the product of this reaction was not a sulphoxide but a compound with a higher mobility on thin-layer chromatograms (in benzene-ethylacetate 3:1) than the starting compound (27).

The reaction product was isolated from unreacted starting compound (27) by means of column chromatography. The infrared spectrum of the product showed disappearance of tosyl absorption bands confirming the formation of a new product and clear vinyl absorption band at 1640 - 1680 cm^{-1} . This was clearly an elimination product (60) an authentic sample of the elimination product was prepared from compound (27) by treatment with potassium tertiary-butoxide under nitrogen at 75° - 80°C for 22 hours. The product of this reaction had same infrared spectrum and also same mobility on thin-layer chromatograms as compound (60).

Other instances of this type of elimination have been reported. Compound (61) was prepared⁶⁰ from 2,3-ethoxymethylidene-5'-O-toluene-p-sulphonyladenosine by treatment with potassium-tertiary-butoxide in tertiary-butyl alcohol followed by removal of blocking groups. A related nucleoside (62) was prepared⁶¹ by a similar method (Fig. 36).

Fig. (33).



(55) R = CH₃, R' = H

(56) R = R' = H, R' = OH

(57) R = R'' = H, R' = OH

Fig. (34).

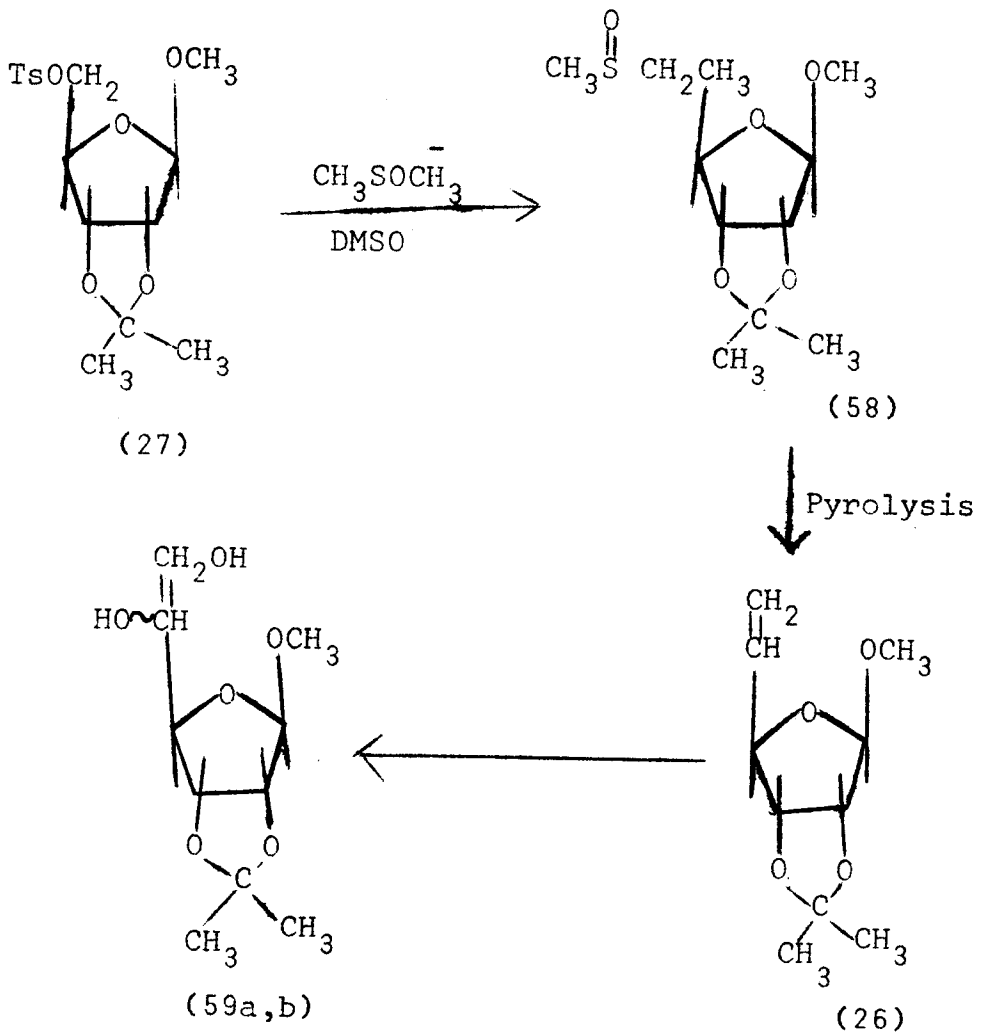


Fig. (35).

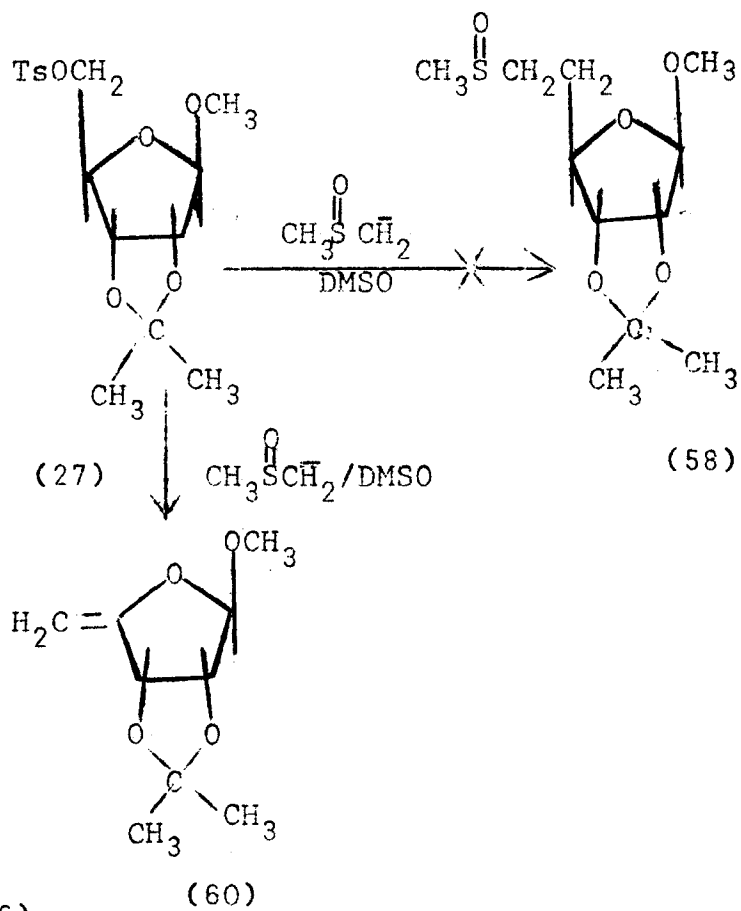
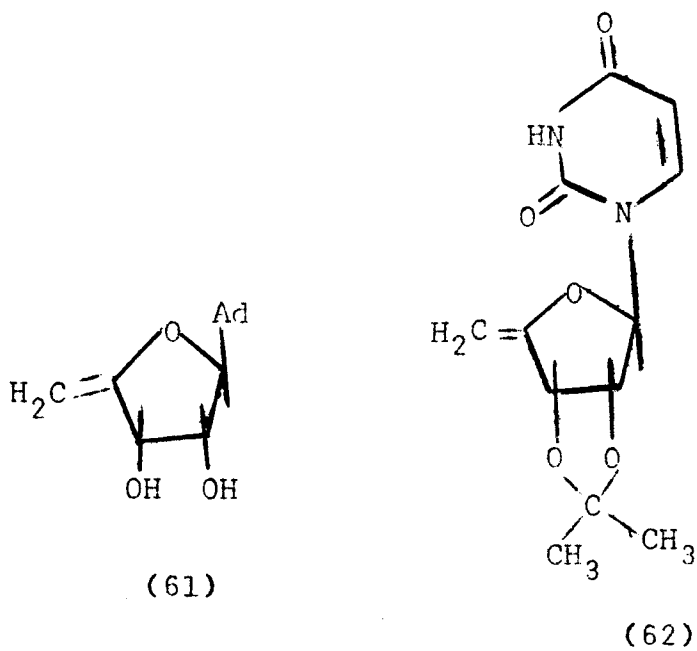


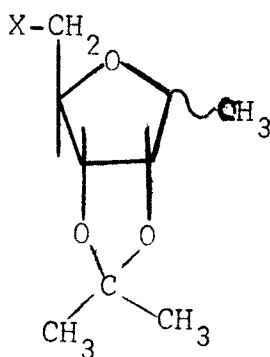
Fig. (36).



Generally primary sugar tosylates present a more sterically hindered $-\text{CH}_2\text{OTs}$ than acyclic sulphonates RCH_2OTs and it is to be expected that SN_2 attack by dimethyl sulphoxide or methyl sulphanyl carbanion will be less easy in the case of sugar sulphonates. The present work infact shows no evidence of nucleophilic attack by these nucleophiles. Using methyl sulphanyl carbanion the competing E_2 reaction is dominant whereas with RCH_2OTs mainly SN_2 is observed. In the reaction where dimethyl sulphoxide containing sodium hydrogen carbonate was used, the complete absence of aldehyde products suggests that nucleophilic attack via a sulphonium salt intermediate does not take place. On the other hand, it is impossible to rule out the possibility of reaction by the mechanism shown in Fig. (20) which does involve initial SN_2 attack by dimethyl sulphoxide (see page 21).

NMR AND MASS SPECTROSCOPIC DATA

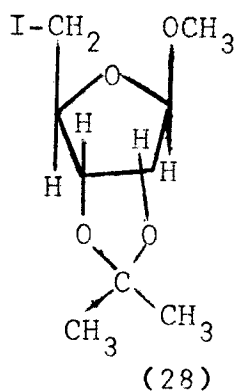
Dr. N. A. Hughes, in a private communication has shown that the α -compounds and β -compounds of general structure (A) may be distinguished by proton NMR. In the case of the β -compounds, the coupling constants $J_{1,2}$ and $J_{3,4}$ are very small ($< \frac{1}{2}$ Hz) so that the H-1 signal shows as a singlet at approximately $\delta 4.8$ to $\delta 4.9$, H-2 and H-3 appear as AB doublets in the range $\delta 4.5$ to $\delta 4.7$ and H-4 appears as a doublet of doublets or in some cases as a triplet in the range $\delta 4.0$ to $\delta 4.3$. In the α -compounds, these coupling constants ($J_{1,2}$ and $J_{3,4}$) are larger and the result is complex H-1, H-2, H-3 and H-4 signals in the $\delta 3.8$ to $\delta 5.0$ region.



(A)

NMR (CCl₄ SOLVENT)

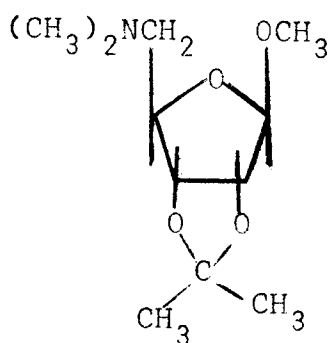
Methyl-5-iodo-5-deoxy-2,3-isopropylidene-β-D-ribofuranoside (28)



-OCH ₃ (3H)	Singlet	δ3.30
>C(CH ₃) ₂ (6H)	doublet	δ1.28, δ1.40
H ₁	singlet	δ4.90
H ₂	AB doublet	δ4.50
H ₃	AB doublet	δ4.64
H ₄	Distorted triplet	δ4.33
-CH ₂ I (2H)	multiplet	δ3.10 - 3.30

The complex nature of the -CH₂I peaks is not unexpected. These two protons are not magnetically equivalent (not in identical environment) and can show different shifts and in addition both are coupled with (H-4).

5-N,N-dimethyl-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside (63)*



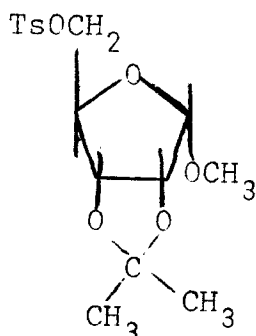
(63)

-OCH ₃ (3H)	singlet	δ3.28
>C(CH ₃) ₂ (6H)	doublet	δ1.27, δ1.40
H ₁	singlet	δ4.80
H ₂	AB doublet	δ4.46
H ₃	AB doublet	δ4.60
H ₄	triplet	δ4.13
-CH ₂ -N (2H)	doublet	δ2.30
-NMe ₂ (6H)	singlet	δ2.20

* This spectrum was provided by Dr. N. A. Hughes and is included for comparison with that of the 5-iodo analogue (28).

Methyl-5-0-tosyl-2,3-0-isopropylidene- α -D-ribofuranoside

(48)

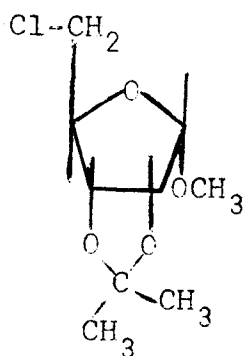


(48)

-OCH ₃ (3H)	singlet	δ3.35
>C(CH ₃) ₂ (6H)	doublet	δ1.20, δ1.38
CH ₃ -Ar (3H)	singlet	δ2.43
-CH ₂ -OTs -H ₄ } (3H)	singlet	δ4.05
H ₁ , H ₂ , H ₃	poorly resolved	δ4.45 - 4.80
Para X-C ₆ H ₄ -Y	a twin pair of doublets	δ7.25 and δ7.70

The assumption has been made that the combined signal at δ4.05 contains the H-4 absorption (rather than any from H-1, H-2, H-3). This is not unreasonable since in general the H-4 absorption in these compounds appears upfield of H-1, H-2 and H-3 absorptions.

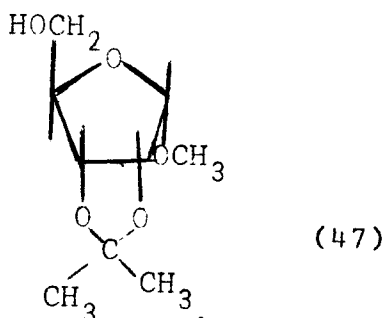
Methyl 5-chloro-5-deoxy-2,3-O-isopropylidene- α -D-ribofuranoside (49).



(49)

$-OCH_3$ (3H)	singlet	δ 3.35
$>C(CH_3)_2$ (6H)	doublet	δ 1.43, δ 1.28
H_1, H_2, H_3, H_4 , (4H)	unresolved	δ 4.1 to δ 4.8
$-CH_2Cl$ (2H)	doublet	δ 3.57

Methyl 2,3-O-isopropylidene- α -D-ribofuranoside (47)



(47)

$-CH_3$ (3H)	singlet	δ 3.40
$>C(CH_3)_2$ (6H)	doublet	δ 1.43, δ 1.27
H_1, H_2, H_3, H_4 (4H)	unresolved	δ 3.9, δ 4.8
$-CH_2-O-$	doublet	δ 3.67 to δ 3.7
HO-	broad approximately singlet	δ 2.2 to δ 3.20

The position of the HO-peak (in compound (47)) varies with the concentration of the sample. A range of $\delta 2.20 - \delta 3.20$ was observed in three different spectra. This peak vanishes after D_2O exchange.

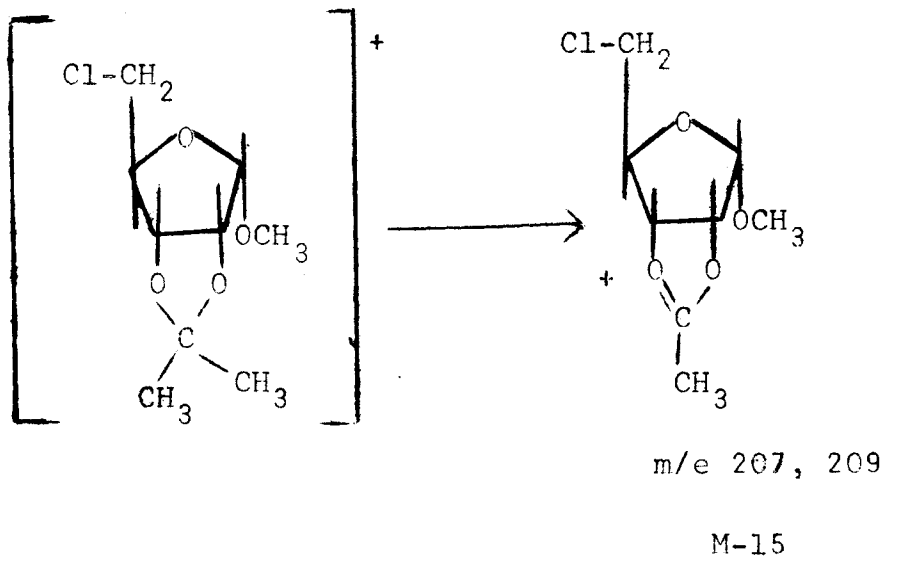
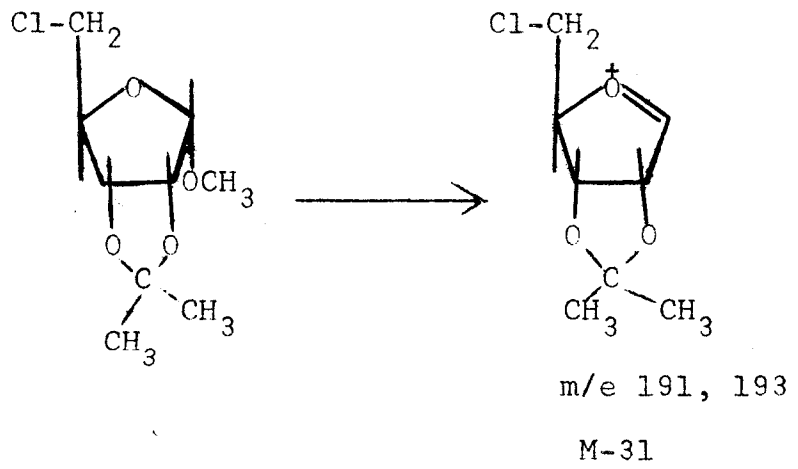
The spectra presented for α - and β -ribofuranosides which are of importance in the present study not only confirm the structures but also illustrate this means of differentiating the α - and β -series.

MASS SPECTRUM

Methyl-5-chloro-5-deoxy-2,3-O-isopropylidene- α -D-ribofuranoside (49).

There was no molecular ion observed. The peaks observed at m/e 191, 193 and m/e 207, 209 have been assigned as the M-31 and M-15 peaks respectively.

The observed doublet peaks at m/e 191, 193 and m/e 207, 209 are due to the characteristic isotope pattern of chlorine. Chlorine consists of two stable isotopes $^{35}_{17}Cl$ and $^{37}_{17}Cl$ in the ratio 3 to 1.



CONCLUDING REMARKS

From the results of this study it is clear that the sugar tosylates and halides investigated do not undergo the Kornblum reaction with dimethyl sulphoxide and sodium hydrogen carbonate to yield aldehydes. Under these reaction conditions, detosylation to yield the corresponding hydroxy sugar was the reaction most commonly observed. Where neighbouring alkoxy or hydroxyl groups are in a position to participate in ejection of a tosyloxy group or halide, rearranged products or anhydro sugars may also be produced. It is possible that no nucleophilic attack by dimethyl sulphoxide is occurring and it is functioning merely as a solvent. In the detosylation, hydrogen carbonate ions may be the effective nucleophile and it would be interesting to investigate the effect of sodium hydrogen carbonate in a non-nucleophilic solvent.

The reaction of methyl sulphanyl carbanion with sugar tosylates has not been fully investigated, but clearly base-induced elimination is predominant in the example studied and is likely to be an important feature with other sugar tosylates and halides.

EXPERIMENTAL

EXPERIMENTAL

General procedures

All evaporations of solvents were carried out in vacuo using a rotary evaporator (Buchi Rotavapor-R). Infrared spectra were obtained on infrared spectrometer UNICAM SP 200G. All melting points reported were taken on Gallenkamp melting point apparatus and the values are uncorrected.

Paper chromatography was performed on Whatman No. 1 paper using the descending front technique and the following solvents were used.

- A. n-butanol; ethanol:water 2:1:1
- B. n-butanol; acetic acid: water 4:1:1
- C. n-butanol; acetic acid: water 4:1:5

Compounds on paper chromatograms were detected with aniline phthalate. Silica gel (Merck Kieselgel 60 grade) was used for column chromatography; silica gel (Merck G grade) was used for thin-layer chromatography. Compounds on thin-layer chromatograms were detected with:

- (i) Iodine
- (ii) Anisaldehyde-sulphuric acid:
(This gives pink and dark spots with sugars after heating for a few minutes at 110^o- 115^oC).
- (iii) 1% diphenylamine in ethanol.
(under u.v. gives white spots with tosylates).

Methyl-5-O-tosyl-2,3-O-isopropylidene- β -D-ribofuranoside (27).

Methyl-5-O-tosyl-2,3-O-isopropylidene- β -D-ribofuranoside (27) was prepared using a method communicated by Dr. Neil Hughes.⁴² Ribose (10g) in dry methanol (50 ml) was treated with concentrated sulphuric acid (0.5 ml). After 1 hour at room temperature, acetone (250 ml) was added. The solution was left for a further one hour, and then neutralized with solid sodium carbonate, filtered and evaporated to dryness. The residue was partitioned between 5% sodium hydrogen carbonate (30 ml) and chloroform (3 x 40 ml). The chloroform extract was dried over anhydrous sodium sulphate, evaporated and benzene (100 ml) was added evaporated to azeotrope out water. The residue in pyridine (30 ml) was treated with p-toluene sulphonyl chloride (16 g) and left for 15 hours at 0° - 4°C, then water (2 ml) and charcoal (decolourising) added. After 2 hours the mixture was filtered and ice-cold water (90 ml) was added to the filtrate, and extracted with ether. The ethereal extracts were washed with 2N sulphuric acid. This was repeated until the washings were strongly acidic to litmus. Finally the extract was washed with dilute sodium hydrogen carbonate solution.

The extract was dried over anhydrous sodium sulphate, filtered and evaporated to a solid (14.44 g). Recrystallisation from isopropyl ether gave (9.26 g) mp $82^{\circ} - 84^{\circ}\text{C}$.⁴²

Attempted preparation of methyl 2,3-O-isopropylidene- β -D-ribosefuranoside (20).

Methyl 2,3-O-isopropylidene- β -D-ribofuranoside (19) (4 g) in dry dimethyl sulphoxide (12.5 ml) was added to a mixture of dimethyl sulphoxide (20 ml) in dry benzene (25 ml) and pyridine (1.6 ml) containing trifluoroacetic acid (0.16 ml). To a stirred solution was added dicyclohexyl carbodiimide (12.5 g) and stirring continued at 5°C for 2 hours. After 2 hours the mixture was left to stir at room temperature overnight. The mixture was then filtered and a solution of oxalic acid (10 g) in methanol (50 ml) was added to the filtrate in small portions with stirring. The resulting suspension was stirred at room temperature for 1 hour and then filtered. The filtrate was washed with saturated sodium hydrogen carbonate solution (3 x 50 ml). The aqueous layer was extracted with ethyl acetate (75 ml). The organic extracts were combined and dried over anhydrous sodium sulphate. Removal of the solvent afforded a syrup which was dissolved in a little acetone and the insoluble dicyclohexyl urea was removed by filtration.

Repetition of this treatment several times followed by removal of the solvent afforded a somewhat mobile syrup (1.26 g). The infrared spectrum of the syrup showed a strong carbonyl absorption at 1730 cm^{-1} but negligible absorption in the hydroxyl region. Thin-layer chromatography (in benzene-ether 2:1) revealed that it consisted of two sugar components in relatively same yields. Attempts to separate the two by column chromatography were unsuccessful.

The reaction on the above tosylate (27) with dimethyl sulphoxide (DMSO).

To a freshly prepared mixture of dimethyl sulphoxide (12 ml) and sodium hydrogen carbonate (1.6 g) under nitrogen and at $175^{\circ} - 180^{\circ}\text{C}$ was added the tosylate (27) (1 g). After 15 minutes at this temperature, the mixture was cooled and poured into cold water (50 ml) and extracted with ether (3 x 20 ml). The ethereal extracts were washed with water (2 x 20 ml) and dried over anhydrous sodium sulphate, filtered and evaporated to a syrup (0.29 g). Thin-layer chromatography (benzene-ether acetate 3:1) showed the presence of the starting material and a lower running compound.

The crude product was chromatographed on a column of silica gel (17 g) and the starting material (0.087 g) was eluted with benzene-ether 9:1. Further elution with benzene-ether 7:3 gave the product (0.102 g). Infrared spectrum of the product showed no carbonyl absorption at 1730 cm^{-1} but hydroxyl absorption at 3420 cm^{-1} . The product was identical (by infrared spectrum and thin-layer chromatography) to methyl 2,3-O-isopropylidene- β -D-ribofuranoside (19).

A portion of the product (20 mg) in 0.1N sulphuric acid (1 ml) was refluxed for 2 hours at 60°C and neutralized with sodium hydrogen carbonate. The hydrolysate was examined by paper chromatography. Only D-ribose could be detected (RFO. 35 in solvent A).

Methyl-5-iodo-deoxy-2,3-O-isopropylidene- β -D-ribofuranoside (28).

Methyl-5-O-tosyl-2,3-O-isopropylidene- β -D-ribofuranoside (27) (2.0 g) and anhydrous sodium iodide (1.666 g) in dry dimethyl formamide (17 ml) were held at $100^{\circ} - 105^{\circ}\text{C}$ for 3 hours. The solution was then poured into water (50 ml) and extracted with ether (3 x 50 ml), dried over anhydrous sodium sulphate and evaporated.

The residue was co-distilled with n-butanol (2 x 20 ml) and then petroleum ether (2 x 40 ml). This afforded a syrup (1.897 g). Thin-layer chromatography showed that this consisted of one major and three minor components. The major component had a slightly higher mobility (in benzene-ethyl-acetate 3:1) than the original tosylate (27). Chromatography on silica gel (100 g) gave the major component (1.8 g) eluted with benzene-ether (9:1). Thin-layer chromatography of the major component revealed the absence of a tosyl group (with reagent (iii)). Infrared spectrum confirmed the absence of the tosyl group. (no peaks at $1610 - 1550 \text{ cm}^{-1}$, 1180 cm^{-1} , and 1190 cm^{-1}).

The n.m.r. data (in carbon tetrachloride) for this product was consistent with the assignment of its structure as methyl 5-iodo-5-deoxy-2,3-O-isopropylidene- β -D-ribofuranoside (28). See page 44.

The reaction of the 5-iodo-5-deoxy derivative (28) with dimethyl sulphoxide (DMSO)

The 5-iodo-5-deoxy derivative (28) (2 g) was added to dimethyl sulphoxide (20 ml) and sodium hydrogen carbonate (3.64 g) at $175^{\circ} - 180^{\circ}\text{C}$ under nitrogen.

After 15 minutes at this temperature, the mixture was cooled and poured into cold water (30 ml) and extracted with chloroform (3 x 40 ml), evaporated and again poured into fresh cold water (30 ml) and then extracted with ether (3 x 40 ml). The ethereal extracts were dried over anhydrous sodium sulphate, filtered and evaporated to a syrup (1.44 g). Thin-layer chromatography (in benzene-ether (1:1)) showed that it consisted of two components, the starting 5-iodo-5-deoxy derivative (28) and a lower running compound. The syrup in benzene (4 ml) was transferred to a column of silica gel (75 g). Elution with benzene-ether (9:1) gave the starting 5-iodo-5-deoxy derivative (28) (0.7892 g) and further elution benzene-ether (2:1) gave the product (0.0564 g). The infrared spectrum of the product showed no carbonyl absorption around 1730 cm^{-1} but strong hydroxyl absorption at 3420 cm^{-1} .

Acid hydrolysis:- A portion of the syrup (37 mg) in 0.1N sulphuric acid (1 ml) was refluxed at 60°C for 2 hours and then neutralized with sodium hydrogen carbonate and paper chromatography in-butanol-ethanol-water (2:1:1) revealed the presence of two free sugars one of which was identified as D-ribose and the other was identified as 5-O-methyl ribose by chromatographic comparison with an authentic sample. (See overleaf) R.f.O. RF/Ribose = 1.4 in solvent A.

Methyl-2,3-O-isopropylidene-5-O-methyl-β-D-ribofuranoside (29) and 5-O-methyl-D-ribose (30)

Methyl 2,3-O-isopropylidene-β-D-ribofuranoside (19) (1.43 g) was stirred in acetone (20 ml) with crushed sodium hydroxide (1.1 g) and dimethyl sulphate (1.5 ml) was added. After heating for 6 hours under reflux, the solution was diluted with water and extracted with chloroform and from the extract a mobile syrup (1.59 g) was obtained. Thin-layer chromatography in benzene-ether (1:1) showed that no starting material remained. Infrared spectrum of the crude product showed no hydroxyl absorption at 3420 cm^{-1} .

Acid hydrolysis:- A portion of the crude product (40 mg) in 0.1N sulphuric acid (1 ml) was refluxed at 100°C for $2\frac{1}{2}$ hours and then neutralized with sodium hydrogen carbonate. Paper chromatography in solvent systems B and C revealed that it consisted of one running higher than D-ribose, with Rfs of 0.54 in solvent B and 0.55 in solvent C compared to Rf ribose of 0.36 in solvent B and 0.35 in solvent C. Rf/R ribose in solvent B was 1.50 and 1.61 in solvent C. This compound was identical by paper chromatography in solvent systems B and C with the 5-O-methyl-D-ribose obtained from

the reaction of the 5-iodo-5-deoxy derivative (28) with dimethyl sulphoxide in the presence of sodium hydrogen carbonate.

Methyl 2,3-O-isopropylidene- α - and β -D-ribofuranoside (19) and (47)

Methyl 2,3-O-isopropylidene- α and β -D-ribofuranoside (19) and (47) were prepared by a method communicated by Dr. Neil Hughes.⁴²

Ribose (10 g) in dry methanol (50 ml) was treated with concentrated sulphuric acid (0.5 ml). After 1 hour at room temperature, acetone (250 ml) and concentrated sulphuric acid (2.5 ml) were added and the solution was left at room temperature for a further 1 hour. The solution was neutralised with solid sodium carbonate, filtered and evaporated to dryness to a syrup (14 g). Thin-layer chromatography (in benzene-ether (1:1)) showed that it consisted of two compounds. The higher running compound was the β -compound while the lower one was the α -compound (47).

Isolation of the α -derivative (47)

The above α, β mixture was dissolved in chloroform (110 ml). Nine (500 ml) separating funnels containing water (110 ml) were set up in series and the chloroform

solution was shaken through all the nine funnels to emerge as chloroform solution number one. A second chloroform (110 ml) was passed through all the nine funnels and emerged as chloroform solution number two. This procedure was repeated with seven more portions of chloroform (110 ml) giving rise to nine portions of chloroform at the end. Finally each aqueous solution in nine funnels was saturated with sodium chloride and extracted with chloroform (3 x 30 ml), the combination of which gave chloroform solution number ten. Thin-layer chromatography (in benzene-ether (1:1)) showed that chloroform solution numbers six to ten contained pure α -derivative, chloroform solutions numbers one to three contained pure β -derivatives and chloroform solutions number four and number five contained a mixture of two. Chloroform solutions number six to ten were then combined and dried over anhydrous sodium sulphate, filtered and evaporated to a syrup (0.8108 g).

Methyl-5-O-tosyl-2,3-O-isopropylidene- α -D-ribofuranoside
(48).

Methyl 2,3-O-isopropylidene- α -D-ribofuranoside (47) (0.8108 g) in pyridine (8.11 ml) was treated with p-toluene sulphonyl chloride (1.2973 g) in pyridine (3 ml) at -10°C for 2 hours.

After 2 hours the solution was left to stir overnight at room temperature. Then 2 drops of water were added and stirring continued for 30 minutes. The solution was then poured into ice-cold water (30 ml) and extracted with chloroform (3 x 35 ml), then washed with 2N sulphuric acid until the washings were strongly acidic to litmus, then washed with saturated sodium hydrogen carbonate and finally with water. The chloroform extract was dried over anhydrous sodium sulphate and evaporated to a syrup (0.8711 g). Thin-layer chromatography (in benzene-ether (1:1)) revealed that it consisted of three components, and no starting material was present. The lower running one gave a positive response (fluorescent white spot) to the spray reagent, diphenylamine in ethanol, and was assumed to be the tosylate (48). The syrup in benzene (5 ml) was chromatographed on silica gel (45 g). Elution with benzene gave a non-carbohydrate material (0.0065 g). Further elution with benzene-ether (9:1) gave a compound which was identified as a 5-chloro sugar (49) (by mass spectroscopy and n.m.r. see page 47) and finally the 5-tosyl compound (48) (0.51 g). Infrared spectrum of the 5-chloro sugar (49) showed no hydroxyl absorption peaks at 3420 cm^{-1} and no tosyl absorption peaks $1610 - 1550\text{ cm}^{-1}$, 1180 cm^{-1} and

1190 cm^{-1} , n.m.r. and mass spectroscopic data is summarized on pages 47 and 49. The infrared spectrum of the 5-tosyl compound (48) showed no hydroxyl absorption at 3420 cm^{-1} but tosyl absorption peaks at 1610 - 1550 cm^{-1} . (n.m.r. and mass spectroscopic data. See pages 47 and 49).

Reaction of methyl-5-0-tosyl-2,3-0-isopropylidene
- α -D-ribofuranoside (48) with dimethyl sulphoxide
(DMSO).

Methyl-5-tosyl-2,3-0-isopropylidene- α -D-ribofuranoside (48) (0.8549 g) was added to dimethyl sulphoxide (7 ml) and sodium hydrogen carbonate (1.276 g) at 100^o - 105^oC under nitrogen. After 5 hours at this temperature, the mixture was cooled and poured into a saturated solution of sodium sulphate (20 ml), extracted with chloroform (3 x 15 ml) and then with ether (3 x 15 ml). The chloroform and ethereal extracts were dried over anhydrous sodium sulphate, filtered and evaporated to a product (2.912 g). Thin-layer chromatography of the product (in benzene-ether (1:1)) showed that it consisted of one major carbohydrate component, running much lower than the starting tosylate (48) and a negligible amount of tosylate (48). The product in benzene (4 ml) was transferred to a column of silica gel (100 g).

Elution with benzene-ether (9:1) gave the starting tosylate (48) (0.0098 g) and further elution with benzene-ether (1:1) gave the major carbohydrate component (0.2014 g). Finally elution with ether gave a non-carbohydrate compound which was identified as dimethyl sulphoxide (by thin-layer chromatography and infrared spectroscopy). The infrared spectrum of the major carbohydrate component showed no carbonyl absorption around 1730 cm^{-1} but a strong hydroxyl absorption at 3420 cm^{-1} , and also an absence of tosyl peaks at $1610\text{--}1550\text{ cm}^{-1}$, 1180 cm^{-1} and 1190 cm^{-1} . The product was found to be identical with methyl 2,3-O-isopropylidene- α -D-ribofuranoside (47) by comparison with an authentic sample prepared above (infrared spectrum and thin-layer chromatography). Nmr spectra confirmed structure (47).

1,2:3,5-Di-O-isopropylidene- α -D-xylofuranose (51)

1,2:3,5-Di-O-isopropylidene- α -D-xylofuranose (51) was prepared by the method of Baker and Schaub.⁵² To 667 ml reagent acetone were added 96% sulphuric acid (3.33 ml) and anhydrous copper sulphate (66.7 g) and then D-xylose (33.33 g). The mixture was stirred briskly (protected from moisture) for 25 hours at room temperature, then filtered. To combined filtrate and washings were made alkaline by rapid addition of 13N

ammonium hydroxide (4 ml). The filtered solution was evaporated to dryness, and the residue was distilled under reduced pressure (0.12 mm Hg) to a colourless oil (37.621 g). Thin-layer chromatography (in benzene-ethyl acetate)(3:1) showed that it consisted of one compound only.

1,2-O-isopropylidene- α -D-xylofuranose (52)

The above 1,2:3,5-Di-O-isopropylidene- α -D-xylofuranose (51) (2.049 g) was warmed until molten, then cooled to room temperature to a syrup. Then 2% hydrochloric acid (11 ml) was added and the mixture was shaken for 25 minutes. When about half the syrup had dissolved the remainder crystallized. The solution was filtered from unreacted starting material, then neutralized with sodium hydrogen carbonate to PH 7-8. The unreacted starting material was treated as above. The combined neutralized solutions were evaporated to dryness in vacuo. The residue was dissolved in chloroform (8 ml). The solution, filtered from inorganic salts and dried over magnesium sulphate, was evaporated to dryness in vacuo leaving (1.068 g) of 1,2-O-isopropylidene- α -D-xylofuranose (52) as a viscous oil. Thin-layer chromatography (in benzene-ethylacetate (3:1)) revealed the presence of a trace of the starting material.

1,2-O-isopropylidene-5-O-tosylsulphonyl- α -D-xylofuranose
(24).

1,2-O-isopropylidene- α -D-xylofuranose (1.1 g) in anhydrous pyridine (5.2 ml) was stirred and cooled to 0°C. With stirring a cold solution of p-toluene sulphonyl chloride (1.11 g) in dichloromethane (5 ml) was added dropwise with exclusion of atmospheric moisture, and in such a way that the temperature did not exceed 0°C. On completion of addition, stirring was continued at 0°C for a further 1 hour. The solution was then left to stir at room temperature overnight. Two drops of water were added and stirring continued for 30 minutes. The solution was then diluted with water and extracted with chloroform. The chloroform extract was washed with 2N sulphuric acid until the washings were strongly acidic to litmus and then washed with a saturated solution of sodium hydrogen carbonate, dried over anhydrous sodium sulphate, filtered and evaporated to a syrup which crystallized immediately on addition of ether. Double recrystallization gave a white crystalline compound (0.3077 g), mp. 132° - 133°C, lit.⁶² mp. 133° - 134°C.

The reaction of the 5-tosylate-xylofuranose derivative (24) with dimethyl sulphoxide

To a freshly prepared mixture of dimethyl sulphoxide (15 ml) and sodium hydrogen carbonate (1.527 g) under nitrogen at 175° - 180°C was added 1,2-0-isopropylidene-5-0-tosyl- α -D-xylofuranose (24) (0.9 g). After 15 minutes at this temperature, the reaction mixture was cooled and poured into cold water (30 ml) and extracted with chloroform (3 x 20 ml). The chloroform extract was dried with anhydrous sodium sulphate, filtered and evaporated to a syrup (1.2634 g).

Thin-layer chromatography (in benzene-ether 1:1) revealed that it consisted of one major sugar component and a minor amount of starting material. The major component was running slightly higher than the starting material. The syrup in benzene (3 ml) was chromatographed on silica gel (25 g). Elution with benzene gave the major component (0.7 g). The infrared spectrum showed no carbonyl absorption and no hydroxyl absorption, and also an absence of tosyl peaks at 1610 - 1550 cm^{-1} and 1190 cm^{-1} . The product was found to be 3:5-anhydro-1,2-0-isopropylidene- α -D-xylofuranose (54) by comparison with an authentic sample (infrared spectrum and thin-layer chromatography).

3:5-anhydro-1,2-O-isopropylidene- α -D-xylofuranose (54)

3:5-anhydro-1,2-O-isopropylidene- α -D-xylofuranose (54) was prepared by the method of Whistler, Luttenegger and Rowell.⁵⁹

Crystalline 1,2-O-isopropylidene-5-O-tosyl- α -D-xylofuranose (24) (1 g) was dissolved in absolute alcohol. (2.5 ml) and freshly prepared sodium methoxide was added. The solution was refluxed for 15 minutes. Sodium toluene sulphonate started precipitating after 5 minutes. The complete reaction mixture was concentrated to dryness under reduced pressure and the solid residue was extracted with 20 ml each of chloroform and water. The chloroform solution was washed twice with water, dried over anhydrous sodium sulphate, and evaporated to a syrup (0.37 g). Thin-layer chromatography (in benzene-ether (1:1)) showed the presence of a trace of the starting material. The syrup was chromatographed on silica gel (25 g). Elution with benzene-ether (9:1) gave (0.2428 g) of the product. Infrared spectrum of the product showed no hydroxyl absorption at 3420 cm^{-1} and no tosyl bands at $1610 - 1550\text{ cm}^{-1}$, 1180 cm^{-1} and 1190 cm^{-1} .

Reaction of methyl-5-O-tosyl-2,3-O-isopropylidene- β -D-ribofuranoside (27) with methyl sulphanyl carbanion

Preparation of methyl sulphanyl carbanion (DMSO⁻)

Sodium hydride in dispersion oil (0.2 g) was washed with petroleum ether (3 x 5 ml) by swirling and allowing the hydride to settle and decanting the liquid portion in order to remove the oil. Traces of petroleum ether were removed by suction. Under nitrogen and with the exclusion of atmospheric moisture dimethyl sulphoxide (3 ml) was added. The reaction mixture was heated to 70^o - 80^oC for 45 minutes. A somewhat cloudy pale yellow grey product was obtained.

Reaction with methyl-5-O-tosyl-2,3-O-isopropylidene- β -D-ribofuranoside (27)

The tosylate (27) (1 g) in tetrahydrofuran (3 ml) was added during 3 minutes to a cool (25^oC) solution of methyl sulphanyl carbanion, and the reaction was left stirring under nitrogen at room temperature over the week-end. The reaction mixture was then poured into water and extracted with chloroform. The chloroform extracts were washed with 2 lots of water and dried over anhydrous sodium sulphate, filtered and evaporated to a pale yellow mobile syrup (0.5637 g).

Thin-layer chromatography (in benzene) showed that it consisted of the starting 5-tosyl compound (27) and a higher running compound. The product was chromatographed on silica gel (25 g). Elution with benzene-ether (9:1) gave the product (0.2587 g). Further elution with benzene-ether 7:3 gave starting material (27) (0.2910 g).

Infrared spectrum of the higher running compound showed a strong absorption at 1665 cm^{-1} which suggests structure (59). Comparison with the sample prepared below showed that the compounds were identical.

Reaction of methyl 2,3-O-isopropylidene-5-O-tosyl- β -D-ribofuranoside (27) with potassium tertiary-butoxide

To tertiary butanol (3.2 ml) under nitrogen was added potassium metal (0.12 g). The mixture was refluxed until all the potassium dissolved. To this solution was added methyl 2,3-O-isopropylidene-5-O-tosyl-ribofuranoside (27) (1 g) in dimethyl sulphoxide (7.6 ml) and the reaction was left to stir at $75^{\circ} - 80^{\circ}\text{C}$ for 22 hours. After 22 hours the mixture was cooled and poured into water (30 ml) and extracted with ether (3 x 20 ml). The ethereal extracts were dried over anhydrous sodium sulphate, filtered and evaporated to a syrup (0.4423 g). Thin-layer chromatography showed that it consisted of one compound. This compound had no tosyl bands at $1610 - 1550\text{ cm}^{-1}$ and 1190 cm^{-1} but had a strong olefinic band at 1665 cm^{-1} .

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