A thesis entitled

"SYNTHETICAL ROUTES TO THIOSUGARS AND RELATED COMPOUNDS"

submitted by

JOHN MICHAEL COX

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ABSTRACT

Part I

It has been shown that monocyclic thioseptanose sugars are formed only where the adoption of a pyranose or furanose ring is not possible. Thus acylated derivatives of 6-deoxy-6-mercapto-D-galactose itself exist as pyranose sugars containing an S-acyl group.

In the 6-deoxy-6-mercapto-3,5-di-O-methylglucose series, which is unable to adopt a pyranose ring system, formation of a thioseptanose ring can be achieved but only accompanied by the retention of the O-furanose ring, giving a bicyclic compound. Thus hydrolysis of 6-deoxy-1,2-O-isopropylidene-6-mercapto-3,5-di-O-methyl-α-D-glucofuranose (which was synthesized by two alternative routes) with mineral acid gives 1,6-anhydro-6-deoxy-6-mercapto-3,5-di-O-methyl-β-D-glucofuranose and the intermolecular 1:6',1':6-dianhydride. The use of aqueous acetic acid, however, merely results in the removal of the isopropylidene group to give the free 6-deoxy-6-mercapto-O-furanose sugar.

6-Deoxy-6-mercapto-2,3,4,5-tetra-O-methyl-D-galactose (prepared from D-galactose *via* a series of dithioacetals)

is shown to exist in a cyclic form and thus to constitute the first example of a monocyclic thioseptanose sugar. In contrast to the thiopyranose, but like the thiofuranose system, it consumes iodine rapidly on titration. The corresponding ethyl glycoside has been obtained, also as an anomeric mixture, by reaction of 6-deoxy-6-mercapto-2,3,4,5-tetra-O-methyl-D-galactose ethylene acetal both with ethanolic hydrogen chloride and with ethereal hydrogen chloride followed by silver carbonate in ethanol.

The first sugar derivative containing a sulphur atom in both a five- and a seven- membered ring, 1,6-anhydro-4,6-dideoxy-4,6-dimercapto-2,3-di-O-methyl-β-D-glucofuranose, is obtained when methyl 4,6-dideoxy-4,6-dimercapto-2,3-di-O-methyl-β-D-glucopyranoside is treated with mineral acid.

Part II

Thietan, tetrahydrothiophen, tetrahydrothiopyran and thiepan are converted into their 2-acetoxy derivatives by reaction with t-butyl peracetate. Except in the first case, deacetylation yields a hemithioacetal, although in solution the seven-membered thiepanol ring exists as the tautomeric mercapto-aldehyde. Among the interesting

properties of these previously unknown analogues of the thiosugars is the spontaneous elimination of water, from the five- and six- membered ring hemithioacetals, to form 4-[(2-thiolanyl)thio] butanal and 5-[(2-thianyl)thio]-pentanal respectively.

ACKNOWLEDGEMENTS

My grateful thanks are due to Professor L. N. Owen, for his help and guidance throughout the course of this work, and to various members of the Organic Chemistry Department for many helpful discussions.

I am also indebted to the Salters' Institute of Industrial Chemistry for the award of a Scholarship and to my fiancée, Miss M. D. Fox, for typing both this thesis and previous reports.

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PART I

Thiosugars

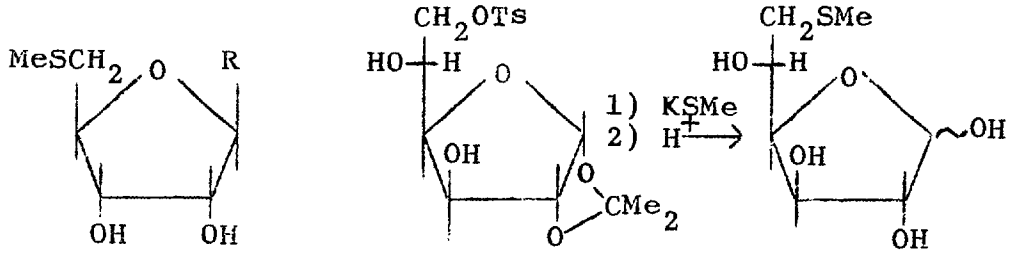
Introduction

Since the subject of thiosugars (in the general sense) has been reviewed by several authors,[1-4] the present literature survey will dwell chiefly on the relatively new class of carbohydrates in which the ring hetero-atom is other than oxygen. As a brief introduction, however, the other classes will receive attention.

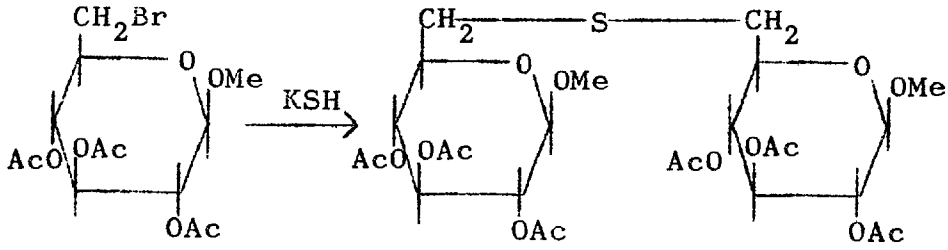
Being relatively easily accessible, the 1-thiosugars, both aldoses and glycosides, have been extensively investigated and it is to these compounds that the reviews devote most space. In contrast, it is only in recent years that much work has been carried out on thiosugars containing sulphur at another position.

Among early examples were the isolation[5] of the yeast nucleoside (1) containing the 5-deoxy-5-methylthio-D-ribofuranose moeity and the synthesis of ω-thiosugars such as 6-deoxy-6-methylthio-D-glucofuranose (2)[6], the di-D-glucose 6,6'-sulphide (3)[7] and 6-deoxy-1,2-O-isopropylidene-6-mercapto-α-D-glucofuranose (4)[8]. The routes to these compounds, as shown in the charts, exemplify two of the standard procedures for the introduction of sulphur, namely the displacement of halide or sulphonyloxy groups

by a sulphur-containing nucleophile, and the scission of epoxides.



[1; R = 9-(6-aminopurinyl)] (2)



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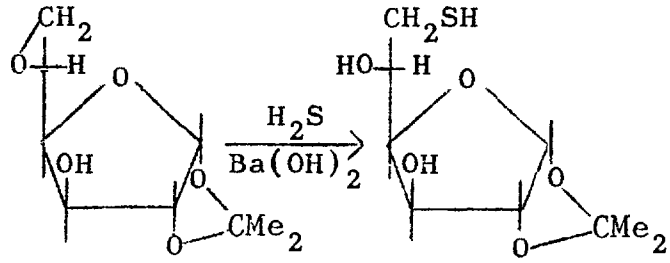
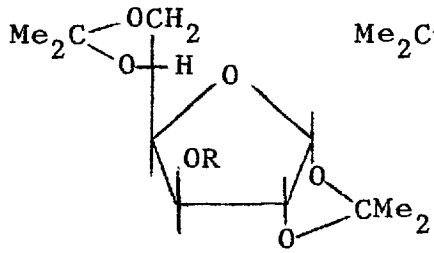
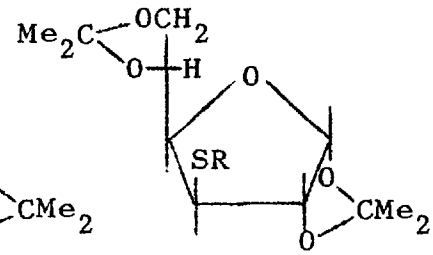
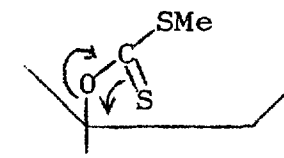


(4)

The first example of a sugar containing sulphur attached to a secondary carbon atom (other than C-1) was reported by Freudenberg[9]. Pyrolysis of the 3-O-[(methylthio)thiocarbonyl]- derivative (5) gave, instead of the expected olefin, the rearranged product (6) which was saponified to give crude 3-deoxy-1,2:5,6-di-O-isopropylidene-3-mercapto-α-D-glucofuranose (7), characterised as the crystalline disulphide and 3-S-methyl ether. The conversion of (5) to (6) presumably involves a four-membered transition state as indicated.





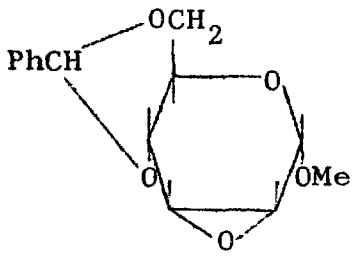


(5; R = CS.SMe) (6; R = CO.SMe)

(7; R = H)

A large number of secondary derivatives have been prepared by the cleavage of an epoxide ring with various thionucleophiles. As attack can be at one of two sites, usually non-equivalent, it is possible that two products

may be formed. However, in a large number of cases, some feature of the molecule causes specificity. In the 2,3-epoxides attached to a locked pyranose ring, it has been shown that the position of attack is such that the product bears <u>trans</u>-diaxial substituents according to the Fürst-Plattner rule.[10, 11] Thus, whereas the alloside (8) is attacked by sodium methyl sulphide at C-2 to give the altroside (9),[12] the corresponding mannoside (10) is cleaved in the opposite manner, giving the 3-methylthio-altroside (11).[13]



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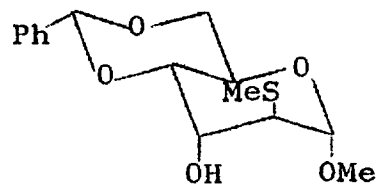

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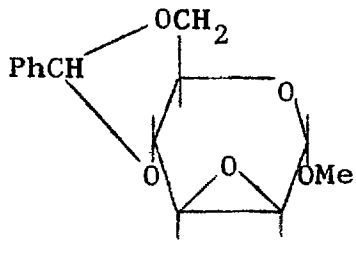

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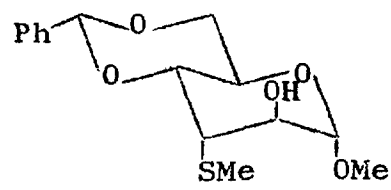


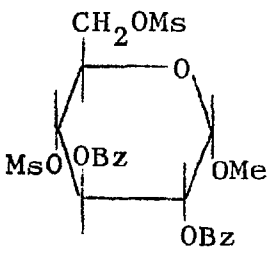
(11)

Baker and his co-workers have found, however, that 2,3-epoxides contained in non-rigid systems are generally attacked at C-3,[4] regardless of configuration, although methyl 2,3-anhydro-β-D-lyxofuranoside does yield a mixture of both products when treated with sodium benzyl sulphide.[14]

If the free thiol is required, this method may be modified by preparing the S-benzyl derivatives since, unlike the S-alkyl ethers, they are readily cleaved, notably by sodium in liquid ammonia. Low yields are usually obtained by the direct action of hydrogen sulphide on epoxides.

The displacement of sulphonyloxy groups from sugars has been thoroughly reviewed by Ragg.[15] Secondary sulphonates, particularly those attached to a ring carbon atom, other than C-1, are much less susceptible to nucleophilic attack than those at a primary position. It is only recently that successful reactions have been recorded,[16, 17, 18] due entirely to the use of dipolar aprotic solvents[19] such as N,N-dimethylformamide. The di-O-methanesulphonate (12) was converted,[20] by treatment with potassium thiocyanate in dimethylformamide, into the 4,6-bisthiocyanate (13). Further reaction with either sodium ethoxide or ethanolic sodium sulphide led, with simultaneous de-O-benzoylation, to the 4,6-dithiol, which

rapidly oxidised to the internal 4,6-disulphide (14).



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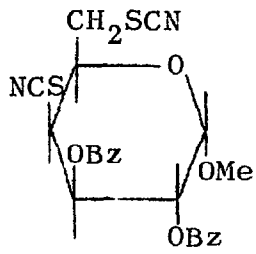

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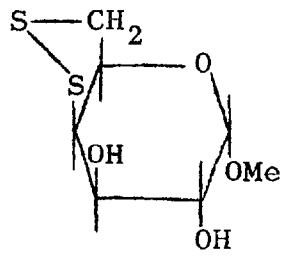
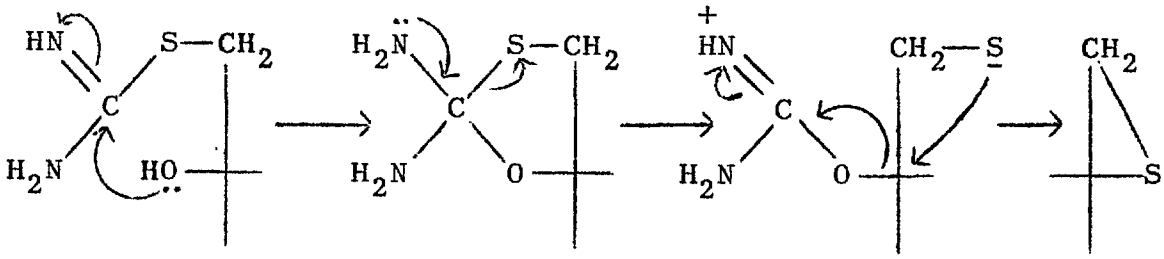


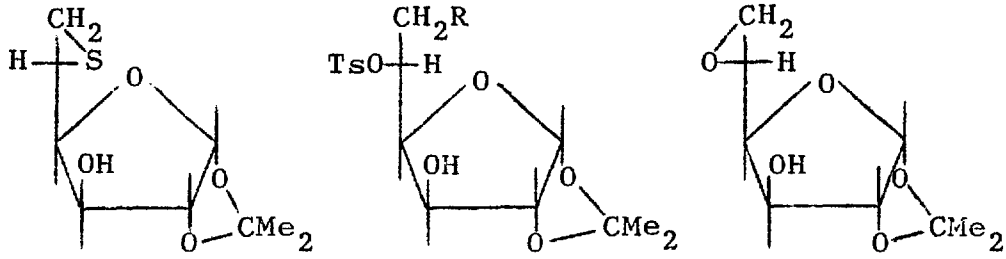
(14)

Further examples are given later, since the introduction of a sulphur atom at a secondary carbon atom (namely C-4) is a necessary step in the synthesis of thiofuranose sugars.

Many syntheses of thiosugars involve the episulphides, which fall into two main classes. The two synthetic routes to the 5,6-episulphides, the first group, are exemplified by the preparation of 5,6-dideoxy-5,6-epithio-1,2-O-isopropylidene-β-L-idofuranose (15)[21, 22]. Reaction of 1,2-O-isopropylidene-5,6-di-O-tosyl-α-D-glucofuranose (16) with potassium thiolacetate in ethyl methyl ketone gave the 6-acetylthio derivative (17).[22] Treatment with sodium methoxide in methanol released the thiolate anion which expelled the sulphonyloxy group with inversion at C-5. The initial step in the alternative route, which involved

treatment of the 5,6-epoxide (18) with thiourea or potassium thiocyanate, is presumed to be the attack of the sulphur atom at C-6. Although the reaction scheme is shown only for thiourea, parallel steps can be written for the attack by thiocyanate.

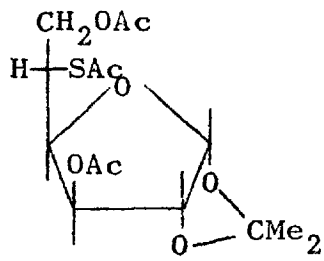




(15) (16; R = OTs) (17; R = SAc) (18)

Although alkaline cleavage may give rise to polymeric products,[22] the episulphide ring can be successfully opened by attack of nucleophiles at C-6. For example, the action

of potassium acetate in acetic anhydride - acetic acid on (15) gave 3,6-di-O-acetyl-5-acetylthio-5-deoxy-1,2-O-isopropylidene-β-L-idofuranose (19).[23, 106] The episulphide (15) was also converted[21] into the trithiocarbonate of the same configuration by reaction with potassium methylxanthate in methanol at room temperature. This trithiocarbonate (20) had, in fact, been prepared[24] earlier by the action of excess potassium methylxanthate in hot methanol on the 5,6-epoxide (18) but it was then thought to be the D-gluco isomer, since the intermediacy[25] of an episulphide, with consequent inversion, had not been recognized.



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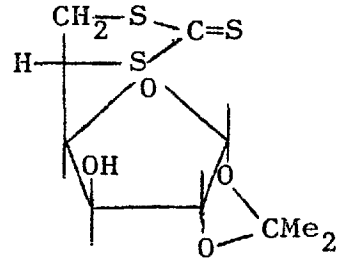
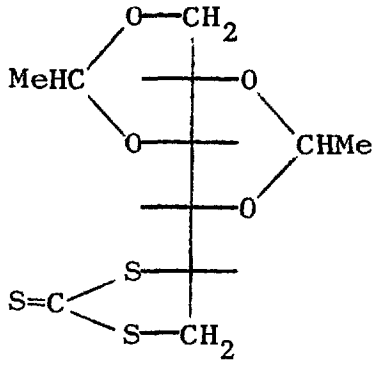


(20)

Since the trithiocarbonates are readily reduced with lithium aluminium hydride,[26] they may be used to introduce the vicinal dithiol grouping into carbohydrates. Thus reduction of 5,6-dideoxy-1,3:2,4-di-O-ethylidene-5,6-(thiocarbonyldithio)-

L-iditol (21) gave the crystalline dithiol in excellent yield. Similarly, a reductive fission of the dithiocarbonate (22) was used[27] to prepare the 4,5-dimercapto-L-xylose derivative (23).



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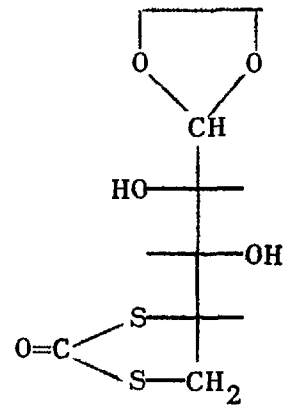

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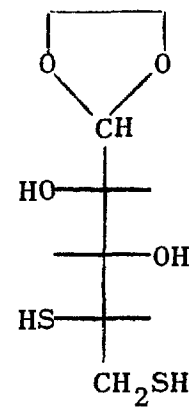
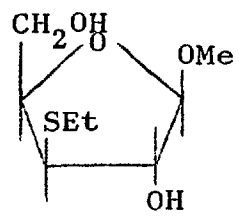


(23)

A second class of episulphides, involving fusion directly on to a carbohydrate ring, has been observed only rarely.[28, 29] Although a low yield of such an episulphide was obtained directly from the epoxide, a three-step process involving cleavage of the epoxide with thiocyanate, conversion of the liberated hydroxyl into a sulphonyloxy group and treatment with base, proved more successful.

The episulphonium ion intermediate has also been utilised, mostly in order to obtain products not accessible

by direct epoxide cleavage. The tendency of nucleophiles to attack the 2,3-epoxides of non-rigid ring systems at C-3 has already been mentioned. The 3-ethylthio derivative (24) yielded,[30] on toluene-p-sulphonylation, the mixture (25). Acetolysis, followed by acetylation, gave a preponderance of the D-arabinoside (26), containing sulphur at C-2. A further example, from the same laboratories, is mentioned later (see p. 34).



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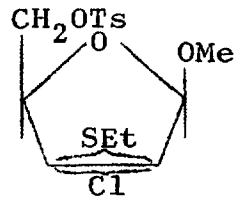

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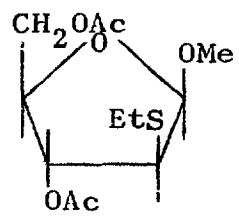
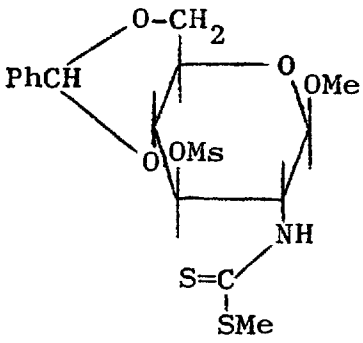


(26)

Since secondary ring sulphonates are difficult to displace and the scission of epoxides and episulphides must give trans- orientated products, the anchimerically assisted displacements of sulphonates have been used to obtain the cis- relationship, particularly for amino-thiols. The glucoside (27) was cyclized[31] with sodium methoxide in methanol to the thiazoline (28) which was reduced with aluminium amalgam. Cleavage of the resulting thiazolidine

with mercuric chloride gave the mercuric complex of the cis- amino-thiol (29). A similar result has been reported by Goodman and his co-workers[32] who cyclized the altroside (30) by boiling it in pyridine. The thiazoline (31) obtained was converted, as above, into the 3-amino-2-mercapto sugar. The use of sodium methoxide resulted, however, in the formation of the aziridine (32).



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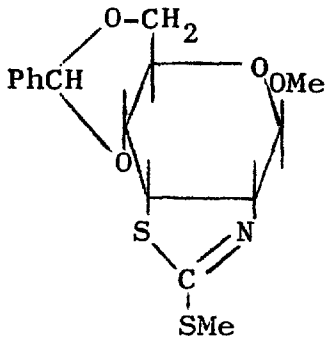

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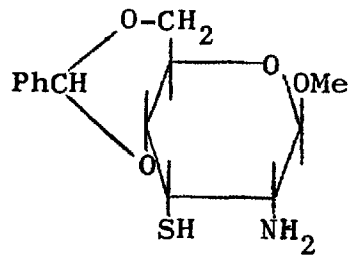

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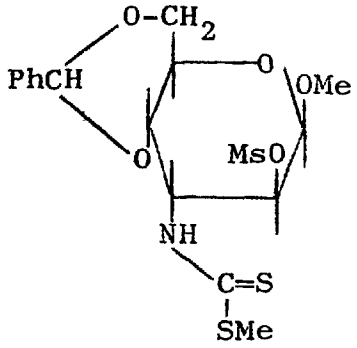

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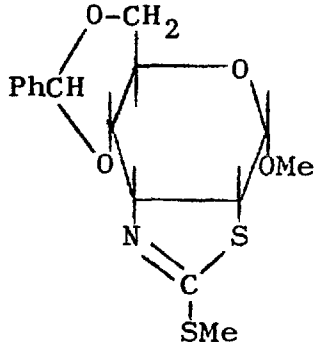

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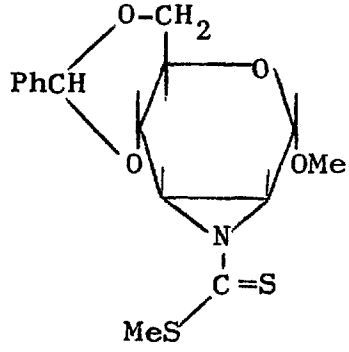
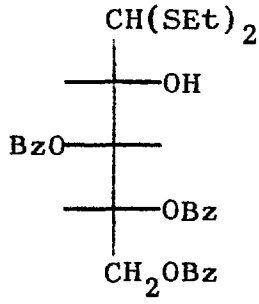


(32)

It has also been reported that the dithioacetals of certain aldose derivatives react further, over long reaction periods, with thiols under acidic conditions to give thioethers. For example, treatment[33] of the D-xylose diethyl dithioacetal (33) with ethanethiol and dry hydrogen chloride in chloroform resulted in the isolation of the thioether (34). Although the position of the new substituent was established by successive debenzoylation, reductive desulphurization and periodate oxidation to propionaldehyde, the configuration at C-2, assumed to be D-xylo in a subsequent publication[34], was not proved. It appears that any free hydroxyl group is subject to replacement, although an early example[35] also involved the introduction of an ethylthio group at C-2. The reaction of 1,2,3,4-tetra-O-acetyl-α-L-arabinopyranose with ethanethiol in the presence of zinc chloride or preferably boron trifluoride etherate yielded,[34] after deacetylation, 5-deoxy-5-ethylthio-L-arabinose diethyl dithioacetal (35). Similarly 3,5,6-tri-O-benzoyl-1,2-O-isopropylidene-α-D-glucofuranose gave a 3,5,6-tri-O-benzoyl-2,4-dideoxy-2,4-diethylthio-D-hexose diethyl dithioacetal.[36]



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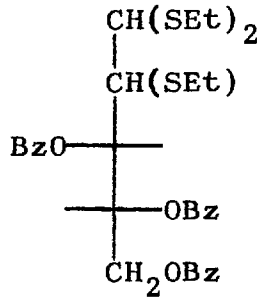

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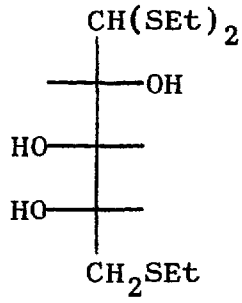


(35)

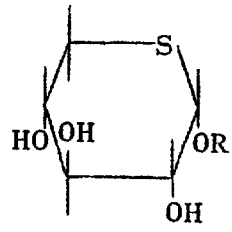
Thiopyranoses

Prior to 1961, carbohydrate derivatives containing a ring heteroatom other than oxygen were unknown.

The first example of such a system, 5-deoxy-5-mercapto-D-xylopyranose (36), was reported both by Schwarz and Yule[37] and Adley and Owen[23, 106]. The former workers[37] obtained the thiocyanate (37) and the Bunte's salt (38) by treatment of the 5-O-tosylate (39) with sodium thiocyanate in acetone, and sodium thiosulphate in dimethylformamide, respectively. The thiol (40) was formed from the thiocyanate by treatment with aqueous sodium sulphide solution, and from the thiosulphate by reduction with potassium borohydride. It has also been prepared by two further routes. Reaction of the tosylate (39) with potassium thiolacetate in dimethylformamide gave[23, 106] a

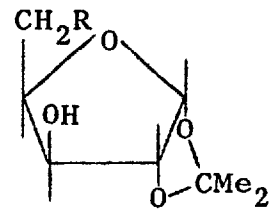
mixture of the thiolacetate (41) and the product of acyl migration (42). Deacetylation of the mixture with sodium methoxide in methanol then afforded the thiol (40), which Whistler[38, 39] derived from the tosylate (39) by treatment first with sodium benzyl sulphide in ethanol, then sodium in liquid ammonia.

Acidic hydrolysis of (40) gave[23, 37, 106] crystalline 5-deoxy-5-mercapto-α-D-xylopyranose (36), the original nomenclature of which, D-xylothiapyranose, has been criticised[4] both because the compound could be adequately described using conventional nomenclature and because the term "thia" should be used to indicate the substitution of a methylene group by sulphur.



(36; R = H)

(43; R = Me)



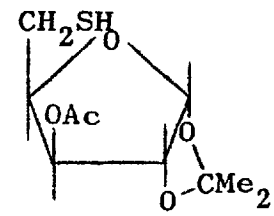
(37; R = SCN)

(38; R = $S_2O_3^-$)

(39; R = OTs)

(40; R = SH)

(41; R = SAc)



(42)

The free sugar (36) titrated only slowly with iodine[23, 106] and the mutarotation[37] was also very slow, both in water and in a potassium hydrogen phthalate solution of pH 4.4, although at pH 6.6 the rate was comparable to that of D-xylose itself!

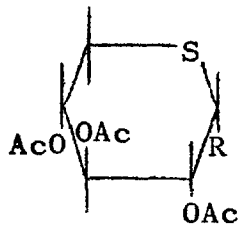
Whereas acetylation of (36) with sodium acetate in acetic anhydride gave[37] a mixture of the anomeric tetra-acetates, the use of acetic anhydride in pyridine led to the isolation[23, 37, 106] of only the dextrorotatory isomer. Since the nuclear magnetic resonance (n.m.r.) spectra of the dextrorotatory and laevorotatory isomers showed[40] coupling constants, $J_{1,2}$, of 2.4 and 8.5 $sec.^{-1}$, they were assumed to be the α- and β- forms respectively. (See also p. 27).

The methyl α-glycoside (43), formed when the thiol (40) was treated with a solution of hydrogen chloride in methanol, absorbed no iodine on titration.[38, 39] Since it also gave the expected quantity of formic acid on oxidation with sodium metaperiodate, the presence of a thiopyranose ring was confirmed. The consumption of greater than the calculated quantity of periodate was attributed to the oxidation of the heterocyclic sulphur atom.[41]

The chemical reactions of (36) are similar to those

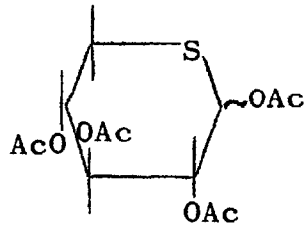
of D-xylose itself. Reaction with aryl amines gave a series of glycosylamines[42] which underwent the Amadori rearrangement to 1-amino-1-deoxy-2-ketoses in the usual manner[43, 44]. 2,3,4-Tri-O-acetyl-5-deoxy-5-mercapto-α-D-xylopyranosyl bromide (44) which was prepared[45] from the tetra-acetate (45)[37] by the action of hydrogen bromide in acetic acid, also reacted normally, the β-methyl glycoside (46) being formed by the treatment of (44) with silver carbonate in methanol and subsequent deacetylation. The corresponding thioglycoside (47), formed by the action first of sodium methoxide, then sodium methyl sulphide on the bromide (44) in methanolic solution, underwent acetylation to the triacetate (48) and methanolysis to the β-glycoside (46). Oxidation[46] of either anomer of methyl 2,3,4-tri-O-acetyl-5-deoxy-5-mercapto-D-xylopyranoside with hydrogen peroxide in glacial acetic acid at 25° led to the corresponding sulphone. Unlike the corresponding 1-O-acetates, from which sulphoxides could not be obtained with any oxidant, the methyl glycosides were oxidised with sodium metaperiodate in methanol-water. Although each can form two diastereoisomeric sulphoxides, the α-glycoside (49) formed mainly one, and the β-anomer (50) two in the ratio of about 3:1. The sulphoxide configurations were tentatively proposed after consideration of the relative dispositions

of the non-bonding orbitals of the glycosidic and sulphoxide oxygen atoms.

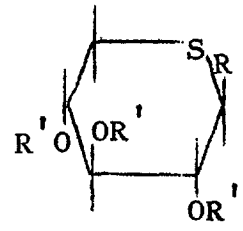


(44; R = Br)

(49; R = OMe)



(45)



(46; R = OMe; R' = H)

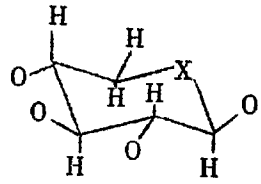
(47; R = SMe; R' = H)

(48; R = SMe; R' = Ac)

(50; R = OMe; R' = Ac)

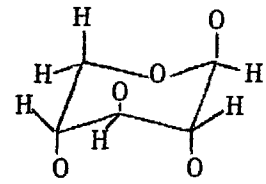
It has been shown[47] by n.m.r. spectroscopy that the replacement of the ring oxygen of the D-xylopyranosides by sulphur has little effect on the preferred ring conformation. In the case of both D-xylopyranosides, consideration of stability factors[48-50] suggested the normal conformation to be <u>C1</u> rather than <u>1C</u> [i.e. (51) rather than (52) in the case of the β-isomer], a nomenclature introduced by Reeves[51]. Methyl β-D-xylopyranoside had been previously shown,[52] by X-ray analysis, to adopt this conformation in the crystalline

state and optical rotation studies[53] provided further confirmation. In the case of both tetra-O-acetyl-D-xylopyranoses, the spin-spin coupling constants observed in the n.m.r. spectra are consistent with those required by the C1 but not the 1C formulation.[54] From Table 1, it can be seen that this is the case for all the compounds investigated[47] including those with sulphur in the ring. A detailed analysis of the additional fine structure in the spectrum of methyl 5-deoxy-5-mercapto-β-D-xylopyranoside (46) showed, without doubt, that H-1, H-2, H-3 and H-4 are all in the axial orientation, as shown in (53). These coupling constants are set out in Table 2.



(51; X = O)

(53, X = S)



(52)

Table 1

Chemical Shifts and Coupling Constants for Anomeric Protons				
Compound	Chemical Shift (τ)		Coupling Const. $J_{1,2}$(c.p.s.)	Dihedral angle* (degrees)
	H-$1_{eq.}$	H-$1_{ax.}$		
D-xylose	4.82	5.45	2.2 7.2	60 148
Methyl β-D-xylopyranoside		5.62	7.2	148
5-Deoxy-5-mercapto-D-xylopyranose	5.0	5.25	2.5 8.2	57 154
Methyl 5-deoxy-5-mercapto-α-D-xylopyranoside	5.35		2.8	55
Methyl 5-deoxy-5-mercapto-β-D-xylopyranoside		5.52	8.4	156

*Calculated from $J_{1,2}$ using the modified Karplus equation.[55]

Table 2

Coupling Constants of Methyl 5-deoxy-5-mercapto-β-D-xylopyranoside (c.p.s.)	
$J_{1ax.,2ax.} = 8.4$	$J_{4ax.,5eq.} = 3.3$
$J_{2ax.,3ax.} = 8.6$	$J_{4ax.,5ax.} = 11.2$
$J_{3ax.,4ax.} = 8.6$	$J_{5ax.,5eq.} = 13.5$

The rates of hydrolysis of various sulphur-containing glycosides have been measured and compared[45, 56] with the oxygen analogues. (See Table 3)

The increased rate of the thiopyranosides [(C) and (D)], compared with the corresponding oxygen compounds [(A) and (B)], was explained by Whistler and Van Es[45] as being due to "the inductive effect of the sulphur releasing electrons to the exocyclic oxygen, thus increasing the concentration of the conjugate acid". This would appear to be both incorrect and unnecessary, since the slower rate of the oxygen analogues can be attributed to the more ready protonation of the ring oxygen than sulphur with consequent loss of the more effective

resonance stabilization (that oxygen affords) of the intermediate carbonium ion[58]. The slow hydrolysis of the 1-thioglycosides, compared with the corresponding oxygen analogues [i.e. (E) with (B), and (F) with (D)], can be explained since the low basicity of sulphur[59] would cause a low concentration of the conjugate acid.

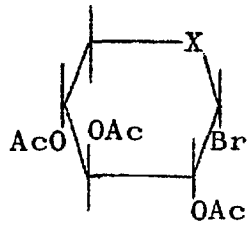
Table 3

Rate of acid-catalysed hydrolysis of glycosides[45]	
Compound	$10^5 k$ ($sec.^{-1}$)
Methyl α-D-xylopyranoside (A)	3.45*
Methyl β-D-xylopyranoside (B)	6.90*
Methyl 5-deoxy-5-mercapto-α-D-xylopyranoside (C)	35.0
Methyl 5-deoxy-5-mercapto-β-D-xylopyranoside (D)	100.0
Methyl 1-deoxy-1-mercapto-β-D-xylopyranoside (E)	3.50
Methyl 1,5-dideoxy-1,5-dimercapto-β-D-xylopyranoside (F)	70.1**

*Measured by Riiber and Sørensen[57].

**Value converted from that given in Ref. 56.

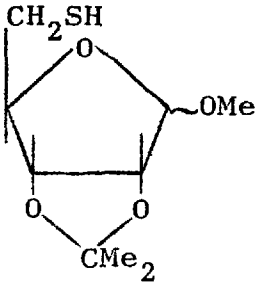
Whistler and Van Es[45] also showed that the rate of methanolysis of the thiopyranosyl bromide (54) was much slower than that of the oxygen analogue (55). This is consistent with α-haloethers being more reactive than α-halosulphides[60] and may be attributed to the greater resonance stabilization of the intermediate carbonium ion by oxygen than by sulphur.



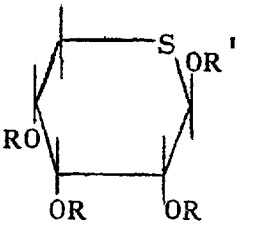
$[54;\ X=S\ :\ 10^5k\ (sec.^{-1}) = 4.36]$
$[55;\ X=O\ :\ 10^5k\ (sec.^{-1}) = 178\ ]$

Other pentose thiopyranosides having the D-*ribo*-[39, 61], 2-deoxy-D-*ribo*-[39], and L-*arabino*-[62] configurations have been prepared by similar routes. There is some confusion, however, over assignments at the anomeric position in one case. Treatment of the thiol (56) with 1% hydrogen chloride in methanol gave a crystalline glycoside, said[39] to be the β-anomer (57), having m.p. 97°, $[\alpha]_D^{25}$ + 18.6° (*c* 0.6, H_2O). This is contradictory to the work of Clayton and Hughes[61] who hydrolysed methyl 5-deoxy-2,3-*O*-isopropylidene-5-mercapto-β-D-ribofuranoside [the β-anomer of (56)] with $^M/_{20}$ aqueous sulphuric acid, giving the thiopyranose (58). On treatment

with methanolic hydrogen chloride this yielded two glycosides, one crystalline, m.p. 122-123°, $[\alpha]_D^{20}$ -246° (c 1.1, MeOH) and the other a syrup characterized as its tri-O-acetate (59), m.p. 64-65°, $[\alpha]_D^{20}$ +227° (c 0.8, MeOH). The crystalline and non-crystalline glycosides were given, on the evidence of optical rotation, the β- (57) and α- (60) formulations respectively. If Whistler's glycoside was, in fact, the α-anomer (60), this could be proved by conversion to the acetylated derivative (59). The presence of the pyranose ring in all these compounds was demonstrated by the lack of thiol activity and by periodate oxidation.

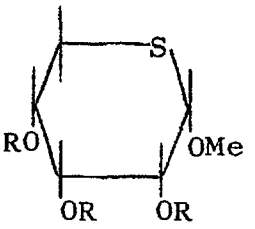


(56)



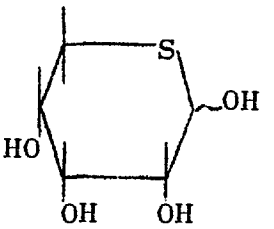
(57; R = H, R' = Me)

(61; R = Ac, R' = Ac)



(59; R = Ac)

(60; R = H)

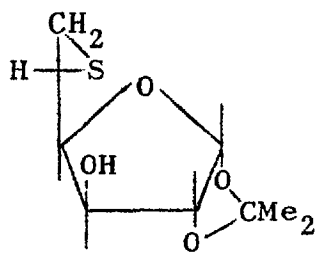


(58)

5-Deoxy-5-mercapto-D-ribopyranose (58), like the corresponding D-xylose compound[23], reacted only slowly with iodine.[61] It was characterized as the crystalline tetra-O-acetate (61), which was assigned the β- configuration on account of its optical rotation, $[\alpha]_D^{20}$ -61° (c 1.0, MeOH). The infra-red (i.r.) spectrum of (61) showed no thiolacetate absorption, thus confirming the presence of an S-pyranose ring.

All the sugars containing a thiopyranose ring discussed above have been pentoses. To obtain such a ring system in a hexose, it is necessary to introduce the sulphur atom at a secondary position which, as pointed out previously, is more difficult.

On treatment with potassium acetate, acetic acid and acetic anhydride, the 5,6-epithio-L-idose (62) was converted into the triacetate (63).[23, 106] Hydrolysis with aqueous acid, followed by acetylation, gave crystalline 1,2,3,4,6-penta-O-acetyl-5-deoxy-5-mercapto-L-idopyranose (64), the ultra-violet (u.v.) and i.r. spectra of which confirmed the absence of an S-acetyl group.



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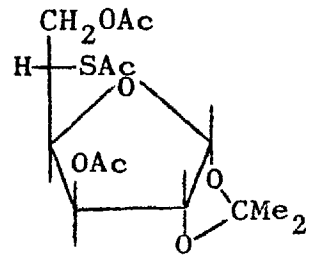

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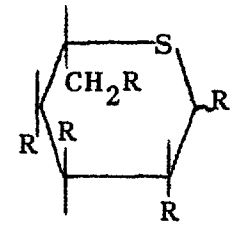
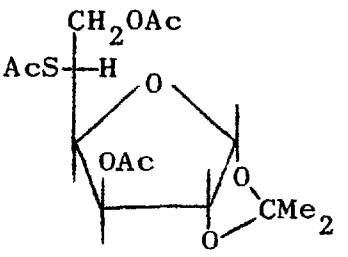
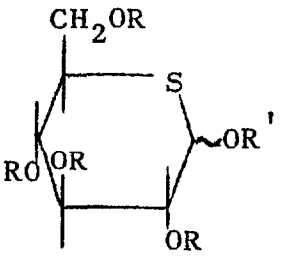


(64; R = OAc)

The triacetate (65), obtained[63] similarly from the D-gluco analogue of (62), underwent acetolysis to give a chromatographically pure syrup showing no thiolacetate absorption in the i.r. or u.v. spectra. The methanolysis of this penta-acetate (66), or the triacetate (65), yielded methyl 5-deoxy-5-mercapto-D-glucopyranoside (67) which showed no thiol activity with iodine in acetic acid and gave the expected one mole of formic acid upon periodate oxidation.



(65)

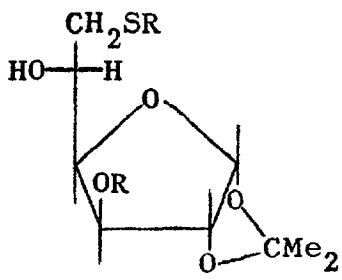


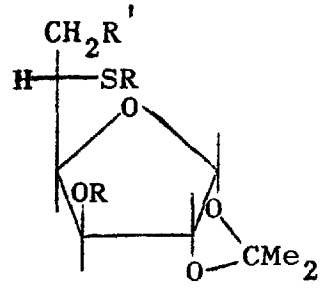
(66; R = R' = Ac)

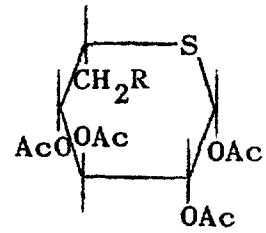
(67; R = H; R' = Me)

A derivative of L-idothiopyranose has also been prepared by Goodman[64] using a somewhat different approach. The benzylthio sugar (68), obtained by cleavage of the appropriate 5,6-epoxide with sodium benzyl sulphide, gave on treatment with thionyl chloride in dichloromethane the 5-benzylthio-6-chloride (69), presumably *via* the chlorosulphite of (68) and a 5,6-episulphonium ion. Further attack of azide ion at C-6, followed by borohydride reduction and debenzylation with sodium in liquid ammonia, yielded the amino-thiol (70) which was isolated and analysed as a complex with mercuric chloride. The *N*-acetate (71), prepared by *N*-acetylation before debenzylation in the preceding scheme, was subjected to vigorous hydrolytic

conditions. The crude solid isolated, which could not be purified, was acetylated to give a low yield of a crystalline penta-acetate exhibiting no S-acetate absorption in the i.r. spectrum. The rotation of the solid, compared to that of its mother liquors, suggested the compound to be 6-acetamido-1,2,3,4-tetra-O-acetyl-5,6-dideoxy-5-mercapto-β-L-idopyranose (72).







(68; R = CH_2Ph) (69; R = CH_2Ph, R' = Cl) (72; R = NHAc)

(70; R = H, R' = NH_2)

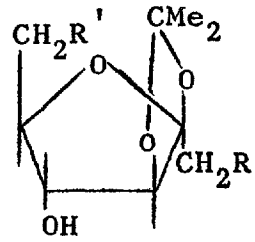
(71; R = H, R' = NHAc)

It should be noted that not only is the thiopyranose structure preferred to the original five-membered oxygen ring, but also to a possible septanose form containing nitrogen as the ring heteroatom.

Although it is possible for a 6-thiohexulose to exist in a pyranose ring, only one example of such a system has

been recorded.[65] Due to steric hindrance, sodium benzyl sulphide displaces only one of the sulphonyloxy groups from 2,3-O-isopropylidene-1,6-di-O-tosyl-β-D-fructofuranose (73) to give the 6-benzylthio ether (74). The 1-deoxy compound (75), formed from (74) by treatment first with lithium aluminium hydride, then sodium in liquid ammonia, decomposed in acid solution to methyl 2-thienyl ketone (76), isolated as its 2,4-dinitrophenylhydrazone. The tosylate (74) was also desulphonylated with sodium amalgam, then debenzylated with sodium in liquid ammonia. The resulting thiol (77) was hydrolysed in acidic solution to give, after chromatography, 6-deoxy-6-mercapto-D-fructose. As with D-xylothiopyranose[23,106], only 80% of the total sulphur could be titrated iodometrically during two hours. Since the i.r. spectrum showed no thiol or carbonyl absorption it was concluded that a major portion of the product was present in the thiopyranose form (78). As the thiol peak is always of very low intensity[66] it would appear, however, that any assignment of ring size is premature.

Tokuyama and his co-workers[67, 68] have investigated the synthesis of thio derivatives of blocked α-L-sorbofuranoses in some detail. For example, they have prepared 6-deoxy-2,3-O-isopropylidene-6-mercapto-α-L-sorbofuranose (79) and the 1,6-dimercapto compound (80) but no attempt was made to hydrolyse either.

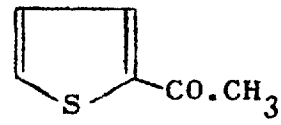


(73; R = R' = OTs)

(74; R = OTs, R' = SCH_2Ph)

(75; R = H, R' = SH)

(77; R = OH, R' = SH)



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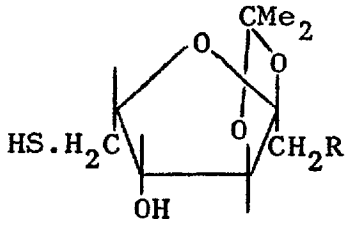
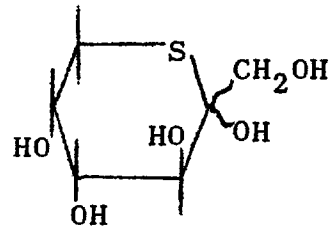


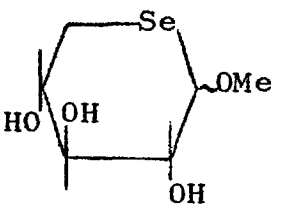
(79; R = OH)

(80; R = SH)

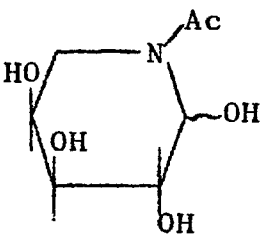


(78)

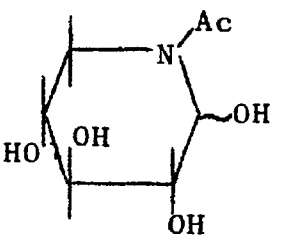
There are now a relatively large number of examples of pyranose sugars containing a ring heteroatom other than oxygen or sulphur. This is usually nitrogen, although methyl 5-deoxy-5-seleno-D-xylopyranoside (81) has been synthesized[69] by a route parallel to that used for the sulphur analogue. Of the nitrogen derivatives, the first examples recorded were 5-acetamido-5-deoxy-L-arabino-pyranose (82)[70] and the analogous compound (83)[71] from D-xylose, both synthesized by J.K.N. Jones and his co-workers. In both cases, the introduction of nitrogen into the molecule was carried out by reaction of the respective 1,2-O-isopropylidene-5-O-tosylates with methanolic ammonia in an autoclave. Hydrolysis of the blocking groups gave, in each instance, a complex mixture separated by chromatography on a cellulose column.



(81)

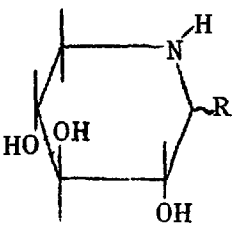


(82)



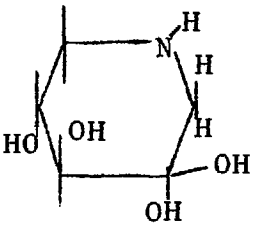
(83)

A compound (84) of this type containing a non-acylated amino group has recently been prepared.[72, 73] It is however extremely acid-sensitive, decomposing to its Amadori-rearrangement product (85) and 3-hydroxypyridine. Since the acid hydrolysis of 5-amino-1,2-O-cyclohexylidine-5-deoxy-D-xylofuranose led only to these unwanted derivatives,[74] a new synthetic method was developed. The bisulphite addition compound (86), prepared[75] from the isopropylidene derivative (87) by treatment with sulphurous acid, cyclized when heated in water to give the sulphonic acid (88). When treated with barium hydroxide solution, (88) gave an immediate precipitate of barium sulphite, and the free amino sugar (84).

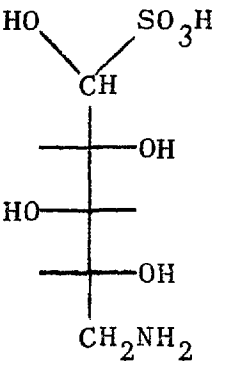


(84; R = OH)

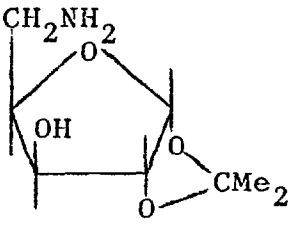
(88; R = SO_3H)



(85)



(86)



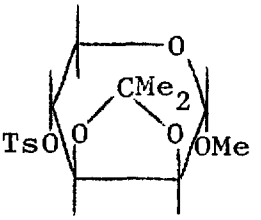
(87)

Little work has been done on the biological significance of replacing a sugar's usual heteroatom by another. However 5-deoxy-5-mercapto-D-glucopyranose has been shown to have bacteriostatic activity and to act as a mild competitive inhibitor for natural D-glucose in fruit flies and Escherichia coli.[76] In a recent paper, Claeyssens[77] has shown that D-xylose derivatives with sulphur or nitrogen in the ring are powerful inhibitors of glycosidase activities.

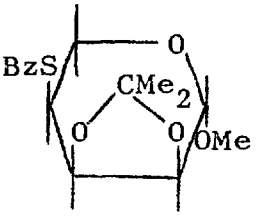
Thiofuranoses

The earliest examples of such a system all involved the pentose sugars, D- and L-ribose. The D-lyxo tosylate (89) was treated[16, 78] with potassium thiolbenzoate in

dimethylformamide to give the 4-thiolbenzoate (90), having the L-ribo configuration. Removal of the isopropylidene group with aqueous acetic acid gave the diol (91) from which was obtained, by acetolysis, 1,2,3,5-tetra-O-acetyl-4-deoxy-4-mercapto-L-ribofuranose (92) as a chromatographically pure syrup. Deacetylation of (92) with methanolic sodium methoxide yielded L-ribothiofuranose (93) which, in contrast to the behaviour of the thiopyranoses,[23, 61, 106] consumed one equivalent of iodine rapidly at room temperature; there was then a relatively slow additional iodine consumption which remained unexplained. The only evidence favouring the thiofuranose (93) compared with the pyranose form is the absence of thiol absorption in the i.r. spectrum. Since this is usually of very low intensity,[66] it would appear that in the free sugar itself, the ring structure was not definitely proved. This criticism obviously does not apply to the acetate (92) or the crystalline tetra-O-p-nitrobenzoate (94), since both showed no thiolester absorption in the i.r. spectrum. The methyl glycoside (95), formed by methanolysis of (93) and characterized as the p-nitrobenzoate (96), gave a negative nitroprusside test confirming the absence of any pyranose isomer.



(89)



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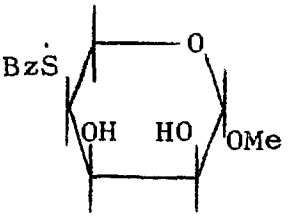
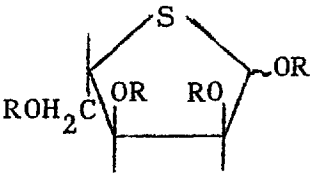


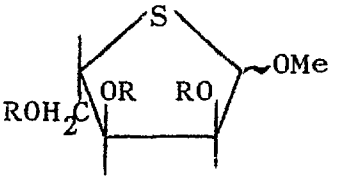
(91)



(92; R = Ac)

(93; R = H)

(94; R = p-nitrobenzoyl)



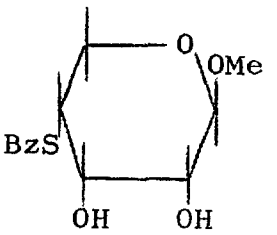
(95; R = H)

(96; R = p-nitrobenzoyl)

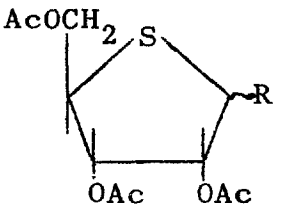
Much of the above work was repeated[16] in the D-ribo series, starting with the commercially less available L-lyxose. For example, acetolysis of methyl 4-benzoylthio-4-deoxy-β-D-ribopyranoside (97) gave the tetra-O-acetate (98) as a chromatographically pure syrup showing no S-acetate absorption in the i.r. spectrum. The crystalline isomer,

obtained by trituration with methanol, was assigned the β- configuration after consideration of the comparative optical rotations of the solid and the anomeric mixture. The D- isomers of (93), (94), (95) and (96) were, however, not prepared by these workers.

The adenine nucleosides of both D- and L-ribothiofuranose were prepared by the action of chloromercuri-6-benzamidopurine on the L-bromide (99) and the D-chloride (100) respectively, followed by deacetylation. The two 4'-thioadenosines were identical in all respects, except that the specific optical rotations were equal and opposite.

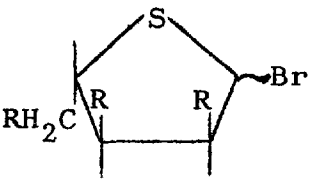


(97)



(98; R = OAc)

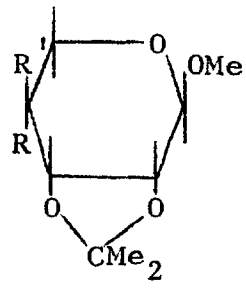
(100; R = Cl)



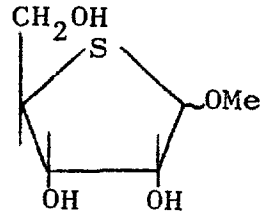
(99; R = OAc)

The first record of methyl D-ribothiofuranoside came, in fact, from Whistler and his co-workers.[17] The thiolacetate (101), formed from the tosylate (102) by

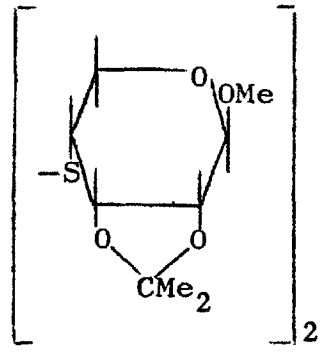
reaction with potassium thiolacetate yielded, on methanolysis, syrupy methyl 4-deoxy-4-mercapto-D-ribofuranoside (103) which showed no thiol activity when tested with sodium nitroprusside. The preparation of D-ribothiofuranose itself was not attempted, although a hydrolysis of the disulphide (104) was carried out.



(101; R = SAc, R' = H)
(102; R = H, R' = OTs)



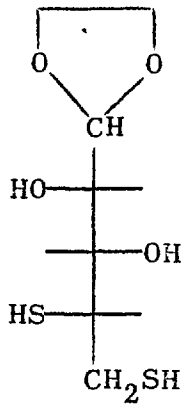
(103)



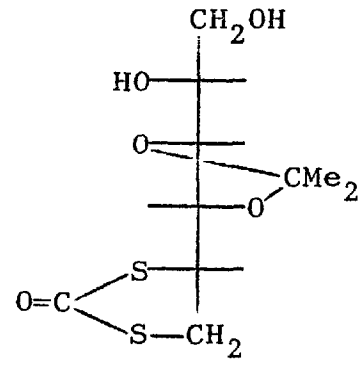
(104)

In general, it appears that an S-pyranose ring is preferred to O-furanose and an S-furanose to O-pyranose due, presumably, to the greater nucleophilicity of sulphur. In sugars containing no sulphur, the preference is usually for the six-membered ring,[79, 80] but there is as yet no direct evidence as to the relative stabilities of the thiopyranose and thiofuranose ring systems. The striking difference between the two is, of course, the rate at which iodine is consumed on titration. The rapid oxidation of the thiofuranose

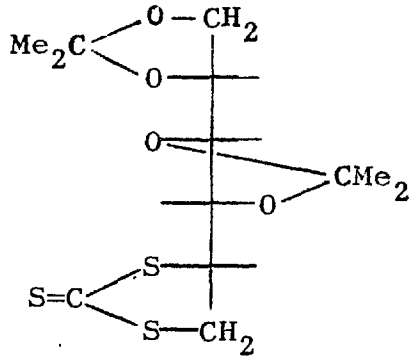
system appears to suggest a very facile equilibrium between the open-chain and cyclic tautomers,[16] whereas the much slower reaction in the pyranoses may well indicate greater stability. A direct comparison between the two forms could be obtained, if a molecule were synthesized in which the thiol groups are in such a position that either mode of cyclization could occur. It is difficult to see how such a molecule could be constructed by a method similar to those described above. However, a synthesis of a 4,5-dimercapto-pentose has been reported[27] although the final stage, the removal of the protecting group from the acetal (105), was not carried out due to lack of material. The L-gulitol dithiocarbonate (106) was prepared from the trithiocarbonate (107) using mercuric acetate in acetic acid followed by the addition of water and a further period of heating. Treatment with lead tetra-acetate cleaved the diol system but left the dithiocarbonate intact, although trithiocarbonates are attacked.[81] Under the acidic conditions necessary to form an ethylene acetal of the resulting L-xylose derivative (108), the 3,4-O-isopropylidene group was removed yielding the acetal (109). Reduction with lithium aluminium hydride gave the dithiol (105) which has only to be hydrolysed to obtain a compound with the desired features.



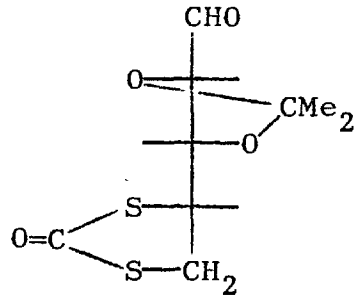
(105)



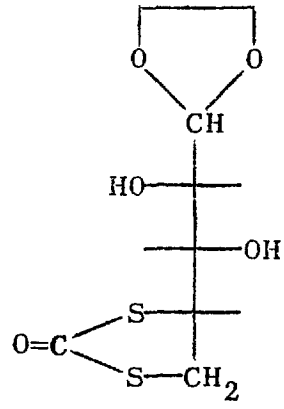
(106)



(107)



(108)

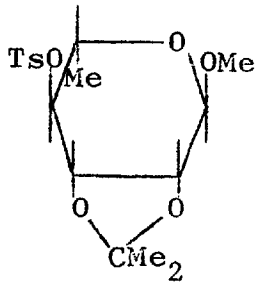


(109)

It is only recently that 4-mercapto-hexoses have been synthesized with the aim of producing a thiofuranose ring system.

The toluene-p-sulphonyloxy group was displaced[18] from methyl 2,3-O-isopropylidene-4-O-tosyl-α-L-rhamno-pyranoside (110)[82] on treatment with potassium thiolbenzoate

in dimethylformamide, although less readily than from the corresponding lyxose derivatives.[16, 17, 78] The thiol (111), obtained from the thiolbenzoate by treatment with sodium methoxide in methanol, was hydrolysed to give 4,6-dideoxy-4-mercapto-L-talofuranose (112), the first unsubstituted thiofuranose to be reported in the crystalline state. The α- configuration, shown, was assigned after consideration of the optical rotation, $[\alpha]_D^{26}$ -130° (c 1.0, MeOH). Like L-ribothiofuranose[16], the talose derivative (112) consumed iodine only slowly at room temperature, although the rate was much in excess of that reported for thiopyranoses.[23, 37, 61] Acetylation of (112) with acetic anhydride in pyridine gave a crystalline tetra-O-acetate showing no S-acetate absorption in the i.r. spectrum.



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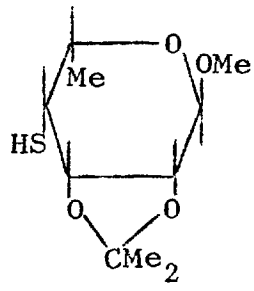
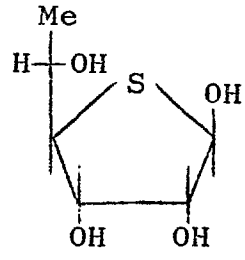
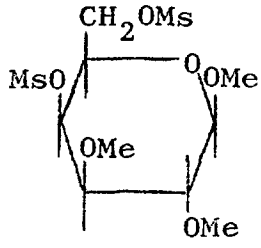


(111)

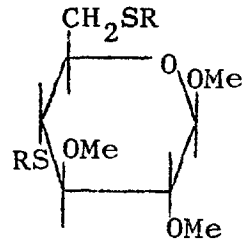


(112)

Neither toluene-p-sulphonyloxy nor methanesulphonyloxy groups can be displaced from the C-4 position of acylated methyl galactopyranosides.[18] However, methyl 4,6-di-O-methanesulphonyl-2,3-di-O-methyl-β-D-galactopyranoside (113) was converted to the D-gluco bisthiolacetate (114) by the action of excess potassium thiolacetate in dimethylformamide. The dithiol (115), obtained by deacetylation, was subjected to an acidic hydrolysis but no firm conclusion was reached, at that time, as to the nature of the products. This reaction has now been investigated further, and the results will be discussed later (p. 92).

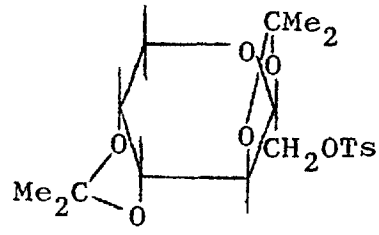


(113)



(114, R = Ac)

(115, R = H)

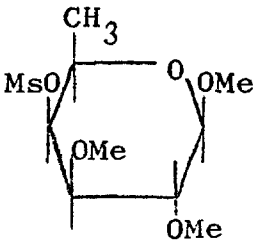


(116)

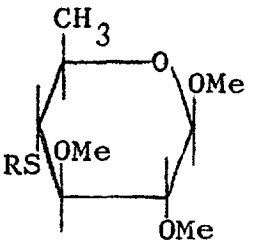
Lithium aluminium hydride is known to react with sulphonate groups in two different ways. Whereas a primary toluene-p-sulphonate is usually[83] cleaved with alkyl-oxygen fission giving a methyl group, those in sterically hindered

positions produce the sugar alcohol. The latter course thus occurs with primary groups when these are extremely hindered [as in 2,3:4,5-di-O-isopropylidene-1-O-tosyl-D-fructo-pyranose (116)[84]], and usually with secondary[85] sulphonates.

Although a large excess of lithium aluminium hydride was necessary to attack even the primary position of the di-O-methanesulphonate (113), the secondary sulphonate group remained intact.[18] The methyl 6-deoxy-4-O-methanesulphonyl-2,3-di-O-methyl-β-D-galactopyranoside (117) formed was converted into the D-gluco thiolacetate (118) by treatment with potassium thiolacetate in dimethylformamide. Acetolysis of (118) gave, after a chromatographic separation, the acetylated thiofuranose (119) which showed no thiolacetate absorption either in the u.v. or the i.r. spectrum. An ethanolysis of the thiol (120), formed by deacetylation of the corresponding thiolacetate (118), was also described. Although the product was not fully characterized, it was tentatively assigned the thiofuranoside structure (121) on the basis of the n.m.r. spectrum and its negative reaction with an alkaline sodium nitroprusside solution.

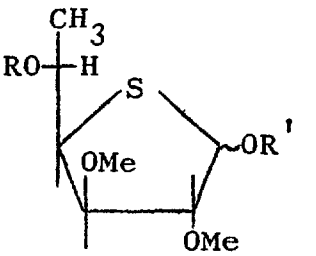


(117)



(118; R = Ac)

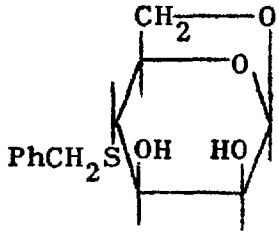
(120; R = H)



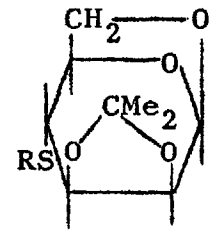
(119; R = R' = Ac)

(121; R = H, R' = Et)

It is known that an epoxide fused to a locked six-membered ring reacts with nucleophiles in such a way as to give the product bearing <u>trans</u>-diaxial substituents (see p. 12). Thus treatment of 1,6:3,4-dianhydro-β-D-talopyranose with sodium benzyl sulphide gave the 4-benzylthio ether (122)[18], as shown by the formation of an isopropylidene derivative (123). When the thiol (124), formed by reduction with sodium in liquid ammonia, was hydrolysed with N sulphuric acid, no decrease in the thiol activity was observed. Since it was thought that a product containing a hydroxyl group at C-1 would rearrange to the thiofuranose form and, by analogy with other such compounds,[16, 18] consume iodine more slowly than a free thiol, the 1⟶6 bridge was presumed intact. When more vigorous conditions were used, extensive decomposition resulted and no identifiable products were reported.



(122)

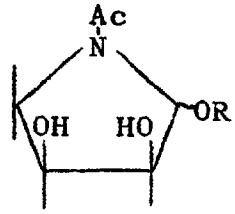


(123, R = CH_2Ph)

(124, R = H)

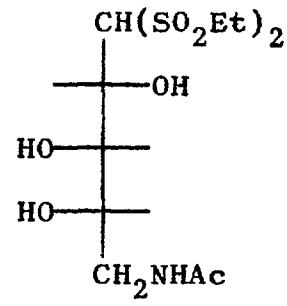
Carbohydrates containing nitrogen in a five-membered ring have also been synthesized. The first example, methyl 4-acetamido-4-deoxy-L-erythrofuranoside (125), was prepared by J.K.N. Jones and his co-worker [86] who cleaved the threo-glycol group of 1-acetamido-1-deoxy-D-ribitol with a limited quantity[87] of sodium metaperiodate and subjected the major product to methanolysis. Hanessian[88] reported, almost simultaneously, the furanose itself (126), which was obtained by an alkaline degradation of 5-acetamido-1,5-dideoxy-1,1-bis(ethylsulphonyl)-aldehydo-L-arabinose (127).

Although both of these examples involve a nitrogen atom attached to a primary position, a facile route to 4-amino-4-deoxy-pentoses (involving the displacement of a 4-O-methane-sulphonyloxy group with azide ion) has now been developed.[89]



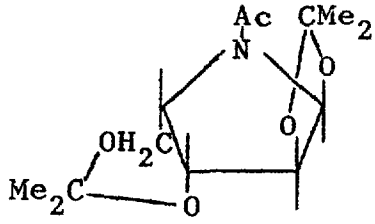
(125; R = Me)

(126; R = H)



(127)

The stable form of most 4-amino sugars, both pentoses and hexoses, appears to contain a six-membered oxygen ring[89,90,91] but the solid di-isopropylidene derivative (128) of 4-acetamido-4-deoxy-L-xylose[89] apparently contains nitrogen in the ring. Consideration of the conformational formulae [(129), drawn in the <u>C1</u> form: (130), drawn in the <u>1C</u> form] shows that a pyranose ring would have to be greatly distorted to accommodate two isopropylidene rings, whereas the four hydroxyl groups attached to a furanose ring are correctly disposed for reaction with acetone.



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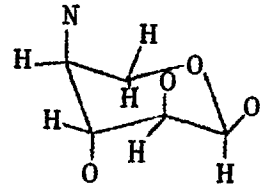

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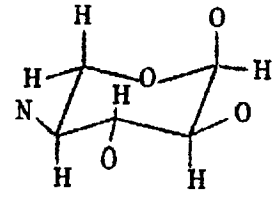
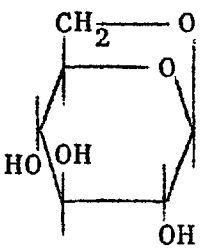


(130)

Thioseptanoses

Since there are very few monocyclic sugar derivatives containing a seven-membered ring, if oxidised and reduced systems are excluded, all septanoses[92] are reviewed.

Although Pringsheim[93, 94] claimed to have obtained D-glucoseptanose by the vigorous acidic hydrolysis of laevoglucosan (131), Reichel[95] concluded that the product was probably 2,4-anhydro-D-glucopyranose. The first authenticated examples were reported by Micheel[92, 96-98]. 2,3,4,5-Tetra-O-acetyl-6-deoxy-6-iodo-D-galactose diethyl dithioacetal (132) formed from 6-deoxy-6-iodo-D-galacto-pyranose by the action first of ethanethiol in concentrated hydrochloric acid, then acetic anhydride in pyridine, was cleaved[92] by treatment with mercuric chloride and cadmium carbonate in aqueous acetone to the hydrate (133). This was cyclized to the septanose (134) by heating it in pyridine and after further acetylation a mixture of the penta-acetates, both crystalline, was obtained. Each was shown to be different from the other five possible D-galactose penta-acetates (two pyranose, two furanose and an aldehydo isomer). The septanose structure was confirmed by conversion[96] into methyl tetra-O-methyl-D-galactoseptanoside, followed by oxidation with nitric acid to tetra-O-methylmucic acid (135).



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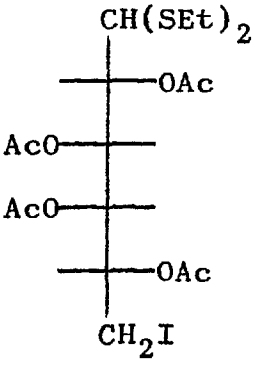

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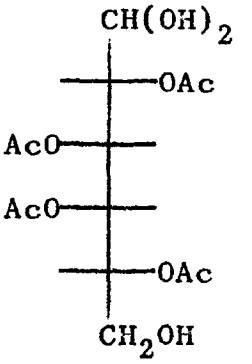

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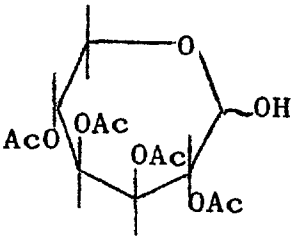

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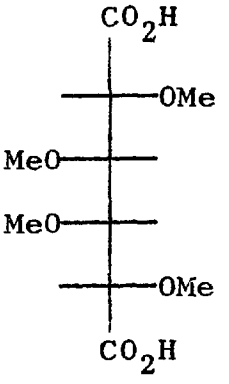

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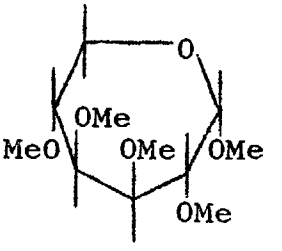


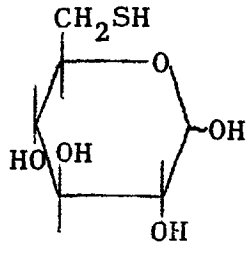
(136)

Neither Micheel[97] nor Riiber[99] were able to detect the presence of any septanose form in the case of D-galactose itself, but the possibility was not excluded. The first direct evidence that it does, in fact, exist largely in the seven-membered ring form was obtained recently.[100] Permethylation of both D-galactose and its methyl glycosides was carried out under various conditions and the total product analysed by gas-liquid chromatography (GLC). When

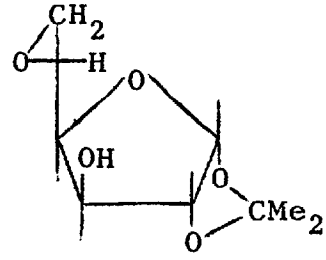
D-galactose was methylated directly with barium oxide, barium hydroxide and methyl iodide in dimethylformamide, the product contained 64.2% of methyl 2,3,4,5-tetra-O-methyl-α-D-galactoseptanoside (136) and 0.7% of its β-anomer. Following its isolation by preparative-scale GLC, the α-anomer was shown to be identical with that previously prepared by Micheel[96]. When permethylation succeeded glycosidation in boiling methanol, no trace of septanoside formation could be seen but the situation with regard to experiments where the glycosidation was performed at 20° or 40°, is not clear. This arises from an apparent discrepancy between the tabulated experimental results and the conclusions drawn in the text.

In 1935, Ohle and Mertens[8] reported that 6-deoxy-6-mercapto-D-glucose (137) was obtained when 1,2-O-isopropylidene-5,6-anhydro-α-D-glucofuranose (138) was treated first with hydrogen sulphide in barium hydroxide solution, then sulphuric acid. A completely different synthesis was carried out by Akagi and his co-workers[101] who introduced sulphur by reacting either the 6-iodo derivative (139) or the corresponding toluene-p-sulphonate (140) with a variety of nucleophilic reagents such as potassium thiolacetate, thiourea and potassium ethylxanthate. The

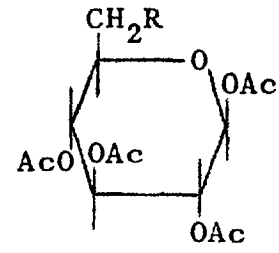
treatment of any of these products [(141), (142) and (143)] with sodium methoxide in methanol resulted in the formation of 6-deoxy-6-mercapto-D-glucose (137). Contrary to the results of Ohle[8], an osazone could be prepared although it decomposed rapidly, and the penta-acetate (141) gave the 1-α-bromide on treatment with hydrogen bromide in acetic acid.



(137)



(138)

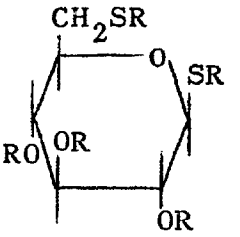


(139; R = I)
(140; R = OTs)
(141; R = SAc)
(142; R = $SCNHNH_2$)
(143; R = SCSOEt)

Although this system has also been studied by other workers, the possibility of any thioseptanose form has neither been mentioned, nor investigated.[102, 103]

The related 1,6-dideoxy-1,6-dimercapto-D-glucose has also been synthesized on two occasions. Although the two routes are quite different, the final step in each was the

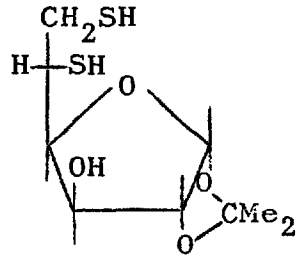
deacylation of a bisthiolester, (144) in one case[104] and (145) in the other[105]. Once again, neither group of workers commented on the possibility of a seven-membered ring.



(144, R = Ac)

(145, R = Bz)

Both of the 6-mercapto sugars above had, at C-5, an oxygen atom capable of forming a pyranose ring. A direct comparison of the stabilities of pyranose and septanose rings, both containing sulphur, would be possible if the structure of a 5,6-dimercapto-hexose were investigated. Unfortunately, although the dithiol (146) was formed when the 5,6-trithiocarbonate (147) was reduced with lithium aluminium hydride, no identifiable product could be isolated from its acid hydrolysis.[106]



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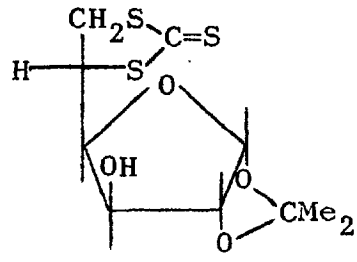
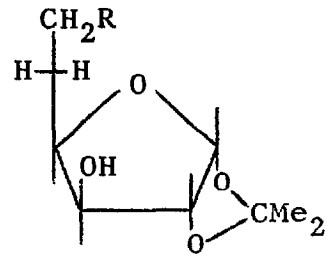


(147)



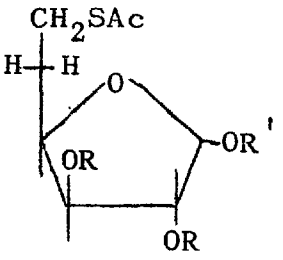
(148; R = SAc)

(149; R = OTs)

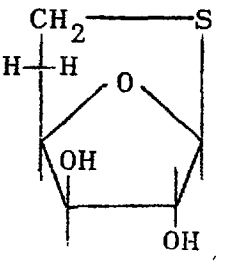
(158; R = OH)

5,6-Dideoxy-6-mercapto-hexoses are also of interest, since the cyclic form must be O-furanose or S-septanose. A precursor of such a compound is the thiolacetate (148), prepared[107] by photocatalysed addition of thiolacetic acid to the 5,6-ene in an anti-Markovnikoff manner. Although it was realised that the acetolysis or methanolysis of (148) might provide useful information regarding relative ring stabilities, there has been no further communication from these workers. However, Whistler[108] has removed the isopropylidene group from (148) formed, in this case, from the 6-O-tosylate (149) by reaction with potassium thiolacetate at 25°, despite the extremely facile formation of a

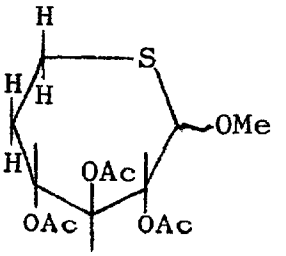
3,6-anhydro compound. The thiolacetate (150), formed by mild acidic hydrolysis of (148) with 20% aqueous acetic acid, gave the 1,6-anhydro derivative (151) on treatment with a strongly acidic ion-exchange resin in either water or methanol, for twenty hours at 65°. Since (151) proved to be an extremely hygroscopic and waxy solid, it was characterized by the formation of a syrupy di-O-acetate and a crystalline di-O-p-nitrobenzoate. On treatment sequentially with aqueous acetic acid, followed by sodium methoxide in methanol, the acidic ion-exchange resin in methanol for only two hours, and acetic anhydride in pyridine, the thiolacetate (148) gave a glycoside which was claimed to be the furanoside (152). It would appear, however, that the seven-membered ring form (153) cannot be eliminated since no evidence which would have distinguished the two (e.g. the presence or otherwise of S-acetyl absorption in the i.r. or u.v. spectra) was presented.



(150; R = R' = H)



(151)



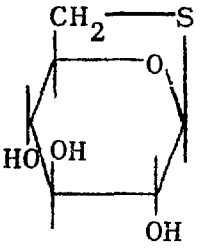
(153)

(152; R = Ac; R' = Me)

Although Akagi[104] had previously prepared 1,6-anhydro-6-deoxy-6-mercapto-β-D-glucopyranose (154), it could not have been made by a route similar to that for (151) since, with 4% hydrochloric acid for two hours at 95°, it is cleaved to 6-deoxy-6-mercapto-D-glucose (137 - p. 56). 2,3,4-Tri-O-acetyl-6-O-tosyl-α-D-glucopyranosyl bromide (155) was converted into either the xanthate (156) or the thiolacetate (157) by treatment with the appropriate nucleophile. The thiol group, produced at C-1 by the action of sodium methoxide in methanol on either (156) or (157), immediately displaced the toluene-p-sulphonyloxy group from C-6 to give the 1,6-anhydro derivative (154) after deacetylation.

Although 5-deoxy-1,2-O-isopropylidene-α-D- glucofuranose (158 - p. 58) formed no 1,6-anhydro derivative when heated under acid conditions,[108] a number of aldohexoses and

ketoheptuloses tend to form 1,6- and 2,7-anhydropyranoses respectively when heated with dilute acids.[109] Since the CH_2OH group must be axial in these derivatives, only those sugars containing more equatorial than axial hydroxyl groups in the 1C [C1 for L-sugars, see (159)] representation of the pyranose ring would be expected to form anhydro derivatives easily. Of these, D-idose (3 eq.) gave a 75% yield; D-altrose (2 eq.), 57%; and D-gulose (2 eq.), 43%. Although D-talose has only one axial hydroxyl group, it is at C-3 and so interacts with the bulky axial substituent at C-6. The instability is reflected in the low yield of anhydro compound (12%) from this sugar. Since glucose has all its hydroxyl groups in an axial orientation, it is not surprising that thiolaevoglucosan (154) reverted to 6-thioglucose on treatment with acid.[104]



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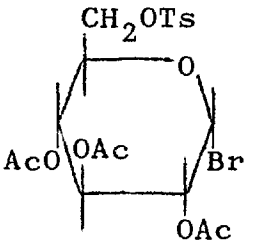

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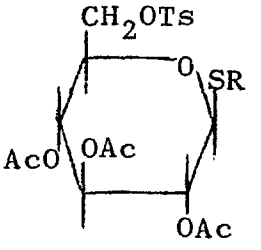
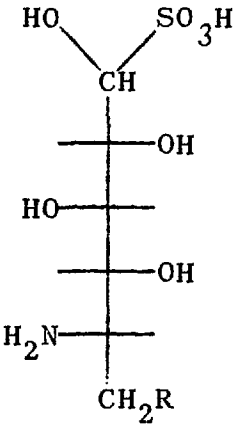
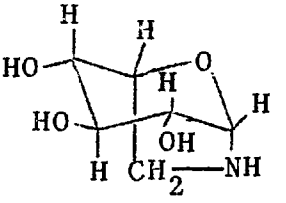


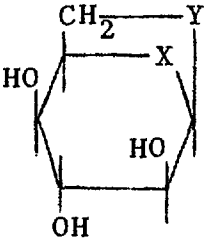
(156; R = CSOEt)

(157; R = Ac)

Certain nitrogen-containing sugars have also been shown to behave similarly.[110] Thus, 6-amino-6-deoxy-L-idose can be cyclized to the idosan (159) simply by concentration of an aqueous solution of the free base. Paulsen[110] has also reported two novel anhydro sugars containing nitrogen in an idopyranose ring. The sulphonic acids [(160) and (161)] are spontaneously and quantitatively converted to the respective anhydro compounds [(162) and (163)] by the action of barium hydroxide.







(160; R = OH)
(161; R = NH_2)

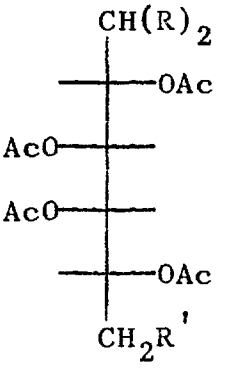
(159)

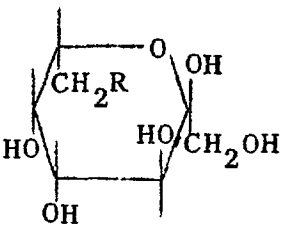
(159; X = O; Y = NH)
(162; X = NH; Y = O)
(163; X = Y = NH)

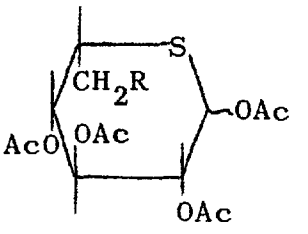
There is only one attempted synthesis of a monocyclic N-septanose sugar on record. J.K.N. Jones[111] obtained the

hydrate (164) by treatment of the dithioacetal (165) with mercuric chloride and cadmium carbonate in aqueous acetone but, in contrast to the case of (166)[92], heating it with pyridine failed to produce any cyclization.

Two other compounds which could have contained a seven-membered nitrogen ring are known. However, 7-acetamido-7-deoxy-α-L-galactoheptulose has been shown to exist as the O-pyranose (167)[112] and a peracetylated 6-acetamido-5,6-dideoxy-5-mercapto-L-idose as the S-pyranose (168)[64].







(164; R = OH; R' = NHAc) (167; R = NHAc) (168; R = NHAc)

(165; R = SEt; R' = NHAc)

(166; R = OH; R' = OH)

DISCUSSION

A preliminary account of part of this work has already been published.[152] Prior to 1963, reports of sugars containing sulphur in the ring were confined exclusively to thiopyranoses. Thiofuranoses have been synthesized more recently in pentose and hexose sugars, but there have been few attempts to incorporate a heteroatom other than oxygen into a seven-membered ring sugar derivative (see pp. 53-63).

In sugars containing no sulphur, the ring form usually favoured is the six-membered pyranose. However, as discussed previously, the preferred form of 4-thioaldoses is the furanose, due to the greater nucleophilicity of sulphur as compared with oxygen. The aim of the work described in the sequel was to synthesize sugars containing sulphur in a seven-membered ring and to do so in such a way as to compare the stability of this system with the smaller rings containing oxygen as the heteroatom.

6-Thiogalactose Series

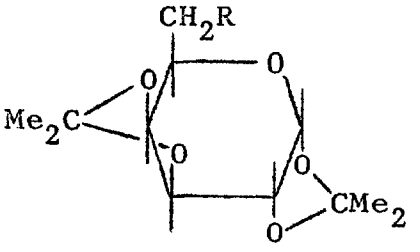
Although 6-deoxy-6-mercaptoglucose had been synthesized by Akagi[101], no evidence was presented relating to the ring

size. Consequently, 6-deoxy-6-mercaptogalactose itself was investigated as an example of a system free to exist as an O-furanose, an O-pyranose or an S-septanose sugar.

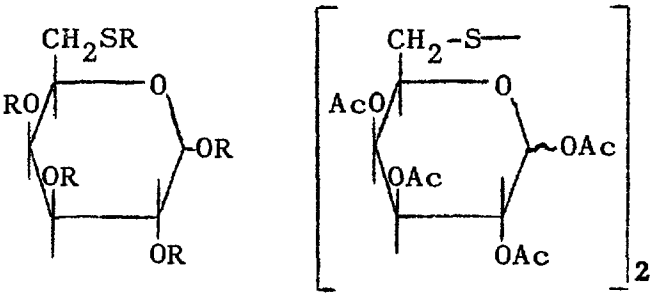
Whilst 6-deoxy-6-iodo-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (169)[113] reacted with potassium thiolacetate in refluxing acetone to give the 6-thiolacetate (170), the toluene-p-sulphonyloxy group of the tosyl analogue (171)[113] was displaced only in dimethylformamide at 100°.

Although deacetylation of (170) with a catalytic amount of sodium methoxide in methanol gave the thiol (172), no pure compound could be obtained when the isopropylidene groups in the latter were removed by acidic hydrolysis. The resultant non-crystalline froth gave no phenylosazone and consumed only 60% of the calculated quantity of iodine upon titration. The action of acetic anhydride in pyridine gave another froth, the u.v. spectrum of which $\left[\lambda_{max.}^{EtOH}\ 227\ m\mu\ (E_{1cm.}^{1\%}\ 19.2)\right]$ showed an apparent molecular extinction coefficient of only 780. Since thiolacetates, in general, exhibit[114] little deviation from a value of 4,000 near 230 mμ, this suggested a purity, with respect to the penta-acetate (173), of approximately 20%. Assuming the remainder to be the disulphide octa-acetate (174), the apparent molecular

weight (M, 664) is in agreement with the experimentally determined value (M, 646), indicating the existence of little, if any, thioseptanose form (175). It would appear that 6-mercaptogalactose is exceptionally susceptible to atmospheric oxidation since, despite the usual precautions being taken during both the hydrolysis and the subsequent acylation, disulphide was the major product.

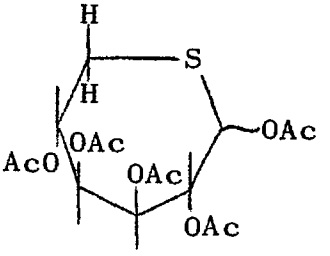


(169; R = I)
(170; R = SAc)
(171; R = OTs)
(172; R = SH)



(173; R = Ac)
(176; R = p-nitrobenzoyl)

(174)



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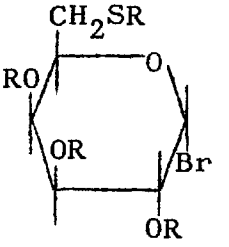


(177; R = p-nitrobenzoyl)

When treated with p-nitrobenzoyl chloride in pyridine, the crude 6-deoxy-6-mercapto-D-galactose, obtained from its di-O-isopropylidene derivative (172) as described above, gave an anomeric mixture of penta-O-p-nitrobenzoates (176). On treatment with hydrogen bromide in acetic acid / chloroform[16], the mixture yielded a bromide which, though rather unstable, was purified by chromatography. Since fractional precipitation gave crops which were both homogeneous, by thin-layer chromatography (TLC), and of identical specific rotation ($+203^{o}$), the bromide was assumed to be the optically pure α-anomer (177). Further treatment of the bromide with silver p-nitrobenzoate in benzene gave, after fifteen hours at room temperature, a mixture containing (by TLC) unchanged bromide, decomposition products and a compound identical to the slower-moving of the two penta-O-p-nitrobenzoates from which the bromide had been prepared. When a longer reaction period was used, an increased number of products was observed, presumably due to the inherent instability of the bromide since a control solution, without the silver salt, also decomposed to a large extent.

Since (176) and (177) exhibited both O-ester and S-ester absorption in the i.r. spectrum, there is no possibility that they exist as the isomeric thioseptanoses.

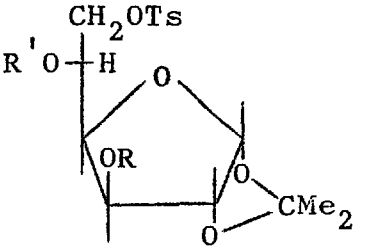
That these were not present in the mother liquors from the reactions was shown by TLC, since the impurities all migrated much more slowly than the major component(s).

3,5-Di-O-methylglucose Series

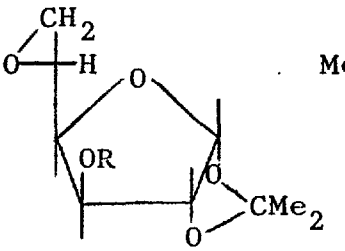
It can be seen from the previous series that an O-pyranose is preferred to an S-septanose ring system. To investigate systems where the usually dominant pyranose ring is absent, it is necessary to prevent ring closure at C-5. This can be achieved by working, for example, either with 5-O-methyl ethers as in the present series or with 5-deoxy sugars[108].

1,2-O-Isopropylidene-6-O-tosyl-α-D-glucofuranose (178) was prepared in the usual manner[115, 116] from D-glucose by acetonation, partial hydrolysis and toluene-p-sulphonylation. Methylation of (178) using silver oxide and methyl iodide in dimethylformamide yielded not the desired 3,5-di-O-methyl ether (179), but 5,6-anhydro-1,2-O-isopropylidene-3-O-methyl-α-D-glucofuranose (180), previously prepared[117] by treatment of the 6-O-tosylate (181) with sodium methoxide in methanol. Despite its extreme sensitivity to base, the tosylate (178) was successfully converted into its di-O-methyl ether (179) by repeated methylation with silver oxide and methyl iodide

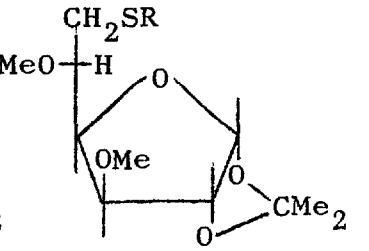
in acetone. This reaction is tedious (taking five to six weeks in all) and costly, (using the relatively expensive reagents, silver oxide and methyl iodide) and the yield is variable, for no apparent reason. Thus, although the thiol (182) was initially prepared by the route being described at present, it is best synthesized by the alternative route described below (pp. 70-73).



(178; R = R' = H)
(179; R = R' = Me)
(181; R = Me, R' = H)



(180; R = Me)
(184; R = H)



(182; R = H)
(183; R = Ac)

Aqueous acetic acid removed, rather surprisingly, not only the isopropylidene group but also the tosylate from (179), giving the known[118, 119] 3,5-di-O-methylglucose. Consequently, the tosylate (179) was converted into the corresponding thiolacetate (183) by the action of potassium

thiolacetate in refluxing acetone. Subsequent deacetylation, using a catalytic quantity of sodium methoxide in methanol, gave the key intermediate (182).

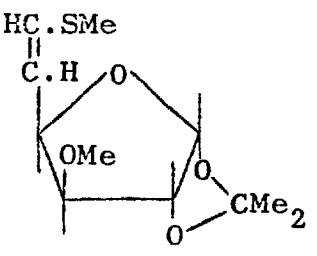
As stated above, this thiol (182) is best prepared by another route not involving methylation of a labile tosylate. Treatment of 1,2-O-isopropylidene-6-O-tosyl-α-D-gluco-furanose (178)[116] with excess sodium methoxide in methanol gave the epoxide (184)[120]. This was cleaved by sodium benzyl sulphide in the usual manner, giving the 6-benzylthio ether (185).

Although methylation of (185) with sodium hydride and methyl iodide in tetrahydrofuran gave a mixture from which no pure compound could be isolated, the spectral evidence suggested that 5,6-dideoxy-1,2-O-isopropylidene-3-O-methyl-6-methylthio-α-D-xylohexofuran-5-enose (186) was the major constituent. The n.m.r. spectrum showed the presence of two olefinic protons (τ3.62 and 4.68, doublets, J = 15 c.p.s.) and an S-methyl group (τ7.72, singlet) but the almost total lack of aromatic protons. The u.v. spectrum [$\lambda_{max.}$ 228 mμ ($E^{1\%}_{1cm.}$ 180) and 240 mμ ($E^{1\%}_{1cm.}$ 154, shoulder)] showed a close similarity to those[121, 122] of vinyl sulphides and the i.r. spectrum ($\nu_{max.}$ 1615 $cm.^{-1}$) was also consistent with such a system. The formation of the S-methyl ether can be explained,

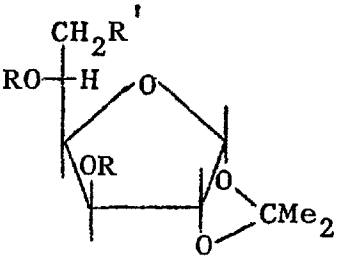
since the sulphonium ion formed by methylation at sulphur would be expected to decompose with the loss of the most stable carbonium ion, namely benzyl. It was estimated, from the intensity of the signals in the olefinic region of the n.m.r. spectrum, that elimination of the newly-formed methoxyl group at C-5 had occurred to an extent of ca. 70%, a figure later confirmed by titration with bromine in carbon tetrachloride. Although a yellow solid was formed during bromination, it underwent rapid decomposition with the liberation of hydrogen bromide.

Unsubstituted vinyl sulphides, CH_2:CHSR, react[123] quantitatively with an ethanolic mercuric chloride solution, at room temperature, to give acetaldehyde diethyl acetal. Even methyl-substituted derivatives, however, require much harsher conditions for cleavage. With as large a substituent as the sugar residue, it was perhaps not surprising therefore that the vinyl sulphide mixture, described above, reacted only partially when heated for nine hours at 75° with mercuric chloride and cadmium carbonate in aqueous dioxan. (The reaction should give rise to an aldehyde in aqueous solution, an acetal in alcohol. Since the liberated hydrogen chloride must be absorbed, if hydrolysis of the isopropylidene group is to be avoided, cadmium carbonate was added.) The i.r.

spectrum showed, besides unchanged vinyl sulphide (1615 $cm.^{-1}$) and the expected aldehyde (1720 $cm.^{-1}$), the presence of an alcohol (3350 $cm.^{-1}$). Since a negative Fehling's test eliminated the possibility that the isopropylidene group had been hydrolysed to some extent, the alcohol was presumably (187), formed by the action of the mercuric salt on the corresponding 6-methylthio derivative. The desired aldehyde (188) could neither be separated from the mixture, nor converted into its 2,4-dinitrophenylhydrazone under conditions which would leave the acid-labile isopropylidene group intact.



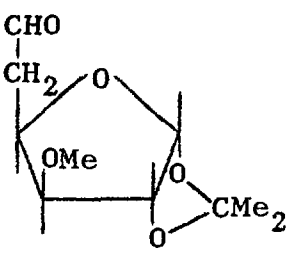
(186)



(185; R = H, R' = SCH_2Ph)

(187; R = Me, R' = OH)

(189; R = Me, R' = SCH_2Ph)



(188)

6-Benzylthio-6-deoxy-1,2-O-isopropylidene-3,5-di-O-methyl-α-D-glucofuranose (189) was finally obtained, in excellent yield, by treatment of the corresponding diol (185) with powdered sodium hydroxide and dimethyl sulphate in tetrahydrofuran[124]. Debenzylation with sodium in liquid ammonia then gave the thiol (182, p. 69), previously synthesized by another route.

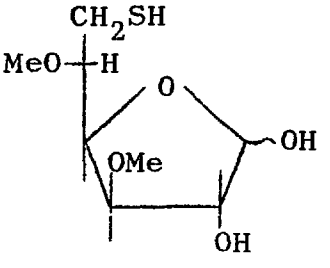
Removal of the isopropylidene group from (182), with 25% aqueous acetic acid, gave the thiol (190). That free thiol, and hence the furanose form, was present was shown by a considerable SH peak at 2560 $cm.^{-1}$ in the i.r. spectrum and the positive reaction with a mixture of sodium nitroprusside and sodium bicarbonate solutions. The n.m.r. spectrum showed two low-field signals, at τ 4.55 and 4.87, together equivalent to one proton and in the ratio of 3:1, presumably due to the anomeric protons of the α- and β-forms respectively. Although the spectrum as a whole was consistent with the compound having retained its furanose ring, it is difficult to envisage how a small proportion of the possible thioseptanose tautomer (191) could be detected.

When the thiol (182) was hydrolysed in the presence of mineral acid (2.5% v/v sulphuric acid in 25% aqueous acetic acid), two different, crystalline, compounds were obtained.

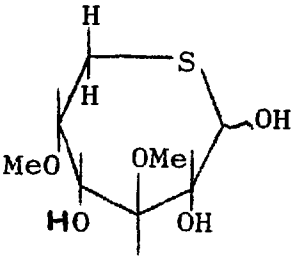
The major product (52%) gave negative Fehling's and nitroprusside tests and consumed no iodine even at 70°. Since a molecular formula of $C_8H_{14}O_4S$ was indicated by elemental analysis and molecular weight determination, the 1,6-anhydro structure (192) was postulated. That only one hydroxyl group was present was confirmed both by the preparation of the corresponding methyl ether (193), as described below, and by n.m.r. spectroscopy. The spectrum showed, in particular, (a) a one-proton singlet, removed by deuteration, at τ 7.01 (b) a one-proton multiplet, due to H-1, at τ 5.08 (c) two one-proton signals at τ 6.65 and 7.1 to 7.4 due to the two methylene protons at C-6. It is interesting to note that the considerable downfield shift of one of the two C-6 protons is observed only in compounds containing a S→C-1 bridge [e.g. (192), (193) and the thiofuranoses (225) and (226) ; see p. 93]. Although the protons are apparently non-equivalent even where rotation about the C-5 / C-6 bond is possible, such as in (185), the resonance positions of both occur in the region τ 7.0 to 7.8 and differ by less than 0.2 p.p.m..

The minor product, isolated in a yield of only ca. 1%, had a much higher melting-point than (192), was almost insoluble in most organic solvents, and gave a negative

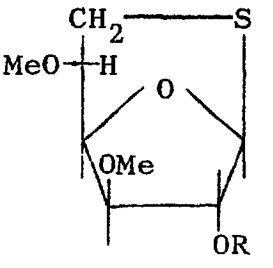
nitroprusside test. That it was not the disulphide from (190) was shown by the analytical data (again indicating an empirical formula of $C_8H_{14}O_4S$), the mass spectrum (giving a molecular weight of 412 rather than 446) and the negative reaction with Fehling's solution. From this evidence, it is clear that the compound must be a di-(6-deoxy-6-mercapto-3,5-di-O-methyl-α-D-glucofuranose)-dianhydride in which the two ring systems are linked via both C-1 atoms. Although there are five possible isomers [the 1:6',1':6- (containing two furanose rings), the 1:2',1':2- and 1:4',1':4- (two thioseptanose rings), and the 1:2',1':6- and 1:4',1':6 (one furanose and one thioseptanose ring) dianhydrides], the retention of the furanose ring system in both (190) and (192) suggests that the 1:6',1':6- structure (194) is the most probable. A distant analogy is that of 'ribose anhydride'[125] which was later shown[126] to be a di-D-ribose dianhydride, although the exact isomeric structure was not proved.



(190)

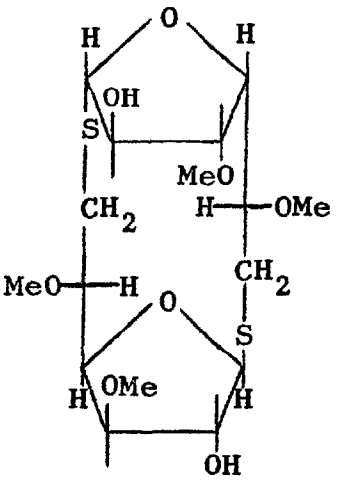


(191)

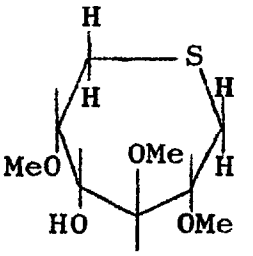


(192; R = H)

(193; R = Me)



(194)



(195)

Since, at this time, no monocyclic thioseptanose had been synthesized, it was hoped that the furanose ring of (192) might be preferentially cleaved to give such a system. Acidic reagents were considered unlikely to succeed because not only had (192) been formed under such conditions, but an analogous compound was obtained by Whistler[108] when the thiolacetate (150) was treated with an acid ion-exchange resin in either methanol or water (see p. 59).

Neither ring is apparently broken by the action of 2N sodium hydroxide solution since thiol was completely absent even after one hour at 100° under nitrogen.

On treatment with an aluminium chloride - lithium aluminium hydride complex in ether, simple ethylene hemithioketals are known[127] to yield hydroxy-thioethers with negligible cleavage of the C-S bond. Although (192) is, itself, unsuitable for such a reaction, its methyl ether (193), readily formed by reaction with sodium hydroxide and dimethyl sulphate in tetrahydrofuran, should be reduced to the 1-deoxy-thioseptanose (195). Unfortunately, no identifiable product could be isolated from the reaction of (193), either with an aluminium chloride - lithium aluminium hydride complex or with aluminium chloride alone.

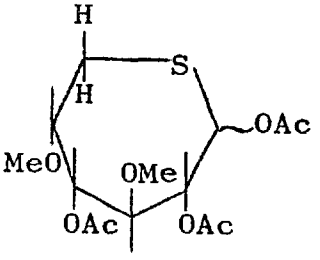
In many of the syntheses of thiopyranose and thiofuranose sugars, the vital step, the introduction of the sulphur atom into the ring, was carried out by means of an acetolysis. 6-Acetylthio-6-deoxy-1,2-O-isopropylidene-3,5-di-O-methyl-α-D-glucofuranose (183, p. 69) was therefore subjected to the action of a mixture of acetic acid, acetic anhydride and sulphuric acid for varying periods of time and at various temperatures. These reactions, and an acetolysis of the bicyclic compound (192), gave extremely complex mixtures, all

apparently of similar qualitative composition (by TLC). Consequently, no compound could be isolated in a yield high enough to allow characterization, although very small amounts of two crystalline derivatives were obtained.

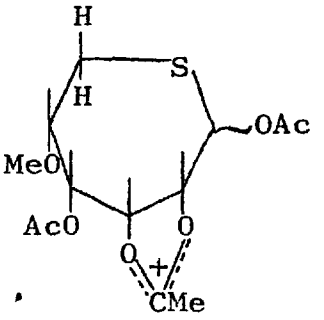
On treatment with the acetolysis mixture for four hours at 0^{o}, (183) yielded a white crystalline compound which exhibited no thiolacetate absorption in its i.r. spectrum. An n.m.r. spectrum showed the presence of two methoxyl (τ 6.55 and 6.68) and three acetoxyl groups (τ 7.94, 7.94 and 7.98) and confirmed the absence of S-acetate, but it could not be interpreted in detail. Whilst much more evidence is obviously required before assigning a structure, the above would appear to suggest the thioseptanose derivative (196) as a possibility.

When the reaction was allowed to proceed for forty-eight hours, a different solid, again exhibiting no thiolacetate absorption in the i.r. spectrum, was isolated. In this case, the n.m.r. spectrum showed very clearly the presence of four acetoxyl groups (τ 7.84, 7.87, 7.92 and 7.93) with only one methoxyl (τ 6.48). Such an occurrence, which has never been reported previously although also now observed in the 2,3,4,5-tetra-O-methylgalactose series (see p. 91), can readily be explained. One might expect a

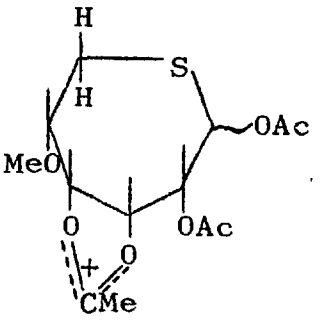
trans- methoxy-acetate, such as (196), to exhibit neighbouring group participation. Each of the two possible orthoester intermediates [(197) and (198)] can then be opened in two directions, giving the gluco-, altro- or gulo- configuration. Since, besides anhydro compounds, the structural variables of the possible products include the stereochemistry and the nature of the substituent at C-3, the stereochemistry at C-4, C-2 and C-1, and two different ring sizes, it is perhaps not surprising that such a complex situation was encountered.



(196)



(197)



(198)

2,3,4,5-Tetra-O-methylgalactose Series

In the preceding series, the furanose ring was retained despite the formation of a seven-membered ring containing sulphur as the heteroatom. This can be avoided by

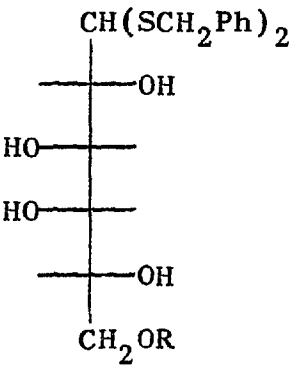
modification of the hydroxyl group at C-4, in addition to that at C-5. Thus, if a 6-deoxy-6-mercapto-2,3,4,5-tetra-O-methylaldose is to exist in other than an acyclic form, it must adopt a thioseptanose ring system.

In order to methylate both the hydroxyl groups usually involved in ring closure, it is necessary to perform the reaction on an acyclic derivative, such as an aldose dithioacetal. The decision to employ the dibenzyl dithioacetals was based on the assumption that they were more likely to be crystalline than the corresponding dimethyl or diethyl compounds.

D-Galactose dibenzyl dithioacetal (199)[128] was synthesized from D-galactose by the action of toluene-α-thiol in the presence of fuming hydrochloric acid.[129]

The action of one equivalent of toluene-p-sulphonyl chloride on (199) in excess pyridine gave not the 6-O-tosylate (200), as reported by Fernández-Bolaños[130], but the 3,6-anhydro derivative (201)[131]. Further reactions using only a small excess of pyridine, with either dioxan or acetone as solvent, resulted in recovery of the dithioacetal (199). An alternative synthesis, involving treatment of 6-O-tosyl-D-galactose[132] with toluene-α-thiol in concentrated hydrochloric acid, gave a crystalline

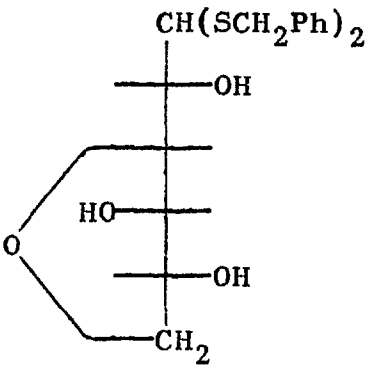
product but this rapidly decomposed on standing. Although the 6-O-methanesulphonate (202) is known,[131] that too was obtained only in such a low yield as to make a different approach to the problem essential.



(199; R = H)

(200; R = Ts)

(202; R = Ms)



(201)

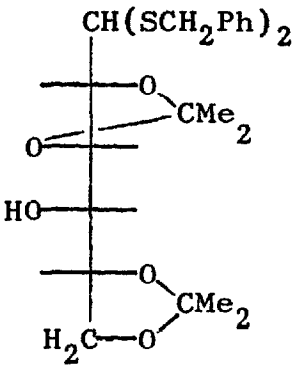
On treatment with acetone and sulphuric acid, the dithioacetal (199) gives a product originally thought[133] to be the 2,3:5,6-di-O-isopropylidene derivative (203). However, Munro and Percival[134] demonstrated that the monomethylgalactose derived by methylation, hydrolysis and demercaptalation was substituted not at C-4, as supposed by Pacsu[133], but at C-6. It was then proposed that the product of acetonation was the 2,3:4,5 isomer (204). Although a recent investigation[135] confirmed that this is, indeed, the

major product, it was suggested that (203) was present as an impurity. When the reaction was repeated, the complex mixture obtained could not be separated and, when subjected to subsequent toluene-p-sulphonylation, failed to yield the 6-O-tosylate (205). It was, however, converted into the corresponding 6-iodo compound (206)[135], in excellent yield, by the action of triphenyl phosphite methiodide[136] in benzene. It would appear[135] that (206) is formed not only from (204), but also from (203), a process which requires the migration of an isopropylidene group.

Before replacing the isopropylidene by methyl groups, it is necessary to displace the labile iodide by a potential thiol group stable to both acidic and basic media. The 6-benzylthio ether (207) was therefore made by treating (206) with sodium benzyl sulphide; this was then hydrolysed with sulphuric acid in aqueous ethanol to the tetraol (208).

A series of methylations, using barium oxide and dimethyl sulphate in dimethylformamide, was carried out, but the yield of the tetra-O-methyl ether (209) was variable (40-60%) even when the critical optimum conditions were employed. Since the isolation procedure was also difficult, an alternative method was sought. Finally, following its successful use in the 3,5-di-O-methylglucose series, a

mixture of powdered sodium hydroxide and dimethyl sulphate in peroxide-free tetrahydrofuran was used and (209) was obtained in 91% yield.



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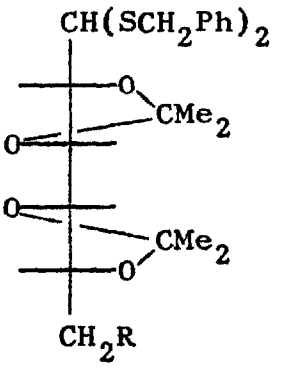
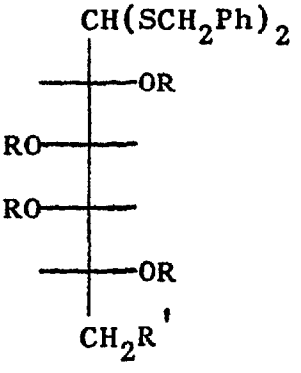


(204; R = OH) (205; R = OTs) (206; R = I) (207; R = SCH_2Ph)



(208; R = H, R' = SCH_2Ph) (209; R = Me, R' = SCH_2Ph)

A debenzylation of (209), using sodium in liquid ammonia, was performed in the hope of obtaining 1,6-dideoxy-1,6-dimercapto-2,3,4,5-tetra-O-methyl-D-galactoseptanose (210), but no product could be isolated except dibenzyl. This may possibly be due to the occurrence either of numerous side-reactions, following the facile removal of the C-1 proton which has been shown to occur in these systems,[137, 138] or of polymerization, common in thiocarbonyl compounds.[139]

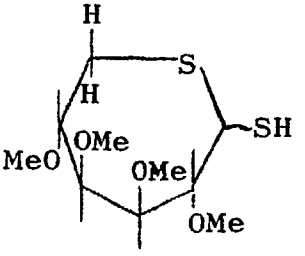
In order to obtain 6-deoxy-6-mercapto-2,3,4,5-tetra-O-methyl-D-galactose, the desired end-product of this series, it is necessary to selectively remove from (209) the groups protecting the thiol at C-6, and the aldehyde at C-1. Since debenzylation afforded no identifiable product, the dithioacetal group must be removed first. Although they are rather more stable than acetals towards acid hydrolysis, it is well known[140] that dithioacetals may be converted into the parent aldehyde or an acetal by treatment with mercuric salts in aqueous or alcoholic solutions respectively. Since the carbonyl group at C-1 must be protected against reduction, ammonolysis and condensation during subsequent debenzylation, it was decided to convert (209) directly into an acetal.

Reaction of the dithioacetal (209) with mercuric chloride, cadmium carbonate, anhydrous calcium sulphate and absolute ethanol gave 6-benzylthio-6-deoxy-2,3,4,5-tetra-O-methyl-D-galactose diethyl acetal (211) as a syrup which could be distilled only with difficulty, even at 10^{-4}mm..

The ethylene acetal (212), prepared by a similar reaction using ethylene glycol in place of ethanol, was obtained in the crystalline state and was consequently used in subsequent stages. Since the dithioacetal (209) is almost insoluble in ethylene glycol even at 100°, a co-solvent

must be used. Unfortunately, the inert solvents which dissolve (209) are themselves immiscible with the glycol. This problem was overcome by the addition of carbon tetrachloride, the quantity of which proved to be critical, with any significant departure from the optimum reducing the yield to zero.

Treatment of the ethylene acetal (212) with sodium in liquid ammonia gave 6-deoxy-6-mercapto-2,3,4,5-tetra-O-methyl-D-galactose ethylene acetal (213) in high yield. Although a solid, its purification was best achieved by chromatography, since no suitable recrystallization solvent could be found.



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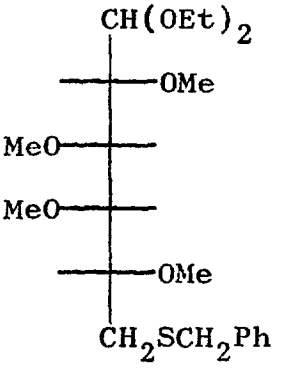
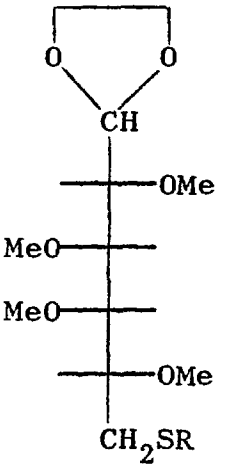


(211)

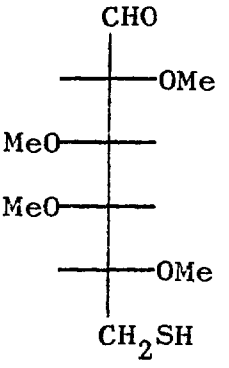


(212; R = CH_2Ph)

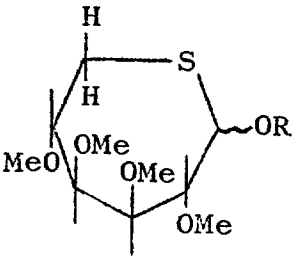
(213; R = H)

When the acetal (213) was hydrolysed with sulphuric acid in aqueous acetic acid, the crude product exhibited negligible absorption in the carbonyl region of the i.r. spectrum, indicating the absence of the aldehydo- derivative (214). The terminal groups of (214) may interact in either an intra- or an inter- molecular fashion to give the thioseptanose sugar (215) or a linear polymer respectively. A total recovery of approximately only 50% from a chromatography would appear to suggest that the latter course was followed to a considerable extent, but the desired monomer (215) was isolated in 24% yield. The n.m.r. spectrum showed no low-field aldehydic proton but exhibited, in particular, two peaks at τ 4.96 and 5.27, in the ratio of approximately 1:1 and together equivalent to one proton, which must be due to the anomeric protons of the α- and the β- forms (see also p. 88). No absorption due to either SH or CHO was visible in the i.r. spectrum, which showed, however, a large peak at 3400 $cm.^{-1}$. Although it is thus obvious that, both in the liquid state and in solution, the tautomer (215) predominates to the exclusion of (214), the equilibrium may be displaced to the latter under suitable reaction conditions. For example, the hemithioacetal reacted rapidly with an aqueous iodine solution, consuming

ca. 80% of the theoretical quantity within a minute and 100% within five minutes, at room temperature. This contrasts with the behaviour of thiopyranoses, which take up iodine only slowly with intermittent heating,[23, 37, 106] but is similar to that of thiofuranose sugars.[16, 18] An additional slow consumption of iodine (finally corresponding to ca. 10% overoxidation after three hours) has also been observed with 4-deoxy-4-mercapto-ribofuranose[16] and some non-carbohydrate hemithioacetals (see pp. 167, 170). A further reflection of the ring stability was provided by the reaction with sodium nitroprusside solution, since this was negative in the presence of sodium bicarbonate but positive with sodium hydroxide.

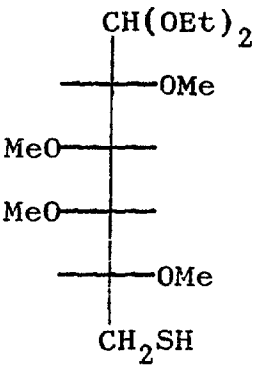


(214)



(215; R = H)

(216; R = Et)



(217)

Ethanolysis of the acetal (213) with 8% hydrogen chloride in ethanol gave, after chromatography, ethyl 6-deoxy-6-mercapto-2,3,4,5-tetra-O-methyl-D-galactoseptanoside (216). That it was not the acyclic diethyl acetal (217) was shown by analysis, the negative nitroprusside test, and the n.m.r. spectrum which showed only three C-Me protons (τ 8.81, triplet, J = 7 c.p.s.). It should be appreciated that had the methyl glycoside been prepared, the n.m.r. evidence would be less clearly defined since the new O-methyl resonance would have been similar to those already present. The spectrum also showed two low-field peaks, at τ 5.48 and 5.75, in a ratio of approximately 1:1 and integrating together to one proton. When it was found that the relative intensities changed considerably when (216) was synthesized by a different route, these were ascribed to the anomeric protons of the α- and β- forms respectively.

Since in many cases, one of the anomeric glycosyl halides, usually the α-, is sufficiently stable that the other cannot be isolated, it is possible to prepare anomerically pure glycosides by reaction with alcohols and silver carbonate.[141] On treatment with anhydrous hydrogen chloride in ether, a reagent which has been used[142] in the synthesis of glycosyl halides, the acetal (213) gave rise

to an inseparable mixture. Further reaction with ethanol and silver carbonate yielded, after a chromatographic purification, the glycoside (216) which was identical to the earlier sample except for two features. In the n.m.r. spectrum the two peaks at τ 5.48 and 5.75, previously of equal intensity, were now in the ratio of 1:3, the high-field signal having gained at the expense of the lower one. This, in fact, provides a confirmation that the two peaks are not due to the C-1 proton, of a single anomer, split by H-2, with $J_{1,2}$ = 16 c.p.s.. The second point of difference was the specific optical rotation, -117^{o} for the first sample and -180^{o} for the second.

Whilst it is realised that the conformational situation is complex even for simple substituted cycloheptanes,[142-144] it should be noted that the results above are consistent with the general behaviour of sugars, in the D-series, containing pyranose rings. In the latter, it is the β- glycoside which (a) is usually formed *via* a 1-halogeno compound, (b) exhibits the higher negative (or less positive) rotation. Also its anomeric proton, being in the axial orientation, appears at a higher field in the n.m.r. spectrum than that of the corresponding α-anomer.[145] However, several exceptions to the generalization, that the chemical shift of

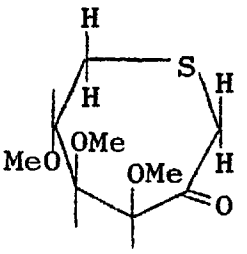
an equatorial proton is greater than that of the corresponding axial proton, have recently been reported.[146]

Although it had been shown conclusively that the glycoside was an anomeric mixture, no separation could be achieved by TLC. Despite the success of GLC on the analytical scale, the limited choice of stationary phases at hand precluded preparative-scale separation.

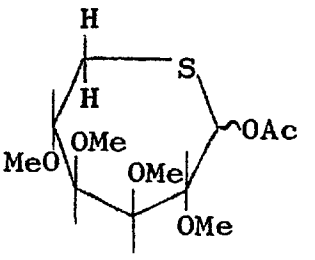
A ketonic impurity, containing no halogen, was observed when the ethylene acetal (213) was treated with hydrogen chloride in both ethanol and ether. It could not be isolated in a pure state and failed to give a solid 2,4-dinitrophenylhydrazone, although reaction was shown to occur (by TLC). Mechanistically, the structure (218) would appear quite possible.

As a final attempt to prepare a crystalline thioseptanose derivative, the glycoside (216) was acetolysed in a mixture of sulphuric acid, acetic anhydride and acetic acid. No identifiable compound could be isolated, although a partial purification was achieved by chromatography. The i.r. spectrum of this material contained both O-acetate and S-acetate absorption, but the n.m.r. spectrum showed the thiolacetate (τ 7.93) to be only a minor constituent. A comparison of the intensities of the signals in the

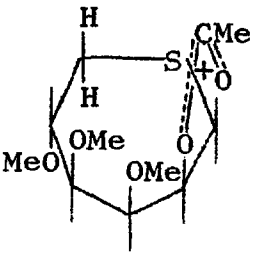
appropriate regions suggested the presence of two acetoxyl and three methoxyl groups. An explanation similar to that offered in the preceding series (p. 79) would appear reasonable. The C-2 methoxyl group may be eliminated from the initially produced 1-acetoxy derivative (219) via the orthoester intermediate (220). This may be cleaved, by the attack of acetic acid, in two directions yielding derivatives of either D-galactose or D-talose, depending upon the stereochemistry at C-2.



(218)



(219)



(220)

4,6-Dideoxy-4,6-dimercaptoglucose Series

Although the glucoside (221) was recently prepared, no firm conclusions were reached as to the structure of any products of its hydrolysis.[18, 147]

Methyl 2,3-di-O-methyl-β-D-galactopyranoside (222),

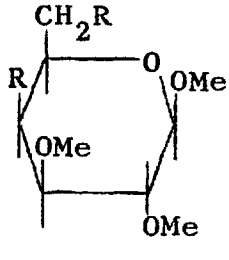
prepared from its 4,6-*O*-benzylidene derivative by treatment with sodium in liquid ammonia, was converted into the dithiol (221) *via* the di-*O*-methanesulphonate (223) and the bisthiolacetate (224), basically as described by Owen and Ragg.[18]

A number of small-scale hydrolyses of (221) were performed to establish the optimum conditions. It was shown by TLC that the glycoside was surprisingly resistant and that extensive decomposition occurred in the time necessary for complete reaction. The consequent partial hydrolysis, in N hydrochloric acid, yielded a complex mixture separated by chromatography into unchanged glycoside (*ca*. 16% recovery), decomposition products retained by the column (*ca*. 30% of the crude yield) and two further components. One of these (*ca*. 15% of the crude yield) gave a positive nitroprusside test, but was still grossly impure and was not investigated further.

The major constituent, isolated in 41% yield, was 1,6-anhydro-4,6-dideoxy-4,6-dimercapto-2,3-di-*O*-methyl-β-D-glucofuranose (225). It gave negative reactions with both alkaline sodium nitroprusside and Fehling's solutions and consumed no iodine on titration, even when heated with a small excess for many hours. The n.m.r. spectrum was

consistent with the proposed structure showing, in particular, (a) a broad one-proton signal, removed by deuteration, at τ6.6 to 6.9 (b) a one-proton doublet, due to H-1, at τ 5.64, $J_{1,2}$ = 2.5 c.p.s. (c) a broad one-proton signal, at τ 7.3 to 7.6, due to one of the two methylene protons at C-6. It should be noted that a large difference in the chemical shifts of the two C-6 protons has been observed only in the spectra of compounds containing a 1→6 bridge (see discussion, p. 74). The above evidence, together with that from the elemental analysis and the molecular weight determination, preclude any structure other than (225).

The anhydro compound was further characterized by the preparation of a crystalline 3,5-dinitrobenzoate (226). This also displayed the strange phenomenon, with regard to the C-6 protons, mentioned above.

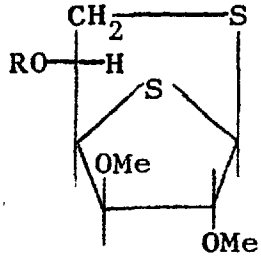


(221; R = SH)

(222; R = OH)

(223; R = OMs)

(224; R = SAc)



(225; R = H)

(226; R = 3,5-dinitrobenzoyl)

These results provide a further example of the tendency of O-pyranose to rearrange to S-furanose derivatives where possible. The further formation of the thioseptanose ring was not unexpected, since it has been observed that two analogous O-furanose compounds undergo this ring closure (see pp. 59, 74).

In summary, although thioseptanose rings were readily formed as part of a bicyclic ring system, monocyclic derivatives, containing a seven-membered sulphur ring, were obtained only where the adoption of a pyranose or furanose ring was not possible.

EXPERIMENTAL SECTION

Bracketed numerals, preceded by the letter "E", refer to the page number in the laboratory notebooks.

Melting-points were determined on a Kofler block, and optical rotations (in a 1 dm. tube) with a Hilger-Watts polarimeter. I.R. spectra of liquids were taken as films, and those of solids in chloroform solution, unless otherwise stated, using a Unicam SP 200 spectrometer. U.V. spectra were determined in ethanolic solution on a Unicam SP 800 instrument and n.m.r. spectra on a Varian A-60 machine in the solvents stated, usually deuterochloroform or carbon tetrachloride. Analyses and osmometric molecular weight determinations were carried out by the Staff of the Microanalytical Laboratory at Imperial College, n.m.r. spectra by Mrs. A.I. Boston, and mass spectra by Mr. P. Boshoff (using an A. E. I. MS-9 spectrometer).

The adsorbent for TLC was silica gel GF_{254} (20 x 5 $cm.^2$ plates) and HF_{254} (7.5 x 2.5 $cm.^2$ plates), or alumina G. (All supplied by E. Merek A.G., Darmstadt). For column chromatography, either silica gel (Hopkin and Williams Ltd., M.F.C.) or alumina (Peter Spence, Grade H) was used.

Evaporations were usually carried out at reduced pressure below 40°, and anhydrous sodium sulphate was used for the drying of solutions, unless otherwise stated. "Petroleum" refers to the fraction b.p. 40-50°, if no boiling-point is quoted.

Thiol estimations were carried out by iodometric titration in aqueous methanol containing a little sulphuric acid.

6-Thiogalactose Series

1,2:3,4-Di-O-isopropylidene-6-O-tosyl-α-D-galactopyranose (E 61, 361)

1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (25.0 g.) was converted, by treatment with toluene-p-sulphonyl chloride in pyridine and acetone, into the 6-O-tosylate (40.0 g., 100%; m.p. 91-93°), as described by Raymond[113]. Recrystallization first from petroleum (b.p. 60-80°), then methanol, gave material, m.p. 93.5-94°. Lit. m.p. 87-89°,[113] 91-92°,[148] and others up to 105°.

6-Acetylthio-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose

Method A (E 7, 17): A mixture of 1,2:3,4-di-O-isopropylidene-6-O-tosyl-α-D-galactopyranose (10.0 g.) and potassium thiolacetate (5.5 g., 2 equiv.) in dry dimethylformamide (70 ml.) was heated at 100°, for 5 hr., under nitrogen. The solvent was removed and the residue dispersed between chloroform and water. The organic phase was washed with water, dried and evaporated to give a yellow oil. Distillation gave the 6-thiolacetate (7.46 g., 97%), b.p. $118^{\circ}/10^{-4}$mm., $[\alpha]_D^{22}$ -15° (c 1.0, $CHCl_3$), n_D^{20} 1.4871, $\nu_{max.}$ 1690 $cm.^{-1}$ (SAc). (Found: C, 52.8; H, 7.0; S, 10.1. $C_{14}H_{22}O_6S$ requires: C, 52.5; H, 6.8; S, 10.05%).

Method B (E 45): A mixture of 6-deoxy-6-iodo-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose[113] (0.50 g., kindly supplied by Prof. L.N. Owen) and potassium thiolacetate (0.31 g., 2 equiv.) in anhydrous acetone (50 ml.) was refluxed for 6 hr., cooled and filtered. The solvent was removed, water (5 ml.) added, and the mixture extracted with chloroform (4 x 10 ml.). The residue (0.43 g., 100%), obtained after the extract had been washed, dried and evaporated, gave an i.r. spectrum identical to that of the previous product.

6-Deoxy-1,2:3,4-di-O-isopropylidene-6-mercapto-α-D-galactopyranose (E 9, 113, 177)

Sodium (85 mg., 0.1 equiv.) was added to a solution of 6-acetylthio-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (11.8 g.) in anhydrous methanol (200 ml.) after it had been flushed out with nitrogen. The solution was allowed to stand under nitrogen for 3 days, neutralized with solid carbon dioxide and evaporated. The residue was dissolved as far as possible in ether, dried, filtered through kieselguhr and evaporated. Distillation gave the thiol (6.7 g., 66%), b.p. $93^{\circ}/10^{-4}$mm., $[\alpha]_D^{22}$ -76° (c 0.9,$CHCl_3$), n_D^{20} 1.4828; $\nu_{max.}$ 2560 $cm.^{-1}$ (SH), absence of $\nu_{max.}$ 1690 $cm.^{-1}$ (SAc). (Found: C, 52.1; H, 7.2; S, 11.9; thiol-S, 11.8. $C_{12}H_{22}O_5S$ requires: C, 52.15; H, 7.3; S, 11.6%).

The acidic hydrolysis of 6-deoxy-1,2:3,4-di-O-isopropylidene-6-mercapto-α-D-galactopyranose (E 307, 439)

6-Deoxy-1,2:3,4-di-O-isopropylidene-6-mercapto-α-D-galactopyranose (2.4 g.) was dissolved in methanol (30 ml.) and water (30 ml.) and 2N sulphuric acid (2 ml.) was added. The solution was stirred at 75° under nitrogen for 5 hr., the exit gases being periodically passed into aqueous Brady's reagent in order to determine the conclusion of the reaction.

The solution was then cooled, passed down a column of Deacidite E ion-exchange resin (20 ml., wet) and evaporated to dryness. The froth (1.7 g.) obtained by evaporating the residue with ethanol could not be crystallized and showed a thiol value of 11% (calc. 16.3%). $\nu_{max.}$ 3450 $cm.^{-1}$ (OH), no C-Me signals in the n.m.r. spectrum (in aqueous methanol).

Attempted osazone formation from the hydrolyzate of 6-deoxy-1,2:3,4-di-O-isopropylidene-6-mercapto-α-D-galactopyranose (E 309)

Most of the methanol was distilled from the still acid hydrolyzate obtained from 6-deoxy-1,2:3,4-di-O-isopropylidene-6-mercapto-α-D-galactopyranose (1.50 g.) as described above. Sodium acetate (4.0 g.) and phenylhydrazine hydrochloride (3.3 g.) were added and the solution refluxed for 1 hr.. It was then cooled, saturated with sodium chloride and extracted with ethyl acetate. The extract was washed with water, dried and evaporated to give a red-brown oil. Trituration with ether gave a yellow solid (0.4 g.,m.p. 99-103° decomp.) which could not be recrystallized. Chromatography, both on silica gel and cellulose proved unsuccessful.

Acetylation of the crude 6-deoxy-6-mercapto-D-galactose (E 311)

Crude 6-deoxy-6-mercapto-D-galactose (0.79 g.) was dissolved in dry pyridine (6 ml.) and acetic anhydride (4 ml.) added. The solution was allowed to stand under nitrogen for 5 days, then poured into ice-water (50 ml.). After 1 hr., the mixture was extracted with chloroform and the extract washed with water, dilute sulphuric acid, water, sodium bicarbonate solution and water again. The solution was dried and evaporated to give a gum (1.35 g.) which could not be induced to crystallize. Chromatography in 75% chloroform in benzene on alumina gave a froth (0.39 g.) which was a mixture of the disulphide octa-acetate with ca. 20% of the acetylated 6-thiogalactose. $\lambda_{max.}$ 227 mμ ($E^{1\%}_{1cm.}$ 19.2); $\nu^{CCl_4}_{max.}$ 1695 $cm.^{-1}$ (SAc), 1740 and 1755 $cm.^{-1}$ (OAc). (Found: M, 646. Calculated: for monomer penta-acetate, 406; for disulphide octa-acetate, 727.).

6-Deoxy-1,2,3,4-tetra-O-p-nitrobenzoyl-6-p-nitrobenzoylthio-αβ-D-galactopyranose (E 441, 461)

p-Nitrobenzoyl chloride (4.5 g.) was added to a solution of crude 6-deoxy-6-mercapto-D-galactose (0.47 g.) in dry pyridine (30 ml.) and the mixture was shaken, under

nitrogen, for 9 days. Then, 30 min. after water (5 ml.) had been added, it was poured into saturated sodium bicarbonate solution (300 ml.). The precipitate, which coagulated on stirring, was filtered off, dissolved in chloroform, washed with water, sodium bisulphate solution and water again, and dried. Evaporation to dryness gave a froth (1.46 g., 70%) which could not be crystallized. TLC (silica gel, chloroform or 10% ether in benzene) showed the presence of two components moving at almost the same rate. These could not be separated either by chromatography or by fractional precipitation from chloroform with methanol. The anomeric mixture had an indefinite m.p., over 150°, and $[\alpha]_D^{24}$ +137° (c 1.2, $CHCl_3$); $\nu_{max.}$ 1675 (thiolester), 1740 (ester). (Found: N, 7.0%; M, 980. $C_{41}H_{27}N_5O_{20}S$ requires: N, 7.4%; M, 940).

6-Deoxy-2,3,4-tri-O-p-nitrobenzoyl-6-p-nitrobenzoylthio-α-D-galactopyranosyl bromide (E 463)

A solution of hydrogen bromide in glacial acetic acid (45%, 20 ml.) was added to a solution of 6-deoxy-1,2,3,4-tetra-O-p-nitrobenzoyl-6-p-nitrobenzoylthio-αβ-D-galactopyranose (0.91 g.) in ethanol-free chloroform (20 ml.) and the mixture allowed to stand for 18 hr.. Chloroform (80 ml.) was then added, and the solution washed with water, dried and

evaporated to give, on trituration with ether, a buff-coloured solid (0.81 g., 99%). Chromatography on silica gel, first in benzene, then in 3% ether in benzene, gave a white solid (0.29 g., 35%). Precipitation from benzene with ether gave several fractions, all having the same specific rotation. The pure amorphous bromide had m.p. ca. 180°, $[\alpha]_D^{25}$ +203° (c 1.1, $CHCl_3$); $\nu_{max.}$ 1675 $cm.^{-1}$ (thiolester), 1740 $cm.^{-1}$ (ester). (Found: C, 47.7; H, 3.0; Br, 9.0; O, 29.9. $C_{34}H_{23}BrN_4O_{16}S$ requires: C, 47.7; H, 2.7; Br, 9.3; O, 29.9%).

Reaction of 6-deoxy-2,3,4-tri-O-p-nitrobenzoyl-6-p-nitrobenzoylthio-α-D-galactopyranosyl bromide with silver p-nitrobenzoate (E 477)

A mixture of 6-deoxy-2,3,4-tri-O-p-nitrobenzoyl-6-p-nitrobenzoylthio-α-D-galactopyranosyl bromide (65 mg.) and silver p-nitrobenzoate (40 mg.) in dry benzene (5 ml.) was stirred for 15 hr. in the absence of light. It was then filtered and the solids washed with benzene. TLC (silica gel, 8% ether in benzene) showed that the filtrate contained unchanged bromide and one of the penta-O-p-nitrobenzoates, presumably the β-isomer, from which the bromide had been prepared. When longer reaction periods were given,

the product was accompanied by decomposition products of the bromide.

3,5-Di-O-methylglucose Series

1,2-O-Isopropylidene-α-D-glucofuranose (E 49)

This was prepared by the method of Mehltretter *et al.*[115], as described in 'Methods in Carbohydrate Chemistry',[149] from anhydrous D-glucose.

Anhydrous D-glucose (200 g.) was acetonated by the action of acetone, containing sulphuric acid, to give 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose. This was partially hydrolysed with $^{N}/_{100}$ hydrochloric acid at 40° for 4 hr., yielding the monoacetone derivative (142 g., 58%), m.p. 160-163°, $[\alpha]_D^{21}$ -11.5° (c 2, H_2O). Lit.[115] m.p. 161°, $[\alpha]_D^{25}$ -12°.

1,2-O-Isopropylidene-6-O-tosyl-α-D-glucofuranose (E 143)

1,2-O-Isopropylidene-α-D-glucofuranose (45.0 g.) was converted, by treatment with toluene-p-sulphonyl chloride in pyridine at 0°, into the 6-O-tosylate (45.6 g., 60%), m.p. 104-106°. Recrystallization from ether-petroleum gave

material m.p. 107-108°. Lit.[116] m.p. 108°.

Since this compound is much more soluble in dichloromethane than in either chloroform or ether, its extraction is best carried out with that solvent.

Attempted methylation of 1,2-O-isopropylidene-6-O-tosyl-α-D-glucofuranose (E 75, 81)

A mixture of 1,2-O-isopropylidene-6-O-tosyl-α-D-glucofuranose (1.0 g.), silver oxide (2.0 g., 3 equiv. per OH), and methyl iodide (4.0 g., 5 equiv. per OH) in dry dimethylformamide (15 ml.) was stirred for 2 days at room temperature, with the addition of more methyl iodide (2.0 g.) after a day. The mixture was filtered and the filtrate evaporated to dryness. The residue was extracted with chloroform, washed with water, dried and evaporated to give a yellow oil. Distillation gave 5,6-anhydro-1,2-O-isopropylidene-3-O-methyl-α-D-glucofuranose[117] (203 mg., 35%), rather than the desired 3,5-di-O-methyl ether. The epoxide had b.p. 100-110° (bath)/10^{-2}mm., $[\alpha]_D^{22}$ -67° (c 1.1, $CHCl_3$), n_D^{23} 1.4571; $\nu_{max.}$ 1600 $cm.^{-1}$, absent. (Found: C, 54.9; H, 7.2; OMe, 14.6; Calc. for $C_{10}H_{16}O_5$: C, 55.5; H, 7.5; OMe, 14.35%). The material gave a positive epoxide test with sodium thiosulphate-phenolphthalein.

Kenner and Richards[117], who prepared this compound from 1,2-O-isopropylidene-3-O-methyl-6-O-tosyl-α-D-glucofuranose by treatment with sodium methoxide in methanol, gave b.p. 98°/0.3 mm., $[\alpha]_D^{21}$ -69.6° (c 2.5, $CHCl_3$), n_D^{17} 1.4586.

1,2-O-Isopropylidene-3,5-di-O-methyl-6-O-tosyl-α-D-glucofuranose (E 155, 166)

A mixture of 1,2-O-isopropylidene-6-O-tosyl-α-D-glucofuranose (25.0 g.), silver oxide (4.5 g.) and methyl iodide (40 ml.) was stirred vigorously at 35-40°. After more silver oxide (5 g. portions) had been added after 2, 4, and 6 hr., acetone was added to decrease the viscosity and the reaction continued for a further 18 hr.. The mixture was filtered through kieselguhr, the solids washed with more acetone, and the combined filtrates evaporated to dryness.

The above procedure, but with 3-4 day reaction periods, was repeated seven times after which the residue (24.2 g.,90%) showed no hydroxyl absorption in the i.r. spectrum. Since this material could neither be crystallized nor distilled, an analytical sample was prepared by chromatography on alumina, using benzene followed by 50% benzene-chloroform. 1,2-O-Isopropylidene-3,5-di-O-methyl-6-O-tosyl-α-D-glucofuranose had $[\alpha]_D^{25}$ -15° (c 1.0, $CHCl_3$), n_D^{25} 1.4926,

$\lambda_{max.}$ 224 mμ (log ε, 4.05); $\nu_{max.}$ 1600, 1380, 1180 $cm.^{-1}$, absence of hydroxyl absorption. (Found: C, 53.65; H, 6.9; S, 8.05; OMe, 15.1. $C_{18}H_{26}O_8S$ requires: C, 53.7; H, 6.5; S, 8.0; OMe, 15.4%).

Acidic hydrolysis of 1,2-O-isopropylidene-3,5-di-O-methyl-6-O-tosyl-α-D-glucofuranose (E 347)

A mixture of 1,2-O-isopropylidene-3,5-di-O-methyl-6-O-tosyl-α-D-glucofuranose (0.60 g.), acetic acid (0.6 ml.) and water (5.4 ml.) was heated at 100° for 2¼ hr. in a stream of nitrogen. The solution was cooled, diluted with methanol (6 ml.) and passed through a column of Deacidite E ion-exchange resin (20 ml., wet). Evaporation gave a gum (0.38 g.), $\lambda_{max.}$ 225 mμ absent, which was distilled to give 3,5-di-O-methyl-D-glucofuranose (0.12 g., 39%), b.p. 140-155° (bath)/10^{-4}mm., $[\alpha]_D^{25}$ -28° (c 0.9, H_2O). (Found: C, 46.8; H, 7.3. Calc. for $C_8H_{16}O_6$: C, 46.1; H, 7.75%). Lit.[119] b.p. 165-170° (bath)/0.04 mm., $[\alpha]_D^{26}$ -20° (c 1.1, H_2O).

6-Acetylthio-6-deoxy-1,2-O-isopropylidene-3,5-di-O-methyl-α-D-glucofuranose (E 221)

A mixture of 1,2-O-isopropylidene-3,5-di-O-methyl-6-O-tosyl-α-D-glucofuranose (20.0 g.) and potassium thiolacetate (11.4 g. 2 equiv.) in anhydrous acetone (400 ml.)

was refluxed, under nitrogen, for 8 hr.. It was evaporated to dryness and the residue distributed between chloroform and water. The organic layer was washed with saturated sodium chloride solution, dried and evaporated to give a yellow oil. Distillation gave the 6-thiolacetate (8.6 g., 57%), b.p. 123-125°/10^{-4} mm., $[\alpha]_D^{21}$ -12° (c 1.3, $CHCl_3$), n_D^{19} 1.4809, $\lambda_{max.}$ 232 mμ (ε, 4060), $\nu_{max.}$ 1695 $cm.^{-1}$ (SAc). (Found: C, 51.3; H, 7.5; S, 10.9. $C_{13}H_{22}O_6S$ requires: C, 50.95; H, 7.2; S, 10.5%).

6-Deoxy-1,2-O-isopropylidene-6-mercapto-3,5-di-O-methyl-α-D-glucofuranose (E 261)

Sodium (30 mg.) was added to a solution of 6-acetylthio-6-deoxy-1,2-O-isopropylidene-3,5-di-O-methyl-α-D-glucofuranose (1.50 g.) in anhydrous methanol (20 ml.), from which the air had previously been displaced with nitrogen. The solution was allowed to stand for 3 days, then neutralized with solid carbon dioxide and evaporated to dryness. The residue was extracted with ether and the extract dried, filtered through kieselguhr and evaporated. Distillation gave the thiol (0.92 g., 71%), b.p. 96°/10^{-4}mm., $[\alpha]_D^{24}$ -38° (c 1.1, $CHCl_3$), n_D^{23} 1.4710, $\nu_{max.}$ 2560 $cm.^{-1}$. (Found: C, 49.8; H, 7.45; thiol-S, 12.2. $C_{11}H_{20}O_5S$ requires: C, 50.0; H, 7.6; thiol-S, 12.1%).

5,6-Anhydro-1,2-O-isopropylidene-α-D-glucofuranose (E 523)

A solution of toluene-p-sulphonyl chloride (84 g.) in dry pyridine (200 ml.) was added dropwise, over a period of 6 hr., to a well-stirred solution of 1,2-O-isopropylidene-α-D-glucofuranose (90 g.)[115] in pyridine (600 ml.) at 0°. The reaction mixture was allowed to stand at 0° for a further 2 hr., then at room temperature for 18 hr.. The solution was stirred for 4 hr. after the addition of water (20 ml.), then evaporated to low bulk below 30°. The residue was dissolved in dichloromethane (see p. 104), washed with water, dilute hydrochloric acid, water, sodium bicarbonate solution, then water again. The dried solution (ca. 500 ml.) was cooled to 0° and a solution of sodium (11.3 g.) in anhydrous methanol (230 ml.) was added with vigorous shaking. The mixture was shaken for a further 15 min., then diluted with water (200 ml.) and neutralized with solid carbon dioxide. The aqueous layer was extracted twice with dichloromethane and the combined organic phases washed, dried and evaporated at room temperature. Recrystallization of the residue, from benzene, gave the epoxide (29.4 g., 36%), m.p. 132-135°. Lit.[120] m.p. 133.5°.

6-Benzylthio-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (E 393, 525)

Toluene-α-thiol (52 ml.) was added to a solution of sodium (7.0 g.) in anhydrous methanol (400 ml.), from which the air had previously been displaced with nitrogen. 5,6-Anhydro-1,2-O-isopropylidene-α-D-glucofuranose (29.4 g.) was added and the solution allowed to stand under nitrogen for 24 hr.. The solution was neutralized with glacial acetic acid (ca. 17 ml.), evaporated to dryness, and the residue distributed between chloroform and water. The aqueous layer was extracted several times with chloroform and the combined organic phases washed with saturated sodium chloride solution, dried and evaporated to dryness. Excess thiol was removed at 100°/0.2 mm. and the crystalline residue chromatographed on silica gel, in benzene followed by 50% ethyl acetate-benzene. The thioether (38.8 g., 82%), which was recrystallized from petroleum (b.p. 60-80°) containing a little chloroform, had m.p. 81.5-82.5°, $[\alpha]_D^{23}$ -4° (c 3.4, $CHCl_3$); $\nu_{max.}$ 3500, 1600 $cm.^{-1}$. (Found: C, 59.2; H, 6.6; S, 10.1. $C_{16}H_{22}O_5S$ requires: C, 58.9; H, 6.8; S, 9.8%). The n.m.r. spectrum (in CCl_4) showed (a) a five-proton group, τ ca. 2.75, due to the aromatic protons (b) two three-proton singlets, τ 8.56 and 8.72, due to the C-Me groups

(c) a two-proton singlet, at τ 6.27, due to the benzylic methylene group (d) a broad one-proton signal, removed by deuteration, at τ 6.37, due to the hydroxylic proton (e) a two-proton group, at τ *ca.* 7.26, due to the C-6 protons (f) a two-proton group, at τ 6.04, due to H-3 and H-4 (g) a one-proton signal, at τ 5.76, due to H-5 and (h) two one-proton doublets, at τ 4.16 and 5.58, due to H-1 and H-2 respectively, J = 3.5 c.p.s..

Attempted methylation of 6-benzylthio-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (E 429)

6-Benzylthio-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (4.0 g.) was dissolved in tetrahydrofuran (70 ml., dried by distillation from lithium aluminium hydride) and sodium hydride (3.5 g. of a 50% suspension in mineral oil, prewashed with anhydrous ether) added. After 1 hr., methyl iodide (25 ml.) was added and the mixture stirred for 5 days at room temperature. After the addition of water (20 ml.), the solution was neutralized with solid carbon dioxide, evaporated to dryness and extracted with chloroform. The extract was washed, dried and evaporated to give a yellow oil (4.4 g.), a sample of which polymerized during high-vacuum distillation.

Chromatography on silica gel, in benzene followed by 50% ethyl acetate in benzene, gave an oil, the major part of which was probably 5,6-dideoxy-1,2-O-isopropylidene-3-O-methyl-6-methylthio-α-D-xylohexofuran-5-enose. For spectral data (n.m.r. spectrum in CCl_4), see p. 70.

Bromination (E 443): A solution of the above vinyl sulphide mixture (96 mg.) in carbon tetrachloride (1 ml.) absorbed 0.70 ml. of a solution of bromine (0.631 g.) in carbon tetrachloride (10 ml. of solution) indicating the olefin to be ca. 70% pure. Although a yellow solid was precipitated, the mixture very quickly blackened with the liberation of hydrogen bromide, as shown both by a strong acid reaction and precipitation with silver nitrate solution.

Hydrolysis (E 445): A mixture of the crude vinyl sulphide above (0.41 g.), mercuric chloride (2.0 g.), cadmium carbonate (1.0 g.), water (4 ml.) and dioxan (10 ml.) was heated at 75° for 9 hr.. It was then filtered, evaporated to dryness and extracted with chloroform. The extract was washed, with saturated sodium chloride solution, dried and evaporated to an oil, $\nu_{max.}$ 3350, 1720 $cm.^{-1}$, which did not give a crystalline 2,4-dinitrophenylhydrazone.

6-Benzylthio-6-deoxy-1,2-O-isopropylidene-3,5-di-O-methyl-α-D-glucofuranose (E 499, 501, 533)

Dimethyl sulphate (8 ml., ca. 2 equiv. per OH) was added dropwise over a period of 1 hr. to a mixture of 6-benzylthio-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (5.0 g.) and finely-powdered sodium hydroxide (5.0 g., ca. 4 equiv. per OH) in peroxide-free tetrahydrofuran (120 ml.). The mixture was stirred, under nitrogen, for 24 hr. at 30°, then water (20 ml.) was added, the bath temperature raised to 65-70° and the solvent evaporated in a stream of nitrogen. After a further 1 hr. at 65°, the mixture was cooled and extracted with chloroform. The extract was washed, dried, evaporated and distilled to give 6-benzylthio-6-deoxy-1,2-O-isopropylidene-3,5-di-O-methyl-α-D-glucofuranose (4.48 g., 83%), b.p. $160^{\circ}/10^{-4}$mm., $[\alpha]_D^{24}$ - 75° (c 1.4, $CHCl_3$), n_D^{19} 1.5201, $\nu_{max.}$ ca. 3600 $cm.^{-1}$ absent, τ (in CCl_4) 6.63 and 6.67, both three-proton singlets, due to O-Me groups. (Found: C, 61.3; H, 7.3; S, 9.3. $C_{18}H_{26}O_5S$ requires: C, 61.0; H, 7.4; S, 9.1%).

When the preparation was carried out on the 38 g. scale, the yield dropped to 63% of purified material.

6-Deoxy-1,2-O-isopropylidene-6-mercapto-3,5-di-O-methyl-α-D-glucofuranose (E 505, 579)

Sodium (2.20 g.) was added, during 30 min., to a stirred mixture of 6-benzylthio-6-deoxy-1,2-O-isopropylidene-3,5-di-O-methyl-α-D-glucofuranose (15.0 g.), anhydrous ether (50 ml.) and liquid ammonia (150 ml.). The mixture was stirred for a further 30 min., then excess sodium was decomposed by the cautious addition of ammonium chloride (14 g.). The solvents were evaporated after 1 hr. and the residue distributed between chloroform and water. The aqueous layer was extracted with chloroform and the combined organic phases washed, dried, evaporated and distilled to give the thiol (8.71 g., 78%), b.p. $96^{\circ}/10^{-4}$mm., (thiol-S, 11.2%; calc. 12.1%). TLC (silica gel, 15% ethyl acetate in benzene or 50% ether-petroleum) showed the product to be identical with that obtained previously by the deacetylation of the corresponding thiolacetate, but contaminated with a small quantity of dibenzyl. The material was suitable for the next stage (p. 114) without further purification.

6-Deoxy-6-mercapto-3,5-di-O-methyl-αβ-D-glucofuranose (E 677)

A mixture of 6-deoxy-1,2-O-isopropylidene-6-mercapto-3,5-di-O-methyl-α-D-glucofuranose (0.43 g.), glacial acetic

acid (15 ml.) and water (45 ml.) was heated, under nitrogen, for 22 hr. at 75°. The solution was evaporated to dryness at room temperature and the residue extracted with chloroform after the addition of an excess of sodium bicarbonate and a little water. The extract was washed with a saturated sodium chloride solution, dried and evaporated. The oil was distilled to give 6-deoxy-6-mercapto-3,5-di-O-methyl-αβ-D-glucofuranose (0.28 g., 77%), b.p. 90-100° (bath)/10^{-4}mm., $[\alpha]_D^{22}$ -25° (c 1.5, $CHCl_3$), n_D^{17} 1.5078; $\nu_{max.}$ 3500 (OH), 2560 $cm.^{-1}$ (SH). (Found: C, 43.1; H, 7.2; thiol-S, 14.3. $C_8H_{16}O_5S$ requires: C, 42.8; H, 7.2; thiol-S, 14.3%). For the n.m.r. spectrum (in $CDCl_3$), see p. 73.

1,6-Anhydro-6-deoxy-6-mercapto-3,5-di-O-methyl-β-D-glucofuranose and di-(6-deoxy-6-mercapto-3,5-di-O-methyl-β-D-glucofuranose)-1,6':1',6-dianhydride (E 281, 543, 549, 573 and 581)

A mixture of 6-deoxy-1,2-O-isopropylidene-6-mercapto-3,5-di-O-methyl-α-D-glucofuranose (8.7 g.), acetic acid (160 ml.), water (650 ml.) and 10% aqueous sulphuric acid (245 ml.) was stirred, under nitrogen, at 95° for 3½ hr.. Sodium acetate (160 g.) was then added to neutralize the

mineral acid and the solution was evaporated to dryness. The residue was distributed between chloroform and water, the aqueous layer extracted with more chloroform and the combined organic phases washed, dried and evaporated to give a semi-solid (6.1 g.). This was extracted with acetone, leaving a small solid residue (A), and the product from the extract was chromatographed on silica gel in 10% acetone in ether, then recrystallized from benzene-cyclohexane, to give the 1,6-anhydro compound (3.49 g., 52%), m.p. 106.5-107°, $[\alpha]_D^{24}$ -117° (c 1.5, $CHCl_3$). (Found: C, 46.8; H, 7.15; S, 15.45%; M, 208. $C_8H_{14}O_4S$ requires: C, 46.6; H, 6.85; S, 15.55%; M, 206). The compound took up no iodine, even at 70°, and gave negative Fehling's and nitroprusside tests. For the n.m.r. spectrum (in $CDCl_3$), see p. 74.

From another hydrolysis of 6-deoxy-1,2-O-isopropylidene-6-mercapto-3,5-di-O-methyl-α-D-glucofuranose (1.0 g.), 12 mg. of the sparingly-soluble compound (A, above) was obtained. This was recrystallized, with difficulty, from a large volume of aqueous methanol to give pure di-(6-deoxy-6-mercapto-3,5-di-O-methyl-β-D-glucofuranose)-1,6':1',6-dianhydride, m.p. 260-270° (decomp.). [Found: C, 46.5; H, 7.1; O, 30.7%; M (mass spect.), 412. $C_{16}H_{28}O_8S_2$ requires: C, 46.6; H, 6.8; O, 31.0; M, 412]. The compound gave negative

tests with both Fehling's and sodium nitroprusside - sodium hydroxide solutions. Due to the extreme insolubility, it is probable that much was rejected with inorganic material during the chloroform extraction.

A solution of the monomeric 1,6-anhydro compound (10 mg.) in methanol (1 ml.) and 2N aqueous sodium hydroxide solution (1 ml.) was heated at 95°, for 1 hr., under nitrogen. The basic solution, which showed no thiol activity when treated with sodium nitroprusside solution, was acidified with dilute sulphuric acid. Titration with aqueous iodine solution showed the absence of any thiol.

1,6-Anhydro-6-deoxy-6-mercapto-2,3,5-tri-O-methyl-β-D-glucofuranose (E 575, 587)

Dimethyl sulphate (1.40 ml.) was added dropwise to a well-stirred suspension of powdered sodium hydroxide (0.90 g.) and 1,6-anhydro-6-deoxy-6-mercapto-3,5-di-O-methyl-β-D-glucofuranose (1.15 g.) in peroxide-free tetrahydrofuran (35 ml.) at 40°, under nitrogen. The mixture was stirred for 24 hr. at 45-50°, then the temperature was raised to 65° and water (13 ml.) was added. After being heated for 1 hr. following the evaporation of the tetrahydrofuran in a stream of nitrogen, the mixture was cooled and extracted

with chloroform. The extract was washed, dried and evaporated to a yellow oil (1.24 g.). Chromatography on silica gel in 50% ether-petroleum, followed by distillation gave the methyl ether (1.14 g., 93%), b.p. $93^{\circ}/10^{-4}$mm., $[\alpha]_D^{23}$ -106° (c 1.0, $CHCl_3$), n_D^{19} 1.5044; $\nu_{max.}$ (in $CHCl_3$), absence of hydroxyl absorption. (Found: C, 49.3; H, 7.4; S, 14.4. $C_9H_{16}O_4S$ requires: C, 49.1; H, 7.3; S, 14.6%). τ (CCl_4) 6.58, 6.62 and 6.65, due to O-Me groups.

Attempted cleavage of the furanose ring of 1,6-anhydro-6-deoxy-6-mercapto-2,3,5-tri-O-methyl-β-D-glucofuranose with lithium aluminium hydride - aluminium chloride (E 595)

White lithium aluminium hydride (13.5 mg.) was added to a stirred solution of anhydrous aluminium chloride (190 mg.) in anhydrous ether (2 ml.) at 0°. After 15 min., a solution of 1,6-anhydro-6-deoxy-6-mercapto-2,3,5-tri-O-methyl-β-D-glucofuranose (0.23 g.) in anhydrous ether (2 ml.) was added slowly at 0°. The mixture was allowed to attain room temperature, then refluxed for 2 hr., cooled, diluted with water (0.3 ml.) and 2N sulphuric acid (2 ml.) and extracted with chloroform (10 ml.). The extract was washed, dried and evaporated to give a multi-component syrup (200 mg.), from which no identifiable product could be isolated by chromatography.

When the reaction was repeated without the metal hydride, a similar result was obtained.

Acetolysis of 6-acetylthio-6-deoxy-1,2-O-isopropylidene-3,5-di-O-methyl-α-D-glucofuranose (E 673, 675, 713)

Acetolyses, using a mixture of acetic acid (20 parts), acetic anhydride (20 parts) and concentrated sulphuric acid (1 part), were carried out with temperature (-20^{o} to $+20^{o}$) and time (40 min. to 2 weeks) as variables. Two typical experiments are described below. In all cases, the complex mixture obtained was shown by TLC (silica gel, 40% ethyl acetate in benzene) to have the same qualitative composition. A similar result was obtained from the acetolysis of 1,6-anhydro-6-deoxy-6-mercapto-3,5-di-O-methyl-β-D-glucofuranose.

A solution of 6-acetylthio-6-deoxy-1,2-O-isopropylidene-3,5-di-O-methyl-α-D-glucofuranose (200 mg.) in acetic acid (5 ml.), acetic anhydride (5 ml.) and concentrated sulphuric acid (0.25 ml.) was allowed to stand at 0^{o} for 4 hr.. After the addition of anhydrous sodium acetate (1.3 g.), the mixture was evaporated to dryness and the residue distributed between chloroform and water. The chloroform layer, together with a further extract of the aqueous phase, was evaporated

to dryness and evaporated several times with methanol. The residue was extracted with chloroform and the extract washed with sodium bicarbonate solution and saturated sodium chloride solution, dried and evaporated to give a dark brown gum (130 mg.); $\nu_{max.}$ 1745 $cm.^{-1}$ (OAc, very strong), 1690 $cm.^{-1}$ (SAc, very weak). Trituration with ether-petroleum gave a white solid (12 mg.) which was recrystallized from carbon tetrachloride - petroleum to give material m.p. 95-96°, $[\alpha]_D^{21}$ +53° (c 0.5, $CHCl_3$); no i.r. absorption for S-acetate. For n.m.r. data (in CCl_4), see p. 78.

An acetolysis of the thiolacetate (0.71 g.) for 48 hr., worked up as above, gave a syrup which was chromatographed on silica gel in 20% ethyl acetate in benzene. A small yield of crystalline material (35 mg.) was obtained by the trituration of some fractions with petroleum. Recrystallization from ether-hexane gave material m.p. 107-108°, $[\alpha]_D^{23}$ +89° (c 1.1, $CHCl_3$); no thiolacetate absorption in the i.r. spectrum. For n.m.r. data (in $CDCl_3$), see p. 78.

2,3,4,5-Tetra-O-methylgalactose Series

D-Galactose dibenzyl dithioacetal (E 19, 223)

A mixture of D-galactose (29 g.), toluene-α-thiol (40 ml.) and fuming hydrochloric acid (30 ml.) was shaken vigorously for 2 hr.. The solid formed was filtered off, dried at 1 mm. for 3 days over potassium hydroxide, triturated with benzene and recrystallized from ethanol to give the dithioacetal (49 g., 74%). Two types of crystal are formed, probably depending on the rate of cooling. Spars, arising from rapid cooling and having m.p. 138-139°, undergo a transition during the melting-point determination to needles, m.p. 144.5-145°, which can also be formed by slow cooling during recrystallization. Lit.[128] m.p. 144°.

Toluene-p-sulphonylation of D-galactose dibenzyl dithioacetal (E 27, 55, 85, 87, 91, 99)

A solution of toluene-p-sulphonyl chloride (2.50 g.) in pyridine (10 ml.) was added dropwise to a solution of D-galactose dibenzyl dithioacetal (5.0 g.) in pyridine (20 ml.) at 0°. After 24 hr. at room temperature, water (9 ml.) was added over 20 min. and the solution allowed to stand for a further 2 hr.. Evaporation gave a residue which was

dissolved in chloroform, washed with acid, base and water in the usual manner, and dried. The crude gum (4.2 g.), obtained by evaporation, was triturated with benzene to yield, not the desired tosylate as claimed by Fernández-Bolaños *et al.*[130], but a small quantity of starting material (*ca.* 70 mg.) and 3,6-anhydro-D-galactose dibenzyl dithioacetal (0.30 g., m.p. 99-101°). Recrystallization from chloroform-petroleum gave pure material, m.p. 99.5-101.5°, $[\alpha]_D^{23}$ -9° (*c* 2.3, pyridine). Lit.[131] m.p. 100°, $[\alpha]_D^{20}$ -11° (*c* 1.94, pyridine). (Found: S, 16.35. Calculated for $C_{20}H_{24}O_4S_2$: S, 16.3%).

The yield of anhydro compound was increased to 1.8 g. (37%) by increasing the reaction time to 3 days.

Several experiments, in which the theoretical quantity of pyridine only was used with acetone or dioxan as the solvent, resulted only in recovery of D-galactose dibenzyl dithioacetal (*ca.* 80%), no tosylate or anhydro compound being isolated.

6-O-Tosyl-β-D-galactopyranose (E 69)

A mixture of 1,2:3,4-di-O-isopropylidene-6-O-tosyl-α-D-galactopyranose (5.0 g.)[113], glacial acetic acid (45 ml.) and water (15 ml.) was heated at 90° for 2 hr.. The solution,

obtained by evaporation at 25° to incipient crystallization, was left overnight yielding the tosylate (1.75 g., 43%), m.p. 124-127° (decomp.). Recrystallization from water gave material m.p. 125-126°. Lit.[132] m.p. 130° (decomp.).

Attempted preparation of 6-O-tosyl-D-galactose dibenzyl dithioacetal (E 73)

Toluene-α-thiol (0.37 ml.) was added to a solution of 6-O-tosyl-β-D-galactopyranose (0.5 g.) in concentrated hydrochloric acid (50 ml.). The mixture was shaken vigorously for 40 min., and the precipitate filtered off, washed with water, dried and triturated with petroleum (50 ml.). The crude product (0.48 g.), m.p. 80-84°, was recrystallized from chloroform-petroleum but appeared to undergo extensive decomposition on drying *in vacuo*. No pure compound could be obtained.

Acetonation of D-galactose dibenzyl dithioacetal (E 21, 233)

D-galactose dibenzyl dithioacetal (100 g.) was dissolved in a chilled solution of concentrated sulphuric acid (35 ml.) and anhydrous acetone (1300 ml.). The reaction mixture was allowed to stand at room temperature for 24 hr., neutralized with gaseous ammonia, filtered to remove the precipitated salts, and evaporated to dryness. Water (500 ml.)

was added and distilled off at 70° to remove traces of acetone and its condensation products. The residue, after being dried by azeotropic distillation with benzene, was extracted with petroleum leaving behind inorganic matter, starting material and monoacetonated product. Evaporation of the solution gave a syrup (109 g. 97%) shown by TLC (alumina, chloroform) to be largely a mixture of two compounds. These have been shown[135] to be the 2,3:4,5- and 2,3:5,6- di-O-isopropylidene derivatives.

Attempted tosylation of the di-O-isopropylidene derivatives of D-galactose dibenzyl dithioacetal (E 29)

A solution of toluene-p-sulphonyl chloride (0.43 g.) in pyridine (2 ml.) was added dropwise to a solution of di-O-isopropylidene-D-galactose dibenzyl dithioacetal (1.0 g.) in pyridine (5 ml.) at 0°. After 30 min. at 0°, and a further 16 hr. at room temperature, water (1 ml.) was added. The mixture was allowed to stand for 45 min., then poured into ice-water (50 ml.). The precipitated oil was extracted with chloroform and the solution was washed with acid, base and water in the usual way, dried and evaporated. The crude syrup (1.26 g.) was shown by TLC (alumina, benzene) to be multi-component and no purification could be achieved.

Triphenylphosphite methiodide (E 162, 235)

A mixture of triphenylphosphite (180 g.) and methyl iodide (125 g.) was refluxed, under anhydrous conditions, for 40 hr.. (After some hours, it is best to seed the solution with previously prepared product). Anhydrous ether was added after cooling the mixture to 30°, and the crystals were filtered off, washed well with ether and dried over phosphorus pentoxide *in vacuo*. The chunky colourless crystals (130 g., 50%), m.p. 135-138° (sealed tube) were extremely deliquescent. Lit.[136] m.p. 146°, after recrystallization.

6-Deoxy-6-iodo-2,3:4,5-di-O-isopropylidene-D-galactose dibenzyl dithioacetal (E 165, 241)

Crude di-*O*-isopropylidene-D-galactose dibenzyl dithioacetal (119 g.), triphenylphosphite methiodide (125 g.) and anhydrous benzene (2 l.) were stirred at 55-60° for 36 hr. with the exclusion of moisture. The solution was cooled and applied to an alumina column (4 kg.). Elution with benzene, evaporation, and recrystallization of the resulting solid from petroleum, gave 6-deoxy-6-iodo-2,3:4,5-di-*O*-isopropylidene-D-galactose dibenzyl dithioacetal (110 g., 76%), m.p. 89-90°, $[\alpha]_D^{24}$ -101° (*c* 1.1, benzene). Lit.[135] m.p. 86.5-87°, $[\alpha]_D^{19}$ -99.9° (*c* 2.1, benzene).

6-Benzylthio-6-deoxy-2,3:4,5-di-O-isopropylidene-D-galactose dibenzyl dithioacetal (E 173, 245)

Toluene-α-thiol (56 ml., 2.6 equiv.) was added to a solution of sodium (10.5 g., 2.5 equiv.) in anhydrous methanol (1500 ml.) from which the air had previously been displaced with nitrogen. 6-Deoxy-6-iodo-2,3:4,5-di-O-isopropylidene-D-galactose dibenzyl dithioacetal (110 g.) was added and the solution refluxed, under nitrogen, for 5 hr.. The residue remaining after evaporation to dryness was extracted with chloroform (2 l.) and the extract washed with 2N sodium hydroxide solution (2 x 500 ml.) and water, dried and evaporated. Although the crude product (115 g., $>$100%) contained some dibenzyl disulphide and toluene-α-thiol, its use in the subsequent stage resulted in a 96% yield overall. Since it could neither be crystallized, nor distilled, 6-benzylthio-6-deoxy-2,3:4,5-di-O-isopropylidene-D-galactose dibenzyl dithioacetal was purified for analysis by chromatography on alumina in 50% benzene-petroleum (b.p. 60-80°). It had $[\alpha]_D^{27}$ -90° (c 1.1, benzene), n_D^{25} 1.5777. (Found: C, 66.4; H, 6.6; S, 15.7. $C_{33}H_{40}O_4S_3$ requires: C, 66.4; H, 6.8; S, 16.1%).

6-Benzylthio-6-deoxy-D-galactose dibenzyl dithioacetal

(E 175, 195, 247)

2N Sulphuric acid (100 ml.) was added to a solution of crude 6-benzylthio-6-deoxy-2,3:4,5-di-O-isopropylidene-D-galactose dibenzyl dithioacetal (115 g.) in ethanol (1750 ml.) and water (150 ml.). The solution was refluxed for 30 hr. in a stream of nitrogen, filtered and cooled. The crystalline product was filtered off, washed with dilute ammonium hydroxide solution and water, and dried at 1 mm. over calcium chloride. After removal of dibenzyl disulphide by trituration with boiling petroleum, the product (90.0 g., 96% over two stages) had m.p. 132-133.5°. Recrystallization first from methanol, then ethyl acetate, gave an analytical sample of 6-benzylthio-6-deoxy-D-galactose dibenzyl dithioacetal, m.p. 132.5-133.5°, $[\alpha]_D^{25}$ +49° (c 1.2, $CHCl_3$), $\nu_{max.}$ (in nujol) 3400 $cm.^{-1}$. (Found: C, 62.7; H, 6.4; S, 18.3. $C_{27}H_{32}O_4S_3$ requires: C, 62.75; H, 6.2; S, 18.6%).

6-Benzylthio-6-deoxy-2,3,4,5-tetra-O-methyl-D-galactose dibenzyl dithioacetal

Method A (e.g. E 217, 243, 369): A series of methylations using barium oxide, barium hydroxide and

dimethyl sulphate in dimethylformamide with variations in time, concentration, and temperature was carried out giving the tetra-O-methyl ether in yields of nil to 60%. Variable reproducibility, with yields from 40-60%, was encountered even when the critical conditions described below were closely followed.

A mixture of 6-benzylthio-6-deoxy-D-galactose dibenzyl dithioacetal (9.0 g.), barium oxide (12.0 g.), barium hydroxide (12.0 g.), dimethyl sulphate (24 ml.) and dimethylformamide (200 ml.) was stirred magnetically, together with some glass balls, for 5 days at 28-30°. Ammonium hydroxide solution (0.880, 90 ml.) was added and stirring continued for a further 4 hr.. The residue, after evaporation to dryness, was extracted with chloroform and the solution washed well with water, dried and evaporated. Trituration with methanol gave a crude solid (6.6 g.) which was recrystallized from methanol giving the tetra-O-methyl ether (5.50 g., 55%), m.p. 79-82°. Further recrystallization from petroleum, then methanol, gave an analytical sample, m.p. 81-82°, $[\alpha]_D^{28}$ +72° (c 1.0, $CHCl_3$); $\nu_{max.}$ (CCl_4) 2820 $cm.^{-1}$ (OMe), absence of hydroxyl absorption. (Found: C, 65.3; H, 7.2; S, 17.1; OMe, 21.9. $C_{31}H_{40}O_4S_3$ requires: C, 65.0; H, 7.0; S, 16.8; OMe, 21.7%).

Method B (E 503, 521): Finely-powdered sodium hydroxide (18.0 g.) was added to a solution of 6-benzylthio-6-deoxy-D-galactose dibenzyl dithioacetal (14.5 g.) in tetrahydrofuran (150 ml., peroxide-free). The mixture was stirred, together with some glass balls, at 30° under nitrogen, whilst dimethyl sulphate (30 ml.) was added dropwise, over a period of 1 hr.. After stirring for a further 24 hr. at 45-50°, water (50 ml.) was added and the solvent evaporated in a stream of nitrogen at 60-65°. After being heated for a further 1 hr. at 65°, the mixture was cooled and extracted with chloroform. The washed and dried extract was evaporated and the solid obtained was recrystallized from methanol. The product (14.6 g., 91%). m.p. 78-81°, was identical with that produced above [mixed m.p. and i.r. spectrum (in CCl_4)].

Reaction of 6-benzylthio-6-deoxy-2,3,4,5-tetra-O-methyl D-galactose dibenzyl dithioacetal with sodium in liquid ammonia (E 237)

A solution of the dithioacetal (1.55 g.) in anhydrous ether (80 ml.) was treated with sodium (1.20 g.) in liquid ammonia (100 ml.). After 6 hr., ammonium chloride was added to destroy the excess sodium and the solvents

evaporated in a stream of nitrogen. The residue was extracted with chloroform and the solution washed with saturated sodium chloride solution, dried, and evaporated. The only pure material which could be isolated was dibenzyl, m.p. 52-53°, as shown by its characteristic u.v. absorption.

6-Benzylthio-6-deoxy-2,3,4,5-tetra-O-methyl-D-galactose diethyl acetal (E 345)

A solution of mercuric chloride (2.75 g.) in anhydrous ethanol (40 ml.) was added to a mixture of 6-benzylthio-6-deoxy-2,3,4,5-tetra-O-methyl-D-galactose dibenzyl dithioacetal (2.76 g.), anhydrous calcium sulphate (2.75 g.), cadmium carbonate (2.75 g.) and anhydrous ethanol (80 ml.). The mixture was stirred under reflux for $5\frac{1}{2}$ hr., filtered, and the solids washed with ethanol. The combined filtrates were evaporated and the residue dissolved in chloroform, washed with water, dried and evaporated. Dissolution in petroleum and filtration through kieselguhr removed any inorganic material still present. The syrup obtained was distilled, only with difficulty, to give the diethyl acetal (1.80 g., 90%), b.p. 170-180° (bath)/10^{-4}mm., $[\alpha]_D^{26}$ -56° (c 1.1, CCl_4), n_D^{20} 1.5018. (Found: C, 60.7; H, 8.85; S, 7.95. $C_{21}H_{36}O_6S$ requires: C, 60.5; H, 8.7; S, 7.7%).

The n.m.r. spectrum (in CCl_4) showed, in particular, five aromatic protons (τ 2.73) and six C-Me protons (two triplets at τ 8.76 and 8.82, J = 7 c.p.s. in both cases).

6-Benzylthio-6-deoxy-2,3,4,5-tetra-O-methyl-D-galactose ethylene acetal (E 225, 531)

A solution of mercuric chloride (30 g.) in dry ethylene glycol (150 ml.) was added to a mixture of 6-benzylthio-6-deoxy-2,3,4,5-tetra-O-methyl-D-galactose dibenzyl dithioacetal (15.0 g.), cadmium carbonate (15 g.), anhydrous calcium sulphate (15 g.) and carbon tetrachloride (15 ml.). The mixture was stirred very efficiently for 13 hr. at 90-100°, cooled and extracted with hot water and chloroform. The aqueous phase was extracted with more chloroform and the combined organic layers washed, dried and evaporated. The crystalline residue was chromatographed, on silica gel (100 g.) in benzene followed by 25% ethyl acetate in benzene, and recrystallized from petroleum (b.p. 60-80°) to give the ethylene acetal (7.38 g., 73%), m.p. 108-109°. Further recrystallization from petroleum (b.p. 60-80°), then methanol, gave an analytical sample, m.p. 110-110.5°, $[\alpha]_D^{24}$ - 63° (c 1.3, $CHCl_3$). (Found: C, 59.2; H, 7.5; S, 8.4%; M, 384. $C_{19}H_{30}O_6S$ requires: C, 59.0; H, 7.8; S, 8.3%; M, 386).

The efficiency of mixing and the quantity of carbon tetrachloride are particularly critical. Recovery of starting material was noted with both too much and too little carbon tetrachloride.

6-Deoxy-6-mercapto-2,3,4,5-tetra-O-methyl-D-galactose ethylene acetal (E 387, 404, 541)

Sodium (1.0 g.) was added in small pieces to a stirred suspension of 6-benzylthio-6-deoxy-2,3,4,5-tetra-O-methyl-D-galactose ethylene acetal (7.0 g.) in anhydrous ether (40 ml.) and liquid ammonia (100 ml.). After a total period of 50 min., ammonium chloride (ca. 7 g.) was added to destroy the excess sodium, and the mixture stirred for a further 30 min.. Having removed the solvents in a stream of nitrogen, the residue was distributed between chloroform and water. The aqueous layer was extracted with more chloroform and the combined organic phases washed with dilute sulphuric acid and water, dried and evaporated. Chromatography on silica gel, in benzene followed by 10% ethyl acetate in benzene, gave the required thiol (4.85 g., 90%), m.p. 55-58°, b.p. 116°/10^{-4}mm., $[\alpha]_D^{21}$ -22° (c 1.1, $CHCl_3$), $\nu_{max.}$ 2460 $cm.^{-1}$ (SH). (Found: C, 48.3; H, 7.8; thiol-S, 10.9. $C_{12}H_{24}O_6S$ requires: C, 48.6; H, 8.2; thiol-S, 10.8%). It was hygroscopic and no satisfactory recrystallization could be achieved.

6-Deoxy-6-mercapto-2,3,4,5-tetra-O-methyl-αβ-D-galacto-septanose (E 643)

6-Deoxy-6-mercapto-2,3,4,5-tetra-O-methyl-D-galactose ethylene acetal (0.50 g.) was dissolved in glacial acetic acid (10 ml.), and water (40 ml.) and 10% v/v aqueous sulphuric acid (15 ml.) were added. The solution was stirred, under nitrogen, for 2 hr. at 90-95°, cooled, and sodium acetate (10 g., hydrated) was added. The residue, following evaporation to dryness, was distributed between water and chloroform. The chloroform layer, together with a further extract of the aqueous phase, was washed with sodium bicarbonate solution and water, dried and evaporated. The crude product (450 mg.) was chromatographed on silica gel in 50% ether-petroleum, followed by ether. One pure component (102 mg., 24%) gave a positive nitroprusside test in sodium hydroxide, but not in sodium bicarbonate, solution. Distillation gave 6-deoxy-6-mercapto-2,3,4,5-tetra-O-methyl-αβ-D-galactoseptanose (95 mg., 22%), b.p. 120-130° (bath)/ 10^{-4}mm., $[\alpha]_D^{22}$ -112° (c 0.27, H_2O), n_D^{19} 1.4996; $\nu_{max.}$ 3400 $cm.^{-1}$ (OH), no absorption in the thiol or carbonyl regions. (Found: C, 47.4; H, 8.2%; M, 237. $C_{10}H_{20}O_5S$ requires: C, 47.6; H, 8.0%; M, 252). For the n.m.r. spectrum (in $CDCl_3$), see p. 86. On titration with iodine, ca. 75% of the

theoretical amount was taken up rapidly, but the calculated amount only after 5 min. (additions being made in 0.04 ml. portions). Thereafter, uptake was very slow and ceased, with 10% overoxidation, after 3 hr..

Ethyl 6-deoxy-6-mercapto-2,3,4,5-tetra-O-methyl-αβ-D-galacto-septanoside

Method A (E 507, 709): A solution of 6-deoxy-6-mercapto-2,3,4,5-tetra-O-methyl-D-galactose ethylene acetal (1.0 g.) in 5% ethanolic hydrogen chloride (125 ml.) was heated, under nitrogen, for $4\frac{1}{2}$ hr. at 70°. The solution was cooled and a little 2N sodium carbonate solution and excess solid sodium carbonate added. The residue, obtained by evaporation to dryness, was distributed between chloroform and water, and the organic phase washed, dried and evaporated. Distillation gave a product (0.57 g., 60%) which was shown by GLC (see below) to contain about 45% of each of the anomeric glycosides and 10% of an unknown ketone. Chromatography on silica gel, in 10% ether in chloroform removed this impurity. A further distillation gave ethyl 6-deoxy-6-mercapto-2,3,4,5-tetra-O-methyl-αβ-D-galacto-septanoside, b.p. 92-93°/10^{-4}mm., $[\alpha]_D^{24}$ -117° (c 0.8, $CHCl_3$), n_D^{20} 1.4820. (Found: C, 51.6; H, 8.5; S, 11.7. $C_{12}H_{24}O_5S$ requires: C, 51.4; H, 8.6; S, 11.4%). For the n.m.r. spectrum (in CCl_4), see p. 88.

Preparative separation of the α- and β- forms could be achieved neither by TLC nor GLC, although the latter technique was partially successful on the analytical scale.

The ketonic fraction failed to yield a solid 2,4-dinitrophenylhydrazone.

Method B (E 598, 687): 6-Deoxy-6-mercapto-2,3,4,5-tetra-O-methyl-D-galactose ethylene acetal (280 mg.) was dissolved in anhydrous ether (50 ml.) which had previously been saturated with hydrogen chloride at 0°. Powdered calcium chloride (0.5 g.) was added and the mixture allowed to stand at 0° for $3\frac{1}{2}$ days. The hydrogen chloride was largely removed by evaporating half of the solvent, adding more ether and evaporating, several times. The mixture was filtered and evaporated to dryness giving a residue presumably containing crude 6-deoxy-6-mercapto-2,3,4,5-tetra-O-methyl-αβ-D-galactoseptanosyl chloride. Anhydrous ethanol (10 ml.) and silver carbonate (2.0 g.) were added and the mixture was stirred for 24 hr., filtered and evaporated. The residue was dissolved in benzene, filtered through kieselguhr and again evaporated. Chromatography on silica gel (40 g.) in 10% ether in chloroform gave pure anomeric glycoside mixture (77 mg., 29%) and a larger quantity (128 mg.) contaminated with approximately 10% of

the ketonic impurity mentioned above. The pure material, b.p. 90-100° (bath)/10^{-4}mm., $[\alpha]_D^{23}$ -180° (c 1.7, $CHCl_3$), n_D^{20} 1.4840, was identical, in the i.r. spectrum and by TLC, to the material obtained by Method A above. For the n.m.r. spectrum (in CCl_4) see p. 89.

Attempted separation of the glycoside mixtures by gas-liquid chromatography (E 705)

(a) Analytical: This was carried out using a Perkin-Elmer F11 instrument fitted with a 2 m. steel column containing Apiezon L on Chromosorb P 60-80 (20:80). At column temperatures of less than 240°, no distinct peaks were observed. At 260°, the optimum temperature, crude material from Method A showed three distinct peaks, although overlapping both with each other and, in one case, with the solvent ($CHCl_3$) peak. The ratio of the peak areas was approximately 45:45:10 at retention times of 2.4, 5.2 and 8.0 minutes. A sample from Method B behaved similarly with a ratio of 3:1 for the first two peaks and an impurity of approximately 10%.

(b) Preparative: Prior to attempting a preparative-scale separation, the analytical procedure was repeated on a Wilkens' Aerograph A700 "Autoprep" instrument using a

20 ft. column packed with (i) 5% SE 30 on Chromosorb P 60-80 (ii) 30% SE 30 on Chromosorb P 60-80 (iii) 30% PDEAS (phenyl diethanolamine succinate) on Chromosorb P 60-80. Using column (i), at the optimum temperature of 250°, three peaks were observed for both glycoside mixtures, but they were very close together and near the solvent peak. Under similar conditions with column (ii), the separation of the ketone was improved but that of the glycosides had vanished. All three compounds were apparently retained on column (iii), even when the recommended maximum temperature was reached.

Acetolysis of ethyl 6-deoxy-6-mercapto-2,3,4,5-tetra-O-methyl-αβ-D-galactoseptanoside (E 743)

A solution of concentrated sulphuric acid (0.5 ml.) in glacial acetic acid (10 ml.) was added at 0° to a solution of the glycoside (0.55 g.) in acetic anhydride (10 ml.) and the mixture allowed to stand at 0° for 13 hr.. Following the addition of anhydrous sodium acetate (2.5 g.), the mixture was evaporated to dryness to give a residue which was extracted with chloroform. The solution was evaporated, first to dryness, then three times with methanol. The crude product was dissolved in chloroform, washed with sodium bicarbonate solution and water, dried and evaporated.

Chromatography on silica gel (70 g.) in benzene, followed by increasing proportions of chloroform in benzene, gave a syrup (260 mg.) which was distilled, b.p. 140-150° (bath)/ 10^{-4}mm., $\nu_{max.}$ 1740 $cm.^{-1}$ (OAc) and 1690 $cm.^{-1}$ (SAc). The composition of this product is discussed on p. 90. The n.m.r. spectrum was recorded in CCl_4.

4,6-Dideoxy-4,6-dimercaptoglucose Series

Methyl 2,3-di-O-methyl-β-D-galactopyranoside (E 697)

This was prepared from methyl 4,6-O-benzylidene-2,3-di-O-methyl-β-D-galactopyranoside[150] (18.30 g., kindly supplied by Dr. P.L. Ragg of this laboratory) by the action of sodium in liquid ammonia.[18] The crude product was used immediately for the subsequent stage.

Methyl 4,6-di-O-methanesulphonyl-2,3-di-O-methyl-β-D-galactopyranoside (E 699)

Crude methyl 2,3-di-O-methyl-β-D-galactopyranoside (prepared from 18.30 g. of the benzylidene derivative, as above) reacted with methanesulphonyl chloride (13 ml.) in pyridine (17 ml.) to give the di-O-methanesulphonate (14.53 g., 65% over two stages), m.p. 123-124°. Lit.[18] m.p. 121-122°.

Methyl 4,6-bisacetylthio-4,6-dideoxy-2,3-di-O-methyl-β-D-glucopyranoside (E 703)

Treatment of methyl 4,6-di-O-methanesulphonyl-2,3-di-O-methyl-β-D-galactopyranoside (14.38 g.) with potassium thiolacetate in dry dimethylformamide, at 110° for 3½ hr., gave the D-gluco- bisthiolacetate (6.56 g., 51%), m.p. 75-76°. Lit.[18] m.p. 75-76°.

Methyl 4,6-dideoxy-4,6-dimercapto-2,3-di-O-methyl-β-D-glucopyranoside (E 717)

Sodium (90 mg.) was added to a solution of methyl 4,6-bisacetylthio-4,6-dideoxy-2,3-di-O-methyl-β-D-glucopyranoside (6.10 g.) in anhydrous methanol (70 ml.). The reaction mixture was allowed to stand under nitrogen for 3 days at room temperature, then neutralized with solid carbon dioxide and evaporated to dryness. An ethereal extract of the residue was dried, filtered through kieselguhr, evaporated and distilled to give the dithiol (3.75 g., 82%), b.p. 111-113°/10^{-4}mm., $[\alpha]_D^{23}$ -35° (c 1.2, $CHCl_3$), n_D^{15} 1.5092. (Found: thiol-S, 25.4. Calc.: 25.2%). Lit.[18] $[\alpha]_D^{20}$ -39° (c 1.1, $CHCl_3$); no b.p. or refractive index recorded.

The yield of 65% obtained previously,[151] was thus improved by the use of more sodium and an increased reaction period.

1,6-Anhydro-4,6-dideoxy-4,6-dimercapto-2,3-di-O-methyl-β-D-glucofuranose (E 757)

A mixture of methyl 4,6-dideoxy-4,6-dimercapto-2,3-di-O-methyl-β-D-glucopyranoside (0.72 g.), water (70 ml.) and concentrated hydrochloric acid (7 ml.) was refluxed, under nitrogen, for $3\frac{1}{2}$ hr. with vigorous stirring. After evaporation to low bulk, sodium bicarbonate (excess) was added and the mixture was extracted with chloroform. The extract was washed with water, dried and evaporated to give a yellow syrup (0.70 g.). This was chromatographed in ether on silica gel (210 g.) to give unchanged glycoside (117 mg.), 1,6-anhydro-4,6-dideoxy-4,6-dimercapto-2,3-di-O-methyl-β-D-glucofuranose (260 mg., 41%) and an impure thiol-active component (113 mg.), probably some tautomer of 4,6-dideoxy-4,6-dimercapto-2,3-di-O-methylglucose. The main component had b.p. 120-125° (bath)/10^{-4}mm., $[\alpha]_D^{24}$ -34° (c 1.9, $CHCl_3$), n_D^{23} 1.5660, $\nu_{max.}$ 3600 $cm.^{-1}$ (OH). It gave a negative Fehling's reaction and consumed no iodine, even at 70°. (Found: C, 43.1; H, 6.1; S, 29.0%; M, 230. $C_8H_{14}O_3S_2$ requires: C, 43.2; H, 6.35; S, 28.85%; M, 222). For the n.m.r. spectrum (in CCl_4), see p. 93.

1,6-Anhydro-4,6-dideoxy-4,6-dimercapto-2,3-di-O-methyl-5-O-(3,5-dinitrobenzoyl)-β-D-glucofuranose (E 777)

A solution of 1,6-anhydro-4,6-dideoxy-4,6-dimercapto-2,3-di-O-methyl-β-D-glucofuranose (60 mg.), 3,5-dinitrobenzoyl chloride (74 mg., 20% excess) and dry pyridine (0.2 ml.) in anhydrous benzene (0.5 ml.) was refluxed, with stirring, for ½ hr. in the absence of moisture. The mixture was then cooled, diluted with chloroform and washed with dilute acid, water, base and water again. The dried solution was evaporated to give a gum (114 mg., 100%) which crystallized on trituration with methanol. It was recrystallized from benzene-ethanol to give the 3,5-dinitrobenzoate (88 mg., 79%), m.p. 167-168°, $[\alpha]_D^{24}$ -42° (c 1.1, $CHCl_3$); $\nu_{max.}$ 1730 (O-ester), 1625 (aromatic), 1555 (asymm. NO_2) and 1350 $cm.^{-1}$ (symm. NO_2). The n.m.r. spectrum (in $CDCl_3$) showed in particular, three aromatic protons (τ 0.72), H-5 (τ 4.60, multiplet), H-1 (τ 5.62, doublet) and two methoxyl singlets (τ 6.43 and 6.47). (Found: C, 43.45; H, 4.0; N, 6.6. $C_{15}H_{16}N_2O_8S_2$ requires: C, 43.3; H, 3.9; N, 6.7%).

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PART II

Hemithioacetals derived from simple mercapto-aldehydes

Cyclic Hemi-acetals, Hemi-ketals and their Sulphur Analogues

Introduction

It has been known for a long time that hydroxy-aldehydes may exist in equilibrium with cyclic hemiacetals. A study of the u.v. absorption spectra of some simple ω-hydroxy-aldehydes, carried out by Hurd and Saunders[1], gave the first semi-quantitative evidence regarding the position of equilibrium (See Table 1, p. 154). This was achieved by comparison of the extinction coefficients at the carbonyl absorption maximum (ca. 290 mμ) with those of the corresponding ω- methoxy-aldehydes.

Since the five-membered ring is under considerable strain due to hydrogen-hydrogen interactions, it is not surprising that rather more free aldehyde exists at equilibrium in the case of 4-hydroxybutanal than in that of 5-hydroxypentanal which may adopt a relatively strain-free six-membered ring. Although seven-membered rings are less favoured on account of both hydrogen interactions and entropy factors, the increase in the proportion of the open-chain tautomer of the hexanal was considered surprisingly large. The apparent decrease in free aldehyde for the octanal did not occur in another solvent and was tentatively ascribed to a failure in attaining true equilibrium.

Table 1

U.V. Absorption Maxima for $HO(CH_2)_nCHO$ in 75% Aqueous Dioxan						
n	% Free aldehyde		Conc^n. (mole. l^{-1})	$\lambda_{max.}$ (mμ)	ε_{25}	ε_{35}
	25^o	35^o				
3	11.4	13.4	0.141	286	1.99	2.34
4	6.1	6.8	0.222	287	1.17	1.30
5	85	89	0.0308	288	16.6	17.2
7	80	*	0.0140	289	16.1	*
8	91	*	0.0178	288	19.1	*

U.V. Absorption Maxima for $MeO(CH_2)_nCHO$ in 75% Aqueous Dioxan					
n	Conc^n. (mole. l^{-1})	$\lambda_{max.}$ (mμ)	ε_{25}	ε_{35}	
3	0.0367	286	17.4	*	
4	0.0383	288	19.2	*	
5	0.0257	289	19.4	*	
7	0.0209	289	20.1	*	
8	0.0361	287	21.1	*	
9	0.0208	290	21.6	*	

*No temperature effect.

Table 2

U.V. Absorption Maxima in Various Solvents								
Solvent	Methyl hexyl ketone		5-hydroxy-pentan-2-one			6-hydroxy-hexan-2-one		
	$\lambda_{max.}$ (mu)	ϵ	$\lambda_{max.}$ (mu)	ϵ	K_T*	$\lambda_{max.}$ (mu)	ϵ	K_T*
Water	-	-	268	24.0	-	270	26.3	-
Aq. alcohol	271	25.5	270	22.5	0.89	270	22.8	0.90
Methanol	275	22.3	-	-	-	-	-	-
n-Butanol	276	21.7	275	12.5	0.58	272	18.7	0.86
Dioxan	277	22.2	278	11.5	0.52	275	15.0	0.68
Chloroform	278	22.2	276	9.5	0.43	-	-	-
CCl_4	281	22.4	-	-	-	275	12.5	0.56
Iso-octane	280	22.5	280	9.3	0.42	-	-	-

*The "tautomeric equilibrium constant, K_T" was derived by dividing the extinction coefficient for the hydroxy-ketone by that for methyl hexyl ketone in the same solvent. Multiplied by 100, it is equivalent to the percentage of open-chain form in the equilibrium mixture.

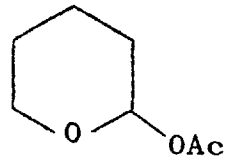
Two keto-alcohols, namely 6-hydroxyhexan-2-one and 5-hydroxypentan-2-one, have more recently been shown[2] to exhibit ring-chain tautomerism by comparing their extinction coefficients at the carbonyl absorption maximum (ca. 275 mμ) with that of methyl hexyl ketone in a variety of solvents. (See Table 2, p. 155).

Table 3

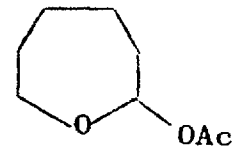
Molar Extinction Coefficients (at 1710 $cm.^{-1}$)			
Solvent	Methyl hexyl ketone	5-hydroxy-pentan-2-one	6-hydroxy-hexan-2-one
Chloroform	372	212	-
CCl_4	304	204	152
Iso-octane	276	177	74

Although the conclusion that they are predominantly open-chain in the polar, and much less so in non-polar, solvents is not unexpected, it would appear that the six-membered is less stable than the five-membered ring. This is in contrast both to the evidence of i.r. spectroscopy in the hydroxy-ketones[2] (see Table 3) and u.v. spectroscopy in the hydroxy-aldehydes.[1] (See Table 1).

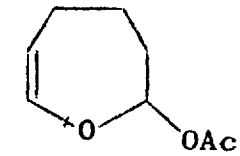
Both ethers and esters of cyclic hemiacetals are well-known and the latter, in particular, have been made by a variety of routes. 2-Acetoxytetrahydrofuran, originally prepared[3] by addition of acetic acid to 2,3-dihydrofuran, has more recently been synthesized[4] by the photochemically catalysed reaction of t-butyl peracetate on tetrahydrofuran in the presence of cuprous bromide. The corresponding tetrahydropyran ester (1) has been obtained both by the addition of acetic acid to 2,3-dihydropyran and the action of acetic anhydride in pyridine on 5-hydroxypentanal itself.[5] 2-Acetoxyoxepan (2) was prepared by the hydrogenation, over palladised charcoal, of the acetate (3) formed by the oxidation of cyclohexene in acetic anhydride solution by oxygen under free-radical initiation.[6]



(1)



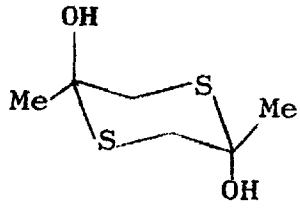
(2)



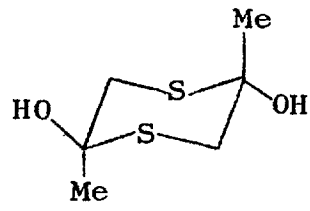
(3)

It is now well-known that α-mercaptoketones often exist in a dimeric form containing a 1,4-dithian ring. The action of sodium hydrogen sulphide on chloroacetone gave two

compounds[7,8] which were proved[9], by i.r. spectroscopy and X-ray crystallography, to be the conformational isomers of 2,5-dihydroxy-2,5-dimethyl-1,4-dithian [(4) and (5)].



(4)

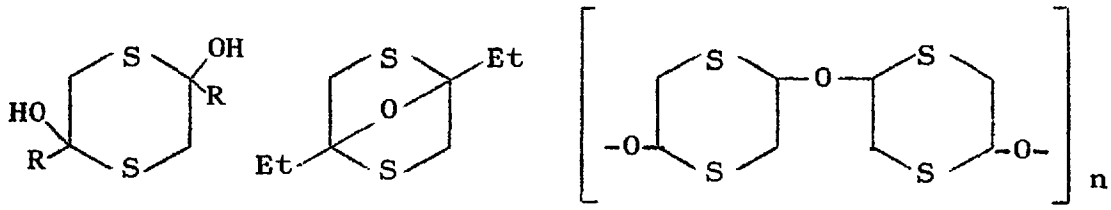


(5)

Similarly 2,5-diethyl-2,5-dihydroxy-1,4-dithian (6), the dimer of 1-mercaptobutan-2-one, has been prepared[10, 11] although it is unstable above -15° giving the 2,5-endoxy derivative (7), corresponding to that obtained when the dimethyl derivative (8) was distilled.[12]

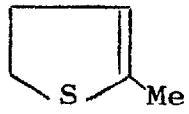
Hesse and Jörder[13] treated chloroacetaldehyde with sodium hydrogen sulphide and obtained 1,4-dihydroxy-1,4-dithian (9) in two forms, only one of which was crystalline. Since the non-crystalline material (formed slowly from the crystalline on standing) could be reconverted by treating with pyridine and each form gave a different crystalline di-O-acetate, they were assumed to be cis- and trans- isomers. Although an attempt was made to prepare an

endoxy compound, dehydration gave only a resin to which a poly-ether structure (10) was assigned.[14]

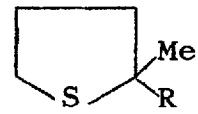


(6; R = Et) (7) (10)
(8; R = Me)
(9; R = H)

The only work which has been done on the possible ring-chain tautomerism of aldehydes or ketones bearing a mercapto substituent other than at the α-position is that of Bacchetti.[15] 5-Mercaptopentan-2-one tended to decompose even at low temperature, and on reduced pressure distillation (at ca. 40-50°) gave 4,5-dihydro-2-methylthiophen (11). Since the mercapto-ketone was also reduced to 2-methyl-tetrahydrothiophen (12) by a Clemmensen reduction, Bacchetti suggested that it was in equilibrium with 2-hydroxy-2-methyl-tetrahydrothiophen (13). However, treatment with diazomethane in ether gave the S-methyl ether (14), identical to that obtained by the action of sodium methyl sulphide on 5-bromopentan-2-one.



(11)



(12; R = H)
(13; R = OH)

$MeS(CH_2)_3COCH_3$
(14)

$AcS(CH_2)_3CHO$
(15)

Bateman and Glazebrook[16] attempted to prepare 4-mercaptobutanal, which is tautomeric with 2-hydroxy-tetrahydrothiophen, but were unsuccessful. They found that 4-acetylthiobutanal (15) was unaffected by cold methanolic sodium methoxide but, not surprisingly, polymerized in hot ethanolic sodium hydroxide solution. Although the diethyl acetal of (15) was deacetylated by treatment with a cold solution of potassium hydroxide in aqueous ethanol, the resulting thiol gave only involatile products when hydrolysed with 2N sulphuric acid.

The first direct evidence concerning the structures of some thiocyclic hemithioacetals will be discussed in the sequel.

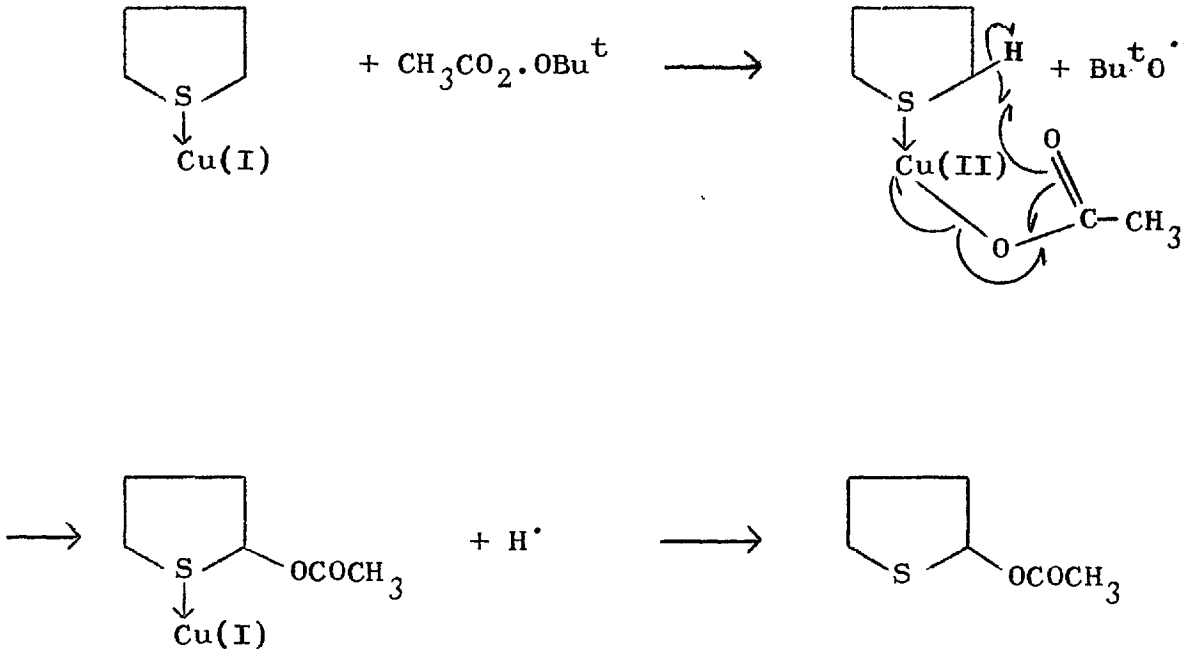
DISCUSSION

The aim of this work was to develop a method of synthesizing the previously unknown ω-mercapto-aldehydes, which may exist in equilibrium with the tautomeric thiocyclic hemithioacetals, and thus provide simple analogues of sugars containing sulphur in the ring. This duality of nature provides two possible routes of attack employing either open-chain or cyclic precursors.

Bateman and Glazebrook[16] attempted a synthesis of 4-mercaptobutanal by the former means, but failed to isolate any product when the groups protecting either the thiol or the carbonyl were removed. (See p. 160). To prepare the desired hemithioacetals directly, it is necessary to introduce an oxygen function, α to the sulphur atom of a cyclic sulphide.

Although tetrahydrothiophen gave[17] a mixture of 2-acetoxytetrahydrothiophen (16) and tetrahydrothiophen 1-oxide when treated with diacetyl peroxide, the sulphoxide may be converted into (16) by the action of acetic anhydride.[18] It has been shown more recently that t-butyl peroxyesters react with various classes of compounds, especially when catalysed by copper ions, to produce

acyloxy derivatives.[19, 20] Thus 2-acetoxytetrahydrothiophen was formed from tetrahydrothiophen by the action of t-butyl peracetate in the presence of cuprous bromide.[21] It has been suggested[22] that the reaction involves a termolecular transition state as shown below. (The curved arrows represent one-electron transfer).



(16)

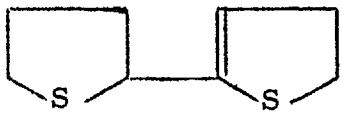
Since tetrahydrothiophen is readily available, the five-membered ring series was investigated initially although parallel work on the thietan, tetrahydrothiopyran and thiepan series was planned.

Tetrahydrothiophen Series

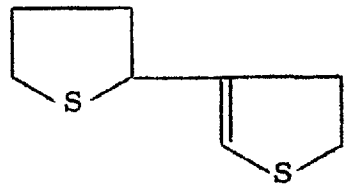
Tetrahydrothiophen was converted into its 2-acetoxy derivative by treatment with t-butyl peracetate in the presence of cuprous chloride, but the large excess of cyclic sulphide used by Sosnovsky[21] was greatly reduced.

Although Horner[18] reported that 2-acetoxy-tetrahydrothiophen (16) underwent acidic hydrolysis giving acetic acid and "a sulphur-containing aldehyde", no evidence was given as to the nature of the latter. When (16) was hydrolysed with 2N hydrochloric acid at 80° for two hours, a product was obtained containing neither a thiol nor a hydroxyl group. It was shown to be identical with the dimer of 2,3-dihydrothiophen obtained when 2-benzoyloxy-tetrahydrothiophen was pyrolysed at 160-170° for two hours.[23] Lawesson[23] claimed to have proved this to be 5-(2-thiolanyl)-2,3-dihydrothiophen (17) from the evidence of a Raney nickel desulphurization, since n-octane can arise from only one of the possible isomers [(17), (18), (19) and (20)], namely (17).

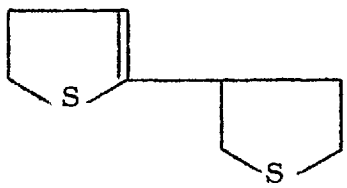
The experimental details show that the hydrocarbon was apparently present in the residue after ethanol and water had been distilled from the filtered reaction mixture. Since octane is known[24, 25] to form ternary azeotropic mixtures with water and the lower alcohols, this evidence must be viewed with suspicion.



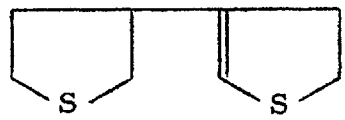
(17)



(18)



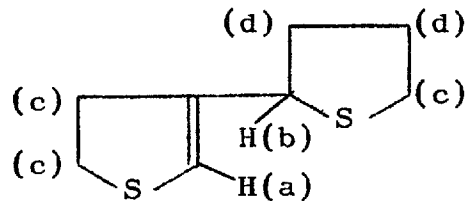
(19)



(20)

Consequently, 2-acetoxytetrahydrothiophen was pyrolysed under similar conditions to give the dimer. An n.m.r. spectrum showed four groups of protons: (a) a one-proton multiplet at τ 4.08 (b) a one-proton triplet at τ 5.91, J = 6 c.p.s. (c) a six-proton group at τ 6.6-7.5 (d) a four-proton group at τ 7.7-8.5. In addition, spin-decoupling experiments, carried out on a Varian HA 100 spectrometer, showed the low-field multiplet to be coupled to a signal with origin at τ 7.38 and the triplet to be coupled at τ 7.94. No evidence of coupling between the low-field multiplet and the triplet could be obtained. Since the chemical shift and multiplicity of the methine proton (τ 5.91) indicates that it is α to a sulphur atom and coupled to only two other protons, two [(19) and (20)] of the possible structures may be rejected. It was hoped to differentiate between (17) and (18) by considering the multiplicity of the olefinic proton since, in the former, it is vicinal to a methylene group and should hence give rise to a triplet. In fact, although he made no further comment, Lawesson[23] described the olefinic proton as a singlet, which would appear to eliminate (17) as a possibility. However, in the present work, this peak was resolved to a six-line multiplet with a total width of only ca. 5 c.p.s..

In order to obtain a model value for the coupling constant of the triplet which would be expected to arise from (17), 2,3-dihydrothiophen was prepared as described by Sosnovsky.[26] Its n.m.r. spectrum showed four groups of protons: (a) a one-proton six-line multiplet at τ 3.94 with $J_{4,5}$ = 6 c.p.s. and $J_{3,5}$ = 1.8 c.p.s. (b) a one-proton six-line multiplet at τ 4.51 with $J_{4,5}$ = 6 c.p.s. and $J_{3,4}$ = 2.6 c.p.s. (c) a two-proton group at τ 6.6-7.0 (d) a two-proton group at τ 7.1-7.5. The olefinic region appeared as an AB quartet when the sample was irradiated at τ 7.28, but no sharp triplet could be obtained for H-4 by irradiation at τ 3.94. Thus, as is the case with 2,3-dihydrofuran,[27, 28] there are certain anomalies, especially the small value of $J_{3,4}$. This makes a definite decision between (17) and (18), on n.m.r. grounds alone, rather hazardous although the olefinic proton present in the dimer exhibits even smaller coupling, consistent with allylic coupling in (18). The evidence, as a whole, would appear to suggest 4-(2-thiolanyl)-2,3-dihydrothiophen (18) as the more likely formulation. The proton resonance positions can then be assigned as shown below.

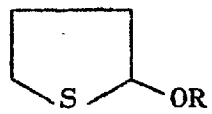


(a) τ 4.08
(b) τ 5.91
(c) τ 6.6-7.5
(d) τ 7.7-8.5

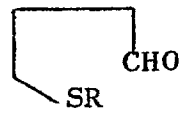
Although the acetate (16) underwent elimination when treated with acid, even at room temperature, it was successfully deacetylated by treatment with a catalytic amount of sodium methoxide in methanol. The resulting thiocyclic hemithioacetal (21) rapidly consumed iodine corresponding to one thiol group and underwent further slow oxidation, over ninety minutes, to an extent of ca. 10%. That (21) does not exist as the tautomeric 4-mercaptobutanal was shown by its i.r. spectrum, in which carbonyl absorption was absent. This was confirmed by n.m.r. spectroscopy which showed the hydroxyl (singlet, τ 7.14) and C-2 (multiplet, τ 4.46) protons, but no trace of any low-field aldehydic signal.

On treatment with α-naphthyl isocyanate in the presence of triethylamine, the hemithioacetal gave rise to the

O-urethane (22). That it was not the S-urethane (23), derived from 4-mercaptobutanal, can be seen from its n.m.r. spectrum which showed (a) a seven-proton complex, due to aromatic protons, at τ 1.7-2.7 (b) a broad one-proton signal, due to NH, at τ 3.0 (c) a one-proton signal at τ 3.67, due to a methine proton (d) a two-proton group at τ 6.8-7.3 (e) a four-proton group at τ 7.5-8.3. The alternative S-urethane would be expected to exhibit an aldehydic, rather than a methine, proton and only two 'normal' methylene protons, since four would then be subject to the deshielding influence of either the sulphur atom or the carbonyl function.

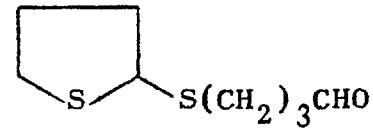


(21; R = H)



(23; R = α-naphthylcarbamoyl)

(22; R = α-naphthylcarbamoyl)



(24)

When 2-hydroxytetrahydrothiophen (21) was allowed to stand in a sealed tube for several weeks, two phases developed. It was found that an almost quantitative conversion into 4-[(2-thiolanyl)thio]butanal (24) had

occurred, presumably by dimerization of two molecules of 4-mercaptobutanal followed by the elimination of one molecule of water. Although the i.r. spectrum showed a strong carbonyl but no hydroxyl absorption and a molecular weight determination confirmed that dimerization had occurred, the structure of (24) is based largely on the evidence of the n.m.r. spectrum. This showed: (a) a one-proton multiplet, due to CHO, at τ 0.17 (b) a one-proton multiplet, due to S.CH.S, at τ 5.46 (c) a six-proton group, due to CH_2.S and CH_2.CO, at τ 6.7-7.6 (d) a six-proton group, due to C.CH_2.C, at τ 7.7-8.4. The dithioacetal (24) consumed two equivalents of iodine, about 80% immediately and the remainder over a period of fifteen minutes, which suggests that it undergoes a hydrolytic cleavage to 4-mercaptobutanal.

The dithioacetal (24) was also obtained, in low yield, when 2-hydroxytetrahydrothiophen (21) was chromatographed on silica gel.

On methylation with dimethyl sulphate and sodium hydroxide in tetrahydrofuran, the hemithioacetal (21) gave largely polymeric products. The presence of a prominent S-methyl peak (τ 7.96, singlet) in the n.m.r. spectrum showed methylation to have occurred on sulphur rather than on oxygen. Since this requires the hemithioacetal to react

in its open-chain form, it is not surprising that the aldehyde function should polymerize under the strongly basic conditions.

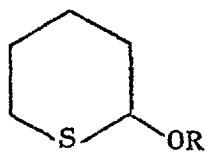
Tetrahydrothiopyran Series

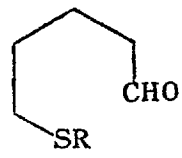
The commercially available cyclic sulphide was converted into its 2-acetoxy derivative (25) by the action of t-butyl peracetate in the presence of cuprous chloride, as previously described for 2-acetoxytetrahydrothiophen.

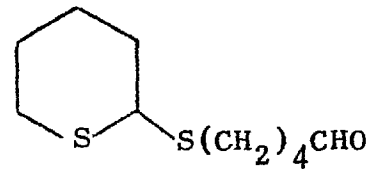
Deacetylation with sodium methoxide in methanol gave 2-hydroxytetrahydrothiopyran (26) as a waxy solid which rapidly liquified. The i.r. spectrum recorded, like the other data, within twenty minutes of distillation, showed a strong hydroxyl peak but negligible carbonyl absorption which suggests that there was little, if any, open-chain tautomer present. The absence of any aldehyde was confirmed by n.m.r. spectroscopy, which showed peaks due to the hydroxyl (τ 6.73, doublet, J = 0.5 c.p.s.) and C-2 (τ 5.08, triplet, J = 3 c.p.s.) protons. The hemithioacetal (26) rapidly consumed iodine corresponding to one thiol group and underwent further slow oxidation to an extent of ca. 10%.

Reaction with α-naphthyl isocyanate, in the presence of triethylamine, gave the O-urethane (27) rather than the

S-urethane (28) derived from 5-mercaptopentanal. This was indicated by the n.m.r. spectrum which showed: (a) a seven-proton group, due to aromatic protons, at τ 1.9-2.7 (b) a broad one-proton signal, due to NH, at τ 3.0 (c) a one-proton signal, due to a methine proton, at τ 4.06 (d) a two-proton group at τ 6.7-7.6 and (e) a six-proton group at τ 7.6-8.6. The alternative S-urethane would be expected to show an aldehydic proton at low-field, rather than the methine proton, and only four 'normal' methylene protons, since four would then be subject to the deshielding influence of either the sulphur atom or the carbonyl function.







(25; R = Ac) (29)

(26; R = H) (28; R = α-naphthylcarbamoyl)

(27; R = α-naphthylcarbamoyl)

Like its lower homologue (see p. 168), 2-hydroxy-tetrahydrothiopyran (26) was converted into a dithioacetal

merely on standing for several weeks. The i.r. spectrum showed a strong carbonyl but no hydroxyl absorption and a molecular weight determination confirmed that dimerization had occurred. The structure of 5-[(2-thianyl)thio]-pentanal (29) was confirmed by its n.m.r. spectrum which showed: (a) a one-proton multiplet, due to CHO, at τ 0.20 (b) a one-proton multiplet, due to S.CH.S, at τ 6.09 (c) a six-proton group, due to CH_2.S and C.CH_2.CO, at τ 6.8-7.8 (d) a ten-proton group, due to C.CH_2.C, at τ 7.8-8.8. This dithioacetal also consumed two equivalents of iodine, about 80% immediately and the remainder over a period of ten minutes, suggesting a hydrolytic cleavage to 5-mercapto-pentanal.

Thiepan Series

Thiepan (30) was synthesized from 1,6-dibromohexane by reaction with sodium sulphide in ethanol, using a simplified version of the method described by Müller and his co-workers[29], and converted into its 2-acetoxy derivative (31) by the action of t-butyl peracetate in the presence of cuprous chloride, as previously described for the lower homologues.

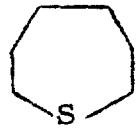
When (31) was deacetylated under the conditions employed for these, no pure compound could be isolated.

However, when the reaction period was decreased to eighteen hours, at ca. 5°, the hemithioacetal (32) was obtained in an almost quantitative yield. Like its oxygen analogue (33)[1], the hemithioacetal was found to have a melting-point varying with the exact history of the sample and to be surprisingly insoluble in most organic solvents. That a facile tautomeric equilibrium exists between the hemithioacetal and 6-mercaptohexanal was demonstrated by i.r. and n.m.r. spectroscopy, iodometric titration and mass spectrometry.

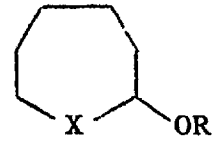
In the solid state (nujol mull), the hemithioacetal displayed a strong hydroxyl peak with negligible absorption in the carbonyl region, but this situation was completely reversed in solution as shown by the i.r. (in chloroform) and n.m.r. (in deuterochloroform) spectra. In methanolic solution, it rapidly consumed one equivalent of iodine without further slow oxidation. The mass spectrum is apparently consistent only with the presence of the cyclic tautomer since the molecular-ion ($^{m}/_{e}$, 132) initially decomposed by the loss of either H_2O (to $^{m}/_{e}$, 114) or CH_2OH (to $^{m}/_{e}$, 101).

The existence of a minute peak at $^{m}/_{e}$ 246 is the only evidence that 2-hydroxythiepan (32) undergoes a transformation

to a dimeric dithioacetal analogous to (24) and (29) since, even when it was allowed to stand for several months, there was little increase in the intensity of carbonyl absorption in the i.r. spectrum. This reluctance to dimerize may possibly be due merely to the decreased rate of diffusion in the solid, as compared with the liquid, state.



(30)



(31; X = S, R = Ac)

(32; X = S, R = H)

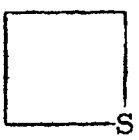
(33; X = O, R = H)

Although too insoluble in petroleum (b.p. 100-110°) to yield an α-naphthyl urethane, the hemithioacetal (32) did react with 3,5-dinitrobenzoyl chloride in pyridine. An i.r. spectrum of the product showed peaks at 2720, 1720 and 1665 $cm.^{-1}$ indicating that, as expected, it was the S-acyl derivative of 6-mercaptohexanal rather than the O-acyl derivative of (32).

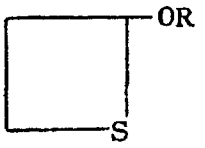
Thietan Series

The commercially available thietan (34) was treated with t-butyl peracetate in the presence of cuprous chloride, as described previously for its homologues. In this case, however, the yield of the desired product (35) was much lower. This may be a reflection of its inherent instability since a considerable involatile residue was obtained even when the initial distillate was further fractionated.

When 2-acetoxythietan (35) was deacetylated with sodium methoxide in methanol for three days at room temperature, only non-volatile material was obtained. Although a small quantity of distillate was collected when the reaction period was decreased to eighteen hours at ca. 5°, it was shown to contain both acetate and alcohol indicating that deacetylation was incomplete. Since the major product was, once again, involatile, it would appear that the rate of decomposition of the hemithioacetal (36) is comparable to the rate of its formation.



(34)



(35; R = Ac)

(36; R = H)

EXPERIMENTAL SECTION

For general notes, see the preface to the experimental section of Part I, p. 95.

Tetrahydrothiophen Series

2-Acetoxytetrahydrothiophen (E 567, 623, 719)

A 50% solution of t-butyl peracetate in benzene (62 ml., ca. 75% theoretical; kindly supplied by Laporte Chemicals Limited) was added over a period of 5 hr. to a refluxing solution of tetrahydrothiophen (27 ml.) and anhydrous cuprous chloride (80 mg.) in anhydrous benzene (70 ml.) under nitrogen. The solution was refluxed for a further 5 hr., cooled, diluted with ether (300 ml.) and extracted with 2N aqueous sodium carbonate solution. The aqueous layer was extracted with benzene (2 x 50 ml.) and the combined organic phases washed well with water, dried and evaporated. Distillation gave 2-acetoxytetrahydrothiophen (24.8 g., 73% based on the quantity of peracetate used), b.p. 66-70°/0.5 mm., n_D^{16} 1.4916, n_D^{20} 1.4891, $\nu_{max.}$ 1735 $cm.^{-1}$ (OAc); τ (in CCl_4) 8.02 (singlet, $COCH_3$), 3.93 (multiplet,H-2). Lit.[21] b.p. 60°/0.1 mm., n_D^{20} 1.4893.

Sosnovsky[21] reported a much poorer conversion of sulphide, presumably due to the use of a much smaller ratio of peracetate to sulphide.

Acidic hydrolysis of 2-acetoxytetrahydrothiophen (E 591, 593)

Method A: A mixture of 2-acetoxytetrahydrothiophen (1.0g.), concentrated hydrochloric acid (3 ml.) and water (18 ml.) was stirred under nitrogen for 2 hr. at 80°. The mixture was cooled, extracted with chloroform (5 x 20 ml.), and the extract washed with water, dried and evaporated. The residue showed $\nu_{max.}$ (CCl_4) 1710, 1630 and 1600 $cm.^{-1}$, but no absorption at 1735 $cm.^{-1}$. On distillation, it partly polymerized but also gave an oil, b.p. ca. 140° (bath)/0.5 mm., n_D^{22} 1.6040; $\nu_{max.}$ 1710 $cm.^{-1}$, much diminished. For the n.m.r. spectrum, see p. 165.

Method B: A mixture of 2-acetoxytetrahydrothiophen (1.0 g.), nitromethane (10 ml.), concentrated hydrochloric acid (0.5 ml.) and water (0.5 ml.) was stirred at room temperature for 20 hr., evaporated and extracted with chloroform. The solution was washed, dried and evaporated to give a residue identical, by TLC (silica gel, 10% ether in petroleum), to that obtained in the previous experiment.

Pyrolysis of 2-acetoxytetrahydrothiophen (E 769)

2-Acetoxytetrahydrothiophen (12.9 g.) was heated, under reflux, for 2 hr. at 150-160°. The mixture was cooled, diluted with ether (ca. 150 ml.) and extracted with 2N sodium hydroxide solution. The aqueous layer was washed with more ether and the combined organic phases washed with water (3 x 30 ml.), dried and evaporated. Distillation gave 4-(2-thiolanyl)-2,3-dihydrothiophen (3.16 g., 42%), b.p. 89°/0.1 mm., n_D^{24} 1.6008. See p. 165 for the n.m.r. spectrum (in CCl_4).

Berglund and Lawesson[23] prepared a dimer b.p. 88-90°/0.02 mm., n_D^{20} 1.6023 by the pyrolysis of 2-benzoyloxytetrahydrothiophen, but concluded it was 5-(2-thiolanyl)-2,3-dihydrothiophen. (See pp. 163-165).

2,3-Dihydrothiophen (E 793)

2-Acetoxytetrahydrothiophen (40 g.) was heated at 150°/765 mm. for 1 hr. and the volatile products were collected. The oil (ca. 4 g.), which separated when excess sodium carbonate solution was added to the mixture, was removed, washed with water, dried and distilled. The 2,3-dihydrothiophen had b.p. 43°/66 mm., n_D^{20} 1.5292. Lit.[26] b.p. 43°/67 mm., n_D^{24} 1.5288. For the n.m.r. spectrum (in CCl_4), see p. 166.

2-Hydroxytetrahydrothiophen (E 651, 723)

Sodium (200 mg.) was added to a solution of 2-acetoxy-tetrahydrothiophen (10.0 g.) in anhydrous methanol (100 ml.). The mixture was allowed to stand, under nitrogen, for 3 days at room temperature, then neutralized with solid carbon dioxide and evaporated. An ethereal solution of the residue was dried, filtered through kieselguhr, evaporated and distilled to give 2-hydroxytetrahydrothiophen (4.78 g., 67%), b.p. $63^{\circ}/0.5$ mm., n_D^{21} 1.5291. (Found: C, 46.2; H, 7.8%, M. 114. C_4H_8OS requires: C, 46.1; H, 7.7%, M, 104. Thiol-S: immediate, 30.8%; after $1\frac{1}{2}$ hr. continuous titration, 33.2%. Calc.: 30.8%). The i.r. spectrum recorded within 20 min. of distillation, as were the n.m.r. and analytical data, showed strong hydroxyl ($\nu_{max.}$ 3400 $cm.^{-1}$) but no carbonyl absorption. For the n.m.r. spectrum (in $CDCl_3$), see p. 167.

When carried out on a smaller scale (ca. 3 g. of the acetate), yields of greater than 80% were achieved.

4-[(2-thiolanyl)thio]butanal (E 607, 659, 685)

When 2-hydroxytetrahydrothiophen was allowed to stand in a sealed tube for several weeks, two phases developed. After eight weeks, the mixture was diluted with chloroform

and dried. The solution was evaporated and the residue distilled to give an almost quantitative yield of the dithioacetal, b.p. $110^{o}/10^{-4}$mm., n_D^{16} 1.5516; $\nu_{max.}$ 1720 $cm.^{-1}$ (CHO), hydroxyl absent. (Found: C, 50.5; H, 7.5; O, 8.4%, M, 203. $C_8H_{14}OS_2$ requires: C, 50.5, H, 7.4; O, 8.4%, M, 190. Thiol-S: immediate, 27%; after 15 min. continuous titration, 33.8%. Calc.: 33.7%). For the n.m.r. spectrum (in $CDCl_3$), see p. 169.

The same compound was obtained, in low yield, when 2-hydroxytetrahydrothiophen was passed through a column of silica gel.

2-(α-naphthylcarbamoyloxy)tetrahydrothiophen (E 617)

A mixture of 2-hydroxytetrahydrothiophen (245 mg., ca. 10% excess), α-naphthyl isocyanate (380 mg.), triethylamine (50 mg.) and petroleum (4 ml., b.p. 100-110°) was heated at 100° for 1 hr. with the exclusion of moisture. The resultant solid was filtered off after dilution of the mixture with light petroleum and extracted with boiling petroleum (40 ml., b.p. 100-110°). On cooling, the extract gave the urethane (280 mg., 46%), m.p. 128-131°, which was recrystallized from di-isopropyl ether to give an analytical sample, m.p. 131-134° (decomp.), $\nu_{max.}$ 1725 $cm.^{-1}$ (NH.CO.O) and

3460 $cm.^{-1}$ (NH). (Found: C, 66.0; H, 5.75; N, 4.9; S, 12.0. $C_{15}H_{15}NO_2S$ requires: C, 65.9; H, 5.5; N, 5.1; S, 11.7%). For the n.m.r. spectrum (in $CDCl_3$), see p. 168.

Methylation of 2-hydroxytetrahydrothiophen (E 731, 741)

Dimethyl sulphate (3.6 ml.) was added slowly, under nitrogen, to a stirred mixture of the hemithioacetal (1.50 g.), powdered sodium hydroxide (2.3 g.) and tetrahydrofuran (50 ml., peroxide-free) at 55-60°. After 22 hr. at 45-50°, water (20 ml.) was added, the temperature raised to 65-70°, and the solvents evaporated in a stream of nitrogen. The aqueous mixture was stirred for a further 1 hr. at 70°, cooled, and extracted with chloroform. The extract was washed, dried and evaporated to an oil which showed no hydroxyl nor carbonyl absorption in the i.r., but did exhibit S-methyl resonance in the n.m.r. spectrum (in CCl_4, see p. 169). On distillation at 10^{-4}mm., only a small quantity was collected, there being a large polymeric residue.

Tetrahydrothiopyran Series

2-Acetoxytetrahydrothiopyran (E 625, 627)

A 50% solution of t-butyl peracetate in benzene (20 ml.) was diluted with anhydrous benzene (40 ml.) and added over a

period of 4 hr., under nitrogen, to a stirred, refluxing mixture of anhydrous cuprous chloride (100 mg.), tetrahydrothiopyran (10.0 g.) and benzene (5 ml.). The solution was heated for a further 5 hr., cooled, diluted with ether (200 ml.) and washed with 2N sodium carbonate solution. The aqueous layer was extracted with more benzene and the combined organic phases washed with water (3 x 20 ml.), dried and evaporated. Distillation of the residue gave 2-acetoxytetrahydrothiopyran (7.98 g., 67% based on the quantity of peracetate used), b.p. 73°/0.3 mm., n_D^{17} 1.4947, $\nu_{max.}$ 1738 $cm.^{-1}$ (OAc); τ (in CCl_4) 7.95 (singlet, $COCH_3$), 4.23 (multiplet, H-2). (Found: C, 52.4; H, 7.5; S, 20.3. $C_7H_{12}O_2S$ requires: C, 52.5; H, 7.55; S, 20.0%).

2-Hydroxytetrahydrothiopyran (E 653, 747)

Sodium (100 mg.) was added to a solution of 2-acetoxytetrahydrothiopyran (4.74 g.) in anhydrous methanol (50 ml.). The reaction mixture was allowed to stand under nitrogen for 4 days, neutralized with solid carbon dioxide and evaporated to dryness. An ethereal solution of the residue was dried, filtered through kieselguhr, evaporated and distilled to give 2-hydroxytetrahydrothiopyran as a waxy solid which rapidly liquified (2.8 g., 80%), m.p. ca. 50°, b.p. 71°/0.3 mm., n_D^{18} 1.5320; $\nu_{max.}$ 3420 $cm.^{-1}$ (OH, very strong), carbonyl

absorption absent. (Found: C, 51.2; H, 8.2%; M, 134. $C_5H_{10}O_5S$ requires: C, 50.8; H, 8.5; M, 118. Thiol-S: immediate, 27%; after 10 min. continuous titration 31.95%. Calc.: 27.1%). For the n.m.r. spectrum (in $CDCl_3$), see p. 170.

5-[(2-thianyl)thio]pentanal (E 655, 681)

Six weeks after its preparation, 2-hydroxytetrahydrothiopyran was distilled to give an almost quantitative yield of 5-[(2-thianyl)thio]pentanal, b.p. $116^o/10^{-4}$mm., n_D^{19} 1.5441; $\nu_{max.}$ 1720 $cm.^{-1}$ (CHO), hydroxyl absent. (Found: C, 54.6; H, 7.9; O, 7.6%, M, 199. $C_{10}H_{18}OS_2$ requires: C, 55.0; H, 8.3; O, 7.3%; M, 218. Thiol-S: immediate, 23.5%; after 10 min. continuous titration, 30.9%. Calc.: 29.4%). For the n.m.r. spectrum (in $CDCl_3$), see p. 172.

2-(α-Naphthylcarbamoyloxy)tetrahydrothiopyran (E 749)

A mixture of 2-hydroxytetrahydrothiopyran (2.2 g., ca. 15% excess), α-naphthyl isocyanate (2.7 g.), triethylamine (ca. 100 mg.) and petroleum (35 ml., b.p. 100-110°) was heated at 110° for $2\frac{1}{2}$ hr., under nitrogen. The resultant solid was filtered off after dilution of the mixture with light petroleum and extracted with boiling petroleum (250 ml., b.p. 100-110°). The solution was evaporated and the residue

crystallized from a mixture of di-isopropyl ether and petroleum. The solid obtained (0.95 g., 21%) was recrystallized from chloroform-petroleum to give the pure urethane, m.p. 122-124° (decomp.), $\nu_{max.}$ 1725 $cm.^{-1}$ (NH.CO.O) and 3460 $cm.^{-1}$ (NH). (Found: C, 67.2; H, 5.8; S, 11.5. $C_{16}H_{17}NO_2S$ requires: C, 66.9; H, 6.0; S, 11.2%). For the n.m.r. spectrum (in $CDCl_3$), see p. 171.

Thiepan Series

Thiepan (E 693)

One solution of 1,6-dibromohexane (100 g.) in absolute ethanol (2 l.) and another of hydrated sodium sulphide (120 g.) in ethanol (2 l.) were added dropwise, with stirring, to refluxing ethanol (4 l.) at the rate of 400 ml. of each solution per day. [The sulphide solution was prepared freshly each day from sodium sulphide nonahydrate (24 g.) and ethanol (400 ml.)]. After the final addition, the mixture was refluxed overnight and evaporated to dryness. A solution of mercuric chloride (120 g.) in water (1500 ml.) was added to the distillate and the white precipitate filtered off. A mixture of this mercuric complex, sodium

hydroxide (80 g.) and water (1 l.) was steam distilled and the product isolated from the distillate as far as possible by physical separation, then by extraction with dichloromethane. Distillation of the dried material gave thiepan (24.55 g., 52%), b.p. 167°/755 mm., n_D^{19} 1.5134. Lit.[29] b.p. 173-174°, n_D^{20} 1.5137. The n.m.r. spectrum (in CCl_4) showed two groups of protons: (a) a four-proton signal at τ 7.2-7.5, due to $C.CH_2.S$ (b) an eight-proton signal at τ 7.9-8.5 due to $C.CH_2.C$.

This yield is equal to that obtained using a somewhat more complex method and much superior to the next highest ever recorded.[30]

2-Acetoxythiepan (E 721, 755)

A 50% solution of t-butyl peracetate in benzene (17 ml.) was diluted with more anhydrous benzene (30 ml.) and added over a period of 3 hr., under nitrogen, to a stirred and refluxing mixture of thiepan (10.0 g.), anhydrous cuprous chloride (100 mg.) and anhydrous benzene (30 ml.). After a further 6 hr., the mixture was cooled, diluted with ether (200 ml.) and extracted with 2N sodium carbonate solution (2x40 ml.). The aqueous phase was extracted with more benzene and the combined organic phases washed until neutral,

then dried and evaporated. Distillation gave 2-acetoxythiepan (7.57 g., 67% based on the quantity of peracetate used), b.p. 65°/0.08 mm., n_D^{24} 1.4974, n_D^{15} 1.5006. $\nu_{max.}$ 1740 $cm.^{-1}$ (OAc). The n.m.r. spectrum (in CCl_4) consists of four groups of protons: (a) a one-proton multiplet, τ 4.10, due to S.CH.OAc (b) a two-proton group, τ 6.8-7.5, due to $S.CH_2.C$ (c) an eight-proton group, τ 7.6-8.6, due to $C.CH_2.C$ (d) a three-proton singlet, τ 8.00, due to $CO.CH_3$. (Found: C, 55.2; H, 7.8; S, 18.7. $C_8H_{14}O_2S$ requires: C, 55.1; H, 8.1; S, 18.4%).

2-Hydroxythiepan (E 761, 765)

Sodium (50 mg.) was added to a chilled solution of 2-acetoxythiepan (2.0 g.) in anhydrous methanol (30 ml.). The solution was sealed under nitrogen and allowed to stand for 18 hr. at ca. 5°. The solution was neutralized with solid carbon dioxide and evaporated to dryness to give a powdery solid. This was washed by trituration with water (3 x 50 ml.) and dried over calcium chloride in vacuo. 2-Hydroxythiepan (1.41 g., 94%) had a m.p. over ca. 4° in the range 100-118° depending on the preparation and on the age of the sample. It was also surprisingly insoluble in most organic solvents, although a 'recrystallization' was achieved from ethyl acetate. The thiepanol showed

$\nu_{max.}$ (nujol), 3350 (OH, strong) and 1720 $cm.^{-1}$ (CHO, very weak); $\nu_{max.}$ (in $CHCl_3$, boiled and filtered solution) 1718 (CHO, very strong), 2720 (CHO) and 3600 $cm.^{-1}$ (OH, very weak). [Found: C, 54.2; H, 8.95; thiol-S, 24.4%; M (mass spect.) 132. $C_6H_{12}OS$ requires: C, 54.5; H, 9.15; thiol-S, 24.25%; M, 132]. The thiol titration, which gave both an immediate absorption and a sharp end-point, was carried out by disolving the compound in boiling methanol (ca. 1 mg. per ml.), cooling rapidly and titrating without added acid.

The action of 3,5-dinitrobenzoyl chloride on 2-hydroxythiepan (E 779)

A solution of 2-hydroxythiepan (0.5 g.) and 3,5-dinitrobenzoyl chloride (0.95 g.) in pyridine (10 ml.) was heated at 90° for 1 hr., cooled and poured into ice-water (200 ml.). The mixture was acidified with concentrated hydrochloric acid and extracted with chloroform. The extract was washed with water, sodium bicarbonate solution and water again, dried and evaporated. The residue was chromatographed on silica gel in chloroform to give a homogeneous syrup (230 mg.), $\nu_{max.}$ 3100 (aromatic CH), 2720 (CHO), 1720 (CHO), 1665 (thiolester), 1625 (aromatic), 1555 and 1350 $cm.^{-1}$ (NO_2). Although it was distilled on a micro-scale to give a syrup, b.p. 160-180° (bath)/ 3 x 10^{-4}mm., n_D^{22} 1.5812, the bulk completely decomposed on heating.

Thietan Series

2-Acetoxythietan (E 783)

A 50% solution of t-butyl peracetate in benzene (28.5 ml.) was diluted with more anhydrous benzene (50 ml.) and added over a period of 4 hr., under nitrogen, to a stirred and refluxing mixture of thietan (10.0 g.), anhydrous cuprous chloride (150 mg.) and anhydrous benzene (10 ml.). The mixture was heated for a further 6 hr., cooled, diluted with ether (300 ml.) and extracted with 2N sodium carbonate solution. The aqueous phase was extracted with benzene and the combined organic phases washed until neutral, then dried and evaporated. Distillation of the residue gave 2-acetoxythietan (4.48 g., 25% based on the quantity of peracetate used), b.p. 85-86°/20 mm., n_D^{23} 1.4855. $\nu_{max.}$ 1740 $cm.^{-1}$ (OAc). τ (in CCl_4) 4.18 (multiplet, H-2), 7.96 (singlet, $COCH_3$). (Found: C, 45.5; H, 6.05; S, 24.2. $C_5H_8O_2S$ requires: C, 45.4; H, 6.1; S, 24.3%).

Deacetylation of 2-acetoxythietan (E 787, 789)

Sodium (50 mg.) was added to a chilled solution of 2-acetoxythietan (1.62 g.) in methanol (10 ml.) and the mixture allowed to stand under nitrogen for 18 hr. at ca. 5°,

then neutralized with solid carbon dioxide and evaporated at 25°. The residue was dissolved in ether, dried, filtered through kieselguhr and evaporated. Distillation of the residual liquid gave an involatile polymeric semi-solid (ca. 1 g.) and a little liquid, b.p. 74-77°/16 mm., $\nu_{max.}$ 3450 $cm.^{-1}$ (OH) and 1740 $cm.^{-1}$ (OAc).

When the reaction period was increased, complete polymerization resulted.

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