A thesis entitled

"STUDIES IN THE THIO-SUGAR FIELD"

submitted by

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ABSTRACT

The literature on thio-sugars, 3,6-anhydro sugars, and nucleophilic displacement reactions of sulphonate esters has been reviewed critically. The following original contributions are presented:

The 1,2:5,6-di-O-isopropylidene-3-thiohexose, described by Freudenberg, has been converted, in several steps, into a 3,6-dideoxy-3,6-epithio-D-glucose derivative, and therefore has the D-gluco configuration. The same 3,6-epithio-compound has also been synthesised from a 6-thio-allose derivative by intramolecular displacement of a tosyl group at C-3 by the thiol anion at C-6.

Methyl 3,6-dideoxy-3,6-epithio-β-D-glucopyranoside has been synthesised by an intramolecular nucleophilic displacement reaction on a 6-thio-3-O-tosyl allopyranoside derivative, and (in contrast to the known 3,6-anhydro analogue) has been shown not to undergo the isomerisation into the furanoside form.

The kinetics of the nucleophilic displacement reactions, using potassium thiolbenzoate in N,N-dimethylformamide, on the 1,2:5,6-di-O-isopropylidene-3-O-tosyl derivatives of galactose, glucose, allose, and gulose, have been determined under pseudo first-order conditions. The relative rates of reaction have been shown to be 1 : 3 : 15 : 59 respectively.

The anomalously slow rate of reaction of 4,6-O-ethylidene-1,2-O-isopropylidene-3-O-tosyl-α-D-galactopyranose with potassium thiolbenzoate in DMF has been explained in terms of the unfavourable conformation of the molecule which inhibits nucleophilic attack by the thiolbenzoate anion. N.m.r. spectroscopy has been used to confirm structures, assign conformations, and to measure the rates of the displacement reactions.

To Hilary

ACKNOWLEDGEMENTS

I would like to take this opportunity of expressing my grateful thanks to my supervisor, Professor L.N. Owen, for his help and guidance given throughout the course of this work.

My thanks are also due to Professor D.H.R. Barton, F.R.S. for the privilege and opportunity of working in his department, and to the Imperial College for the generous gift of a research assistantship for the past three years.

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INTRODUCTORY

REVIEW

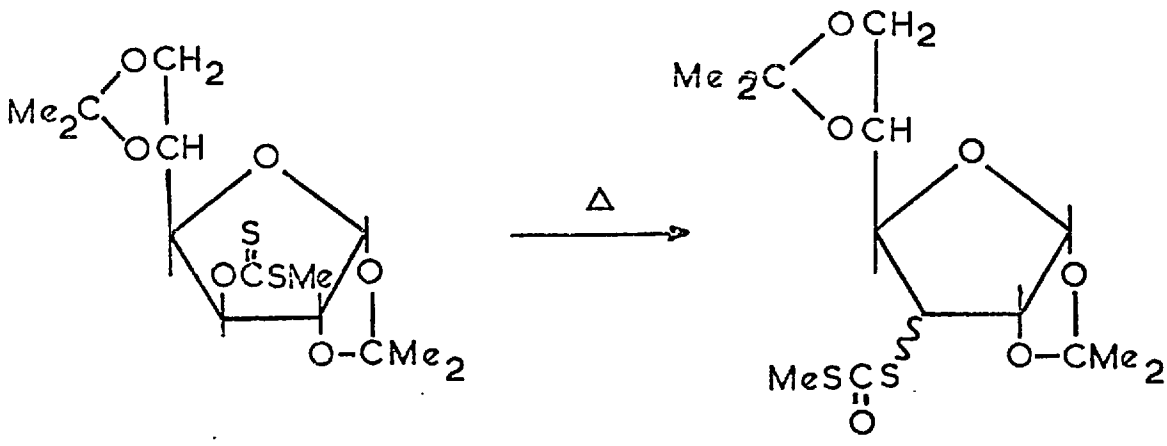
THIO-SUGARS

Thio-sugars have been reviewed by several authors[1,2,3,4]. These compounds have found important applications in the synthesis of deoxy sugars, and their biological action when incorporated into drugs, and other biologically important molecules is of potential interest. Nearly all naturally occurring thio-sugars are thioglycosides, but these are excluded from the present review which will deal with aldoses having one or more oxygen atoms (other than at the anomeric position) replaced by sulphur.

The general methods available for the synthesis of thio-sugars can be summarised as:-

1. Pyrolysis of xanthates,
2. Opening of anhydro rings with thionucleophiles,
3. Conversion of anhydro-sugars into episulphides, and the opening of episulphide rings,
4. Use of photochemical procedures, and
5. Nucleophilic displacement of sulphonate esters.

1. The most documented archetype of this synthetic approach was discovered by accident[5]. Pyrolysis of the 3-*S*-methyl xanthate (1) derived from di-*O*-isopropylidene glucose yielded a 3-thio rearranged product (2).



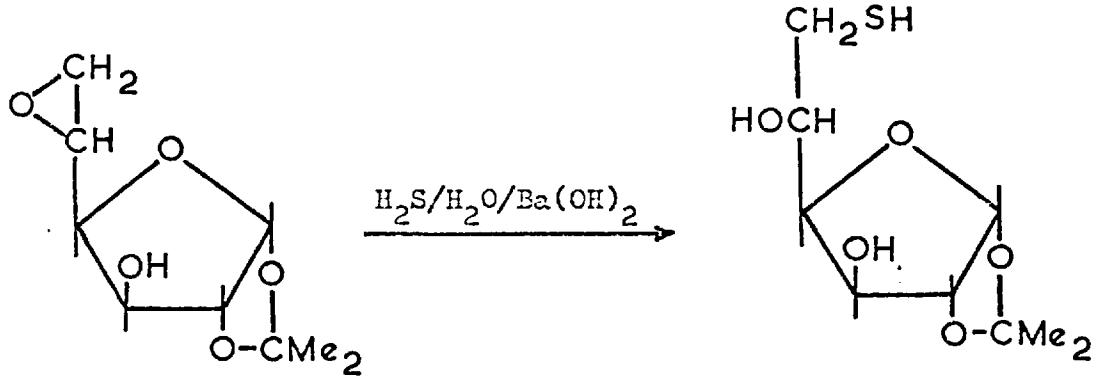
(1) (2)

Several other S- methyl xanthates have been prepared[6] and a thermal rearrangement has been reported in the arabinose series[7]. Neither the original workers[5], nor some later workers[8] were able to determine the absolute configuration about C-3 in compound (2). This question was settled using n.m.r. techniques by Horton[9], and the present research, which was in progress at the time, has corroborated this result by both spectroscopic and chemical evidence.

2. By the reaction of a variety of thio-nucleophiles on an epoxide, the following thio-sugars have been prepared: 6-thio-D-glucose[10], 5-thio-L-idose[11], 3-thio-D-altrose[12], 3-thio-D-xylose[13], 3-thio-D-arabinose[14], 2-thio-D-xylose[14], and 2-thio-D-altrose[15].

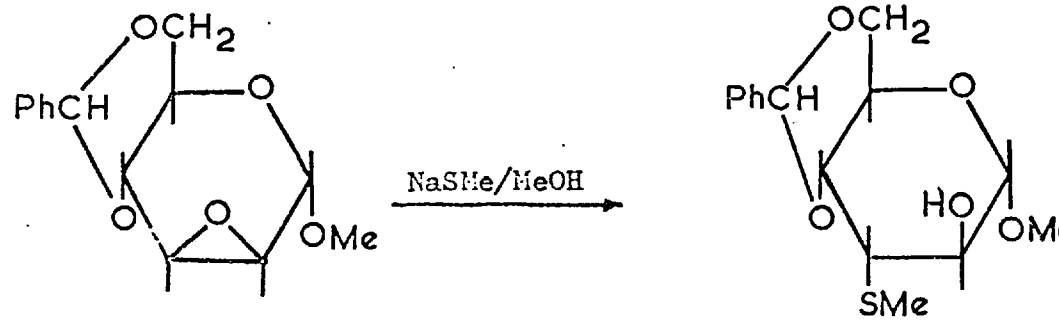
As would be expected, 5,6-anhydro sugars undergo ring opening at the primary position in the anhydro-ring to afford the 6-thio derivatives[10,11]. For example, treatment of 5,6-

anhydro-1,2-O-isopropylidene-α-D-glucofuranose (3) with hydrogen sulphide in mild base yields the 6-thiol (4)[10].



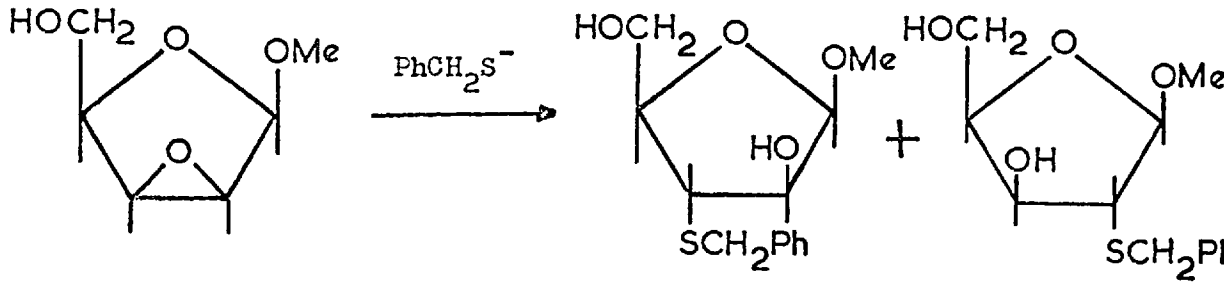
(3) (4)

Endocyclic anhydro rings in pyranose sugars often react with thio-nucleophiles to give mixtures, but in a conformationally rigid system the product is that which would be predicted from diaxial opening of the anhydro-ring[12,13,15]. For example, the conformationally very stable methyl 2,3-anhydro-4,6-O-benzylidene -α-D-mannopyranoside (5) is converted solely into the 3-thio altrose derivative (6)[12].



(5) (6)

Mixtures are usually formed in furanose systems. Thus methyl 2,3-anhydro-β-D-lyxofuranoside (7) on treatment with benzylmercaptide ions gives 3-thio-D-arabino (8), and 2-thio-D-xylo (9) derivatives in the ratio 2:3[14].



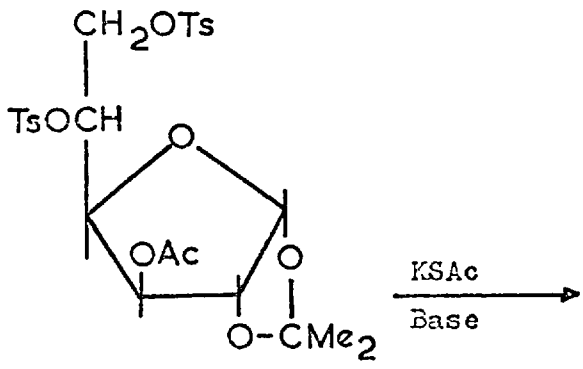
(7) (8) (9)

A molecular model of the anhydro sugar (7) shows that the anhydro -ring forces the furanose ring into a conformation approaching planarity, and in fact the anhydro-ring is almost sterically symmetrical for nucleophilic attack.

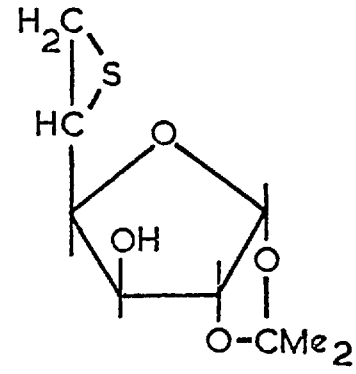
3. Sugar episulphides can be synthesised by several routes. Displacement of the primary tosylate group with thiolacetate in the D-glucose derivative (10), and treatment with base yields the L-idose derivative (11)[16].

Treatment of an anhydro sugar with thiourea yields an epithio sugar with inversion of configuration[16,17,18,19].

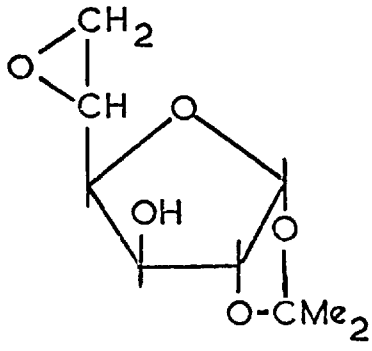
When the 5,6-anhydro-D-glucose (12) and 5,6-anhydro-L-idose (13) derivatives are reacted with thiourea, the corresponding L-ido (14) and D-gluco (15) compounds are formed[17,18,19].



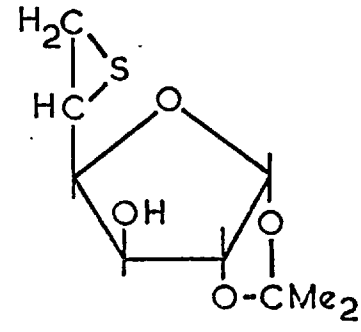
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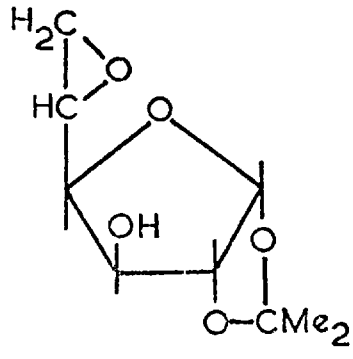
(11)



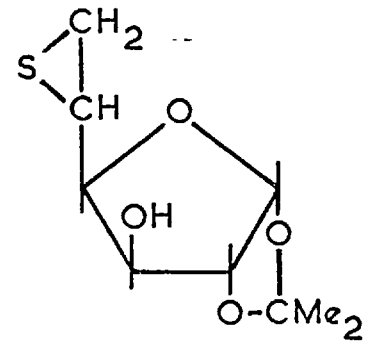
(12)



(14)

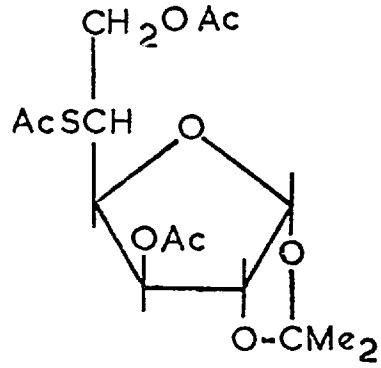


(13)



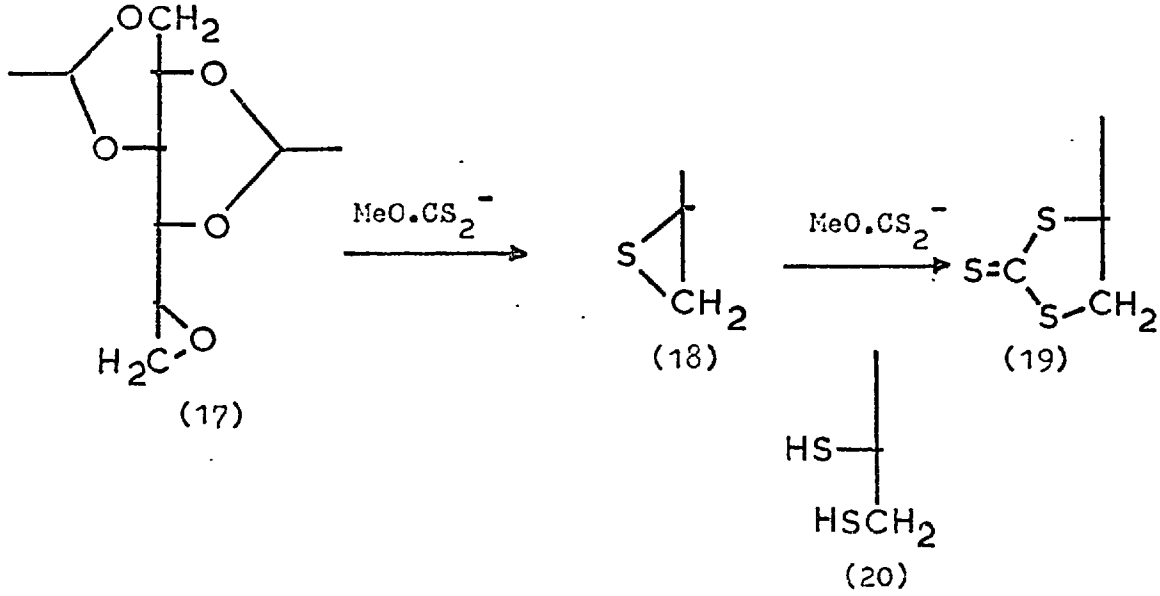
(15)

Ring opening of such episulphides usually occurs by nucleophilic attack at the primary position; thus compound (15) undergoes ring opening with acetic acid / acetic anhydride to give the useful 5-thio-sugar (16)[18,19].



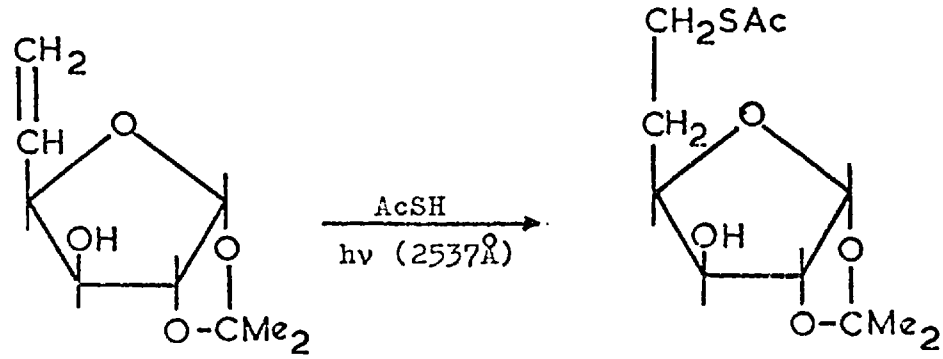
(16)

Creighton and Owen[16] also showed the reaction of anhydro sugars with xanthates gives inverted trithiocarbonates. Reduction of such trithiocarbonates is a useful synthetic route to vicinal dithiols[20], the configuration of the reduced product being unequivocal for a terminal trithiocarbonate.



(17) (18) (19) (20)

4. Little work on the photochemical approach has appeared in the literature, and the method appears to be of rather limited scope. However a good example was described by Horton and Turner[21]. Thiolacetic acid was found to add, in an anti-Markownikoff fashion, to the unsaturated compound (21) to give the 6-S-acetyl-5-deoxy derivative (22).



(21) (22)

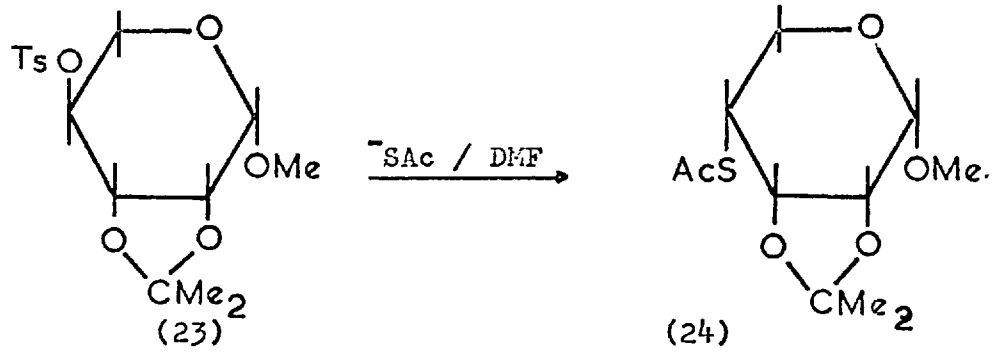
5. Nucleophilic displacement of sulphonate esters provides a very convenient synthetical route to thio-sugars. To date the literature has described the syntheses of 4-,5-, and 6-thio sugars by this method.

a) 4-Thio-sugars

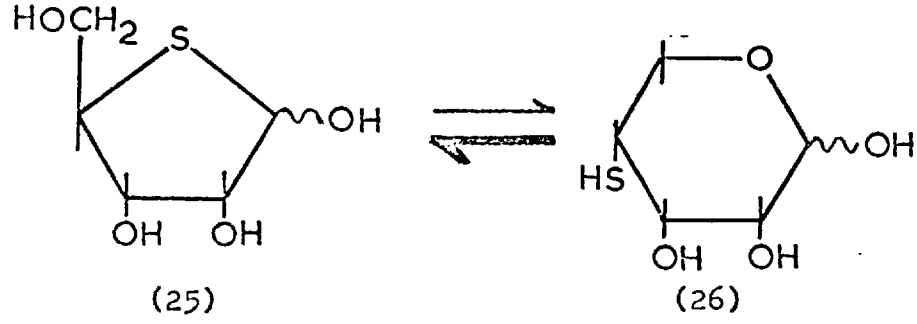
Using the anionic thionucleophiles, thiolbenzoate and thiolacetate, 4-thio-L-ribose[22] and 4-thio-D-ribose[23,24] have been prepared. For example, displacement of the tosyl group in methyl 2,3-O-isopropylidene-4-O-toluene-p-sulphonyl-β-L-lyxopyranoside (23) with thiolacetate occurs with inversion to give the 4-thio-D-ribose derivative (24)[24].

As a general rule, displacement of secondary tosylates,

without neighbouring group participation, occurs with inversion of configuration, and thus stereospecific syntheses can be achieved.



An interesting phenomenon observed[22,23,24] with these 4-thio sugars was that the free sugars existed in a labile equilibrium between the S-thiofuranose, and the O-pyranose forms; for example (25) ⇌ (26).

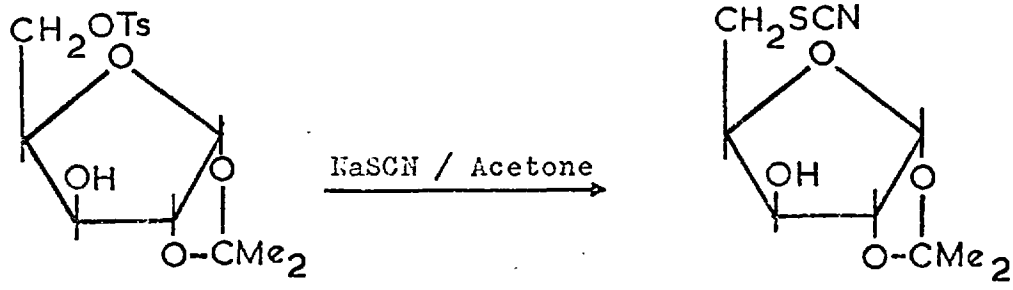


The equilibrium favoured the thiofuranose form (25)[22,23].

b) 5-Thio-sugars

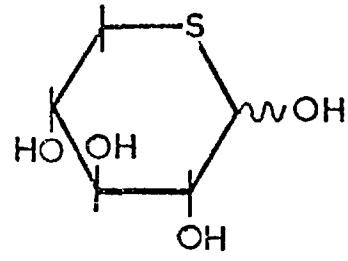
The first sugars in which the hemiacetal ring oxygen was replaced by sulphur were 5-thio sugars[25,26,27]. Displacement of the primary tosylate by thiocyanate in the D-xylofuranose

compound (27) gave the 5-thio derivative (28)[25].



(27) (28)

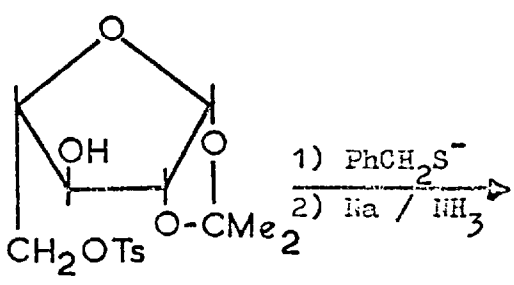
Mild alkaline hydrolysis of (28) followed by treatment with acid gave the 5-thiopyranose (29)



(29)

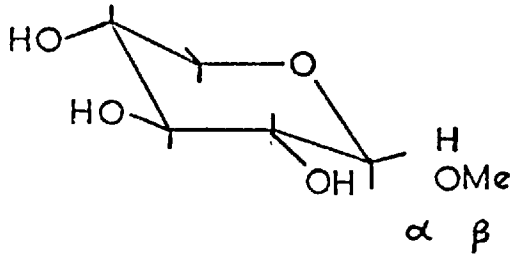
Subsequent papers[28,29] reported the same compound, and analogous thiopyranoses based on other aldopentoses[30,31,32]. Thus treatment of the 5-tosyl-L-arabinose compound (30) with benzylmercaptide ion, followed by removal of the benzyl group with sodium in liquid ammonia gave the 5-thio-L-arabinose derivative (31)[32]. Acid-catalysed methanolysis of the thiol (31) gave an anomeric mixture of the methyl thiopyranosides; there being no evidence for furanoside formation. There is overwhelming

experimental support for saying that free 5-thio sugars exist in the 5-S-thiopyranose ring form[25-32].

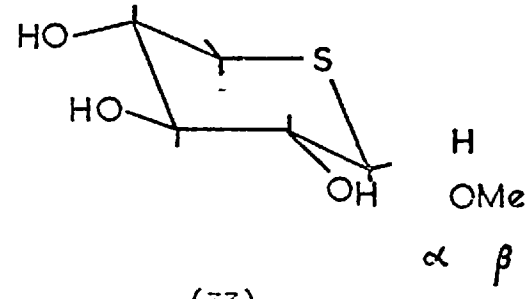


(30) (31)

Using the original theoretical work of Reeves[33], the ring conformations of methyl α- and β-xylopyranosides (32) and the analogous thiopyranosides (33) were studied by Whistler and co-workers[34].



(32)

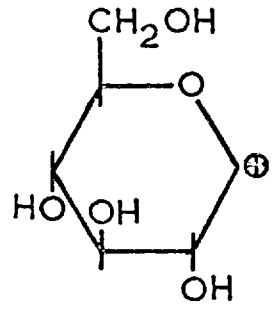


(33)

N.m.r. spectra showed that the ring conformation was not altered appreciably by replacement of oxygen with sulphur, and also that (32) and (33) both existed in the C1 conformation shown.

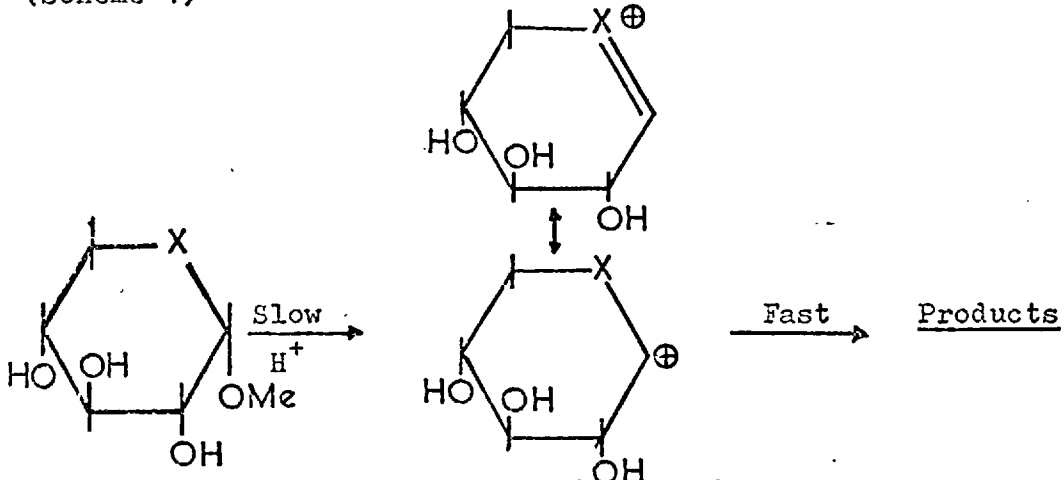
The 5-thioxylopyranose system [e.g. (33)] has been a most useful theoretical model for studies on the acid-catalysed hydrolysis of glycosides[35,36,37]. Previous workers[38,39] had

postulated mechanisms for glycosidic hydrolysis consistent with the intermediacy of a cyclic carbonium ion (34)



(34)

The kinetics investigations[35-37] carried out on the xylose derivatives (32) and (33) were consistently in accord with the intermediacy of a cyclic carbonium ion in the mechanism (scheme 1)

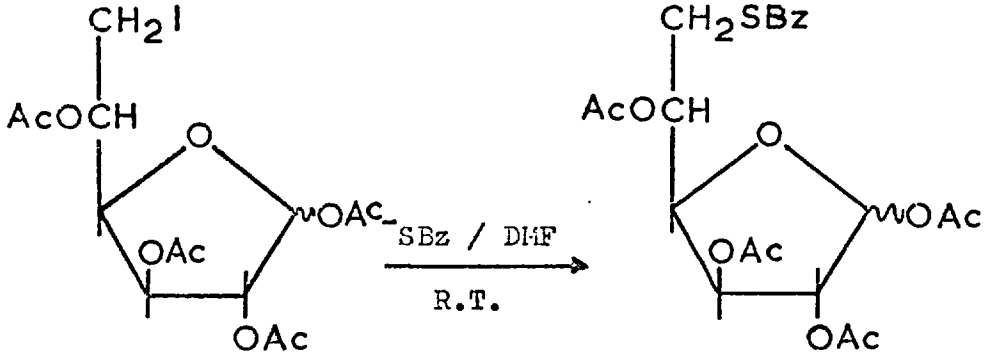


Scheme 1 X=O, or S.

c) 6-Thio-sugars

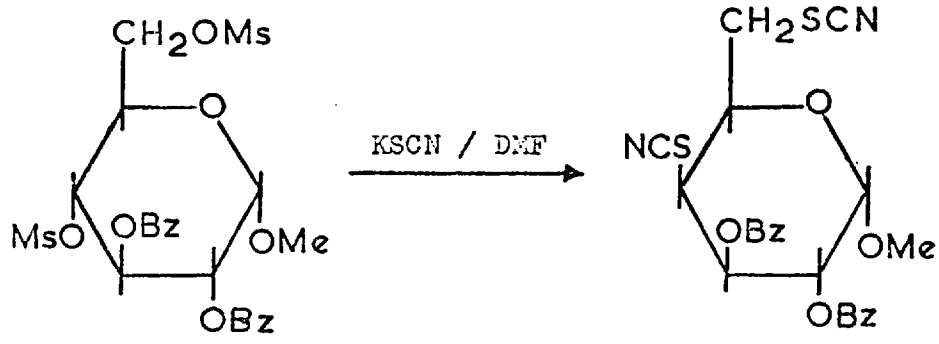
6-Thio-sugars are easily synthesised as the quite facile displacement of primary sulphonates and halides is the step in which sulphur is introduced into the sugar molecule.

Thionucleophilic displacements at C-6 are equally as favourable in furanose compounds[40,41,42], as in pyranose derivatives[43,44], and open-chain molecules[45]. The excellent nucleophilic properties of thiolbenzoate ions in DMF were well illustrated by Kocourek and co-workers[41], who were able to displace the 6-iodide in the glucose compound (35) at room temperature. The yield of the 6-thio derivative (36) was 65%.



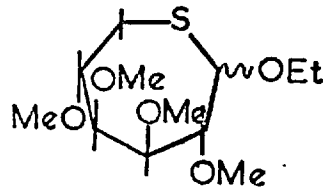
(35) (36)

A 4,6-dithio-D-galactose compound (38) has recently been synthesised[44] by direct S_N2 displacement of the glucose 4,6-dimesylate (37) with thiocyanate, and a 4,6-dithio-D-glucose derivative has been prepared[45].



(37) (38)

It has been shown[46] that a free 6-thio-aldohexose exists in the pyranose ring form with no detectable thioseptanose form being present. The thioseptanose (39) was prepared however, only after blocking positions 4 and 5 in the sugar. Thus thioseptanoses are thermodynamically less stable than 5-O-pyranose sugars.



(39)

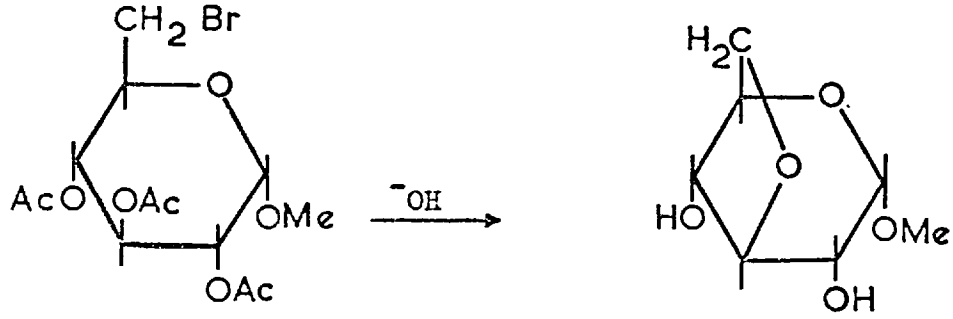
3,6-ANHYDRO SUGARS

Introduction:

Most of the literature on 3,6-anhydro sugars has been concerned with derivatives of D-glucose and D-galactose. Apart from aldehydo-forms, all the derivatives described have a common characteristic, namely that they exist in either a cis-fused [5,6]-bicyclic ring form (pyranose sugar), or a cis-fused[5,5]-bicyclic ring form (furanose sugar). Thus there is no record, for example, of 3,6-anhydro-D-allose, which in a furanose or pyranose form would contain a trans-fused bicyclic system.

[5,6]-Bicyclic systems:

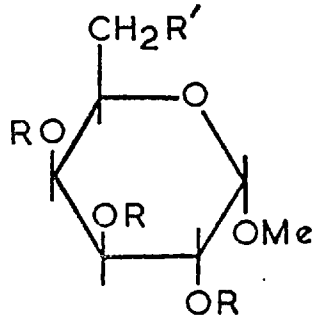
All the preparations of 3,6-anhydro-pyranose sugars involve the intramolecular nucleophilic displacement of good leaving-groups such as tosylate and halide. Methyl 3,6-anhydro-α-D-glucopyranoside was prepared by Fischer and Zach[47]. Treatment of methyl 2,3,4-tri-O-acetyl-6-bromo-6-deoxy-α-D-glucopyranoside (40) with base yielded methyl 3,6-anhydro-α-D-glucopyranoside (41)



(40) (41)

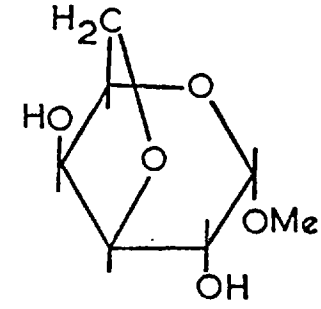
Although (41) was hydrolysed in aqueous acid to the free sugar, the latter was not characterised thoroughly.

Methyl 3,6-anhydro-α-D-galactopyranoside and methyl 3,6-anhydro-α-D-mannopyranoside have been prepared, by exactly similar procedures, by Valentin[48,49]. For example, in the galactose series, methyl α-D-galactopyranoside (42) was selectively tritylated at position 6, and then acetylated to yield (43). Treatment of (43) with phosphorus tribromide gave the 6-bromo compound (44) which on treatment with barium hydroxide gave the 3,6-anhydro derivative (45).



	R	R'
(42)	H	OH
(43)	Ac	OTrityl
(44)	Ac	Br

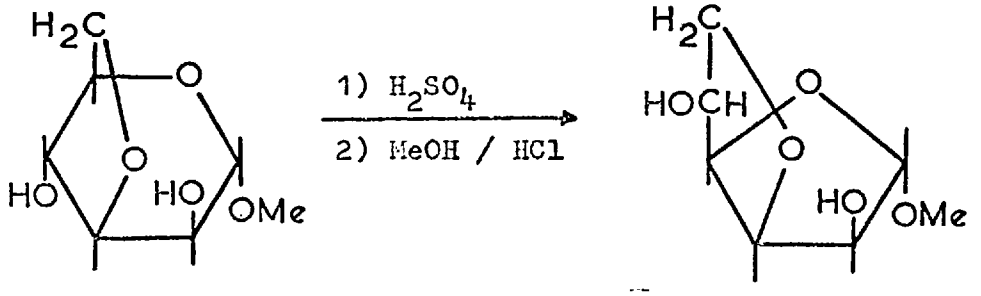
$\xrightarrow{Ba(OH)_2}$



(45)

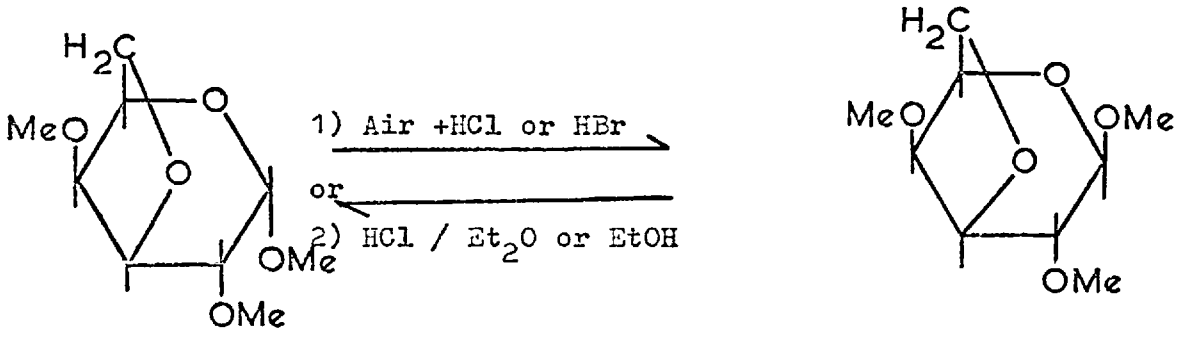
Another method of preparing methyl 3,6-anhydro-α-D-galactopyranoside (45) was described by Ohle[50] who treated methyl 6-C-toluene-p-sulphonyl-α-D-galactopyranoside with base.

Valentin in 1932[48] made the important discovery that the 3,6-anhydro bridge had profound effects on the chemistry of 3,6-anhydro sugars. Both Valentin[48] and Ohle[50] noted that the 3,6-anhydro ring was stable to acid, and that the 3,6-anhydro ring weakened the pyranose ring to such an extent that the compounds gave positive tests with Schiff's reagent, and exhibited mutarotation. A further very interesting observation was made by Valentin[49] who showed that methyl 3,6-anhydro-α-D-mannopyranoside (46) could be converted into methyl 3,6-anhydro-α-D-mannofuranoside (47) *via* acid catalysed hydrolysis, and acid catalysed methanolysis.



(46) (47)

The properties of 3,6-anhydro-D-galactose, and 3,6-anhydro-D-glucose were carefully studied by Haworth and his co-workers[51,52]. Haworth[51] found that methyl 3,6-anhydro-2,4-di-O-methyl-α-D-galactopyranoside (48) could be anomerised, with great facility, into the β-form (49), and vice versa, using a trace of acid as a catalyst.

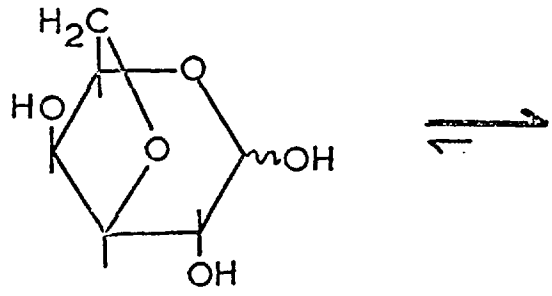


(48) (49)

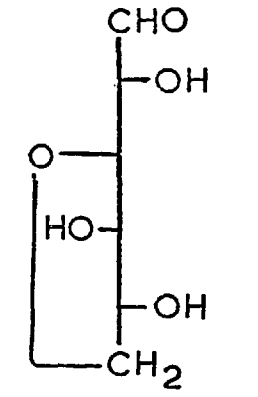
As this transformation could be performed in the absence of methanol, there could be no intermediate free sugar, though it was found that in methanol solution both the α- and β-anomers could be converted into the dimethyl acetals. This clearly indicates that the 3,6-anhydro bridge governs the chemical properties of the sugar pyranose ring. The isomerisation was later discussed by Foster et. al.[54] in conformational terms. Haworth[51] also confirmed that free 3,6-anhydro sugars restored the colour to Schiff's reagent, and caused an immediate decolourisation of neutral aqueous potassium permanganate solution, and on this basis postulated that these 3,6-anhydro sugars existed not in the hemiacetal form (50), but rather in the open-chain aldehydic form (51).

An even more interesting result was described by Haworth and his co-workers[52] who showed that methyl 3,6-anhydro-α- and β-D-glucopyranosides (52) underwent instantaneous conversion into the α- and β-D-glucofuranosides (53) without any isom-

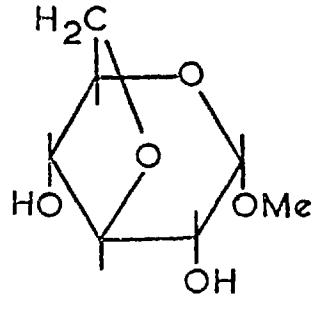
erisation at C-1.



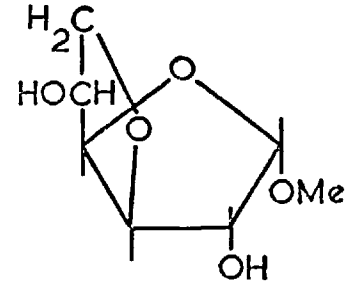
(50)



(51)



α-series



(52) (53)

This isomerisation was effected by a solution of hydrogen chloride in ether and chloroform, or by using methanolic acid. Haworth and his co-workers[52] rationalised these observations in terms of strain in the 1,5 pyranose ring, caused by the 3,6-anhydro bridge. They pointed out that the [5,6] -bicyclic system was more strained than the [5,5]-bicyclic system. Thus the interconversion of pyranoside to furanoside has its driving force in the relief of ring strain in the pyranose

form of the 3,6-anhydro sugar. Stacey and co-workers[53] supported the conclusions of Haworth, and showed that the pyranoside - furanoside interconversion was equally facile in the 2-deoxyglucose series. In summary, the properties of 3,6-anhydro pyranose sugars of special interest are as follows:

1. The α- and β- forms of methyl 3,6-anhydro-D-pyranosides are almost instantaneously interconvertable in the presence of a trace of an acid catalyst.

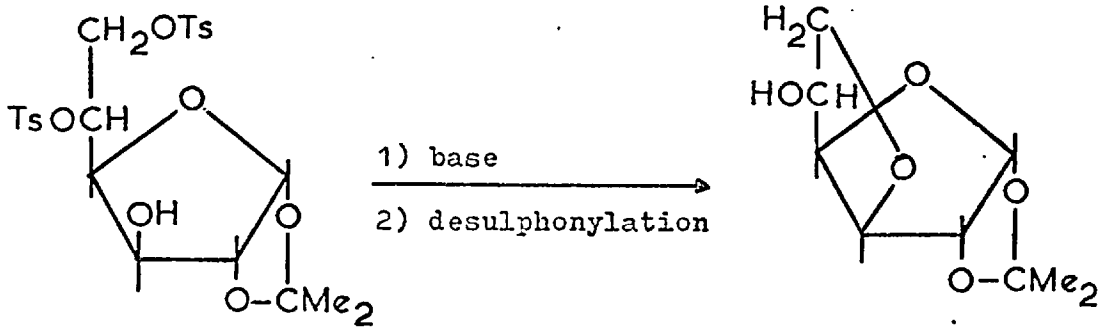
2. The α- and β- forms of methyl 3,6-anhydro-D-glucopyranosides can be converted into the methyl 3,6-anhydro-D-glucofuranosides without any anomerisation. The analogous derivatives of D-galactose do not undergo this isomerisation on steric grounds, as galactose has the "wrong" configuration at C-4, and consequently the furanose form would contain the highly strained trans-[5,5]-bicyclic system.

3. The α- and β- forms of methyl 3,6-anhydro-D-galactopyranosides can be transformed into the open-chain 3,6-anhydro-dimethyl acetals. There is some experimental support for describing the free sugars having a 3,6-anhydro bridge as being in the open-chain aldehydic form.

4. The 3,6-anhydro ether bridge is much more stable than the hemiacetal ring. The 3,6-anhydro bridge will withstand hot strong acid, whereas the glycosidic group is exceptionally acid-labile.

[5,5]-Bicyclic systems:

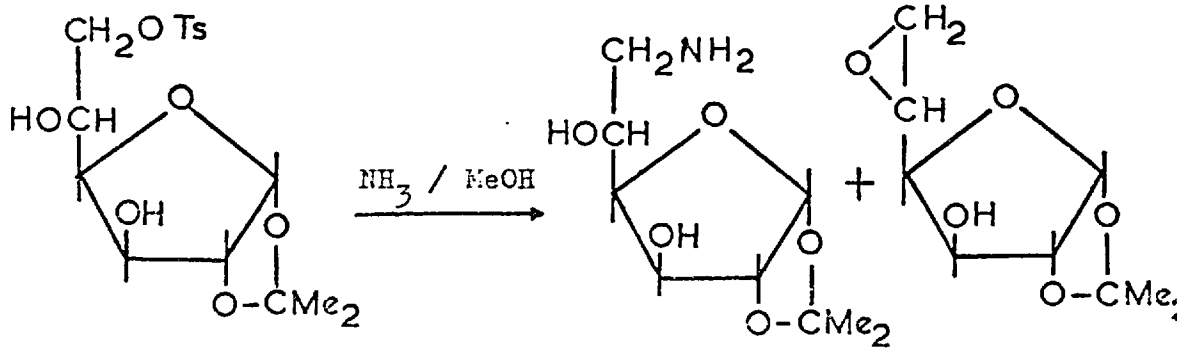
A great deal of the early work on 3,6-anhydro-furanose sugars was done by Ohle and his school, who prepared 3,6-anhydro -1,2-O-isopropylidene-α-D-glucofuranose (55) by treatment of 1,2-O-isopropylidene-5,6-di-O-toluene-p-sulphonyl-α-D-glucofuranose (54) with base[55].



Ts = p-CH_3.$C_6H_4SO_2$

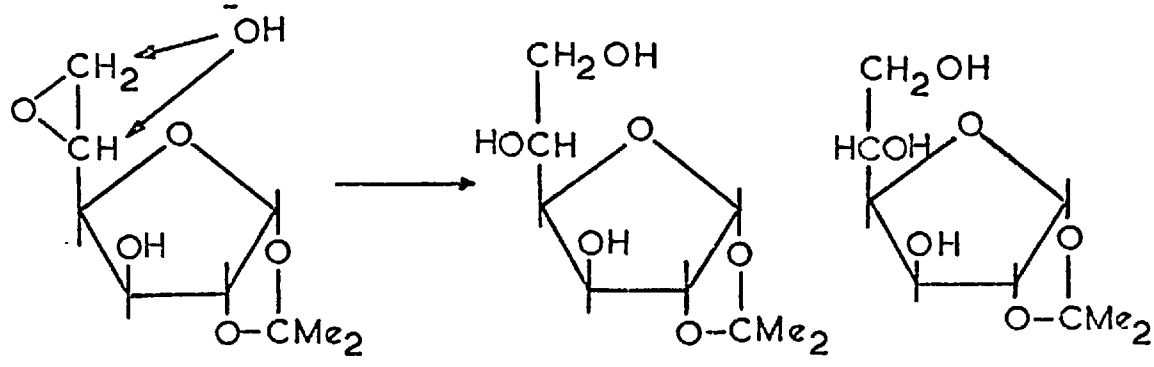
(54) (55)

Ohle found that for a 3,6-anhydro bridge to be formed, the 5-hydroxyl group had to be substituted. Treatment of 1,2-O-isopropylidene-6-O-toluene-p-sulphonyl-α-D-glucofuranose (56) with methanolic ammonia, in the cold, yielded the 6-amino derivative (57), and the 5,6-anhydro compound (58)[56].



(56) (57) (58)

The reactions of the 5,6-anhydro compound (58) were studied further by Ohle and von Vargha[57]. They showed that in their previous work[56], the 6-amino compound (57) was derived from the 5,6-anhydro compound (58) by nucleophilic ring opening with ammonia. They also treated the 5,6-anhydro compound (58) with base under more forcing conditions and obtained, according to their paper[57], no 3,6-anhydro derivative, but rather a mixture of 1,2-O-isopropylidene-α-D-glucofuranose (59) and the L-idose analogue (60).

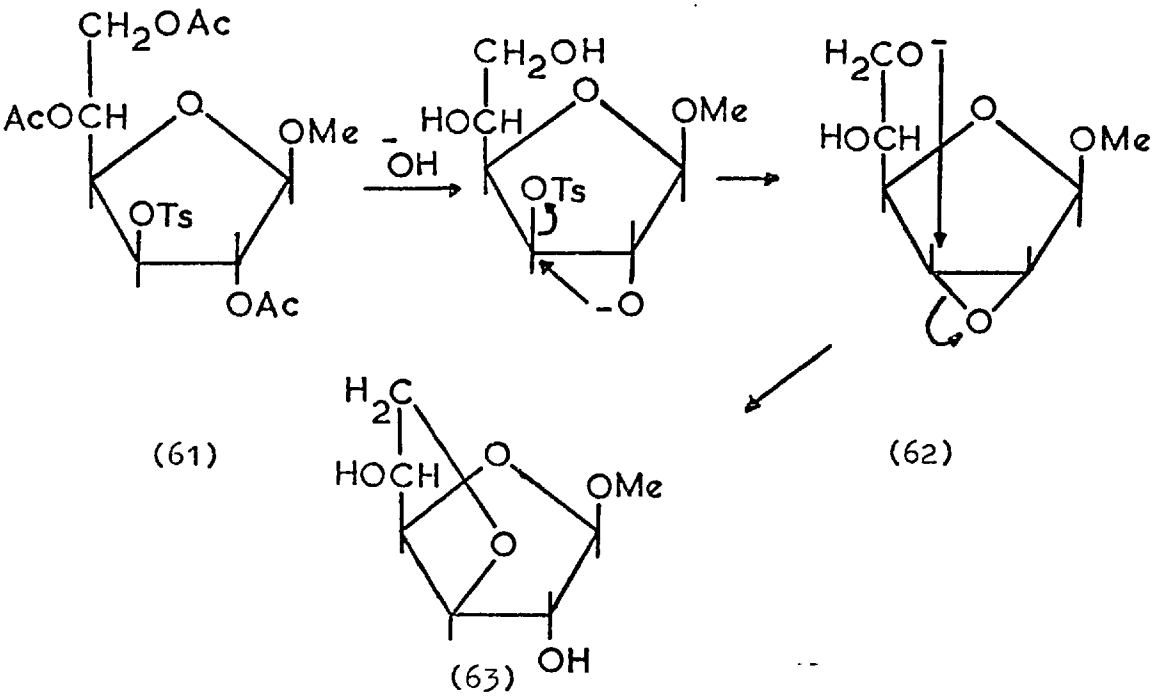


(59) (60)

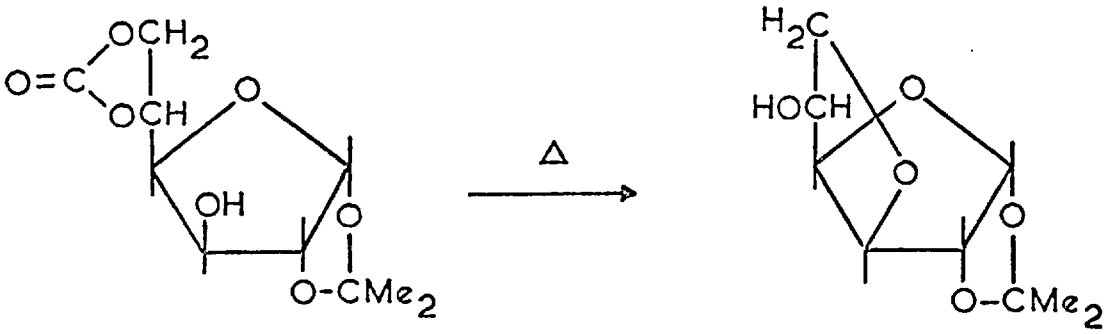
These results must be questioned as Reichstein and co-workers[58] showed that base-treatment of the 5,6-anhydro compound (58) yielded three products; 1,2-O-isopropylidene-α-D-glucofuranose, a dimeric product, and 3,6-anhydro-1,2-O-isopropylidene -α-D-glucofuranose.

The preferred formation of 3,6-anhydro rings rather than three-membered anhydro-rings has been shown by Percival[59]. Work by Ohle and Wilcke[60] has indicated the generality of this postulate, and of course the observations of Reichstein and

his colleagues[58] have given strong experimental corroboration. Treatment of methyl 2,5,6-tri-O-acetyl-3-O-toluene-p-sulphonyl -β-D-glucofuranoside (61) with sodium hydroxide solution yielded methyl 3,6-anhydro-β-D-glucofuranoside (63); the reaction presumably proceeding via the 2,3-anhydro allose derivative (62).

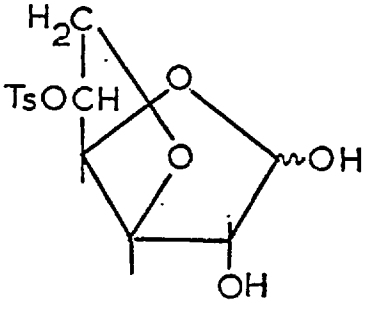


A simple preparation of 3,6-anhydro-1,2-O-isopropylidene- -α-D-glucofuranose was described by Freudenburg and co-workers[61]. Starting with 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose, they prepared the 3-O-chloroformyl derivative (via the 3-sodio derivative), and left this compound in the atmosphere at room temperature, whence it was converted into the 5,6-carbonate (64). Heating (64) at high temperature gave the 3,6-anhydro compound (55) in good yield.



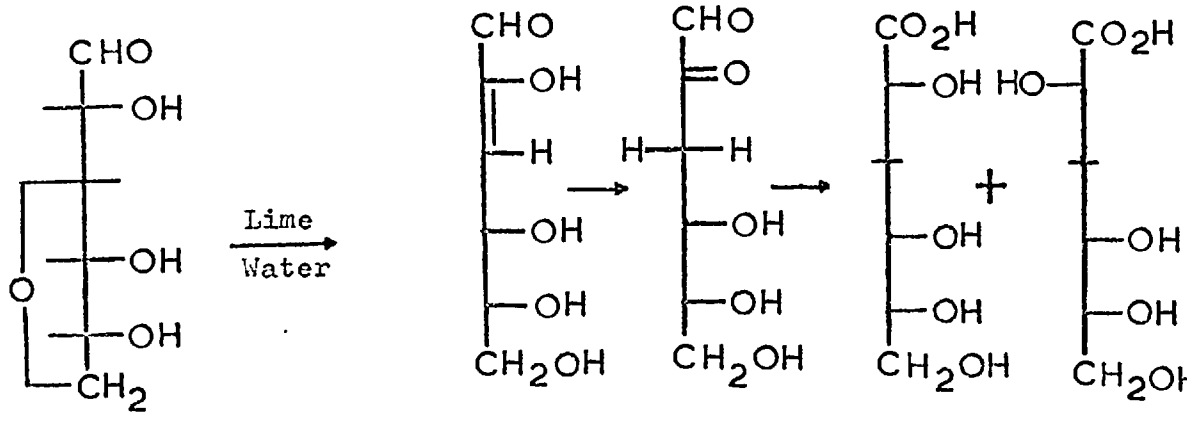
(64) (55)

3,6-Anhydro-D-glucose has been described by a number of the before-mentioned authors. The free sugar reduces Fehling's solution strongly[58], and most authors [55,58] have considered the free sugar as existing in the open-chain aldehydic form rather than the hemiacetal form. Ohle and Euler[62] showed that 3,6-anhydro-5-O-toluene-p-sulphonyl-D-glucose exhibited mutarotation in absolute ethanol, and considered this compound to exist in an equilibrium between the open-chain form and the furanose hemi-acetal ring form (65).



(65)

The acid stability of the 3,6-anhydro bridge was shown by many authors, and not until 1957 was there a reported method for its fission[63]. Treatment of 3,6-anhydro-glucose with lime water yielded a mixture of 3-deoxy-D-gluconic and 3-deoxy-D-mannonic acids, (66) and (67) respectively.



(66) (67)

In conclusion it is possible to say that the 3,6-anhydro bridge profoundly alters the normal chemistry of the rest of the sugar molecule. The hemi-acetal sugar ring becomes thermodynamically less stable than in ordinary sugars. In fact the presence of the 3,6-anhydro bridge greatly increases the tendency for the sugar to adopt the open-chain form.

NUCLEOPHILIC DISPLACEMENT REACTIONS OF SULPHONATE ESTERS

The volume of published work on this topic is so immense that this review must necessarily be somewhat selective.

The displacement of sugar sulphonates can be categorised under the following divisions:

1. Displacements on open-chain compounds,
2. Displacements on furanose compounds,
3. Displacements on pyranose compounds,
4. Displacements with neighbouring group participation, and
5. Displacements with molecular rearrangement of the substrate.

Classes 2. and 3. can be sub-divided into further categories depending on the primary or secondary nature of the sulphonate group. Secondary sulphonates exhibit differences in reactivity depending on (a) whether they are sterically exo or endo, (b) whether they are ring sulphonyl derivatives, or side-chain derivatives, and (c) whether they are axial or equatorial in conformation.

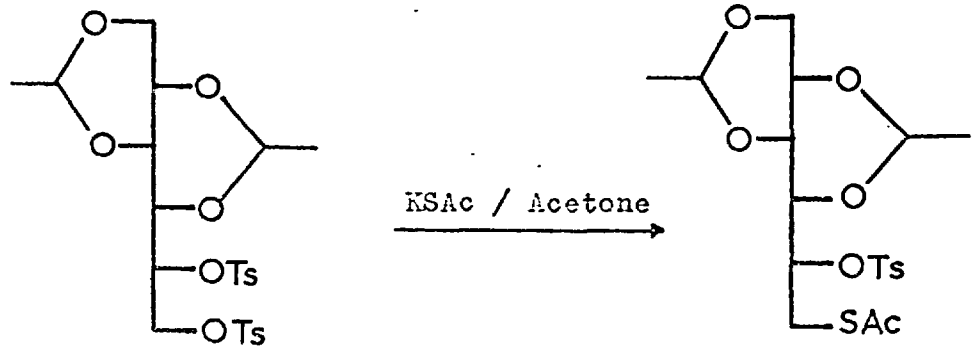
As a general rule, primary sulphonyloxy groups are the most easily displaced. These reactions are usually performed in solvents such as acetone, ethanol or 2-methoxyethanol, and require both short reaction periods and moderate temperatures. Secondary sulphonates are much less reactive than primary derivatives, and displacements are usually carried out in dipolar aprotic solvents such as DMF, DMSO, N-methylpyrollidone,

and hexamethylphosphorictriamide (HMPT hereafter), and often require high reaction temperatures and substantial reaction times (several days in some cases). As a rule, pyranose ring sulphonates are more reactive than furanose ring compounds, and endo-sulphonates are generally much more susceptible to displacement than the analogous exo-derivatives.

Although most nucleophilic displacements of sulphonates occur via an S_N2 mechanism with concomitant inversion of configuration at the reactive site, this rule is by no means universal, and it is always desirable to prove the stereochemistry of the product.

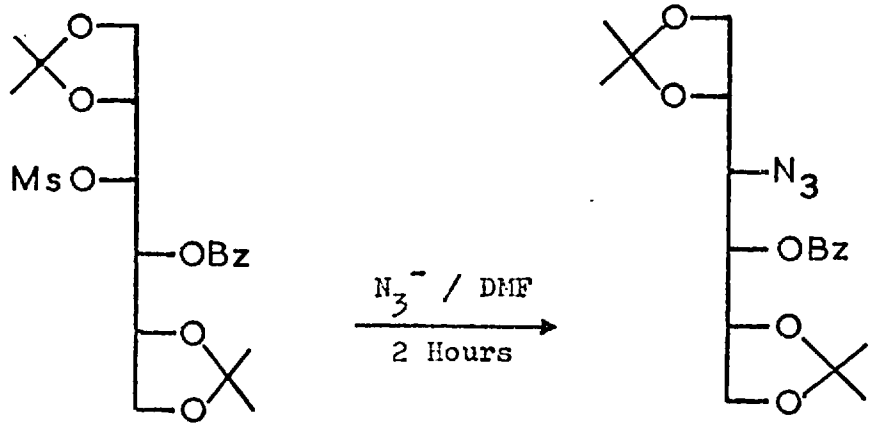
1. Displacements on Open-chain Compounds:

As far as reactions with thio-nucleophiles are concerned, the paper by Chapman and Owen[64] firmly established the generalisation that primary sulphonates are more reactive towards nucleophilic displacement than secondary sulphonates. Using potassium thiolacetate in refluxing acetone, only the primary sulphonate of the D- sorbitol derivative (68) could be displaced to give the 6-thio compound (69).



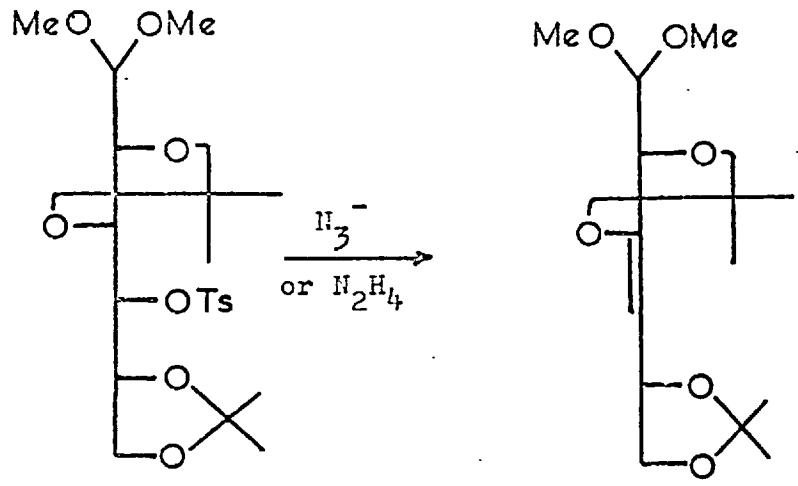
(68) (69)

Subsequent work by Baker[65,66] and his school has shown that the secondary sulphonates in open-chain sugars are best displaced in reaction media such as DMF. For example, the 3-O-methanesulphonyl derivative (70) could be converted into the 3-azido-3-deoxy-D-altrose compound (71) with complete inversion at C-3; there being no evidence of anchimeric assistance from the 4-O-benzoyl group[65].



(70) (71)

Unfortunately, not all displacements occur smoothly and result in the desired product, and this has recently been highlighted by the work of Paulsen[67]. Attempted nucleophilic displacements by hydrazine, and azide ion, on the 4-O-tosyl-glucose compound (72) gave as the major product the 3,4-dehydro compound (73), and not the expected amino compounds.

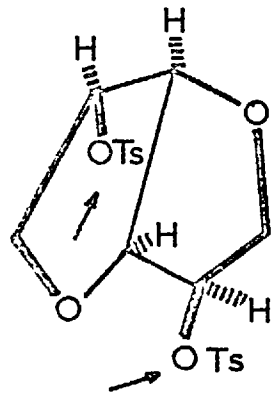


(72) (73)

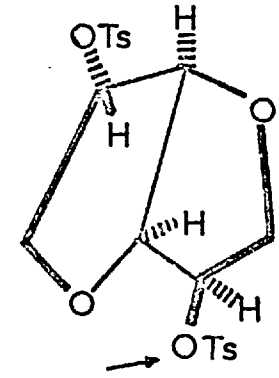
2. Displacements on Furanose Compounds:

The differences in reactivity of the endo- and exo-tosylates were elegantly described by Cope[68]. Three 1,4:3,6-dianhydrohexitols were prepared, and the ditosylates were prepared in each case. The D-mannitol compound (74) has two endo-tosyl groups, and both were displaced in refluxing acetone with acetate ion. The D-glucitol derivative (75) has one endo-, and one exo-tosyl group, and under the same reaction conditions only the endo-tosylate could be displaced. The L-iditol compound (76) having two exo-tosyl groups was unreactive under the same reaction conditions.

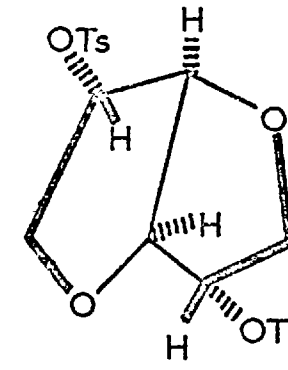
The exo-tosyl group of 1,2:5,6-di-O-isopropylidene-3-O-tosyl-α-D-glucofuranose is very resistant to displacement by ionic nucleophiles[69,70], the reaction being characterised by either detosylation or extensive decomposition. The former effect was also noted by Reichstein[71,72]. In the glucose



(74)



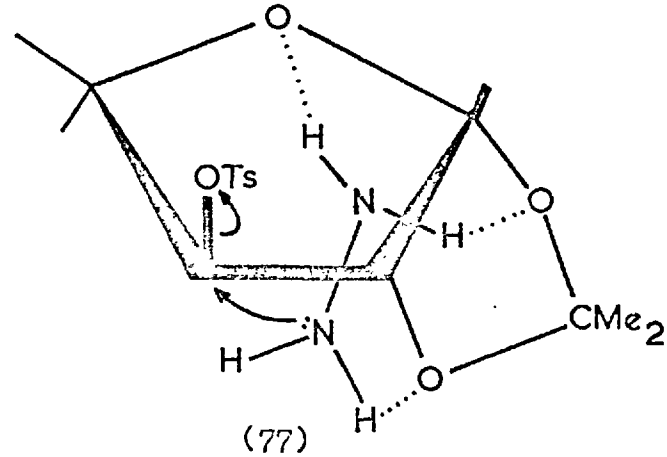
(75)



(76)

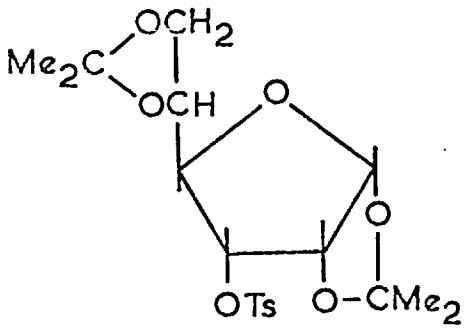
(The tosyl groups marked (⟶) are the ones displaced)

compound mentioned above, the incoming anion experiences electrostatic repulsions from the ring oxygen atom, and the oxygen atoms on C-1, and C-2[70]. However the 3-O-tosyl group can be displaced by hydrazine[73] - a neutral molecule - with inversion of configuration[74]. The relative ease of this displacement has been rationalised[70] in terms of a tridentate H-bonded complex (77) which is ideally set up for pseudo intramolecular displacement.

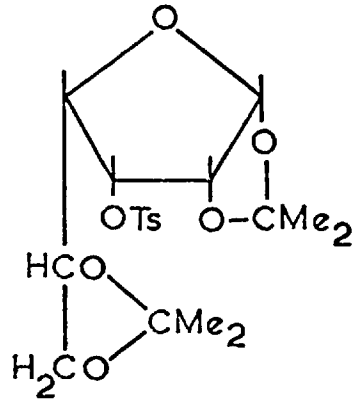


(77)

Recently the ease of displacement of the endo-tosyl groups in the analogous D-allose (78)[75,76,77], and D-gulose (79)[78,79] compounds has been demonstrated. The ionic nucleophiles used were fluoride, azide, and benzoate.

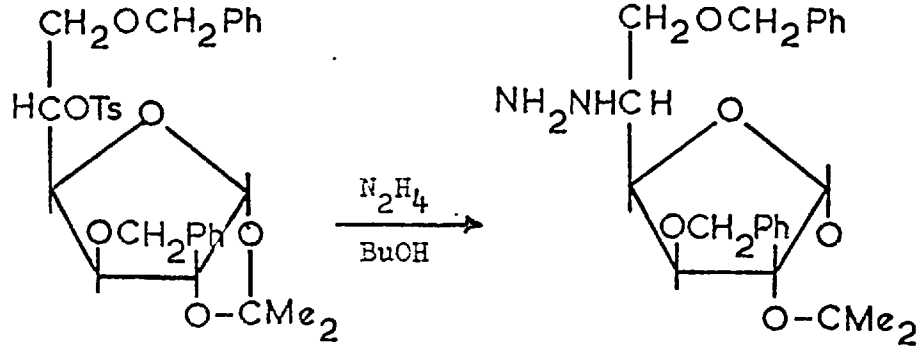


(78)



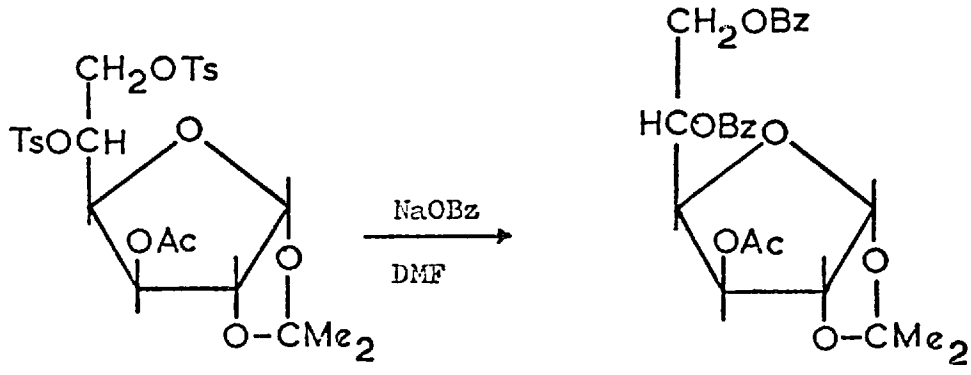
(79)

Exocyclic (side-chain) secondary sulphonates are usually quite difficult to displace[80,81,82], and elimination is often a competing reaction[80]. The 5-O-tosyl-L-idose derivative (80) undergoes displacement with hydrazine to give compound (81), but does not react with ionic nucleophiles[81].



(80) (81)

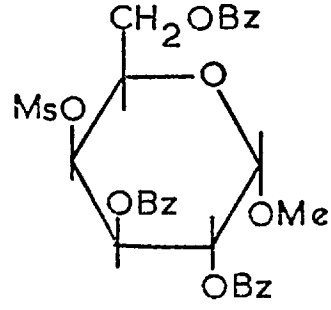
The successful displacement of exocyclic secondary sulphonates requires severe conditions[82], for example, treatment of the D-glucose compound (82) with sodium benzoate in boiling DMF is required to convert it into the L-idose compound (83).



(82) (83)

3. Displacements on Pyranose Compounds:

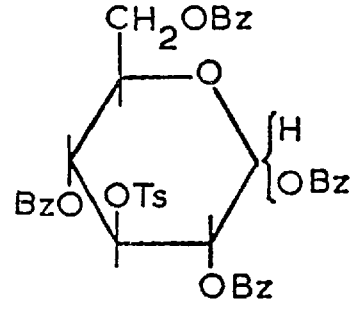
The displacement of secondary sulphonates is little affected by the conformation of the departing sulphonate except in some fairly rare cases, which are discussed later in section 5. The axial sulphonate in compound (84) is displaced with ease by azide ion in DMF[83].



(84)

Using the 4-O-sulphonyl derivatives of D-glucose, and D-galactose, it has been shown[84] that the straightforward displacement of sulphonates is as facile whether the departing group is axial or equatorial in conformation. These results are supported by Richardson[85] who showed that there was no direct correlation between the conformation of a sugar hydroxyl group, and its reactivity.

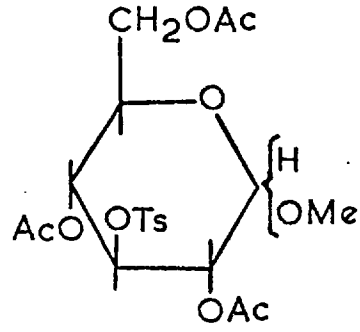
Steric hindrance to the approach of the incoming nucleophile is a major factor encountered in displacement reactions. For instance, the α- and β- anomers of the 1,2,4,6-tetra-O-benzoyl-3-O-tosyl-glucose compounds (85), and (86) were subjected to displacements under identical conditions[86].



(85) α-anomer
(86) β-anomer

The α-anomer was completely unreactive, whereas the sulphonate in the β-anomer underwent smooth S_N2 displacement yielding only one compound. Both (85) and (86) exist in the C1 conformation, and in (85), the benzoyloxy group at position 1 is axial, and thus hinders the approach of the incoming

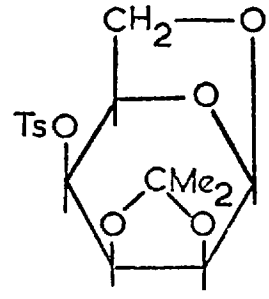
nucleophile to such an extent as to prohibit displacement of the 3-O-tosyl group. Similar results have recently been reported by Angyal and his co-workers[87]. They found a ratio of about 4:1 between the rates of displacement of the 3-O-tosyl groups in the β- and α- methyl glucopyranosides (87) and (88); the β-anomer being the more reactive.



(87) β-anomer

(88) α-anomer

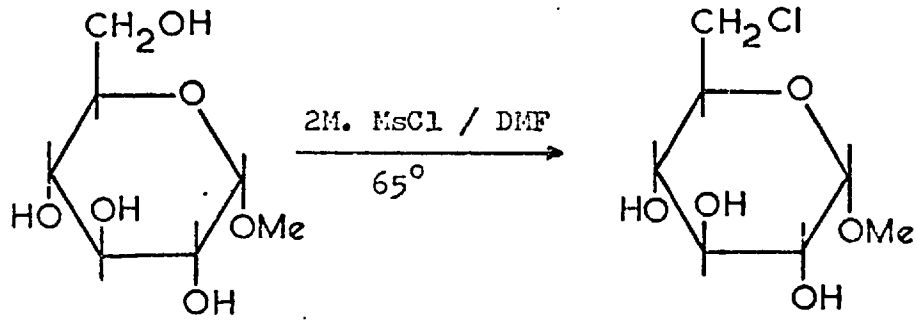
Another important factor which may influence considerably the reactivity of a sulphonate ester is the steric congestion associated with the transition state. Horton and his colleagues have synthesised[88] several secondary tosyl derivatives of 1,6-anhydro-pyranose compounds, e.g. (89),



(89)

and they have shown that these esters are completely unreactive, and thus such a bicyclo-[3,2,1]-system as (89) involves a too severe steric hindrance to the achievement of a transition state having five groups round one carbon atom.

Nucleophilic displacements of primary sulphonates is usually easy compared to secondary sulphonate esters[43,84,89]. For example, treatment of methyl α-D-glucopyranoside (90) with two equivalents of mesyl chloride in DMF at 65° gives a 97% yield of the 6-chloro compound (91)[89].

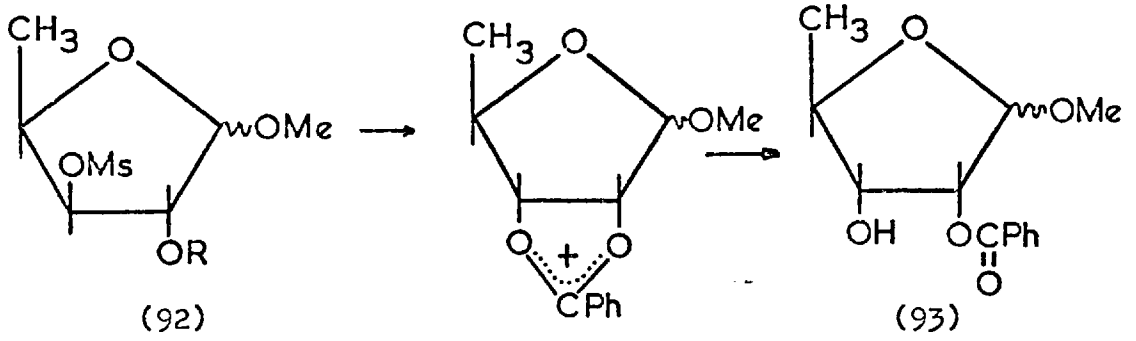


(90) (91)

Some primary sulphonates, however, are surprisingly resistant, as exemplified by the relative unreactivity at the primary position in galactopyranose compounds. This topic has been thoroughly studied by Nadkarni and Williams[90], and the effect has been explained in terms of electronic repulsions experienced by negative nucleophiles from the lone pairs of electrons of the ring oxygen, and the <u>axial</u> C-4 oxygen atom.

4. Displacements with Neighbouring Group Participation:

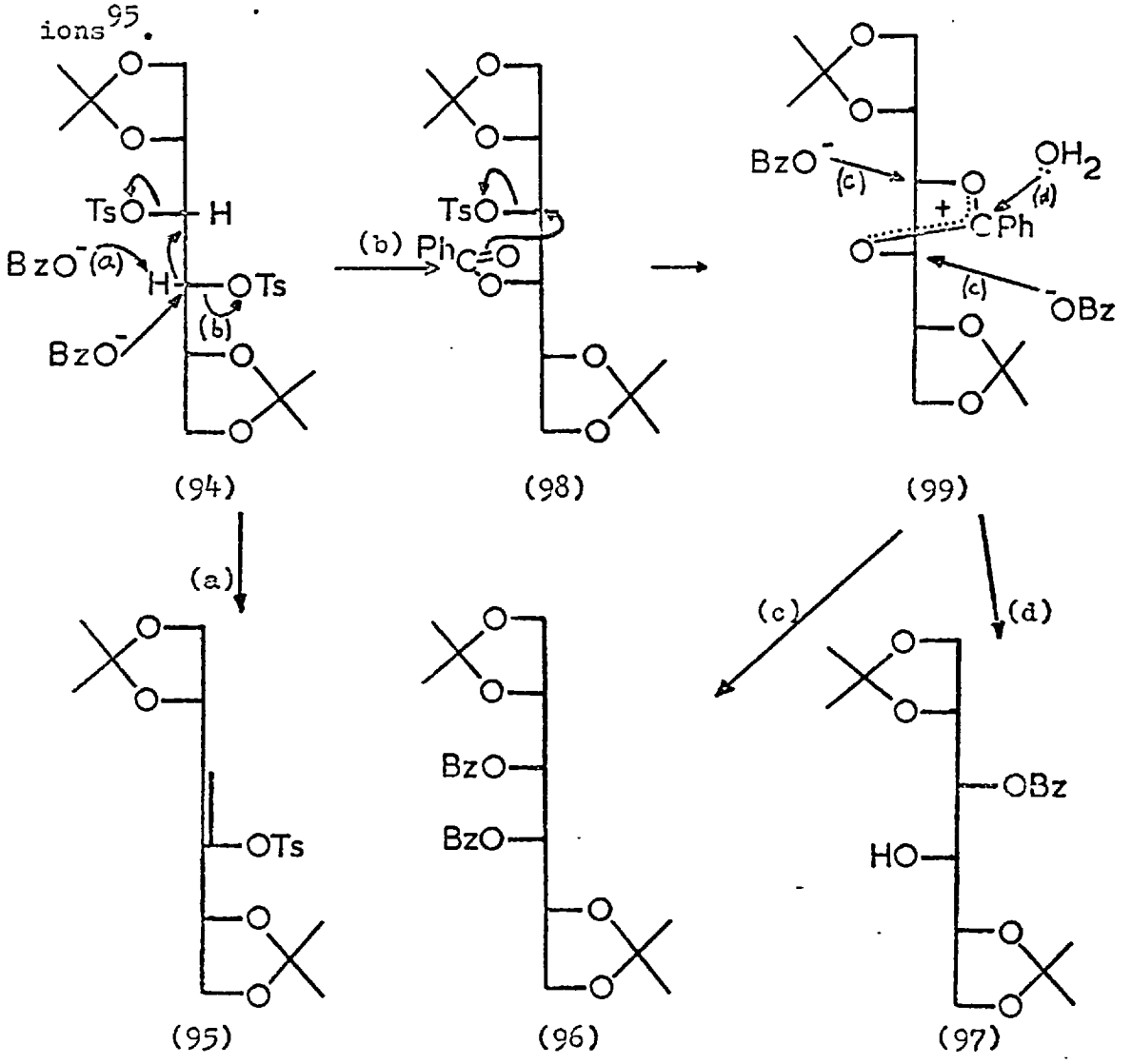
The whole subject of neighbouring group participation has been the subject of a most excellent review[91]. Neighbouring group participation usually manifests itself either in increased rates of reaction, or in anomalous stereochemical control of a reaction. For example, the 3-O-methanesulphonate (92, R=COPh) is easily displaced by benzoate ions in DMF to give compound (93), whereas compound (92, R=CH_2Ph) is very much more resistant to displacement, and gives a mixture of products[92].



In many compounds a competition can exist between direct displacement, and anchimerically assisted displacement. The extent of the occurence of direct displacement depends on the nucleophilicity of the attacking anion[94]. Thus less anchimeric assistance occurs when using azide ion than when using benzoate ion, azide ion being the stronger nucleophile.

Foster and Webber and their co-workers have done some interesting work on open-chain compounds[94,95]. A complex

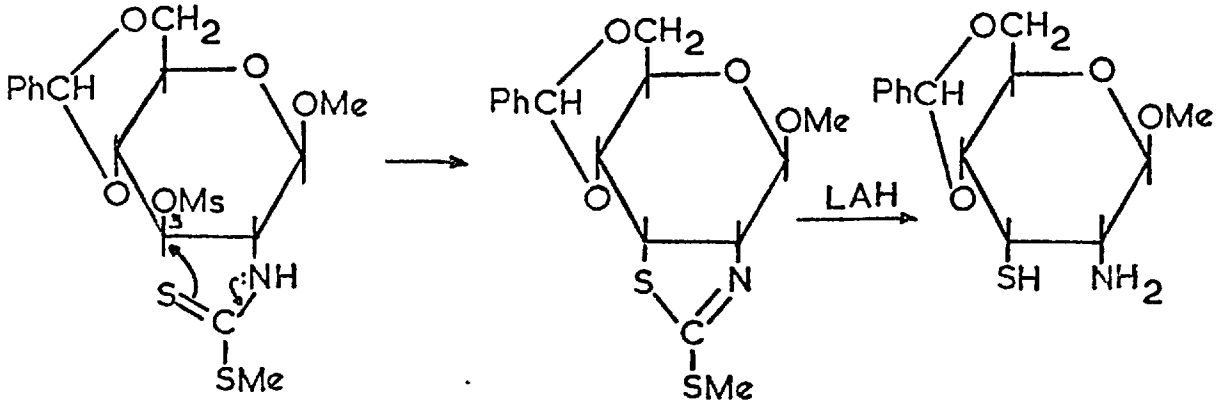
mixture of products (95 - 97) was obtained when the D-mannitol derivative (94) was subjected to displacement with benzoate ions[95].



The course of the reaction is visualised as proceeding by initial displacement of one of the tosyl groups by benzoate to yield (98). Anchimeric displacement of the second tosyl group gives the oxonium ion (99) which reacts further by pathways (c) and (d) to give (96) and (97).

Neighbouring group participation by methyl and benzyl

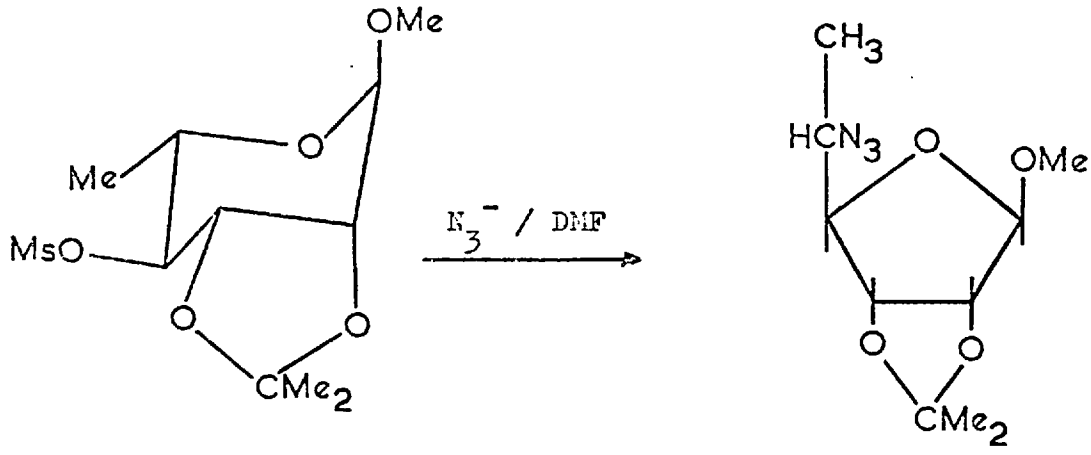
ether groups has been demonstrated in nucleophilic displacement reactions[96,97]; however the use of complex participating groups is of more synthetic interest and utility[98,99]. By using a dithiocarbamate derivative of glucosamine (100), zu Reckendorf and Bonner[98] were able to prepare the 2-amino-2-deoxy-3-thio-D-allose compound (102) after LAH reduction of the intermediate thiazole derivative (101).



(100) (101) (102)

5. Displacements with Molecular Rearrangement of the Substrate:

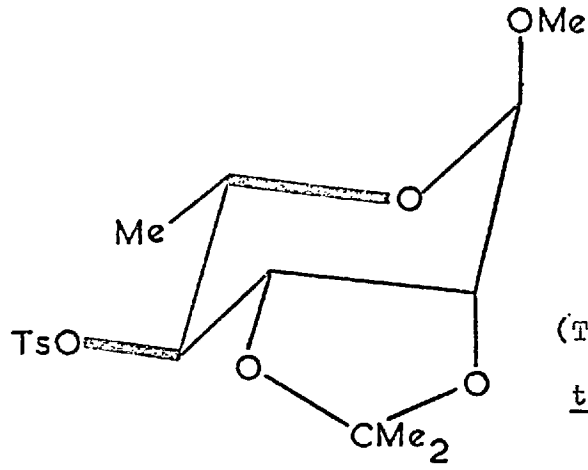
The first documented examples[100,101] of this type of reaction were reported in 1966, and involved the contraction of a pyranoside to a furanoside during the displacement reaction with retention of configuration at C-5 and inversion at C-4 in the hexose. Thus treatment of the α-L-rhamnopyranoside (103) with azide in DMF yields the α-L-talofuranoside (104). In the above examples[100,101], and further examples[102,103] of the ring contractions of carbohydrates, it will be noted that there is a trans-antiparallel relationship[100,104] between



(103) (104)

the C-4 sulphonate bond and the C-5 ring oxygen bond. Owen[104] has suggested an explanation for the stereochemistry of these reactions (viz. inversion at C-4, and retention of configuration at C-5) in terms of a two stage process. First, there is a migration of the sulphonyloxy group from C-4 to C-5 concerted with ring contraction. This intramolecular displacement by the ring oxygen involves inversion at C-4 and C-5. The second stage of the process is the normal S_N2 displacement at C-5 which occurs with inversion at this position. Thus the configuration of C-5 is the same in the starting material and in the ring contracted product because of a double inversion at that position.

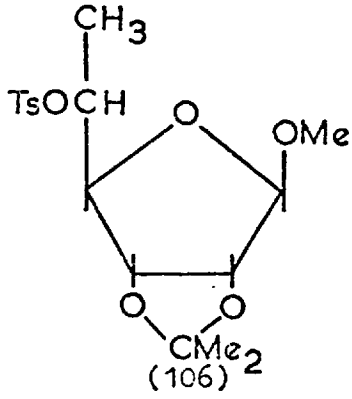
For example, the α-L-rhamnopyranoside (105) exists in the 1C conformation with the tosylate C-4 bond, and the C-5 ring oxygen bond in a trans-antiparallel relationship. According to Owen's theory[104], such a compound could undergo



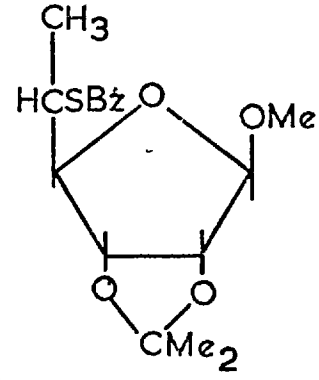
(Thickened bonds are trans-antiparallel)

(105)

displacement by a two stage process, and the intermediate would be the β-D-allofuranoside (106), which on reaction with thiolbenzoate would yield the 5-thio-α-L-talose compound (107)[103] and not the 4-thio-L-talose compound as originally reported[45].

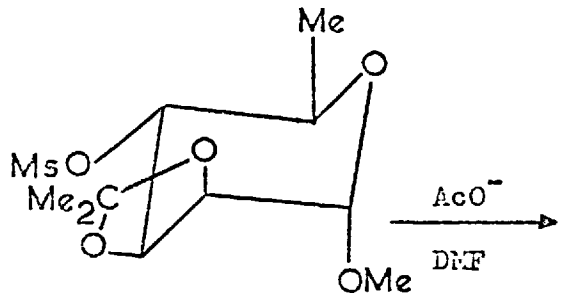


(106)



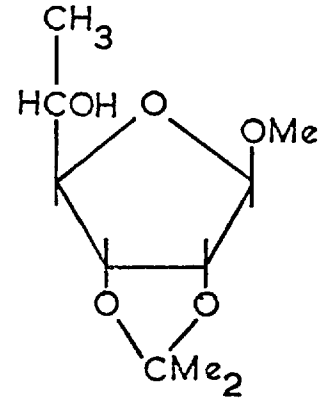
(107)

Direct experimental evidence[101] has supported Owen's theory[104] since the double-inverted, ring contracted intermediate (109) has been isolated as an artefact, via hydrolysis of the sulphonate ester, from the displacement reaction on the D-rhamnose compound (108).



(108)

D-rhanno



(109)

6-deoxy-L-allo

D I S C U S S I O N

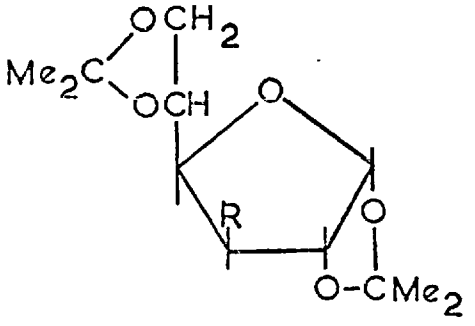
A N D

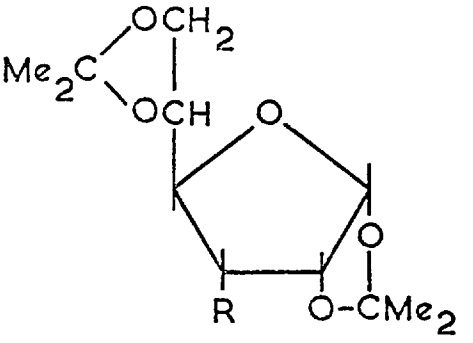
R E S U L T S

Part 1

One of the objectives of the present investigation was to confirm the supposed gluco configuration of the 3-thio compound originally described by Freudenberg[5] (see Introductory Review page [8]). 1,2:5,6-Di-O-isopropylidene-D-glucose was therefore converted into the 3-O-methylxanthate (110a) and the thermal rearrangement of this into the 3-thio compound (110b) was carried out both by the modified method described by Overend and co-workers[8] (in which the xanthate is heated in boiling diphenyl ether) and by the heated-tube process recommended by Cerny and his colleagues[105]; the latter method was found to give better yields. The rearranged product (110b) was then reduced to the thiol (110c) with lithium aluminium hydride.

The availability of 1,2:5,6-di-O-isopropylidene-α-D-allofuranose (which was required for other experiments to be described later) made it of interest to prepare the corresponding 3-O-methylxanthate (111a) and study its pyrolysis. It was found that its rearrangement occurred much less readily than with the gluco compound, only a very poor yield of the 3-thio compound (111b) being obtained. This difference in reactivity is analogous to that encountered in the S_N2 displacement reactions of endo compared with exo sulphonates in other bicyclic systems[68].





(110a) R=O.CS.SMe

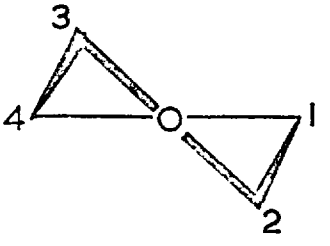
(110b) R=S.CO.SMe

(110c) R=SH

(111a) R=O.CS.SMe

(111b) R=S.CO.SMe

It has been pointed out (page 9) that n.m.r. spectral evidence has recently been presented which supports the allocation of the gluco configuration to Freudenberg's rearranged product. Independent evidence, on similar grounds, has been obtained in the present work. The n.m.r. spectra of compounds (110b) and (111b) are shown in Fig. 1. The spectrum of the 3-thio-D-glucose compound has 2-H as a doublet, it being solely coupled to 1-H. Extensive investigations[106] on 1,2-O-isopropylidene furanose sugars have shown that the sugar ring is puckered. C-1, C-4, and the ring oxygen define the plane of the ring with C-2 and C-3 almost symmetrically below and above this plane.



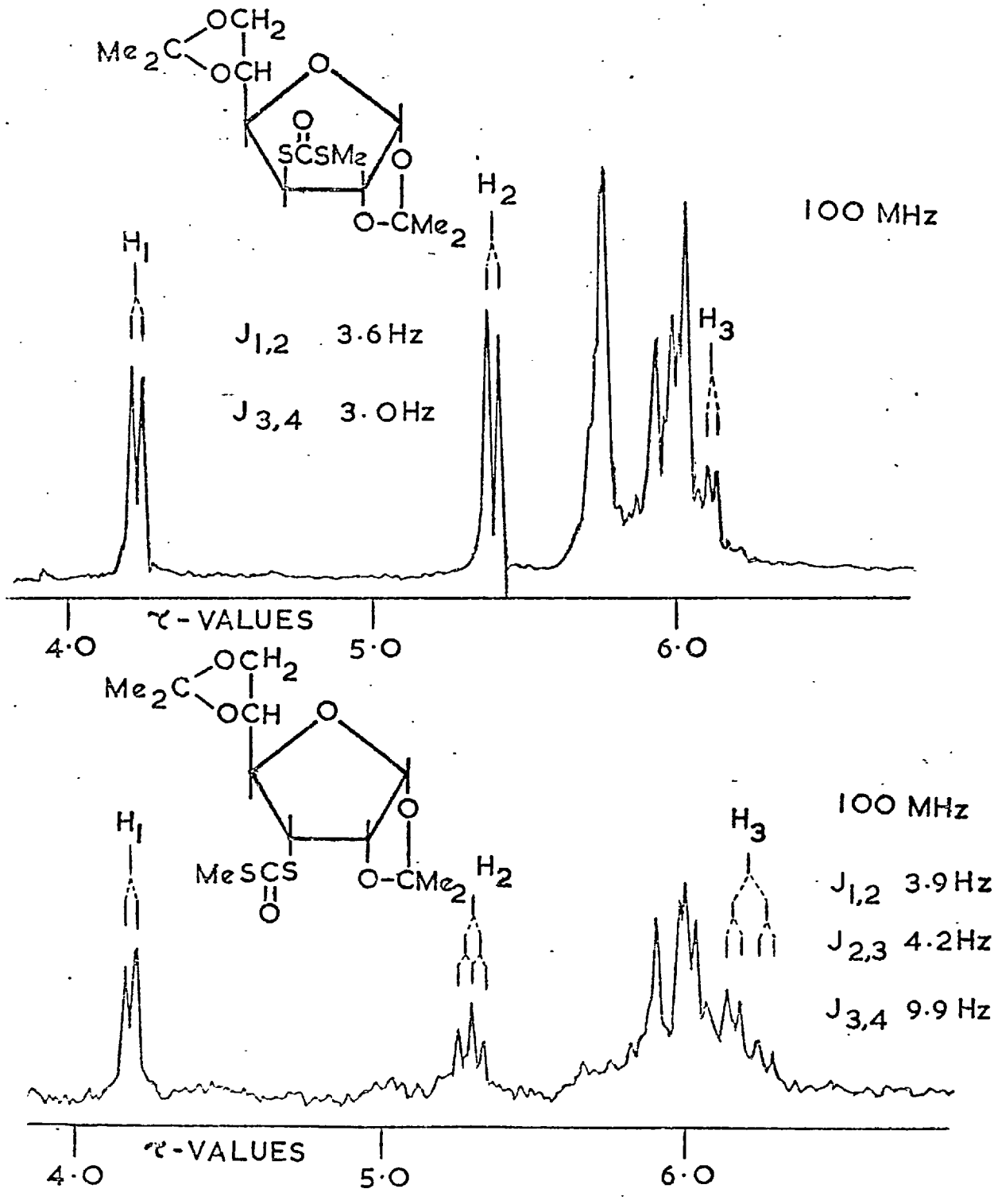
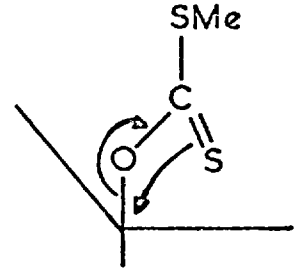

OCH2
Me2C
OCH
O
SCSMe
O
O-CMe2
H1
H2
H3
100 MHz
J1,2 3·6 Hz
J3,4 3·0 Hz
τ-VALUES
4·0
5·0
6·0
OCH2
Me2C
OCH
O
MeSCS
O
O-CMe2
H1
H2
H3
100 MHz
J1,2 3·9 Hz
J2,3 4·2 Hz
J3,4 9·9 Hz
τ-VALUES
4·0
5·0
6·0

Fig. 1

From the inspection of molecular models of such a puckered ring, it can be seen that, if the configuration at C-2 and C-3 is threo, the dihedral angle between 2-H and 3-H,as observed by looking along the C-2 - C-3 bond axis, is almost 90°. This value of the dihedral angle corresponds to a zero coupling between 2-H and 3-H[107,108,109]. When, however, the sugar has the erythro configuration at C-2 and C-3 then the dihedral angle between 2-H and 3-H is approximately 45-50°, and as shown in Fig. 1 the n.m.r. signal due to 2-H is then split by coupling to both 1-H and 3-H. The two configurations are thus clearly differentiated, and Freudenberg's 3-thio sugar is shown to be the D-gluco configuration from a simple inspection of the spin-multiplicity of the 2-H signal.

The thermal isomerisation clearly involves an intramolecular nucleophilic reaction having a four-centre transition state:



Further spectral evidence supporting the D-gluco configuration of the 3-thiohexose is given by the n.m.r. data for the free thiol (110c)-Fig. 2 and its disulphide derivative (Fig. 3). In these compounds a zero 2-H to 3-H coupling was observed indicating that the thiol group at C-3,

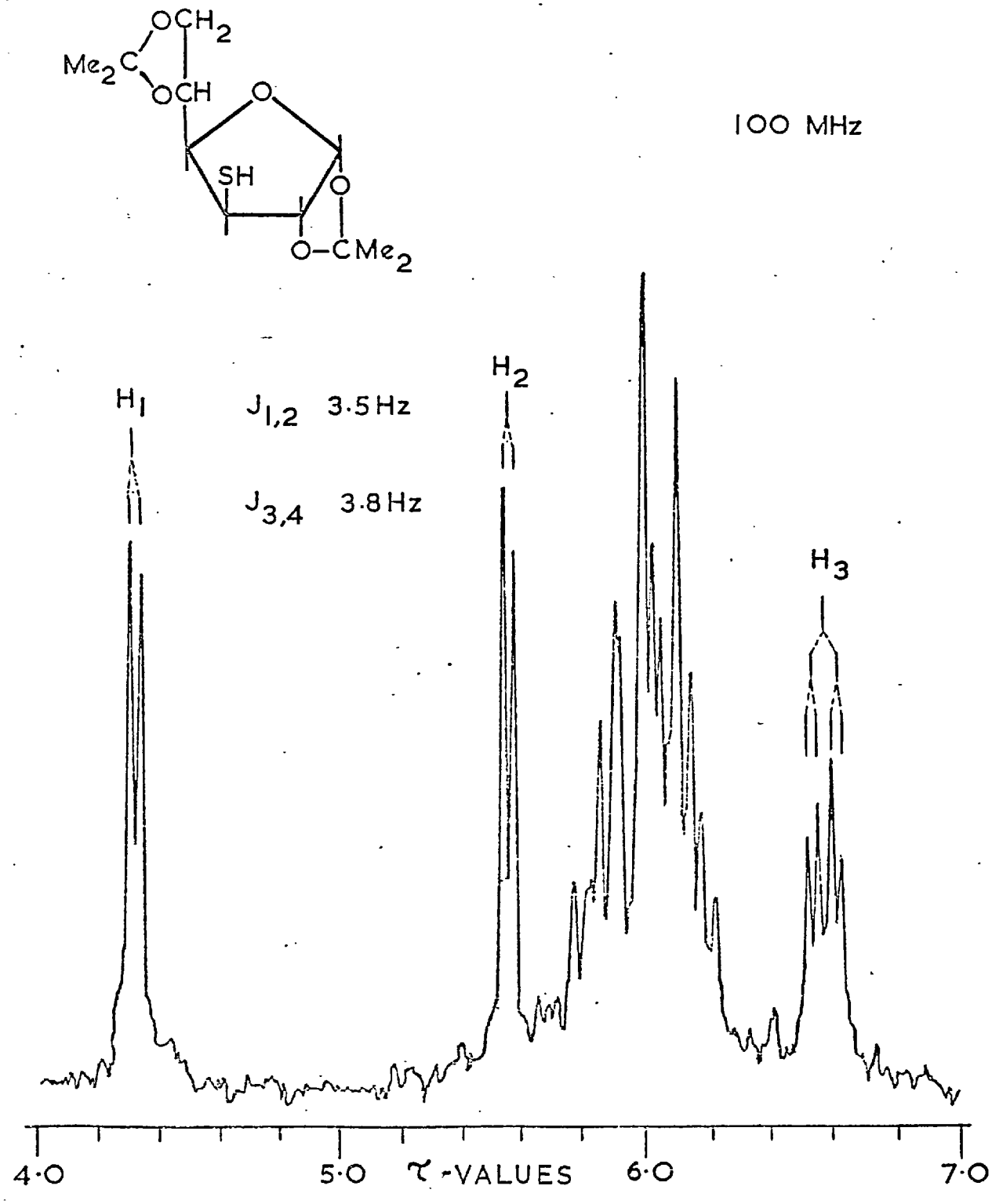

OCH2
Me2C
OCH
O
SH
O
O–CMe2
100 MHz
H1
J1,2 3.5 Hz
J3,4 3.8 Hz
H2
H3
4·0
5·0
τ-VALUES
6·0
7·0

Fig. 2

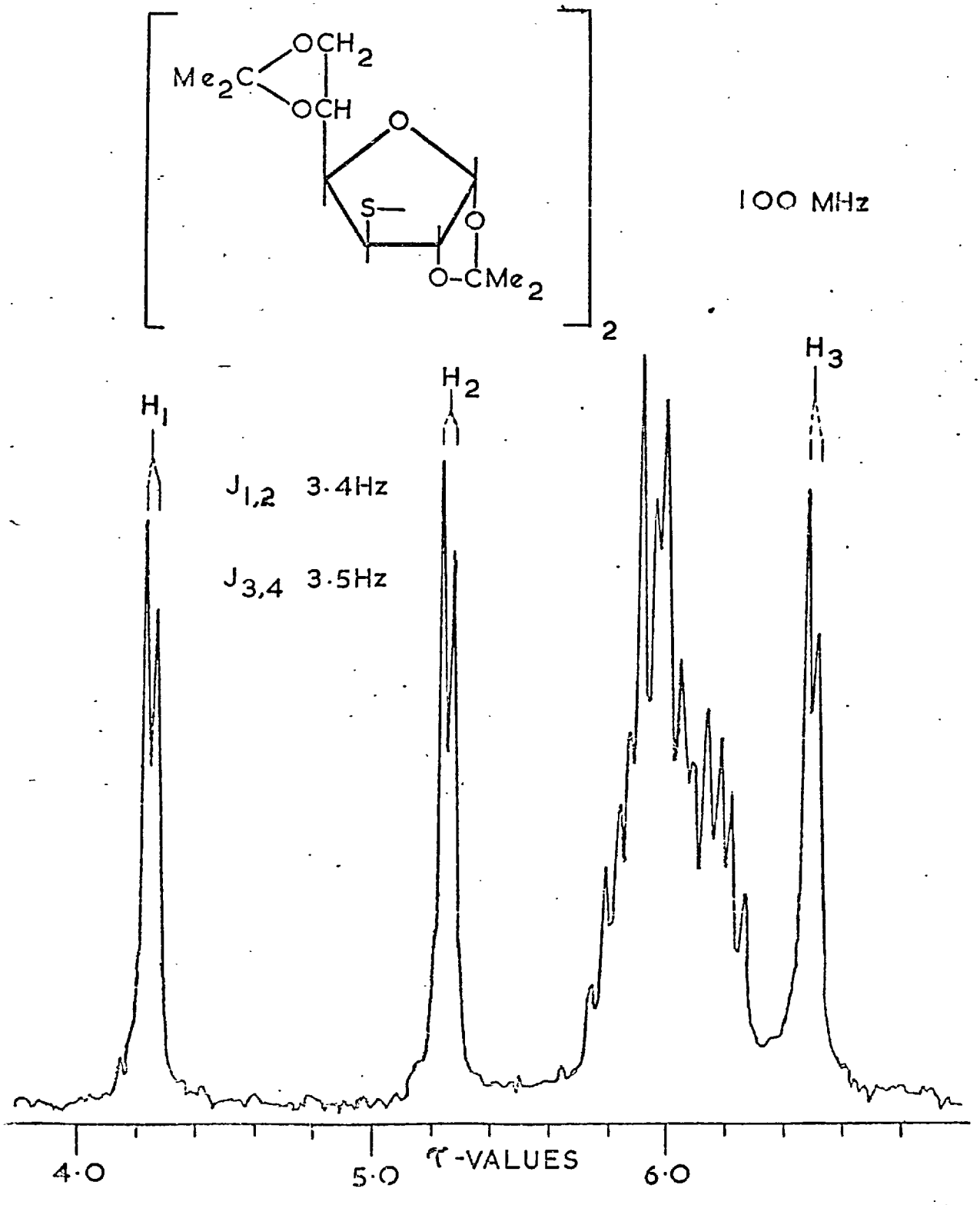

Me2C
OCH2
OCH
O
S
O
O-CMe2
2
100 MHz
H1
H2
H3
J1,2 3·4Hz
J3,4 3·5Hz
4·0
5·0
τ-VALUES
6·0

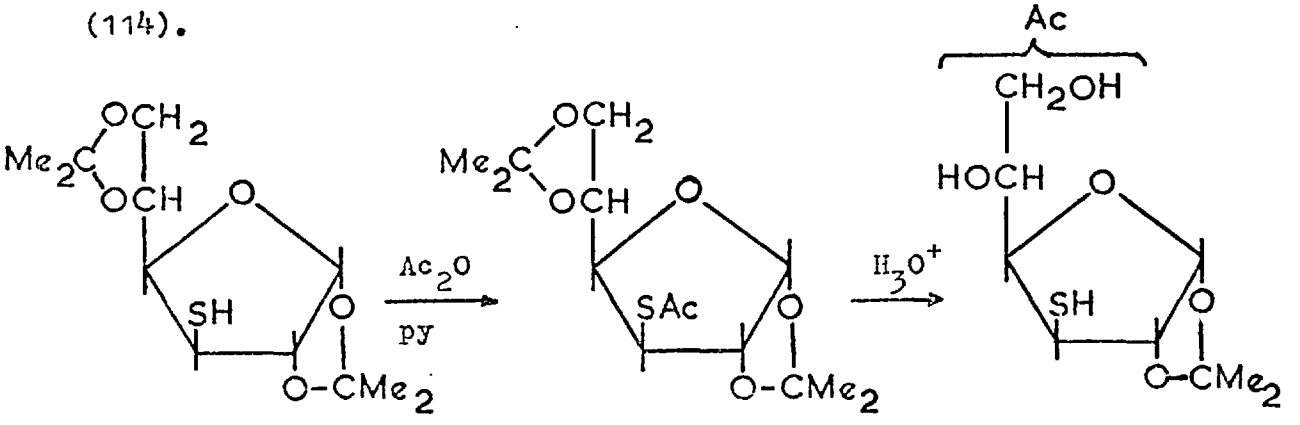
Fig. 3

and the hydroxyl group at C-2 were trans. The double doublet at τ 6.56 in Fig. 2 was the cause for some initial speculation as to its assignment, but the point was resolved when the spectrum of the disulphide (Fig. 3) was at hand. The larger coupling in the double doublet signal is due to a coupling between the thiol proton and 3-H. This coupling appears to be a fairly general phenomenon[110].

In spite of these data, from which the absolute configuration can be inferred, a direct chemical proof of the configuration was thought desirable. The rationale of this was to form a 3,6-epithio bridge from the 3-thio sugar. If the configuration of the 3-thiohexose were D-gluco, the formation of the 3,6-bridge would give a compound containing two mutually cis-fused five membered rings and should occur easily. Formation of the 3,6-epithio bridge if the compound were a 3-thio-D-allose derivative would lead to a trans-fused [5,5]-bicyclic system which would normally be considered highly strained, although such systems have been described[111].

3-Thio-D-glucofuranose Series:

Treatment of 1,2:5,6-di-O-isopropylidene-3-thio-α-D-glucofuranose (112) with acetic anhydride - pyridine yielded the 3-S-acetyl derivative (113). When (113) was partially hydrolysed in methanol and dilute sulphuric acid, the 5,6-O-isopropylidene ring was removed, but the acetyl group in the molecule distributed itself over the 5-OH, 6-OH, and 3-SH groups. (114).

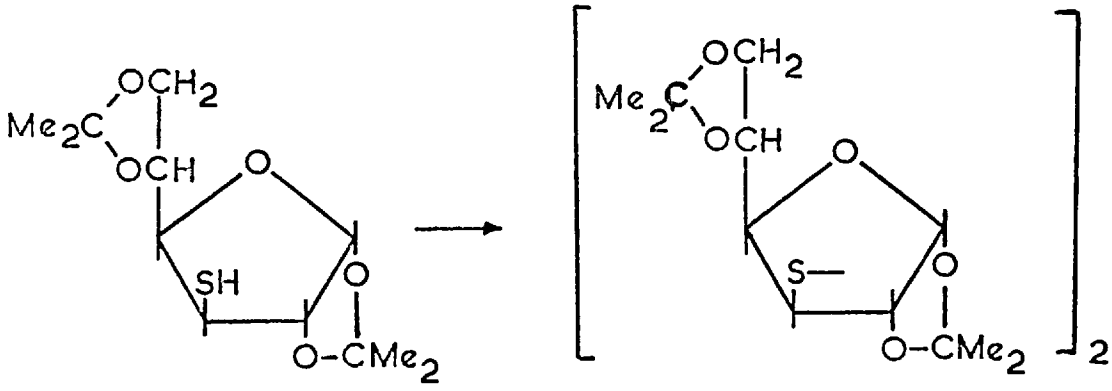


(112) (113) (114)

A separation of this mixture of O- and S-acetyl compounds was accomplished, but the synthetic usefulness of the achievement was thwarted by the rapid equilibration of the S-acetyl compound into the mixed O- and S-acetyl compounds, and also by the facile oxidation of the free thiol into the disulphide.

The next method of protecting the sulphur at C-3 was to convert the thiol into the relatively inert disulphide. The disulphide was chosen because of its ease of preparation, its unreactivity, and its facile conversion into the thiol under suitably mild conditions[112,113]. The oxidising agent

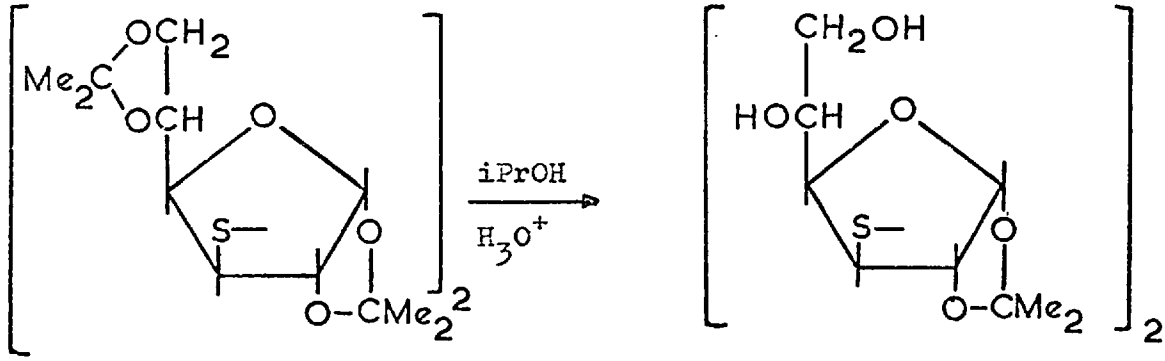
used to convert the thiol (115) in alkaline solution into the disulphide (116) was either iodine or air, and both were equally effective.



(115) (116)

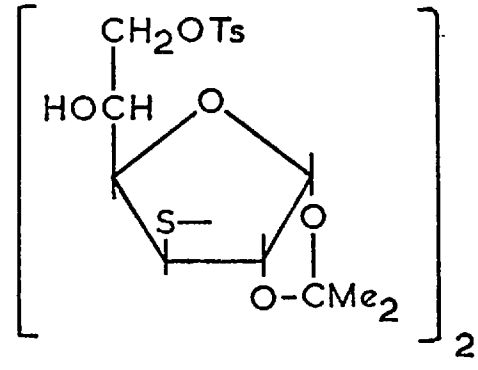
Once the 3-thiol group had been protected as the disulphide (116), the next stage was to effect a selective removal of the 5,6-O-isopropylidene ring. This step proved to be quite difficult because of the very low solubility of the disulphide (116)in water-miscible solvents, and on account of the intricacy in stopping the reaction before the 1,2-O-isopropylidene group was removed. It was found that the solubility of the disulphide (116) in alcohol solvents increased in the order MeOH < EtOH < nPrOH < isoPrOH < nBuOH. However, n-butanol is not completely miscible with one third of its volume of water, and so isopropanol was the solvent used. The solid disulphide (116) was added to a stirred solution of isopropanol and 1.6% aqueous sulphuric acid (8:3 v/v) maintained at ca. 30°. When the solution had become homogeneous

the reaction was stopped and the product, bis-[3-deoxy-1,2-O-isopropylidene-α-D-glucofuranose] -(3,3')-disulphide (117) was obtained in good yield.



(117)

Tosylation of (117) with an excess of tosyl chloride did not give the bis-5,6-di-O-tosyl compound but rather the bis-6-O-tosyl compound only (118), as evidenced by its found molecular weight (762).



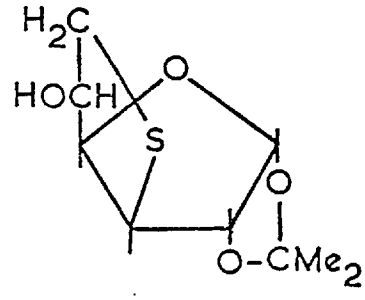
(118)

This reaction can readily be explained on consideration of a molecular model. The primary hydroxyl group will be the

more reactive in (117), and thus compound (118) will be readily formed. In compound (118), there is a very bulky group at C-3 in the sugar ring, namely another sugar ring bonded through the disulphide bridge, and there is a bulky group at C-6. On steric grounds, the 6-O-tosyl group will be anti to the sugar ring and will eclipse (or nearly so) the 5-hydroxyl group. Thus for steric reasons the 5-hydroxyl group is not esterified. In fact a similar effect was noted[114] in 1,2-O-isoproylidene-3,6-di-O-tosyl-α-D-glucofuranose which could only be tosylated with difficulty at C-5.

The disulphide bond in compound (118) was unaffected by methanolic borohydride even though this reagent will normally cleave disulphides[112]. The only reasonable explanation for this lack of reactivity seems to be that the disulphide bridge and some other parts of the molecule (118) in close proximity are heavily solvated and hence the solvated BH_4^- ion cannot approach the S-S bond sufficiently close for a reaction to occur. The use of LAH to cleave the disulphide linkage was done with some hesitancy as it is known[115] that primary tosylates are easily replaced by hydride ion. However a paper by H.C. Brown and his associates[113] has indicated the conditions under which a disulphide linkage could be cleaved without the loss of a primary tosyloxy group. Thus when (118) was treated with LAH in THF at 0°, fission of the disulphide linkage occurred with concomitant cyclisation and loss of the 6-tosyloxy

group to give the 3,6-epithio compound (119).



(119)

The n.m.r. spectrum of (119) is illustrated in Fig. 4 overleaf. The furanose ring size is indicated by the characteristic[106] position of the anomeric proton at τ 4.06. By the techniques of double and triple resonance[117], a complete first-order interpretation of the spectrum was possible. A very important point to note is that there is no 2-H - 3-H coupling. This lack of coupling ($J_{2,3} = 0$) was found in the 3-thio compounds illustrated in Figs. 1(a), 2, and 3, which did not however have the constraint of the 3,6-epithio bridge upon the furanose ring. The fact that $J_{2,3}$ is zero indicates that the formation of the 3,6-epithio bridge leaves the furanose ring virtually unaltered in geometry. The inference from this is that the cis-fused[5,5]-bicyclic system as found in compound (119) is virtually strain-free.

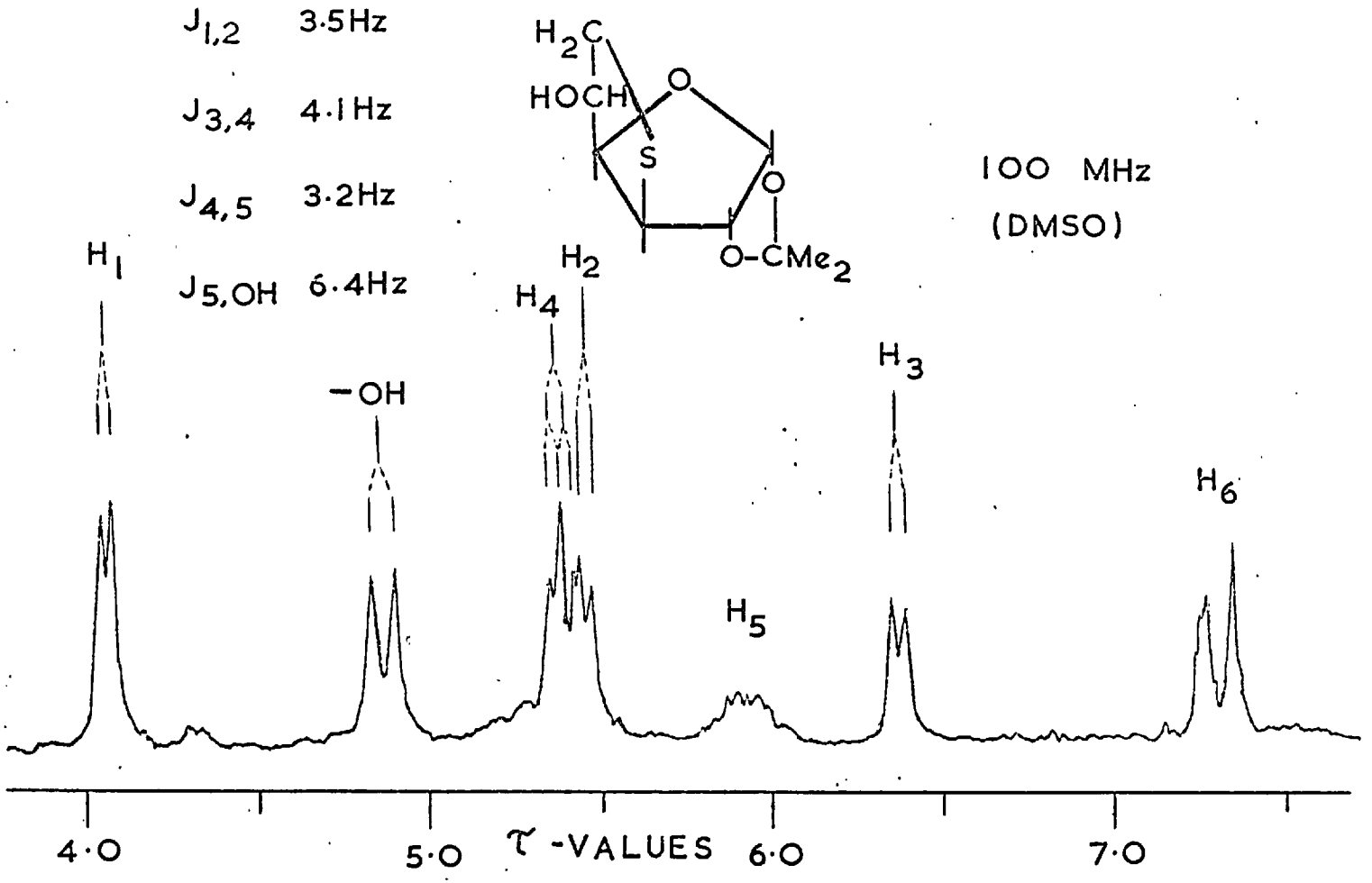
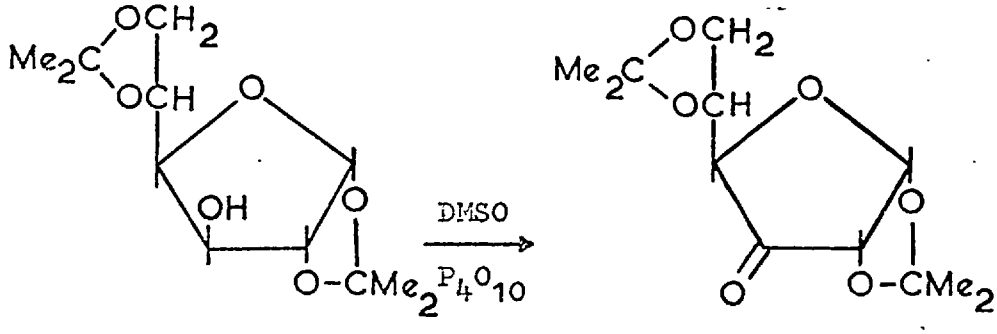

$J_{1,2}$ 3·5Hz
$J_{3,4}$ 4·1Hz
$J_{4,5}$ 3·2Hz
$J_{5,OH}$ 6·4Hz
H_2C
HOCH
O
S
O
O-CMe$_2$
100 MHz
(DMSO)
H_1
H_2
H_4
H_3
H_6
−OH
H_5
4·0
5·0
τ -VALUES
6·0
7·0

Fig. 4

6-Thio-D-allofuranose Series:

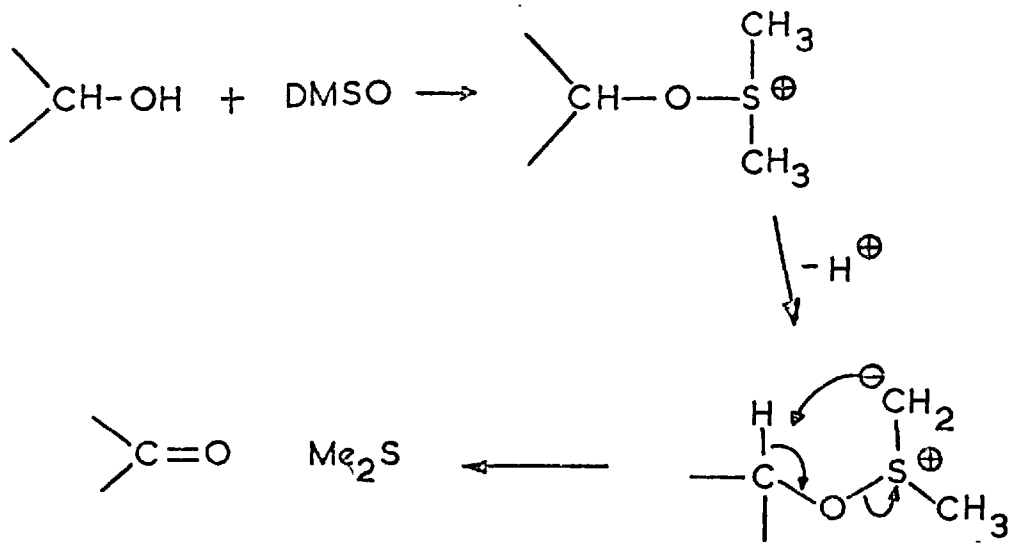
The synthesis of 3,6-dideoxy-3,6-epithio-1,2-O-isopropylidene-α-D-glucofuranose (119) described above was effected by the intramolecular nucleophilic displacement of a 6-O-tosyl group by a 3-thio anion. In the D-allose series, an intramolecular nucleophilic displacement of a 3-O-tosyl group by a 6-thio anion would be expected to yield the same 3,6-epithio compound (119).

Oxidation of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (120) with DMSO / P_4O_{10}[75,117,118] gave the 3-oxo sugar (121) in 65% yield. Variable yields were reported by earlier workers, and the reaction is certainly unpredictable. The best method for performing the reaction was to keep the amount of phosphorus pentoxide down to a minimum, and to prepare the DMSO / P_4O_{10} reagent before adding the glucose compound.



(120) (121)

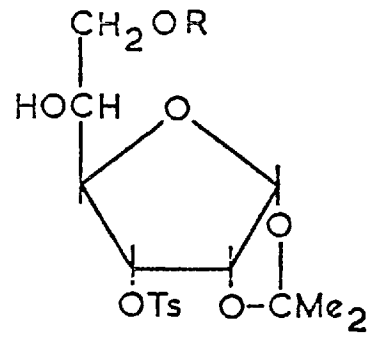
The mechanism proposed for this reaction by Epstein and Sweat[119] is illustrated below:



Borohydride reduction of (121) proceeds in a stereospecific manner[120]; the sole product being the D-allo isomer of (120). The 1,2:5,6-di-O-isopropylidene-α-D-allofuranose was converted into its tosylate, and then the 5,6-O-isopropylidene group was selectively removed under standard conditions[114] to give the crystalline 1,2-O-isopropylidene-3-O-tosyl-α-D-allofuranose (122). This reaction was straightforward and simple to perform because the product (122) is a nicely crystalline solid, and is easily purified. The analogous reaction in the 3-O-tosyl glucose series (described later in this thesis) presented many more experimental difficulties.

Compound (122) was smoothly converted into the 3,6-di-O-tosyl compound (123) which was the key intermediate in the synthesis of the 6-thio allose compounds.

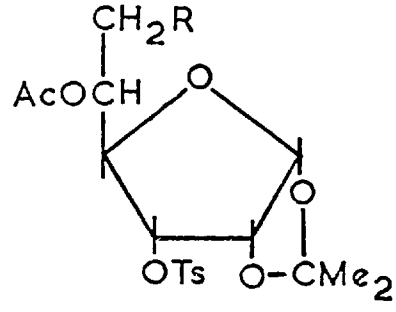
Reaction of (123) with potassium thiolacetate in refluxing acetone, followed by acetylation of the intermediate product



(122) R=H

(123) R=Ts

gave a mixture of the 5-O-acetyl-6-S-acetyl derivative (124), and the 5,6-di-O-acetyl compound (125).



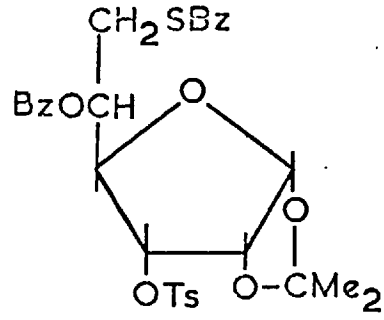
(124) R=SAc

(125) R=OAc

The formation of (125) is presumably due to the presence, as an impurity, of compound (122) in the sample of ditosylate (123) used in the reaction.

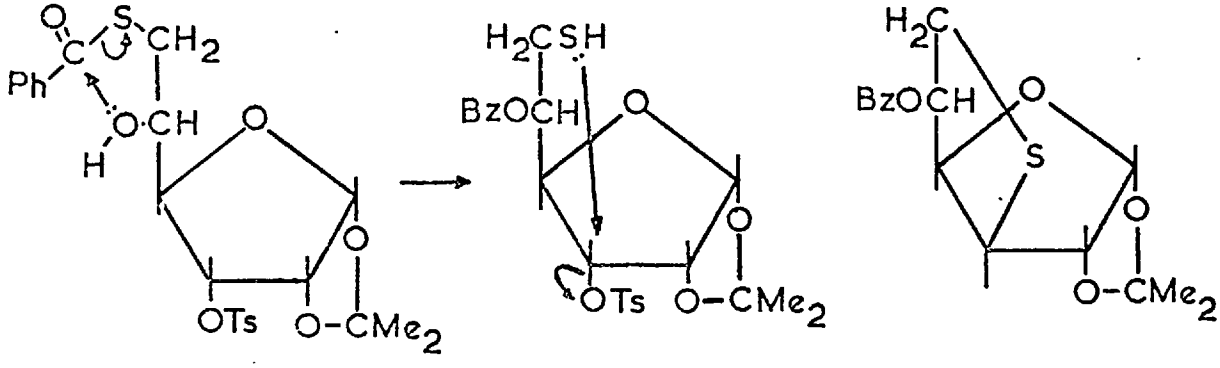
Using a better thio-nucleophile and a higher reaction

temperature, namely potassium thiolbenzoate in refluxing ethanol, compound (125) was converted (after benzoylation) into the 5-O-benzoyl-6-S-benzoyl compound (126) in good yield, there being no evidence for any 5,6-di-O-benzoyl compound.



(126)

However a second compound was formed which was found to be the 5-O-benzoyl-3,6-dideoxy-3,6-epithio derivative (127). The formation of this compound can be visualised as involving the initial formation of a 6-S-benzoyl compound, an intramolecular acyl migration, and then an intramolecular cyclisation as illustrated below:



(127)

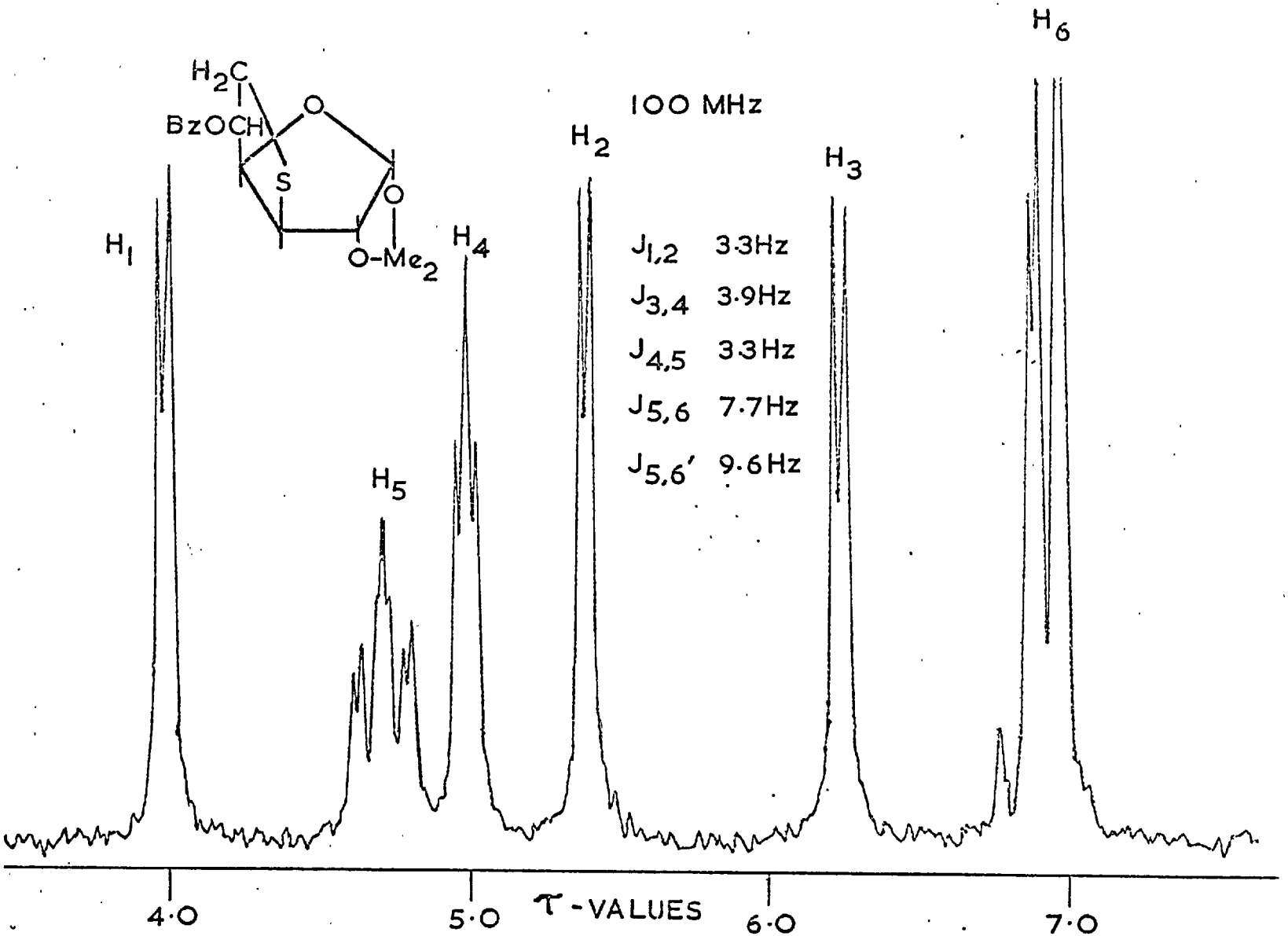

H6
H2C
BzOCH
O
S
O
O-Me2
100 MHz
H2
H3
H1
H4
J1,2 3·3Hz
J3,4 3·9Hz
J4,5 3·3Hz
J5,6 7·7Hz
J5,6' 9·6Hz
H5
4·0
5·0
τ-VALUES
6·0
7·0

Fig. 5

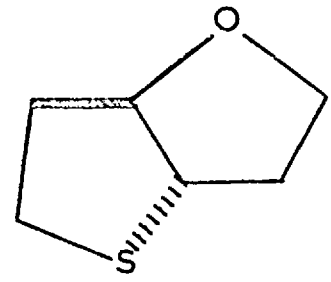
The n.m.r. spectrum of (127) is illustrated overleaf (Fig. 5), and again shows $J_{2,3} = 0$, indicative of a virtually strain-free ring system. It will also be noted that the protons at C-3, and C-6 which are directly bonded to the sulphur atom experience a positive shielding effect in the n.m.r.

Saponification, under mild conditions, of the 5-O-acetyl-6-S-acetyl compound (124) and the 5-O-benzoyl-6-S-benzoyl compound (126) gave a 3,6-epithio bridged compound which was identical (spectra, m.p., mixed m.p.) with the compound (119) prepared from 3-thioglucose - Freudenberg's 3-thiohexose. Thus the absolute configuration of Freudenberg's 3-thio sugar has been shown to be D-gluco by the unambiguous synthesis of a cis-fused [5,5]-bicyclic compound (119) by two different procedures.

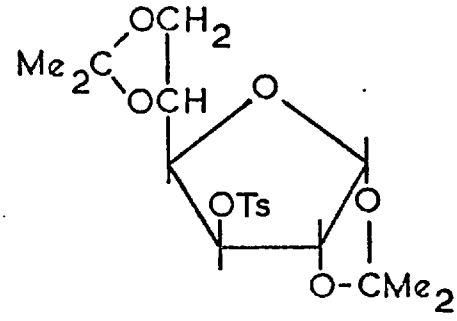
6-Thio-D-glucofuranose Series:

Since the work of Owen and Peto[111] had shown that a trans-3-thia-bicyclo-[3,3,0]-octane system could easily be prepared and that this system was acid-stable, it was speculated that it might be possible to prepare a trans-2-oxa-6-thia-bicyclo-[3,3,0]-octane system (128) in the sugar field.

Treatment of 1,2:5,6-di-O-isopropylidene-3-O-tosyl-α-D-glucofuranose (129) with aqueous acetic acid effected the removal of the 5,6-O-isopropylidene group[114]. This reaction was not as straightforward as the literature indicated. The



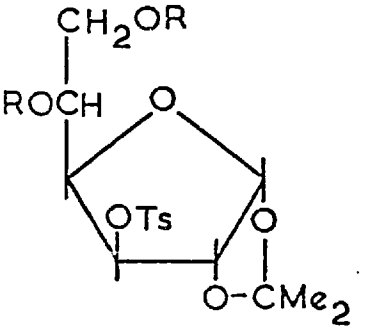
(128)



(129)

point of "half-hydrolysis" was not too easy to monitor and the product from the reaction was a recalcitrant gum which was difficult to purify completely. When the 1,2-O-isopropylidene compound (130) was tosylated under literature conditions[114], the only crystalline product obtained was the 3,5,6-tri-tosylate[60] (131).

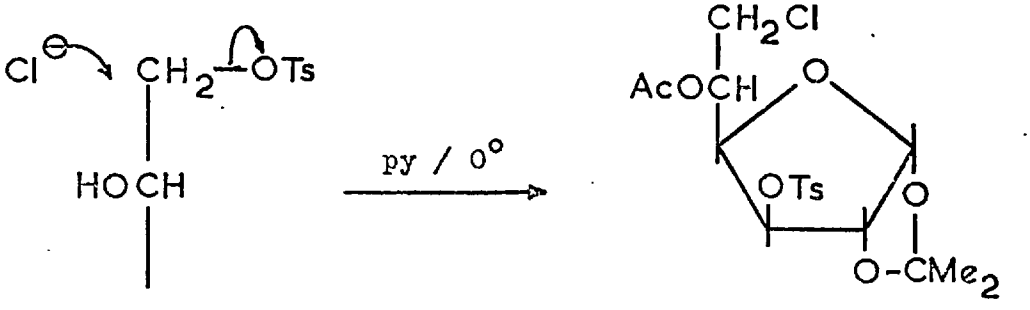
Using more controlled conditions, and only 1 equivalent of tosyl chloride (see Experimental Section, page 128), compound (130) was tosylated at the primary position, and the 5-hydroxyl group was then acetylated. Extensive purification



(130) R=H

(131) R=Ts

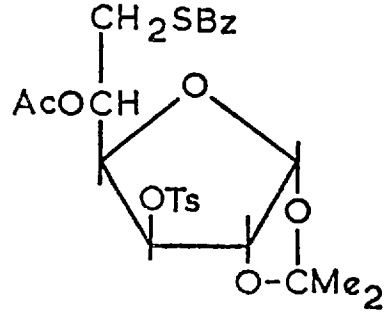
of this reaction mixture gave unexpectedly the 5-O-acetyl-6-chloro-6-deoxy compound (132). This compound must have arisen by tosylation at C-6, followed by intermolecular nucleophilic displacement of the tosyloxy group by chloride ion. This illustrates the extreme ease of displacement of the primary tosyloxy group in the glucofuranose series.



(132)

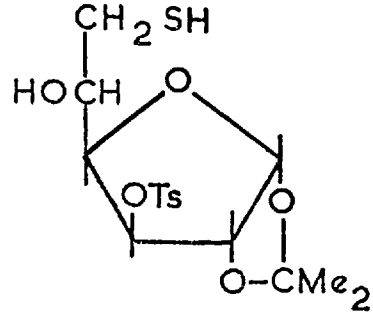
The chlorine at the primary position in (132) was somewhat

more resistant to displacement than the tosyloxy group had been. Compound (132) was unaffected by potassium thiolbenzoate in refluxing acetone, but underwent ready conversion into the 5-O-acetyl-6-S-benzoyl compound (133) in DMF at 70°.



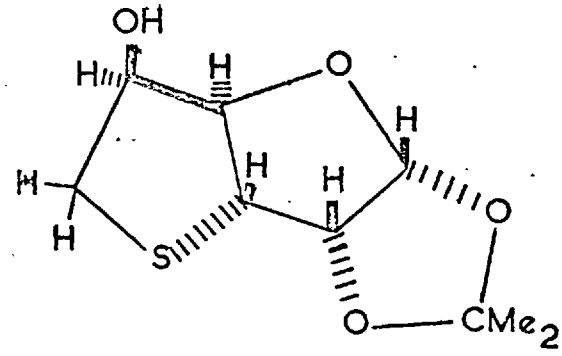
(133)

When compound (133) was saponified under exactly the same experimental conditions as (124) and (126), no cyclisation to give 3,6-dideoxy-3,6-epithio-1,2-O-isopropylidene-α-D-allofuranose occurred at all. The product of the reaction was shown by infra-red and n.m.r. spectroscopy to be the 6-thiol-3-O-tosyl compound (134).



(134)

A simple explanation for the lack of 3,6-epithio bridged compound can be inferred from an examination of molecular models. The 1,3-dioxolan ring causes the furanose ring to be puckered with C-3 lying above the plane of the ring as defined by C-1,C-4, and the ring oxygen atom. The furanose ring is fairly rigidly held in this puckered geometry and the formation of a trans-fused [5,5]-bicyclic system such as (135) would involve too strained a ring system for the molecule to be stable.



(135) 3,6-epithio-D-allo

In summary, the total evidence to show that Freudenberg's pyrolytic xanthate rearrangement occurs with retention of configuration is:-

1. N.m.r. evidence on the rearranged glucose xanthate, and on the thiol and disulphide derived therefrom indicates that the lack of coupling between 2-H and 3-H in the 1,2-O-isopropylidene furanose ring is uniquely in accord with the configuration at C-2 and C-3 being the threo configuration.

2. The formation of the same cis-fused 3,6-epithio furanose system from both a 3-thio-6-O-tosyl-glucofuranose compound, and a 6-thio-3-O-tosyl-allofuranose derivative.

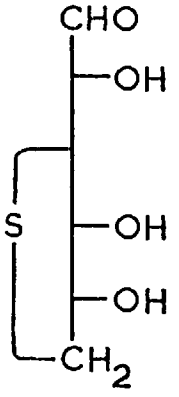
3. The lack of any trans-fused 3,6-epithio furanose compound from a 6-thio-3-O-tosyl-glucofuranose derivative.

Part 2

The Chemistry of 3,6-dideoxy-3,6-epithio Sugars:

1. Furanose Compound:

3,6-Dideoxy-3,6-epithio-D-glucose was prepared by treatment of 3,6-dideoxy-3,6-epithio-1,2-O-isopropylidene-α-D-glucofuranose (119) with hot mineral acid. The n.m.r. spectrum of the reaction mixture showed no resonances to the low field side of τ 3.8. Thus the open-chain form of the sugar (136) can be excluded.



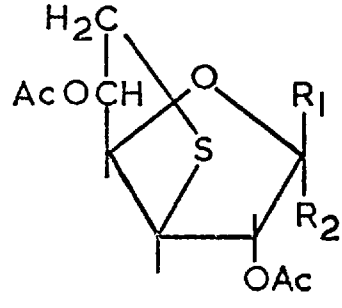
(136)

As a matter of interest, an authentic sample of 3,6-anhydro-D-glucose (kindly supplied by Professor L.N. Owen) was examined by n.m.r. spectroscopy in the same solvent (DMSO d^6) as was used for the 3,6-epithio compound. There was no evidence at all for describing the 3,6-anhydro-D-glucose as an open-chain aldehyde in DMSO solution. Previous workers[51,55] have described 3,6-anhydro-D-glucose as an open-chain aldehyde

because it gave chemical reactions diagnostic of an aldehyde (i.e. restored the colouration to Schiff's reagent). However it seems more correct to describe 3,6-anhydro-glucose as a furanose sugar in a labile equilibrium with its open-chain form, the hemiacetal ring form being just the more stable.

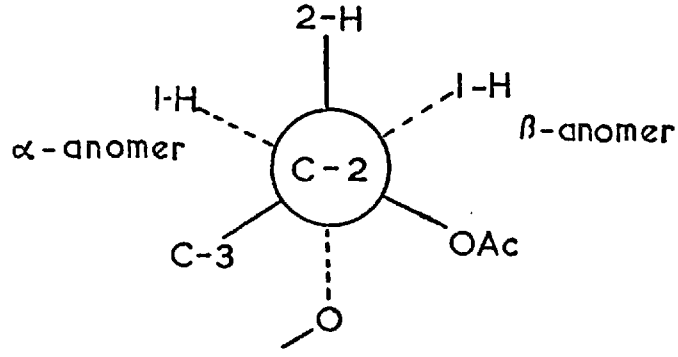
The exact ring size adopted by the 3,6-epithio-glucose was deduced from a close examination of the n.m.r. spectrum of the 1,2,5-tri-O-acetyl derivative. The work of Lemieux and Stevens[121] has indicated that there is a chemical shift difference Δ of ca. 0.2 to 0.6 p.p.m. between the τ-values for the β- and α-anomers of hexopyranose pentaacetates in chloroform, the α-anomer always being at the lower field.

Acetylation of the 3,6-epithio compound gave an oil, the spectrum of which indicated it to be an anomeric mixture of the α-furanose (75%) and β-furanose (25%) (137), $\Delta\beta$-α being 0.33 p.p.m. The coupling constants $J_{1,2}$ indicated that the sugar ring was furanoid in size. In the α-anomer, $J_{1,2}$ was 4.4 Hz, and in the β-anomer, $J_{1,2}$ was essentially zero.



(137) R_1=H, R_2=OAc 75%
R_2=H, R_1=OAc 25%

In the pyranoid ring structure, the sugar would have been in the 1C conformation, and in such a geometry the coupling 1-H to 2-H would have been virtually identical in either anomer as the conformation as viewed along the C-2 - C-1 bond axis is such as to make the dihedral angle between 1-H and 2-H almost the same in either anomer.

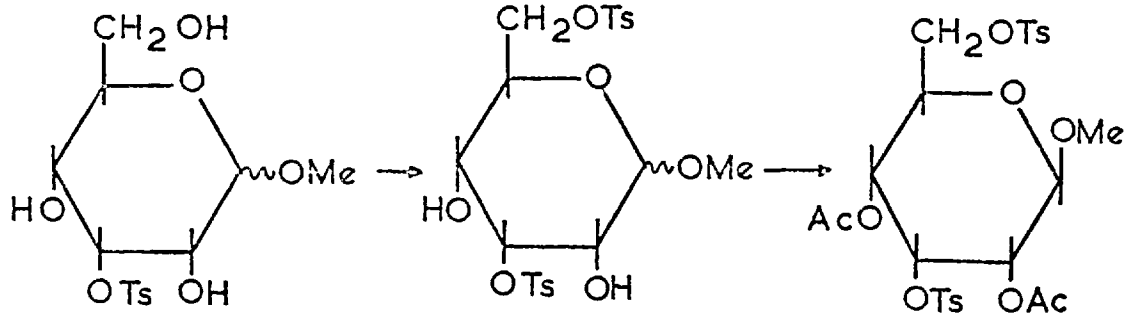


The chemical shifts and the values of $J_{1,2}$ of the anomeric protons (α- τ 3.46; β- τ 3.79) were unequivocally in accord with the sugar in a furanose form (137)

2. Pyranose Compound:

1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-allofuranose was subjected to a "Fischer-glycosidation" using the general conditions described for the glucose analogue by Angyal and his co-workers[87]. The product, methyl 3-O-tosyl-D-allopyranoside (138) could not be crystallised, and so it was converted into the 3,6-di-O-tosyl compound (139)

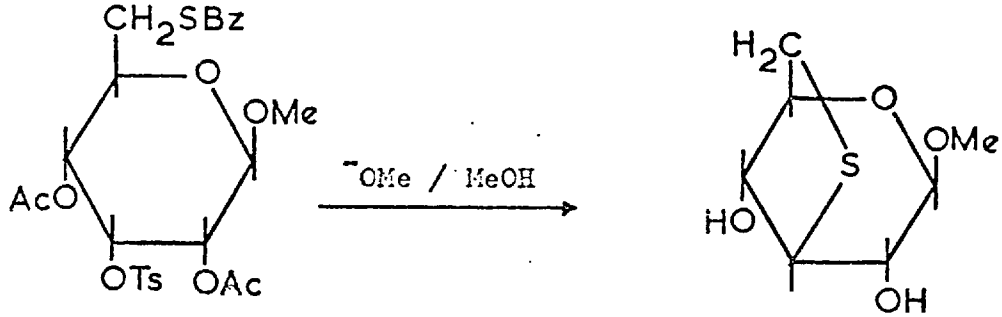
under the standard conditions[123], and thence by acetylation into the fully esterified sugar (140), which was crystalline.



(138) (139) (140)

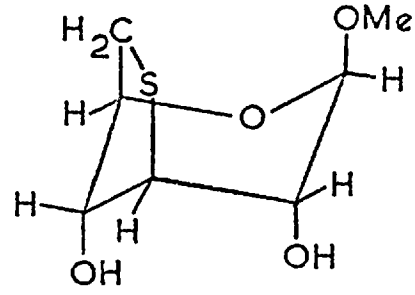
The anomeric configuration of compound (140) could not be inferred from any spectral or optical data, but the question was settled in favour of the β-configuration from the value of the optical rotation of the 3,6-dideoxy-3,6-epithio glycoside to be described later.

As was expected[43,89], the displacement of the 6-O-tosyl group in compound (140) occurred with great ease using potassium thiolbenzoate in boiling acetone. The resulting solid 6-S-benzoyl compound (141) on treatment with methoxide gave the crystalline 3,6-epithio glycoside (142) in good yield.



(141) (142)

The n.m.r. spectrum of (142) is illustrated overleaf. It is almost certain that the conformation of (142) will be the 1C conformation (143) and it is impossible from the value



(143)

of $J_{1,2}$ to establish the anomeric configuration, as this coupling constant would be about the same for both anomers. The optical rotation, $[\alpha]_D^{22}$ -65°, provided the only tangible evidence. The values of the optical rotations of methyl 3,6-anhydro-α-D-glucopyranoside and methyl 3,6-anhydro-β-D-glucopyranoside, as given by Haworth, Owen, and Smith[52], are +56° (H_2O) and -138°(H_2O) respectively. Assuming that the oxygen bridge and the sulphur bridge do not make any profound difference upon the optical rotations of exactly analogous compounds containing such bridging systems, then the observed optical rotation of (143) is in accord with it being β in anomeric configuration.

A very interesting point concerning the n.m.r. spectrum (Fig. 6) of (143) is the symmetrical quartet signal at τ 5.08

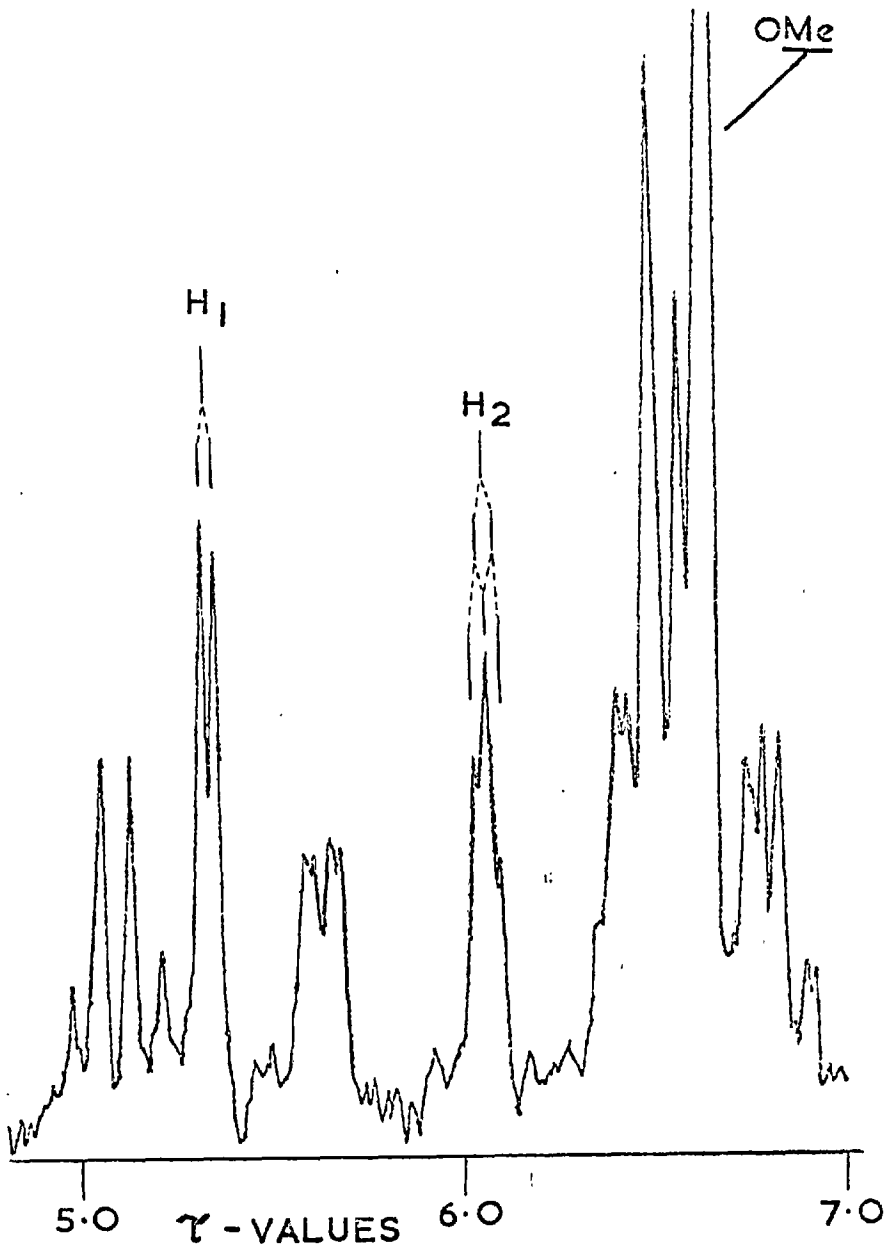
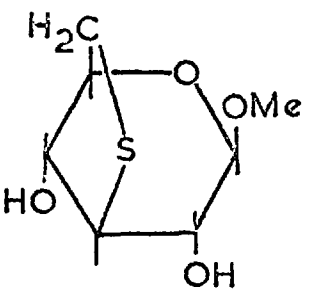


Fig. 6



100 MHz

$J_{1,2}$ 3·3 Hz

$J_{2,3}$ 3·0 Hz

due to 5-H. The appearance of this resonance can only be explained if $J_{4,5} = J_{5,6} = J_{5,6'}$.

When methyl 3,6-dideoxy-3,6-epithio-β-D-glucopyranoside (143), the thio-analogue of methyl 3,6-anhydro-β-D-glucopyranoside, was treated with a solution of hydrogen chloride in AnalaR chloroform no rearrangement to the furanoside form of (143) was observed. There was a very small change in the observed angular rotation, presumably due to slight hydrolysis of the glycoside, but the only crystalline compound obtained from the reaction mixture was the starting material. There was no evidence for any rearranged compound.

In their paper[52] of 1941, Haworth and his colleagues discussed the driving force for the pyranoside → furanoside isomerisation in the 3,6-anhydro series in terms of ring strain. On assembling a molecular model of methyl 3,6-anhydro-D-glucopyranoside, it is apparent that the 3,6-anhydro bridge does put a considerable strain onto the pyranose ring. However the furanose isomer of the 3,6-anhydro compound exhibits virtually no ring strain at all, and thus the relief of ring strain would seem to be the driving force for the isomerisation.

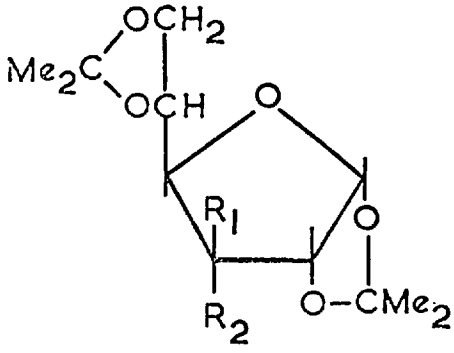
The internuclear C-O bond distance is approximately 1.50 Å, whereas the internuclear C-S bond distance is about 1.80 Å. The increased size of the 3,6-epithio bridge over the oxygen analogue causes far less ring strain in the pyranose sugar

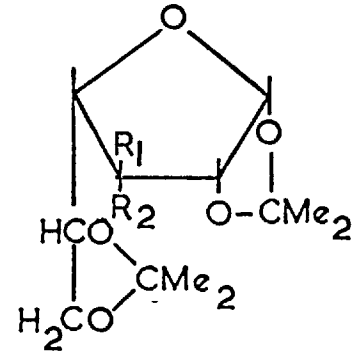
ring. This can be seen quite clearly from inspection of molecular models. Apart from these considerations, there is the enigmatic sulphur atom in the bridge. Previous work[111] has shown the apparent stability of trans-fused [5,5]-bicyclic systems containing a sulphur atom. It may be that the sulphur atom is capable of reducing the C-S-C bond angle in slightly strained systems such as (143), and thus removing the driving force for the pyranoside → furanoside rearrangement. Valence-shell expansion of the sulphur atom[123], which would involve the 3d orbitals to some extent in bonding, and thus allow more flexibility in the bond-angle at the sulphur atom, might be a contributory factor in the cause of the lack of any rearrangement.

Part 3

1. Furanose system:

The four diastereoisomeric compounds studied were the 1,2:5,6-di-O-isopropylidene-3-O-toluene-p-sulphonyl derivatives of glucose (144), allose (145), galactose (146), and gulose (147); the stereochemistry thus differed only at C-3 and C-4, and the purpose of the work was to see the effect of these variations on the reactivity of the sulphonyloxy group towards displacement by thiolbenzoate ion.





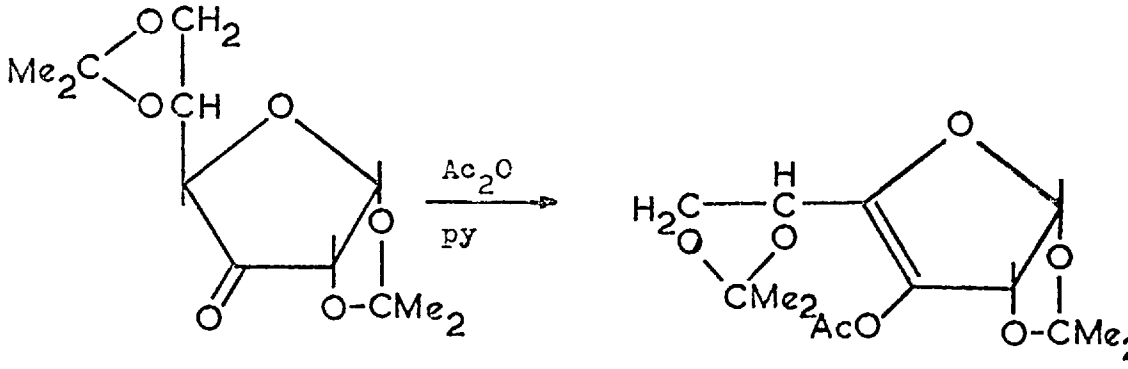
(144) R_1=OTs, R_2=H (gluco)

(145) R_1=H, R_2=OTs (allo)

(146) R_1=OTs, R_2=H (galacto)

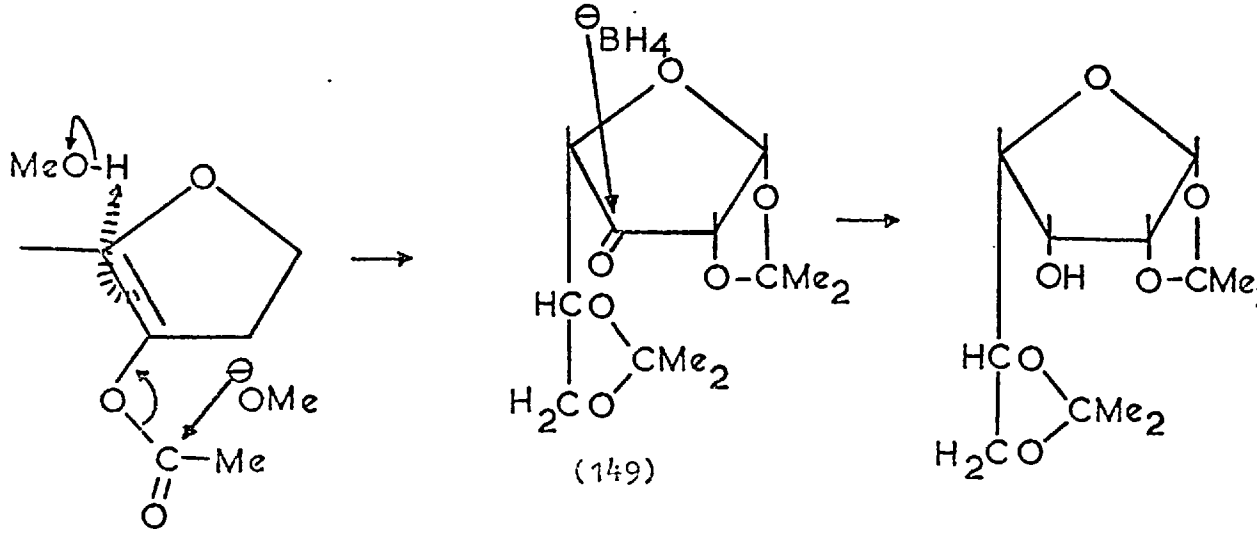
(147) R_1=H, R_2=OTs (gulo)

The precursor of (147), 1,2:5,6-di-O-isopropylidene-α-D-gulofuranose, was prepared by zu Reckendorf's method[124]. The essential step is the generation of two asymmetric centres at C-3 and C-4 from the enol-acetate (148) (derived from the 3-oxo sugar (121), page 62) using methanolic sodium borohydride. The formation of the gulose derivative can be rationalised as

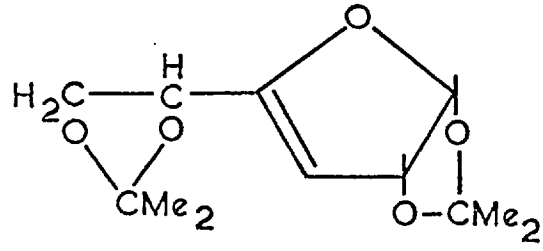


(121) (148)

involving a basic hydrolysis (MeOH / BH_4^- is basic) of the ester to give the transient enol. This ketonises, picking up a proton at C-4 from the less hindered side of the molecule, i.e. the "top-side" of the molecule. The intermediate 3-oxo sugar (149), 1,2:5,6-di-O-isopropylidene-α-D-xylo-hexofuranos-3-ulose, is then reduced by the borohydride, the approach of the reagent being from the less hindered exo side of the molecule.



1,2:5,6-Di-O-isopropylidene-α-D-galactofuranose was prepared from D-glucose by the trans elimination of toluene-p-sulphonic acid from 1,2:5,6-di-O-isopropylidene-3-O-tosyl-α-D-glucofuranose to give the 3,4-unsaturated compound (150)[125,126] and the cis hydration of this compound via hydroboration[127].



(150)

A byproduct obtained from this reaction on one occasion was a 3,3' ether. N.m.r. evidence indicated that the molecule was composed of two 1,2:5,6-di-O-isopropylidene furanose units, and the mass spectrum showed that the compound had a M.W. of 502, consistent with the dimeric structure. Although the configuration of each unit was not established, several alternative configurations are possible. The dimer could have arisen via hydrolysis of the glucose tosylate by soda-lime and then reaction of the 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose so formed with the glucose tosylate at the reaction temperature of 210°. On this hypothesis, the configurations of the dimer units would be gluco and allo. The dimer could also have arisen at a later stage in the preparation

of 1,2:5,6-di-O-isopropylidene-α-D-galactofuranose. It is possible that the dimer was formed during the hydrolysis of the reaction product derived from the reaction of the unsaturated sugar (150) and diborane. On this hypothesis, one of the dimer units must have the galacto configuration and the configuration of the other unit could be either galacto or gulo.

Several trial displacement reactions were performed using 1,2:5,6-di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-glucofuranose (and its D-allose stereoisomer) and potassium thiolbenzoate in a mole ratio of 1:5. The reactions were carried out in DMF solution, and at reflux temperature (ca. 159°). Samples were taken at regular intervals, diluted with water, and extracted with chloroform. Such samples were investigated by infra-red spectroscopy, which showed that displacement was occurring in the glucose series as seen by monitoring the "carbonyl region" (1650 - 1750 cm^{-1}) for the appearance of the thiolbenzoate absorption. However care must be exercised in this respect, as DMF itself absorbs at ca. 1680 cm^{-1} (tertiary amide), and dibenzoyl disulphide is also present as an impurity. When the glucose tosylate and potassium thiolbenzoate were reacted for two hours at reflux temperature and then the reaction worked-up, a solid was eventually obtained. The n.m.r. spectrum of the solid showed it to be a mixture of unreacted tosylate (ca. 40%), and allose thiolbenzoate (ca. 60%). This result was a useful

pointer for indicating the approximate half-life of this reaction.

A thiolbenzoate displacement reaction was attempted on 1,2:5,6-di-O-isopropylidne-3-O-methanesulphonyl-α-D-gluco-furanose. The reaction was characterised by extensive decomposition, and no recognisable product could be obtained from this reaction. The use of mesylates was not pursued.

Trial experiments were performed on the glucose tosylate using the thio-nucleophiles, thiolacetate ion and thiolbenzoate ion. It was found that the latter was superior in ability to displace the sulphonyloxy group. Presumably thiolacetate ion is a poorer nucleophile than thiolbenzoate ion as the former could not displace the *exo* tosylate group in the glucose compound.

Initial qualitative experiments on the glucose and allose compounds (144) and (145) indicated that the reactions were occurring *via* an S_N2 mechanism with inversion of configuration. The allose tosylate was converted into the 3-S-benzoyl *gluco* derivative, which was also synthesised by benzoylation of the 3-thio-glucose compound (110c). Thus the stereochemistry of the product obtained from displacement of the allose tosylate group was proved. N.m.r. evidence indicated that the reaction of thiolbenzoate ion on the glucose and gulose tosylates (144) and (147) also occurred with inversion of configuration at C-3.

Initially the progress of the displacement reaction was

observed by infra-red spectroscopy. However as mentioned above this method was not fool-proof. The reaction was hence followed by n.m.r. spectroscopy, the loss of tosylate being monitored rather than the formation of S-benzoyl compound. The reason for observing the disappearance of tosylate was the unavoidability of having dibenzoyl disulphide as an impurity in the kinetics sample, and thus scanning the aromatic region of the spectra would give erroneous results. The n.m.r. spectral data were obtained on crude total reaction products. No attempt was made to purify the kinetics samples at all as this might result in the loss of tosylate or S-benzoyl derivative , thus altering the ratio of the two and giving erroneous results.

For a pseudo first-order reaction,

$$\frac{dx}{dt} = -k_{obs}\, x$$

$$\therefore \int \frac{dx}{x} = -k_{obs} \int dt$$

$$\therefore \log_{10} x = -k_{obs} / 2.303 \cdot t \quad \ldots\ldots\ldots\ldots (1)$$

For a second-order reaction, the reaction rate is given by:

$$V = k_2 \,[\text{Tosylate}]\,[\text{KSBz}]$$
$$= k_{obs}\,[\text{Tosylate}]$$

$$\therefore k_2 = k_{obs} / [KSBz] \quad \ldots\ldots\ldots\ldots\ldots\ldots(2)$$

The results of the kinetics experiments were treated graphically as follows, the logarithm, to the base 10, of the percentage (α) of tosylate remaining in solution (ordinate) was plotted against the reaction time. The straight-line graph (pseudo first-order kinetics) gave a value for k_{obs}, the first-order rate constant - equation (1), and the value for k_2 could be obtained using equation (2).

The kinetics experiments were performed under pseudo first-order conditions (1:10 mole ratio of tosylate to potassium thiolbenzoate), and Fig. 7 illustrates the data obtained on the four compounds (144)-(147). These results were obtained under identical conditions, the temperature of the oil-bath in which these experiments were carried out being constant at 178°, and the average internal temperature of the solutions being ca. 156°.

The second-order rate constants for the four sugars under these conditions were:

Aldose	k_2 ($mol^{-1} sec^{-1} litre$)	Relative RATE
Galactose	3.71×10^{-5}	1
Glucose	1.11×10^{-4}	3
Allose	5.65×10^{-4}	15
Gulose	2.19×10^{-3}	60

The first point to note from Fig. 7 is the anomalous

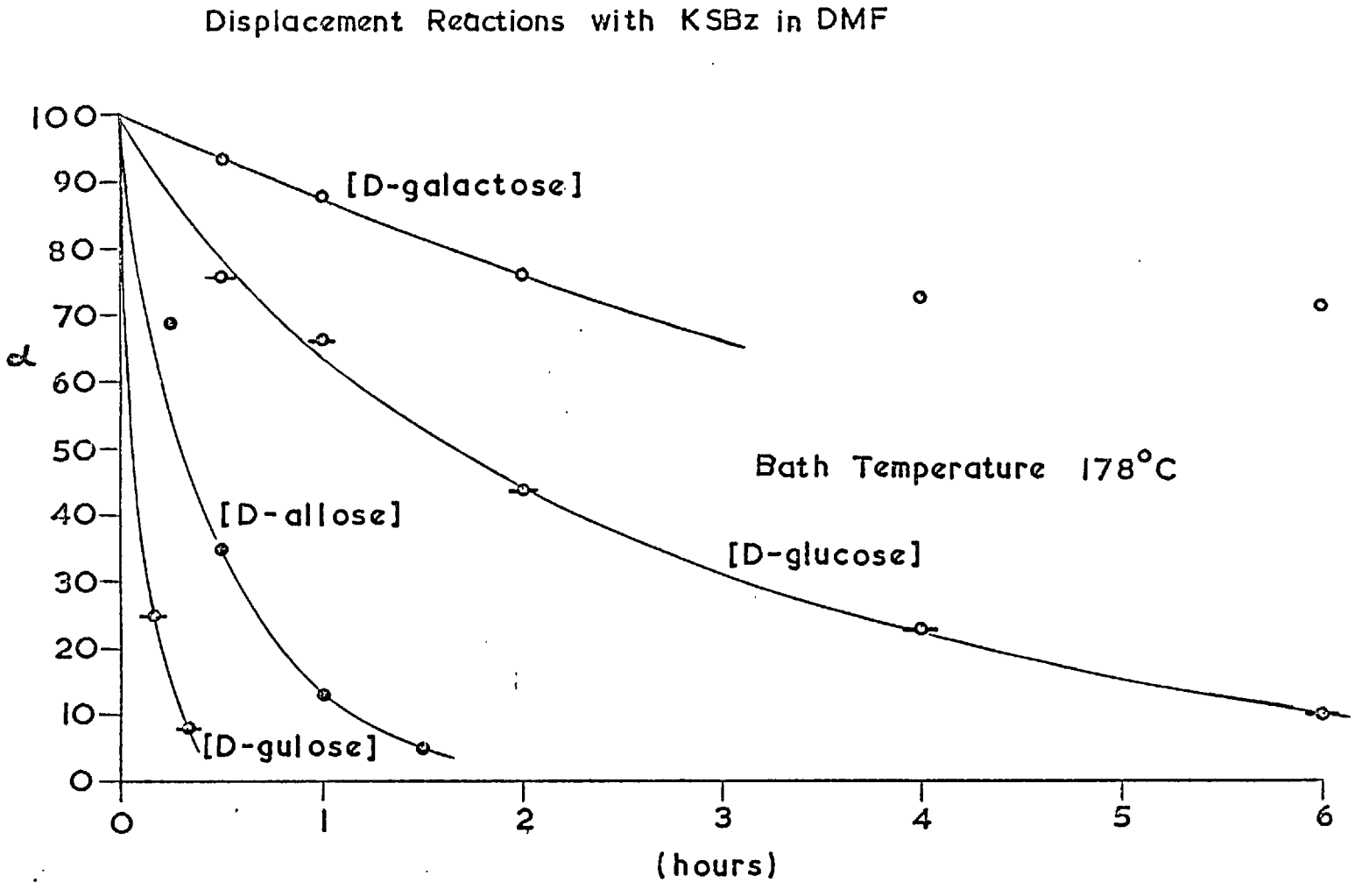
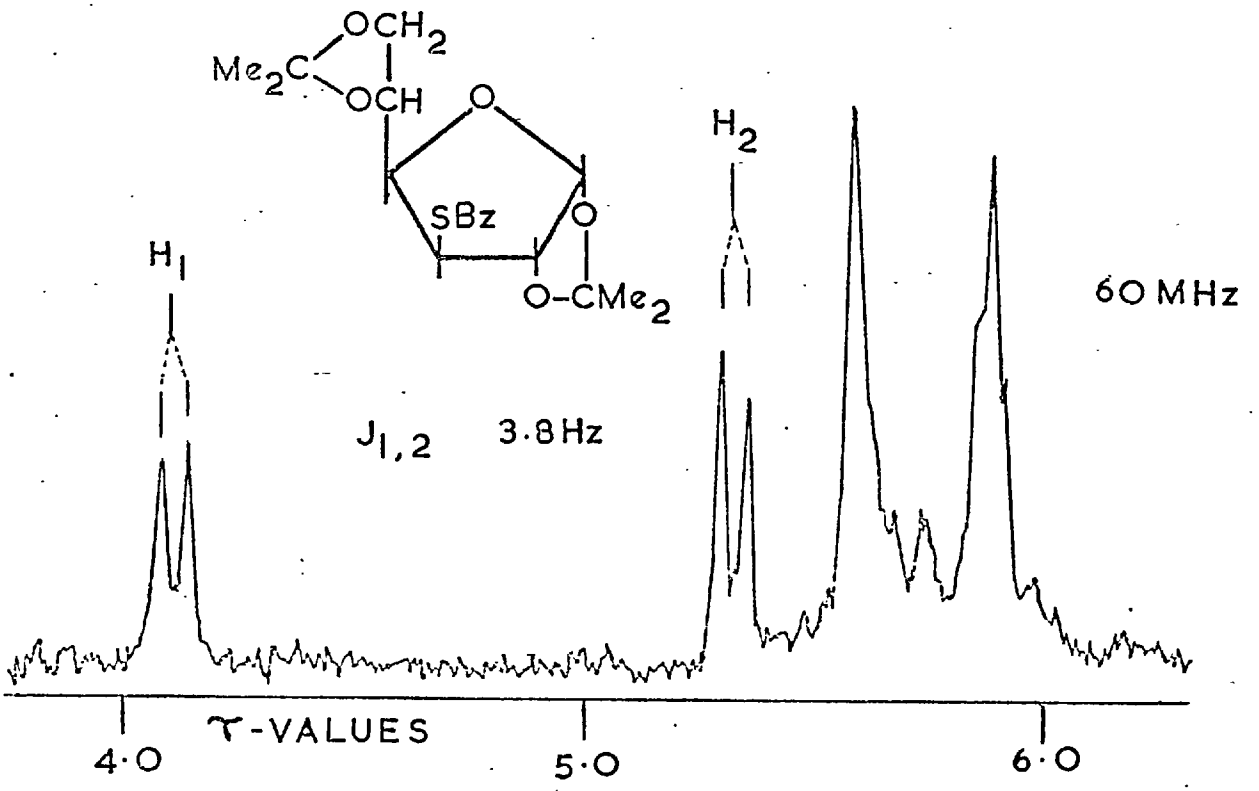

Displacement Reactions with KSBz in DMF
100
90
80
70
60
50
40
30
20
10
0
α
[D-galactose]
[D-allose]
[D-gulose]
[D-glucose]
Bath Temperature 178°C
0
1
2
3
4
5
6
(hours)

Fig. 7

result obtained for the D-galactose compound. The kinetics results showed a discontinuation in the normal α v t plot at about 2 hours of reaction. These results were double-checked and found to be an intrinsic property of this system. The value of k_2 for the galactose compound was calculated from the slope of the plot of $\log_{10}\alpha$ against t, the value of t being from 0 to 2 hours.

The kinetics data for the galactose compound were determined also in HMPT when the results gave a second-order rate constant k_2 of 6.67×10^{-4} mol^{-1} sec^{-1} litre; the internal temperature being 148.5°. When compared to the value of k_2 (3.71×10^{-5}) obtained in DMF with the internal temperature at 156.3°, these data indicate the superiority of HMPT as a solvent for S_N2 displacement reactions compared to D.M.F. With HMPT as solvent, there was no apparent divergence from pseudo first-order kinetics. However in both kinetics experiments, no pure 3-S-benzoyl gulose derivative could be obtained from the reaction mixture. These experiments on the galactose compound were characterised by a much greater tendency for decomposition than occurred with the other stereoisomers, which reacted smoothly with the potassium thiolbenzoate to give isolable inverted products. That from the allose derivative was identical with 3-S-benzoyl-1,2:5,6-di-O-isopropylidene-3-thio-α-D-glucofuranose prepared by benzoylation of 1,2:5,6-di-O-isopropylidene-3-thio-α-D-glucofuranose. Fig. 8 shows the


OCH2
Me2C
OCH
O
SBz
O
O-CMe2
H1
H2
60 MHz
J1,2 3.8Hz
τ-VALUES
4·0
5·0
6·0

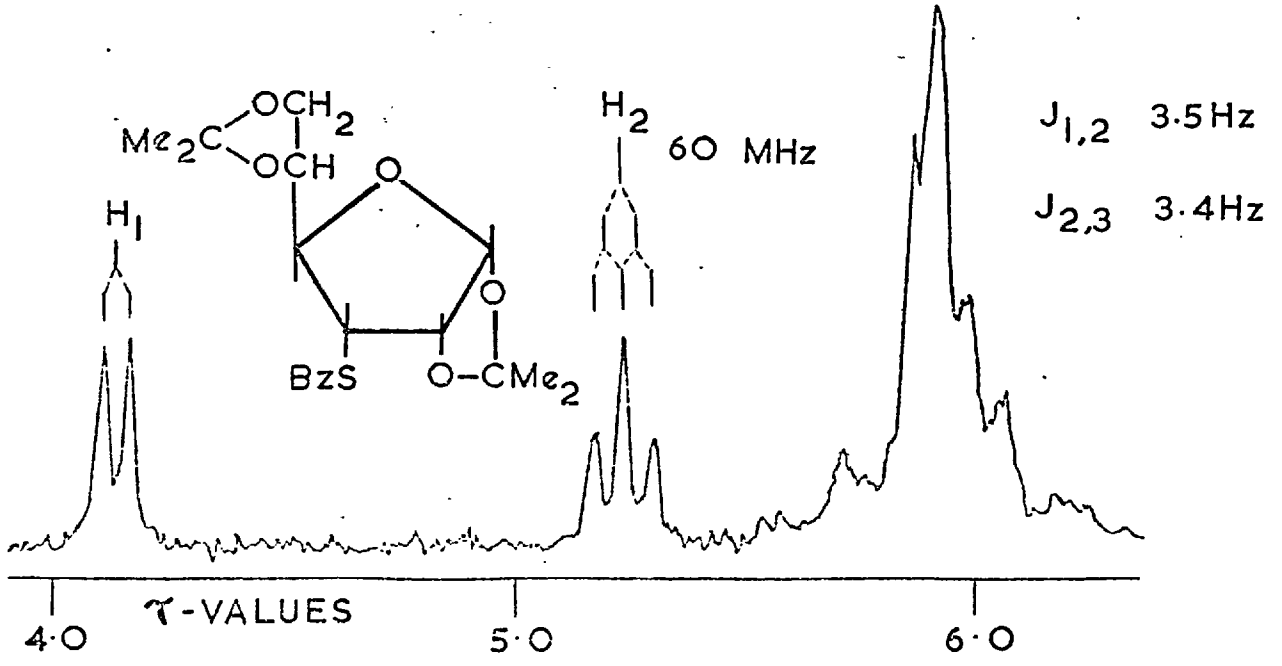
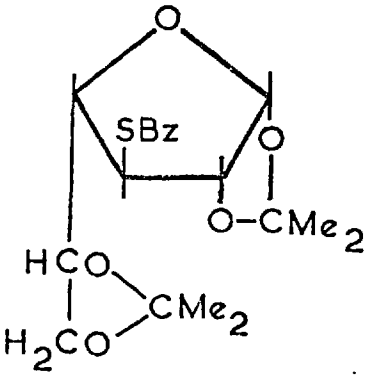

OCH2
Me2C
OCH
O
BzS
O
O-CMe2
H1
H2
60 MHz
J1,2 3.5Hz
J2,3 3.4Hz
τ-VALUES
4·0
5·0
6·0

Fig. 8

n.m.r. spectra of this thiolbenzoate and of the analogous 3-S-benzoyl allose derivative, prepared by S_N2 displacement on 1,2:5,6-di-O-isopropylidene-3-O-tosyl-α-D-glucofuranose. The lack of coupling between 2-H and 3-H is indicative of the D-gluco configuration, and the triplet resonance for 2-H, in the lower spectrum, indicates the D-allo configuration. Incidently this work has yielded another piece of evidence to show that Freudenberg's 3-thiohexose is D-gluco in absolute configuration.

The n.m.r. spectrum (Fig. 9) of 3-S-benzoyl-1,2:5,6-di-O-isopropylidene-3-thio-α-D-galactofuranose, isolated from the displacement reaction on the gulose toluene-p-sulphonate, shows that there is a small coupling (1.4 Hz) between 2-H and 3-H. Thus it appears that the bulky benzoylthio group at C-3 distorts the furanose ring somewhat. In fact the furanose ring becomes more flattened out, and thus 2-H and 3-H no longer have a dihedral angle of 90°.

The relatively facile S_N2 displacement of the endo tosyloxy group in 1,2:5,6-di-O-isopropylidene-α-D-allofuranose by ionic nucleophiles has been well documented[75,76,77]. Using azide ion as the nucleophile, Stacey and his co-workers[75] obtained a 50% yield of the inverted 3-azido-D-glucose derivative after 4 hours refluxing in DMF. The data in Fig. 7 indicate that by using thiolbenzoate ion as the nucleophile, the half-life of the reaction with the allose tosylate is



100 MHz

$J_{1,2}$ 3·9Hz

$J_{2,3}$ 1·4Hz

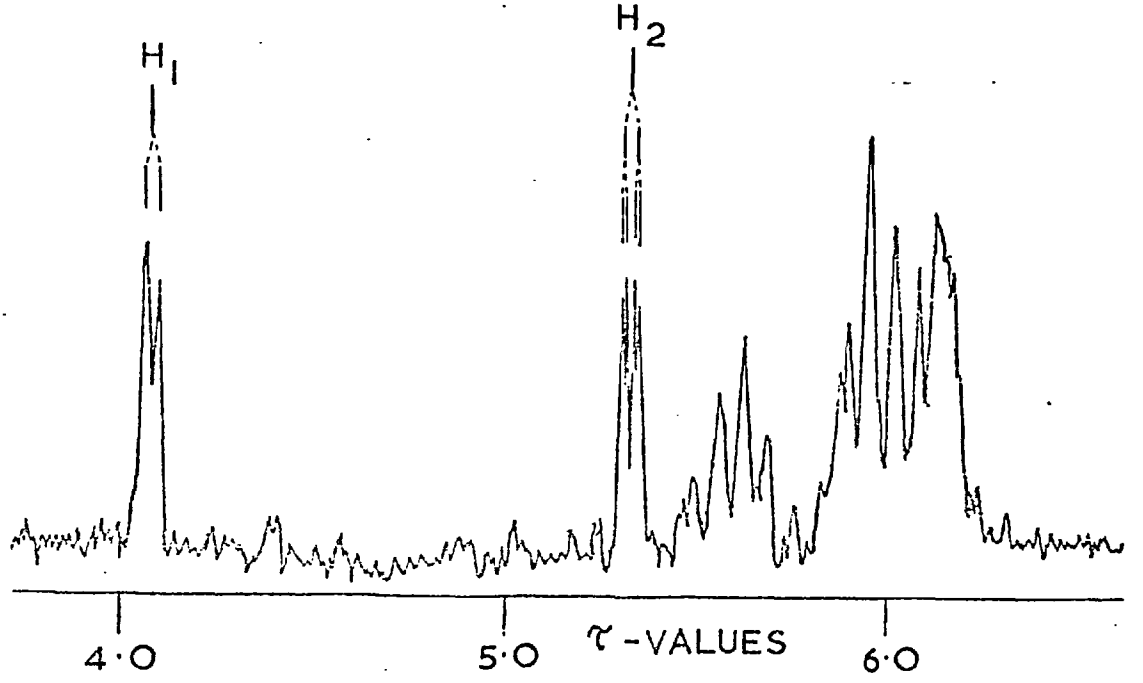


Fig. 9

about 20 minutes.

The reactivity of the 3-O-tosyl glucose compound, though less than that of the allose isomer, is quite unexpected. The rate ratio allose : glucose is only 5 : 1, whereas a much higher ratio would have been expected in view of the known[69] lack of reactivity of the endo tosyloxy group in the glucose compound towards benzyl sodium sulphide.

Recently there have appeared two reports[78,79] of nucleophilic displacement reactions on the 3-O-tosyl gulose derivative (147). Using azide ion as the nucleophile and refluxing DMF as the reaction medium, the gulose derivative was converted into a 3-azido-galactose derivative in 4 hours[79]. Using sodium benzoate in DMF at 140°, the reaction took 84 hours to be complete[79]. These reaction times, when compared with the reaction time (ca. 30 min.) observed when using potassium thiolbenzoate in refluxing DMF, indicate the superiority of the latter system for facile S_N2 displacement reactions. The other recent paper[78] described the displacement of the tosyloxy group in (147) by fluoride ion. The reaction was characterised by a marked tendency for the tosylate (147) to undergo elimination to give the 3,4-unsaturated compound (150). The large amount of byproduct formed must be due in some measure to the basicity of the fluoride ion, but more recent work[67] on an acyclic sugar derivative has shown that elimination can be dominant even when displacement reactions

are attempted with azide ion. The surprisingly high rate of reaction of the glucose compound (144) cannot, however, be explained by the occurrence of any side reactions, because the n.m.r. spectra of the kinetics samples were checked against the spectrum of the analytically pure 3-S-benzoyl-allose compound, and the spectrum of the sample of crude product collected after 8 hours' reaction in refluxing DMF was peak-for-peak identical to that of the pure material.

However to investigate the glucose and allose compounds more thoroughly it was decided to obtain some thermodynamical data on these compounds by measuring the reaction rates at various temperatures. The results are illustrated in Figs. 10 and 11.

For the glucose tosylate, the accumulated kinetics data are:

k_2 m^{-1} s^{-1} l.	$\log_{10} k_2$	Internal Temperature T^oC	T^oK	$1/T \times 10^3$
1.11×10^{-4}	-3.955	154.8	428.0	2.336
3.49×10^{-5}	-4.457	136.5	409.7	2.441
2.00×10^{-5}	-4.699	125.4	398.6	2.509

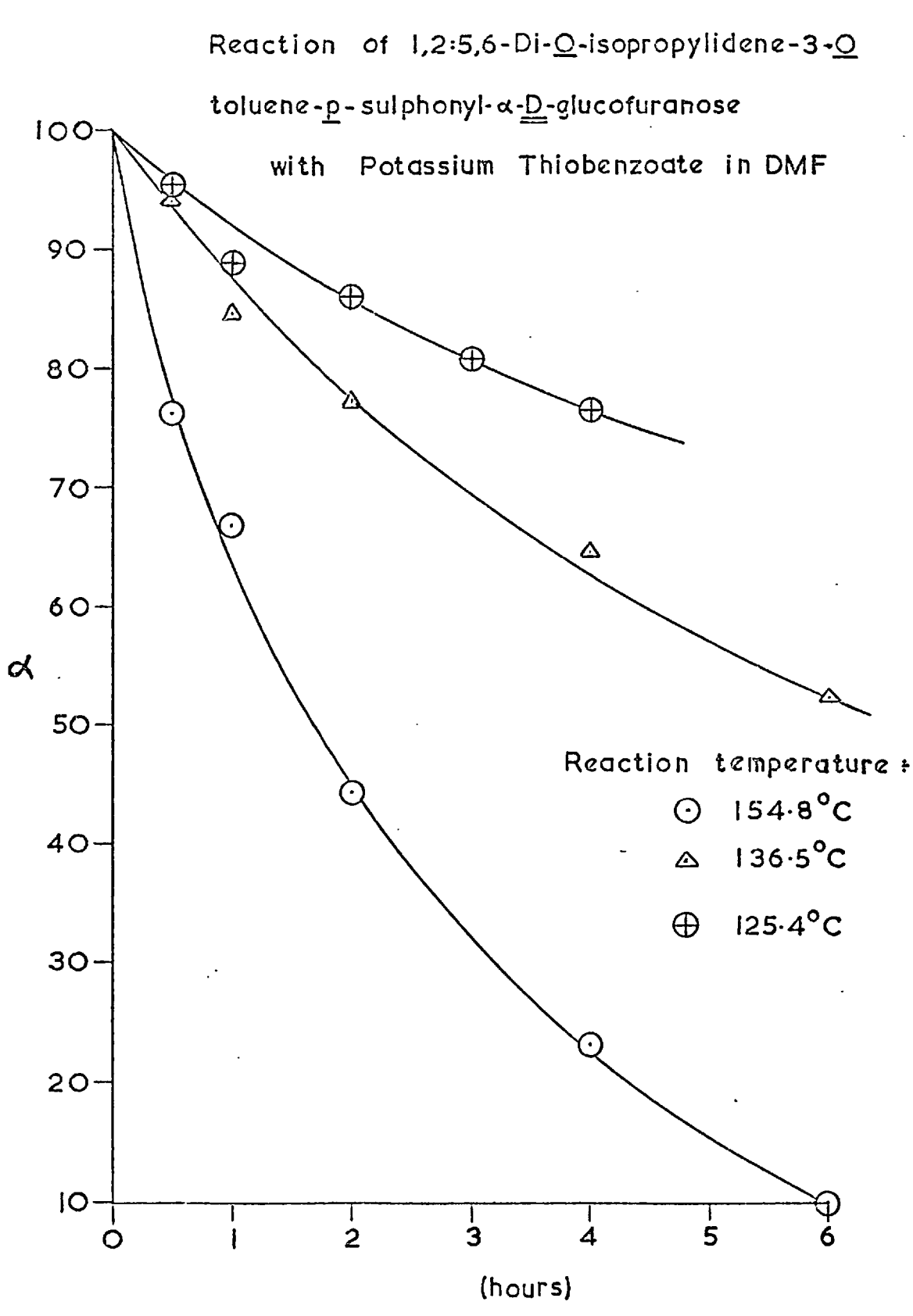

Reaction of 1,2:5,6-Di-O-isopropylidene-3-O
toluene-p-sulphonyl-α-D-glucofuranose
with Potassium Thiobenzoate in DMF
100
90
80
70
60
50
40
30
20
10
α
0
1
2
3
4
5
6
(hours)
Reaction temperature :
154·8°C
136·5°C
125·4°C

Fig. 10

For the allose tosylate, the accumulated kinetics data are:

k_2 m^{-1} s^{-1} l.	$\log_{10} k_2$	Internal Temperature T^oC	T^oK	$1/T \times 10^3$
5.65×10^{-4}	-3.248	157.2	430.4	2.324
1.72×10^{-4}	-3.765	140.0	413.2	2.420
8.00×10^{-5}	-4.097	125.6	398.8	2.508

The Arrhenius plot for the glucose tosylate is illustrated overleaf (Fig. 12). These data give a value of 20.4 ± 1 Kcal. mol^{-1} for the activation energy of the reaction. Substitution of this value for Ea and of the values listed in the table into the Arrhenius equation, $k = Ae^{-Ea/RT}$, gives an average value for the pre-exponential factor of 2.1×10^6. The Arrhenius plot for the allose tosylate is illustrated in Fig. 13, and the values for the activation energy and the average pre-exponential factor are 21.5 ± 2 Kcal. mol^{-1}, and 3.9×10^7 respectively. Within experimental error, the activation energies for the glucose and allose tosylates are the same.

Hulett[128] has described the activation energy as a composite function of several terms:

(a) a bonding term, Eb due to stretching bonds in the reactants and forming new ones in the transition state;

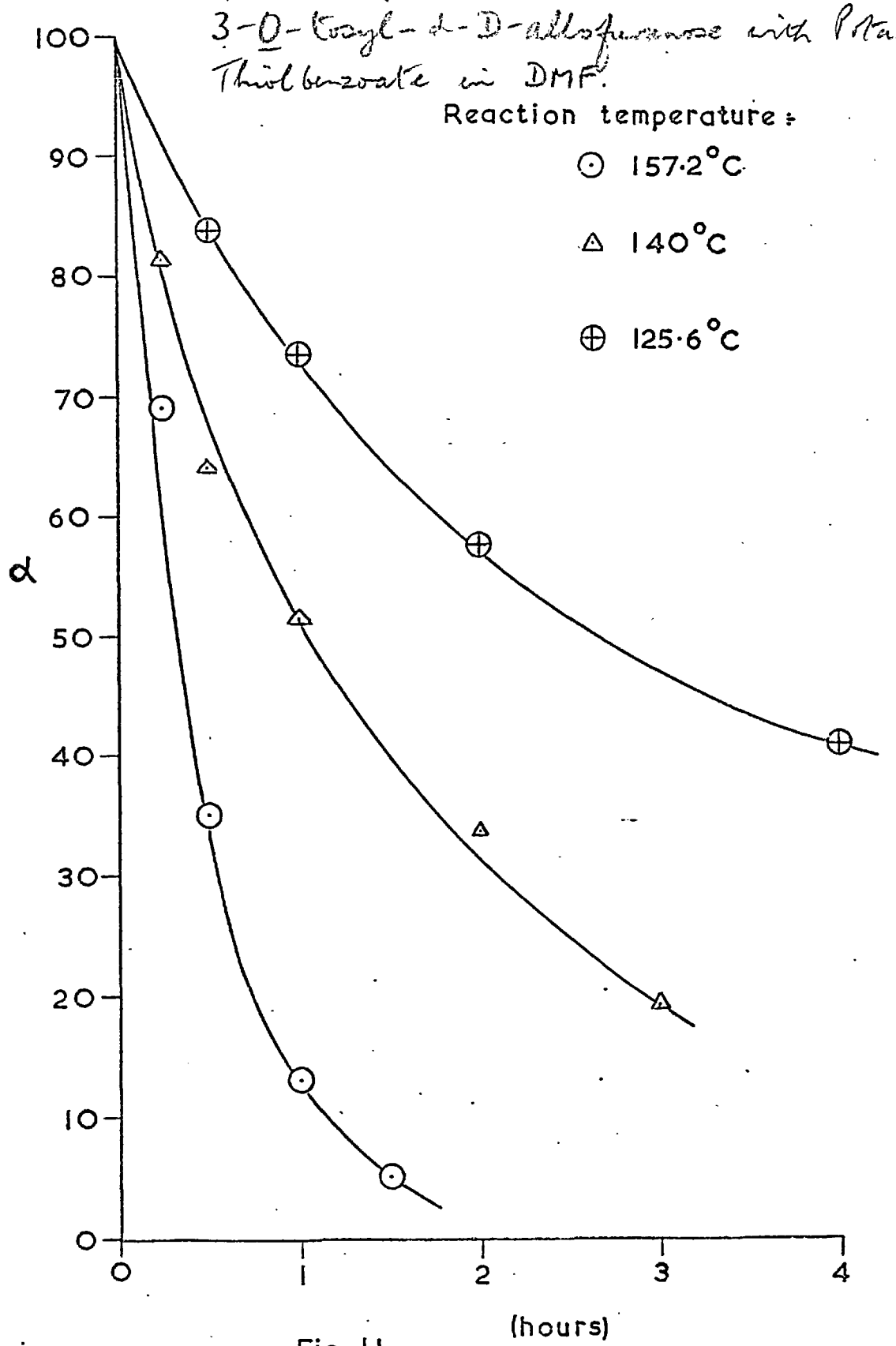

Reaction of 1:2-5:6-Di-O-isopropylidene 3-O-tosyl-α-D-allofuranose with Potassium Thiolbenzoate in DMF.
Reaction temperature:
⊙ 157·2°C
△ 140°C
⊕ 125·6°C
α
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
(hours)

Fig. 11

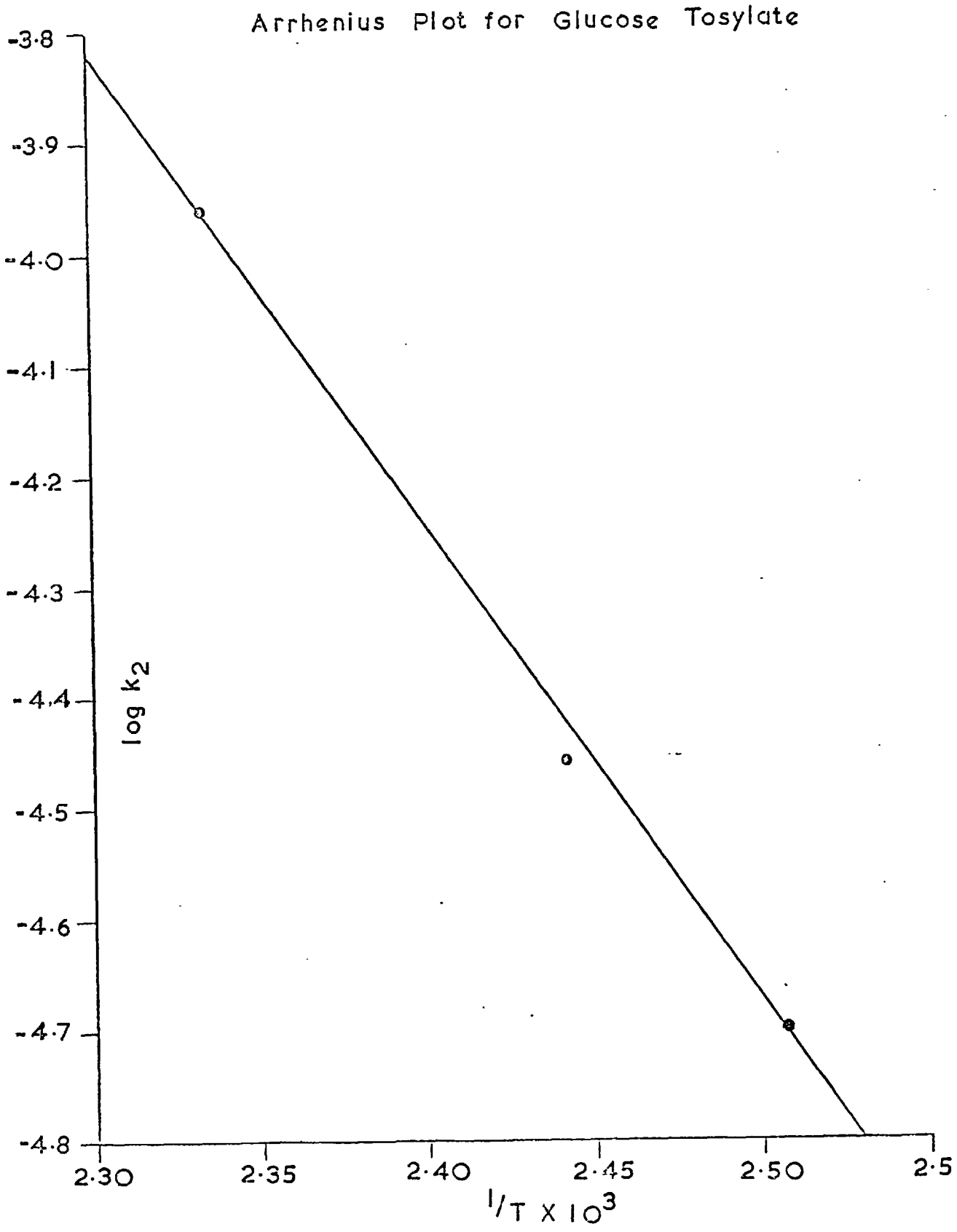

Arrhenius Plot for Glucose Tosylate
-3·8
-3·9
-4·0
-4·1
-4·2
-4·3
-4·4
-4·5
-4·6
-4·7
-4·8
log k2
2·30
2·35
2·40
2·45
2·50
2·55
1/T X 10^3

Fig. 12

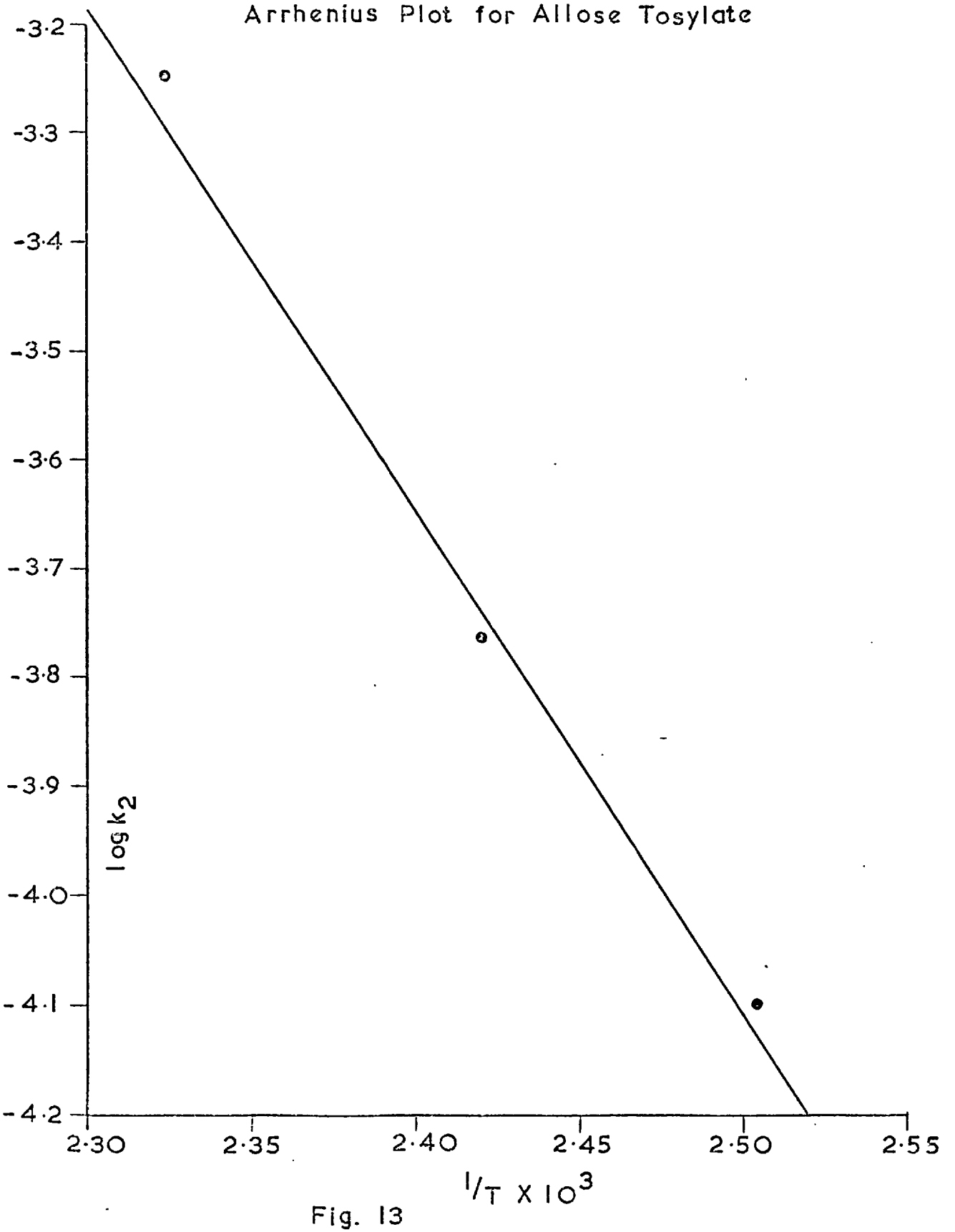

Arrhenius Plot for Allose Tosylate
-3·2
-3·3
-3·4
-3·5
-3·6
-3·7
-3·8
-3·9
-4·0
-4·1
-4·2
log k2
2·30
2·35
2·40
2·45
2·50
2·55
1/T X 10^3

Fig. 13

(b) Er from repulsion forces between unbonded atoms or groups at close range;

(c) Ee from electrostatic interactions between the reactants; and

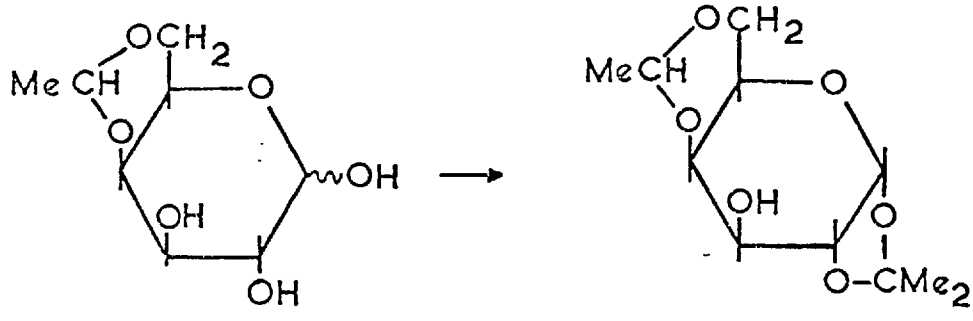
(d) Es due to varying degrees of solvation of the reactants and the transition state.

The displacement reactions on the glucose and allose tosylates are mechanistically identical, and one would expect the terms Eb and Es to be identical for the two reactions. However as the activation energies for the two reactions are equal within experimental error, it would appear that the sum of the terms Er and Ee is about equal in both reactions.

The pre-exponential factor A is often divided into a true collision number Z multiplied by a "probability factor" P ranging from 10^{-8} to 10^{6} [128]. Small values of P are thought to arise when the steric restrictions on a reaction are rather severe. Thus the explanation for the differing rates of reaction of the glucose and allose tosylates is that the stereochemistry of the molecule (exo, and endo respectively) governs the rate of reaction, and that the solvation of the ground and transition states, and repulsions between the thiolbenzoate ion and various atoms of the molecule is a constant factor in the reactions.

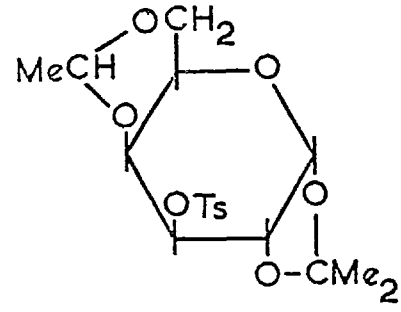
2. Pyranose system:

No quantitative kinetics work has been reported on 3-O-tosyl pyranose compounds, and, as a direct comparision with the preceding work, a simple kinetics investigation was attempted. The substrate chosen was the known[129,130] galactose compound (153). In common with the furanose compounds, this compound has a 1,2-O-isopropylidene ring system. Compound (153) was prepared by treatment of D-galactose with paraldehyde containing a trace of acid. The 4,6-O-ethylidene compound (151) was reacted with acetone using fused zinc chloride as a catalyst to give the 3-hydroxy compound (152)



(151) (152)

Compound (152) was not isolated, but tosylated directly. However the final product was a mixture of two components, the desired product (153), and 1,2:3,4-di-O-isopropylidene-6-O-tosyl-α-D-galactopyranose. The byproduct presumably arises via acetal exchange (ethylidene→acetaldehyde; acetone → isopropylidene) catalysed by the zinc chloride.



(153)

Fig. 14, overleaf, shows the kinetics data obtained under the same "pseudo first-order" conditions.

k_2 (mol^{-1} sec^{-1} litre)	Internal Temperature (°C)
2.62×10^{-5}	139.5
3.28×10^{-5}	161.0

A ready explanation for the very low rates of reaction of the galactose compound (153) was apparent on examining the high-resolution n.m.r. spectrum of (153), which is illustrated in Fig. 15. A first-order analysis, assisted by extensive spin-decoupling, gave the values of the coupling constants $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$. From these values, the geometry of the molecule could be deduced, and it was found that the sugar ring existed in a slightly flattened "boat" conformation, with C-5, C-1, and the ring oxygen atom almost planar. This

Displacement Reaction (KSBz / DMF) on

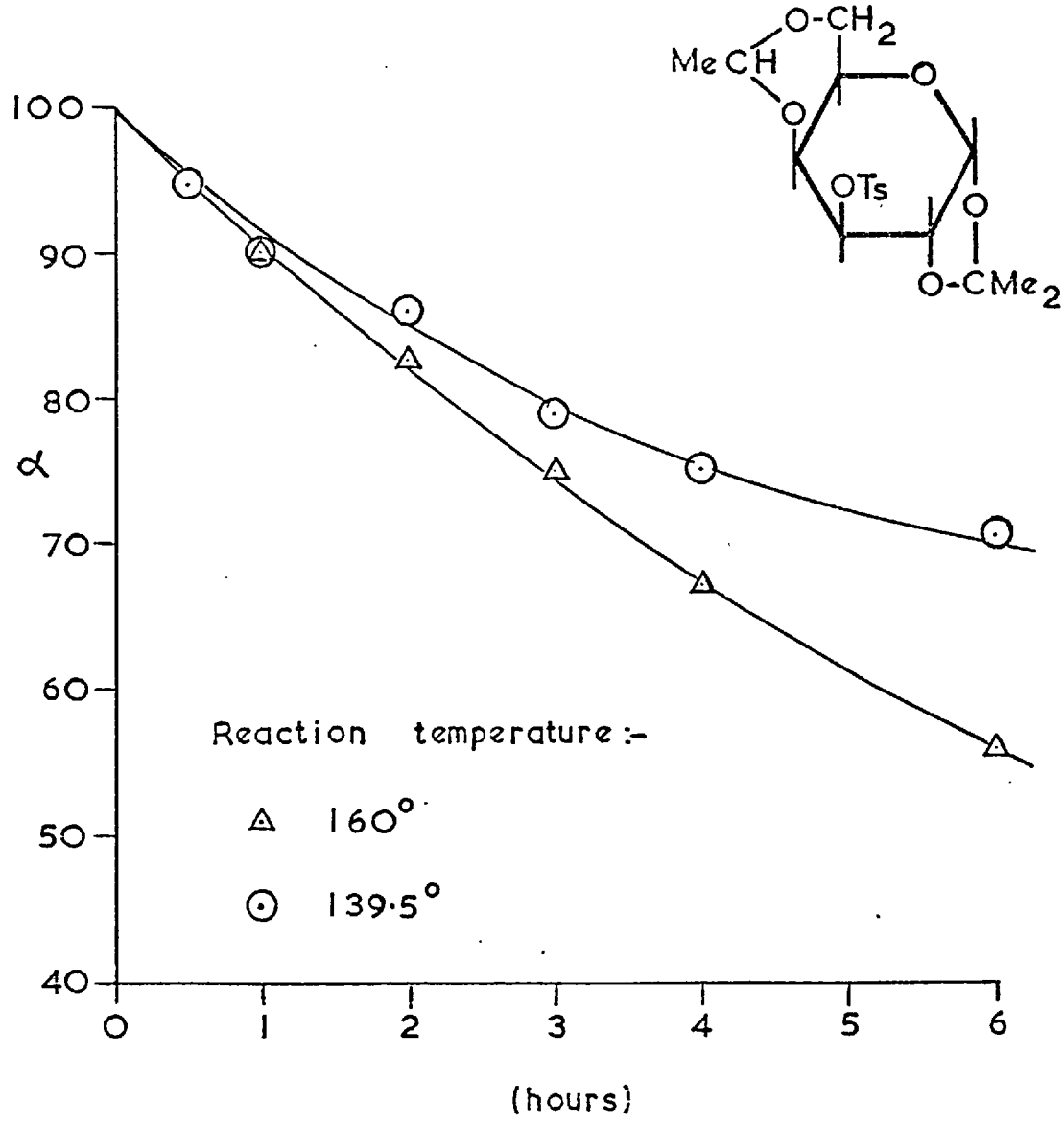


Fig. 14

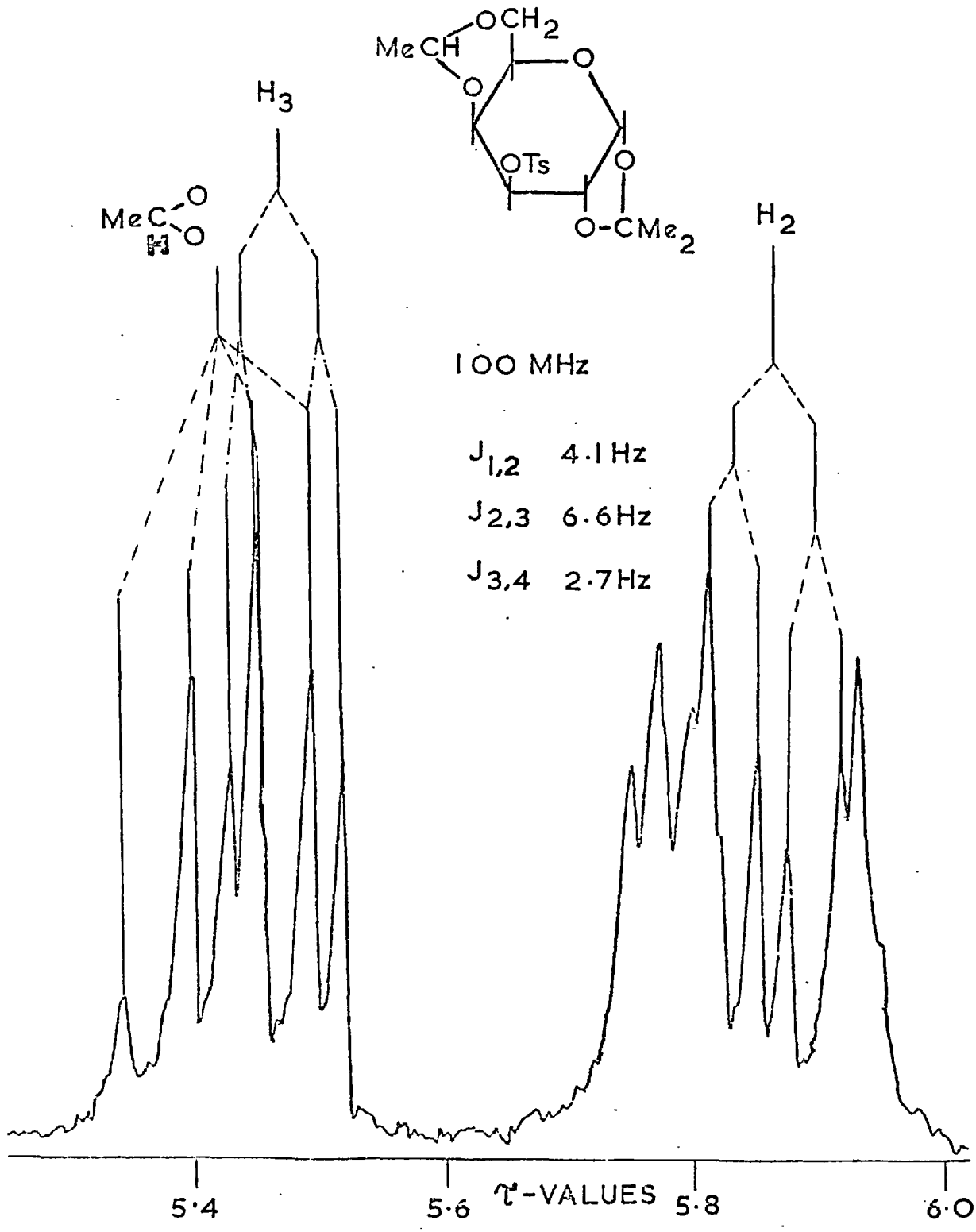

OCH2
MeCH
O
O
O
OTs
O
O-CMe2
H3
MeC
O
H
O
H2
100 MHz
J1,2 4·1 Hz
J2,3 6·6 Hz
J3,4 2·7 Hz
5·4
5·6
τ-VALUES
5·8
6·0

Fig. 15

particular conformation forces the C-3 tosyloxy group to point away from the ring oxygen atom. Thus the approach of the thiolbenzoate ion towards C-3 would be hampered by very severe steric hindrance from the 1,2-O-isopropylidene group and 5-H, and by severe electronic repulsions from the ring oxygen and C-2 oxygen atoms.

Solvent Effects:

The four main kinds of strong solvent-solute interactions are:

(a) ion-dipole;

(b) dipole-dipole;

(c) π-complex formation; and

(d) hydrogen-bonding.

In protic solvents, anions are solvated by ion-dipole interactions and a superimposed interaction due to mutual polarisability of the anion and the solvent molecule. In dipolar aprotic solvents, there is no significant contribution to solvation by hydrogen-bonding[131], and in fact most anions are much less solvated in dipolar aprotic solvents than in protic solvents. However, polarisable charged transition states are more solvated in dipolar aprotic solvents than in protic solvents[132].

The quantitative evaluation of two dipolar aprotic solvents was carried out on the glucose tosylate (144) using

the two solvents DMF, and HMPT. The kinetics data are illustrated in Fig. 16.

Solvent	k_2 (mol^{-1} sec^{-1} litre)
HMPT	7.88×10^{-5}
DMF	3.49×10^{-5}

Hence k_{HMPT} / k_{DMF} is 2.26

The reaction,

$$nBuBr + N_3^- \longrightarrow nBuN_3 + Br^-$$

has been studied by Delpuech[133], and some of his results are given below:

Solvent	k_{25} (m^{-1} sec^{-1} l.)	E (Kcal. m^{-1})
DMF	2.37×10^{-2}	16.45
HMPT	1.75	13.40
MeOH	8.61×10^{-6}	21.18

The comparatively small rate ratio of 2.26 would seem to imply that any lowering of the activation energy was small, probably being due to the terms Ee and Es.

The kinetics work which has been described illustrates the high nucleophilic strength of the thiolbenzoate ion in dipolar aprotic solvents. Thus it appears that the system KSBz / DMF or KSBz / HMPT should find fairly general utility for nucleophilic displacement reactions in the synthesis of thio sugars.

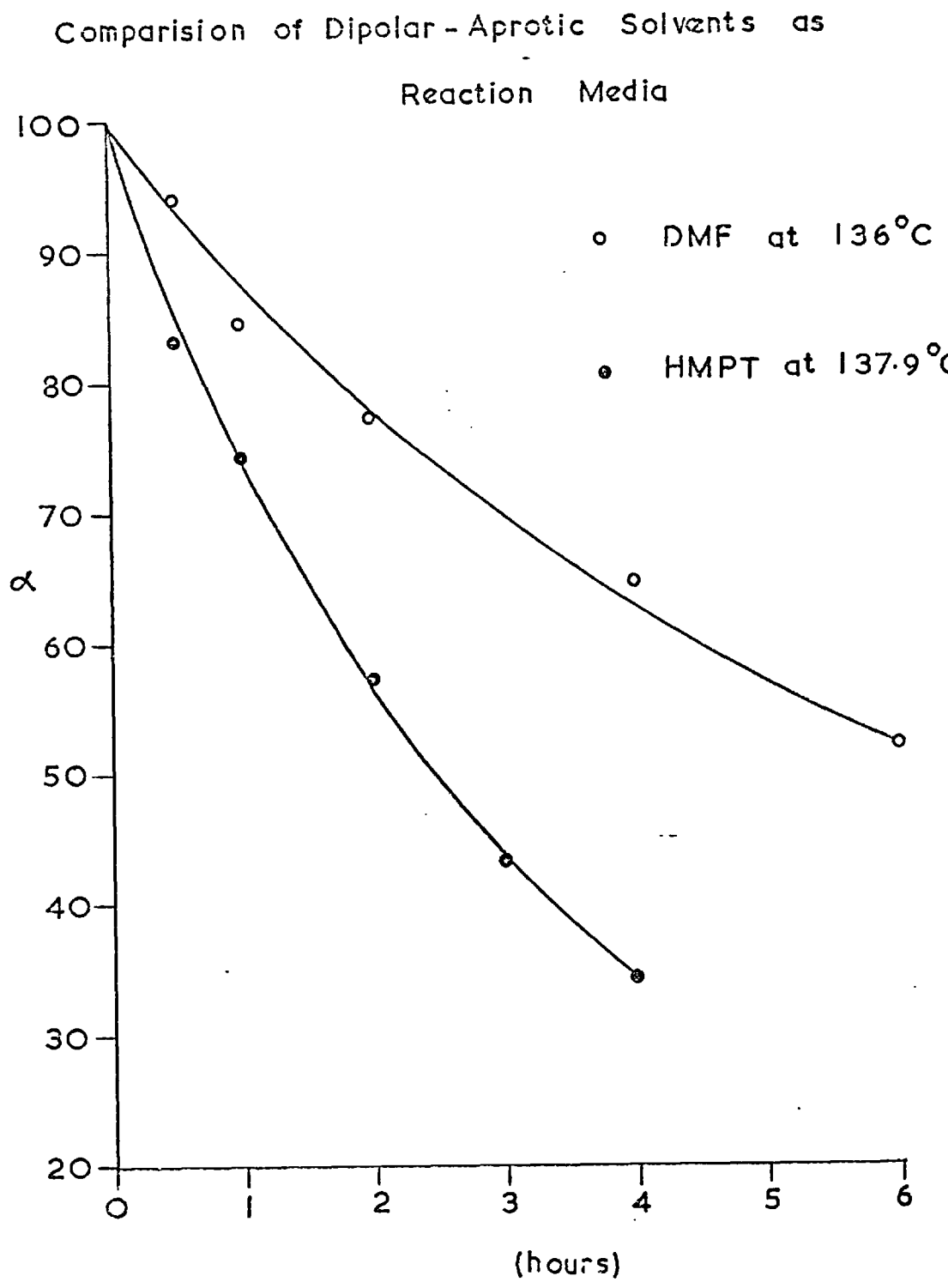

Comparision of Dipolar-Aprotic Solvents as Reaction Media
100
90
80
70
60
50
40
30
20
α
o DMF at 136°C
HMPT at 137.9°C
0
1
2
3
4
5
6
(hours)

Fig. 16

EXPERIMENTAL

SECTION

The figures in parentheses, shown throughout this section, refer to the page references in the original laboratory notebooks.

Infra-red spectra were run on a Unicam S.P.200 instrument. Ultra-violet spectra were determined on a Unicam S.P.800 instrument with AnalaR ethanol as the solvent. Nuclear magnetic resonance spectra were determined on either a Varian A 60 spectrometer (Mrs. A.I. Boston) or a Varian HA 100 spectrometer (Mr. P.N. Jenkins); the solvent, unless otherwise stated, being deuteriochloroform and with tetramethylsilane as internal reference. Mass-spectra were determined (Mr. P. Boshoff) on an E.M.I. MS9 double-focussing instrument.

Thin layer chromatograms were performed on Kieselgel GF_{254} (E. Merck Ltd.), detection being by iodine vapour, and column chromatographies were carried out using silica gel M.F.C. (Hopkins & Williams Ltd.).

Melting points were determined using a Kofler micro-stage apparatus, and are uncorrected. Evaporations were performed under reduced pressure, and at temperatures below 50°.

Part 1

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (1)

This compound was prepared by the method described by O.T. Schmidt[134]. D(+) glucose (250 g.)(dried in vacuo at 60° for 2 hours) was mixed with AnalaR grade acetone (1,600 ml.), and the reaction mixture was then transfered to a dry-box. Zinc chloride stick (200 g.) was pulverised, and added to the mixture, which was then treated with syrupy orthophosphoric acid (10 ml.). The mixture was stirred for 30 hours at room temperature, and then neutralised by the addition of sodium hydroxide (142 g.) in water (142 ml.). The solution was filtered, and the concentrated filtrate was diluted with water (250 ml.), and extracted with chloroform (3x250 ml.). Concentration of the organic extract yielded a solid which was recrystallised from petroleum (b.p. 80-100°) to give the product (170.3 g.); m.p. 109-111° (lit.[134] m.p. 110-111°); $[\alpha]_D^{22}$ -12.0° (c 2.0 $CHCl_3$).

1,2:5,6-Di-O-isopropylidene-3-O-([methylthio]-thiocarbonyl)-α-D-glucofuranose (11)

The preparation of the title compound has been described by several groups of workers[5,6,8]. Sodium hydride (50% suspension in oil - 30 g.) was washed with, and stored over petroleum (b.p. 60-80°). This suspension was treated with

1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (112 g.) in anhydrous ether (600 ml.), and the solution was stirred for 6 hours. With vigorous stirring, carbon disulphide (120 ml.) was added slowly. The reaction mixture was stirred for 18 hours at room temperature, and then methyl iodide (36 ml.) was added. After being stirred for a further 6 hours, the mixture was filtered, and the product isolated by fractional distillation (130.1 g.; 87%); b.p. 135-150° / 0.4 m.m.; m.p. 58-59° (from petroleum (b.p. 60-80°)); λ_{max} 280 n.m. (ϵ 11,300); lit.: m.p. 58.60° [6], and λ_{max} 283 n.m. (ϵ 8,000)[8].

1,2:5,6-Di-O-isopropylidene-3-S-([methylthio]-carbonyl)-3-thio-α-D-glucofuranose

(a) Pyrolysis of xanthate in diphenyl ether[8] (7)

1,2:5,6-Di-O-isopropylidene-3-O-([methylthio]-thiocarbonyl)-α-D-glucofuranose (13.42 g.) was mixed with diphenyl ether (14.35 g.) and refluxed in an atmosphere of dry, oxygen-free nitrogen for 6 hours. The resulting dark-brown liquid was fractionally distilled to yield the title compound (2.52 g.); b.p. 160-170° / 1.0 m.m.; m.p. 148-149° (from ethanol); λ_{max} 248.5 n.m. (ϵ 6,600). Recyclisation of the lower boiling fraction gave a further yield of the title compound (0.2 g.).

(b) Pyrolysis of xanthate - hot-tube method[105] (17)

1,2:5,6-Di-O-isopropylidene-3-O-([methylthio]-thiocarbonyl)-α-D-glucofuranose (49.6 g.) was heated by an air-blower, and

slowly passed down a silica tube (internal diameter ca. 10 m.m.) at 510°. The apparatus was maintained under a vacuum of ca. 20 m.m. Recrystallisation of the solid product from ethanol gave the title compound (35%); m.p. 147-149°; λ_{max} 248 n.m. (ϵ 6,900). One recyclisation of the material recovered from the mother liquors gave a further yield of the product (12.5%); ν_{max} 1712, 1660, 1388, and 1378 cm^{-1} (CCl_4); n.m.r. spectrum see Fig. 1.

1,2:5,6-Di-O-isopropylidene-3-thio-α-D-glucofuranose (43, 63)

1,2:5,6-Di-O-isopropylidene-3-S-([methylthio]-carbonyl)-3-thio-α-D-glucofuranose (5.0 g.) was dissolved in dry ether (100 ml.), and with cooling and stirring, a solution of lithium aluminium hydride (2.0 g.) in dry ether (60 ml.) was slowly added. After the completion of this addition, the solution was refluxed for 1 hour. The excess reducing agent was destroyed by the cautious addition of ethyl acetate. The reaction mixture was poured into an ice-cold solution of glacial acetic acid (20 ml.) in water (400 ml.), and extracted with ether (1 litre). The organic layer was dried over $MgSO_4$, evaporated, and distilled to yield the product (3.16 g.); b.p. 112-114° / 0.15 m.m.; ν_{max} 2550 (SH), 1390, and 1380 cm^{-1} (liq. film); n.m.r. spectrum see Fig. 2.

3-S-acetyl-1,2:5,6-di-O-isopropylidene-3-thio-α-D-glucofuranose (45)

1,2:5,6-Di-O-isopropylidene-3-thio-α-D-glucofuranose (1.95 g.) was acetylated with acetic anhydride (1.5 g.) in dry pyridine (3 ml.), the reactants being stirred at room temperature for 3 days. Water (15 ml.) was then added, and the solution was extracted with ether (4x40 ml.). The ether layer was washed with sodium bicarbonate solution, and water, dried over Na_2SO_4, evaporated and distilled to yield the product (1.79 g. - 80%); b.p. 133-137° / 0.35 m.m.; n_D^{19} 1.4836; $[\alpha]_D^{22}$ -43.5° (c 1.3 $CHCl_3$); λ_{max} 229 n.m. (ε 3,800); ν_{max} 1695 (SAc) cm^{-1} (liq. film); τ 4.36 (1H, doublet, $J_{1,2}$ = 3.4 Hz, 1-H), 5.57 (1H, doublet, 2-H), 7.65 (3H, singlet, -SAc), and 8.51, 8.63, and 8.72 (12H, singlets, acetal groups, integrated ratios 1:1:2)(CCl_4).

(Found: C, 52.81; H, 6.68; S, 9.56. $C_{14}H_{20}O_6S$ requires C, 52.81; H, 6.96; S, 10.07%).

Attempted preparation of 3-S-acetyl-1,2-O-isopropylidene-3-thio-α-D-glucofuranose (49)

A mixture of 3-S-acetyl-1,2:5,6-di-O-isopropylidene-3-thio-α-D-glucofuranose (464 mg.), methanol (8 ml.), and aqueous sulphuric acid (3 ml., 1.6% w/v) was stirred at room temperature for 6 hours. Barium carbonate was then added, and the stirring continued for 3 hours. Filtration and evaporation of the

solution yielded an oil (295 mg.); ν_{max} 3500, 1740, 1695, 1390, 1380, and 1220 cm^{-1} (CCl_4). T.l.c. (ethyl acetate - benzene, 4:1 v/v) showed there to be three components in the oil (Rf's 0.95, 0.85, and 0.55). A column chromatography was carried out using the same solvent system as eluant, and the slowest moving component was isolated; ν_{max} 3500, 1735 (OAc), 1695 (SAc), 1390, 1380, and 1220 cm^{-1} (CCl_4). The t.l.c. on this chromatography fraction, using the solvent system above, indicated the presence of five components in the sample.

Bis-(3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose)-(3,3')-disulphide (121, 29)

1,2:5,6-Di-O-isopropylidene-3-thio-α-D-glucofuranose (6.32 g.) was mixed with methanol (40 ml.), and 2N sodium hydroxide solution (15 ml.). Air was drawn through the solution for 18 hours. The solid product was separated by filtration, and recrystallised from ethanol to give the disulphide (4.93 g.); m.p. 165-165.5°; $[\alpha]_D^{21}$ -281° (c 0.5 $CHCl_3$) (lit.[5] m.p. 163°, $[\alpha]_D^{21}$ -330° in $C_2H_2Cl_4$); λ_{max} 250 n.m. (ϵ 360); ν_{max} 1390, 1380 (CCl_4); n.m.r. spectrum see Fig. 3.

Acid Hydrolysis of bis-(3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose)-(3,3')-disulphide (83)

Bis-(3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose)-(3,3')-disulphide (200 mg.) was dissolved in isopropanol (16 ml.) with slight warming, and treated with aqueous sulphuric acid (6 ml., 1.6% w/v). The solution was heated to about 30° and stirred (accidently it was heated to 70° for about 2 minutes). After 2 hours, the solution was homogeneous, and was left at room temperature for 15 hours. Barium carbonate was added, and after a further 2 hour's of stirring, the solution was filtered and evaporated. Crystallisation of the residue from petroleum (b.p. 40-60°) gave bis-(3-deoxy-D-glucopyranose)-(3,3')-disulphide. No melting point could be recorded for this compound as it decomposed below its m.p.

(Found: C, 37.05; H, 5.65; S, 16.13. $C_{12}H_{22}O_{10}S_2$ requires C, 36.92; H, 5.68; S, 16.43%). Freudenberg and Wolf[5] quote S, 15.83%.

The hydrolysis was therefore repeated under milder conditions.

Bis-(3-deoxy-1,2-O-isopropylidene-α-D-glucofuranose)-(3,3')-disulphide (107)

Bis-(3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose)-(3,3')-disulphide (109 mg.) was added to isopropanol (8 ml.) and aqueous sulphuric acid (3 ml., 1.6% w/v). The solution

was maintained at ca. 33° for 26 hours, by which time the solution was completely clear and homogeneous. Addition of barium carbonate, filtration, and evaporation, yielded the product (56 mg.); m.p. 188-189° (from ethyl acetate); $[\alpha]_D^{22}$ -320° (c 1.3 EtOH); ν_{max} 3450 (OH, broadened peak), and 1390 cm^{-1} ($CHCl_3$).

(Found: C, 45.95; H, 6.26; S, 12.94. $C_{18}H_{30}O_{10}S_2$ requires C, 45.95; H, 6.43; S, 13.62%).

Improved synthesis of bis-(3-deoxy-1,2-O-isopropylidene-α-D-glucofuranose)-(3,3')-disulphide (179)

1,2:5,6-Di-O-isopropylidene-3-thio-α-D-glucofuranose (1 g.) was mixed with methanol (5 ml.), and sulphuric acid (5 ml., 0.8% w/v), and the reactants were stirred for 12 hours, and left a further 24 hours at room temperature. An excess of barium carbonate was added, and the solution was boiled and filtered. The filtrate was evaporated in a stream of air under reduced pressure. A white solid (470 mg.) separated out from an oil (230 mg.). Recrystallisation of the solid from ethanol - petroleum (b.p. 40-60°) gave the title compound; m.p. 186-188°. After exposure to air, the oil (230 mg.) solidified to yield a light-yellow solid; m.p. 186-188°, which was a second crop of the product.

Bis-(3-deoxy-1,2-O-isopropylidene-6-O-toluene-p-sulphonyl-α-D-glucofuranose)-(3,3')-disulphide (135,307)

Toluene-p-sulphonyl chloride (3 g.) in anhydrous pyridine (15 ml.) was slowly added to a cooled solution of bis-(3-deoxy-1,2-O-isopropylidene-α-D-glucofuranose)-(3,3')-disulphide (1.12 g.) in anhydrous pyridine (10 ml.), the addition taking 1 hour. The solution was then stirred for 20 hours at room temperature, and then poured into ice-water. The material slowly solidified during 3 months; ν_{max} 3500, 1600, 1385, 1195, and 1185 cm^{-1} (CCl_4); mol. wt. in chloroform 761.4, $C_{32}H_{42}O_{14}S_4$ requires mol. wt. of 778.

T.l.c. on the impure material, using chloroform - ethyl acetate (1:1 v/v) as eluant, indicated the presence of four components: Rf's 0.85, 0.6, 0.3, and 0.0. Preparative column chromatography gave the pure 6,6'-di-O-tosyl compound as a glass.

(Found: C, 49.38; H, 5.20; S, 16.78. $C_{32}H_{42}O_{14}S_4$ requires C, 49.35; H, 5.44; S, 16.47%).

3,6-Dideoxy-3,6-epithio-1,2-O-isopropylidene-α-D-glucofuranose (381, 453)

(a) The reduction of the above disulphide was first attempted by the general method described by Benn[112]. Bis-(3-deoxy-1,2-O-isopropylidene-6-O-toluene-p-sulphonyl-α-D-glucofuranose)-(3,3')-disulphide (280 mg.) was dissolved in anhydrous methanol

(25 ml.). The solution was maintained in an atmosphere of dry, oxygen-free nitrogen, and with stirring, sodium borohydride (500 mg.) was gradually added. The solution was left at room temperature for 30 minutes, and then refluxed for 4 hours. The reaction mixture was poured into water (ca. 50 ml.), extracted with ethyl acetate (200 ml.), and evaporated to an oil. Infra-red evidence indicated that the oil was the unchanged starting material.

(b) This selective reduction was performed under the general conditions as described by H.C. Brown[113]. Bis-(3-deoxy-1,2-O-isopropylidene-6-O-toluene-p-sulphonyl-α-D-glucofuranose)-(3,3')-disulphide (250 mg.) in THF (25 ml.) at 0° was treated slowly with a solution of lithium aluminium hydride (ca. 90 mg.) in THF (10 ml.). The mixture was stirred at 0° for 2 hours, then the excess of hydride was cautiously destroyed by the addition of ethyl acetate. 2N Aqueous sodium hydroxide (an excess) was added, and the solution was refluxed for 30 minutes. Extraction with chloroform (4x30 ml.), drying over $MgSO_4$, and evaporation yielded as oil which was crystallised from petroleum (b.p. 60-80°) to give the title compound; m.p. 112-114°; ν_{max} 3600. 3450. 1390, and 1380 cm^{-1} (CCl_4); n.m.r. see Fig. 4. This compound was identical (m.p., and mixed m.p.) with the compound described on page 127).

1,2:5,6-Di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose

(123, 173, 215, 465)

Dimethyl sulphoxide (500 ml., dried over molecular sieve, type 4A - B.D.H.) was cautiously treated with phosphorus pentoxide (16.4 g.) with cooling, and then 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (50 g.) was added. The order of addition of these reagents as suggested by Onodera and co-workers[117, 118] was found not to be as effective as the above procedure. The reaction mixture was stirred for 3 days at room temperature. The solution was then slowly poured into a well-stirred solution of saturated sodium bicarbonate (ca. 1 litre - an excess). The work-up procedures as described by Brimacombe and Stacey[75], and Onodera and co-workers[118] proved to be less effective. This solution was extracted with chloroform (ca. 1.5 litres), the organic layer then being washed, dried over $MgSO_4$, and distilled to yield the title compound (31.32 g., 63%); b.p. 128-129° / 1 m.m.; n_D^{20} 1.4589.

1,2:5,6-Di-O-isopropylidene-α-D-allofuranose

(133, 177, 295, 471)

1,2:5,6-Di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose (42.2 g.) was dissolved in 70% aqueous ethanol (200 ml., v/v), and at room temperature, sodium borohydride (25 g.) was gradually added with stirring. After completion of this addition, the solution was stirred for a further 30 minutes,

and then diluted with water (200 ml.). The solution was extracted with ethyl acetate (ca. 3 litres); the organic phase being dried ($MgSO_4$), evaporated, and crystallised from benzene - petroleum (b.p. 60-80°) to yield the product (31.5 g.); m.p. 75-77° (lit.[120] m.p. 76-77°); τ ($CDCl_3$) 4.21 (1H, doublet, $J_{1,2}$ = 3.7Hz, 1-H), 5.40 (1H, triplet, 2-H), 5.95 (1H, singlet, OH), and 8.42, 8.55, and 8.62 (12H, singlets, integrated ratios 1:1:2, acetal methyl groups).

1,2:5,6-Di-O-isopropylidene-3-O-([methylthio]-thiocarbonyl)-α-D-allofuranose (137)

1,2:5,6-Di-O-isopropylidene-α-D-allofuranose (5 g.) was added to sodium hydride (1.5 g., of a 50% oil suspension, washed with petroleum (b.p. 60-80°), and ether), in anhydrous ether (70 ml.). After stirring for 4 hours, carbon disulphide (5 ml.) was added, and after a further 20 hours stirring, methyl iodide (4 ml.) was added. Filtration of the reaction mixture and evaporation of the filtrate gave an oil, which on distillation yielded the product (5.42 g.); b.p. 164-174° / 1.0 m.m.; m.p. 50-51° (from petroleum (b.p. 40-60°)); $[\alpha]_D^{25}$ +144° (c 1.36 $CHCl_3$); λ_{max} 280 n.m. (12,700); ν_{max} 1390, 1380, and 1210 (broad) cm^{-1} (CCl_4); τ ($CDCl_3$) 4.16 (1H, doublet, $J_{1,2}$ = 3.8Hz, 1-H), 4.40 (1H, double-doublet, $J_{2,3}$ = 5Hz, $J_{3,4}$ = 7.6Hz, 3-H), 5.00 (1H, double-doublet, 2-H), 5.53 - 6.18 (4H, multiplet, 4-H, 5-H, and 2 6-H protons),

7.39 (3H, singlet, SMe), 8.45, 8.59, and 8.67 (12H, singlets, acetal groups integrated ratios 1:1:2).

(Found: C, 48.09; H, 6.47; S, 18.19. $C_{14}H_{22}O_6S_2$ requires C, 47.98; H, 6.33; S, 18.30%).

1,2:5,6-Di-O-isopropylidene-3-S-([methylthio]-carbonyl)-3-thio-α-D-allofuranose

(a) Pyrolysis in diphenyl ether[8] (151)

The xanthate (5.2 g.) was dissolved in diphenyl ether (7 g.) and the warmed solution was de-gassed four times under reduced pressure. This solution was then refluxed under nitrogen for 4 hours, and then the products were isolated by fractional distillation under reduced pressure. It was noted that on this and subsequent diphenyl ether pyrolyses on this compound, a great deal of decomposition was occurring. Infra-red evidence indicated that no rearrangement of the xanthate had occurred.

(b) Hot-tube method[105] (185 then 203)

The xanthate (7.9 g.) was passed down a heated tube maintained at 510°, the apparatus being maintained at a pressure of ca. 20 m.m.

Infra-red evidence indicated thatsome rearrangement had occurred. The product was partially purified by column chromatography (chloroform - benzene (1:1 v/v) as eluant). A final purification by preparative t.l.c. (chloroform as

eluant) yielded the title compound (15 mg.) as an oil; ν_{max} 1710, and 1645 (S.CO.S), 1385, and 1375 cm^{-1} (CCl_4); n.m.r. spectrum see Fig.1.

(Found: C, 48.53; H, 6.48. $C_{14}H_{22}O_6S_2$ requires C, 47.98; H, 6.33%).

1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-allofuranose (145)

1,2:5,6-Di-O-isopropylidene-α-D-allofuranose (2.9 g.) in anhydrous pyridine (25 ml.) was treated with toluene-p-sulphonyl chloride (3.65 g.) in anhydrous pyridine (30 ml.), the addition being carried out with stirring and cooling. After the addition, which took 30 minutes, the reactants were left at room temperature for 4 days. The solution was then diluted with water (20 ml.), and poured into ice-water (500 g.). The solid was collected, washed, and recrystallised from ethanol to yield the title compound (3.82 g.); m.p. 121° (lit.[75] m.p. 121°); ν_{max} 1600, 1390, 1195, and 1185 cm^{-1} (CCl_4); τ ($CDCl_3$) 2.10 - 2.65 (4H, multiplet, aromatic), 4.21 (1H, doublet, $J_{1,2}$ = 3.5Hz, 1-H), 5.36 (2H, multiplet, 2-H, and 3-H), 7.54 (3H, singlet, Ar-Me), 8.46, 8.66, and 8.70 (12H, singlets, acetal groups, integrated ratios 1:1:2).

1,2-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-allofuranose

(195)

The general procedure used in this experiment was similar to that described by Chle and Dickhaeuser[114]. 1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-allofuranose (3.03 g.) was mixed with glacial acetic acid (108 ml.) and water (42 ml.). After being shaken for 30 minutes, the reaction mixture was left for 2 days at room temperature. The clear solution was then evaporated at 30-35° / 1m.m. The white solid residue was collected and recrystallised from ethanol to yield the product (1.88 g.); m.p. 130°; $[\alpha]_D^{24}$ +50° (c 0.34, acetone); ν_{max} 3450, 3390, 1600, 1190, and 1180 cm^{-1} (nujol mull).

(Found: C, 51.27; H, 5.73; S, 8.54. $C_{16}H_{22}O_8S$ requires C, 51.33; H, 5.92; S, 8.56%).

1,2-O-isopropylidene-3,6-di-O-toluene-p-sulphonyl-α-D-allofuranose

(201)

1,2-O-Isopropylidene-3-O-toluene-p-sulphonyl-α-D-allofuranose (500 mg.) in dry pyridine (5 ml.) was treated with toluene-p-sulphonyl chloride (269 mg. 1.05 mol.) in dry pyridine (5 ml.). The addition was performed with vigorous stirring and cooling, and after the addition, the reaction mixture was stored in a refrigerator for 20 hours. Water (5 ml.) was added, and after 30 minutes the solution was poured into ice-water (100 g.) yielding the crude product (680 mg.). Recrystallisation

from ether - petroleum (b.p. 60-80°) gave pure title compound (190 mg.); m.p. 117-118°; $[\alpha]_D^{26}$ +70° (c 0.69 EtOH); ν_{max} 3520, 1600, 1385, 1185, and 1175 cm^{-1} (nujol mull); τ ($CDCl_3$) 2.02 - 2.69 (8H, multiplet, aromatic), 4.30 (1H, doublet, $J_{1,2}$ = 3.5Hz, 1-H),5.18 - 6.10 (7H, multiplet, other ring protons and OH), 7.55 (6H, singlet, Ar-Me), 8.43 and 8.73 (6H, singlets, acetal group).

(Found: C, 52.46; H, 5.53; S, 12.09. $C_{23}H_{28}O_{10}S_2$ requires C, 52.26; H, 5.34; S, 12.13%).

5-O-Acetyl-6-S-acetyl-1,2-O-isopropylidene-6-thio-3-O-toluene-p-sulphonyl-α-D-allofuranose (217, 237)

1,2-O-Isopropylidene-3,6-di-O-toluene-p-sulphonyl-α-D-allofuranose (910 mg.) and potassium thiolacetate (1.01 g.) were reacted for 18 hours in refluxing AnalaR acetone (100 ml.) in an atmosphere of dry, oxygen-free nitrogen. The acetone was then distilled off, and the residue was acetylated using pyridine (70 ml.) and acetic anhydride (4 ml.). After two days, the mixture was treated with ice-water (50 g.), and extracted with ether (800 ml.). Evaporation of the washed and dried ether extracts yielded an oil, which on t.l.c., using chloroform as eluant, showed 8 spots.

A column chromatography was performed, and the first fraction yielded the title compound (127 mg.); m.p. 123-124° (from ethanol); $[\alpha]_D^{23}$ +57° (c 0.1 $CHCl_3$); ν_{max} 1745 (OAc),

1695 (SAc), 1660, 1390, 1380, 1190, 1180, and 1170 cm^{-1} (CCl_4); τ ($CDCl_3$) 2.13 - 2.64 (4H, multuplets, aromatic); 4.30 (1H, doublet, $J_{1,2}$ = 3.4Hz, 1-H), 7.56 (3H, singlet, Ar-Me), 7.70 (3H, singlet, -SCOMe), 7.98 (3H, singlet, -OAc), 8.51, and 8.76 (6H, singlets, acetal group).

(Found: C, 50.56; H, 5.49; S, 13.20. $C_{20}H_{26}O_9S_2$ requires C, 50.62; H, 5.52; S, 13.52%).

A second, slower-moving component was 5,6-di-O-acetyl-1,2-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-allofuranose (118 mg.); m.p. 91° (from EtOH - petroleum (b.p. 40-60°); $[\alpha]_D^{22}$ +89° (c 0.98 $CHCl_3$); ν_{max} 1745 (OAc), 1390, 1380, 1190, and 1180 cm^{-1} (CCl_4); τ ($CDCl_3$) 2.15 - 2.66 (4H, multiplets, aromatic), 4.34 (1H, doublet, $J_{1,2}$ = 3.6Hz, 1-H), 7.56 (3H, singlet, Ar-Me), 7.96 and 7.98 (6H, singlets, -OAc's), 8.51 and 8.76 (6H, singlets, acetal group).

(Found: C, 52.46; H, 5.70; S, 7.44. $C_{20}H_{26}O_{10}S$ requires C, 52.38; H, 5.72; S, 6.99%).

5-O-Benzoyl-6-S-benzoyl-1,2-O-isopropylidene-6-thio-3-O-toluene-p-sulphonyl-α-D-allofuranose (337)

1,2-O-Isopropylidene-3,6-di-O-toluene-p-sulphonyl-α-D-allofuranose (3.31 g.) was refluxed with potassium thiolbenzoate (6.62 g.) in absolute ethanol (50 ml.) in an atmosphere of dry, oxygen-free nitrogen for 6 hours. The ethanol was then removed under nitrogen, and the residue was benzoylated

(in the usual manner) using pyridine and benzoyl chloride. The solution was then diluted with water, and extracted with ether (6x75 ml.). The washed and dried organic phase was evaporated, and the residue was taken up in methanol and decolourised with charcoal.

A white solid (3.5 g.) crystallised from the methanol solution, and was identified as dibenzoyl disulphide. The remaining oil (obtained from the mother liquors after evaporation of the methanol) was chromatographed using chloroform as eluant. Tubes 45-52 were combined, and recrystallisation from ethanol gave 5-O-benzoyl-3,6-dideoxy-3,6-epithio-1,2-O-isopropylidene-α-D-glucofuranose (180 mg.); m.p. 113°; $[\alpha]_D^{23}$ +47° (c 1.23 $CHCl_3$); ν_{max} 1718 (OBz), 1600, 1388, and 1378 cm^{-1} (CCl_4); n.m.r. spectrum see Fig. 5.

(Found: C, 59.63; H, 5.65; S, 9.94. $C_{16}H_{18}O_5S$ requires C, 59.61; H, 5.63; S, 9.94%).

The eluates from tubes 53-72 were combined and evaporated to a solid which on recrystallisation fron ethanol gave the title compound (710 mg.); m.p. 131.5-132.5°; $[\alpha]_D^{21}$ +117° (c 0.44 $CHCl_3$); ν_{max} 1720, 1670 (SBz), 1390, 1380, 1193, and 1180 cm^{-1} (CCl_4); τ ($CDCl_3$) 1.90 - 2.90 (14H, multiplet, aromatic), 4.28 (1H, doublet, $J_{1,2}$ = 3.5Hz, 1-H), 7.62 (3H, singlet, Ar-Me), 8.45 and 8.69 (6H, singlets, acetal group).

(Found: C, 60.09; H, 4.93; S, 10.75. $C_{30}H_{36}O_9S_2$ requires C, 60.19; H, 5.05; S, 10.71%).

3,6-Dideoxy-3,6-epithio-1,2-O-isopropylidene-α-D-glucofuranose

5-O-Benzoyl-6-S-benzoyl-1,2-O-isopropylidene-6-thio-3-O-toluene-p-sulphonyl-α-D-allofuranose (187 mg.) was dissolved in anhydrous methanol (50 ml.), and treated with sodium (ca. 30 mg.). The reaction mixture was maintained in an atmosphere of dry, oxygen-free nitrogen for 24 hours. The solution was then poured into chloroform (200 ml.), and this solution was washed with water (3x150 ml.). Evaporation of the dried organic phase yielded an oil which was crystallised from petroleum (b.p. 60-80°) to give the product; m.p. 114.5-115°; $[\alpha]_D^{22}$ +75° (c 0.56 EtOH).

(Found: C, 49.67; H, 6.19; S, 15.00. $C_9H_{14}O_4S$ requires C, 49.51; H, 6.46; S, 14.69%).

1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-glucofuranose (57, 445, 527)

A solution of toluene-p-sulphonyl chloride (114 g.) in dry pyridine (200 ml.) was added dropwise onto 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (104 g.). The reactants were stirred for 24 hours at room temperature, and then cautiously added to ice-water (3 litres). The solid which was obtained was recrystallised from ethanol to give the product (124.4 g., lit.[126] yield 136 g.); m.p. 120-121° (lit.[135] m.p. 120-121°).

1,2-O-Isopropylidene-3-O-toluene-p-sulphonyl-α-D-glucofuranose (521)

1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-glucofuranose (15 g.) was treated with a mixture of glacial acetic acid (225 ml.) and water (75 ml.). The reaction mixture was left at room temperature for 5 days and then evaporated under vacuum at 30-33°. The resulting oil was dissolved in chloroform (300 ml.) and this solution was washed with bicarbonate solution, and water. Evaporation of the dried organic layer gave the title compound as an oil (11.3 g.). No lit.[114] m.p. was given.

5-O-Acetyl-6-chloro-6-deoxy-1,2-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-glucofuranose (529, 559)

1,2-O-Isopropylidene-3-O-toluene-p-sulphonyl-α-D-glucofuranose (11.3 g.) was dissolved in dry pyridine (50 ml.), and with stirring and ice-cooling, a solution of toluene-p-sulphonyl chloride (6.7 g., 1.1 mol.) in pyridine (40 ml.) was added over 30 minutes. The reaction mixture was maintained at room temperature for 2 days, then diluted with chloroform (300 ml.). This solution was washed with N acetic acid (2x100 ml.) and water, and the dried and evaporated organic phase gave a crude product which was chromatographed ($CHCl_3$ as eluant). The purified product (4.7 g.); ν_{max} 3550, 1600, 1390, 1195, 1185, and 1170 cm^{-1} (CCl_4); was acetylated at

room temperature with a mixture of acetic anhydride (15 ml.) and pyridine (20 ml.). After 24 hours, the reaction was worked-up in the usual manner to yield an oily product, which was purified by chromatography ($CHCl_3$ as eluant). The first eluted fraction was crystallised from ethanol - petroleum (b.p. 60-80°), and was not the expected 3,6-di-O-tosyl compound, but rather 5-O-acetyl-6-chloro-6-deoxy-1,2-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-glucofuranose(1.12 g.); m.p. 114°; $[\alpha]_D^{22}$ -14° (c 0.55 $CHCl_3$); ν_{max} 1740, 1600, 1390, 1360, 1240, 1190, and 1170 cm^{-1} (CCl_4); τ ($CDCl_3$) 2.20 - 2.66 (4H, multiplets, aromatic), 4.13 (1H, doublet, $J_{1,2}$ = 3.7Hz, 1-H), 6.15 (2H, multiplet, 2 6-H protons), 7.56 (3H, singlet, Ar-Me), 7.98 (3H, singlet, OAc), 8.48, and 8.70 (6H, singlets, acetal group).

(Found: C, 49.77; H, 5.35; Cl, 8.28; S, 7.34. $C_{18}H_{23}O_8ClS$ requires C, 49.72; H, 5.33; Cl, 8.15; S, 7.37%).

5-O-Acetyl-6-S-benzoyl-1,2-O-isopropylidene-6-thio-3-O-toluene-p-sulphonyl-α-D-glucofuranose (587, 601)

(a) (585) 5-O-Acetyl-6-chloro-6-deoxy-1,2-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-glucofuranose (500 mg.) and potassium thiolbenzoate (500 mg.) were reacted in boiling acetone for 6 hours in an atmosphere of dry, oxygen-free nitrogen. After work-up in the usual manner, the oily residue was found to be the starting material.

(b) (587, 601) A mixture of 5-O-acetyl-6-chloro-6-deoxy-1,2-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-glucofuranose (500 mg.) and potassium thiolbenzoate (1 g.) in dry DMF (30 ml.) was maintained at 70°in an oil-bath for 12 hours, the reaction being carried out in an atmosphere of dry, oxygen-free nitrogen. The reaction mixture was diluted with water (100 ml.) and this solution was extracted with petroleum (b.p. 60-80°) (4x100 ml.). The dried organic extracts were evaporated to an oil which was partially purified by chromatography ($CHCl_3$ as eluant). Evaporation of the eluted fractions gave an oil which was crystallised from ether - petroleum (b,p. 60-80°) to yield the product (131 mg.); m.p. 118° (from $CHCl_3$ - petroleum (b.p. 60-80°)); $[\alpha]_D^{22}$ -36° (c 0.53 $CHCl_3$); ν_{max} 1745, 1670 (SBz), 1600, 1390, 1360, 1235, 1190, and 1170 cm^{-1} (CCl_4); τ ($CDCl_3$) 1.86 - 2.75 (9H, multiplet, aromatic), 4.11 (1H, doublet, $J_{1,2}$ = 4Hz, 1-H), 7.57 (3H, singlet, Ar-Me), 8.10 (3H, singlet, OAc), 8.52 and 8.71 (6H, singlets, acetal group).

(Found: C, 55.87; H, 5.55; S, 11.90. $C_{25}H_{28}O_9S_2$ requires C, 55.95; H, 5.26; S, 11.95%).

Saponification of 5-O-acetyl-6-S-benzoyl-1,2-O-isopropylidene-6-thio-3-O-toluene-p-sulphonyl-α-D-glucofuranose (603)

A solution of the tosylate (71 mg.) in dry methanol (10 ml.) was treated with sodium (ca. 20 mg.) in an atmosphere of dry,

oxygen-free nitrogen. The reaction mixture was stirred at room temperature for 24 hours, refluxed for 2 hours, and then cooled and neutralised with solid carbon dioxide. Removal of the methanol under nitrogen yielded a solid which was extracted with chloroform. Evaporation of the chloroform solution yielded 1,2-O-isopropylidene-6-thio-3-O-toluene-p-sulphonyl-α-D-glucofuranose as an oil; ν_{max} 3530, 2500 (SH), 1600, 1390, and 1190 cm^{-1} ($CHCl_3$); τ ($CDCl_3$) 4.13 (1H, doublet, $J_{1,2}$ = 3.5Hz, 1-H), 7.55 (3H, singlet, Ar-Me), 8.53 (3H, singlet, acetal group methyl), 8.72 (4H, broadened singlet, acetal Me, and thiol proton).

This thiol was to be characterised as the disulphide, but all the product was lost when a centrifuge tube collapsed whilst in use.

Part 2

The preparation of 3,6-dideoxy-3,6-epithio-1,2-O-isopropylidene-α-D-glucofuranose was described on page 127 .

3,6-Dideoxy-3,6-epithio-D-glucose (505)

3,6-Dideoxy-3,6-epithio-1,2-O-isopropylidene-α-D-glucofuranose (20 mg.) was treated with 2N hydrochloric acid (4 ml.) at 100° for 2 hours. The reaction mixture was neutralised by the addition of excess barium carbonate, centrifuged, and

the supernatant liquid evaporated to dryness in vacuo. The resulting solid was extracted with boiling ethanol (5 ml.), and this extract was evaporated to an oil. The n.m.r. spectrum of this oil indicated the total lack of any aldehydic proton, but the resolution of this spectrum was not good enough for any detailed analysis to be made.

1,2,5-Tri-O-acetyl-3,6-dideoxy-3,6-epithio-αβ-D-glucofuranose (543)

3,6-Dideoxy-3,6-epithio-D-glucose (ca. 6 mg.) was dissolved in pyridine (2 ml.) and treated with a mixture of acetic anhydride (1 ml.) and pyridine (1 ml.). Work-up in the usual manner yielded a light-brown oil; ν_{max} 1750, 1235, and 1070 (cyclic ether) cm^{-1} (CCl_4); τ ($CDCl_3$) 3.46 (3/4 H, doublet, $J_{1,2}$ = 4.4Hz, 1-H (α-anomer)), 3.79 (1/4 H, slightly broadened singlet, 1-H (β-anomer)), 6.29 and 6.33 (1H, doublets, 3-H for α- and β-anomers), 7.00 (2H, multiplet, 2 6-H protons), 7.91 and 7.92 (9H, singlets, OAc groups). This spectrum was obtained using the C.A.T. attachment on the H.A. 100 instrument.

There was insufficient of this material for a successful micro-analysis.

Methyl 2,4-di-O-acetyl-3,6-di-O-toluene-p-sulphonyl-β-D-allopyranoside (475 - 487 - 491)

1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-allofuranose (40 g.) was added to a 2% (w/v) solution of hydrogen chloride in anhydrous methanol, and the solution was refluxed for 28 hours. It was then treated with an excess of solid sodium bicarbonate, filtered, and evaporated. The oily product was dissolved in chloroform and filtered (this removed some insoluble toluene-p-sulphonic acid). This crude intermediate (20 g.) in dry pyridine (170 ml.) was treated with a solution of toluene-p-sulphonyl chloride (10.9 g., 1.1 mol.) in dry pyridine (50 ml.). The reaction was performed at room temperature, and the mixture was stirred for 2 days. This second intermediate, which was not isolated, was then acetylated by the addition of a mixture of acetic anhydride (20 ml.) and pyridine (30 ml.). The reaction mixture was stirred at room temperature for 36 hours. The solution was poured into iced sodium bicarbonate solution (ca. 1 l. saturated) and the whole was refrigerated overnight. The organic material, which separated as a heavy oil, was isolated, dissolved in ether (300 ml.) and this solution was washed with water (3x300 ml.). Evaporation of the dried organic layer yielded an oil which crystallised from ethanol to give the product (4.25 g.); m.p. 165°; $[\alpha]_D^{22}$ +6.6° (c 1.82 $CHCl_3$); ν_{max} 1750, 1600, 1230, 1195, and 1185 cm^{-1} (CCl_4);

τ ($CDCl_3$) 2.20 - 2.86 (8H, multiplets, aromatic), 6.62 (3H, singlet, OMe), 7.60 (6H, singlet, Ar-Me), 8.06 and 8.11 (6H, singlets, OAc).

(Found: C, 51.20; H, 5.19; S, 10.73. $C_{25}H_{30}O_{12}S_2$ requires C, 51.19; H, 5.16; S, 10.93%).

Methyl 2,4-di-O-acetyl-6-S-benzoyl-6-thio-3-O-toluene-p-sulphonyl-β-D-allopyranoside (535)

Methyl 2,4-di-O-acetyl-3,6-di-O-toluene-p-sulphonyl-β-D-allopyranoside (1.06 g.) and potassium thiolbenzoate (2 g.) were mixed, AnalaR acetone (100 ml.) was added, and the solution was refluxed for 24 hours under an atmosphere of dry, oxygen-free nitrogen. After filtering the reaction mixture, the filtrate was diluted with chloroform (300 ml.) and this solution was washed with water (3x100 ml.), dried over $MgSO_4$, and evaporated. The oily residue was crystallised from ether to yield the product (630 mg.); m.p. 134-135°; $[\alpha]_D^{21}$ -18° (c 1.33 $CHCl_3$); ν_{max} 1750, 1670 (SBz), 1600, 1230, 1195, and 1185 cm^{-1} (CCl_4); τ ($CDCl_3$) 2.00 - 2.84 (9H, multiplets, aromatic), 6.55 (3H, singlet, OMe), 7.61 (3H, singlet, Ar-Me), 7.95 and 8.08 (6H, singlets, OAc).

(Found: C, 54.11; H, 5.27; S, 11.31. $C_{25}H_{28}O_{10}S_2$ requires C, 54.34; H, 5.11; S, 11.61 %).

Methyl 3,6-dideoxy-3,6-epithio-β-D-glucopyranoside (555, 583)

Methyl 2,4-di-O-acetyl-6-S-benzoyl-6-thio-3-O-toluene-p-sulphonyl-β-D-allopyranoside (309 mg.) in dry methanol (10 ml.) was treated with sodium (ca. 40 mg.) in an inert atmosphere. The reaction mixture was stirred and refluxed for 8 hours. After the addition of an excess of solid carbon dioxide, the reaction mixture was evaporated to dryness under nitrogen. The solid residue was extracted with chloroform (2x50 ml.). Evaporation of the chloroform solution, and crystallisation of the oil from chloroform - petroleum (b.p. 60-80°) yielded the product (58 mg.); m.p. 100-101°; $[\alpha]_D^{22}$ -65° (c 0.76 $CHCl_3$); ν_{max} 3500 cm^{-1} (CCl_4); n.m.r. spectrum see Fig. 6.

(Found: C, 43.77; H, 6.43. $C_7H_{12}O_4S$ requires C, 43.74; H, 6.30%).

Resistance of Methyl 3,6-dideoxy-3,6-epithio-β-D-glucopyranoside towards Acid-catalysed Rearrangement (629)

Methyl 3,6-dideoxy-3,6-epithio-β-D-glucopyranoside (32 mg.) was dissolved in AnalaR chloroform (2 ml.), and this solution was treated with a solution of dry hydrogen chloride in chloroform (0.4 ml., 0.12N). Polarimetric observation showed a small change in the rotation from - 0.39° (initial reading) to - 0.32° (after 1 hour, and constant thereafter). After 4 hours the solution was evaporated under vacuum to give a brown solid which was taken up in hot carbon tetrachloride containing

a little chloroform; then petroleum (b.p. 60-80°) was added in sufficient quantity to produce a slight turbidity in the solution. Cooling this solution gave a solid (12.4 mg.) identical (m.p., n.m.r. spectrum) with the starting material.

Part 3

1,2:5,6-Di-O-isopropylidene-3-O-methanesulphonyl-α-D-glucofuranose (73)

A solution of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (20 g.) in dry pyridine (60 ml.) was treated with methanesulphonyl chloride (9 ml.), the reaction mixture being stirred, and maintained in an ice-bath during the addition. After stirring for a further 16 hours, the solution was poured into ice-water (800 g.) and the solid so obtained was recrystallised from aqueous methanol to yield the product (18.1 g.); m.p. 79-80° (lit.[136] m.p. 83-84°)

3-O-Acetyl-1,2:5,6-di-O-isopropylidene-α-D-erythro-hex-3-enofuranose (209)

A mixture of 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranose-3-ulose (22.8 g.), redistilled acetic anhydride (30 ml., n_D^{24} 1.3880), and dry pyridine (50 ml.) was maintained at 60° for 17 hours in an oil-bath. The bulk of the solution was reduced to ca. 30 ml. by evaporation under reduced pressure, and then the residue was fractionally distilled to give the product (23 g., 87%); b.p. 134-136° / 0.9 m.m.; m.p. 53-55° (from petroleum (b.p. 60-80°)) (lit.[124] m.p. 62-63°); ν_{max} 1750 (OAc), 1635 (C=C-OAc), 1390, 1380, and 1220 cm^{-1} (CCl_4). The n.m.r. spectrum has been fully described[124],

but the resonance at τ 5.31 due to 5-H is a triplet, and not a doublet as reported.

1,2:5,6-Di-O-isopropylidene-α-D-gulofuranose (325)

3-O-Acetyl-1,2:5,6-di-O-isopropylidene-α-D-erythro-hex-3-enofuranose (9.55 g.) in anhydrous methanol (150 ml.) was treated with sodium borohydride (5.1 g.), the solution being cooled and stirred. After the completion of the borohydride addition, the solution was left for 20 minutes, then diluted with water (300 ml.) and the resulting solution was extracted with chloroform (3x250 ml.). Evaporation of the washed and dried ($MgSO_4$) extracts gave an oil which on dilution with ether and petroleum (b.p. 60-80°) gave the product (1.64 g.); ν_{max} 3450 cm^{-1} (CCl_4). This material was converted directly into the 3-tosylate.

1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-gulofuranose (327)

An intimate mixture of toluene-p-sulphonyl chloride (3 g.) and 1,2:5,6-di-O-isopropylidene-α-D-gulofuranose (1.6 g.) was treated with dry pyridine (30 ml.), and the reaction mixture was stirred at room temperature for 7 days. Water (2 ml.) was added, and after 20 minutes the solution was poured into ice-water (200 g.). Separation and recrystallisation (from ethanol) of the solid, yielded the product (1.71 g.); m.p. 121-123° (decomp.) (lit.[79] m.p. 122-123° (decomp.)).

3-Deoxy-1,2:5,6-di-O-isopropylidene-α-D-erythro-hex-3-enofuranose (319, 531)

Soda-lime (120 g., 14-22 mesh) was mixed with 1,2:5,6-di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-glucofuranose (30 g.) and made into an intimate mixture. Half of this mixture was used at a time, and poured into a 100 ml. r.b. flask which was then equipped with a knee-bend, air-condenser, receiver-adaptor, and a 50 ml. r.b. flask. The apparatus was kept at 0.5 m.m. pressure, and the reaction flask was immersed in an oil-bath at 210°. The product (10.2 g.), lit.[126] yield = 12.2 g., slowly distilled over and solidified. The product was dissolved in petroleum (b.p. 60-80°) (400 ml.), and the organic phase was washed with water (3x100 ml.). Evaporation of the dried organic yielded an oil which was used for the next stage.

1,2:5,6-Di-O-isopropylidene-α-D-galactofuranose (321, 553)

The method used is that as described by Paulsen and Behre[127]. 3-Deoxy-1,2:5,6-di-O-isopropylidene-α-D-erythro-hex-3-enofuranose (6 g.) in dry THF (20 ml.) was treated with diborane diluted with dry nitrogen. The diborane was prepared by the addition of a solution of sodium borohydride (3 g.) in dry diglyme (50 ml.), to a stirred solution of boron trifluoride etherate (12 g.) in dry ether (100 ml.). The diborane was evolved over a period of 2½ hours. The THF

solution was cautiously treated with aqueous THF (ca. 20 ml., 1:1 v/v), and then with 2N sodium hydroxide solution (18 ml.), followed by 100 volume hydrogen peroxide (8 ml.). The solution was evaporated to dryness, water (100 ml.) was added, and the solution was extracted with ether (4x100 ml.). Evaporation of the dried organic extracts yielded an oil which solidified. Chromatography of this solid, using ether - petroleum (b.p. 40-60°) (1:1 v/v) as eluant, yielded firstly some di-isopropylidene glucose tosylate (ca. 600 mg.) evidently carried through from the first stage. Further elution, with methanol, then gave the title compound (550 mg.) which after crystallisation from petroleum (b.p. 60-80°) had m.p. 96°; lit. m.p. 97.5-98°.

On one occasion, a third product was obtained which was shown to be composed of two 1,2:5,6-di-O-isopropylidene furanose units bonded together as a 3-3' ether; m.p. 138-141°; $[\alpha]_D^{24}$ -8° (c 1.9 $CHCl_3$); τ ($CDCl_3$) 4.15 (2H, doublet, $J_{1,2}$ = 3.3Hz, 1-H), 5.43 - 6.05 (12H, multiplet, 2-H, 3-H, 4-H, 5-H, and 2 6-H protons), 8.44, 8.52, 8.57, 8.67, and 8.70 (24H, singlets, acetal groups); mass-spectrum M^+ m/e 502, $(M-15)^+$ m/e 487.

(Found: C, 57.50; H, 7.51. $C_{24}H_{38}O_{11}$ requires C, 57.36; H, 7.62%).

The configuration of each unit in the ether was not established.

1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-galactofuranose (333,563)

1,2:5,6-Di-O-isopropylidene-α-D-galactofuranose (1.06 g.) and toluene-p-sulphonyl chloride (1.17 g.) were mixed together, and the mixture was treated with dry pyridine (7 ml.). The reactants were stirred at room temperature for 24 hours, then diluted with water (25 ml.). The solid was separated, and recrystallised from ethanol to give the product (1.14 g.); m.p. 95°; $[\alpha]_D^{25}$ -14° (c 0.5 $CHCl_3$); τ ($CDCl_3$) 2.20 - 2.68 (4H, multiplets, aromatic), 4.21 (1H, doublet, $J_{1,2}$ = 4Hz, 1-H), 5.37 (2H, multiplet, 2-H, and 3-H), 5.77 - 6.53 (4H, multiplet, 4-H, 5-H, and 2 6-H), 7.58 (3H, singlet, Ar-Me), 8.50, 8.67, and 8.73 (12H, singlets, acetal groups, integrated ratios 1:1:2).

(Found: C, 55.10; H, 6.59; S, 7.67. $C_{19}H_{26}O_8S$ requires C, 55.05; H, 6.34; S, 7.73%).

4,6-O-Ethylidene-α-D-galactopyranose (577)

D-Galactose (100 g.) was suspended in distilled paraldehyde (400 ml.) contained in a 500 ml. r.b. flask, and concentrated sulphuric acid (1.0 ml. exactly) was added. The mixture was vigorously stirred for 24 hours, filtered, and the solid collected was extracted with boiling methanol (ca. 250 ml.) containing ammonia (3 ml., d, 0.88). Cooling the methanol solution for 48 hours gave the product (24.8 g.); m.p. 184°

(lit.[129, 130] m.p. 185°).

4,6-O-Ethylidene-1,2-O-isopropylidene-α-D-galactopyranose (591)

4,6-O-Ethylidene-α-D-galactopyranose (20 g.) was added to a solution of granulated zinc chloride stick (50 g.) in AnalaR acetone (500 ml.). The reaction mixture was vigorously stirred at room temperature, and after 3 days, zinc chloride (10 g.) was added. A further portion of zinc chloride (10 g.) was added after a day's further stirring. After 5 days' total stirring, the mixture was added to a solution of sodium carbonate (82 g.) in water (2 l.). The solution was filtered, and the solid was extracted with boiling acetone (2x300 ml.). The combined filtrates were evaporated to remove acetone and extracted with chloroform (5x100 ml.). Evaporation of the dried extracts gave an oil (9.8 g.) which was used in the next stage without further purification.

4,6-O-Ethylidene-1,2-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-galactopyranose (599)

4,6-O-Ethylidene-1,2-O-isopropylidene-α-D-galactopyranose (9.8 g., crude) in dry pyridine (10 ml.) was treated, at room temperature and with stirring, with a solution of toluene-p-sulphonyl chloride (10.6 g.) in dry pyridine (60 ml.). After stirring for 24 hours, the reaction mixture was heated

at 80° for 20 minutes, cooled, and poured into ice-water (1.5 Kg.). An oily solid was obtained which was recrystallised from ethanol to give crude title compound (5.1 g.). Trituration of this solid with ether - petroleum (b.p. 40-60°) (1:1 v/v) gave the title compound (1.5 g.) as an insoluble component. The ether - petroleum was removed under vacuum, and the residue was chromatographed using ether - petroleum (b.p. 40-60°)(1:1 v/v) as eluant. The first fraction obtained was 1,2:3,4-di-O-isopropylidene-6-O-toluene-p-sulphonyl-α-D-galactopyranose (1.5 g.); m.p.'s (from MeOH) 91°, 92°, and 101-102° (lit.[137] m.p.'s 89-91°, 91-92°, 102-103°, and 104-105°. The second fraction was recrystallised from methanol to give the title compound (0.47 g.); m.p. 116-117° (lit.[129] m.p. 116-118°); ν_{max} 1600, 1380, 1205, 1190, and 1175 cm^{-1} (CCl_4); τ ($CDCl_3$) 2.16 - 2.69 (4H, multiplets, aromatic), 4.25 (1H, doublet, $J_{1,2}$ = 4.1Hz, 1-H), 5.44 (1H, quartet, J = 5.1Hz, methine proton in ethylidene group), 5.47 (1H, double doublet, $J_{2,3}$ = 6.6Hz, $J_{3,4}$ = 2.7Hz, 3-H), 5.88 (1H, double doublet, 2-H), 5.74 - 5.98 (2H, multiplet, 4-H, and 5-H), 6.13 - 6.33 (2H, multiplet, 2 6-H), 7.59 (3H, singlet, Ar-Me), 8.69 (3H, doublet, methyl group in ethylidene ring), 8.72, and 8.73 (6H, singlets, acetal group). A small part of this spectrum is illustrated in Fig. 15.

3-S-Benzoyl-1,2:5,6-di-O-isopropylidene-3-thio-α-D-allofuranose

(131)

1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-glucofuranose (8.0 g.) was reacted for 4 hours with potassium thiolbenzoate (17.0 g.) in refluxing DMF (100 ml.) under an atmosphere of dry, oxygen-free nitrogen. The reaction mixture was reduced in bulk to ca. 60 ml., diluted with water, and extracted with chloroform (1 l.). Evaporation of the dried extracts, and purification (charcoal, and chromatography - chloroform as eluant) gave the crude product. The crude material was purified by a further chromatography using ether - petroleum (b.p. 40-60°) (1:4 v/v) as eluant. The eluant was collected and crystallised from petroleum (b.p. 60-80°) to yield the product; m.p. 80-81°; $[\alpha]_D^{25}$ +113° (c 0.51 $CHCl_3$); λ_{max} 239 (10,800) and 267 (8,800)n.m.; ν_{max} 1670 (SBz), 1385, and 1380 cm^{-1} (CCl_4); n.m.r. see Fig. 8.

(Found: C, 59.93; H, 6.12; S, 8.36. $C_{19}H_{24}O_6S$ requires C, 59.98; H, 6.36; S, 8.43%).

3-S-Benzoyl-1,2:5,6-di-O-isopropylidene-3-thio-α-D-glucofuranose

(a) From glucose thiol (167)

1,2:5,6-Di-O-isopropylidene-3-thio-α-D-glucofuranose (730 mg.) in dry pyridine (2 ml.), was benzoylated using a solution of benzoyl chloride (600 mg.) in dry pyridine (8 ml.). After 20 hours stirring, the mixture was diluted with water

(10 ml.), and extracted with ether (150 ml.). The extracts were washed with sodium bicarbonate solution, and water, and then dried. Evaporation of the organic layer gave a solid which was crystallised from petroleum (b.p. 60-80°) to give the product (550 mg.); m.p. 108-108.5°; $[\alpha]_D^{24}$ -37° (c 1.0 $CHCl_3$); λ_{max} 239 (10,200), 244 (9,700), and 264 (8,600) n.m.; ν_{max} 1670 (SBz), 1390, and 1380 cm^{-1} (CCl_4); n.m.r. see Fig. 8.

(Found: C, 60.17; H, 6.37; S, 8.36. $C_{19}H_{24}O_6S$ requires C, 59.98; H, 6.36; S, 8.43%).

(b) From allose tosylate (147)

1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-allofuranose (3.8 g.) and potassium thiolbenzoate (8.1 g.) were reacted in refluxing DMF (48 ml.) for 4 hours under an atmosphere of dry, oxygen-free nitrogen. The solution was diluted with water (200 ml.) and extracted with chloroform (5x150 ml.). The chloroform extract was decolourised (charcoal), and chromatographed using ether - petroleum (b.p. 40-60°) (1:4 v/v) and then ether as eluants. The crude product was distilled (143-147° / $1x10^{-4}$ m.m.) and then recrystallised from petroleum (b.p. 60-80°) to give the product (212 mg.). This compound was identical (infra-red, and n.m.r. spectra) with the authentic sample described under (a).

3-S-Benzoyl-1,2:5,6-di-O-isopropylidene-3-thio-α-D-galactofuranose (347)

The residue from a kinetics experiment (ref. no. 341 p.151) in which 1,2:5,6-di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-gulofuranose was treated with potassium thiolbenzoate in DMF was diluted with methanol and decolourised, and the resulting solution was extracted with chloroform (500 ml.). Evaporation of the dried organic extracts gave an oily solid which was extracted with boiling petroleum (b.p. 40-60°) (2x15 ml.). Cooling the petroleum extract yielded long needles of the product; m.p. 122-123°; $[\alpha]_D^{25}$ +12° (c 0.5 $CHCl_3$); ν_{max} 1665 (SBz), 1390, and 1380 cm^{-1} (CCl_4); n.m.r. see Fig. 9.

(Found: C, 60.06; H, 6.31; S, 8.20. $C_{19}H_{24}O_6S$ requires C, 59.98; H, 6.36; S, 8.43%).

Quantitative Kinetics Experiments

All the experiments that are described in this section were carried out with a tosylate / potassium thiolbenzoate mole ratio of 1:10; i.e. pseudo first-order conditions. The reaction medium was either dry DMF or dry HMPT, and the reactions were performed in a thermostatically controlled oil-bath. An atmosphere of dry, oxygen-free nitrogen was used for all the experiments.

The potassium thiolbenzoate and the DMF were mixed

together in the reaction flask which was heated in the oil-bath to within 5° of the final temperature of the reactants. The tosylate was then added quickly, and the reaction vessel shaken to ensure homogeneity of the solution. At prescribed intervals during the reaction, samples of the solution (ca. 1.5 - 3 ml.) were withdrawn and poured into chloroform (ca. 80 ml.) immediately. The chloroform solution was then washed with water (2x100 ml.), dried, and evaporated. The resulting oil was kept for at least 30 minutes at ca. 10^{-4} m.m. and was then analysed by n.m.r. spectroscopy using the graphical integration curve for the aromatic methyl of the tosylate (ca. τ 7.60), and the methyl groups in the acetal groups (ca. τ 8.5 - 8.7) to determine the percentage (α) of tosylate in the sample.

1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-glucofuranose (401) Tosylate, 2.0 g., potassium thiolbenzoate, 8.75 g., DMF, 50 ml., bath temperature, 178°, average internal temperature, 154.8 ±0.2 °.

Time (hours)	% tosylate remaining (α)	n.m.r. of sample
½	76	97
1	67	98
2	44	99
4	23	100
6	10	101

(411) Tosylate, 2.0 g., potassium thiolbenzoate, 8.75 g., DMF, 50 ml., bath temperature, 142°, average internal temperature, 136.5 ± 0.3°.

Time (hours)	α (%)	n.m.r. of sample
½	94	102
1	85	103
2	77	104
4	65	105
6	52	106

(459) Tosylate, 2.0 g., potassium thiolbenzoate, 8.75 g., HMPT, 50 ml., bath temperature, 143°, average internal temperature, 137.9 ± 0.1°.

Time (hours)	α (%)	n.m.r. of sample
½	83	114
1	74	115
2	57	116
3	43	117
4	34	118

(497) Tosylate, 2.0 g., potassium thiolbenzoate, 8.75 g., DMF, 50 ml., bath temperature, 126°, average internal temperature, 125.4 ± 0.4 °.

Time (hours)	α (%)	n.m.r. of sample
½	96	127
1	89	128
2	86	129
3	81	130
4	77	131

(257) Tosylate, 2.0 g., potassium thiolacetate, 3.0 g., DMF, 50 ml., bath temperature, 178°, initial internal temperature, 162°.

Evidence from the n.m.r. spectra of samples taken during the course of this reaction, showed that no displacement of the tosylate was occurring at all. This particular reaction was characterised by extensive decomposition of the tosylate.

1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-allofuranose

(367) Tosylate, 2.0 g., potassium thiolbenzoate, 8.75 g., DMF, 50 ml., bath temperature, 178°, average internal temperature, 157.2 ± 0.4°.

Time (hours)	α (%)	n.m.r. of sample
1/4	69	81
½	35	82
1	13	84
1½	5	85

(375) Tosylate, 2.0 g., potassium thiolbenzoate, 8.75 g., DMF, 50 ml., bath temperature, 143°, internal temperature, 140°.

Time (hours)	α (%)	n.m.r. of sample
1/4	81	87
½	64	88
1	51	89
2	34	90
3	19	91

(369) Tosylate, 1.68 g., potassium thiolbenzoate, 7.36 g., DMF, 42 ml., bath temperature, 128°, average internal temperature, 125.6 ± 0.2°.

Time (hours)	α (%)	n.m.r. of sample
½	84	93
1	73	94
2	58	95
4	41	96

1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-gulofuranose

(341) Tosylate, 1.5 g., potassium thiolbenzoate, 6.57 g., DMF, 37.5 ml., bath temperature, 178°. No internal temperature was recorded for this experiment.

Time (minutes)	α (%)	n.m.r. of sample
10	25	65
20	8	66

1,2:5,6-Di-O-isopropylidene-3-O-tosyl-α-D-galactofuranose

(565) Tosylate, 0.5 g., potassium thiolbenzoate, 2.19 g., DMF, 12.5 ml., bath temperature, 178°, average internal temperature, 156.3 ± 0.3°.

Time (hours)	α (%)	n.m.r. of sample
½	94	155
1	88	156
2	76	157
4	73	158
6	72	159

(593) Tosylate, 0.5 g., potassium thiolbenzoate, 2.19 g., HMPT, 12.5 ml., bath temperature, 150°, average internal temperature, 148.5 ± 0.5°.

Time (hours)	α (%)	n.m.r. of sample
½	27	167
1	10	168

No 3-S-benzoyl-1,2:5,6-di-O-isopropylidene-3-thio-α-D-gulofuranose could be isolated on work-up of the residues of the above two reactions. Chromatography of the residue from the last experiment yielded dibenzoyl disulphide, the starting tosylate, and HMPT only.

4,6-O-Ethylidene-1,2-O-isopropylidene-3-O-tosyl-α-D-galactopyranose

(617) Tosylate, 0.5 g., potassium thiolbenzoate, 2.2 g., DMF, 15 ml., bath temperature, 140°, internal temperature, 139.5°.

Time (hours)	α (%)	n.m.r. of sample
½	95	178
1	90	179
2	86	180
3	79	181
4	75	182
6	70	183

(621) Tosylate, 0.5 g., potassium thiolbenzoate, 2.2 g., DMF, 15 ml., bath temperature, 178°, average internal temperature 161 ± 0.5°.

Time (hours)	α (%)	n.m.r. of sample
1	90	185
2	83	186
3	75	187
4	67	188
6	56	189

No pure 3-S-benzoyl-4,6-O-ethylidene-1,2-O-isopropylidene-3-thio-α-D-gulopyranose could be isolated from the residues of the last two experiments.

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