

APPROACHES TO THE SYNTHESIS OF GLYCOSIDES

A thesis submitted by
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ABSTRACT

In a search for better synthetic routes to *O*- and *S*-glycosides, a number of mercury(II) containing derivatives of 1-thio- $\underline{\underline{D}}$ -glucose were synthesised, and their reactions with thiols and acids were investigated as well as their pyrolytic behaviour. A new route to *O*-acetylated glycosyl thiols involving specific *S*-deacetylation of peracetylated 1-thioglycoses was developed by the conversion of 1-thio- β - $\underline{\underline{D}}$ -glucopyranose pentaacetate into tetra-*O*-acetyl-1-*S*-phenylmercury(II)thio- β - $\underline{\underline{D}}$ -glucopyranose and subsequent demercuration of this by hydrogen sulphide.

A range of acylated alkyl and aryl 1,2-*trans*-1-thioglycosides was prepared by one step processes from peracylated 1,2-*trans*-related sugars by a procedure which involved the use of equimolar proportions of thiols together with boron trifluoride. A similar procedure was used to obtain benzoylated 1,2-*cis*-*O*-glucosides from penta-*O*-benzoyl- β - $\underline{\underline{D}}$ -glucopyranose.

Partial desulphurisation of acetylated glucosyl phenyl disulphide with tris(diethylamino)phosphine led to both phenyl tetra-*O*-acetyl-1-thio- α - $\underline{\underline{D}}$ -glucopyranoside and the α,β -linked thiotrehalose peracetate.

Phenyl 1-thiohex-1-enopyranosid-3-ulose esters were obtained from the light induced reactions of *N*-bromosuccinimide with acetylated and benzoylated phenyl 1-thiogluco- and galacto-pyranosides; the acetylated 1-thioglycosides gave mixtures of 2-*O*-acetyl and 2-*O*-monobromoacetyl 1-enosid-3-uloses. Methyl hexuronate derivatives were brominated α to the carbonyl function by *N*-bromosuccinimide, and a new synthetic route to $\underline{\underline{L}}$ -ascorbic acid has been proposed following the successful bromination of methyl tri-*O*-acetyl-2,6-anhydro- $\underline{\underline{L}}$ -gulonate.

CHAPTER ONE

INTRODUCTION

GENERAL INTRODUCTION

The work described in this thesis was undertaken with the general aim of finding better methods for the synthesis of *O*- and *S*-glycosides; of particular interest was the preparation of such compounds in their 1,2-*cis* configurations since the methods available when this work was initiated in 1972 were far from satisfactory.

As an understanding of the synthetic goals and of the synthetic methods already available is necessary for the design of possible new methods, the remainder of this chapter is devoted to a review of the relevant aspects of *O*- and *S*-glycosides.

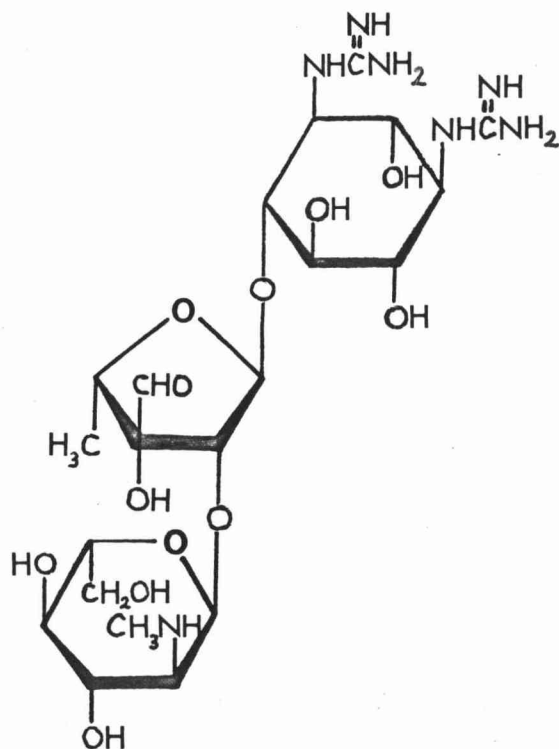
O-GLYCOSIDES

Introduction

O-Glycosides comprise one of the major groups of naturally occurring organic materials.¹ It is the *O*-glycosidic bond which links the monosaccharide units of oligo- and polysaccharides, these being regarded by convention as combinations of up to ten, and more than ten monosaccharide units respectively. *O*-Glycosides with non-carbohydrate aglycons are widely distributed in Nature, most frequently in plant material.^{2,3,4,5} Here the aglycon is often phenolic or steroidal, the phenolic group of compounds including the flavonoid glycosides which are the basis of many plant pigments, and the steroidal group of compounds including the physiologically important saponins, solanum alkaloids and cardiac glycosides. The sugar moieties of these plant glycosides can be either monosaccharides or oligosaccharides.

From the metabolic products of micro-organisms have come a number of important glycosides which exhibit antibiotic properties.⁶ The first of these to be discovered, in 1944, was streptomycin (1) (see below).

Unusual sugar units occur frequently in these compounds, and this is exemplified by streptomycin (1) which contains the amino-sugar 2-deoxy-2-(methylamino)- $\underline{\text{L}}$ -glucose and the branched-chain deoxy-sugar streptose, as well as the diaminocyclitol derivative streptidine.



streptomycin (1)

Oligosaccharides, as well as being bound to non-carbohydrate aglycons, occur free in Nature,⁷ and in this form have as their main biological role the provision of a soluble and thus biologically mobile energy source. Two important examples are the animal disaccharide lactose, which is the major carbohydrate component of mammalian milks, and the plant disaccharide sucrose, which as cane-sugar forms the basis of a large industry.

Natural polysaccharides are generally high molecular weight polymers.^{8,9} Starch and glycogen are the major storage forms of plants and animals respectively, while other polysaccharides are major structural components in plants (e.g. cellulose), insects and micro-organisms. Other macromolecules have been shown to contain carbohydrate sub-units

which are implicated in their biological roles; the blood group substances, for instance, are glycoproteins in which the carbohydrate constituents contribute to the immunological specificity of the different types.

The search for synthetic routes to these natural products and their analogues has been the greatest single challenge to carbohydrate chemists; several reviews of the extensive literature in this field have recently appeared.^{9,10,11,12} While the routes available for the synthesis of 1,2-*trans*-related-*O*-glycosides are generally satisfactory, those available for 1,2-*cis*-*O*-glycosides (generally α -glycosides) have until very recently been low yielding or unreliable. The problem of preparing 1,2-*cis*-*O*-glycosides has been described by Umezawa *et al.*,¹³ as the most important facing carbohydrate chemists, and work in this area has received added impetus from the recognition that 1,2-*cis*-*O*-glycosidic bonds are of widespread occurrence in natural antibiotics^{14,15} (for example, streptomycin (1) shown above).

Most approaches presently available for the synthesis of 1,2-*cis*-*O*-glycosides rely upon either the displacement of a group at C-1, or the suitable modification of a sugar unit after the glycosidic bond has been formed. The review which follows has been divided mainly into these two sections; a third class of reaction, the alkylation of anomeric hydroxy-groups, has been included so that this approach to the synthesis of *O*-glycosides may be compared to the alkylation of anomeric sulphydryl groups which is discussed in a later section on the synthesis of *S*-glycosides (p.32).

Ideally a satisfactory synthetic route should involve a high yielding condensation between equimolar proportions of a glycosylating agent and the alcohol from which the aglycon is derived, and it should result in a product with a desired ring size and anomeric configuration. It is with these criteria in mind that the presently available syntheses of 1,2-*cis*-*O*-glycosides are critically reviewed below.

The Available Syntheses of 1,2-*cis*-O-Glycosides

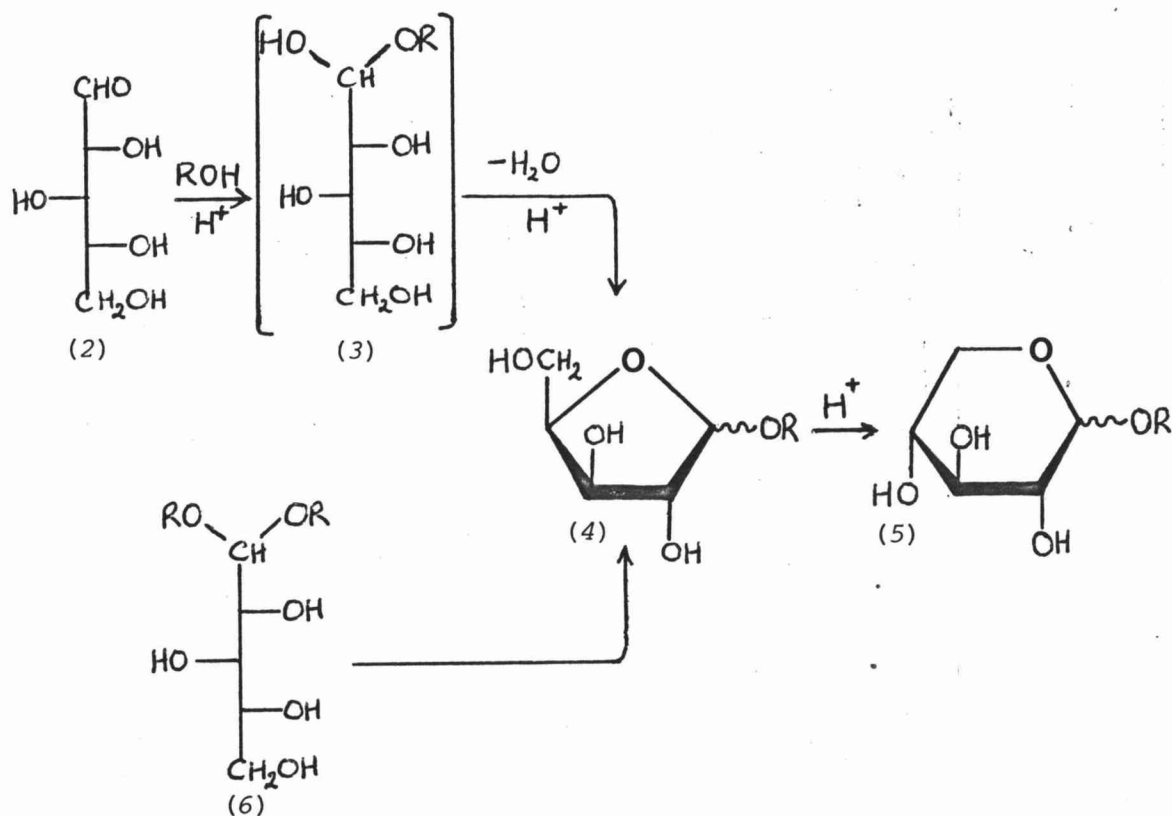
- A By Displacements of Groups from the Anomeric Centre
- A1 Intramolecular displacements

There are three approaches to glycoside synthesis, starting from the free sugar, the dialkyl acetal, or the dithioacetal, which, because they involve the ring closure of acyclic intermediates in the glycoside-forming steps, are appropriately classified in this section.

The most direct method of obtaining simple glycosides is by application of the acid catalysed alcoholysis of free sugars (the Fischer Synthesis)^{10,11} and while the reaction has been known for a long time, the mechanism has not yet been fully elucidated. The most likely glycosidation step appears to be the cyclisation of an acyclic hemiacetal intermediate [e.g. (3) in Scheme 1, which depicts the alcoholysis of D-xylose (2)]. The anomeric furanosides (4) are formed as kinetically controlled products. Initially the 1,2-*cis*-furanoside is the major product, but rapid anomerisation of this causes the thermodynamically more stable 1,2-*trans*-furanoside to become the preponderant product by the time a significant proportion of the free sugar has been converted into glycosides. If the reaction is allowed to continue anomeric pyranosides (5) are formed as the thermodynamically favoured products of the reaction.

While this method has been used as a main route to the furanosides (the anomers can be separated by chromatography on anion exchange resins), and while it is ideal for the synthesis of several specific pyranosides (e.g. methyl α -D-glucopyranoside, for which this method is the basis of the commercial preparation), it is severely restricted by the need to employ the alcohol as solvent, and the fact that the product mixtures contain furanosides and pyranosides in both anomeric forms.

Dialkyl acetals [such as that of xylose (2) in Scheme 1] give furanosides (4) in an acid catalysed ring closure analogous to that postulated in the Fischer Synthesis.¹¹ However in this case the faster rate of conversion of starting material to furanoside permits the 1,2-*cis*-furanoside to be the preponderant product at a stage when most of



Scheme 1

the acetal has reacted.¹⁶ This advantage does not seem to have been exploited preparatively, presumably because the preparation of the dialkyl acetals requires several moderately yielding steps.

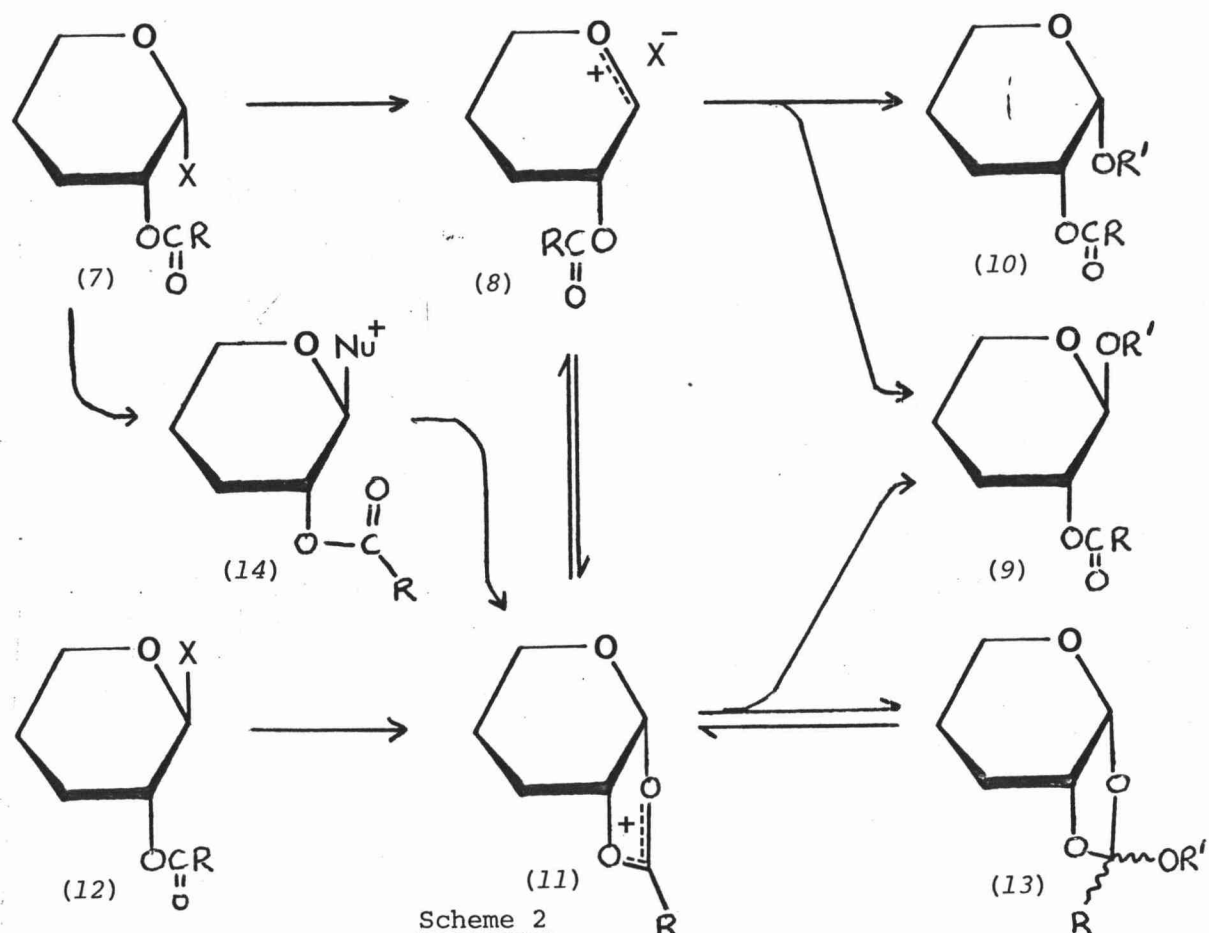
For most sugars (with the definite exception of D-glucose) the mercury (II) ion assisted alcoholysis of the dialkyl dithioacetals in neutral conditions is a further method involving a ring closure step, this time of a monothioacetal derivative, which yields the anomeric glycofuranosides. Unfortunately the preponderant anomer is always the 1,2-*trans*-glycofuranoside.¹⁷ This reaction and the mechanism involved is discussed in greater detail in a later section on thioglycoside synthesis (p. 24).

A2 Intermolecular displacements in the presence of participating groups at C-2

A2a The use of acylated glycosyl halides and orthoesters:

Because of their reactivity and the fact that they give products of specific ring size, the acylated glycosyl halides are amongst the most important glycosylating agents. The acetylated or benzoyleated glycosyl bromides or chlorides are most commonly used, the iodides being too reactive, and the fluorides too stable.

Alkyl and aryl glycosides can be prepared using the condensation of an acylated glycosyl halide either with an alcohol or phenol in the presence of silver, mercury or cadmium salts (the Koenigs-Knorr Synthesis), or with an alkali metal salt of a phenol (the Michael Synthesis) but both processes are limited in the sense that they generally lead to 1,2-*trans*-glycosides.^{11,12} The characteristics of glycosylation reactions with acylated glycosyl halides are discussed with reference to Scheme 2. For simplicity, in this and other schemes in the Introduction, the substituents on positions other than C-1 and C-2 of the pyranoid structures have been omitted. Also, it can be assumed that similar schemes can generally be drawn to represent the reactions of furanoid derivatives.



Acylated 1,2-*cis*-glycosyl halides (7) generally react by unimolecular processes to give the intermediates (8), however the halide ion probably shields the side of the pyranoid ring from which it departs since the products are usually 1,2-*trans*-glycosides (9). 1,2-*cis*-Glycosides (10) can be produced in varying and unpredictable but nevertheless synthetically useful amounts, along with the 1,2-*trans*-isomers, by the use of highly polar solvents (acetonitrile, nitromethane) and catalysts having strongly complexing anions (mercury (II) bromide and cyanide).¹² These reaction conditions presumably stabilize the glycosylation (8) sufficiently to allow nucleophilic attack by alcohol from both sides of the pyranoid ring. Competitive formation of the acetoxonium ion intermediate (11) probably also occurs under these conditions, but not at a rate sufficient to preclude synthesis of the 1,2-*cis*-glycoside.

In glycosylations with acylated 1,2-*trans*-glycosyl halides (12) the acyloxy group at C-2 generally participates in the displacement of the halide ion, giving the acyloxonium ion intermediate (11). Nucleophilic attack on this by the alcohol then affords mainly the 1,2-*trans*-glycoside (9), but under some conditions it can also give the 1,2-orthoester (13). The 1,2-orthoesters themselves are useful glycosylating agents, giving 1,2-*trans*-glycosides (9) via the regeneration of the acyloxonium ion intermediates (11).¹²

Acylated glycosyl halides rarely undergo displacement reactions which show 2nd order kinetics. However, the use of some insoluble silver compounds in certain solvents (particularly diethyl ether) causes the absorption of the 1,2-*cis*-glycosyl halide (7) and permits the direct conversion of this into a 1,2-*trans*-glycoside (9) by reaction with an alcohol in a concerted "push-pull" mechanism.^{12,18,19}

The analogous S_N2 reactions of acylated 1,2-*trans*-glycosyl halides should lead to 1,2-*cis*-glycosides, but although Lemieux and Hayami²⁰ recognised conditions under which tetra-*O*-acetyl- β -D-glucopyranosyl chloride underwent nucleophilic attack much faster than it dissociated with C-2 acetoxy group participation, no further investigations have since been reported. That this is so must be due to the fact that acylated 1,2-*trans*-glycosyl halides are difficult to prepare and isomerise under mild reaction conditions,⁹ as they generally have their C-1 halogens

equatorially disposed, and are thus thermodynamically less stable than their 1,2-*cis* counterparts. This is an example of the influence of the "anomeric effect",²¹ which stabilizes an electronegative substituent on C-1 in the axial relative to the equatorial orientation, and this effect is of major importance in the design of glycosylation reactions.

A bimolecular mechanism is also indicated in the formation of orthoesters (13) from acylated 1,2-*cis*-glycosyl halides (7). Intermediates of type (14) can be produced by employing strongly nucleophilic solvents which cannot form strong bonds (e.g. collidine, tetrahydrofuran), and these intermediates can be converted via the acyloxonium ion intermediates (11) to the orthoesters (13).

Until recently the preparation of 1,2-*cis*-glycosides from acylated 1,2-*cis*-glycosyl halides under the conditions described above, although requiring the separation of mixtures of anomers, was the best available method,¹² and it has been utilized in particular for the synthesis of many 1,2-*cis*-disaccharides. Generally however acylated glycosyl halides and 1,2-orthoesters, for the reasons outlined above, are more suited to the preparation of 1,2-*trans*-glycosides.

A2b The use of peracylated sugars

The C-1 acyloxy group of a peracylated sugar can be specifically displaced with the aid of an acid catalyst. For similar reasons to those outlined for acylated glycosyl halides, displacements of the acyloxy-groups by alcohols or phenols lead mainly to 1,2-*trans*-glycosides, but in the acidic conditions subsequent anomerisation may occur to yield 1,2-*cis*-glycosides.

A fusion method, using phenols to obtain acylated aryl glycosides, was introduced by Helferich and Schmitz-Hillebrecht²². When zinc chloride or toluene-*p*-sulphonic acid are used as the acid catalysts, acylated aryl 1,2-*trans*-glycosides are the usually isolated products, but unless optimum conditions are found anomerisation occurs and both anomers are produced. A longer heating time with zinc chloride favours the anomerisation to the thermodynamically stable acylated aryl 1,2-*cis*-

glycoside.¹¹ Other acid catalysts (e.g. phosphorous oxychloride, sulphuric acid, tin(IV) chloride, aluminium chloride and boron trifluoride) have been successfully used to yield the 1,2-trans-anomers.¹¹

The extension of this method to the preparation of alkyl glycosides has received scant attention. The volatility of the lower aliphatic alcohols rules out a fusion reaction, and only reactions in inert solvents have been reported. Zemplen²³ used ferric chloride in chloroform to catalyse the reactions of octa-O-acetyl- α -cellobiose (and -maltose) with approximately equivalent amounts of ethanol, and claimed the production of ethyl hepta-O-acetyl- α -cellobioside (and -maltoside) as crude, poorly characterised solids. Lemieux and Shyluk,²⁴ from the reaction of equivalent amounts of penta-O-acetyl- β -D-glucose and methanol in chloroform or benzene solution in the presence of 0.5 or more equivalents of tin(IV) chloride, isolated 50-60% yields of methyl tetra-O-acetyl- β -D-glucopyranoside. The unfractionated product contained, in addition to the β -glucoside (62%), α -acetochloroglucose (16%), no detectable penta-O-acetyl- α -D-glucose, and undoubtedly some α -glucoside in the highly dextro-rotatory remaining fraction.

Peracylated sugars offer advantages in that they are readily obtained starting materials, but their use in 1,2-cis-glycoside synthesis has been limited by the high proportions of 1,2-trans-glycosides generally produced under the applied conditions.

A3 Intermolecular displacements in the presence of non-participating groups at C-2

A3a The use of glycosyl halides

It should be possible to obtain 1,2-cis-glycosides from 1,2-trans-glycosyl halides providing that neighbouring group participation from the substituent on C-2 can be eliminated, and that the displacement at C-1 of halide ion by alcohol can occur with a Walden inversion.

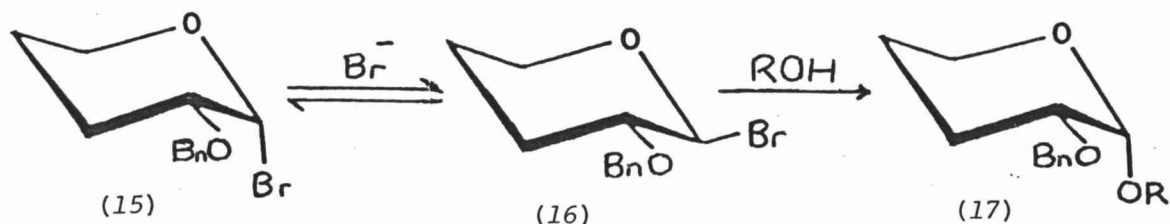
The benzyl ether group is the most widely used non-participating group, because benzylated derivatives are readily prepared and the group is quite chemically stable. The only disadvantage in using benzyl

ether groups is that their removal can only be accomplished under mild conditions by catalytic hydrogenation, a technique which can be time consuming and difficult.²⁵

When benzylated 1,2-*cis* or 1,2-*trans*-glycosyl halides are treated with alcohols under typical S_N1 conditions (e.g. solvolysis in the presence of soluble silver salts²⁶), mixtures of anomeric glycosides are obtained, the yields of 1,2-*cis*-glycosides being generally only moderate.¹² However, in combination with conditions which promote S_N2 reactions (e.g. non-polar solvents, insoluble silver salts), benzylated 1,2-*trans*-glycosyl halides yield 1,2-*cis*-glycosides as predicted. Unfortunately, considerable quantities of 1,2-*trans*-glycosides can be produced concurrently due to the isomerisation of the starting material to its more stable 1,2-*cis*-anomer before reaction with alcohol. A variety of other non-participating groups on C-2 (e.g. nitrate, hydroxy, trichloroacetoxy, and chlorosulphate) have been of some value in 1,2-*cis*-glycoside synthesis in further examples of this approach.

Preparatively, 1,2-*trans*-glycosyl halides are difficult to obtain free of their 1,2-*cis*-anomers, and as mentioned before they isomerise readily during reaction. Thus the most satisfactory approach so far developed for the synthesis of 1,2-*cis*-glycosides is the "halide ion catalysed glycosidation reaction". Ishikawa and Fletcher²⁷ reported that the anomeric 2-*O*-benzylated glycosyl bromides are brought into facile equilibrium by the catalytic effect of added bromide ions. Although the equilibrium mixture obtained contains largely the 1,2-*cis*-glycosyl bromide (15) due to the "anomeric effect", the 1,2-*trans*-anomer (16) is considerably more reactive, and under methanolysis conditions Ishikawa and Fletcher found the reaction to proceed largely via the 1,2-*trans*-anomer (16) with inversion at C-1 to give the methyl 1,2-*cis*-glycoside (17, R=CH₃) (See Scheme 3).

Lemieux and co-workers²⁸ developed general conditions for the halide ion catalysed glycosidation, in which a 1,2-*cis*-glycosyl halide in dichloromethane containing equimolar proportions of ethyl diisopropyl amine (to prevent the solution becoming acidic) and tetraethylammonium



Scheme 3

bromide (as catalyst), reacts with an equimolar proportion of an alcohol to give almost exclusively the 1,2-*cis*-glycoside. They then applied the method to highly efficient syntheses of a number of important oligosaccharides.^{29,30}

That this method is applicable relies upon the fact that the 1,2-*trans*-glycosyl halide is considerably more reactive than the corresponding 1,2-*cis*-anomer. This is a result of the "anomeric effect" (i.e. participation from the lone pair electrons of the ring oxygen) which not only lowers the relative ground state energy of the 1,2-*cis*-anomer, but also specifically stabilises the intermediate involved in 1,2-*cis*-glycoside formation.²⁸

One problem with the halide ion catalysed glycosidation procedure is that the reactions of benzylated glycosyl chlorides with alcohols at room temperature are extremely slow, and even those with the more reactive bromides are relatively slow. The limitation that the interconversion of the anomeric glycosyl halides must occur at a substantially greater rate than the glycosidation reaction, has meant that attempts to increase the reaction rate by heating or by using electrophilic metal salts result in decreased specificity for the 1,2-*cis*-glycoside.

A3b The use of glycosylating agents having other electronegative leaving groups

The rate of glycosidation reactions has been increased by

converting benzylated glycosyl chlorides or bromides into the more reactive triflates,^{31,32} iodides,³³ tosylates,^{32,34} *p*-bromophenylsulphonates³² and mesylates.³⁵ Some success has been achieved in obtaining 1,2-*cis*-glycosides from these derivatives; in the case of the iodides and tosylates, anomerisation to and then reaction from the 1,2-*trans*-anomers appears to occur in a manner analogous to that proposed for the halide ion catalysed glycosidation (Section A3a). However, the high reactivity of these derivatives makes them difficult to work with, and the ready intervention of reactions either from the 1,2-*cis*-anomers or via glycosyl carbonium ions generally ensures that the products contain 1,2-*trans*-glycosides.

The hydroxy-group at C-1 of 2,3,4,6-tetra-*O*-benzyl- α -D-glucose can be activated by *p*-nitrobenzenesulphonylation³⁶ or chlorodiphenylsilylation.³⁷ Displacement reactions lead to 1,2-*trans*-glycosides mainly, and as yet no analogous 1,2-*trans*-1-hydroxy-sugars are available for attempting 1,2-*cis*-glycoside synthesis.

Recently Kochetkov and co-workers³⁸ investigated the reaction of the *p*-nitrophenate anion with trimethylsilylated 1,2-*cis*-glucosyl phosphate, and observed initial formation of the 1,2-*trans*-glucoside and its subsequent anomerisation to the 1,2-*cis*-glucoside. Because phosphate is employed as the leaving group in biosynthetic pathways, and because 1,2-*cis*-glycosides are readily produced in Nature, this approach may hold further interest in the future.

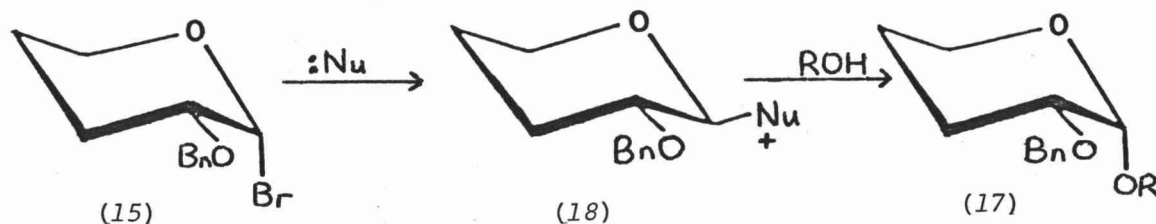
At present no electronegative leaving group can offer any advantage over bromide, when the latter is coupled with halide ion catalysis, for the synthesis of 1,2-*cis*-glycosides.

A3c Exploitation of the "reverse anomeric effect".

One problem inherent in attempting to use a 1,2-*trans*-glycosylating agent bearing a strongly electronegative equatorial leaving group is that it is less thermodynamically stable than its 1,2-*cis*-anomer due to the "anomeric effect" and thus extensive anomerisation often occurs before and during a displacement reaction.⁹ Positively charged substituents on C-1, however, are stabilised in the equatorial position by both steric and electrostatic effects, the latter being called the "reverse anomeric effect".⁹ Scheme 4 depicts the attempts made to

take advantage of these effects in glycoside synthesis.

Benzylated 1,2-*cis*-glycosyl bromides (15) have been successfully treated with powerful nucleophiles such as tertiary amines and phosphines to give 1,2-*trans*-onium compounds (18). Methanolysis of the ammonium salts gives methyl 1,2-*cis*-glycosides (17; R=CH₃) in good yield in an overall double inversion from the bromides (15),⁴⁰ but disappointingly the phosphonium and ammonium salts have proved too unreactive to be of value for glycosylating equimolar proportions of complex alcohols, and the specificity for the 1,2-*cis*-glycoside (17) is generally low under anything other than optimized conditions.^{41,42}



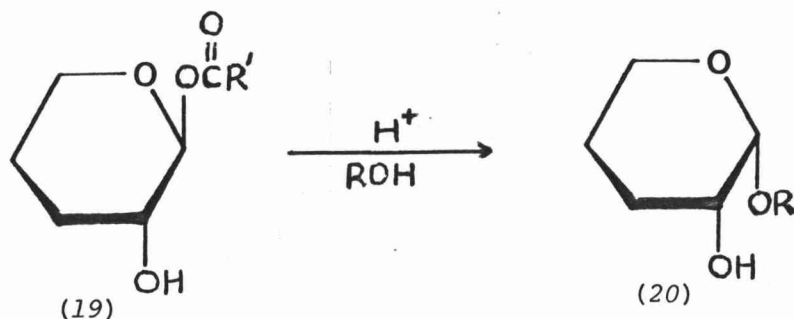
Scheme 4

A3d Acid assisted displacements

Helferich and co-workers⁴³ have shown that 1,2-*trans*-1-*O*-acyl-glycopyranoses (19) are alcoholysed with inversion at C-1 to 1,2-*cis*-glycosides (20) using methanesulphonic acid as catalyst to assist the displacement of the acyloxy group (Scheme 5). It was also found that tetra-*O*-acetyl-1-*O*-benzoyl and mesitoyl- β -D-glucopyranose both give methyl α -D-glucopyranoside upon methanolysis with the same catalyst, which is consistent with the removal of the acetyl protecting groups having occurred faster than the subsequent displacement reaction at C-1.⁴⁴

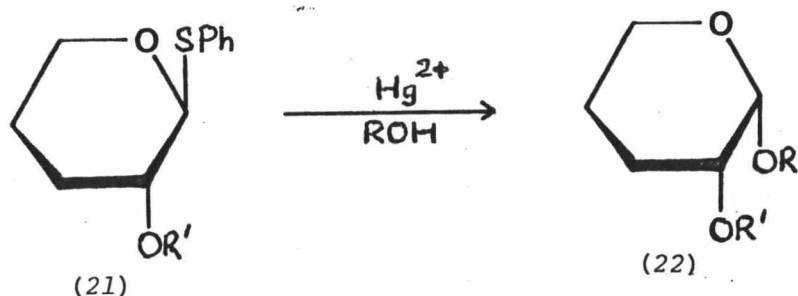
The reaction has only been reported under alcoholysis conditions,

and subsequent or concomitant anomerisation occurs under the acidic reaction conditions to give the equilibrium mixtures of the 1,2-*cis* and 1,2-*trans*-anomers in much the same way as if the free sugars had been used (see p.4).



Scheme 5

Ferrier and co-workers⁴⁵ have developed a much more promising approach using the specific Lewis acid affinity of mercury (II) ions for divalent sulphur. Thus 1,2-*cis*-glycosides (22) are obtained with fairly high specificity by condensing equimolar proportions of alcohols and the readily available phenyl 1,2-*trans*-1-thioglycosides (21) in the presence of mercury (II) ions (Scheme 6).



Scheme 6

The unprotected derivatives (21, R'=H) can be used with simple

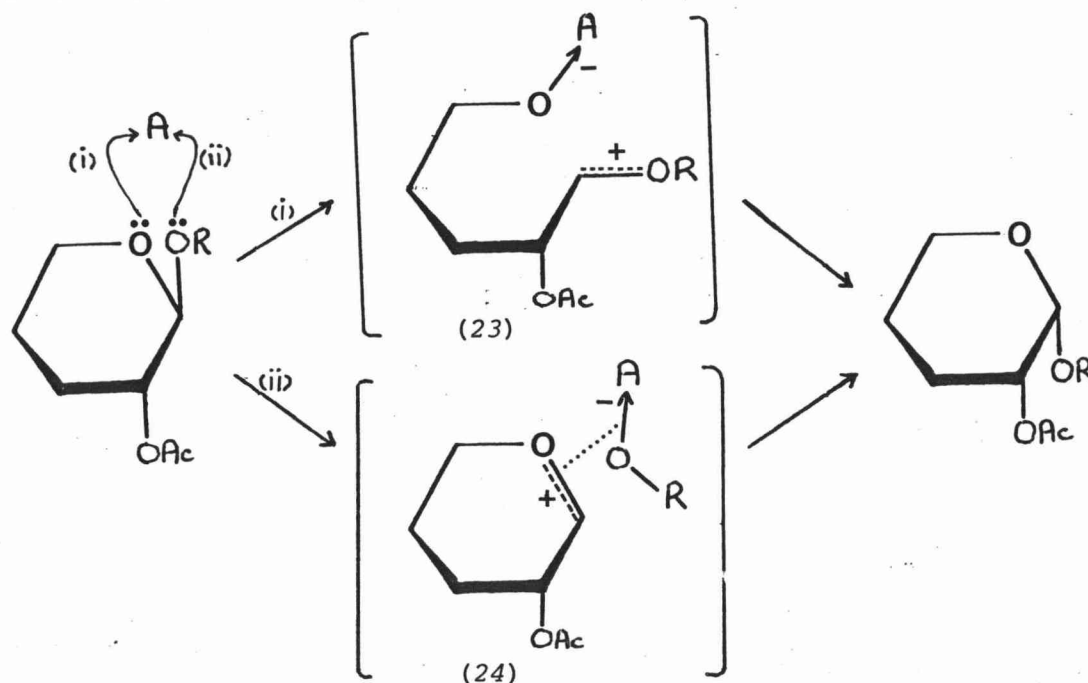
alcohols, but benzylated derivatives (21, $R'=\text{CH}_2\text{Ph}$) must be used for condensations with more complex alcohols.

Acetylated derivatives (21, $R'=\text{COCH}_3$) do not readily undergo reaction under these conditions.

B By Modifications of Available Glycosides

B1 Anomerisations

The readily synthesised acylated alkyl 1,2-*trans*-glycosides are often the thermodynamically unfavoured anomers, and in the presence of an acid catalyst can be made to give an equilibrium mixture from which the 1,2-*cis*-anomers can be isolated in good yield. While the mechanism of such anomerisations has been conclusively shown to be intramolecular,⁴⁶ two alternatives have been proposed (Scheme 7). Lindberg⁴⁷ postulated cleavage of the C-1 to ring oxygen bond to give the acyclic intermediate (23), whereas Lemieux⁴⁸ suggested the formation of the ion-pair (24) by cleavage of the C-1 to alkoxy-group bond. Both intermediates can collapse to either of the anomeric glycosides.



Scheme 7

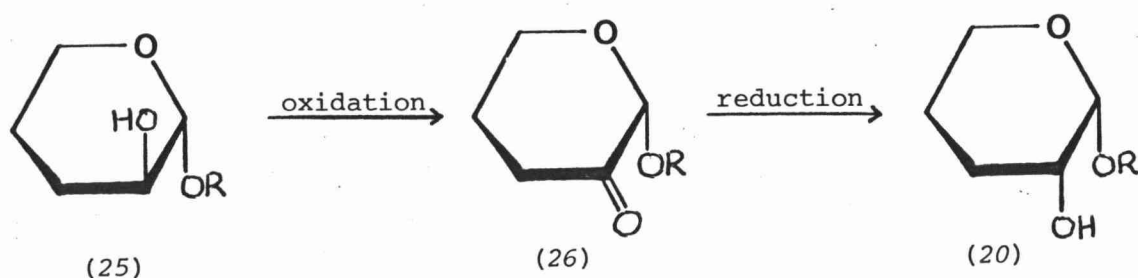
The "anomeric effect", which favours the glycoside with an axial alkoxy-group at C-1, in many cases ensures that the desired acylated 1,2-*cis*-glycoside is present to the extent of 80 to 90% in the equilibrated mixture. Peracetylated 1,2-*trans*-glycosides have been anomerised in chloroform or benzene solution using a variety of acid catalysts, but the Lewis acids titanium tetrachloride^{49,50} and boron trifluoride^{51,52} have found most general use. Acetylated disaccharides with $\beta(1\rightarrow6)$ linkages can be anomerised into the $\alpha(1\rightarrow6)$ linked anomers by this method.^{53,54} It appears that benzoylated glycosides are more readily anomerised than their acetylated analogues,⁵⁵ and this fact is exploited in this thesis (p. 56).

Aryl 1,2-*trans*-glycosides are generally resistant to anomerisation under the conditions employed in the previous examples,⁴⁶ although phenyl tetra-*O*-acetyl- α -D-glucopyranoside has been obtained in 25% yield by treating its β -anomer in chloroform with antimony pentachloride.⁵⁴ Anomerisations of aryl glycosides can best be achieved during their synthesis from peracetylated sugars under fusion conditions, as has been mentioned (p. 8).

B2 Reductions of glycosid-2-uloses

A number of 1,2-*cis*-glycoside syntheses have been developed recently which rely upon the stereoselective reduction of a 2-keto-function. This approach has been used to epimerise glycosides in which a 1,2-*trans*- linkage has been established by traditional methods, and in which the C-2 hydroxyl could be specifically deprotected. Thus oxidation of a 1,2-*trans*-glycoside (25) followed by stereoselective reduction of the glycosid-2-ulose (26) leads to the 1,2-*cis*-glycoside (20) (Scheme 8). Several oligosaccharides containing α -D-glucosyl and β -D-mannosyl bonded units have been synthesised in good yield from α -D-mannosyl and β -D-glucosyl anomers in this manner.^{56,57}

Lemieux and co-workers⁵⁸ have developed an effective 1,2-*cis*-glycoside synthesis which makes use of the *cis*-directing influence of the C-2 nitroso-substituent in glycosylation reactions. As shown

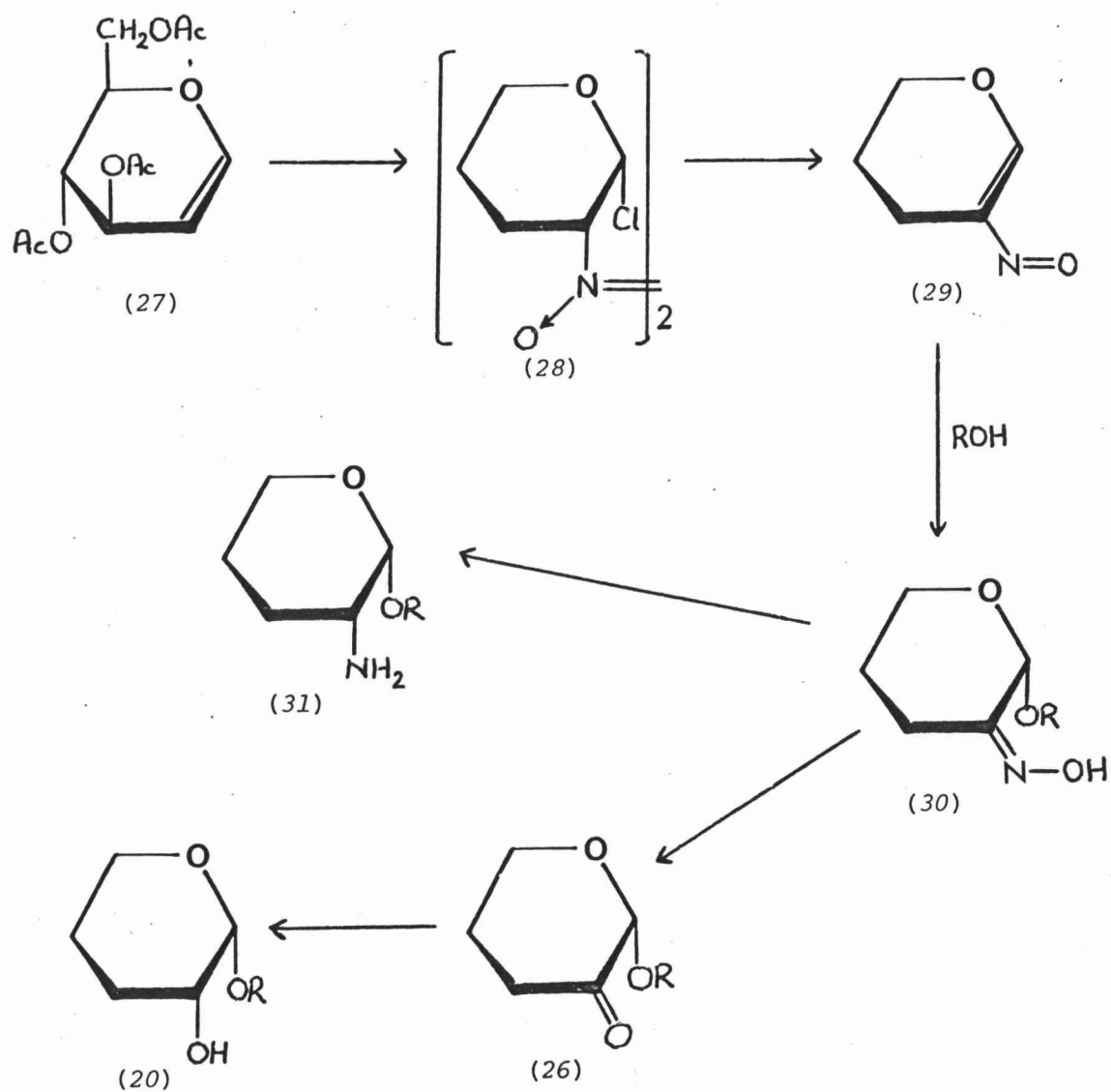


Scheme 8

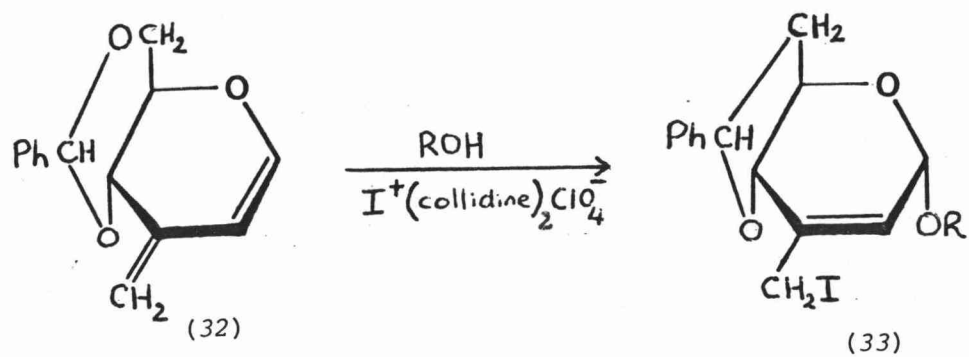
in Scheme 9, nitrosyl chloride adds to the readily available glycals (e.g. (27), tri-*O*-acetyl- $\underline{\underline{D}}$ -glucal) to give the dimeric 2-deoxy-2-nitroso-glycosyl chlorides (28). These can be used to glycosylate even complex alcohols in dimethylformamide at room temperature by a process which involves elimination to give the intermediate (29) followed by 1,4-addition of alcohol. The 2-oximino- α - $\underline{\underline{D}}$ -glycosides (30) are obtained in high yield, and the excellent stereospecificity achieved is regarded as being due to stereoelectronic effects; steric effects from the nitroso-group and electronic effects from the ring oxygen.⁵⁹ The 2-oximino-derivatives (30) can be readily converted into the glycosid-2-uloses (26).

Suitable stereospecific reductions of the 2-oximino- and 2-keto-groups of derivatives (30) and (26) would provide routes to the 1,2-*cis*-2-amino-2-deoxy-glycosides (31) and the 1,2-*cis*-glycosides (20) respectively. Highly stereoselective methods have been developed to generate the α - $\underline{\underline{D}}$ -gluco configuration from 2-keto- and 2-oximino- α - $\underline{\underline{D}}$ -arabino-precursors, and several disaccharides including analogues of the kanamycin antibiotics have been synthesised in this way. At this stage, however, the methods available to reduce certain derivatives are still of low stereospecificity; thus α - $\underline{\underline{D}}$ -lyxo-hexopyran-2-ulosides give mixtures of α - $\underline{\underline{D}}$ -galactosides and α - $\underline{\underline{D}}$ -talosides.⁵⁸

In a novel but complex synthesis of sucrose, Iley and Fraser-Reid⁶⁰ also employed the stereoselective reduction of a glycosid-2-ulose to get a 1,2-*cis*-glucopyranoside. It is interesting to note that they



Scheme 9



Scheme 10

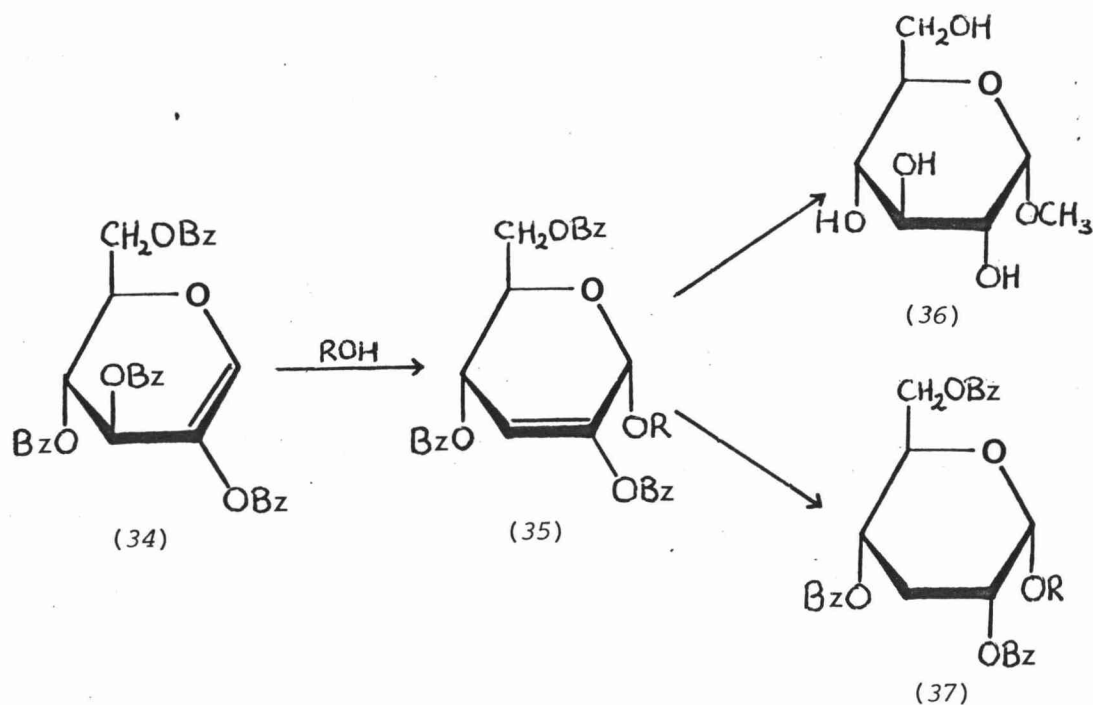
established their α -D-glucosidic bond in an earlier step involving a 1,4-addition to the diene (32) in which they claim stereoelectronic control ensures predominant formation of the α -D-glycoside (33) (Scheme 10). This bears a close analogy to the above work of Lemieux and co-workers. Removal of the 3-C-iodomethyl group of (33) via decarbonylation, and subsequent *cis*-hydroxylation of the 2,3-double bond gave an α -D-mannoside. The required α -D-glucoside was then obtained by the epimerisation of the C-2 hydroxyl.

B3 Modifications of 2,3-unsaturated glycosides

Both D-glycal and 2-hydroxy-D-glycal esters undergo rearrangement reactions in the presence of alcohols and with borontrifluoride as acid catalyst to give 2,3-unsaturated glycosides with predominantly the α -D-configuration. Although the products of 1,2-additions to D-glycal esters have found use in the synthesis of 2-deoxy- α -D-glycosides,¹⁰ these will not be considered here.

The 2-hydroxy-D-glycal esters hold some promise for the synthesis of 1,2-*cis*-glycosides. Ferrier *et al.*⁶¹ condensed tetra-O-benzoyl-1-deoxy-D-arabino-hex-1-enopyranose (34) with equimolar proportions of alcohols to get the 2,3-unsaturated glycoside (35) in largely the α -D-configuration (Scheme 11). It has been mentioned¹⁰ that methyl α -D-glucopyranoside (36) can be obtained via hydroboration of the methyl glycoside (35, R=CH₃), but this procedure has not been fully developed. Alfredsson and Garegg⁶² similarly obtained a 2,3-unsaturated glycoside (35, R = a monosaccharide derivative) from which they obtained the 3-deoxy- α -D-glycoside (37) on catalytic hydrogenation.

The stereospecificity of the formation of the α -D-glycosidic linkage by this method is only fair, and better stereoselective conditions for additions to the 2,3-unsaturated bond are needed before a wider use of this approach can be expected.



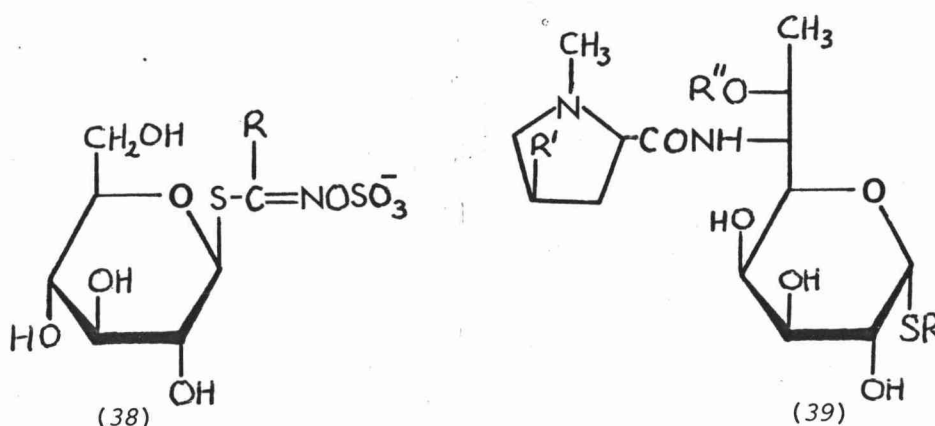
Scheme 11

C By Alkylations of Anomeric Hydroxy - Groups

There are relatively few reports on the direct alkylation of 1-hydroxy -glucoses leading to 1,2-*cis*-glycosides. It might seem that the alkylation of a suitably protected 1,2-*cis*-1-hydroxy-glucose would lead to a 1,2-*cis*-glycoside. Peralkylation conditions, and even more specific conditions however give, at best, anomeric mixtures of glycosides or 1,2-*trans*-glycosides.¹⁰ That this is so is presumably an indication of the facility with which glycoses anomerise under most reaction conditions, and that 1,2-*trans*-glycoses which usually have equatorial hydroxy -groups at C-1 undergo alkylation much faster than the 1,2-*cis*-glycoses which usually have axial hydroxy -groups at C-1.

S-GLYCOSIDESIntroduction

In contrast to the widespread occurrence of *O*-glycosidic bonds in Nature, relatively few compounds with *S*-glycosidic bonds have been reported. The glucosinolates, (38) derivatives of 1-thio-D-glucose where R can be a wide variety of substituents, constitute the largest class of natural thioglycosides. They are found most frequently in plants of the *Cruciferae* family which includes many important food plants (e.g. cabbage).⁶³



Lincomycin [(39), R = methyl, R' = propyl, R'' = H] and celesticetin [(39), R = 2-(salicyloxy)-ethyl, R' = H, R'' = methyl] are the metabolic products of two different micro-organisms of the *Streptomyces* family, and they are important, commercially produced antibiotics.^{64,65} Lincomycin analogues in which the methylthio-group is replaced by an ethylthio- or butylthio-group can be obtained by modifying the micro-organism's fermentation medium, and these modified compounds show slightly enhanced activities.^{66,67} It would thus be desirable to have good synthetic routes to the 1,2-*cis*-1-thioglycosides so that further modified antibiotics of this type could be obtained. It is also desirable that a variety of phenyl 1-thioglycosides should be readily

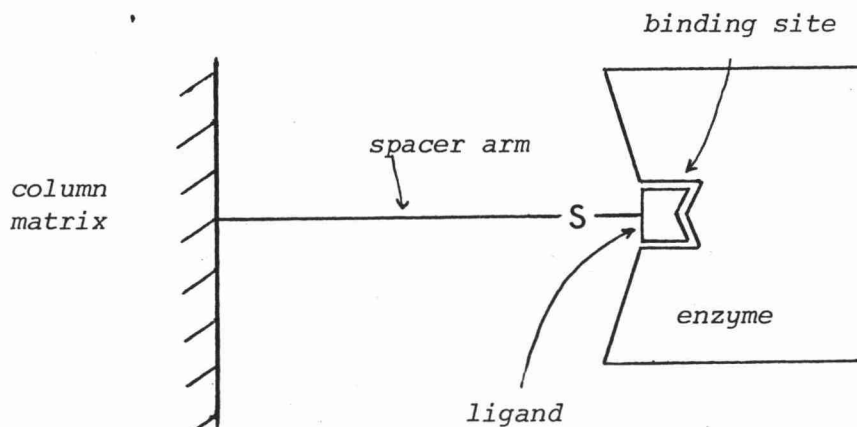
available because of their use in a potentially versatile synthesis of *O*-glycosides (see p. 14).

Thioglycosides and their synthetic availability are also of importance in several areas of biochemical research. The property of thioglycosides which has led to the majority of biochemical applications is their action as competitive glycosidase inhibitors - that is, they are substrate analogues which retain the binding properties of the substrates but not their susceptibility to catalytic cleavage.⁶⁸⁻⁷² It is a direct consequence of the substitution of sulphur for oxygen at the anomeric centre that *S*-glycosides show a greater resistance to both enzymic and acid catalysed hydrolysis than do *O*-glycosides.^{73,74}

Thioglycosides have been found to induce the production of glycosidases by micro-organisms,^{75,76} and the synthesis of thioglycosides for use in the study of this phenomenon has been reported.⁷⁷ A series of *n*-alkyl 1-thio- β -D-xylopyranosides has also been synthesised,⁷⁸ and used in a systematic study of β -D-xylosidase specificity;⁷⁹ simple thioglycosides have been used in a recent investigation of a membrane transport system,⁸⁰ and a 1-thio- β -D-xyloside with a diazoketone group in the aglycon, suitable for photolytic generation of a carbene, has been synthesised for the purpose of labelling the active site of a glycosidase.⁸¹

Work in this University⁸² on the enzymes of the gut of *Halotis iris* (the New Zealand Paua) required the purification of glycosidase components by affinity chromatography. Widespread interest in this method of enzyme purification appears to have stemmed from the work of Cuatrecasas et al.^{83,84} Enzymes are chromatographed on a gel consisting of an inert polymeric meshwork (column matrix) to which bio-specific ligands are covalently attached, usually via "spacer arms". The majority of immobilised ligands used to date have been competitive enzyme inhibitors,⁸⁵ and the use of a thioglycoside as an immobilised ligand should allow the specific retention of the related glycosidase on the column (Scheme 12).

An example of β -galactosidase purification using the above approach has appeared,⁸³ but in an excellent critical review of bio-affinity chromatography O'Carra⁸⁵ has revealed this to be an example of



Scheme 12

non-biospecific affinity chromatography, the binding being due to the hydrophobic spacer arm rather than the immobilized ligand; two similar reports of *N*-acetylhexosaminidase purification^{71,72} may also be subject to the same censure.

The ligands required for such affinity chromatography are thus thioglycosides substituted in their aglycons with reactive groups which permit their subsequent attachment to a matrix support. The preparation of such thioglycosides has received some attention, and all the major synthetic routes to be reviewed later in this chapter have been used. The functional groups most commonly employed have been those of aromatic^{68,70-72,78,86} or aliphatic^{86,87} primary amines, although a number of alkyl⁸⁸ and aryl⁸⁹ 1-thio- β -D-galactopyranosides substituted in the aglycon with a variety of reactive groups have been reported.

The methods that are presently available for the synthesis of 1-thioglycosides adopt similar approaches to those for the synthesis of related *O*-glycosides and they will be reviewed similarly. Differences between the methods for *O*- and *S*-glycoside synthesis are due mainly to the greater nucleophilicity of thiols than alcohols and of thiolate anions than alkoxide anions, and the fact that bivalent sulphur has an affinity for "soft" acids such as mercury (II) ions while oxygen has an affinity for "hard" acids such as protons. The need for a variety of 1,2-*cis*- and 1,2-*trans*-1-thioglycosides is apparent from the above considerations, and so the available syntheses of these compounds are critically reviewed below.

The Available Syntheses of 1,2-*cis* and 1,2-*trans*-1-Thioglycosides

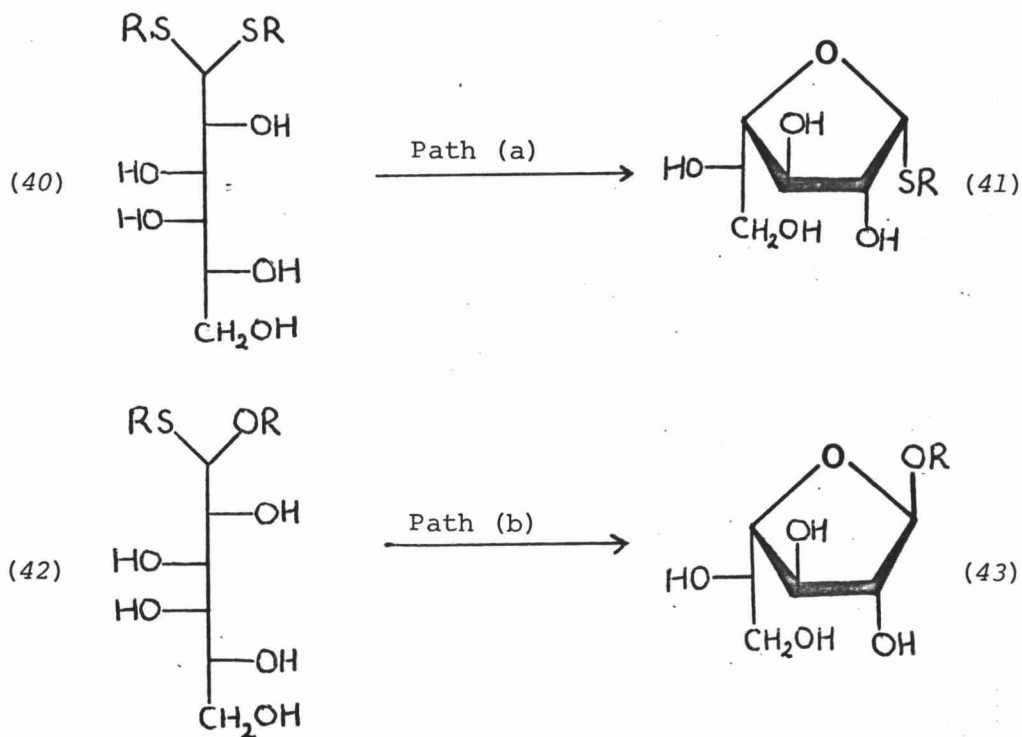
- A By Displacements from the Anomeric Centre
 A1 Intramolecular displacements

As shown in Scheme 13 for derivatives of D-galactose, the mercury (II) ion assisted displacement of an alkylthio-group from C-1 of the acyclic dithioacetal (40) can occur either with intramolecular participation from the C-4 hydroxy-group to give the thiofuranoside (41), or with intermolecular participation from the solvent to give the monothioacetal intermediate (42) which can subsequently give either the furanoside (43) (in alcohol) or the free sugar [(43), R = H] (in water) by a further mercury (II) ion assisted ring closure. Why path (a) should lead to a 1,2-*cis*-anomer and path (b) to a 1,2-*trans*-anomer is not yet understood.

It can be readily appreciated that the balance between competing inter- and intramolecular displacements is likely to vary between different sugars. With most sugars (e.g. galactose, mannose and xylose) the intermolecular pathway is at least significant and the isolation of 1,2-*cis*-1-thioglycofuranosides by this approach is difficult at best.^{17,20} Glucose, however, is an exception and this approach does represent a general route to the 1-thio- α -D-glucofuranosides.

Modifications of this approach using non-participating solvents may prove valuable. Ethyl 5-*O*-benzoyl-1-thio- β -D-arabinofuranoside has been prepared in 67% yield by a mercury (II) ion assisted ring closure reaction in acetone,⁹¹ and phenyl 1-thio- α -D-glucofuranoside has been directly isolated in 31% yield after a similar reaction in acetonitrile.⁹² The extent to which this modification is applicable however, remains undetermined.

A related approach has been used to obtain several 1,2-*cis*-1-thio-glycopyranosides. It is sometimes possible to isolate these products from the mixtures obtained when free sugars,⁹⁴⁻⁹⁸ their dithioacetals^{96,99,100} or their 1-thiofuranosides¹⁰¹ are brought into equilibrium with thiols and concentrated hydrochloric acid. Although D-mannose derivatives appear particularly liable to form 1-thiopyranosides,⁹⁵



Scheme 13

the isolable yields in these reactions are generally low, and sometimes preparative chromatography is necessary for the separation of anomeric mixtures. The only reason such a difficult approach has found such frequent use is that 1,2-*cis*-1-thioglycopyranosides are not easily obtained in any other way.

A2 Intermolecular displacements in the presence of participating groups at C-2

A2a The use of acetylated glycosyl halides

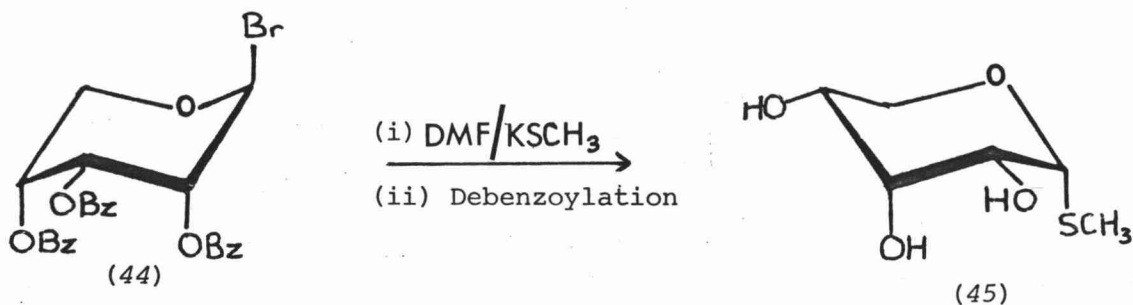
The reaction of an acylated 1,2-*cis*-glycosyl halide with an alkali metal salt of a thiol, for the same reasons discussed in the corresponding section on *O*-glycoside synthesis (page 6) generally leads to a 1,2-*trans*-1-thioglycoside. The first syntheses using this approach were reported by Fischer and Delbruck¹⁰² and by Schneider et al.,¹⁰³ who prepared acetylated aryl and alkyl 1-thio-β-D-glucopyranosides respectively from tetra-*O*-acetyl-α-D-glucopyranosyl bromide. Improvements developed by Purves¹⁰⁴ rendered the reaction homogeneous and ensured the stability of the acetyl protecting groups under the reaction conditions. The

method then allowed the direct synthesis in good yield of many 1,2-*trans*-1-thioglycopyranosides from the peracetylated sugars without isolation of the intermediate glycosyl bromides, and at present this constitutes the major route to such thioglycosides.

The disadvantages in this approach are the intermediacy of reactive and sometimes quite unstable glycosyl halides, and the possibility of competing elimination reactions which could occur on treating these with base (i.e. thiolate anions); both of these factors are of particular concern for furanosyl derivatives.

The analogous reactions of acylated 1,2-*trans*-glycosyl halides in protic solvents also lead to 1,2-*trans*-1-thioglycosides¹⁰⁵ (see p. 7). However, 1,2-*cis*-1-thioglycosides are obtained from bimolecular displacement reactions when the nucleophilicity of the thiolate anions is enhanced by the use of dipolar aprotic solvents, which are effective in the order HMPT (hexamethyl phosphoric triamide) > DMF (dimethyl formamide) > acetone.¹⁰⁶

One difficulty with this approach is the poor accessibility and low stability of many acylated 1,2-*trans*-glycosyl halides (p. 7). Tri-*O*-benzoyl- β -D-ribofuranosyl bromide (44) is an exception; on treatment with sodium methanethiolate in DMF followed by debenzoylation it gave only methyl 1-thio- α -D-ribofuranoside (45) (Scheme 14).⁹⁷ The first report of an analogous use of a thermodynamically unfavoured halide was made by Tejima and co-workers¹⁰⁷ who condensed tetra-*O*-acetyl- β -D-glucopyranosyl chloride with potassium benzyl and methyl xanthates in acetone, but the derivatives of 1-thio- α -D-glucose that they subsequently obtained were reported in unspecified yields.



Scheme 14

Bannister⁶⁵ has made use of the fact that the unstable 1,2-*trans*-glycosyl bromide is the initial product formed in the reaction of bromine with either anomer of an acetylated alkyl 1-thioglycoside in an inert solvent. Glycosyl halides prepared in this way were then treated with thiourea in dipolar aprotic solvents and the isothiuronium salts obtained were converted into anomeric mixtures of the acetylated methyl 1-thioglycosides by the method of Cerny and co-workers (see p. 32). That the 1,2-*cis*-anomers were present in these mixtures to the extent of only 35% at best (when HMPT rather than DMF was used as solvent) is presumably because of the lower nucleophilicity of thiourea in comparison to thiolate anions generally.

From the few reports discussed above it would seem that 1,2-*cis*-1-thioglycosides might be available from appropriate application of these procedures, and further examination of this hypothesis is being undertaken, but will not be reported here.

A2b The use of peracylated sugars

The methods already described for obtaining *O*-glycosides from peracylated sugars involving the specific displacements of anomeric acyloxy-groups with the aid of acid catalysts (see p. 8) have been adapted to the synthesis of *S*-glycosides, and again the 1,2-*trans*-anomers are the major products obtained.

The fusion procedure developed by Helferich and Schmitz-Hillebrecht¹¹ for the preparation of aryl glycosides was first extended to the preparation of aryl 1-thioglycosides by Hurd and Bonner.¹⁰⁸ By heating penta-*O*-acetyl- β -D-glucopyranose with thiophenol (5 mol. equiv.) and toluene-*p*-sulphonic acid (ca. 0.05 mol. equiv.) at 100° for 1 hour they obtained phenyl tetra-*O*-acetyl-1-thio- β -D-glucopyranoside, but only in 14% yield. They found zinc chloride to be an even less successful acid catalyst. Other workers have since reported the use of fusion reactions to permit the preparation in satisfactory yield of anomeric mixtures containing mainly the acetylated *p*-nitrophenyl 1,2-*trans*-1-thioglycosides.^{68,69,98} Isolation of the minor 1,2-*cis*-1-thioglycosides has been achieved on some occasions by preparative chromatography before⁶⁸ or after^{98,109} deacetylation of the crude products.

A modified approach which employs the thiol as solvent is suitable for the preparation of simple alkyl 1-thioglycosides. The use of ethanethiol as solvent and zinc chloride as acid catalyst has permitted the synthesis of the acetylated ethyl 1,2-*trans*-1-thio-glycopyranosides of glucose,^{110,111} galactose,¹¹⁰ mannose,¹¹¹ xylose¹¹² and maltose¹¹³ in good yield from the peracylated sugars in their 1,2-*trans*-configurations. Lemieux and Brice^{110,111} reported that the rate of reaction was much slower when the peracylated sugars in their 1,2-*cis*-configurations were used, although they claim that the major products were still the 1,2-*trans*-1-thioglycosides. However, their report¹¹¹ that negligible ethyl tetra-*O*-acetyl-1-thio- β -D-mannopyranoside was produced in the ethanethiolysis of penta-*O*-acetyl- β -D-mannopyranose was disputed^{90,114} when the α - and β - anomers were isolated in 32% and 14% yield respectively in a repetition of the reported experiment. That the 1,2-*trans*-glycosyl acetate is more reactive under these circumstances is primarily due to the anchimeric assistance supplied by the C-2 acetoxy-group in the displacement of the C-1 acetoxy-group; also, when the C-1 acetoxy-group is equatorial, the reactivity of this anomer is additionally enhanced by its higher ground-state energy.

Brigl and Schinle¹¹⁵ found, when attempting ethanethiolyses using hydrochloric acid as catalyst, that too rapid deacetylation of the penta-*O*-acetyl-D-glucopyranoses occurred, and that the penta-*O*-benzoyl-D-glucopyranoses were unreactive under the conditions.

A further modification to this general approach is the use of inert solvents. Benzene, chloroform-dichloromethane, or ether were used in various zinc chloride catalysed syntheses of the anomeric forms of 2-methylprop-2-yl 1-thio-D-glucopyranoside and -pyranoside, but in each reaction a large excess of thiol was employed.¹¹⁶ Bose and co-workers^{117,118} reported that the stannic chloride catalysed reaction of a peracetylated sugar with the appropriate arylthiol (2 mol. equiv.) in boiling benzene was suitable for the preparation of the anomeric phenyl, *p*-tolyl, and σ -nitrophenyl tetra-*O*-acetyl-1-thio-D-glycopyranosides of glucose and galactose; they crystallised the 1,2-*trans*-anomers in moderate to poor yields, and isolated the 1,2-*cis*-anomers in low yields by preparative chromatography. Further improvements using this modification of the acid catalysed thiolysis of peracylated sugars to prepare 1,2-*trans*-1-thioglycosides are reported in this thesis (p. 50).

A2c The use of 1,2-anhydro-derivatives

In alkaline solution a C-2 hydroxy-group can participate in the displacement of a *trans*-related leaving group from C-1 with the formation of a 1,2-anhydro-intermediate; this has similar stereochemical consequences to those observed for C-2 acyloxy-group participation (p. 7). Thus when Baker and co-workers⁹¹ treated an anomeric mixture of 3,5-di-*O*-benzoyl-D-arabinofuranosyl chlorides with sodium ethanethiolate in ethanethiol they obtained, after debenzoylation, only ethyl 1-thio- α -D-arabinofuranoside. Jennings¹¹⁹ similarly invoked the intermediacy of 1,2-anhydro-derivatives in the formation of ethyl 1,2-*trans*-1-thioglycosides from the chlorosulphated 1,2-*trans*-D-lyxo- and xylo-pyranosyl chlorides upon treatment with sodium ethanethiolate and iodide in methanol; rapid initial removal of the chlorosulphate protecting groups would be expected under these conditions.

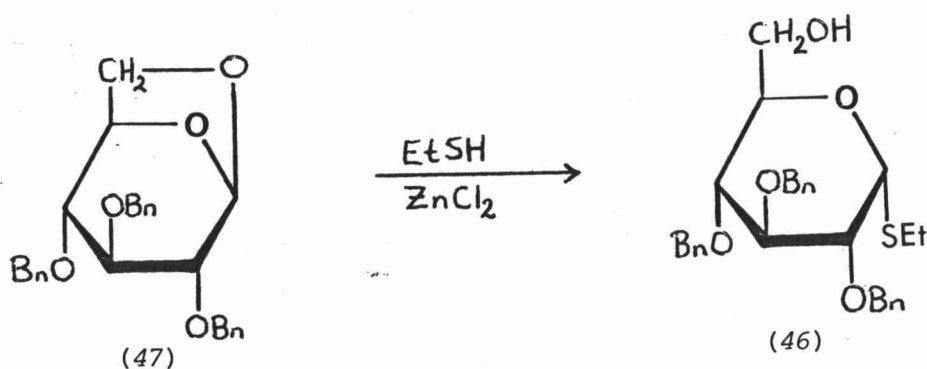
Brigl's anhydride (3,4,6-tri-*O*-acetyl-1,2-anhydro- α -D-glucose) gave only the 1,2-*trans*-product on treatment with ethanethiol and zinc chloride.¹¹⁴ In contrast its reaction with thiophenol alone followed by acetylation gave both anomers of phenyl tetra-*O*-acetyl-1-thio-D-glucopyranoside;¹²⁰ C-6 acetoxy-group participation or the intermediacy of a glycosyl cation may be involved in this case.

A3 Intermolecular displacements in the presence of non-participating groups on C-2

The removal of protecting groups from benzylated 1-thioglycosides appears unlikely to constitute a viable route to the unprotected 1-thioglycosides because the normal debenzylation procedures, such as catalytic hydrogenation, also cause desulphurisation. However the use of simple alkyl thio-groups as temporary, specifically displaceable protecting groups for the anomeric centre, in conjunction with the use of benzyl ether groups for hydroxy-functions, has received some attention.^{121,122} Also, benzylated phenyl 1-thioglycosides are required for the synthesis of complex *O*-glycosides by the method of Ferrier et al.⁴⁵ (see p. 14).

While derivatives suitable for the above uses can sometimes be obtained by the benzylation of 1-thioglycosides⁴⁵ prepared by the other routes discussed in this chapter, the application of methods analogous to those used to prepare benzylated *O*-glycosides (see p. 9) will probably prove a more versatile approach. Thus Anderson and co-workers¹²¹ have prepared partially and fully benzylated derivatives of phenyl and 3-phenylpropyl 1-thio- β -D-glucopyranoside by condensing 1,2-*cis*-glycosyl bromides and chlorides with thiolate anions; the reaction therefore appears to occur predominantly with inversion at C-1.

Zen and co-workers¹²² prepared ethyl 2,3,4-tri-*O*-benzyl-1-thio- α -D-glucopyranoside (46) by treating 1,6-anhydro-2,3,4-tri-*O*-benzyl- β -D-glucopyranose (47) with zinc chloride in ethanethiol (Scheme 15). This derivative, after the C-6 hydroxy-group has been protected by *p*-nitrobenzoylation, can be used to generate a glycosyl bromide (through reaction with bromine, see p. 27) which is suitable for the synthesis of (1 \rightarrow 6) linked oligosaccharides.¹²²



Scheme 15

While the C-2 hydroxy-group can act as a participating group in some situations (p. 29), this can be avoided by the use of acetone as solvent to enhance the nucleophilicity of the thiolate anion (p. 26); thus Tejima and co-workers¹⁰⁷ were able to isolate products with a 1,2-

cis-configuration after acetylating the products from the reactions of 3,4,6-tri-*O*-acetyl- β -D-glucopyranosyl chloride with potassium thiolacetate and potassium benzyl and methyl xanthate. However the relative difficulty of preparing suitable glycosyl chlorides with free C-2 hydroxy-groups makes this approach one of little appeal.

- B By Modifications of Available Compounds Having *S*-Glycosyl Units
 B1 Anomerisations

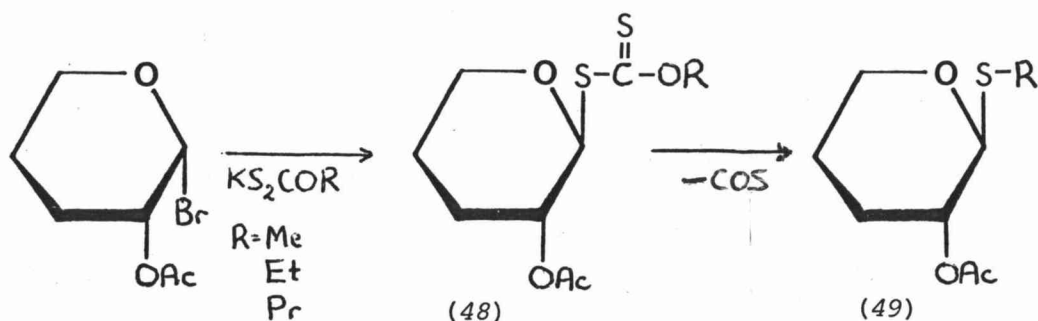
The anomerisation of acylated alkyl 1,2-*trans*-glycosides has provided a useful route for the preparation of simple 1,2-*cis*-*O*-glycosides (see p. 15). The "anomeric effect" in *S*-glycosides is similar to, though somewhat smaller than, that in *O*-glycosides,¹²³ presumably because of the fact that sulphur is both larger and less electronegative than oxygen. However, relatively few examples have been reported where anomerisation has been used to prepare a 1,2-*cis*-1-thioglycoside. Ferrier and co-workers¹¹² used titanium tetrachloride in chloroform to anomerise ethyl tri-*O*-acetyl-1-thio- β -D-xylopyranoside into a mixture containing 53% of the α -anomer; isolation of this required deacetylation and preparative chromatography. Mercury (II) bromide in boiling xylene has been used to catalyse the anomerisation of both 2-(tetra-*O*-acetyl-1-thio- β -D-glucopyranosyl)-4-phenyl-oxazole and -thiazole, and the α -anomers have been subsequently isolated in 30 and 5% yields respectively.¹²⁵

Because the "anomeric effect" is relatively less for *S*-glycosides, anomerised mixtures still contain significant proportions of the 1,2-*trans*-anomers, and hence it seems unlikely that this method could be developed into an efficient practical route to the 1,2-*cis*-1-thioglycosides. It has also been found that conditions capable of anomerising *O*-glycosides sometimes have no effect on the more acid stable *S*-glycosides.⁶⁵

- B2 Decompositions of glycosyl xanthates

Tejima and co-workers¹²⁶ found that under suitable conditions acetylated glycosyl xanthates (48) could be made to eliminate carbonyl sulphide to produce acetylated 1-thioglycosides (49) (Scheme 16), and

satisfactory results were obtained with the methyl, ethyl and benzyl esters. This new method of obtaining 1-thioglycosides provides an interesting alternative in that the aglycon (R) is provided initially in the form of an alcohol (ROH) which, for the synthesis of more complex examples, may be more readily available than the corresponding halide (RX) or thiol (RSH). At this stage the reaction has not been fully investigated as a potential synthetic method, but would seem to have interesting potential.



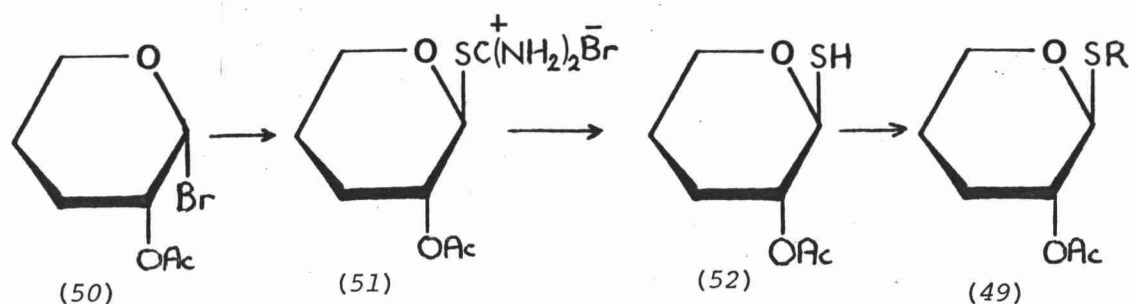
Scheme 16

C By Alkylations of Anomeric Sulphydryl Groups

The first examples of this approach were reported by Schneider and co-workers who obtained firstly ethyl 1-thio-β-D-glucopyranoside from the condensation of the sodium salt of 1-thio-β-D-glucopyranose with ethyl iodide,¹²⁷ and later methyl tetra-O-acetyl-1-thio-β-D-glucopyranoside from the methylation of tetra-O-acetyl-1-thio-β-D-glucopyranose with diazomethane.¹²⁸

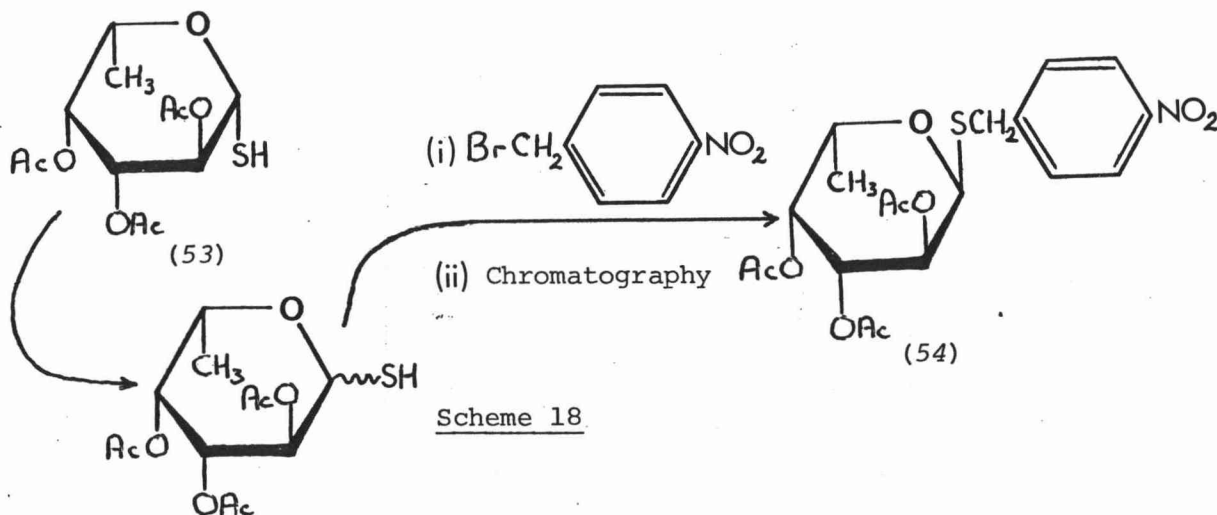
A general method incorporating this approach (Scheme 17) was developed by Cerny and co-workers, and it has been extensively used for the synthesis of alkyl and aryl 1,2-trans-1-thioglycosides (49). In this method acetylated 1,2-trans-glycosyl bromides (50) are condensed with thiourea to form isothiuronium salts (51) which are readily decomposed to acetylated 1,2-trans-glycosyl thiols (52) by the use of

aqueous sodium metabisulphite;¹²⁹⁻¹³² these thiols are then condensed with alkyl halides^{129,132} or aryl diazonium salts¹³³ to give 1-thioglycosides (49) in good yield.



Scheme 17

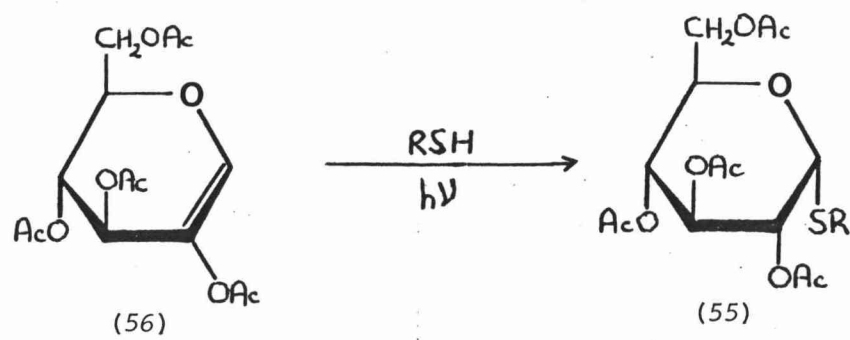
In the above approach mutarotation of the C-1 sulphydryl group is avoided so that a 1,2-*trans*-configuration in the product is assured. However, when a sample of tri-*O*-acetyl-1-thio-β-L-fucopyranose (53) was first equilibrated in 90% ethanol and then alkylated, a small quantity of the 1-thio-α-L-fucopyranoside (54) was obtained from the product mixture by preparative chromatography (Scheme 18).¹³⁴



Scheme 18

D By Photochemical Additions to 2-Hydroxy-glycal Esters

High yields of acetylated ethyl and propyl 1-thio-α-D-glucopyranosides (55), have been reported from the photochemical additions of thiols to tetra-*O*-acetyl-1-deoxy-β-D-arabino-hex-1-enopyranose (56) (Scheme 19).¹³⁵ Whether this approach will find more general applicability remains to be determined.

Scheme 19

CHAPTER TWO

MERCURY (II) CONTAINING 1-THIOGLUCOSE DERIVATIVES

INTRODUCTION

The affinity of mercury (II) ions for bivalent sulphur has been of value in the synthesis of 1,2-*cis*-O-glycosides from phenyl 1,2-*trans*-1-thioglycopyranosides (p.14), but the usefulness of this approach for glycosylating molar equivalents of complex alcohols has been limited by the slow rates of reactions and by the need to employ non-participating protecting groups. As this approach involved intermolecular reaction between three species, a significant enhancement in the rate of reaction could be expected if the reaction could be made bimolecular or intramolecular. Because phenylmercury (II) alkoxides were synthetically available reagents¹³⁶ which combined two of the required species, the reactions undergone between 1-thioglycose derivatives and phenylmercury (II) salts were investigated.

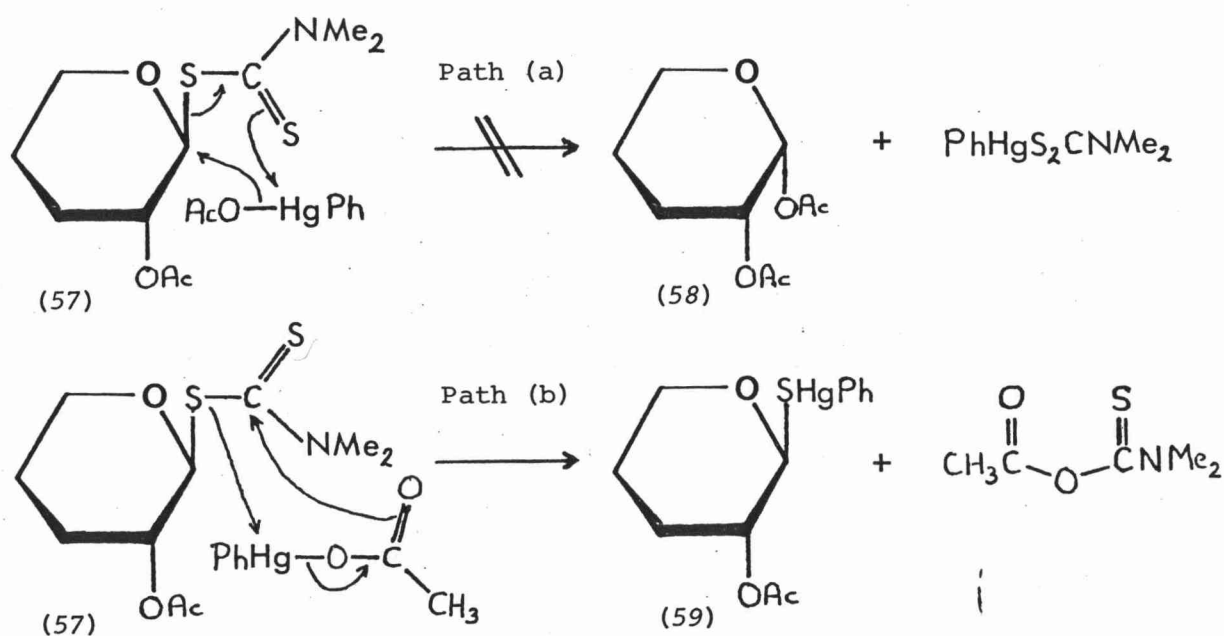
The carbohydrates reported in this chapter are all derivatives of D-glucopyranose, and for simplicity their substituents on positions other than C-1 and C-2 have been omitted from most Schemes.

RESULTS AND DISCUSSION

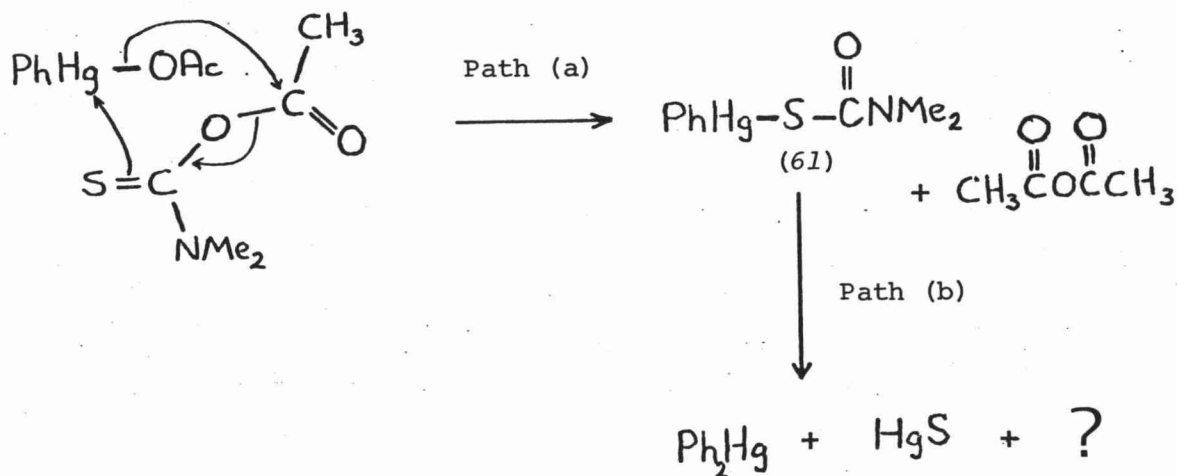
The initial reaction investigated was that between tetra-O-acetyl- β -D-glucopyranosyl *N,N*-dimethyldithiocarbamate (57) and phenylmercury (II) acetate; the envisaged reaction involved the production of penta-O-acetyl- α -D-glucopyranose (58) via a six-membered transition state as shown in path (a) of Scheme 20. It was soon evident, however, that rather than the C-1 to S bond being broken, the C to S single bond in the ester function was being broken with the formation of tetra-O-acetyl-1-S-phenylmercury(II)thio- β -D-glucopyranose (59) as shown in path (b) of Scheme 20. This result is due, in part, to the known retardation of reactions at the anomeric centre caused by C-2 acetoxy-groups.²⁰ Thus

while β -D-glucopyranosyl *N,N*-dimethyldithiocarbamate is known to give methyl α -D-glucopyranoside^{on} treatment with mercury (II) ions in methanol,¹³⁷ acetylated 1-thioglycopyranosides are generally reluctant to undergo mercury (II) ion assisted displacement reactions at C-1 under conditions which are suitable for analogous reactions involving the unprotected derivatives.^{45,94}

The rest of this chapter describes the further examination of the synthesis and possible synthetic utility of mercury (II) containing 1-thiogluco derivatives.



Scheme 20



Scheme 21

Syntheses of Mercury (II) Containing 1-Thiogluucose Derivatives

Tetra-*O*-acetyl-1-*S*-phenylmercury(II)thio-β-D-glucopyranose (59) was isolated in up to 70% yield from the reaction of dimethyldithiocarbamate (57) with phenylmercury (II) acetate (2 mol. equiv.) in boiling methanol, the product crystallising from the reaction solution after a black precipitate of mercury (II) sulphide had been removed by filtration. An 82% yield of compound (59) was similarly obtained from the diethyldithiocarbamate (60).

After removal of compound (59), the mother liquors from a reaction involving the dimethyldithiocarbamate (57) were further investigated, and three further products were isolated pure: diphenylmercury in 33% yield from phenylmercury (II) acetate, a small quantity of triphenylmethanol, and an even smaller quantity of a compound tentatively characterised as *S*-phenylmercury (II) *N,N*-dimethylthiocarbamate (61).

The production of *S*-phenylmercury (II) *N,N*-dimethylthiocarbamate (61) can be rationalised as resulting from reaction of the anhydride produced in path (b) of Scheme 20 with a second molar equivalent of phenylmercury (II) acetate as shown in path (a) of Scheme 21. Diphenylmercury and mercury (II) sulphide are probably formed by the disproportionation of a phenylmercury (II) thio-compound such as that shown in path (b) of Scheme 21 for compound (61). Phenylmercury (II) compounds have been shown to disproportionate into diphenylmercury and mercury (II) compounds in a variety of circumstances,^{138,139} and this type of reaction has even been used in a commercial process for the recovery of mercury from organomercurials.¹⁴⁰ A particularly close analogy is seen in the decomposition of bis[phenylmercury (II)] sulphide in boiling alcohol (Scheme 22).¹⁴¹



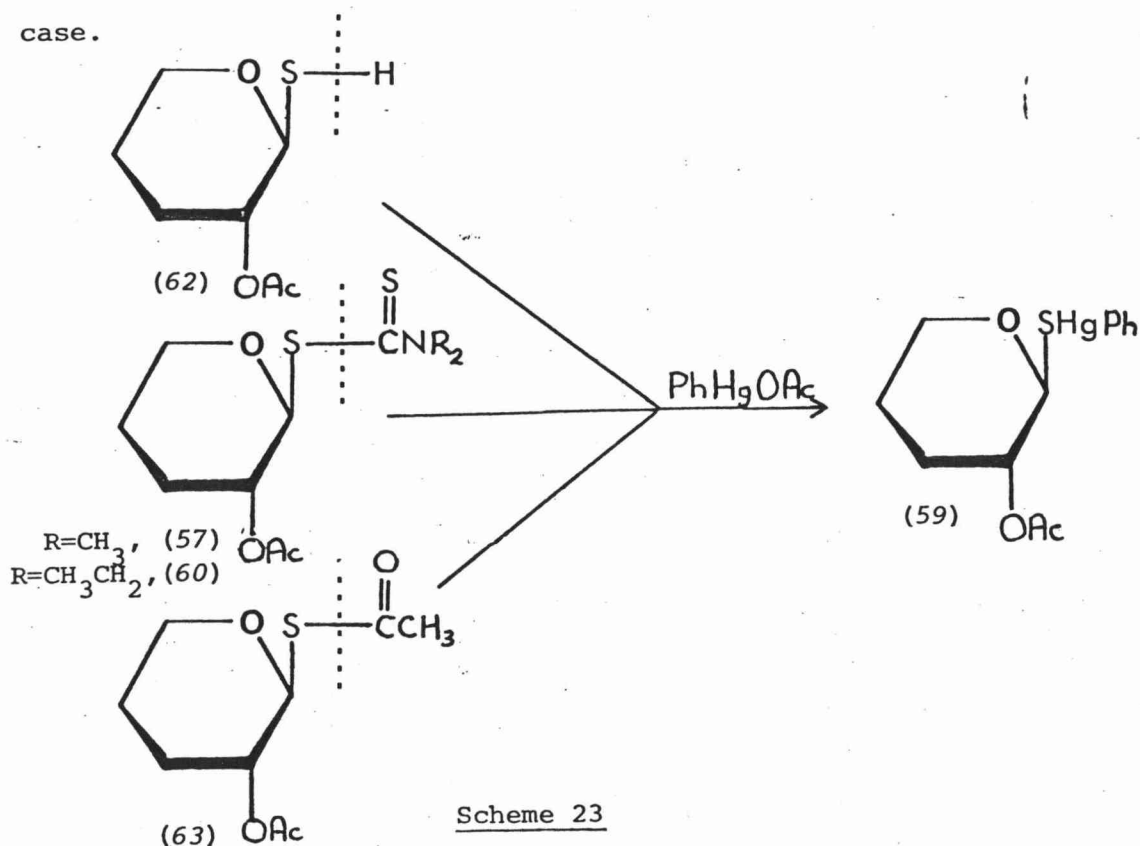
Scheme 22

Triphenylmethanol probably arose from the solvent (methanol) by way of successive radical substitutions; the initial substitution product

would be benzyl alcohol and this would preferentially undergo further reaction due to benzylic radical stabilisation. Phenylmercury (II) acetate has been shown to be a source of radicals upon photolysis¹⁴² and in the presence of reducing agents,¹⁴³ and may well be the radical source in this case.

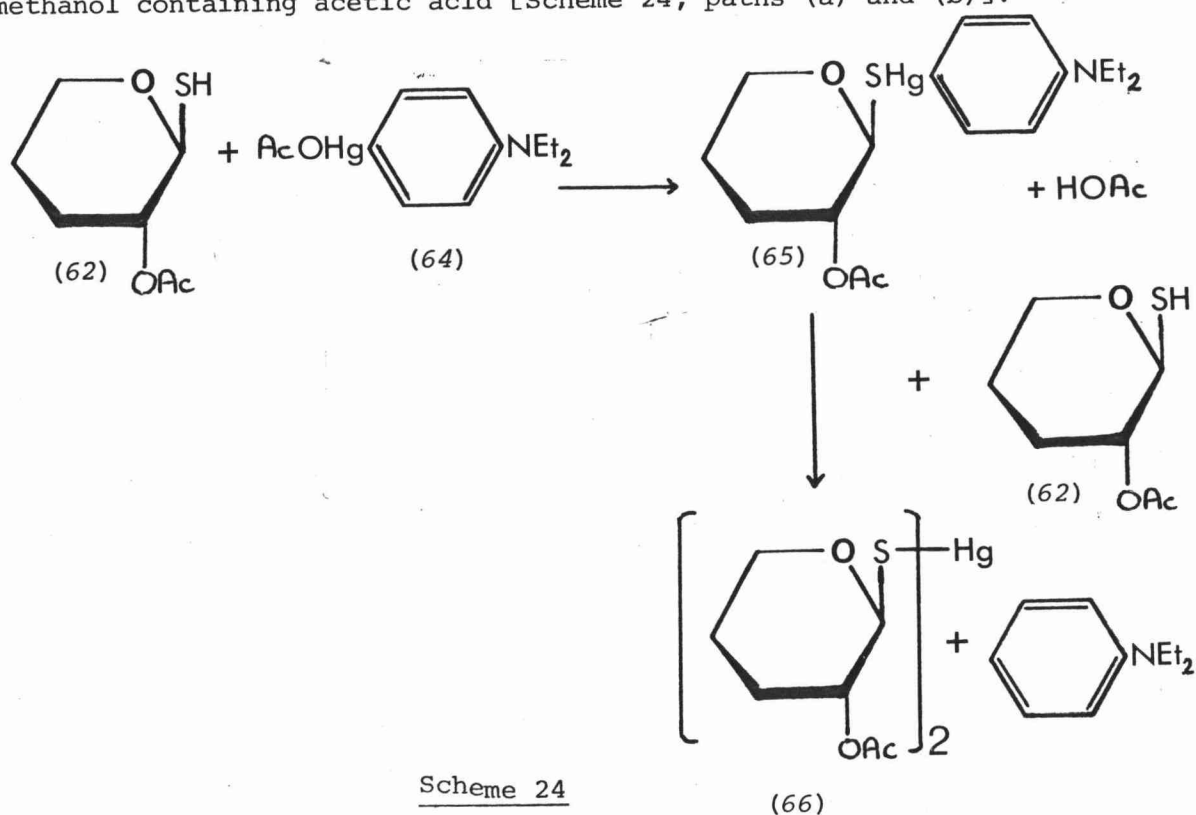
The structure of tetra-*O*-acetyl-1-*S*-phenylmercury(II)thio-β-D-glucopyranose (59) was confirmed by its synthesis in 82% yield from tetra-*O*-acetyl-1-thio-β-D-glucopyranose (62) and phenylmercury (II) acetate. Analogous condensations between complex organo-mercury (II) hydroxides or acetates and polyhydroxyalkyl thiols (e.g. 1-thiosorbitol) have been employed in the search for non-toxic organo-mercurial diuretics.^{144,145} The same compound (59) was also obtained from 1-thio-β-D-glucopyranose pentaacetate (63) and phenylmercury (II) acetate (1 mol. equiv.); cleavage of the thiolester function in preference to reaction at the anomeric centre has also been observed in the reaction of compound (63) with bromine in an inert solvent, when the sulphenyl bromide was produced;¹⁴⁶ acetylated alkyl 1-thioglycosides in contrast yield glycosyl bromides (see p. 27).

The four preparations so far revealed are summarised in Scheme 23, and the position of bond cleavage is indicated by a dotted line in each case.



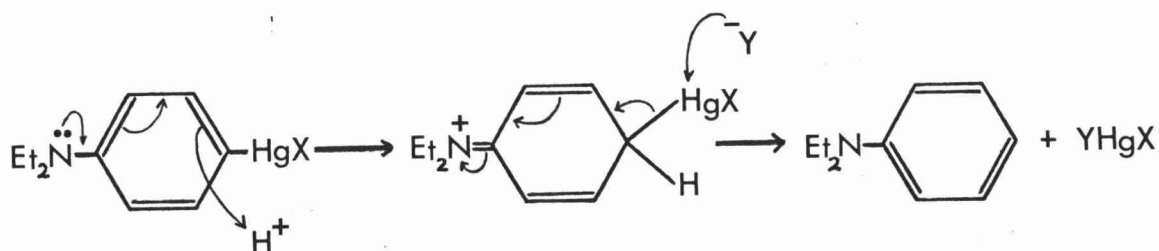
Reactions analogous to those outlined in Scheme 23, but using the readily accessible and easily purified *p*-diethylaminophenylmercury (II) acetate (64), were suitable for the preparation of tetra-*O*-acetyl-1-*S*-*p*-diethylaminophenylmercury(II)thio-β-D-glucopyranose (65) when suitable reaction conditions were employed. Thus compound (65) was obtained in 84% yield when the dimethyldithiocarbamate (57) was treated with compound (64) (2 mol. equiv.) in methanol at room temperature. Although the solution developed an intense black colour, under these mild conditions no mercury (II) sulphide precipitated. When similar reaction mixtures were heated under reflux, however, an oily black material (which could be converted into a filterable black precipitate on treatment with ether) was formed, and the major carbohydrate product was bis(tetra-*O*-acetyl-1-thio-β-D-glucopyranosyl)mercury (II) (66), which was isolated in 77% yield when only 1 mol. equiv. of compound (64) was employed.

Similarly, compound (65) was isolated in 88% yield from the direct condensation of tetra-*O*-acetyl-1-thio-β-D-glucopyranose (62) and *p*-diethylaminophenylmercury(II) acetate (64) (1.0 mol. equiv.) at room temperature in methanol containing triethylamine [Scheme 24, path (a)]. Again, however, when the mixture was briefly heated in ethanol in the absence of triethylamine the major carbohydrate product, isolated in 60% yield, was bis(tetra-*O*-acetyl-1-thio-β-D-glucopyranosyl)mercury(II) (66). This same compound (66) was obtained in 63% yield when the glycosyl thiol (62) and compound (64) (0.5 mol. equiv.) were heated under reflux in methanol containing acetic acid [Scheme 24, paths (a) and (b)].



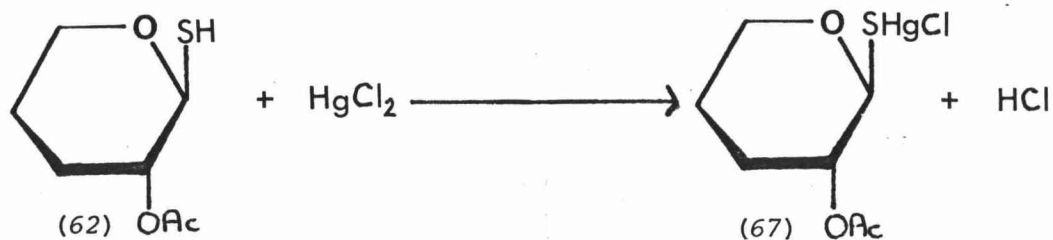
Scheme 24

It appears that, although compound (65) is the product initially formed in the above reactions, under all but the mildest conditions its carbon-mercury bond is readily broken and compound (66) is the resulting product. The greater lability of the carbon-mercury linkages in such *p*-diethylamino-substituted as compared to the unsubstituted phenylmercury (II) derivatives, particularly under acidic conditions, has been observed before,¹⁴⁷ and is due to the strong electron-donating effect of the diethylamino-group as shown in Scheme 25.



Scheme 25

The identity of bis(tetra-*O*-acetyl-1-thio- β -D-glucopyranosyl) mercury(II) (66) was confirmed by its separated synthesis in 79% yield from mercury(II) acetate and tetra-*O*-acetyl-1-thio- β -D-glucopyranose (62) (2 mol. equiv.) in a reaction which constituted a double substitution at mercury. As, however, Schneider and Bansa¹⁴⁸ had reported that a single substitution at mercury occurred in the condensation of compound (62) with an equimolar proportion of mercury(II) chloride to give tetra-*O*-acetyl-1-*S*-chloromercury(II)thio- β -D-glucopyranose (67) (Scheme 26), a similar attempt was made to prepare the analogous acetoxymercury derivative.



Scheme 26

For this purpose equimolar proportions of compound (62) and mercury(II) acetate were mixed in methanol. An uncharacterised white solid rapidly precipitated, and by chromatographic separation of the remaining reaction products were obtained compound (66) (46% yield), and a syrup which was shown by n.m.r. analysis to be a mixture of the 3,4,6-tri-*O*-acetyl- α -D-glucopyranosyl *endo*- and *exo*- 1,2-(methylorthoacetates) (68) and methyl tetra-*O*-acetyl- α -D-glucopyranoside (69) in the ratio 2:10:3 (35% yield). That a chloromercury(II) but not an acetoxy-mercury(II) derivative can be prepared in this manner is an indication of the greater lability of mercury-oxygen bonds relative to mercury-chlorine bonds. The formation of the methyl glucoside and orthoacetates is of interest in that it constitutes a rare example of mercury assisted displacement of sulphur from C-1 in the presence of a C-2 acetoxy-group (see p. 2), and because the glucoside is the unexpected α -anomer, formed by direct displacement at C-1.

Reactions of Mercury(II) Containing 1-Thiogluucose Derivatives

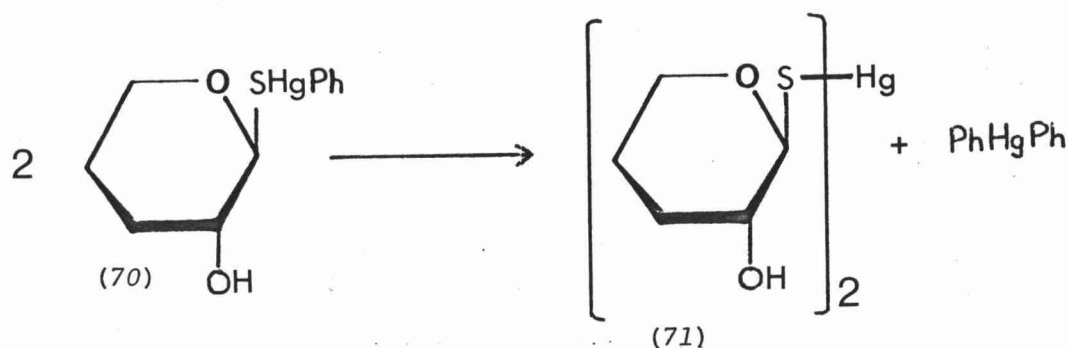
The reactivities of the acetylated compounds (59), (65) and (66) were investigated under a variety of conditions to ascertain if they could be used synthetically.

A The Effects of Alcohol

All three compounds above were synthesised in, and could be recrystallised from alcohols, and could not be used as glycosylating reagents. It is possible that the *p*-diethylaminophenylmercury derivative (65) decomposes on silica gel t.l.c. plates to give the bithiogluco-syl mercury derivative (66) since both these compounds have identical chromatographic properties, with compound (65) displaying in addition a fast and a slow moving non-carbohydrate u.v.- absorbing component. An attempt to cause this decomposition by heating compound (65) with an equal weight of silica gel in methanol under reflux for 15 min led only to compound (65) being recovered in 83% yield.

B Deacetylations

Deacetylations of compounds (59) and (66) proceeded smoothly to give 1-*S*-phenylmercury(II)thio- β -D-glucopyranose (70) and bis(1-thio- β -D-glucopyranosyl)mercury(II) (71) respectively. When compound (70) was dissolved in water it slowly, but quantitatively, disproportionated as shown in Scheme 27. Both mercurated 1-thioglucoses are soluble in water, and it is presumably the precipitation of diphenylmercury which drives the reaction to completion; compound (70) can be recrystallised from organic solvents in which diphenylmercury is soluble. This is another example of the remarkable ability of phenylmercury(II) compounds to disproportionate (see p.37).

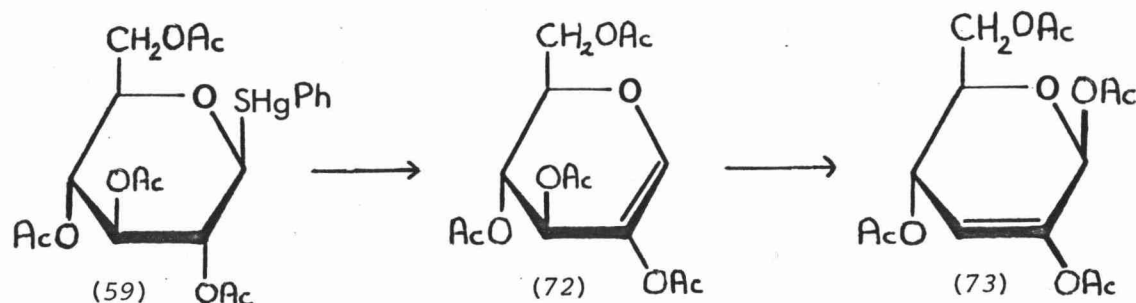


Scheme 27

C Thermolyses

The possibility of extruding mercury(II) sulphide from tetra-*O*-acetyl-1-*S*-phenylmercury(II)thio- β -D-glucopyranose (59) and thereby synthesising a C-glycoside, led to the investigation of the thermolysis of this compound. Reaction occurred too slowly in boiling toluene or xylene, but after 32 h in boiling mesitylene a black solid had formed, and the syrupy carbohydrate product obtained on processing the reaction mixture was shown by n.m.r. analysis to be a 3:1 mixture of tetra-*O*-acetyl-2-hydroxy-D-glucal (72) and 1,2,4,6-tetra-*O*-acetyl-3-deoxy- β -D-erythro-hex-2-enopyranose (73). The products, depicted in

Scheme 28, were thus formed following an elimination between C-1 and C-2 rather an extrusion of mercury(II) sulphide. The former product (72) is known to rearrange to the latter product (73) under thermolysis conditions,¹⁴⁹ and by further heating the initial mixture, this time in nitrobenzene, another syrup was obtained and was shown by n.m.r. analysis to be a 1:3 mixture of these two compounds respectively.



Scheme 28

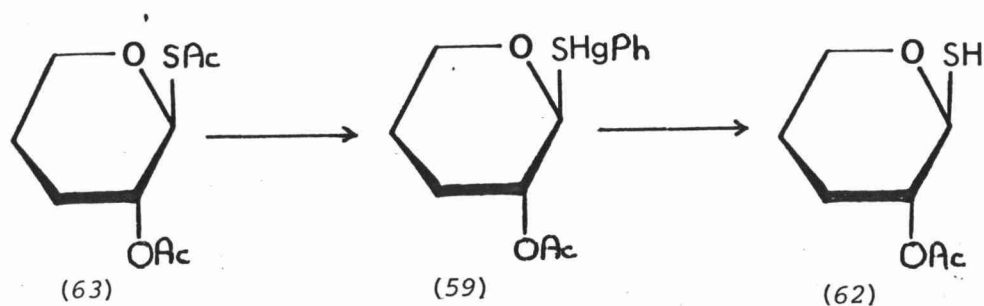
An attempt was made to synthesise compound (73) directly by thermolysis of compound (59) in nitrobenzene, but the reaction was not as clean in this solvent. Although the unsaturated products were formed, β -D-glucopyranosyl 1-thio- β -D-glucopyranoside octaacetate (74) was isolated in 14% by direct crystallisation, and some metallic mercury was observed. Similar thermolysis of bis(tetra-O-acetyl-1-thio- β -D-glucopyranosyl)mercury(II) (66) in nitrobenzene gave a complex mixture of products from which only bis(tetra-O-acetyl-1-thio- β -D-glucopyranosyl)disulphide (75) was isolated, in 7% yield.

D Reactions with Hydrogen Sulphide

To find conditions under which the acetylated mercury(II) containing 1-thiogluco derivatives could be demercurated, their reactions with hydrogen sulphide were investigated. Mercury(II) sulphide was rapidly precipitated when a solution of either tetra-O-acetyl-1-S-p-diethylaminophenylmercury(II)thio- β -D-glucopyranose (65) or bis(tetra-O-acetyl-1-thio- β -D-glucopyranosyl)mercury(II) (66) was treated with

hydrogen sulphide, and tetra-*O*-acetyl-1-thio-β-D-glucopyranose (62) was obtained in 65% and 70% yield from the respective reaction solutions. Diethylaniline was also obtained as a product in the former case. While *p*-diethylaminophenylmercury(II) acetate (64) has been similarly shown to give mercury(II) sulphide with hydrogen sulphide,¹⁴⁷ phenylmercury(II) acetate, which has a much less labile carbon-mercury bond, has been shown to form bis[phenylmercury(II)]sulphide.¹⁴¹ Thus when an ethanol solution of tetra-*O*-acetyl-1-*S*-phenylmercury(II)thio-β-D-glucopyranose (59) was treated with hydrogen sulphide a yellow solid was immediately precipitated and, although a small amount of compound (59) remained unreacted for a reason not yet understood, compound (62) was isolated in 81% yield from the reaction solution. However, when a chloroform solution of compound (59) was treated with hydrogen sulphide, mercury(II) sulphide was precipitated over a period of five days, and the product isolated from the reaction solution appeared to be a mixture of compound (62) and diphenylmercury. While bis[phenylmercury(II)]-sulphide is insoluble in ethanol, it is soluble in chloroform,¹⁴¹ and only its gradual disproportionation into mercury(II) sulphide and diphenylmercury as shown in Scheme 22 permits the above demercuration in chloroform to go to completion.

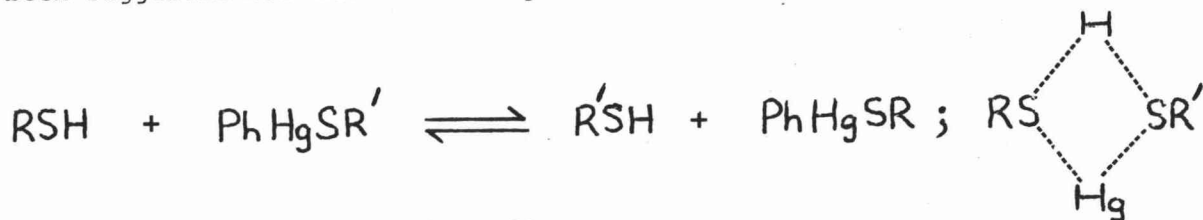
A new general method for the preparation of acetylated glycosyl thiols involving specific *S*-deacetylation is revealed by the results summarised in Scheme 29 for 1-thio-D-glucose derivatives. The thiol (62) can be obtained from the pentaacetate (63), via demercuration of the phenylmercury derivative (59), in an overall 60% yield, the latter two compounds being stable, easily purified and excellently crystalline. A potential advantage of this route would be its applicability to the synthesis of acetylated 1,2-*cis*-glycosyl thiols, from which 1,2-*cis*-1-thioglycosides could be prepared, although a method of preparing the required acetylated 1,2-*cis*-1-thioglycoses has yet to be found. While acetylated 1,2-*trans*-glycosyl thiols can be prepared by the procedure developed by Cerny and co-workers (p. 32), attempts by Bannister (p. 27) to extend this to the preparation of the 1,2-*cis*-analogues were not very successful.



Scheme 29

E Reactions with Other Thiols

The equilibrium shown in Scheme 30 is known to be facile at room temperature for simple aromatic thiols and their derivatives, and the four centre transition state shown on the right in Scheme 30 has been suggested for the interchange.¹⁵⁰

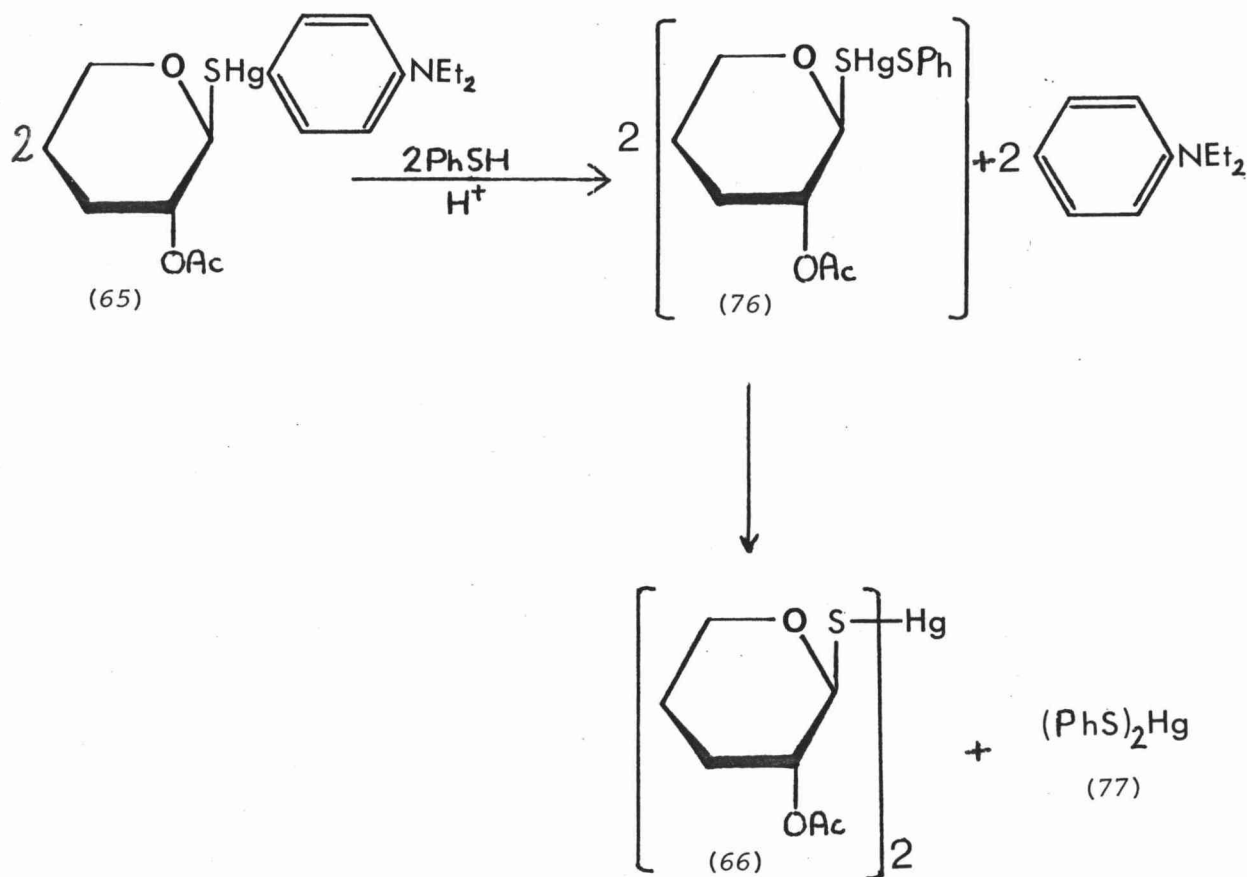


Scheme 30

It was found that tetra-*O*-acetyl-1-*S*-phenylmercury(II)thio-β-D-glucopyranose (59) and thiophenol were brought into a similar equilibrium after being heated in methanol for 30 min, and when a 20-fold excess of thiophenol was used the mixture contained largely tetra-*O*-acetyl-1-thio-β-D-glucopyranose (62) and phenylmercury(II)thiophenol, with the latter crystallising in 86% yield from the cooled solution.

When tetra-*O*-acetyl-1-*S*-*p*-diethylaminophenylmercury(II)thio-β-D-glucopyranose (65) was heated with thiophenol (1 mol. equiv.) in methanol containing acetic acid, the carbon-mercury bond was broken as depicted in Scheme 25 (in the case $Y = PhS$). However, rather than the unsymmetrical mercury derivative (76) shown in Scheme 31 being obtained, the two symmetrical products, namely bis(phenylthio)mercury(II) (77) and the bithiogluco sylmercury derivative (66), were obtained in 82% and 71% yield respectively. Whether such unsymmetrical derivatives are inherently less

stable than the symmetrical derivatives, or whether the reaction is displaced by the precipitation of compound (77) is not known.



Scheme 31

From separate reactions of the *p*-diethylaminophenylmercury derivative (65) and the bithioglucoylmercury derivative (66) with excess of thiolacetic acid in methanol at room temperature, tetra-*O*-acetyl-1-thio-β-D-glucopyranose (62) was isolated in 86% yield on both occasions.

F Reactions with Acetic Acid

Tetra-*O*-acetyl-1-*S*-phenylmercury(II)thio-β-D-glucopyranose (59) was reasonably stable to acetic acid. On prolonged heating of this compound in ethanol containing acetic acid a gradual decomposition occurred,

with the precipitation of a fine black solid and the formation of at least three new compounds (t.l.c.). Even after 30 h, however, 11% of compound (59) could be recovered by direct crystallisation, so the reaction was not further investigated.

As would be expected, tetra-*O*-acetyl-1-*S*-*p*-diethylamino-phenylmercury(II)thio- β -D-glucopyranose (65) was considerably more susceptible to acidic conditions. The major product formed on treatment with boiling methanolic acetic acid was bis(tetra-*O*-acetyl-1-thio- β -D-glucopyranosyl)mercury(II) (66) (isolated in 45% yield); thus, as observed in all the previous reactions of such derivatives, solvent does not appear to participate in product formation.

N.m.r. Spectra of the Glucosyl Dithiocarbamates

The n.m.r. spectrum of a chloroform-*d* solution of tetra-*O*-acetyl- β -D-glucopyranosyl *N,N*-dimethyldithiocarbamate (57) displayed the complex one proton low-field resonance shown in Figure 1.

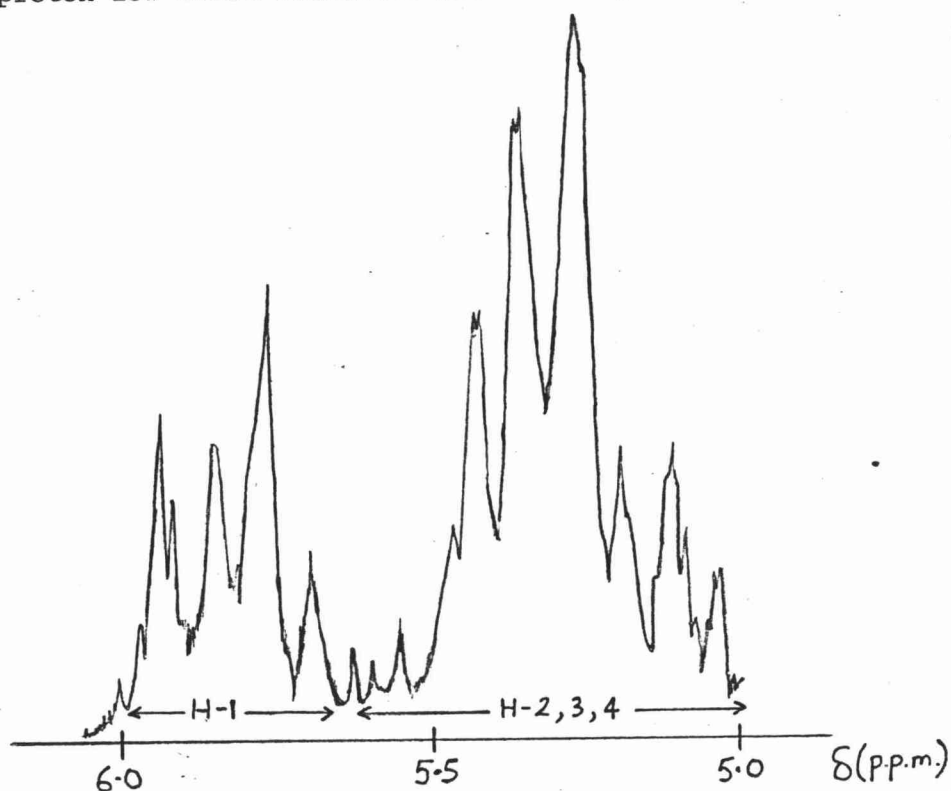


Figure 1. The n.m.r. spectrum of compound (57) at 25° in chloroform-*d*.

The diethyl analogue (60) and the di-*n*-butyl analogue (78) also displayed very similar complex one proton low-field resonances in chloroform-*d* solution at 25°. Because it seemed probable that these resonances were due to the anomeric protons in these compounds, and yet were not the simple doublets expected, the n.m.r. spectrum of compound (57) was recorded in a variety of solvents and at different temperatures; if the complexity of the low-field resonance was due to an equilibrium mixture of isomeric forms, then such variations should cause a change in the equilibrium position and hence in the observed resonance.

Surprisingly the low-field resonance observed for a dimethylsulphoxide-*d*⁶ solution of compound (57) was a simple one proton doublet (*J* 10Hz) as shown in Figure 2.

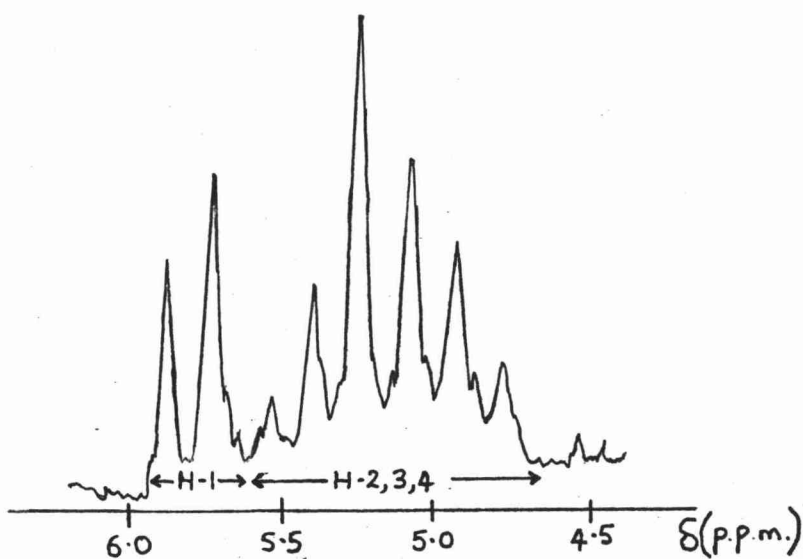


Figure 2. The n.m.r. spectrum of compound (57) at 25° in dimethylsulphoxide-*d*⁶.

resonances of compound (57) or its analogues.

At 25° in all three solvents, two singlets were observed for the *N*-methyls of compound (57) (e.g. at δ 3.34 and 3.51 in chloroform-*d*), but these resonances were observed to coalesce to a broad singlet by 60°, and to sharpen progressively as the temperature rose above this. This phenomenon is due to hindered rotation about the C-N bond, and has been discussed generally for dithiocarbamate esters by Lemire and Thompson,¹⁵¹ and for glycosyl *O*-thiocarbamates by Horton and Prihar.¹⁵²

CHAPTER THREE

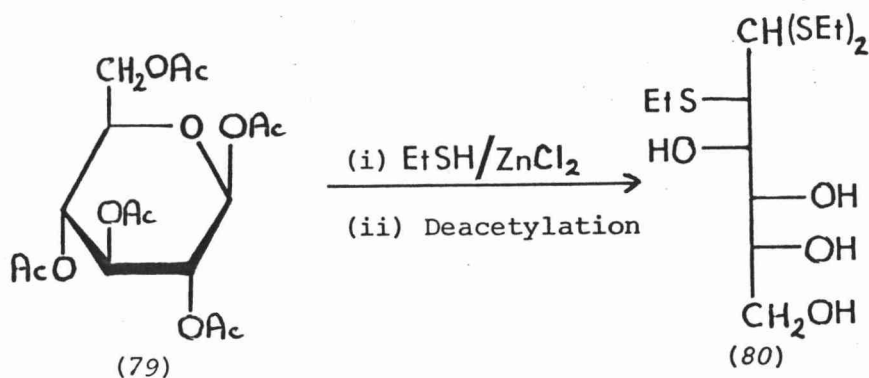
1,2-trans-S- AND 1,2-cis-O-GLYCOSIDES FROM PERACYLATED SUGARS

Introduction

While 1,2-trans-1-thioglycosides have been produced by several different approaches, as outlined in Chapter One (p. 24-34), their synthesis on a preparative scale has been essentially restricted to just two methods: (a) condensations of acylated glycosyl halides with salts of thiols (p. 25), and (b) alkylations of acetylated glycosyl thiols (p. 32). Both of these methods, however, involve converting the readily available peracylated sugars into reactive and sometimes unstable (see p. 26) acylated glycosyl halides. An alternative approach employing the acid catalysed displacement of an anomeric acyloxy-group by a thiol was thus attractive, because not only would it avoid the intermediacy of a glycosyl halide, but it would also represent a single step synthesis.

Attempts by other workers to employ this approach have not been entirely satisfactory (see p. 27). While good yields of acetylated ethyl 1-thioglycosides were obtained by employing zinc chloride as catalyst and ethanethiol as solvent, the use of such large excesses of thiols is undesirable when derivatives of more complex or less volatile thiols are required, and also because most thiols have strong unpleasant odours. In addition, substitutions at other than the anomeric centres of peracetylated sugars can occur in the presence of an excess of thiol. From the zinc chloride catalysed ethanethiolysis of penta-O-acetyl- β -D-glucopyranose (79) or its α -anomer (58), Lemieux¹¹⁰ obtained, after isolation of the β -thiopyranoside and deacetylation of the mother liquors, a small amount of 2-deoxy-2-ethylthio-D-mannose diethyl dithioacetal (80) (Scheme 32). This compound, in which the configuration at C-2 has only recently been established,¹⁵³ is the result of a migration of an ethylthio-group from the anomeric centre to C-2, via a 1,2-episulphonium ion. Similar migration to C-4 and C-5 have been observed in the boron trifluoride or zinc chloride catalysed ethane- or methane-thiolyses of the

β -D-ribofuranose, β -D-ribopyranose or α -L-arabinopyranose tetraacetates.¹⁵⁴⁻¹⁵⁶



Scheme 32

The difficulties associated with this general approach to the synthesis of 1-thioglycosides should be overcome if the method could be modified to employ equimolar proportions of peracetylated sugars and thiols in inert solvents, but no such general procedure has been reported. Conditions were thus developed under which such a modified approach could be applied to the synthesis of 1,2-*trans*-1-thioglycosides on a preparative scale, and these are reported in this chapter.

RESULTS AND DISCUSSION

The Choice of a Catalyst and a Solvent

The Lewis acid boron trifluoride, available as its diethylether complex, appeared to be the most suitable catalyst. Boron trifluoride has been used as its anisole complex in benzene solution,¹⁵⁷ as its acetic acid complex in acetic anhydride - acetic acid solution,¹⁵⁸ and free or as its diethylether complex in chloroform solution,¹⁵⁹ to catalyse the anomerisation of penta-O-acetyl-D-glucopyranose; it has also been used as catalyst in the anomerisation of acetylated 1,2-*trans*-O-glycosides (p. 15), in the synthesis of acetylated aryl 1,2-*trans*-O-glycosides from peracetylated sugars,^{108,157} and even in the Fischer Synthesis (p. 4) of an allyl glycoside.¹⁶³ While other Lewis acid catalysts such as aluminium chloride,¹⁶⁰ tin(IV) chloride (see p. 9)^{51,161} and titanium(IV) chloride^{51,55,161,162} are known on some occasions to

generate glycosyl chlorides in such reactions, boron trifluoride, which is a stronger acid,⁵¹ does not exhibit any side reactions due to the relative stability of the boron-fluorine bonds.

Chloroform was chosen as the solvent for most of the reactions reported herein. In order to avoid competing deacetylation and ethyl glycoside formation, however, the few percent of ethanol generally added to commercially available chloroform to stabilise it against photochemical degradation was removed. Benzene and dichloromethane, which are more easily purified, are useful alternative solvents.

Syntheses of 1,2-trans-1-Thioglycosides

From initial experiments it was found that both the α -anomer (58) and the β -anomer (79) of penta-*O*-acetyl- $\underline{\underline{D}}$ -glucopyranose, on treatment with thiophenol (1.7 mol. equiv.) and boron trifluoride diethyletherate (1.8 mol. equiv.) in chloroform solution, gave phenyl tetra-*O*-acetyl-1-thio- β - $\underline{\underline{D}}$ -glucopyranoside (81) as the main product, but that in keeping with earlier results (p. 28), the β -anomer (79) was found to react much the faster. After 30 days at room temperature the reaction mixtures were processed to yield crude products from which the β -thiogluco-*s*ide (81) was obtained pure after several recrystallisations in 45% and 36% yield from the α - and β -pentaacetates (58) and (79) respectively. Phenyl tetra-*O*-acetyl-1-thio- α - $\underline{\underline{D}}$ -glucopyranoside (82) was also present in the reaction products, and was isolated from the mother liquors of the reaction involving the β -pentaacetate (79) in 8% yield, along with further β -thiogluco-*s*ide (81) (6%), by chromatographic methods.

A general synthetic procedure was then adopted which involved the use of a peracetylated 1,2-trans-related sugar derivative, a slight molar excess of a thiol, and a quantity of boron trifluoride diethyletherate sufficient to afford a convenient reaction rate as determined by t.l.c. analysis. In Table 1 are listed all the 1-thioglycosides isolated crystalline by this method, along with the conditions and efficiencies of their preparations. Of these preparations, only those of compounds (83), (90), (63), (91), and (92) were considered to vary from the basic procedure sufficiently to warrant further description in the experimental section.

This procedure was shown to be applicable to the synthesis of acetylated and benzoylated phenyl 1-thioglycosides of pentoses, hexoses and hexuronic acid derivatives. While those reactions involving acetylated derivatives proceeded satisfactorily at room temperature, that involving the benzoylated derivative was best carried out under reflux in a nitrogen atmosphere. In the preparation of methyl (phenyl 2,3,4-tri-*O*-acetyl-1-thio- β -D-glucopyranosid)uronate (86) it was important for the reaction to be taken to completion, otherwise the product was contaminated with unreacted methyl(tetra-*O*-acetyl- β -D-glucopyran)uronate (93), which, because of its low solubility in cold alcohol, could not be removed from the product by recrystallisation.

Acetylated allyl, benzyl and ethyl 1-thioglycosides were also synthesised using this procedure. The allyl 1-thioglycosides were of particular interest because of their potential use as ligands in affinity chromatography (p. 22), and whereas the β -thiogalactoside (88) was readily obtained crystalline, the β -thioglucoside (94) resisted crystallisation despite the use of a seed and the fact that t.l.c. and n.m.r. evidence indicated it had been formed as the major product in a smooth reaction. Ethyl tetra-*O*-acetyl-1-thio- β -D-glucopyranoside (90) was also of interest because of its use in the synthesis of tetra-*O*-acetyl- β -D-glucopyranosyl bromide, and hence possibly of 1-thio- α -D-glucosides (p. 27).

These acid catalysed reactions were not completely stereospecific and small proportions of 1,2-*cis*-1-thioglycosides were observed as slightly more mobile components than the major 1,2-*trans*-products on t.l.c. With thiophenol the initial reaction mixtures were resistant to further reaction, but when ethanethiol, boron trifluoride diethyletherate and penta-*O*-acetyl- β -D-glucopyranose (79) were allowed to react for a prolonged time, considerable anomerisation occurred and an equal mixture of ethyl tetra-*O*-acetyl- α -D-glucopyranoside (95) and its β -anomer (90) was eventually obtained. All reactions were thus monitored by t.l.c. and were stopped as soon as initial thioglycosidations were complete.

1-Thio- β -D-glucopyranose pentaacetate (63) was also synthesised using thiolacetic acid in this procedure, a convenient reaction rate being achieved when the reaction solution was heated under reflux in a nitrogen atmosphere. The crude product was, however, discoloured and contained

Table 1 Syntheses of 1-Thioglycosides

Compound	Concentration of starting material (% in CHCl ₃)	Thiol (mol.equiv)	BF ₃ etherate (mol.equiv.)	Time (h)	CRUDE PRODUCT ^a		CHARACTERISATION		
					Yield (%)	[α] _D (° in CHCl ₃)	found m.p. [α] _D (° in CHCl ₃)	ref.	lit.
Phenyl tetra-O-acetyl-1- thio-β-D-glucopyranoside (81)	20	1.2	5	5	71	-14	117-118 -16	104	117 -17
Phenyl tetra-O-benzoyl-1- thio-β-D-glucopyranoside (83)	6	1.05	1	4 (reflux)	81	-	167-168 +34 (acetic acid)	b	- -
Phenyl tetra-O-acetyl-1-thio- β-D-galactopyranoside (84)	20	1.1	3	43	69	+4	73-76 +5	164	70.5 - +5
Phenyl tetra-O-acetyl-1-thio- β-D-xylopyranoside (85)	20	1.1	1.5	1.5	56	-	79-80 -55	104	78 -59
Methyl (phenyl tri-O-acetyl- 1-thio-β-D-glucopyranosid)- uronate (86)	17	1.2	2.7	18	76	-	119-120 -20	165	119-120 -22
Phenyl 2,5-di-O-acetyl-1- thio-β-D-glucofuranosiduron- 3,6-lactone (87)	20	1.05	4	2.5	62	-23	115-116 -32 (ethanol)	c	- -

(Cont. over)

(Table 1 cont.)

Allyl tetra-O-acetyl-1-thio- β -D-galactopyranoside (88)	4	1.05	10	2	58	-	88-89	+11	132	88-89	+7
Benzyl tetra-O-acetyl-1-thio- β -D-glucopyranoside (89)	50	1.3	0.2	46	70	-89	102-103	-92	129	100-101	-91
Ethyl tetra-O-acetyl-1-thio- β -D-glucopyranoside (90)	50	1.1	0.22	35	83	-21	82-84	-26	110	82-83	-28
1-Thio- β -D-glucopyranose pentaacetate (63)	8	1.1	3.0	6 (reflux)	55	-	118-120	+8	166	118	+11
Phenyl tetra-O-benzyl-1-thio- α -D-glucopyranoside (91) ^d	3	1.2	5.6	2.5	-	-	81-82 (ethanol)	+154	-	-	-
Phenyl tetra-O-benzyl-1-thio- β -D-glucopyranoside (92) ^d	3	1.2	5.6	2.5	-	-	91-92	+3	45	92-93	+1

Notes: a, Isolated by direct crystallisation.

b, Calculated for $C_{40}H_{32}O_9S$: C, 69.8; H, 4.7; S, 4.7. Found: C, 69.8; H, 4.7; S, 4.7%.c, Calculated for $C_{16}H_{16}O_7S$: C, 54.5; H, 4.6; S, 9.1. Found: C, 54.7; H, 4.7; S, 9.1%.

d, Isolated by p.l.c. as described in the experimental section.

penta-*O*-acetyl- α -D-glucopyranose (58) (20% as judged by t.l.c. and n.m.r.), and an alternative synthesis of compound (63) via tetra-*O*-acetyl- α -D-glucopyranosyl bromide (96) was more satisfactory (p. 89). An attempt to prepare a β -thiogluco-side by application of the acid catalysed procedure to *p*-nitrothiophenol and penta-*O*-acetyl- β -D-glucopyranose (79) was unsuccessful, with a mixture containing appreciable proportions of the α -pentaacetate (58) and α -thiogluco-side (t.l.c. and n.m.r. evidence) being produced instead. These results reveal a limitation of this acid catalysed procedure: poorly nucleophilic thiols allow anomerisations to compete with thiogluco-sidations. A mixture was also obtained when tetra-*O*-acetyl-1-thio- β -D-glucopyranose (62) and β -pentaacetate (79) were used in this procedure, and the main two components of this had t.l.c. mobilities identical to those of the β -D-glucopyranosyl 1-thio- α and β -D-glucopyranoside octaacetates (97) and (74), and were probably formed following initial anomerisation of the thiol (62).

This procedure was also applied to the reactions of thiophenol with two compounds not having C-2 acyloxy-groups. 1,3,4,6-Tetra-*O*-acetyl- α -D-glucopyranose (98) did not give a 1-thiogluco-side with an unsubstituted hydroxy-group at C-2. The major product, isolated in 38% yield, was phenyl tetra-*O*-acetyl-1-thio- β -D-glucopyranoside (81), and reaction therefore occurred with acetyl migration from C-1 to C-2, probably via a 1,2-acetoxonium ion and displacement of this from C-1 by thiophenol. Similar ester migrations have been observed in other reactions.^{166,167} The C-1 hydroxy-group of 2,3,4,6-tetra-*O*-benzyl- α -D-glucose (99) was readily displaced in this procedure to produce a mixture of the anomeric phenyl tetra-*O*-benzyl-1-thio- β -D-glucopyranosides from which the α -anomer (91) and the β -anomer (92) were isolated in 50% and 17% yield respectively after p.l.c. Once a seed crystal had been obtained as above, its use permitted direct isolation of the α -anomer (91) in 31% yield. Because phenyl 1-thio- α -D-glucopyranoside is difficult to obtain,⁹⁹ the above represents a viable preparation of compound (91) which is of potential use in 1,2-*trans*-*O*-glycoside synthesis.⁴⁵

Syntheses of 1,2-*cis*-*O*-Glucosides

When commercial grade chloroform, which contained a few percent of ethanol, was used as the solvent in an attempt to prepare phenyl tetra-*O*-

benzoyl-1-thio - β -D-glucopyranoside (83) by the boron trifluoride catalysed procedure (p. 52), only benzoylated ethyl glucosides were obtained. It was thus discovered that benzoylated glucosides could be produced by heating equimolar proportions of an alcohol and penta-O-benzoyl- β -D-glucopyranose (100) in chloroform or benzene under reflux in the presence of boron trifluoride diethyletherate as catalyst.

The use of ethanol in this reaction led to the formation of ethyl tetra-O-benzoyl- β -D-glucopyranoside (101) as the first major product, but this anomerised on continued heating of the reaction mixture, and ethyl tetra-O-benzoyl- α -D-glucopyranoside (102) became the final major product. When reactions such as this were processed at appropriate times, high yields of crystalline materials containing either the β -glucoside (101) or the α -glucoside (102) as the predominant component were obtained. Unfortunately, repeated recrystallisations of these anomeric mixtures did not remove the minor components, and an anomerically pure sample of the α -glucoside (102) was only obtained following a chromatographic separation.

Similar results were obtained when propan-2-ol was used in this procedure, although in this case anomerisation was competitive with glucosidation, and the reaction was continued until prop-2-yl tetra-O-benzoyl- α -D-glucopyranoside (103) became the major product. The more rapid anomerisation of the benzoylated prop-2-yl than ethyl β -D-glucopyranoside is paralleled by observations made by Lindberg⁵¹ on the boron trifluoride catalysed anomerisation of their acetylated analogues. While an almost pure sample of the α -glucoside (103) was obtained by repeated recrystallisation of the crude product, a chromatographic separation was again required to achieve complete anomeric purity.

It is probable that similar reactions employing acetylated derivatives could be performed (c.f. the tin(IV) chloride catalysed β -glucoside formation on p. 9), although competitive deacetylation may be a problem since this was observed when penta-O-acetyl- β -D-glucopyranose (79) was treated with boron trifluoride diethyletherate in commercial chloroform which contained an undetermined quantity of ethanol.

The experiments reported here, which take advantage of the greater stability under acidic conditions of benzoyl protecting groups

relative to their acetyl counterparts, represent the first applications of a procedure combining glucosidation with anomerisation which is suitable for aliphatic alcohols (*c.f.* the fusion syntheses of acetylated phenolic glycosides on p. 8). Because this procedure yields products rich in the poorly accessible α -glycosides, it may prove to be of considerable synthetic value.

CHAPTER FOUR

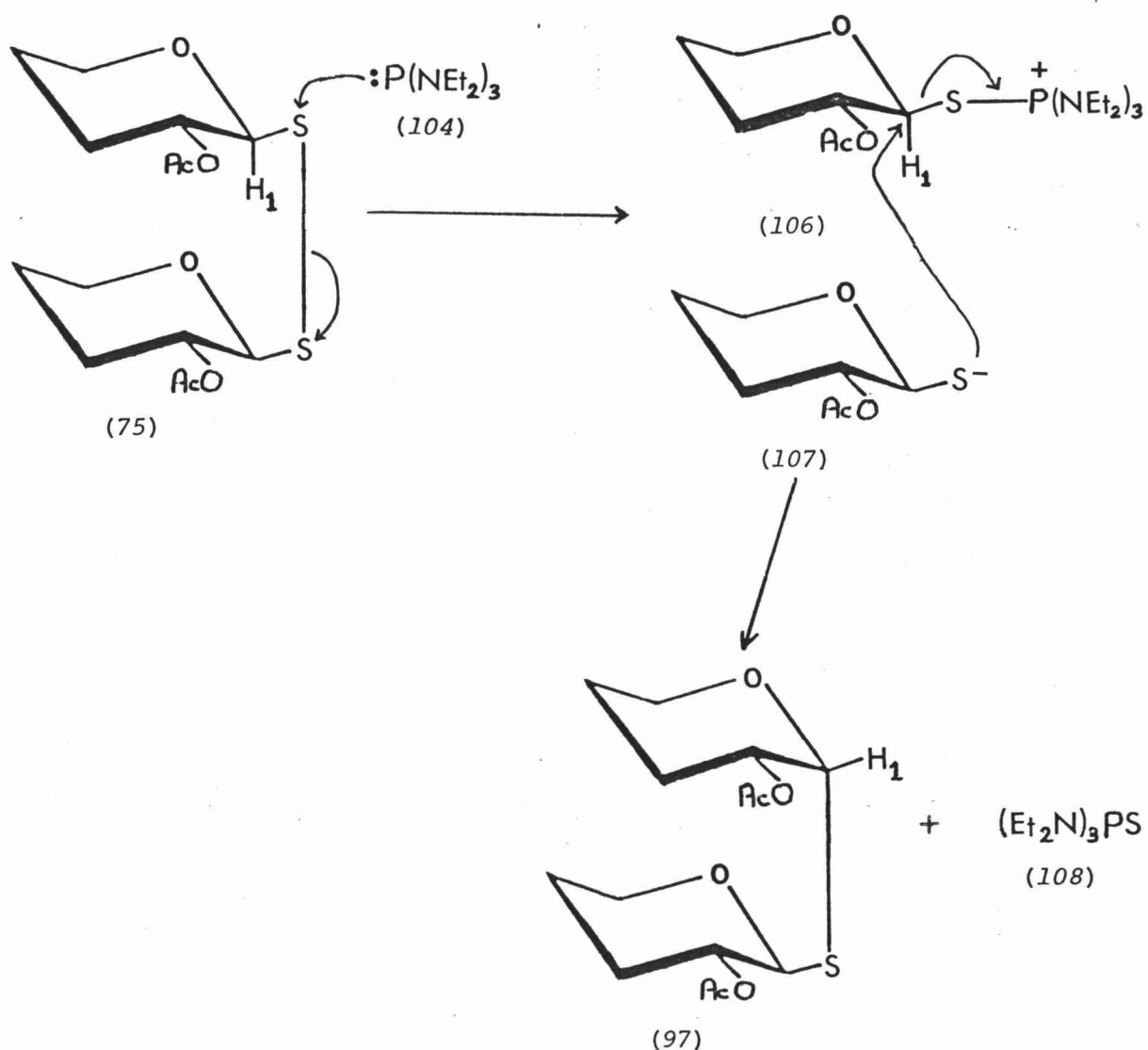
SYNTHESES OF 1,2-CIS-1-THIOGLYCOSIDES

INTRODUCTION*

A recent report by Harpp and Gleason¹⁶⁹ concerning the facile partial desulphurisations of organic disulphides with the strongly nucleophilic reagent tris(diethylamino)phosphine (104) included the intriguing reaction summarised in Scheme 33, by which the β,β -disulphide (75) was converted into α,β -sulphide (97). The mechanism for this reaction appeared, from detailed studies involving partial desulphurisations of simple disulphides, to involve initial nucleophilic cleavage of the disulphide bond to give the charged intermediates (106) and (107), followed by attack by anion (107) at C-1 of (106) with displacement of tris(diethylamino)phosphine sulphide (108) and inversion at the anomeric centre. The apparent lack of participation by the C-2 acetoxy-group of (106) in the displacement of the phosphine sulphide (108) is most interesting because, while such bimolecular displacements leading to products with 1,2-*cis*-configurations have been observed (p. 7 and 26), they are definitely a rare occurrence, and this is taken to indicate that, in the non-polar solvent used (benzene), (106) and (107) are held together by electrostatic attraction as a close ion-pair before reaction.

The possibility that analogous partial desulphurisations of unsymmetrical disulphides might give rise to inaccessible 1,2-*cis*-1-thioglycosides led to a reinvestigation of the above reaction, and to the synthesis, and examination under these reaction conditions, of a suitable unsymmetrical disulphide.

* All carbohydrates reported in this chapter are acetylated derivatives of D-glucopyranose, and for simplicity their substituents on positions other than C-1 and C-2 have been omitted from all Schemes.



Scheme 33

RESULTS AND DISCUSSION

Partial Desulphurisation of Bis(tetra-O-acetyl-β-D-glucopyranosyl) disulphide (75)

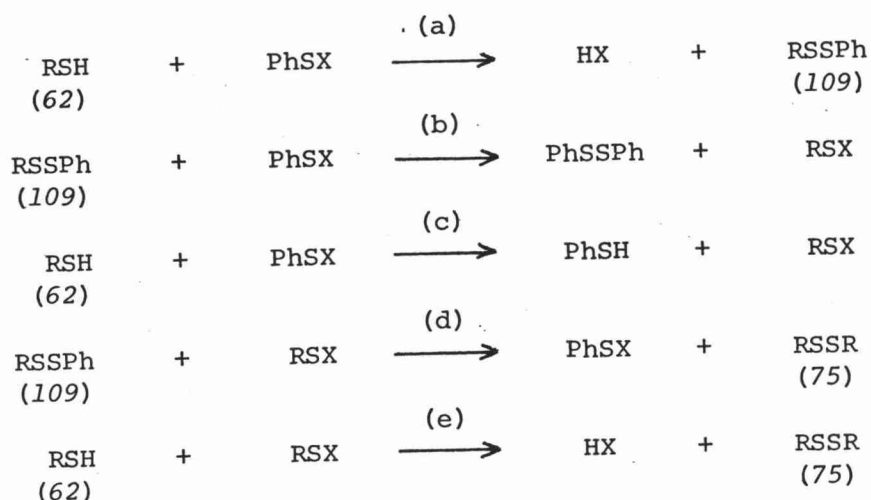
The reaction of symmetrical disulphide (75) with tris(diethylamino)-phosphine (104) in boiling benzene gave one major and at least seven minor carbohydrate products as judged by t.l.c. Direct crystallisation procedures gave the expected β-D-glucopyranosyl 1-thio-α-D-glucopyranoside octaacetate (97) in 52% yield. This result was in agreement with that of Harpp and Gleason¹⁶⁹ who reported isolating this α,β-sulphide (97)

by this desulphurisation method in 47% yield (or 84% "crude yield") but who only reported the one proton low-field doublet observed for its equatorial anomeric proton (H_1 in Scheme 33) by way of characterisation.

Synthesis and Partial Desulphurisation of an Unsymmetrical Disulphide

Phenyl tetra-*O*-acetyl- β -D-glucopyranosyl disulphide (109) was chosen as a suitable unsymmetrical disulphide because its partial desulphurisation as depicted in reactions (a) and (c) of Scheme 35 would lead to the difficultly accessible phenyl tetra-*O*-acetyl-1-thio- α -D-glucopyranoside (82).⁹⁹ Of the two methods that have been reported for the synthesis of disulphide (109), the condensation of benzenesulphenyl chloride (113) with tetra-*O*-acetyl-1-thio- β -D-glucopyranose (62)¹⁷⁰ was more attractive than that between tetra-*O*-acetyl- β -D-glucopyranosyl sulphenyl bromide (114) and thiophenol¹⁷¹ because of the greater stability of the aromatic sulphenyl halide. Application of the former method led to a product containing mainly the glucosyl phenyl disulphide (109) along with some bis(tetra-*O*-acetyl- β -D-glucopyranosyl)disulphide (75), these two compounds being isolated in 60% and 6% yield respectively by fractional crystallisation. When this reaction was repeated using benzenesulphenyl bromide (115), however, the product contained both disulphides (109) and (75) in significant proportions, and these compounds were isolated in 14% and 26% yield respectively.

An explanation of these results is contained in Scheme 34. The sulphenyl halide (PhSX) which is involved in condensation reaction (a) to produce the required unsymmetrical disulphide (109), can also enter the exchange reactions (b) and (c) to produce the glucosyl sulphenyl halide (RSX). This can then generate the symmetrical disulphide (75) in either a further exchange (d), or the condensation (e). Benzenesulphenyl chloride (113) participates less readily in these exchange reactions than does benzenesulphenyl bromide (114) presumably because the former has a stronger halogen-sulphur bond. Exchange reactions involving sulphenyl halides and disulphides similar to those shown in reactions (b) and (d) have been reported before,¹⁷² and the symmetrical disulphide (75) was also observed



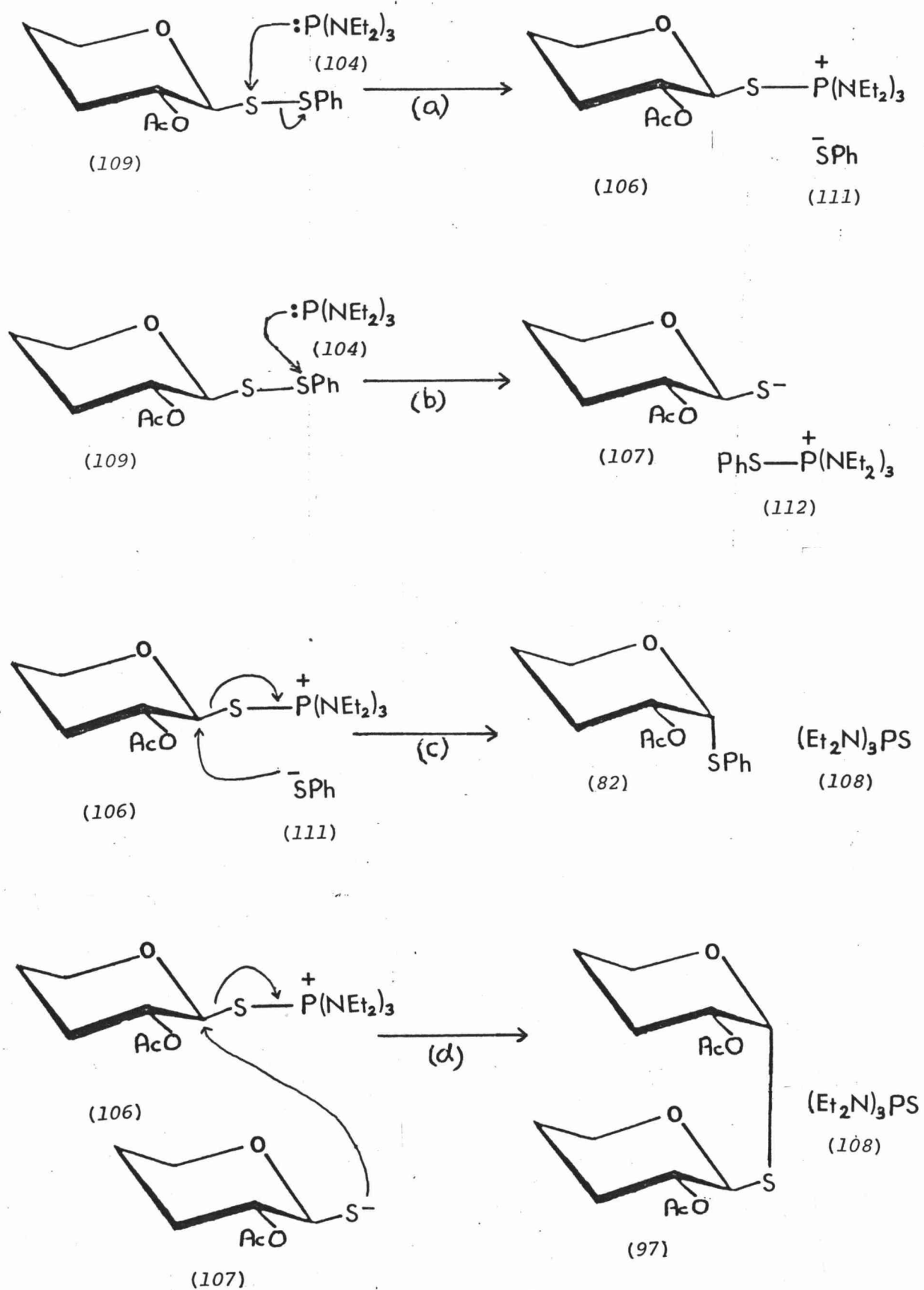
Scheme 34

(R = tetra-O-acetyl- β -D-glucopyranosyl)

as a minor product in the reaction of the glucosyl sulphenyl bromide (114) with thiophenol.¹⁷¹

The reaction of the glucosyl phenyl disulphide (109) with tris-(diethylamino)phosphine (104) in boiling benzene gave as major products in about equal proportions, not only the desired phenyl tetra-O-acetyl-1-thio- α -D-glucopyranoside (82) but also β -D-glucopyranosyl 1-thio- α -D-glucopyranoside octaacetate (97). The latter was isolated in 29% yield by direct crystallisation, but the α -thiogluco-side (82) was obtained pure in only 11% yield after p.l.c. and recrystallisation, although it was shown (n.m.r.) to be present in 42% yield in the syrup initially isolated by p.l.c. which was a mixture of tris(diethylamino)phosphine sulphide (108) and α -thiogluco-side (82) in the ratio 2:3. A number of other minor carbohydrate products were detected (t.l.c.) in this reaction mixture, but none in sufficient quantity to permit identification or isolation.

An explanation for the production of α,β -sulphide (97) which is consistent with the desulphurisation mechanism proposed by Harpp and Gleason¹⁶⁹ is shown in Scheme 35. Initial nucleophilic cleavage of the disulphide (109) can occur in two ways [i.e. reactions (a) and (b)]. While the ion pair (106) and (111) can recombine with elimination of the phosphine sulphide (108) to give the α -thiogluco-side (82) [reaction (c)], it is not possible for the ion pair (107) and (112) to react similarly



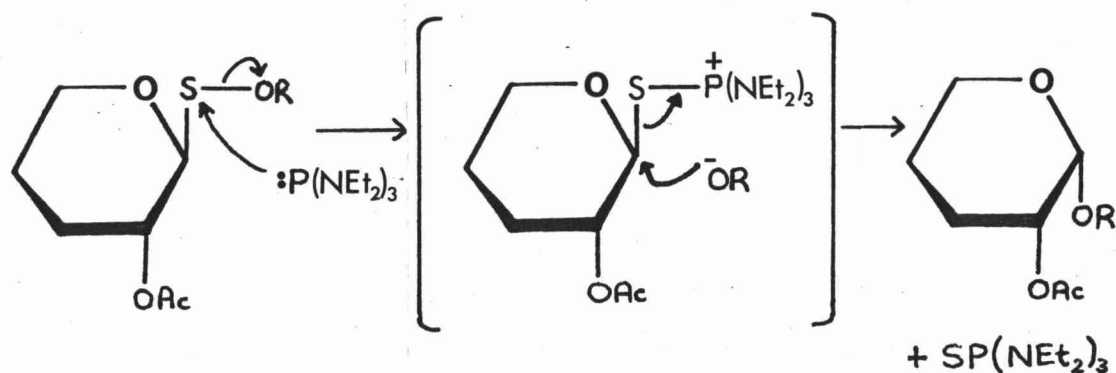
Scheme 35

since this would require a nucleophilic substitution at an aromatic carbon atom. The thiolate anion (107), however, appears to compete with thiophenate anion (111) for the cation (106), reaction (d) leading to the formation of the α,β -sulphide (97). Similar scrambling with the production of symmetrical sulphides has been observed in the partial desulphurisations of unsymmetrical benzylic disulphides¹⁷³ and unsymmetrical cystine derivatives.¹⁷⁴ Thus, while aminophosphine partial desulphurisation appears to proceed without C-2 acetoxy-group participation, this general approach does not appear to be applicable to the general synthesis of 1,2-*cis*-1-thioglycosides (*i.e.* unsymmetrical sulphides) on a preparative scale because of the simultaneous production of symmetrical sulphides.

CHAPTER FIVE

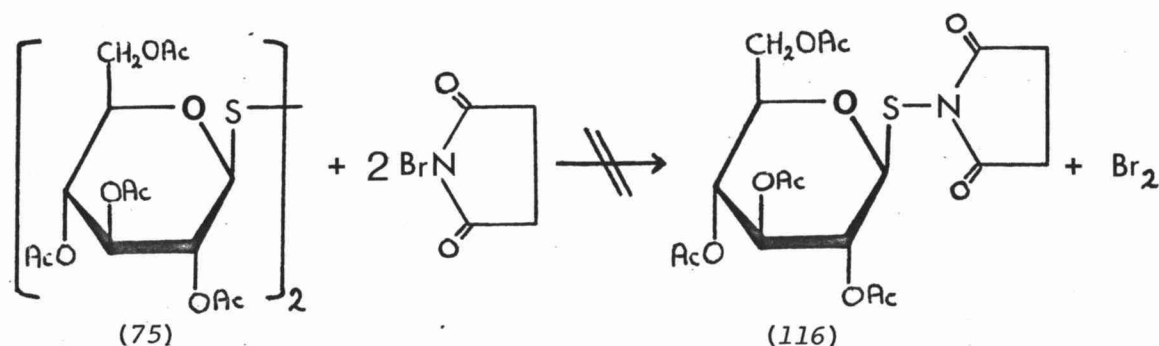
REACTIONS INVOLVING *N*-BROMOSUCCINIMIDEIntroduction

If aminophosphines were able to desulphurise sulphenate esters (RSOR') in the same way that they desulphurise disulphides (RSSR'), as discussed in Chapter 4, then the generalised reaction in Scheme 36 would constitute a new route to 1,2-*cis*-*O*-glycosides. It is possible for either desulphurisation or deoxygenation to occur on treating sulphenate esters with trivalent phosphorous compounds. Barton and co-workers originally reported¹⁷⁵ that *O*-alkyl-*t*-butylsulphenates (good models for glycosyl esters) were desulphurised to ethers by the use of tri-*n*-butylphosphine, but later¹⁷⁶ they were not able to reproduce these results and found instead only deoxygenation and sulphides as products. It was considered, however, that the use of highly nucleophilic aminophosphine might favour the desulphurisation process.¹⁷⁷

Scheme 36

Hence, an attempt was thus made to prepare an *O*-alkyl-(tetra-*O*-acetyl- β -D-glucopyranosyl)sulphenate, the envisaged synthetic route involving initial preparation of the *N*-(glucosylthio)succinimide derivative

(116), as shown in Scheme 37, and subsequent formation of the sulphenate ester from this by nucleophilic displacement of succinimide ion from sulphur by alkoxide ion. Although Groebel¹⁷⁸ found that a variety of *N*-(alkyl- and aryl-thio)succinimides were produced in good yield by the reactions of disulphides with *N*-bromosuccinimide (NBS) in boiling carbon tetrachloride containing the radical initiator benzoyl peroxide, when an analogous reaction between bis(tetra-*O*-acetyl- β -D-glucopyranosyl)disulphide (75) and NBS was attempted, much of the disulphide remained unreacted even though the NBS was converted to succinimide. Thus, each molecule of disulphide (75) which did undergo reaction apparently suffered several hydrogen abstractions.

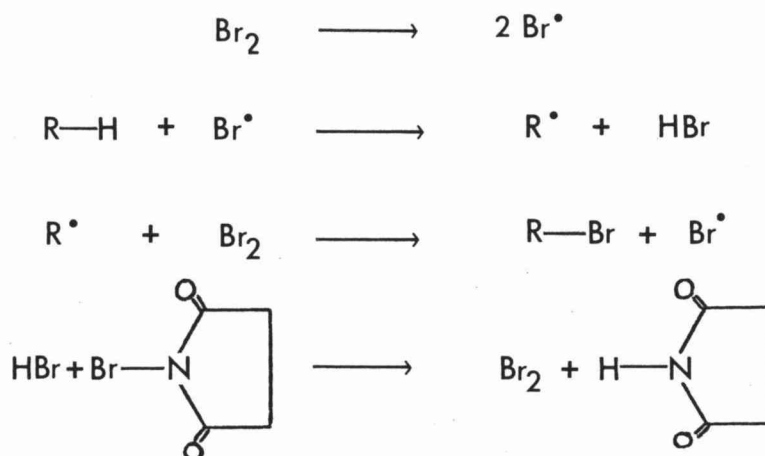


Scheme 37

So as to assist with the elucidation of this complex process, the effect of NBS on the less complex model compound phenyl tetra-*O*-acetyl-1-thio- β -D-glucopyranoside (81) was chosen for an initial study. While the reactions of NBS with this and other carbohydrate derivatives have not assisted in the search for better routes to the *O*- and *S*-glycosides (p. 1), they have proved to be sufficiently novel to warrant the intensive investigations which are reported in this chapter.

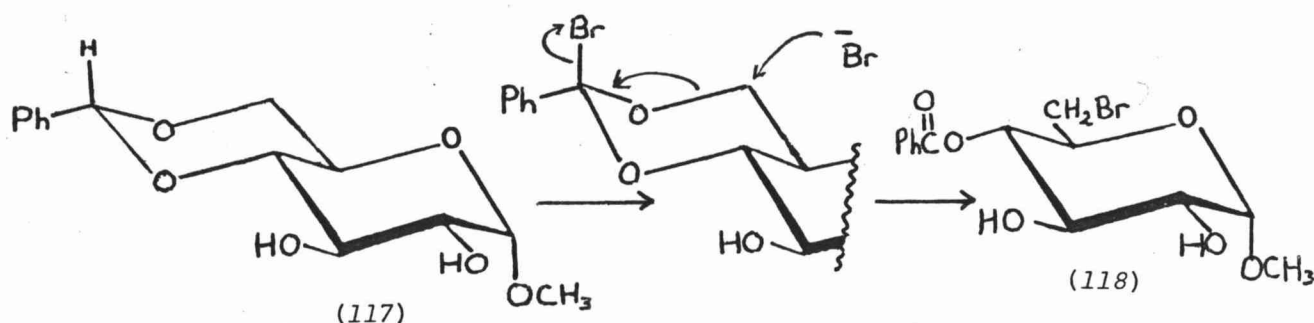
NBS is a versatile brominating reagent, acting under free radical conditions (e.g. in the presence of a radical initiator such as benzoyl peroxide, or under the influence of white light) as shown in Scheme 38, bromine molecules and atoms being gradually released as the reaction

proceeds.¹⁷⁹ Although NBS is capable of brominating even relatively unreactive aliphatic compounds,¹⁸⁰ its greatest advantage (over, for example, bromine) rests in its ability to selectively brominate particular activated sites. Thus NBS accomplishes allylic or benzylic brominations, while not causing double bond additions or aromatic substitutions.¹⁸¹



Scheme 38

Perhaps the most significant application of NBS to carbohydrate chemistry has been in the bromo-sugar synthesis developed by Hanessian and co-workers.¹⁸² They found that 4,6-*O*-benzylidenehexopyranosides [e.g. (117)] yielded 4-*O*-benzoyl-6-bromo-6-deoxy-derivatives [e.g. (118)] on reaction with NBS under radical conditions, and postulated as one possible mechanism, that shown in Scheme 39 involving an initial radical bromination of a benzylic site, followed by an ionic displacement process at the primary carbon atom. Derivatives in which a benzylidene acetal group bridged two secondary positions also underwent reaction, but isomeric bromobenzoates were obtained as a result of bromine being incorporated at both of the secondary carbon atoms involved. This method of preparing bromo-sugars is finding wide application.¹⁸³



Scheme 39

Other applications of NBS in the carbohydrate field involve its ability (i) to act as an oxidising agent,^{184,185} (ii) in combination with triphenylphosphine, to cause replacement of a primary hydroxy-group with bromine,¹⁸⁶ or (iii) to brominate allylic¹⁸⁷ or benzylic¹⁸⁸ sites in the usual way.

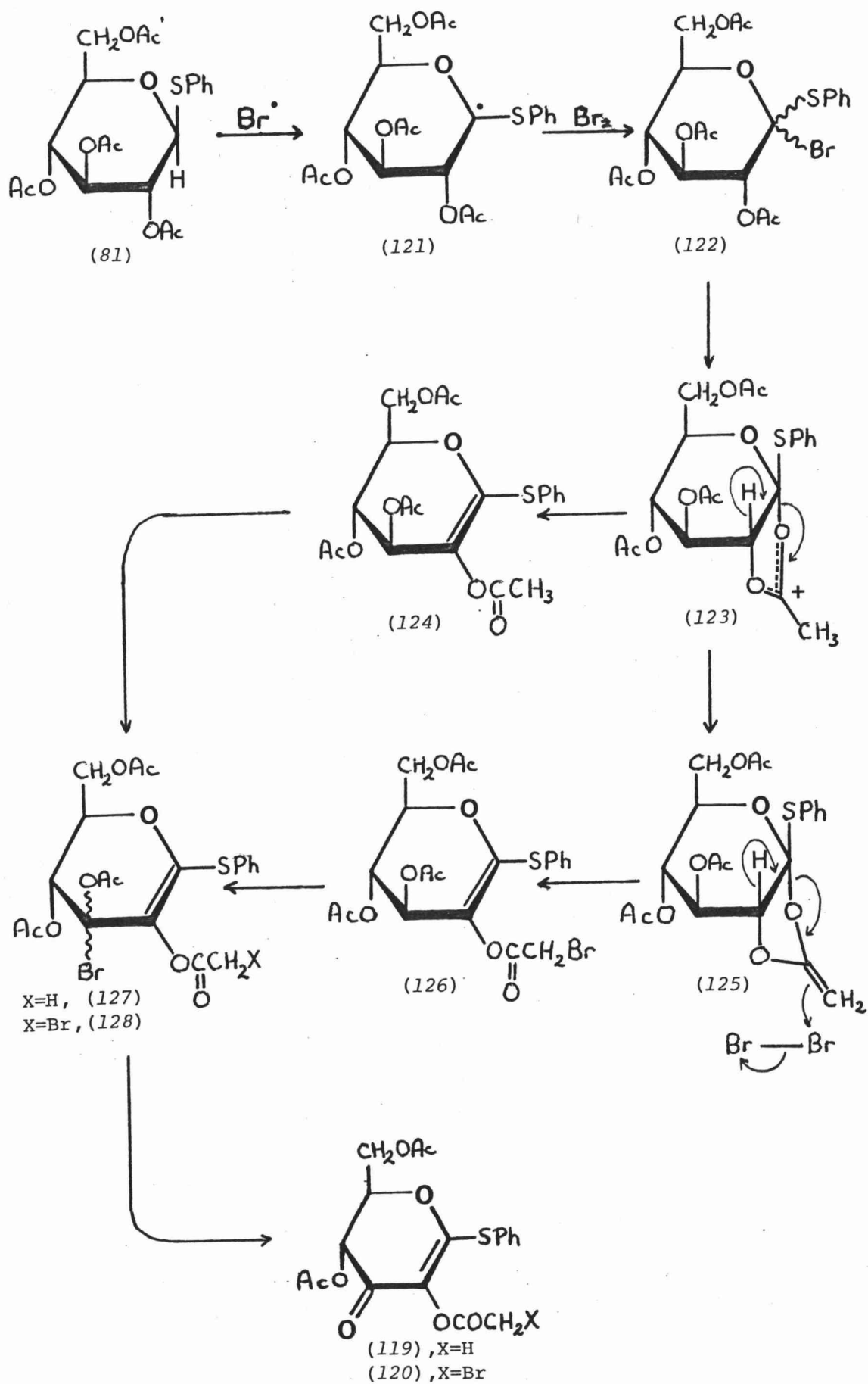
RESULTS AND DISCUSSION

Reactions of NBS with 1-Thioglycosides

From the reaction of phenyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (81) with NBS (3 mol. equiv.) in boiling carbon tetrachloride under the influence of an incandescent bulb, a crystalline mixture of phenyl 2,4,6-tri-*O*-acetyl-1-thio-D-erythro-hex-1-enopyranosid-3-ulose (119) and what appeared (see later) to be its 2-*O*-monobromoacetyl analogue (120) in the ratio 3:1 was obtained in a 45% yield. The components of this mixture could not be separated by repeated recrystallisation, and pure samples of the enosiduloses were obtained only by chromatographic separation. The mother liquors from the reaction were shown (t.l.c.) to contain a number of products and were not further investigated.

The remarkable transformations occurring in this reaction can be understood in terms of the mechanism set out in Scheme 40. Since the production of the enosiduloses (119) and (120) can be rationalised in terms of either a wholly radical or a combination of radical and ionic processes, each of which can occur in either a stepwise or a concerted manner, and since there is no evidence available to suggest which of these alternatives is the more likely, the steps depicted in Scheme 40 were postulated only because of their relative simplicity.

The reaction was dependent on a strong flux of visible light; in the dark it did not proceed, while in diffuse light there was competitive formation of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (96) from the reaction of the β-thioglycoside (81) with bromine¹⁸⁹ (p. 27). This indicates that the initial step in the reaction is a radical process, which is considered to be the bromination of the β-thioglycoside (81) at C-1 [(81)→(121)→(122)]. Although no examples of reactions involving NBS and monothioacetals have been encountered in the literature, some simple



Scheme 40

acetals,^{190,191} especially those which are additionally activated by being benzylic^{182,191} or having an α -keto-function,¹⁹² undergo reactions which involve initial brominations of their acetal centres (see Scheme 39) analogous to that proposed for the thioacetal centre of β -thioglucoside (81). Presumably because of the greater reactivity of the benzylic sites in acetylated *m*-ethylphenyl glycosides¹⁸⁸ and *O*-benzylidenated methyl glycosides (see p. 67), the anomeric centres in these compounds were unaffected during reactions with NBS under free radical conditions. *S*-Glycosides would be expected to be more susceptible than *O*-glycosides to hydrogen abstraction from the anomeric centre, however, since a sulphur atom is known to stabilise an adjacent carbon radical better than an oxygen atom.¹⁹³

The bromination of the C-2 acetoxy-group is apparently a competing reaction which does not interfere with the overall transformation, and this suggests the intermediacy of acetoxonium ion (123), which can be formed following loss of bromide ion from (122), and which can collapse with loss of a proton from C-2 before [(123) \rightarrow (124)] or after [(123) \rightarrow (125) \rightarrow (126)] bromination of the methyl group. The intermediacy of an acetoxonium ion has similarly been invoked to explain the perchlorination of the C-2 acetoxy-group in the reaction of penta-*O*-acetyl- β -D-glucopyranose (79) with phosphorous pentachloride.^{110,194} The two enosides (124) and (126) can then undergo allylic bromination to give (127) and (128), and these can eliminate acetyl bromide to produce the required enosiduloses (119) and (120).

Because the competitive bromination of the C-2 acetoxy-group would be eliminated by employing benzoyl protecting groups, the reaction of phenyl tetra-*O*-benzoyl-1-thio- β -D-glucopyranoside (83) with NBS was attempted, and as expected, the sole product was phenyl 2,4,6-tri-*O*-benzoyl-1-thio-D-*erythro*-hex-1-enopyranosid-3-ulose (130), (see Scheme 41) which was isolated in 76% yield.

Since the enosiduloses (119), (120) and (130) are formed from the β -thioglucosides with loss of chirality at C-1, they should be equally well obtainable from the reactions of the tetraacetate (82) and the tetra-benzoate (131) of phenyl 1-thio- α -D-glucopyranoside with NBS. As expected, the tetraacetate (82) did yield a crystalline mixture of the enosiduloses (119) and (120), and the tetrabenzoate (131) did yield the enosidulose

(130), but a most significant difference was the *ca.*, ten times slower rates of reactions of these α -thiogluco-sides as compared with their β -counterparts. In contrast to the faster abstraction of equatorial than axial hydrogens from cyclohexanol derivatives, it has been shown that the axial acetal hydrogen of a 2-methoxy-tetrahydropyran derivative undergoes a photochemically induced abstraction about eight times faster than does the equatorial hydrogen of an isomeric derivative, the axial hydrogen abstraction evidently being assisted by participation by the ring oxygen's lone-pair electrons in the bond breaking step¹⁹⁵ (*c.f.* p. 11). Similarly, the overall rates of enosidulose formation are evidently determined by the initial radical processes in which the axial anomeric hydrogens of the β -thiogluco-sides are more readily abstracted than the equatorial anomeric hydrogens of the α -thiogluco-sides.

Analogous results were obtained from the light catalysed reactions of 1-thio- $\underline{\text{D}}$ -galactose derivatives with NBS.

The reaction employing phenyl tetra-*O*-acetyl-1-thio- β - $\underline{\text{D}}$ -galactopyranoside (84) yielded a crystalline mixture of phenyl 2,4,6-tri-*O*-acetyl-1-thio- $\underline{\text{D}}$ -threo-hex-1-enopyranosid-3-ulose (132) (see Scheme 41) and a compound which appeared (see later) to be its 2-*O*-monobromoacetyl analogue (133) in the ratio 3:1 in 36% yield. Because these two components had nearly identical mobilities on t.l.c., no attempt was made to separate them by chromatography. The minor component was removed from the mixture by repeated recrystallisation, however, and a pure sample of the threo-enosidulose (132) was obtained in 18%. After removal of the initial crystalline mixture, the mother liquors were shown (t.l.c.) to contain a number of products and were not further investigated. As expected, the reaction of phenyl tetra-*O*-benzoyl-1-thio- β - $\underline{\text{D}}$ -galactopyranoside (134) with NBS gave phenyl 2,4,6-tri-*O*-benzoyl-1-thio- $\underline{\text{D}}$ -threo-hex-1-enopyranosid-3-ulose (135) (see Scheme 41) as the sole product, isolated in 83% yield.

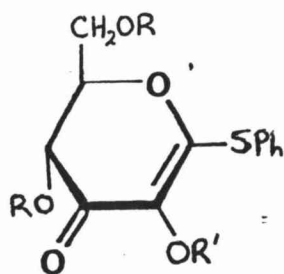
The reaction products so far described as enosiduloses can alternatively be considered as 2-phenylthio- derivatives of 2,3-dihydropyran-4-one (136) (the non-carbohydrate numbering system of which is shown in Scheme 41). A review of recent literature (1965 on) revealed over fifty examples of 2,3-dihydropyran-4-one derivatives, but no examples of such derivatives with an oxy- or thio- linked substituent at position 2 (the "anomeric position") were encountered. A comparison of the spectral characteristics of these reported derivatives with those of the enosiduloses reported here (n.m.r., Table 2; u.v., Table 3; and i.r., Table 4), however,

provided confirmation of the structures assigned to the latter. To avoid confusion, all such 2,3-dihydropyran-4-one derivatives which will be considered in the following discussion are shown in Scheme 41, along with their literature references, and will be referred to as 1-enopyran-3-ulose derivatives with the carbohydrate numbering system shown for compound (137).

The assumption that the competitive acetoxy-group brominations which occurred during enosidulose formation from the acetylated thioglucosides involved the C-2 rather than the C-4 or C-6 acetoxy-groups was made on the basis that a simple mechanistic interpretation of the reaction was available (Scheme 40), and that it was the down-field acetoxy-group resonances (assigned to the "vinylic" C-2 acetoxy-groups) which were missing from the n.m.r. spectra of the monobromoacetate derivatives (120) and (133). The assignments of the resonances in the range $\delta 1.8-2.1$ to "aliphatic" acetoxy-groups and those in the range $\delta 2.2-2.3$ to "vinylic" acetoxy-groups were corroborated by the chemical shifts observed for acetoxy-groups in related 1-enopyran-3-ulose derivatives; the "vinylic" acetoxy-groups of compounds (137), (138), (139), and (140) occur at $\delta 2.19$, 2.28 , 2.20 and 2.22 respectively, whereas the "aliphatic" acetoxy-group of compound (140) occurs at $\delta 2.11$.

It can be seen from the n.m.r. data in Table 2 that while compounds (119), (120) and (130), in which the substituents on C-4 and C-5 are *trans*-related, have $J_{4,5} = 12\text{Hz}$, compounds (132), (133) and (135), in which the substituents on C-4 and C-5 are *cis*-related, have $J_{4,5} = 3.5\text{Hz}$. The difference in the magnitude of $J_{4,5}$ can be understood in terms of half-chair conformations for the 1-enopyran-3-ulose rings, the two possible conformers for compounds (119) and (132) being depicted in Scheme 42. The large coupling constant in compound (119) implies that it exists in the 4H_5 conformation (119a), which has a large H-C-C-H dihedral angle, $\phi_{4,5}$, rather than in the 5H_4 conformation (119b), which has a relatively small dihedral angle, $\phi_{4,5}$. Although both conformers (132a) and (132b) for enosidulose (132) have relatively small dihedral angles, $\phi_{4,5}$, consistent with the small coupling constant, $J_{4,5} = 3.5\text{Hz}$, the 4H_5 conformer (132a) in which the C-4 acetoxy-group adopts a quasi-axial orientation is considered to be the more probable by analogy to the following observations:

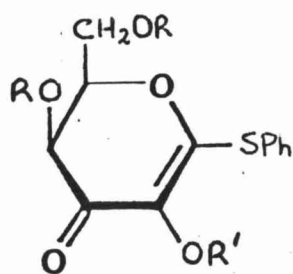
- (i) in cyclohexanone derivatives electronegative substituents α to the carbonyl functions are stabilised in axial orientations (in which dipole



(119), R=R'=Ac

(120), R=Ac, R'=COCH₂Br

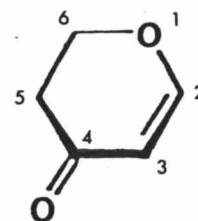
(130), R=R'=Bz



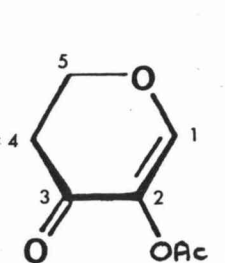
(132), R=R'=Ac

(133), R=Ac, R'=COCH₂Br

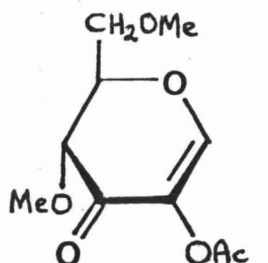
(135), R=R'=Bz



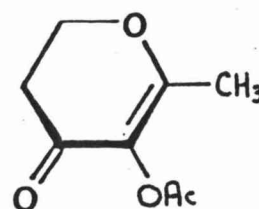
(136)



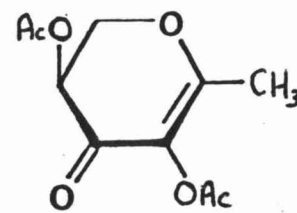
(137) 189 196



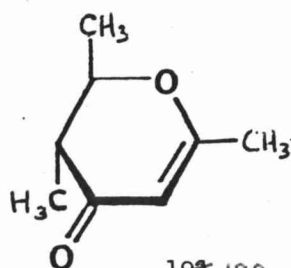
(138) 190 197



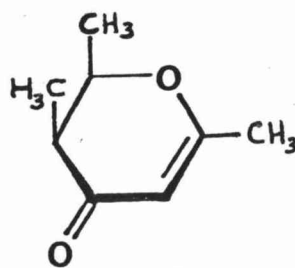
(139) 191 198



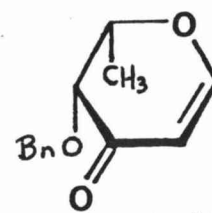
(140) 191 198



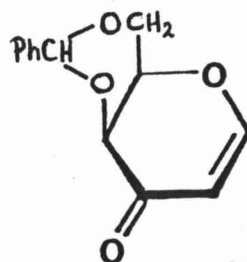
(141) 192 199



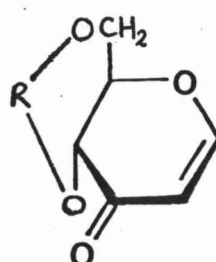
(142) 192 199



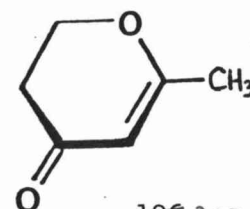
(143) 193 200



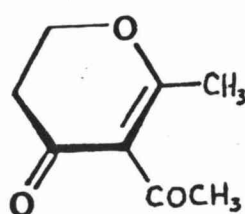
(144) 194 201



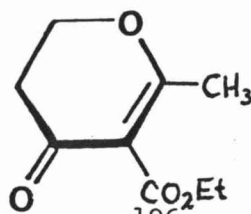
(145), R=PhCH 194 201

(146), R=CH₃CH 194 201(147), R=(CH₃)₂C 195 202

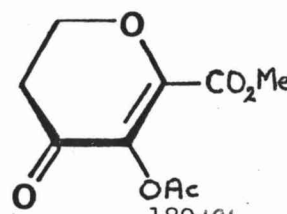
(148) 196 203



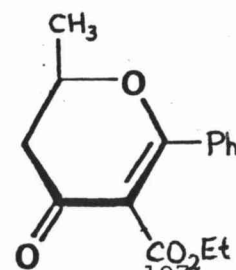
(149) 196 203



(150) 196 203



(151) 189 196



(152) 197 204

Scheme 41

Table 2 N.m.r. data for the hex-1-enopyranosid-3-uloses (δ , in chloroform-*d*)

Assignment	Multiplicity ^a	Compounds			
		(119) ^b	(132) ^b	(130)	(135)
-OCOCH ₃ (aliphatic)	{ S	1.92	1.83	-	-
	{ S	2.11	2.09	-	-
-OCOCH ₃ (vinyllic)	S	2.20	2.21	-	-
H-6	q	4.04			4.43
H-6'	q	4.30	4.0-4.3	4.3-4.7	4.70
H-5	oct	4.74	4.67	5.00	5.06
H-4	d	5.50	5.45	5.95	5.89
PhS-	m	7.2-7.6	7.1-7.5	-	-
PhS-, σ - and <i>m</i> -PhCO ₂ -	m	-	-	7.0-7.7	6.9-7.6
<i>m</i> -PhCO ₂ -	m	-	-	7.7-7.3	7.6-8.2

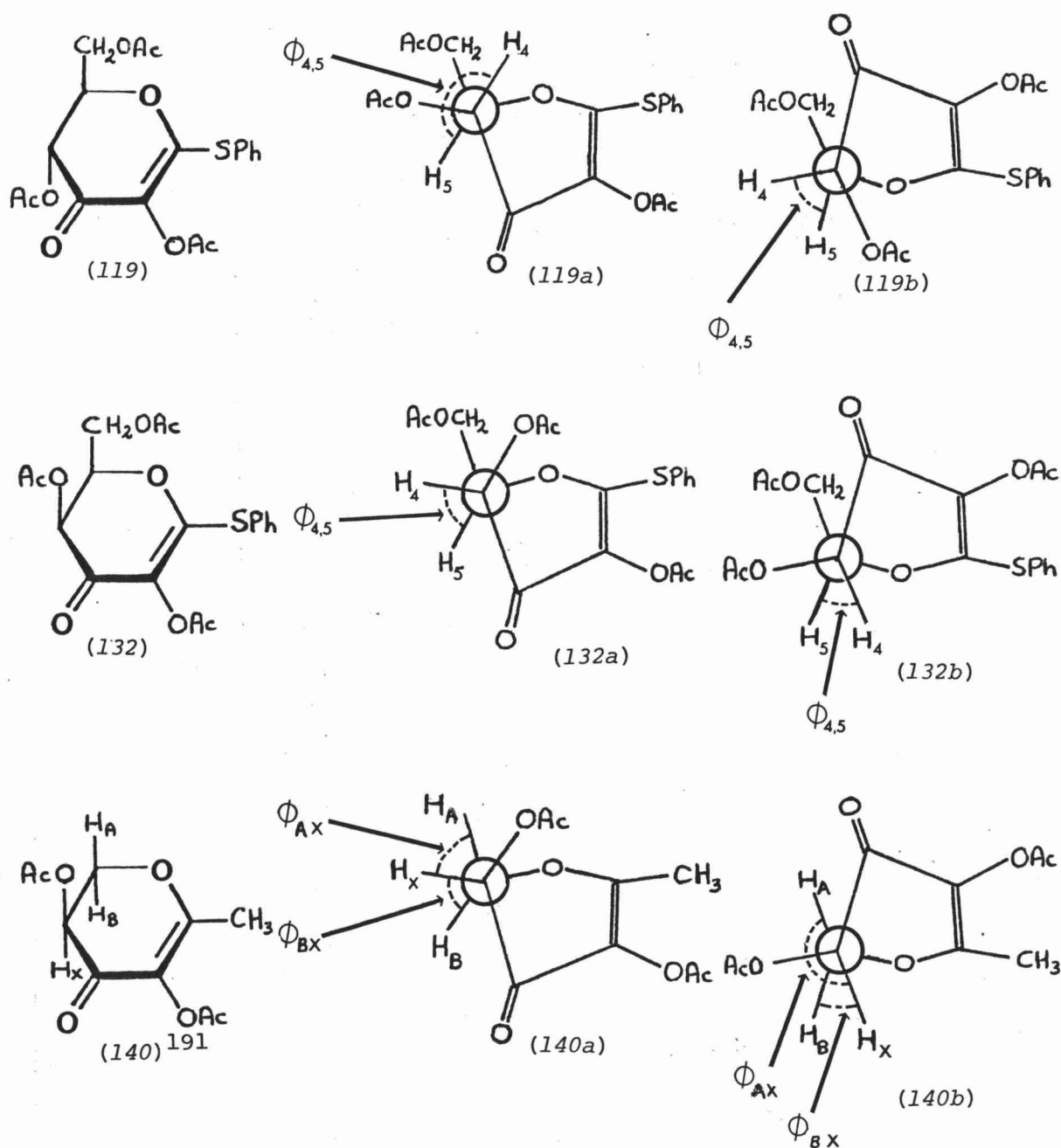
Coupling Constants (Hz)

$J_{4,5}$	12	3.5	12	3.5
$J_{5,6}$	2.7	5.5	4.3	4.5
$J_{5,6'}$	4.8	6	4.7	6.5
$J_{6,6'}$	12	-	-	12

Notes: a, s=singlet, d=doublet, q=quartet, oct=octet, m=multiplet

b, The n.m.r. spectra of monobromoacetates (120) and (133) are identical in every respect to those (119) and (132) respectively, except that the vinyllic 3-proton acetoxy-group resonances in the latter two were replaced by 2-proton bromoacetoxy-group singlets at δ 3.95 and δ 4.00 respectively.

repulsions are minimised) relative to equatorial orientations;²⁰⁷
(ii) Mills and co-workers¹⁹⁸ were able to conclude that compound (140) also existed in the 4H_5 conformation (140a), in which the acetoxy-group is in a quasi-axial orientation, from the near equality of the observed J_{AX} (6Hz) and J_{BX} (8Hz) which was consistent with the nearly equal dihedral angles, ϕ_{AX} and ϕ_{BX} , of conformer (140a) rather than the large and small dihedral angles, ϕ_{AX} and ϕ_{BX} , of the alternative 5H_4 conformer (140b) (see Scheme 42). Obviously, the other enosiduloses mentioned above exist in the 4H_5 conformation as well.



Scheme 42

Large and small coupling constants, $J_{4,5}$, have been similarly reported for related 1-enopyran-3-ulose derivatives with *trans*- and *cis*-related substituents respectively on C-4 and C-5, and on some occasions these values have been rationalised as above in terms of half-chair conformations.^{198,199,201,205} The *trans*- and *cis*- isomers (141) and (142) thus had $J_{4,5} = 13$ and 3.5 Hz respectively, while the *trans*-compound (138) had the particularly large $J_{4,5} = 17.5$ Hz, and the *cis*-compounds (143) and (144) had $J_{4,5} = 2$ Hz. The H-4 doublets recorded for the acetylated enosiduloses (Table 2) occurred in the region δ 5.45-5.00, and, as would be expected, the Hx quartet in compound (137) (see Scheme 42) was centred near this at δ 5.41.

In Table 3 are listed the u.v. absorption bands associated with the β -keto-enol chromophores which have been observed in this work for the enosiduloses and which have been reported for some related 1-enopyran-3-ulose derivatives. While the unsubstituted $O=C-C=C-O$ - chromophore absorbs in the λ_{\max} 260-270 nm region, the enosiduloses absorb in the λ_{\max} 301-312 nm region, and with greater intensity. Although resonance structures can be drawn to show how C-2 acetoxy-, acetyl- and carboethoxy-substituents can be in conjugation with the β -keto-enol system, these substituents have been observed to have relatively little effect on the absorption maxima [e.g. a shift to longer wavelength of only 7nm was observed in going from the 1-methyl-compound (148) to its 1-methyl-2-acetyl-analogue (149)]. Such substituents on C-1, however, do participate to a greater extent in conjugation, and a shift to longer wavelength of 18nm was observed in going from the 2-acetoxy-compound (137) to its 2-acetoxy-1-carbomethoxy-analogue (151). In addition 1-C-phenyl substituted 1-enopyran-3-ulose derivatives [e.g. (152)] absorb in the λ_{\max} 290-300 nm region.¹⁹⁹ Thus, while the C-2 acetoxy- and benzyloxy-substituents on the enosiduloses would not be expected to influence greatly the u.v. absorption band, it is quite consistent that conjugation of the C-1 phenylthio-substituent with the β -keto-enol system should be responsible for the ca., 40 nm bathochromic shift. In compounds (132) and (135), where the C-4 and C-5 substituents are *cis*-related, λ_{\max} is at longer wavelength by 5 and 9 nm than in the *trans*-analogues (119) and (130) respectively; similarly λ_{\max} is at longer wavelength by 4 nm in the *cis*-compound (144) than in its *trans*- analogue (145). As all of these compounds would appear to adopt the 4H_5

conformation (p.72), the bathochromic shift observed in going from a *trans*- to a *cis*- compound must be the result of the C-4 substituent changing from a quasi-equatorial to a quasi-axial orientation. A similar bathochromic shift is observed for the absorption maxima of cyclohexanone derivatives in which an electronegative substituent α to the carbonyl function goes from an equatorial to an axial orientation,²⁰⁷ but it is realised that in this case the absorptions are due to $n \rightarrow \pi^*$ transitions, while those observed for the enosiduloses are $\pi \rightarrow \pi^*$ transitions.

Table 3 U.v. absorptions for the β -keto-enol chromophores in the hex-1-enopyranosid-3-uloses and some related compounds.

Hex-1-enopyranosid-3-uloses			1-Enopyran-3-uloses ^a			
Compound	λ_{\max}^b (nm)	ϵ	Compound	λ_{\max}^c (nm)	ϵ	Compound λ_{\max}^c (nm) ϵ
			<u>1,2-unsubstituted^d</u>			<u>2-C-acetyl derivatives</u>
(119)	301	20,500	(144)	266	9,900	(149) 271 10,800
(130)	303	17,000	(145)	262	8,400	<u>2-C-carboethoxy-derivative</u>
(132)	306	21,500	(146)	260	7,000	(150) 266 11,900
(135)	312	20,800	(147)	260	8,050	<u>1-C-carbomethoxy-derivative</u>
			(148)	264	15,300	(151) 285 8,100
			<u>2-C-acetoxy-derivatives</u>			<u>1-C-phenyl derivative</u>
			(137)	267	7,900	(152) 290 13,530
			(138)	266	14,500	

Notes: a, Refer to Scheme 41 for structure and literature references.

b, In chloroform.

c, In ethanol.

d, Compound (148) has a 1-C-methyl group.

The i.r. spectra of the enosiduloses (Table 4) reveal bands in the 1720-1780 cm^{-1} and the 1675-1690 cm^{-1} regions which can be assigned to the carbonyl stretching vibrations of the ester and β -keto-enol functions respectively. Although most of the bands observed in the 1565-1605 cm^{-1} region can be assigned to the C=C stretching mode of the β -keto-enol function split by solid state coupling effects, bands due to the C=C stretching vibrations of the phenylthio- or benzyloxy- substituents are also expected to appear in this region since the i.r. spectrum (nujol mull) of phenyl tetra-O-acetyl-1-thio- β -D-glucopyranoside (81) contains a weak band at ca., 1590 cm^{-1} , and those of both phenyl tetra-O-benzoyl-1-thio- β -D-glucopyranoside (83) and penta-O-benzoyl- β -D-glucopyranose (100) reveal small sharp bands at 1580 and 1600 cm^{-1} . In comparison, the acetoxy-group carbonyl absorptions for the 1-enopyran-3-ulose derivatives (140), (141), (142), (143) and (151) all occur in the 1759-1765 cm^{-1} region, which is in the centre of the appropriate range recorded above. For the great majority of 1-enopyran-3-ulose derivatives encountered in the literature, including all those depicted in Scheme 41, $\nu(\text{C=O st.})$ and $\nu(\text{C=C st.})$ associated with the β -keto-enol function were in the regions 1655-1700 cm^{-1} and 1590-1630 cm^{-1} respectively. While the enosiduloses' C=O st., bands also fall within the former region, their C=C st., bands occur at slightly lower frequencies than those in the latter region. Although the i.r. spectral bands in 1-enopyran-3-ulose derivatives appear to be less sensitive than the corresponding u.v. spectral bands to increased conjugation of the β -keto-enol function with C-1 substituents [e.g. compound (137) has ν 1670 and 1620 cm^{-1} , and its 1-carbomethoxy-analogue (151) has ν 1689 and 1620 cm^{-1}], this observed decrease in the enosiduloses' $\nu(\text{C=C st.})$ is very probably due to increased conjugation with the C-1 phenylthio- substituent.

The enosidulose monobromoacetates (120) and (133), either in a purified state or in a crystalline mixture with their unbrominated analogues (119) and (132), underwent decompositions, presumably initiated by the production of hydrogen bromide on storage for several months at room temperature. Purified samples of the acetylated enosiduloses (119) and (132) were considerably more stable, however, and the benzyolated enosiduloses (130) and (135) were stable on storage at room temperature for over a year.

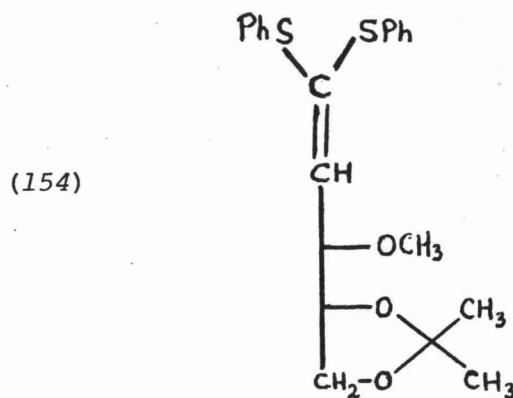
Table 4 I.r. absorptions in the 1500-2000 cm^{-1} region for the hex-1-enopyranosid-3-uloses (cm^{-1} , nujol mull)^a

Assignment	Compounds					
	(119)	(120)	(132)	(130)	(135)	(135) ^b
Ester	1780s	1765sh	1775sh	1750m	1745sh	1730s
C=O st.	1760s	1750s	1755s	1730s	1735s	
	1740sh	1735sh	1739sh		1720m	
β -keto-enol C=O st.	1680s	1680s	1675s	1690s	1695m	1680s
					1675m	
β -keto-enol and aromatic C=C st.	1565sh	1580s	1575s	1590w	1605sh	1600m
	1570s			1580w	1595w	1595sh
	1575sh			1570sh	1580sh	1565m
					1570m	

Notes: a, s=strong, m=medium, w=weak, sh=shoulder

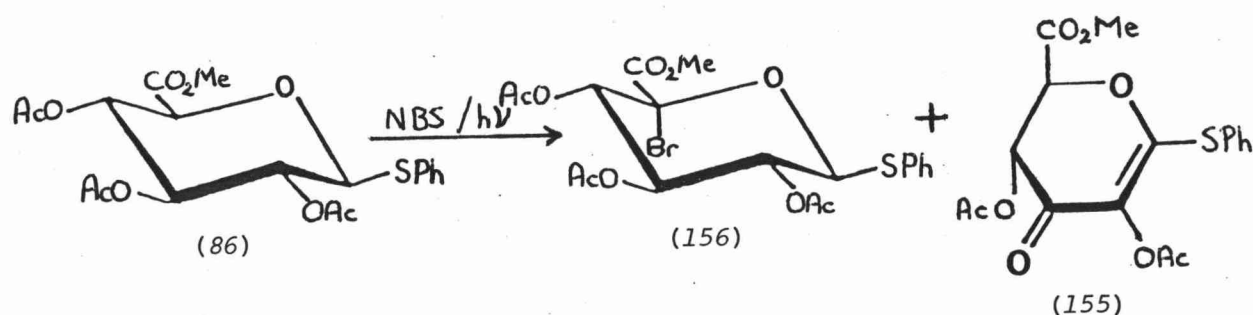
b, in chloroform solution

Although the enosiduloses might appear to have potential value as intermediates in the syntheses of modified carbohydrates, initial experiments indicated that the benzoyletated enosidulose (130) was relatively inert, being recovered unchanged after heating in ethanol under reflux with (i) mercury(II) acetate, (ii) 2,4-dinitrophenyl hydrazine, or (iii) pyridine-acetic anhydride. More vigorous treatment, such as heating in pyridine under reflux succeeded only in causing complete decomposition. The ketene dithioacetal (154), shown below, which contains two vinylic phenylthio-groups, was similarly found to be surprisingly unreactive - notably towards mercury(II) chloride.²⁰⁶



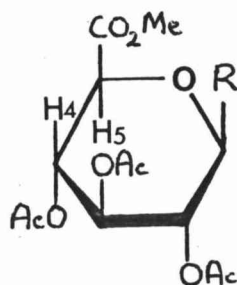
The possibility of preparing enosiduloses from other 1-thioglycoside derivatives was investigated. The light catalysed reaction of NBS with phenyl tri-*O*-acetyl-1-thio- β -D-xylopyranoside (85) was shown by t.l.c. to proceed smoothly to give four new products, two more mobile and two less mobile than the thioxyloside (85), and all detected as bright yellow spots (characteristic of the enosiduloses so far described) on spraying and heating the t.l.c. plates, but this more complex mixture was not further investigated. When methyl (phenyl tri-*O*-acetyl-1-thio- β -D-glucopyranosid)uronate (86) was subjected to the NBS reaction conditions, the two products shown in Scheme 43 were formed smoothly, and were isolated following p.l.c. The major component, a syrup which resisted crystallisation, was considered to be the expected methyl (phenyl 2,4-di-*O*-acetyl-1-thio-D-erythro-hex-1-enopyranosid-3-ulos)uronate (155) since its n.m.r. spectrum included resonances for an "aliphatic" (δ 2.09) and a "vinylic" (δ 2.19) acetyl group, and two doublets for H-4 and H-5. The relatively low value of $J_{4,5}$ (5.5Hz) in this derivative with *trans*-related substituents on C-4 and C-5 probably indicates a quasi-diaxial half-chair conformation. The possibility that this syrup also contained the 2-*O*-monobromoacetyl analogue of (155) could not be eliminated since the methoxy-group resonance (δ 3.71) may hide a small monobromoacetate signal. The other reaction product was methyl (phenyl tetra-*O*-acetyl-5-C-bromo-1-thio- β -D-glucopyranosid)uronate (156) which was isolated crystalline in 12% yield. The assumption that bromination had occurred at the C-5 position was made because this position is α to the C-6 carbonyl function and would thus be expected to be activated with regard to free-radical bromination, and because the resonance observed at δ 3.8-4.3 for H-5 in the starting material (86) (discussed below) was absent in the n.m.r. spectrum of (156). Although the ten peak resonance, δ 4.7-5.8, observed in the 60MHz n.m.r. spectrum of compound (156) could not be assigned more specifically than as being due to H-1,2,3 and 4 (despite the aid of a complementary spectrum obtained in benzene- d^6), the peak separations (ca., 9Hz) were consistent with the four protons being *trans*-axially related. Although the stereochemistry at C-5 in compound (156) has not been determined, it has been tentatively assumed to be that shown in the anomer in Scheme 43, which would be the thermodynamically favoured product, since the substituents on C-5 would

be subject to the "anomeric effect" of the adjacent ring oxygen; this effect favours a bromine atom in an axial orientation (p. 8), and a carbomethoxy-group in an equatorial orientation.²⁰⁸ It must be stated, however, that although the C-5 bromination was demonstrated to be a radical process [no reaction was observed (t.l.c.) when compound (86) and NBS were heated in carbon tetrachloride in the dark], there is no reason to believe that it could not have led to the kinetic product with the alternative configuration at C-5. The novelty of this bromination process led to its further study, and the results of this are described in the next section.



Scheme 43

During this work the 60MHz n.m.r. spectra of methyl (phenyl tri-*O*-acetyl-1-thio-β-D-glucopyranosid)uronate (86), methyl (phenyl tri-*O*-acetyl-β-D-glucopyranosid)uronate (157) and methyl tetra-*O*-acetyl-β-D-glucopyranuronate (93) (see below) were recorded in chloroform-*d*. The *H*-5 resonances in these compounds were expected to be doublets with *J*_{4,5} about 9Hz, but were found to be complex one-proton multiplets centred at δ4.0, 4.2 and 4.15 respectively. Virtual coupling²⁰⁹ appears to be responsible for this greater multiplicity, and it has similarly been invoked to explain the splitting observed in the *H*-5 multiplets centred at δ4.3 in certain methyl (aryl tri-*O*-acetyl-β-D-glucopyranosid)uronates²¹⁰ and at δ4.1 and 4.2 in methyl tri-*O*-acetyl-1-bromo- and 1-chloro-β-D-glucopyranuronates.^{211,212}



(86), R=SPh

(157), R=OPh

(93), R=OAc

Reactions of NBS with methyl esters of carbohydrate acid derivatives

It was apparent from the simultaneous production of the enosidulose (155) and the 5-C-bromo-derivative (156) as described in the preceeding section, that the initial hydrogen abstractions from C-1 or C-5 of compound (86) were competing reactions. Evidently the presence of a C-1 phenylthio-substituent activated the anomeric centre, while a C-5 carbomethoxy-substituent activated C-5. The reactions of NBS with compounds containing only carbomethoxy- substituents were thus investigated, in the hope of effecting uncomplicated bromination reactions. When methyl tetra-O-acetyl- β -D-glucopyranuronate (93) was subjected to the light catalysed reaction with NBS, the sole product was methyl tetra-O-acetyl-5-C-bromo- β -D-glucopyranuronate (158) (see Figure 3) which was isolated in 68% yield. The radical nature of this bromination reaction was confirmed when it was found not to proceed in the absence of light unless benzoyl peroxide, a radical initiator, was added to the reaction mixture. That bromination had occurred at C-5 rather than at the anomeric centre was determined by consideration of the n.m.r. spectra shown in Figure 3; while the C-1 protons of compounds (93) and (158) are clearly distinguishable as low-field doublets at δ 5.97 and δ 6.25 respectively, no resonance analogous to that of the C-5 proton of compound (93) at δ 4.1-4.35 (see p. 81) is seen in the spectrum of compound (158). Again, the stereochemistry at C-5 in compound

(158) has not been determined, but is assumed to be that shown in Figure 3, with the bromine substituent axial, for the reasons previously discussed (p. 80).

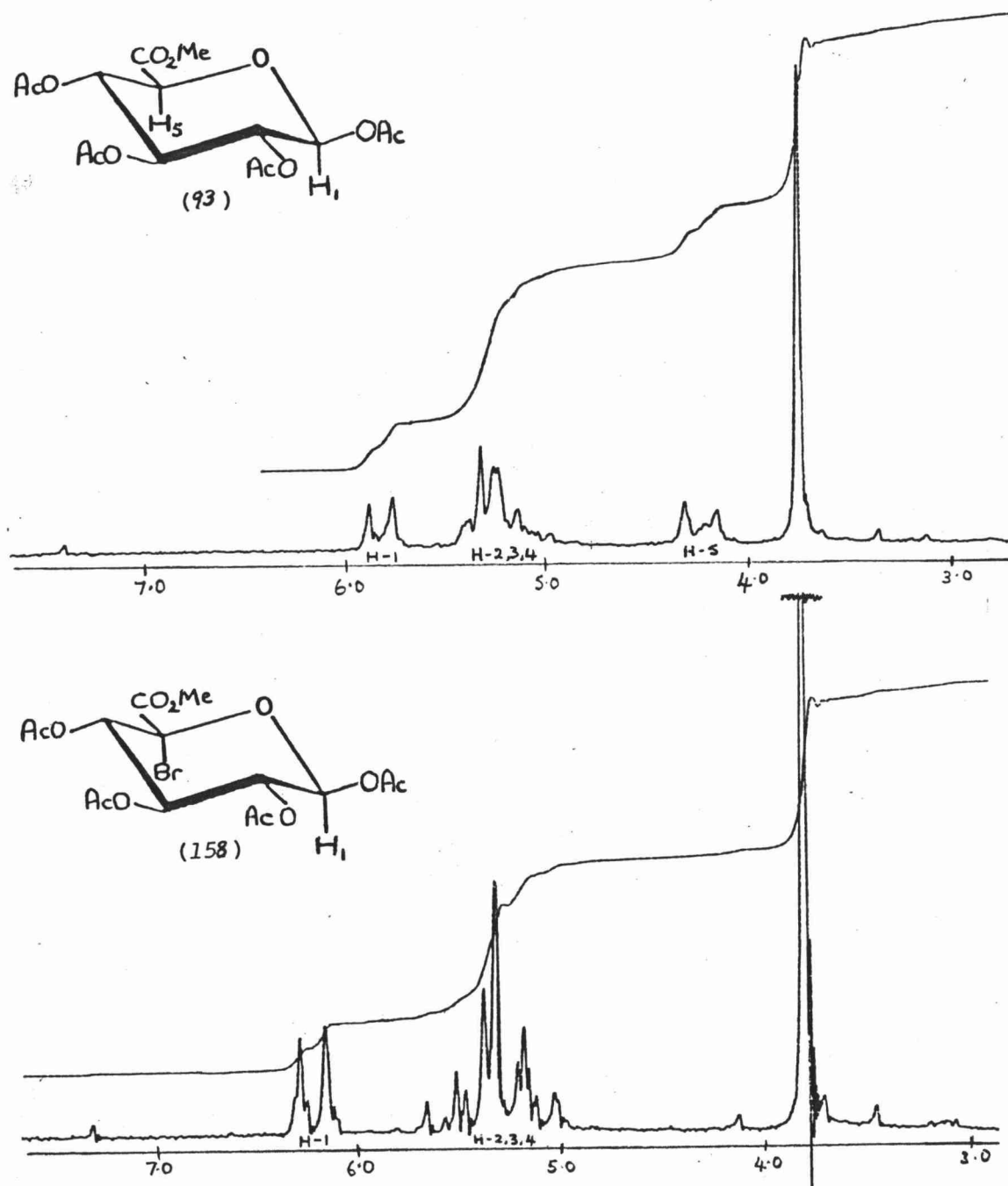
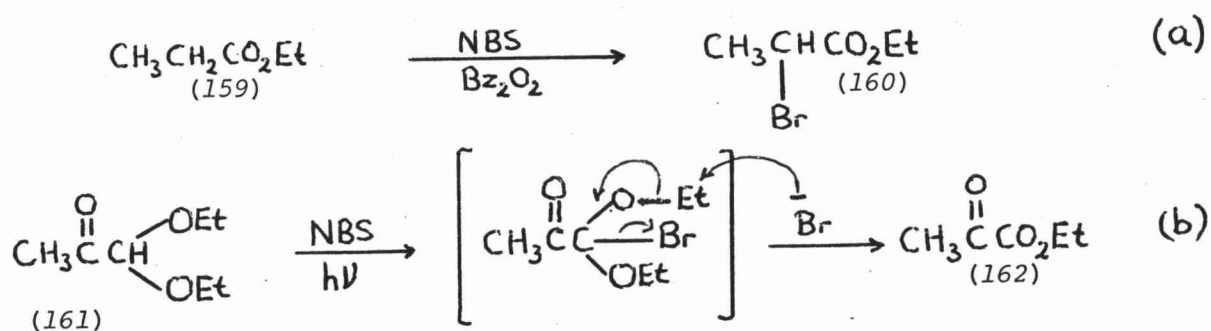


Figure 3. The 60MHz n.m.r. spectra of compounds (93) and (158) in chloroform-*d*.

Surprisingly few examples have been encountered in the literature of brominations α to carbonyl groups such as those reported here which led to compounds (156) and (158). The reaction of ethyl

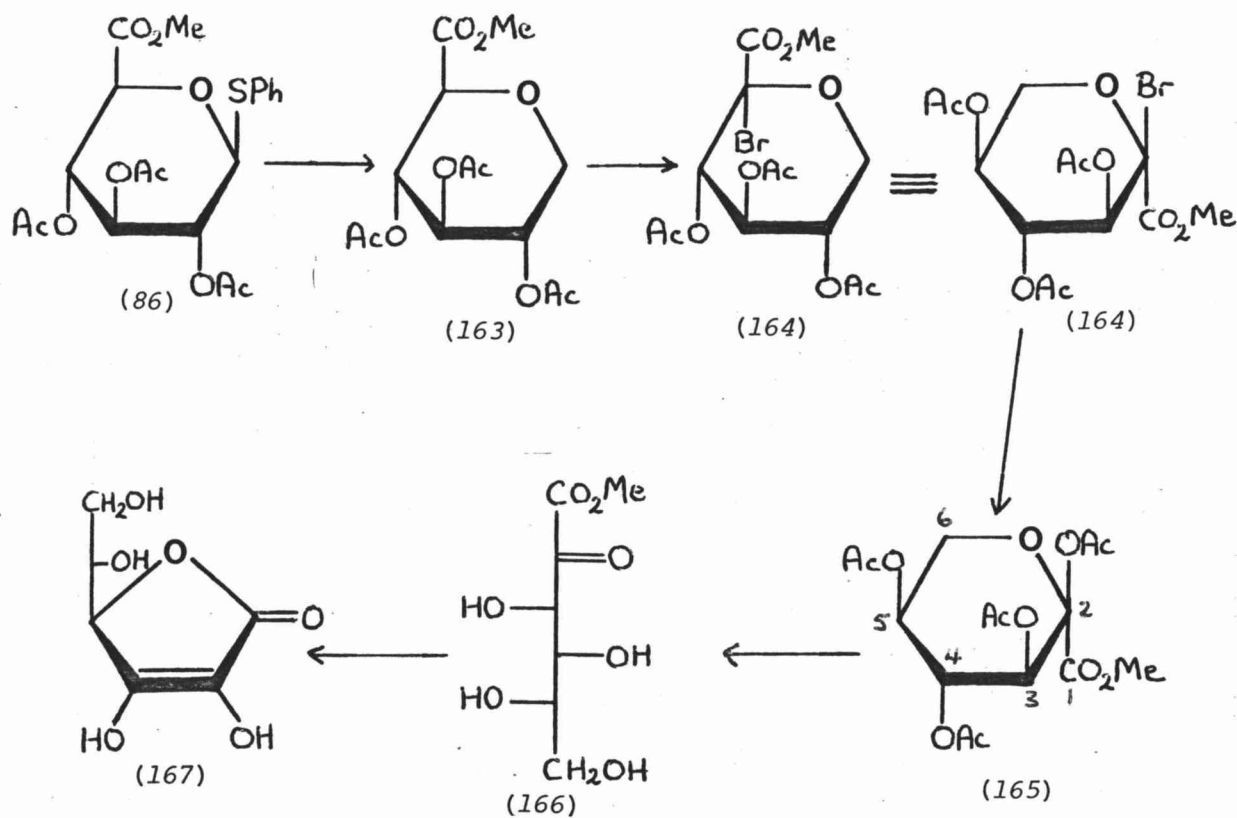
propanoate (159) with NBS under free radical conditions (i.e. in the presence of benzoyl peroxide), however, led to a 42% yield of the α -brominated product (160) [Scheme 44, reaction (a)], although ethyl acetate was unreactive under these conditions.¹⁸⁰ Dialkylacetals of α -ketoaldehydes [e.g. (161) in Scheme 44, reaction (b)] apparently also undergo α -bromination on reaction with NBS under the influence of a 250 watt drying lamp, but the initial products react further (as shown in Scheme 44) to yield α -ketoesters [e.g. (162)].¹⁹² NBS has also been used to effect α -bromination of acid chlorides,²¹³ but these reactions have been shown to involve ionic rather than radical processes, and are therefore not relevant. Apparently, the only previous observations of free radicals being generated by removal of hydrogen atoms from C-5 of either hexopyranose or hexopyranuronic acid units were made during e.s.r. studies of the effects of γ -irradiation from ^{60}Co .²¹⁴



Scheme 44

Finally, methyl tri-*O*-acetyl-2,6-anhydro- $\underline{\underline{L}}$ -gulonate (163), which was synthesised by Raney nickel desulphurisation of methyl (phenyl tri-*O*-acetyl-1-thio- β - $\underline{\underline{D}}$ -glucopyranosid)uronate (86), was subjected to the reaction with NBS and yielded methyl tri-*O*-acetyl-2-bromo-2-deoxy- α - $\underline{\underline{L}}$ -xylo-hex-2-ulo-pyranosonate (164) as shown in Scheme 45. Again, the configuration at the tetrasubstituted carbon atom (C-2) in compound (164) has not been determined, but has been assumed to be that shown below for the thermodynamically favoured anomer in which the bromine would adopt an axial orientation (see p. 80). This product was identical (m.p., $[\alpha]_D$, and n.m.r.) to that

obtained by Tokuyama and co-workers^{196,215} from the reaction of methyl tetra-O-acetyl- α -L-xylo-hex-2-ulopyranosonate (165) with bromine and red phosphorous, a process which is expected to have yielded the thermodynamic product.²¹⁶ It is envisaged that acetolysis of bromide (164) to tetraacetate (165) [preliminary results indicate that mercury(II) acetate in acetic acid is a suitable reagent], and subsequent deacetylation of this, would yield methyl L-xylo-hex-2-ulosonate (166) from which L-ascorbic acid (167) has been synthesised²¹⁷ (Scheme 45). This procedure therefore opens a new synthetic route to Vitamin C.



Scheme 45

CHAPTER SIX

EXPERIMENTAL

General Methods

Melting points were determined using a Gallenkamp melting point apparatus and were uncorrected.

Optical rotations were determined for solutions within the concentration range 1-5 g/100 ml in chloroform containing 2% methanol (unless otherwise stated), in a 1 dm tube, and using a Hilger standard polarimeter.

Microanalyses were performed by Professor A.D. Campbell and his associates, University of Otago.

I.r. spectra were recorded for Nujol mulls on Unicam SP200 and SP1000 spectrophotometers.

U.v. spectra were recorded on a Shimadzu UV200 instrument.

N.m.r. spectra were recorded in chloroform-d (unless otherwise stated), with tetramethylsilane as internal standard, on a Hitachi-Perkin Elmer R20 60MHz instrument operating at 34°.

Solutions were evaporated under reduced pressure at 40°; water azeotropic mixtures at <65°.

High resolution mass spectra were recorded by Dr G.J. Wright, University of Canterbury, on an AEI MS902 spectrometer, while low resolution mass spectra were recorded on Micromass 12F and AEI MS30 instruments.

Purification of Solvents

Chloroform for use in t.l.c., or as a solvent for boron trifluoride catalysed reactions, was first shaken with a small amount of concentrated sulphuric acid, and then purified according to the method of Evans and Reynold.²¹⁸ All other solvents were purified as recommended by Perrin, Armarego, and Perrin.²¹⁹ The light petroleum used in this work was the fraction b.p. 60-68°.

Preparation and Purification of Certain Reagents

(a) N-Bromosuccinimide (NBS) and N-chlorosuccinimide:

The proportions of active halogen in samples of these reagents were determined by titrating with thiosulphate, the iodine liberated by the reactions of NBS or NCS with acidic solutions of potassium iodide. NBS was rapidly recrystallised from water (500 ml per 50 g), and NCS was rapidly recrystallised from benzene (500 ml per 50 g).²¹⁹ The samples were found to have the following percentage activities: commercial NBS, 90.0; recrystallised NBS, 100.0; commercial NCS, 64.4; recrystallised NCS, 91.3%.

(b) Others:

Allyl mercaptan, boron trifluoride diethyletherate, diethylaniline, and thiolacetic acid were distilled under reduced pressure in a nitrogen atmosphere. Tris(diethylamino)phosphine (104) was prepared as described by Harpp and Gleason.²²⁰

Analytical Thin-layer Chromatography (t.l.c.)

Silica gel GF₂₅₄ supplied by Merck was used as the absorbent for t.l.c. plates (length, 20 cm). Components were detected under an ultraviolet lamp at 254 nm and/or by spraying with ethanol- concentrated sulphuric acid-anisaldehyde 93:5:2 followed by heating on a hotplate.

Preparative Thin-layer Chromatography (p.l.c.)

P.l.c. was performed on 1 m x 20 cm plates coated to a thickness of 0.75 mm with silica gel GF₂₅₄. Components were detected under an ultraviolet lamp at 254 nm. Loadings used were 0.5 g - 1 g per plate when good separations were required, components being extracted from the silica gel by elution with ethanol.

Column Chromatography

Silica gel M.F.C. supplied by Hopkin and Williams was used as the packing material, and the loadings were 1 g of mixture to 50-100 g.

Chromatography Solvents

The following solvent mixtures (vol/vol) were employed in this work.

- A 1% methanol in chloroform
- B 2% methanol in chloroform
- C light petroleum-ether, 1:2
- D light petroleum-dichloromethane
- E light petroleum-ethyl acetate, 2:1
- F 2% ethanol in dichloromethane
- G light petroleum-ethyl acetate, 4:1

Benzoylation Reaction Procedures

Carbohydrate derivatives were benzoylated in pyridine with benzoyl chloride, and the mixtures were allowed to stand at room temperature for at least 12h before being tipped onto stirred crushed ice. Benzoic acid and benzoic anhydride are formed in this process, and these contaminate the benzoyl esters (t.l.c. evidence) which are often initially obtained as syrups. These syrups are therefore purified (a) by washing their solutions in chloroform with aqueous sodium bicarbonate, and (b) by adding methanol to their solutions in pyridine, and removing the methyl benzoate so formed by co-distillation with water.

Preparations of Standard Materials

(a) Carbohydrate Derivatives

The peracetates of α -D-glucopyranose, β -D-glucopyranose,

β -D-xylopyranose and β -D-galactopyranose were prepared by standard methods.²²¹ Penta-O-benzoyl- β -D-glucopyranose (100) was prepared by the method of Fletcher *et al.*,²²² and was recrystallised from acetic acid.

Methyl tetra-O-acetyl- β -D-glucopyranuronate (93) was prepared by the method of Bollenback *et al.*²²³ Recrystallised from ethanol it had m.p. 175-176°, $[\alpha]_D + 8^\circ$ [Lit.,²²³ m.p. 176.5-178°, $[\alpha]_D + 7.4^\circ$].

Tri-O-acetyl- β -D-glucurono-3,6-lactone (168) was prepared by the method of Tsou and Seligman.²²⁴ Recrystallised from ethanol containing acetic acid (10% by vol.) it had m.p. 192-194°, $[\alpha]_D + 91^\circ$ [Lit.,²²⁴ m.p. 193-194°, $[\alpha]_D 89.6^\circ$].

1,3,4,6-Tetra-O-acetyl- α -D-glucopyranose (98) was prepared by the method of Helferich and Zirner.²²⁵ Recrystallised from ether it had m.p. 98-99°, $[\alpha]_D + 135^\circ$ [Lit.,²²⁵ m.p. 98-100°, $[\alpha]_D + 141^\circ$].

2,3,4,6-Tetra-O-benzyl- α -D-glucose (99) was prepared by the method of Pfaffli, Hixon and Anderson.¹²¹ Recrystallised from methanol it had m.p. 151-152° $[\alpha]_D + 19^\circ$ [Lit.,²²⁶ m.p. 150-151°, $[\alpha]_D + 20.7^\circ$].

Tetra-O-acetyl-1-thio- β -D-glucopyranose (62) was prepared by the method of Cerny and co-workers (see p. 32) and was obtained as the lower melting isomorph, m.p. 73-76°, $[\alpha]_D + 5.5^\circ$ [Lit.,¹³⁰ m.p. 75° or 115° $[\alpha]_D + 5.8^\circ$], δ 1.97 (6H, s, 2xOAc), 2.04 (6H, s, 2xOAc), 2.30 (1H, d, $J_{1,S}$ 9Hz, exchangeable with D₂O, SH), 3.7 (1H, m, H-5), 4.15 (2H, m, H-6,6'), 4.51 (1H, t, $J_{1,2}$ 9Hz, H-1; d after D₂O shake) and 4.72-5.25 (3H, m, H-2,3,4).

1-Thio- β -D-glucopyranose pentaacetate (63) was prepared from penta-O-acetyl- β -D-glucopyranose (79) by generating tetra-O-acetyl- α -D-glucopyranosyl bromide (96) *in situ* and then treating this in chloroform with potassium hydroxide and thiolacetic acid in ethanol under the general conditions described by Purves (see p. 25); it had m.p. 117-118°, $[\alpha]_D + 14^\circ$ [Lit.,¹⁶⁶ m.p. 118°, $[\alpha]_D + 10.7^\circ$]. This compound was also synthesised by a new route as reported on p.109.

Bis(tetra-O-acetyl- β -D-glucopyranosyl)disulphide (75) was prepared by oxidation of compound (62) in ethanol with hydrogen peroxide (100 vols) in the manner described by Cerny and co-workers.¹³⁰ It had m.p. 141-143° $[\alpha]_D - 153^\circ$ [Lit.,²²⁷ m.p. 142-143°, $[\alpha]_D - 156^\circ$], and displayed the n.m.r. spectral characteristics already reported for this compound.²²⁸

Alternatively compound (62) could be oxidised by shaking its chloroform solution with aqueous sodium bicarbonate and iodine until the evolution of gas ceased; an 80% yield of compound (75) could be obtained in this way, and after recrystallisation from methanol it had the same constants as reported above. When this above iodine oxidation was attempted in the absence of bicarbonate, concomitant deacetylation was observed.

Phenyl 1-thio- β -D-glucopyranoside (169) was obtained by deacetylation of the tetraacetate (81), which itself was obtained either by the method of Purves¹⁰⁴ or by the acid catalysed thiolysis procedure (p. 54). Recrystallised from ethyl acetate containing a little methanol it had m.p. 130-131°, $[\alpha]_D - 67^\circ$ (\underline{c} 1.5 in H₂O) [Lit.,¹⁰⁴ m.p. 133°, $[\alpha]_D - 71^\circ$ (\underline{c} 2 in H₂O)].

Phenyl 1-thio- α -D-glucopyranoside (170) was prepared from the diphenyl dithioacetal as described by Collins and Whitton²²⁹ and recrystallised from ethanol it had m.p. 154-156°, $[\alpha]_D + 303^\circ$ (\underline{c} 0.6 in H₂O), $[\alpha]_D + 263^\circ$ (\underline{c} 0.7 in C₆H₅N) [Lit.,⁹⁹ m.p. 156-157°, $[\alpha]_D + 258^\circ$ (\underline{c} 0.6 in C₆H₅N)].

Phenyl tetra-O-acetyl-1-thio- α -D-glucopyranoside (82) was obtained by acetylation of compound (170) and recrystallised from ethanol it had m.p. 90-91°, $[\alpha]_D + 230^\circ$ [Lit.,⁹⁹ m.p. 91-92°, $[\alpha]_D + 234^\circ$], δ 2.01, 2.02, 2.04, and 2.11 (4s, acetyl), 3.98 (H-6, $\underline{J}_{6,6}$, 12Hz, $\underline{J}_{5,6}$ 2Hz), 4.33 (H-6', $\underline{J}_{5,6}$, 4.5Hz), 4.55 (H-5, $\underline{J}_{4,5}$ 9Hz), 5.46 (H-4, $\underline{J}_{3,4}$ 9.5Hz), 5.06 (H-3, $\underline{J}_{2,3}$ 9.5Hz), 5.09 (H-2, $\underline{J}_{1,2}$ 5Hz) and 5.92 (H-1). The δ - and \underline{J} -values reported for this compound²²⁹ are compatible with those observed here, except that that reported for H-4 (δ 5.66) would appear to be incorrect.

Phenyl 1-thio- β -D-galactopyranoside (171) was obtained by deacetylation of the tetraacetate (84) (see p. 54). The crude product was recrystallised (x2) by heating it under reflux with calcium sulphate (anhydrous) in propan-2-ol and filtering the solution before allowing it to cool to room temperature, whereupon it gave fine white needles m.p. 102-104°C, $[\alpha]_D - 52^\circ$ (\underline{c} 2 in CH₃OH) [Lit.,⁸⁹ m.p. 94-95°, $[\alpha]_D - 53.4^\circ$ (\underline{c} 0.5 in CH₃OH);²³⁰ m.p. 99-100°] (Found: C, 52.0; H, 5.8; S, 11.3. C₁₂H₁₆O₅S requires C, 52.9; H, 5.9; S, 11.8%), δ (C₆H₅N) 5.18 (1H, d, $\underline{J}_{1,2}$ 10Hz, H-1). Repeated determinations of the m.p. of this analysed sample and of other similar samples indicated that the m.p. varied to higher temperatures (up to 120°) depending upon the rate at which the sample was heated.

Sodium N,N-dimethyldithiocarbamate dihydrate (172). - A solution of dimethylamine (90 ml, 33% w/w in ethanol) and carbon disulphide (34 ml, 1.1 mol. equiv.) in ethanol (100 ml) was added to a solution of sodium hydroxide (20 g, 1.0 mol. equiv.) in water (30 ml) cooled in an ice-bath. The sodium salt (172) crystallised on keeping the solution at 0° and then at -20° as white needles (22.5 g, 69%) (Found: C, 20.2; H, 5.6; N, 7.8. $C_3H_6NNaS_2 \cdot 2H_2O$ requires C, 20.1; H, 5.6; S, 7.8%).

Tetra-O-acetyl-β-D-glucopyranosyl N,N-dimethyldithiocarbamate (57). - Penta-O-acetyl-β-D-glucopyranose (79) (95.8 g) was dissolved in chloroform (200 ml) and hydrogen bromide (80 ml, 40% w/v in glacial acetic acid) was added. After 1h the excess of acid was removed by washing once with water. Sodium N,N-dimethyldithiocarbamate dihydrate (172) (48.3 g, 1.1 mol. equiv) in ethanol (200 ml) was added to the organic phase, and the solution was heated under reflux for 0.5h. The chloroform was removed, and the remaining liquor (150 ml) was poured into water (1.5 l) and left overnight. Compound (57) was collected as a white powder (80.8 g, 73%) by filtration. A sample recrystallised (x2) from methanol gave fine needles m.p. 111-113°, $[\alpha]_D + 29^\circ$ [Lit., ¹³⁷ m.p. 114°, $[\alpha]_D + 25.8^\circ$], n.m.r. (p. 47).

Tetra-O-acetyl-β-D-glucopyranosyl N,N-diethyldithiocarbamate (60). - Penta-O-acetyl-β-D-glucopyranose (79) (39.6 g) was treated with hydrogen bromide (25 ml, 40% w/v in glacial acetic acid) and then sodium N,N-diethyldithiocarbamate trihydrate (29.1 g, 1.3 mol. equiv.), and was processed as described for the preparation of compound (57). The crude product obtained was a red syrup, which was dissolved in light petroleum-ether and filtered to remove a black residue. The light orange solution was kept at 0° for 3 days during which time a small yield of compound (60) separated as crude yellow crystals (4.5 g, 9%). Recrystallised from ethanol it had m.p. 82-86°, $[\alpha]_D + 35^\circ$ [Lit., ¹³⁷ m.p. 83-85°, $[\alpha]_D + 33^\circ$], n.m.r. (p. 47).

Tetra-O-acetyl-β-D-glucopyranosyl N,N-di-n-butyldithiocarbamate (78). - A solution of sodium N,N-di-n-butyldithiocarbamate was prepared by mixing a solution of sodium hydroxide (6.2 g) in ethanol (100 ml) and water

(10 ml) with carbon disulphide (9.35 ml, 1.02 mol. equiv.) and di-n-butylamine (20 g, 1 mol. equiv.) at 0°. This solution was then mixed with an ethanol solution of the syrup obtained by treating penta-O-acetyl-β-D-glucopyranose (79) (20.5 g, 0.34 mol. equiv.) in chloroform with hydrogen bromide (15 ml, 45% w/v in glacial acetic acid) and, after 1h at room temperature, washing the solution free of excess acid and removing the solvent. The mixture was heated under reflux for 1h and was then poured into a large excess of water. The small amount of syrup which separated was subsequently induced to crystallise by keeping its ethanol solution at -20° for a week, whereupon the dibutyldithiocarbamate (78) was formed as large white crystals (1.7 g, 6%). Recrystallised from methanol it had m.p. 86-89°, $[\alpha]_D - 31^\circ$ (Found: C, 51.6; H, 7.2; N, 2.8; S, 12.2. $C_{23}H_{37}NO_9S_2$ requires C, 51.6; H, 7.0; N, 2.6; S, 12.0%). No attempt was made to improve this preparation, and the product was only used in an n.m.r. study (p. 47).

Tetra-O-acetyl-1-S-phenylmercury(II)thio-β-D-glucopyranose (59). -

(a) From tetra-O-acetyl-β-D-glucopyranosyl N,N-dimethyldithiocarbamate (57). Compound (57) (10 g) and phenylmercury(II)acetate (14.9 g, 2 mol. equiv.) were heated under reflux in methanol (150 ml) for 30 min, during which time a black precipitate formed. This solid was removed by filtration and was shown from an x.r.d. spectrum of a powder sample (Philips PW 1050/25 X-ray diffractometer with Cu K_α radiation, filtered with nickel) to be mercury(II) sulphide; the three major peaks in order of decreasing intensity corresponded to d-spacings of 3.35, 2.06, 1.76 and 2.91 Å; mercury(II)sulphide, cubic, has d-spacings of 3.38, 2.07 and 1.76 Å according to ASTM file no. 6-261. The clear filtrate at room temperature yielded the acetylated phenylmercurythioglucose (59) as white needles (9.1 g, 64%). Recrystallised from methanol it had m.p. 147-148.5°, $[\alpha]_D - 85.5^\circ$ (c 7 in CHCl₃) (Found: C, 37.3; H, 3.9; S, 5.3. $C_{20}H_{24}HgO_9S$ requires C, 37.5; H, 3.8; S, 5.0%). The n.m.r. data are listed in Table 5. Repetitions of the above experiment resulted in compound (59) being obtained in yields of from 59 to 70%; the methanolic liquors remaining after isolation of compound (59) gradually decomposed at room temperature depositing a yellow solid which itself went black.

Three other products were isolated from the reaction described above; diphenylmercury(II) was obtained by crystallisation on further cooling the reaction liquors, and a compound tentatively assigned as S-phenylmercury(II)thio- N,N-dimethylthiocarbamate (61) and triphenylmethanol were obtained by subjecting a portion of the remaining liquors to p.l.c. (benzene) and extracting bands with R_F 0.40 and 0.11.

Diphenylmercury(II) (3.9 g) was isolated as a crude white solid on cooling the reaction liquors obtained after crystallisation of compound (59) to -20° . After purification on a column of silica gel with benzene as eluting solvent, and recrystallisation from methanol it had m.p. $124-125^\circ$ [Lit., ²³¹ m.p. $122-124^\circ$] (Found: C, 40.7; H, 2.9. $C_{12}H_{10}Hg$ requires C, 40.6; H, 2.8%). The n.m.r. spectrum revealed only aromatic protons. A further quantity of diphenylmercury(II) [0.6 g, 33% total from phenylmercury(II) acetate] was shown to be present in the reaction product by p.l.c.

The p.l.c. band with R_F 0.40 gave a small amount of a syrup which partially crystallised. This fraction retained the pungent odour associated with the unfractionated reaction mixture and its n.m.r. spectrum was complex. When this fraction was recrystallised from light petroleum however, the odour was observed to remain in the filtrate, and one further recrystallisation yielded triphenylmethanol as white crystals with m.p. $161-162^\circ$ [Lit., ²³² m.p. $161-162^\circ$] (Found: C, 87.7; H, 6.5. $C_{19}H_{16}O$ requires C, 87.7; H, 6.2%) δ 7.3 (m, aromatic), ν_{max} 3450 cm^{-1} (OH), m/e 260 (M , 33), 183 ($M-Ph$, 95) and 105 ($M-Ph-PhH$, 100%). The product was shown to be identical to an authentic sample of triphenylmethanol by i.r. and mixed m.p.

The p.l.c. band with R_F 0.11 gave a small amount of a syrup which crystallised on standing and on recrystallising this from light petroleum a compound, tentatively assigned as S-phenylmercury(II) N,N-dimethylthiocarbamate (61), was obtained as large white needles with m.p. $74-76^\circ$ (Found: C, 28.9; H, 3.5; N, 3.9. $C_9H_{11}HgNOS$ requires C, 28.4; H, 2.9; N, 3.7%), δ 2.99 (6H, broad s, NMe_2) and 7.23 (5H, m, aromatic), ν_{max} 1587 cm^{-1} (s). A microtest for sulphur was positive. The white crystals were observed to blacken on storage for several months at room temperature. A second, higher melting compound was observed to be present in the recrystallisation filtrate, but it could not be isolated pure.

(b) From tetra-O-acetyl- β -D-glucopyranosyl N,N-diethyldithiocarbamate (60). Compound (60) (1.20 g) and phenylmercury(II) acetate (1.69 g, 2. mol. equiv.) were heated under reflux in methanol (40 ml) for 30 min. A black precipitate formed and this was removed by hot filtration through celite. White needles of compound (59) (1.32 g, 82%) crystallised on cooling the clear liquor to 0°. Recrystallised (x2) from methanol these had m.p. 147-148°, $[\alpha]_D -85^\circ$. The i.r. and n.m.r. spectra of this product were identical to those of the product obtained using the dimethyldithiocarbamate (57).

(c) From tetra-O-acetyl-1-thio- β -D-glucopyranose (62). Compound (62) (1.0 g) in warm ethanol (20 ml) was mixed with phenylmercury(II) acetate (0.815 g, 1 mol. equiv.) in warm ethanol (25 ml). White needles of compound (59) formed on standing the solution at room temperature, and were collected by filtration after the mixture had been cooled to 0°. The product (1.34 g, 76%) without recrystallisation, had m.p. 146-148°, $[\alpha]_D -85^\circ$, and its i.r. spectrum was identical to those of the products derived from the glycosyl dithiocarbamates.

(d) From 1-thio- β -D-glucopyranose pentaacetate (63). Compound (63) (1.1 g) and phenylmercury(II) acetate (0.91 g, 1 mol. equiv.) were heated under reflux in ethanol (25 ml) for 40 min. T.l.c. (solvent A) indicated that compound (63) (R_F 0.45) had been replaced by largely one new carbohydrate derivative (R_F 0.55) identical to compound (59). A small yellow precipitate was filtered from the hot solution and on being allowed to cool to room temperature the filtrate yielded compound (59) as white needles (1.30 g, 75%). Recrystallised from methanol it had m.p. 147-149°, $[\alpha]_D -83^\circ$. The product was shown to be identical to that obtained before by mixed m.p. and n.m.r.

p-Diethylaminophenylmercury(II) acetate (64). - Mercury(II) acetate (15.5 g) in water (90 ml) was added to a mixture of N,N-diethylaniline (8.0 g, 1.1 mol. equiv.) and ethanol (20 ml). After the homogeneous solution had been stirred for a few minutes compound (64) separated as a voluminous white precipitate (14.8 g, 68%). Recrystallised (x2) from benzene-light petroleum it formed needles m.p. 103-105° [Lit., ²³³ m.p. 105°] (Found: C, 35.2; H, 4.3; N, 3.5. $C_{12}H_{17}HgNO_2$ requires C, 35.3; H, 4.2; N, 3.4%), δ 1.13 (6H, t, CH_3), 2.05 (3H, s, $OCOCH_3$), 3.30

(4H, q, NCH_2), 6.58 (2H, d, aromatic) and 7.06 (2H, d, aromatic).

Tetra-O-acetyl-1-S-p-diethylaminophenylmercury(II) thio- β -D-glucopyranose (65).-

(a) From tetra-O-acetyl- β -D-glucopyranosyl N,N-dimethyldithiocarbamate (57). Compound (57) (1.66 g) and p-diethylaminophenylmercury(II) acetate (64) (3.0 g, 2 mol. equiv.) were dissolved in methanol (50 ml) by slightly warming and swirling the mixture. After this solution had stood for 2h at 20° , and then 30 min. at 0° , the acetylated p-diethylaminophenylmercury(II) thioglucose (65) was filtered off as a white crystalline solid (1.69 g) from a dark black liquor. A second crop of greyish crystals (0.52 g, 84% total) was obtained on further standing the liquors at 0° . Recrystallised (x2) from methanol it had m.p. $150-152^\circ$, $[\alpha]_D -86^\circ$ (Found: C, 40.6; H, 5.0; N, 2.1; S, 4.8. $\text{C}_{24}\text{H}_{33}\text{HgNO}_9\text{S}$ requires C, 40.5; H, 4.7; N, 2.0; S, 4.5%). The n.m.r. data are listed in Table 5.

(b) From tetra-O-acetyl-1-thio- β -D-glucopyranose (62). Compound (62) (5.0 g) and p-diethylaminophenylmercury(II)acetate (64) (5.6 g, 1 mol. equiv.) were separately dissolved in methanol (200 ml total) containing triethylamine (4 ml total, 2.1 mol. equiv.) and the solutions were mixed. At 20° the solution soon deposited the acetylated p-diethylaminophenylmercury(II)thioglucose (65) as white platelets (8.65 g, 88%), with the same i.r. spectrum as that of previously characterised material. Recrystallised from methanol it had m.p. $148-150^\circ$, $[\alpha]_D -85^\circ$. In a repetition of the above experiment scaled up 3-fold the use of 1.2 mol. equiv. of triethylamine was found to be equally effective, and compound (65) was obtained in 87% yield.

Bis(tetra-O-acetyl-1-thio- β -D-glucopyranosyl)mercury(II) (67). -

(a) From tetra-O-acetyl- β -D-glucopyranosyl N,N-dimethyldithiocarbamate (57). Compound (57) (13.6 g) and p-diethylaminophenylmercury(II) acetate (64) (12.0 g, 1 mol. equiv.) were heated under reflux in methanol (150 ml) for 2.5 h. The methanol was then removed, and the black syrup was extracted with boiling ether (200 ml). The black solid which precipitated was removed by filtration through celite. When the colourless etherial filtrate was cooled to -20° , bis(tetra-O-acetyl-1-thio- β -D-glucopyranosyl)mercury(II) (66) crystallised as a white solid (10.2 g), and a second crop (0.5 g,

77% total) was obtained by reducing the volume of the filtrate and again cooling it to -20° . Recrystallised (x3) from methanol it had m.p. ca., 95° (indefinite m.p. observed because it became a viscous syrup on melting), $[\alpha]_D -59^{\circ}$ (Found: C, 36.0; H, 4.1; S, 8.8. $C_{28}H_{38}HgO_{18}S_2$ requires C, 36.3; H, 4.1; S, 6.9%). The n.m.r. data are listed in Table 5.

(b) From p-diethylaminophenylmercury(II)acetate (64) and tetra-O-acetyl-1-thio- β -D-glucopyranose (62). Compound (62) (1.0 g) and compound (64) (0.56 g, 0.5 mol. equiv.) were heated under reflux for 30 min. in methanol (25 ml) containing acetic acid (2% by vol., 6.4 mol. equiv.). When the solution was cooled to 0° ; bis(tetra-O-acetyl-1-thio- β -D-glucopyranosyl)-mercury(II) (66) crystallised as a white solid (0.80 g, 63%). Recrystallised from methanol it had m.p. ca., 95° (indefinite m.p. as viscous syrup formed), $[\alpha]_D -60^{\circ}$. This product was shown to be identical to previously characterised material by i.r. and mixed m.p.

In a separate experiment, in an attempt to prepare the acetylated p-diethylaminophenylmercury(II)thioglucose (65), compound (62) (1.0 g) and compound (64) (1.12 g, 1 mol. equiv.) were briefly heated under reflux

and when the solution was cooled to 0° , compound (66)

Table 5. The n.m.r. spectral data of the acetylated mercury containing 1-thiogluco^se derivatives, recorded at 60MHz in chloroform-d; chemical shifts (δ) relative to tetramethylsilane.

Assignment	Compound: (<u>59</u>)	(<u>66</u>)	(<u>67</u>)
OAc	1.95 (3H)	1.98 (3H)	2.00 (12H)
	2.01 (6H)	2.00 (6H)	2.10 (12H)
	2.06 (3H)	2.10 (3H)	
H-5 ^{<u>a</u>}	3.8	3.8	3.8
H-6,6' ^{<u>b</u>}	4.18	4.15	4.18
H-1,2,3,4	<u>ca.</u> , 5.15 ^{<u>c</u>}	<u>ca.</u> , 5.15 ^{<u>c</u>}	<u>ca.</u> , 5.0 ^{<u>d</u>}
Aromatic	7.39 ^{<u>d</u>}	6.67 (<u>d</u> , <u>J</u> 8Hz)	-
		7.19 (d)	
N-CH ₂ CH ₃	-	1.15 (t, <u>J</u> 7Hz)	-
N-CH ₂ CH ₃	-	3.35 (q)	

Notes: a broad multiplet, width 25 to 30Hz
b multiplet, mainly two peaks, width ca 12Hz
c complex broad multiplet, width 40Hz
d narrow band

that the reaction was complete immediately after final additions and that two new products, R_F 0.45 (u.v. - absorbing) and R_F 0.65 (non-u.v. - absorbing), had been formed. The mobile component had the same mobility as compound (62) but the two could be distinguished by standing the developed t.l.c. plate in iodine vapour; in this way compound (62) was oxidised to disulphide which was then seen as a characteristic purple-red spot on subsequently spraying and heating the plate, and was thus shown to be absent from the reaction mixture.

The white solid (0.54 g) was removed by filtration (x2) through an asbestos pad. The filtrate was reduced to a clear light yellow syrup (1.81 g), and this was subjected to p.l.c. (solvent B). Two fractions A and B, corresponding to the two main components, were extracted, the non-u.v.-absorbing fraction B was obtained by extracting all the material above the u.v.-absorbing band.

Fraction A, R_F 0.45, was shown by n.m.r. and t.l.c. to be bis(tetra-O-acetyl-1-thio- β -D-glucopyranosyl)mercury(II) (66) (0.89 g, 46%). The white needles obtained after crystallisation and then recrystallisation of this fraction from methanol had m.p. ca., 95° (indefinite m.p. as viscous syrup formed), $[\alpha]_D -59^\circ$.

Fraction B, R_F 0.65, was indicated by n.m.r. to be a mixture of the 3,4,6-tri-O-acetyl- α -D-glucopyranosyl endo- and exo-1,2-(methylorthoacetates) (68) and methyl tetra-O-acetyl- α -D-glucopyranoside (69) in the ratio 2:10:3, the spectrum revealing δ 1.57 (CCH_3) and 3.42 (OCH_3) for endo- (68) [Lit., ^{234,235} 1.57 and 3.45]; 1.70 (CCH_3), 3.27 (OCH_3) and 5.70 (H-1, d, $J_{1,2}$ 5Hz) for exo- (68) [Lit., ^{234,235} 1.72, 3.29 and 5.74 ($J_{1,2}$ 5Hz)]; 3.40 (OCH_3) for (69) [Lit., ^{236,237} 3.42, c.f. 3.52 for the β -anomer of (69)]. Compound (69) and its β -anomer were prepared in this laboratory by acetylating available samples of the methyl glucosides and were confirmed to have resonances at δ 3.40 and 3.50 respectively. Fraction B was a syrup (0.52 g, 35%) which resisted crystallisation and was homogeneous on t.l.c.

Very similar product mixtures were obtained when the above experiment was varied either by rapidly mixing methanolic solutions of the reactants at room temperature and then warming to complete the reaction, or by gradually adding a solution of compound (62) in methanol to a boiling solution of mercury(II) acetate in methanol.

1-S-Phenylmercury(II)thio- β -D-glucopyranose (70). - Tetra-O-acetyl-1-S-phenylmercury(II)thio- β -D-glucopyranose (59) (3.69 g) was deacetylated using catalytic amounts of sodium methoxide in methanol. When t.l.c. indicated complete conversion to a single new component, the solution was neutralised with acid resin, filtered, and reduced to a volume of 15 ml. 1-S-Phenylmercury(II)thio- β -D-glucopyranose (70) crystallised from this solution at 0° as a white solid (1.45 g, 53%). Recrystallised from

methanol it had m.p. 173-174° (decomp.) when heated rapidly to near its m.p., $[\alpha]_D -7.7^\circ$ (c 1 in CH₃OH) (Found: C, 30.8; H, 3.5; S, 6.6. C₁₂H₁₆HgO₅S requires C, 30.5; H, 3.4; S, 6.8%). The compound decomposes slowly on heating at temperatures below its m.p.

To confirm the assignment of compound (70) a sample (0.115 g) was reacetylated with acetic anhydride (3 ml) in pyridine (3 ml). After the reaction solution had stood at room temperature for 19h it was poured onto ice-water (400 ml) and tetra-O-acetyl-1-S-phenylmercury(II)thio-β-D-glucopyranose (59) was obtained as a white powder (0.130 g, 84%). Recrystallised from methanol it had m.p. 146-148°, $[\alpha]_D -85^\circ$, and was shown to be identical to previously characterised material by i.r. and mixed m.p.

Bis(1-thio-β-D-glucopyranosyl)mercury(II) (71). - Bis(tetra-O-acetyl-1-thio-β-D-glucopyranosyl)mercury(II) (66) (7.5 g) was deacetylated using catalytic amounts of sodium methoxide in methanol (100 ml). When the reaction solution was left at 0° bis(1-thio-β-D-glucopyranosyl)mercury(II) (71) was deposited as a white solid (4.2 g, 88%). Recrystallised from methanol - water it was obtained as white needles m.p. 184-187° (decomp.) when rapidly heated to near its m.p., $[\alpha]_D -5.9^\circ$ (c 5 in H₂O) (Found: C, 24.5; H, 3.7; S, 11.7. C₁₂H₂₂HgO₁₀S₂ requires C, 24.2; H, 3.8; S, 10.9%). The compound decomposed slowly on heating at temperatures below its m.p.

To confirm the assignment of compound (71) a sample (0.165 g) was reacetylated with acetic anhydride (5 ml) in pyridine (5 ml). After the reaction mixture had been shaken at room temperature for 18h it was poured onto ice-water and bis(tetra-O-acetyl-1-thio-β-D-glucopyranosyl)mercury(II) (66) was obtained as a white powder (0.195 g, 75%). Recrystallised from methanol it had m.p. ca., 95° (indefinite m.p. as viscous syrup formed), $[\alpha]_D -59^\circ$, and was shown by i.r. to be identical to previously characterised material.

Disproportionation of 1-S-phenylmercury(II)thio-β-D-glucopyranose (70). - When a solution of compound (70) in water was allowed to stand at room temperature a white precipitate was observed to form slowly, and this was

shown to be diphenylmercury(II). In order to investigate this reaction further, compound (70) (0.68 g) was shaken with water (40 ml) and chloroform (5 ml) for 3.5 days, during which time all the solid dissolved. Paper chromatography (solvent, ethylacetate-pyridine-water 8:2:1; developing spray, periodate-permanganate) indicated that compound (70) (R_F 0.74) had been completely converted to a single new component corresponding to bis(1-thio- β -D-glucopyranosyl)mercury(II) (71) (R_F 0.14). Further chloroform was added and the aqueous and organic layers were separated.

The organic layer was dried with anhydrous sodium sulphate, and yielded diphenylmercury (0.25 g, 97%) on removal of the solvent. This product was shown to be identical to previously characterised material by i.r., and recrystallised from methanol it had m.p. and mixed m.p. 122-124° (see p. 93).

The aqueous layer yielded compound (71) as a white solid (0.42 g, 98%) on removal of the solvent. Recrystallised from methanol-water it was obtained as white needles (0.35 g) m.p. ca., 180° (decomp.), $[\alpha]_D -5.4^\circ$ (c 3 in H₂O), and with an i.r. spectrum identical to that of previously characterised material. A sample (0.24 g) was reacylated with acetic anhydride (3 ml) in pyridine (3 ml). After the reaction mixture had been shaken at room temperature for 3.5 days it was poured into water (200 ml) and bis(tetra-O-acetyl-1-thio- β -D-glucopyranosyl)mercury(II) (66) was obtained as a white solid (0.38 g, 86%) which was shown to be identical to previously characterised material by i.r. Recrystallised from ethanol it had m.p. ca., 95° (indefinite m.p. as viscous syrup formed), $[\alpha]_D -60^\circ$.

Thermolysis of tetra-O-acetyl-1-S-phenylmercury(II)thio- β -D-glucopyranose (59). -

(a) In mesitylene. Compound (59) (0.25 g) was heated under reflux in mesitylene (7 ml) for 32h, during which time a black solid was deposited. T.l.c. indicated almost complete conversion of compound (59) into a single slightly more mobile non-u.v.-absorbing carbohydrate component which was visualised as a bright yellow spot on spraying and heating the plate. This product was obtained as a syrup (A) after purification by chromatography on a column of silica gel (solvent C).

Syrup (A) resisted crystallisation. It was subsequently heated under reflux in nitrobenzene (5 ml) for 70 min, after which the blackened

solution was treated with charcoal. The new product which was then obtained, after purification by chromatography as above, was a bright yellow syrup (B) (0.065 g) which again resisted crystallisation.

The n.m.r. spectra (see Table 6) indicated that syrup (A) was a 3:1 mixture of tetra-O-acetyl-2-hydroxy-D-glucal (72) and 1,2,4,6-tetra-O-acetyl-3-deoxy-β-D-erythro-hex-2-enopyranose (73) respectively, and that syrup (B) represented a 50% overall yield of a 1:3 mixture of the same two components.

(b) In nitrobenzene. Compound (59) (1.46 g) was dissolved in nitrobenzene (10 ml) which was then heated under reflux for 75 min, during which time a black solid precipitated and some metallic mercury was deposited on the condenser. The nitrobenzene was then removed by vacuum distillation (1 mm of Hg, 60°), and the blackened residue was dissolved in ethanol and treated with charcoal. The only product which could be directly crystallised from the ethanol solution of the crude product was β-D-glucopyranosyl 1-thio-β-D-glucopyranoside octaacetate (74) (0.11 g, 14%); recrystallised (x2) from methanol it was obtained as white needles m.p. 174-176°, $[\alpha]_D -40^\circ$ [Lit., ²³⁸ m.p. 175-176°, $[\alpha]_D -38^\circ$] (Found: C, 48.7; H, 5.3; S, 4.5. C₂₈H₃₈O₁₈S requires C, 48.4; H, 5.5; S, 4.6%). A t.l.c. study (solvent C) indicated that compound (74) had been a minor component (R_F 0.08) in the crude product, and that the major non-u.v.-absorbing carbohydrate component had the same characteristics (R_F 0.60, visualised as a bright yellow spot) as the product obtained in the thermolysis in mesitylene.

Thermolysis of bis(tetra-O-acetyl-1-thio-β-D-glucopyranosyl)mercury(II) (66). - Compound (66) (1.39 g) was heated under reflux in nitrobenzene (5 ml) for 5h. The solvent was then removed in vacuo and the remaining black syrup was taken up in ether and filtered to remove a black solid (which is apparently chloroform soluble). The ether was then removed to leave a red syrup (0.93 g) which was shown (t.l.c.) to contain a number of products. After two applications of p.l.c. only one pure fraction could be obtained, and on crystallisation from methanol this gave bis(tetra-O-acetyl-β-D-glucopyranosyl) disulphide (75) as white needles (72 mg, 7%) m.p. 142-143°. This product was shown to be identical to authentic material by t.l.c. and mixed m.p. (see p. 89). In a separate experiment

Table 6. The n.m.r. spectral data of the syrups obtained from thermolyses of compound (59), recorded at 60MHz in chloroform- d , chemical shifts (δ) relative to tetramethylsilane.

Assignment	Experimental Values		Literature Values	
	Syrup A	Syrup B	Compound (72) ²³⁹	(73) ²⁴⁰
Acetyl	2.06 2.10 2.15 ^a	- 2.08 2.14	-	-
H-5,6,6'	4.3	4.3	-	-
H-4 (m)	ca., 5.25	ca., 5.30	5.26	5.35
H-3 (d)	5.56 (J 4Hz) 5.97 (J 5Hz) ^a	5.56 ^a 5.97 (J 5Hz)	5.62 (J _{3,4} 4Hz)	6.01 (J _{3,4} 5.5Hz)
H-1 (s)	6.40 ^a 6.63	6.40 6.63 ^a	6.69	6.44

Notes: a the peaks were those of the minor component and were judged to represent 25% of the mixture.

the disulphide (75) was shown by t.l.c. to be stable under the reaction conditions, being the only carbohydrate present after a sample had been heated under reflux in nitrobenzene for 5h.

Reactions of hydrogen sulphide. -

(a) With tetra-O-acetyl-1-S-p-diethylaminophenylmercury(II)thio- β -D-glucopyranose (65). Compound (65) (2.4 g) was dissolved in chloroform (50 ml) and hydrogen sulphide was bubbled into the solution. An immediate blackening occurred and t.l.c. (solvent A) after 0.5 h indicated compound (65) (R_F 0.20, centre of streak, moderately u.v.-absorbing) had been replaced by a single new carbohydrate component (R_F 0.60). The reaction

mixture was allowed to stand at room temperature overnight, after which a fine black precipitate had separated from a colourless solution. The precipitate was so fine that direct filtration was difficult, but it was easily removed by eluting the mixture with chloroform down a short column of silica gel (7 cm x 2 cm diameter). The first 50 ml yielded a syrup (0.46 g) which was identical to diethylaniline (R_F 0.98) on t.l.c. (solvent A); further elution with chloroform (150 ml) and then chloroform containing 5% methanol (50 ml) yielded a colourless syrup which partially crystallised (1.4 g). Crystallised from methanol (10 ml) this gave tetra-O-acetyl-1-thio- β -D-glucopyranose (62) as prisms (0.80 g, 65%), m.p. 114-117°, $[\alpha]_D + 6.5^\circ$ [Lit., see p. 89].

(b) With bis(tetra-O-acetyl-1-thio- β -D-glucopyranosyl)mercury(II) (66). Compound (66) (1.7 g) was dissolved in chloroform (50 ml) and ethanol (50 ml) and hydrogen sulphide was bubbled into the solution. After the blackened solution had stood overnight at room temperature, t.l.c. indicated the presence of a single new carbohydrate derivative. Elution of the reaction mixture down a short column of silica gel with chloroform removed the black material. The syrup obtained on removal of the solvent crystallised from methanol to give tetra-O-acetyl-1-thio- β -D-glucopyranose (62) (0.94 g, 70%). Recrystallised from methanol it had the m.p. 74-75°, $[\alpha]_D + 5.3^\circ$. The n.m.r. and i.r. spectra were identical to those of authentic material (see p. 89).

(c) With compound (59) in ethanol. Compound (59) (5.0 g) was dissolved in hot ethanol (60 ml) and hydrogen sulphide was passed into this solution for an hour. A yellow solid was precipitated within the first 5 min, and after the solution had been allowed to stand at room temperature overnight t.l.c. (solvent A) indicated that it contained largely a single new carbohydrate component, but that a small amount of compound (59) remained unreacted. The yellow solid (1.95 g) was removed by filtration, and was assumed to be bis[phenylmercury(II)]sulphide in 85% yield. The filtrate was reheated and resaturated with hydrogen sulphide on several occasions over the next 3 days, but, although a further very small amount of a mixture of white and black solids was obtained, the remaining trace of compound (59) could not be removed. The hot solution was then filtered through a celite pad, and the colourless filtrate was reduced to a syrup

which crystallised from ethanol (20 ml) at 0° to give tetra-O-acetyl-1-thio- β -D-glucopyranose (62) as white crystals (2.31 g, 81%), $[\alpha]_D -1.7^{\circ}$. T.l.c. indicated this product to be largely a single component, with just a faint trace of compound (59). Recrystallised (x2) from methanol it had m.p. and mixed m.p. $114-116^{\circ}$ $[\alpha]_D + 3^{\circ}$ (see p. 89).

(d) With tetra-O-acetyl-1-S-phenylmercury(II)thio- β -D-glucopyranose (59) in chloroform. Compound (59) (1.0 g) was dissolved in chloroform (70 ml) and hydrogen sulphide was bubbled into the solution. A fine black solid was slowly precipitated and after 5 days t.l.c. (solvent A) indicated that compound (59) had eventually been completely replaced by a single new carbohydrate component. The solid was removed by filtration through a celite-asbestos pad and the filtrate was reduced to a syrup which crystallised from methanol to give white needles (0.57 g), $[\alpha]_D -10^{\circ}$ (c 2 in CHCl_3). T.l.c. indicated this product to contain a component identical to tetra-O-acetyl-1-thio- β -D-glucopyranose (62), but the n.m.r. spectrum, although displaying the characteristic signals of this compound (see p. 89), revealed in addition an aromatic resonance. A probable explanation is that the product was a mixture of compound (62) and diphenylmercury in the ratio 3:2.

Reaction of tetra-O-acetyl-1-S-phenylmercury(II)thio- β -D-glucopyranose (59) with thiophenol. - Compound (59) (1.0 g) was dissolved in methanol (25 ml) containing thiophenol (3.2 ml, 20 mol. equiv.). Fine crystals began forming quickly. The mixture was heated under reflux for 30 min and was then allowed to cool to room temperature. Phenylmercury(II) thiophenol was then collected by filtration as white plates (0.30 g) and two further crops (0.22 g, 86% total) were obtained on cooling the filtrate to 0° then -20° . The product had m.p. $101-104^{\circ}$ [Lit.,²⁴¹ m.p. 103.5°] and was shown to be identical to authentic material by mixed m.p. and i.r. (the authentic sample was prepared from sodium thiophenate and phenylmercury(II)chloride by the method of Leandri and Spinelli²⁴²).

T.l.c. indicated the remaining liquors contained a major carbohydrate component identical to tetra-O-acetyl-1-thio- β -D-glucopyranose (62). The syrup obtained on removal of the solvent crystallised from methanol (3 ml) at 0° , giving a white solid (0.125 g) which t.l.c. and n.m.r. indicated to be a mixture of phenylmercury(II)thiophenol and compound (62) in the ratio 3:1, increasing the yield of the former to nearly 100%. Attempts to isolate compound (62) pure from the remaining liquors were unsuccessful.

When this experiment was repeated with less thiophenol (6.4 mol. equiv.), t.l.c. indicated that only partial conversion to compound (62) had occurred, and compound (59) was recovered in 47% yield.

Reaction of tetra-O-acetyl-1-S-p-diethylaminophenylmercury(II)thio- β -D-glucopyranose (65) with thiophenol and acetic acid. - Compound (65) (1.0 g) was heated under reflux for 20 min in methanol (25 ml) containing acetic acid (1.7% by vol., 5.3 mol. equiv.) and thiophenol (0.58% by vol., 1 mol. equiv.). The colourless solution, on cooling to 20°, deposited bis(phenylthio)mercury (77) as white crystals (0.24 g, 82%). This product was shown to be identical to authentic material by i.r., and recrystallised from chloroform-methanol it had m.p. 149-150° [Lit.,²⁴³ m.p. 150-152°]. (Authentic material was prepared by condensing the appropriate amounts of thiophenol and mercury(II) acetate). The filtrate, on being cooled to 0°, yielded bis(tetra-O-acetyl-1-thio- β -D-glucopyranosyl)mercury(II) (66) as white needles (0.46 g, 71%). This product was shown to be identical to authentic material by i.r., and recrystallised (x2) from methanol it had m.p. ca., 95° (indefinite m.p. as viscous syrup formed), $[\alpha]_D$ -65°. No explanation has been found for the anomalously low optical rotation of this sample (c.f. $[\alpha]_D$ -59°, p. 95); the t.l.c. mobility and the n.m.r. spectrum of this sample were identical to those of previously obtained samples, and it was found that a further recrystallisation altered nothing.

Reaction of thiolacetic acid. -

(a) With bis(tetra-O-acetyl-1-thio- β -D-glucopyranosyl)mercury(II) (66). Compound (66) (1.0 g) was dissolved in methanol (25 ml) containing thiolacetic acid (1% by vol., 3.3 mol. equiv.), and the solution became bright yellow. The solution was allowed to stand at room temperature for 2h, and was then set aside at 0° overnight, whereupon tetra-O-acetyl-1-thio- β -D-glucopyranose (62) was obtained as yellowish crystals (0.34 g); a second crop (0.33 g, 86% total) was obtained on standing the filtrate at -20°. I.r., n.m.r., and t.l.c., indicated the product to be identical to authentic material. Recrystallised from methanol it had m.p. ca., 73°, resolidifying and melting again at 113-114°, $[\alpha]_D$ + 4.7° [Lit., see p. 89].

(b) With tetra-O-acetyl-1-S-p-aminophenylmercury(II)thio-β-D-glucopyranose (65). Compound (65) (1.0 g) was dissolved in methanol (50 ml) containing thiolacetic acid (1% by volume, 5.0 mol. equiv.). A fine yellow solid began to form after a few minutes at room temperature, but, after this was removed by filtration, further precipitate formed on keeping the filtrate at room temperature. After 3 days at room temperature the solution was again filtered, and t.l.c. (solvent B) then indicated the absence of compound (65) and the presence of largely one product corresponding to tetra-O-acetyl-1-thio-β-D-glucopyranose (62). The faintly yellow filtrate was then reduced to a volume of 10 ml and set aside at 0°, whereupon compound (62) crystallised as white needles (0.31 g) m.p. 115-118°; a second crop of slightly crude needles (0.13 g, 86% total) was obtained on addition of a little water to the filtrate after removal of the first crop. T.l.c. (solvent C) indicated both crops to be identical to authentic compound (62). Recrystallised from methanol it had m.p. 118-119°, $[\alpha]_D + 8.7^\circ$ [Lit., see p. 89].

Reaction of acetic acid. -

(a) With tetra-O-acetyl-1-S-phenylmercury(II)thio-β-D-glucopyranose (59). Compound (59) (0.43 g) was heated under reflux in a mixture of ethanol (10 ml) and acetic acid (2 ml). The reaction was monitored by t.l.c., and this indicated that at least three less mobile carbohydrate products were being formed, but that even after 30h, at which time the reaction was stopped, some starting material was still present. A fine black solid precipitated during the reaction. The syrup obtained on removal of the solvents yielded compound (59) (0.05 g, 11%) on crystallisation from methanol; the identity of the recovered material was confirmed by m.p., mixed m.p., and t.l.c.

(b) With tetra-O-acetyl-1-S-p-diethylaminophenylmercury(II)thio-β-D-glucopyranose (65). Compound (65) (2.0 g) was heated under reflux for 30 min in methanol (20 ml) containing acetic acid (2% by vol., 2.5 mol. equiv.). A grey precipitate which formed was removed by filtration of the hot solution. The filtrate, when kept at -20°, yielded bis(tetra-O-acetyl-1-thio-β-D-glucopyranosyl)mercury(II) (66) as a white solid (0.59 g, 45%). Recrystallised (x2) from methanol-water it had m.p. ca., 95° (indefinite m.p. as viscous syrup formed), $[\alpha]_D -60^\circ$ (see p. 95).

General procedures for boron trifluoride catalysed thiolyses. -

The carbohydrate starting materials, which were mostly peracetylated 1,2-trans-related glycosyl esters, were dissolved in chloroform (or sometimes, where specified, benzene), and the thiols and then boron trifluoride diethyletherate were added, and the solutions were left at room temperature (or heated under reflux). T.l.c. (solvent D for benzoates, solvent E for acetates) was used to determine when the starting materials had reacted fully at which time the solutions were washed with either excess saturated aqueous sodium hydrogen carbonate, or aqueous sodium hydroxide (2 mol. equiv. per mole of boron trifluoride), and then with water. The acidic reaction mixtures generally developed intense red colourations, but after these had been neutralised as above, they were generally light yellow. Drying of the organic solutions and removal of the solvent gave residues from which the compounds named in Tables 1 and 2 (p. 54) [with the exception of compounds (91) and (92) which were separated by chromatographic methods] were obtained by direct crystallisation procedures. The mother liquors contained appreciable proportions of the α -thioglycosides which were consistently observed as more mobile components than their β -anomers on t.l.c.; also present on many occasions were components corresponding to the carbohydrate starting materials, but which were probably their α -anomers from which they are indistinguishable on t.l.c.

Phenyl tetra-O-acetyl-1-thio- β -D-glucopyranoside (81). -

(a) From penta-O-acetyl- α -D-glucopyranose (58) and its β -anomer (79).

In initial experiments the anomeric acetates were separately dissolved in chloroform (30% solution), thiophenol (1.7 mol.equiv.) and then boron trifluoride diethyletherate (1.8 mol. equiv.) were added, and the solutions were allowed to stand at room temperature in the dark. T.l.c. indicated that whereas the β -acetate (79) had undergone complete reaction within 2 days, some of the α -acetate (58) remained unreacted after 10 days, although the latter was absent from its reaction solution after 30 days at which time both reactions were processed (p.107) to yield crude crystalline masses. The product from α -pentaacetate (58), $[\alpha]_D^{+25}$, was a mixture of β -thioglucoside (81) and its α -anomer (82) in the approximate ratio (n.m.r. analysis) 3:1, and recrystallised (x2) from

ethanol it yielded pure phenyl tetra-O-acetyl-1-thio- β -D-glucopyranoside (81) (45%), m.p. 116-118°, $[\alpha]_D -16^\circ$ (see Table 1, p. 54). The product from β -pentaacetate (79), $[\alpha]_D +14^\circ$, was a mixture of the same compounds in the approximate ratio 5:1, and recrystallised (x3) from ethanol it likewise yielded pure β -thioglucoside (81) (36%), m.p. 117-118°, $[\alpha]_D -16^\circ$. The filtrate obtained during the first recrystallisation of the crude product in the case of the β -pentaacetate (79) reaction was subjected to p.l.c. and yielded further β -thioglucoside (81) (5%) and also phenyl tetra-O-acetyl-1-thio- α -D-glucopyranoside (82) (8%), m.p. 91-92°, $[\alpha]_D +228^\circ$ (see p. 90).

(b) From 1,3,4,6-tetra-O-acetyl- α -D-glucose (98). Compound (98) (1.0 g) was dissolved in chloroform (10 ml) and thiophenol (0.35 g, 1.1 mol. equiv.) and then boron trifluoride diethyletherate (2.05 g, 5 mol. equiv.) were added. After 1h at room temperature, t.l.c. (solvent E) indicated complete conversion to a major (R_F 0.50) and two minor (R_F 0.63 and 0.29) u.v.-absorbing carbohydrate components. The solution was processed (p.107) yield a colourless syrup which gave the β -thioglucoside (81) as white needles (0.48 g, 38%) from ethanol. Recrystallised from ethanol it had m.p. 117-118°, $[\alpha]_D -15^\circ$ and was shown to be identical to authentic material (see Table 1, p. 54) by t.l.c., n.m.r., and mixed m.p. Examination of the mother liquors by t.l.c. revealed compound (81) to be still the major component.

Phenyl tetra-O-benzoyl-1-thio- β -D-glucopyranoside (83). -

(a) From penta-O-benzoyl- β -D-glucopyranose (100). β -Penta benzoate (100) (5.0 g), thiophenol (1.05 mol. equiv.) and boron trifluoride diethyletherate (1.0 mol. equiv.) were heated in chloroform under reflux in a nitrogen atmosphere for 4h as set out in Table 1 (p. 54). The reaction solution was processed (p.107) to yield a light yellow syrup which gave the tetrabenzoate (83) as white solid (4.0 g, 81%) on treatment with ethanol (50 ml). Recrystallised from acetic acid this had the physical constants reported in Table 1. When the above reaction was repeated with the use of 3 mol. equiv. of boron trifluoride, the reaction was complete in 1.5h.

(b) From phenyl-1-thio- β -D-glucopyranoside (169). Compound (169) (0.5 g) was treated with pyridine (3 ml) and benzoyl chloride (3 ml) and the

reaction mixture was processed in the usual way (p. 88) to yield a light yellow syrup which crystallised from acetic acid (10 ml) to give the tetrabenzoate (83) as small needles (1.02 g, 80%). Recrystallised from acetic acid it had m.p. 168-169°, $[\alpha]_D + 31^\circ$.

Allyl tetra-O-acetyl-1-thio-β-D-glucopyranoside (94). - The reaction was carried out as described before (p.107) using penta-O-acetyl-β-D-glucopyranose (79) (2.9 g) allyl mercaptan (0.55 g, 1.0 mol. equiv.) and boron trifluoride diethyletherate (10.5 g, 10 mol. equiv.) in chloroform (25 ml). After 1h at room temperature, t.l.c. (solvent E) indicated compound (79) (R_F 0.27) was largely replaced by a major (R_F 0.42) and a minor (R_F 0.49) new carbohydrate component, and the solution was then processed (p.107) to yield a colourless syrup, $[\alpha]_D + 17.5^\circ$. This syrup could not be induced to crystallise, despite the use of a seed of authentic β-thioglucoside (94), m.p. 53-56°, $[\alpha]_D + 2.6^\circ$ [Lit.,¹²⁹ m.p. 53-55°, $[\alpha]_D - 0.5^\circ$] which, prepared as described by Cerny and Pacak¹²⁹ was itself found difficult to crystallise. T.l.c. and n.m.r. comparisons of this syrup with the authentic sample, however, indicated it to be largely the β-thioglucoside (94).

Reaction of ethanethiol with penta-O-acetyl-β-D-glucopyranose (79). - When compound (79), ethanethiol and boron trifluoride were allowed to react in chloroform solution as set out in Table 1, p. 55, ethyl tetra-O-acetyl-β-D-glucopyranoside (90) was subsequently isolated in high yield (83%). However when the experiment was repeated using 3 mol. equiv. of boron trifluoride diethyletherate for 24h, the product obtained after processing the reaction solution (p.107) crystallised from ether-light petroleum as a mixture of ethyl tetra-O-1-thio-α-D-glucopyranoside (95) and its β-anomer (90) in the ratio 1:1, the white needles (74%) having $[\alpha]_D + 79^\circ$ [α -anomer,¹¹⁰ + 194°; β -anomer,¹¹⁰ -28°; calc., +83°] and δ 5.60 (0.5H, d, $J_{1,2}$ 5Hz, H-1 of the α-anomer).

1-Thio-β-D-glucopyranose pentaacetate (63). - Penta-O-acetyl-β-D-glucopyranose (79) (5.0 g) was heated with thiolacetic acid and boron trifluoride diethyletherate in chloroform under reflux in a nitrogen

atmosphere as set out in Table 1 (p. 55). After 6h t.l.c. (solvent E) indicated a major (R_F 0.40) and a minor (R_F 0.33) component corresponding to compound (63) and penta-O-acetyl- α -D-glucopyranose (58) respectively. The reaction mixture was processed (p.107) to yield a red syrup, the n.m.r. spectrum of which was similar to that of compound (63) but in addition revealed a resonance at δ 6.26 (d, $J_{1,2}$ 3.5Hz, H-1) for a 20% presence of α -pentaacetate (58). Crystallised from ethanol this syrup yielded compound (63) as a brownish crystalline solid (2.9 g, 55%) which after treatment with activated charcoal recrystallised from ethanol as white needles (2.2 g) with the physical constants reported in Table 1. This compound (63) has also been prepared by standard methods (see p. 89).

Reaction of p-nitrothiophenol with penta-O-acetyl- β -D-glucopyranose (79). - A solution of compound (79) (4.0 g), p-nitrothiophenol (1.7 g, 1.07 mol. equiv.) and boron trifluoride diethyletherate (7.3 g, 5 mol. equiv.) in chloroform was allowed to stand at room temperature. T.l.c. (solvent E) indicated the reaction to be slow relative to that with thiophenol, and was only complete after 7 days at which time the mixture contained at least five significant components, two of which had identical mobilities to the β -thiogluco-side (kindly supplied by Dr G. Bethell) and the α -pentaacetate (58). The reaction solution was processed (p.107) to yield a yellow syrup, whose n.m.r. spectrum contained two low field doublets δ 6.24 (J 4Hz) and 6.16 (J 5Hz) consistent with those expected if the mixture contained α -pentaacetate (58) and α -thiogluco-side.

Reaction of tetra-O-acetyl-1-thio- β -D-glucopyranose (62) with β -pentaacetate (79). - β -Pentaacetate (79) (2.0 g) and thiol (62) (1.87 g, 1.0 mol. equiv.) were treated in chloroform (25 ml) with boron trifluoride diethyletherate (3.6 g, 5 mol. equiv.). After 5 days at room temperature, t.l.c. (solvent E) indicated that four less mobile carbohydrate products had been formed, but that trace components identical to the thiol (62), and either of the anomeric pentaacetates (58) and (79) were also present. The two major components of this mixture had the same t.l.c. characteristics as those of β -D-glucopyranosyl 1-thio- α -D-glucopyranoside octaacetate (74) (p.114) and β -D-glucopyranosyl 1-thio- β -D-glucopyranoside octaacetate (97) (p.101). The mixture was not further investigated.

Phenyl tetra-O-benzyl-1-thio- α -D-glucopyranoside (91). - 2,3,4,6-Tetra-O-benzyl- α -D-glucose (99) (0.6 g), thiophenol and boron trifluoride diethyletherate were allowed to react in chloroform solution as set out in Table 1 (p. 55). After 2.5h when t.l.c. (chloroform) indicated compound (99) had been replaced by a major (R_F 0.60) and a minor (R_F 0.50) new component, the reaction solution was processed (p.107) to yield a colourless syrup which resisted crystallisation, and which was thus fractionated by p.l.c. (chloroform-light petroleum, 10:3). The more mobile component, phenyl tetra-O-benzyl-1-thio- α -D-glucopyranoside (91) (0.35 g, 50%), crystallised from ethanol as white needles, and recrystallised from ethanol had the physical constants reported in Table 1. (Found: C, 76.1; H, 6.5; S, 5.3. $C_{40}H_{40}O_5S$ requires C, 75.9; H, 6.4; S, 5.1%), δ 7.2 (25H, m, aromatic), 5.60 (1H, d, $J_{1,2}$ 3.5Hz), 4.1 to 5.1 (9H, m, $PhCH_2$ and one carbohyd. ring proton), and 3.4 to 4.0 (5H, m, carbohyd. ring protons). The other component, phenyl tetra-O-benzyl-1-thio- β -D-glucopyranoside (92) (0.12 g, 17%), crystallised from ethanol as needles also, and had the physical constants reported in Table 1.

When the above reaction was repeated on a scale using compound (99) (1.0 g), the use of a seed permitted compound (91) to be crystallised directly as needles (0.36 g, 31%), $[\alpha]_D + 150^\circ$.

Ethyl tetra-O-benzoyl- α -D-glucopyranoside (102). - Penta-O-benzoyl- β -D-glucopyranose (100), ethanol (0.15 g, 1.2 mol. equiv.) and boron trifluoride diethyletherate (0.41 g, 1.0 mol. equiv.) were heated under reflux in benzene (75 ml) for 4h, during which time t.l.c. (solvent D) indicated that compound (100) (R_F 0.53) was initially replaced by a component (R_F 0.45) which was then itself largely replaced by another component (R_F 0.60). The bright green solution was processed (p.107) to yield a colourless syrup which crystallised from ethanol to give a mixture of ethyl tetra-O-benzoyl- α -D-glucopyranoside (102) and its β -anomer (101) in a ratio of 4:1 as fine white needles (1.47 g, 83%), $[\alpha]_D + 78^\circ$ [α -anomer, $+93^\circ$; β -anomer, $+20.5^\circ$; calc., $+78.5^\circ$], R_F (solvent D) 0.60 (major) and 0.45 (minor). Two recrystallisations from ethanol increased the specific rotation to $+82^\circ$, corresponding to a 6:1 mixture of these same compounds. A pure sample of the α -anomer (102) was obtained by subjecting a sample of the above mixture to p.l.c. (solvent E), and recrystallised

from ethanol it became fine white needles, m.p. 120-122°, $[\alpha]_D +93^\circ$
(Found: C, 69.5; H, 5.4. $C_{36}H_{32}O_{10}$ requires C, 69.2; H, 5.2%).

Ethyl tetra-O-benzoyl-β-D-glucopyranoside (101). - Penta-O-benzoyl-β-D-glucopyranose (100) (2.0 g), ethanol (0.15 g, 1.15 mol. equiv.) and boron trifluoride diethyletherate (0.41 g, 1.0 mol. equiv.) were heated under reflux in chloroform (30 ml) for 1h, by which time t.l.c. (solvent D) indicated that compound (100) had been replaced by a major and a minor new component, the former being the less mobile. The reaction solution was processed (p.107) to yield a colourless syrup which crystallised on standing with ethanol for one week to give a mixture of the β-glucoside (101) and its α-anomer (102) in the ratio 6:1 as a white solid (1.2 g, 67%), $[\alpha]_D +30^\circ$ [calc., +30.9; refer to previous experiment], R_F (solvent D) 0.45 (major) and 0.60 (minor). Recrystallisation of this from ethanol containing a little chloroform yielded a further white solid (0.56 g), m.p. 137-144°, judged from t.l.c. and rotation ($[\alpha]_D +24^\circ$) to be a 20:1 mixture of these same anomers [Lit.,²⁴⁴ m.p. 144-146°, $\alpha_D +20.5^\circ$ for the pure β-glucoside (101)].

Prop-2-yl tetra-O-benzoyl-α-D-glucopyranoside (103). - Penta-O-benzoyl-β-D-glucopyranose (100) (3.0 g), propan-2-ol (0.30 g, 1.2 mol. equiv.) and boron trifluoride diethyletherate (0.90 g, 1.5 mol. equiv.) were heated under reflux in benzene (50 ml) for 1h, by which time t.l.c. (solvent D) indicated compound (100) had been replaced largely by a new more mobile component. The light green solution was processed (p.107) to yield a colourless syrup (2.5 g). A sample of this syrup (0.8 g) was subjected to p.l.c. (solvent E), and the major fraction obtained yielded prop-2-yl tetra-O-benzoyl-α-D-glucopyranoside (103) which crystallised from ethanol as fine white needles (0.34 g, 12% of total), m.p. 132-134°, $[\alpha]_D +92^\circ$ (Found: C, 69.8; H, 5.2. $C_{37}H_{34}O_{10}$ requires C, 69.6; H, 5.4%). The remaining syrup was crystallised from ethanol with the aid of a seed to yield a mixture of the α-glucoside (103) and its β-anomer in the ratio 20:1, as a white solid (0.8 g, 30% of total), $[\alpha]_D +88^\circ$ [α-anomer, +92°; β-anomer,²⁴⁴ +11.4°; calc., +88°]. Recrystallised twice from ethanol the product had $[\alpha]_D +91^\circ$, but t.l.c. indicated a persistent trace of the less mobile β-glucoside.

Benzenesulphenyl bromide (115) and chloride (113). - Solutions of these reagents were prepared by adding thiophenol in benzene over 15 min to stirred suspensions of NBS or NCS (1 mol. equiv. of active material p. 87) in benzene, precautions being taken to exclude moisture. After a further 20 min the fuming red solutions of (115) or the yellow solutions of (113) were decanted from precipitates of succinimide and used immediately.

Phenyl tetra-O-acetyl- β -D-glucopyranosyl disulphide (109). -

(a) From benzenesulphenyl chloride (113). A solution of compound (113) in benzene (120 ml), prepared from thiophenol (1.6 ml), was added to tetra-O-acetyl-1-thio- β -D-glucopyranose (62) (5.0 g, 0.88 mol. equiv.), whereupon t.l.c. (solvent B) indicated that thiol (62) (R_F 0.57) had been replaced by a major (R_F 0.77) and a minor (R_F 0.40) new carbohydrate component. After removal of solvent, the crude product was crystallised from ethanol at room temperature to give fine white needles which were judged from t.l.c. and n.m.r. evidence to be almost pure glucosyl phenyl disulphide (109) (3.92 g, 60%). Recrystallised from ethanol it had m.p. 117-126°, $[\alpha]_D -223^\circ$ [Lit., ²⁴⁵ m.p. 117-118°, $[\alpha]_D -228^\circ$; ¹⁷¹ m.p. 123-124°, $[\alpha]_D -241^\circ$] (Found: C, 50.7; H, 5.0; S, 13.4. $C_{20}H_{24}O_9S_2$ requires C, 50.8; H, 5.1; S, 13.6%), and displayed the n.m.r. spectral characteristics already reported for this compound.¹⁷¹

The filtrate obtained after removal of compound (6) yielded large clear needles at 0° which were judged by t.l.c. and n.m.r. to be almost pure bis(tetra-O-acetyl- β -D-glucopyranosyl)disulphide (75) (0.28 g, 6%). Recrystallised from methanol it had m.p. 142-143°, $[\alpha]_D -151^\circ$ [Lit., see p. 89]. The remaining liquor yielded a further white solid (0.48 g) at -20° which was shown by t.l.c. and n.m.r. to be a mixture of disulphides (109) and (75) in the ratio 1:1. The total yield of carbohydrate material recovered was thus 72%. When the above reaction was repeated on a scale employing thiol (62) (20 g) a 65% yield of glucosyl phenyl disulphide (109) was obtained.

(b) From benzenesulphenyl bromide (115). When the above reaction was repeated using a benzene solution of compound (115), prepared from thiophenol (1.6 ml), t.l.c. indicated that, while the same two products had been formed, the less mobile symmetrical disulphide (75) was the major product. The crude reaction product crystallised from ethanol as a white solid (3.9 g) which was judged by t.l.c. and n.m.r. (the two disulphides have distinct H-6,6' resonances) to be a mixture of disulphides (109) and

(75) in the ratio 1:2. Recrystallisation of this from ethanol (60 ml) gave, at room temperature, bis(tetra-O-acetyl- β -D-glucopyranosyl)-disulphide (75) (1.32 g, 26%), and the filtrate from this at 0° gave phenyl tetra-O-acetyl- β -D-glucopyranosyl disulphide (109) (0.93 g, 14%). T.l.c. and n.m.r. indicated these two products to be largely pure, and after recrystallisation from methanol each had the same physical constants as those reported for the same compounds in part (a).

Partial desulphurisation with tris(diethylamino)phosphine (104). -

(a) General processing procedure. Because it was found that strongly basic aminophosphine residues were able to cause deacetylation of the products during processing of partial desulphurisation mixtures, the benzene reaction solutions were initially washed with dilute hydrochloric acid into which the aminophosphine (104) was shown to be extracted.

(b) Of bis(tetra-O-acetyl- β -D-glucopyranosyl)disulphide (75).

Disulphide (75) (2.0 g) and aminophosphine (104) (1.0 g, 1.5 mol. equiv.) were heated in benzene (50 ml) under reflux in a nitrogen atmosphere for 1.5h, after which time t.l.c. (solvent B) indicated the absence of β , β -disulphide (75) (R_F 0.37, weakly u.v.-absorbing) and the presence of one major carbohydrate product (R_F 0.38, non-u.v.-absorbing) along with a number of other minor products. The benzene solution was washed with dilute hydrochloric acid, then water, dried, and reduced to a red syrup. This yielded β -D-glucopyranosyl 1-thio- α -D-glucopyranoside octaacetate (97) from ethanol as a white solid (1.0 g, 52%) which was shown to contain largely a single component on t.l.c. Recrystallised from ethanol it gave white needles (0.77 g, 40%), m.p. 168-169°, $[\alpha]_D^{+109}$, δ 2.00, 2.02 and 2.10 (24H, acetyl), 3.7 (2H, broad m, H-5), 4.0-5.5 (11H, carbohyd. ring protons), and 5.93 (1H, d, $J_{1,2}$ 5Hz, H-1e) [Lit., ^{107,169} m.p. 170°, $[\alpha]_D^{+115}$, δ 6.0 (d, J 5Hz)].

(c) Of phenyl tetra-O-acetyl- β -D-glucopyranosyl disulphide (109).

Disulphide (109) (2.5 g) and aminophosphine (104) (2.1 g, 1.6 mol. equiv.) were heated in benzene (25 ml) under reflux in a nitrogen atmosphere for 0.75h, after which time the solution was washed with dilute hydrochloric acid (x2) then water, dried, and reduced to a yellow syrup, which was shown by t.l.c. (solvent B) to contain two main carbohydrate products, R_F 0.64 (u.v.-absorbing) and R_F 0.38 (non-u.v.-absorbing). The less

mobile component, β -D-glucopyranosyl 1-thio- α -D-glucopyranoside octaacetate (97), crystallised from this mixture in methanol, being obtained as a crude white solid (two crops, 0.54 g, 29%) which was largely a single component on t.l.c. Recrystallised (x2) from ethanol it gave fine white needles, m.p. 169-170°, $[\alpha]_D +110^\circ$ with an n.m.r. spectrum identical to that of previously characterised material. The remaining liquors were reduced to a red syrup (2.8 g) which was subjected to p.l.c. (solvent B). The major u.v.-absorbing band yielded a syrup (1.4 g) which appeared from its n.m.r. spectrum to be a mixture of tris(diethylamino)phosphine sulphide (108) and phenyl tetra-O-acetyl-1-thio- α -D-glucopyranoside (82) in the ratio 2:3, and which thus represented a 42% yield of the latter. Crystallised from methanol it yielded a white solid (0.47 g) which was shown by n.m.r. to be a mixture of the same compounds in the ratio 1:15, and recrystallised from methanol it gave a pure sample of the α -thioglucoside (82) as white needles (0.25 g, 11%), m.p. 86-88°, $[\alpha]_D +225^\circ$ [Lit., see p. 90], which was identical with authentic material (mixed m.p., n.m.r.). A number of minor carbohydrate products were formed in this reaction, but attempts to isolate any of them by p.l.c. proved unsuccessful, only complex mixtures being obtained.

Reaction of bis(tetra-O-acetyl- β -D-glucopyranosyl)disulphide (75) with NBS. - Compound (75) (0.5 g), NBS (0.25 g, 2 mol. equiv.), and benzoyl peroxide (0.006 g, 0.04 mol. equiv.) were heated in carbon tetrachloride (20 ml) under reflux in the presence of diffuse light. The solution developed an orange colour, presumed to be due to bromine, but after 4h t.l.c. (solvent B) indicated that disulphide (75) was still the major carbohydrate component and that a number of minor products had been formed. On allowing the solution to cool to room temperature, succinimide was deposited as white plates (0.094 g, 61%), $\delta_{2.8}(s, NCH_2)$ the i.r. spectrum of which was identical to that of an authentic sample of succinimide. Recrystallised from carbon tetrachloride it had m.p. 122-125° [Lit.,²³² m.p. 126].

General procedures for NBS reactions. - Unless otherwise stated, all reactions were performed under the influence of white light from a 250 watt heat lamp positioned 10 cm from the glass reaction flask. The reaction

mixtures were heated under reflux until, in most cases, the NBS (which sinks in carbon tetrachloride) had been converted into succinimide (which floats in carbon tetrachloride), or until t.l.c. indicated that the reaction was complete. After the mixtures were cooled to room temperature, succinimide was removed by filtration, and the filtrates were reduced in vacuo to syrups. Bromine, which was often generated in these reactions, was simultaneously evaporated during the latter step. The syrups were then taken up in chloroform, washed with water (1xhot, 1xcold), dried with sodium sulphate (anhydrous), and finally taken to dryness.

Spectral data for the hex-1-enopyranosid-3-ulose derivatives. -

The n.m.r., u.v., and i.r. spectra for these derivatives are summarised in Table 2 (p. 74), Table 3 (p. 76), and Table 4 (p. 79) respectively.

Phenyl 2,4,6-tri-O-acetyl-1-thio-D-erythro-hex-1-enopyranosid-3-ulose (119) and its 2-O-monobromoacetyl analogue (120). -

(a) From phenyl 2,3,4,6-tetra-O-acetyl-1-thio- β -D-glucopyranoside (81). Compound (81) (5.0 g) and NBS (6.2 g, 3.0 mol. equiv.) were heated under reflux in carbon tetrachloride (350 ml) for 20 min. T.l.c. (solvent A) indicated that compound (81) (R_F 0.52) had been completely replaced by two new carbohydrate components (R_F 0.38 and 0.47) which showed up as bright yellow spots on t.l.c. plates after spraying and heating. The mixture was processed (p. 115) to yield a light yellow syrup which crystallised from ethanol to give white crystals (2.1 g). The n.m.r. spectrum contained a singlet at δ 3.95 (0.5H, bromoacetyl) and a singlet at δ 2.20 (2.25H, acetyl), consistent with the product being a 3:1 mixture of the title compounds (119) and (120). Repeated recrystallisations from methanol or ethanol failed to alter the ratio of the products significantly, even though large well formed crystals could be grown. A t.l.c. investigation of the mother liquors after removal of the crystalline product, indicated that a large number of components were present, and although two had the same mobilities as the title compounds, the mixture was so complex it was not further investigated.

A sample of the above crystalline product was subjected to p.l.c. (solvent F) and the two fractions were isolated and crystallised from ethanol.

The triacetate (119) was obtained from the less mobile fraction as white needles, m.p. 117-118°, $[\alpha]_D^{20} +293^\circ$ (c 1 in CHCl_3) (Found: C, 55.0; H, 4.6; S, 8.0%, M^+ 394.0729. $\text{C}_{18}\text{H}_{18}\text{O}_8\text{S}$ requires C, 54.8; H, 4.6; S, 8.1%, M^+ 394.0722).

The crystalline product obtained from the more mobile fraction was repurified by p.l.c. (solvent A) and the major fraction obtained was crystallised from ethanol to yield the monobromoacetate (120) as white needles. T.l.c. and n.m.r. indicated the absence of the triacetate (119) but it was noticed that the monobromoacetate (120) partially reacted on contact with silica gel to give a much less mobile component (R_F 0.20). Recrystallised from ethanol it had m.p. 109-112°, $[\alpha]_D^{20} +258^\circ$ (c 0.8 in CHCl_3) (Found: C, 46.0; H, 3.6; S, 6.7; Br, 16.5%, M^+ (^{79}Br), 471.9816. $\text{C}_{18}\text{H}_{17}\text{BrO}_8\text{S}$ requires C, 45.7; H, 3.6; S, 6.8; Br, 16.9%, M^+ (^{79}Br), 471.9828).

The above experiment was repeated under a variety of conditions, employing β -thioglucoside (81) (1.0 g) and NBS in carbon tetrachloride (70 ml) under the influence [except in one instance, see (v) below] of white light from the 250 watt heat lamp, and the following conclusions were drawn: (i) the addition of barium carbonate (5 mol. equiv.) did not change the course of the reaction, nor improve the yield; (ii) the removal of bromine formed in the reaction by the use of a thimble containing copper powder suspended in the condenser did not affect the reaction; (iii) when only 1 mol. equiv. of NBS was used, the reaction did not go to completion; (iv) although slight variations were observed in the ratio of compounds (119) and (120) present in the products obtained from different reactions, in all cases both compounds were present in significant proportions; (v) in the absence of light, no detectable reaction occurred during heating under reflux for 10h, and compound (81) was recovered unchanged (as determined by mixed m.p. and t.l.c.) in 74% yield.

(b) From phenyl tetra-O-acetyl-1-thio- α -D-glucopyranoside (82). Compound (82) (1.0 g) and NBS (2.0 g, 5.0 mol. equiv.) were heated under reflux in carbon tetrachloride (70 ml) for 2.5h. It was noted that the development of colour and the appearance of succinimide occurred at a slower rate than for the reaction of the corresponding β -compound (81). T.l.c. (solvent F) indicated that the compound (82) had been converted into two new compounds which showed up bright yellow on spraying and heating. The mixture was processed (p.115) to yield a light yellow syrup which

crystallised from ethanol to give solid white crystals (0.24 g). T.l.c. and n.m.r. indicated that the product was a mixture of the title compounds (119) and (120), identical to that obtained from the β -compound (81), except that in this case the components were present in a ratio of 3:2.

Reaction of NBS with phenyl tetra-O-acetyl-1-thio- β -D-glucopyranoside (81) in diffuse light. - Compound (81) (1.6 g) and NBS (2.6 g, 4.0 mol. equiv.) were heated under reflux in carbon tetrachloride (30 ml) under the influence of diffuse light only (neon lighting and winter sun through the windows). After 1.5h, t.l.c. (solvent E) indicated the presence of largely one new non-u.v.-absorbing carbohydrate component (R_F 0.58) of greater mobility than compound (81). The mixture was then processed (p.115) to yield a yellow syrup, a portion of which was subjected to column chromatography (silica gel, solvent E) and yielded two major fractions A and B. Fraction A was a non-u.v.-absorbing carbohydrate (t.l.c.) which was identical (n.m.r. and t.l.c.) to an authentic sample of tetra-O-acetyl- α -D-glucopyranosyl bromide (96) (prepared by the method of Fischer²⁴⁶), and it crystallised from ethanol as white needles, m.p. 96-100°, $[\alpha]_D +182^\circ$ [Lit.,¹⁸⁹ m.p. 88-89°, $[\alpha]_D +201^\circ$]. Although these constants are in poor agreement, the i.r. spectrum of these crystals was identical to that of the authentic bromide (96), and no effort was made to further purify the small sample that had been obtained. Fraction B was a u.v.-absorbing non-carbohydrate (t.l.c.) which crystallised on removal of solvent. Recrystallisation of this from ethanol yielded N-(phenylthio)-succinimide (173), m.p. 113-116° [Lit.,¹⁷⁸ m.p. 116°] which had the same n.m.r. spectrum and t.l.c. mobility as an authentic sample prepared by the method of Groebel.¹⁷⁸

Phenyl tetra-O-benzoyl-1-thio- α -D-glucopyranoside (131). - Phenyl 1-thio- α -D-glucopyranoside (170) (0.44 g) (see p. 90) was treated with pyridine (3 ml) and benzoyl chloride (3 ml) and the reaction mixture was processed in the usual way (p.115) to yield a light yellow syrup which crystallised from ethanol to give the α -thioglucoside (131) as a cream solid (1.05 g, 95%). Recrystallised (x2) from acetic acid-ethanol it became fine white needles, m.p. 130-132°, $[\alpha]_D +109^\circ$ (Found: C, 69.5; H, 4.7; S, 4.8. $C_{40}H_{32}O_9S$ requires C, 69.8; H, 4.7; S, 4.7%), δ 7.7-8.2 (8H, m, σ -PhCO₂-), 7.0-7.7 (17H, m, m - and p -PhCO₂-, PhS-),

5.4-6.4 (4H, m, H-1,2,3,4), 4.8-5.2 (1H, m, H-5), and 4.4-4.7 (2H, m, H-6).

Phenyl 2,4,6-tri-O-benzoyl-1-thio-D-erythro-hex-1-eno-pyranosid-3-ulose (130). -

(a) From phenyl tetra-O-benzoyl-1-thio-β-D-glucopyranoside (83).

Compound (83) (5.0 g) and NBS (3.9 g, 3.0 mol. equiv.) were heated under reflux in carbon tetrachloride (200 ml) for 15 min. T.l.c. (solvent G) indicated that compound (83) (R_F 0.42) had been replaced by a single new component (R_F 0.30) which showed up as a bright yellow spot on spraying and heating. The mixture was processed (p.115) to yield a light yellow syrup which crystallised from ethanol to give the tribenzoate (130) as a white solid (3.2 g, 76%). Recrystallised, twice from ethanol containing a minimum of acetic acid, and then from glacial acetic acid, it had m.p. 165-166° (indefinite start to melting range as it softened from ca. 155°), $[\alpha]_D^{+336}$ (c 1.7 in CHCl_3) (Found: C, 68.5; H, 4.3; S, 5.5. $\text{C}_{33}\text{H}_{24}\text{O}_8\text{S}$ requires C, 68.3; H, 4.2; S, 5.5%).

(b) From phenyl tetra-O-benzoyl-1-thio-α-D-glucopyranoside (131).

Compound (131) (0.40 g) and NBS (0.52 g, 5.0 mol. equiv.) were heated under reflux in carbon tetrachloride (30 ml). The progress of the reaction was monitored by t.l.c. (solvent G) and only after 2.5h was the replacement of compound (131) (R_F 0.50) by a single new component (R_F 0.30), which showed up bright yellow on spraying and heating, judged to be complete. The mixture was then processed (p.115) to yield a light yellow syrup which crystallised from ethanol to give the tribenzoate (130) as a white solid (0.24 g, 71%). Recrystallised from acetic acid and then ethanol-acetic acid it had m.p. 162-164° (indefinite start to melting range as it softened from ca 155°), $[\alpha]_D^{+330}$ (c 0.8 in CHCl_3). T.l.c. and n.m.r. indicated this product to be identical to that obtained from β-compound (83).

Phenyl 2,4,6-tri-O-acetyl-1-thio-D-threo-hex-1-enopyranosid-3-ulose (132). -

Phenyl tetra-O-acetyl-1-thio-β-D-galactopyranoside (84) (8.5 g) and NBS (10.3 g, 3.0 mol. equiv.) were heated under reflux in carbon tetrachloride (350 ml) for 15 min. The mixture was processed (as on p.115, but without washing with water), and the resulting syrup was crystallised from ethanol (70 ml) at 0° to yield white crystals (2.9 g). T.l.c. (solvent F) indicated this to be largely a single component (R_F 0.29), but the n.m.r.

spectrum contained a singlet at $\delta 4.00$ (bromoacetyl) and a comparatively reduced singlet at $\delta 2.21$ (acetyl), consistent with the product being a 36% yield of a mixture of the title compound (132) and its 2-O-mono-bromoacetyl analogue (133) in the ratio 3:1. Recrystallisation (ethanol x1, methanol x2) of this gave a pure sample of the triacetate (132) as chunky white crystals (1.4 g, 18%), m.p. $119-120^\circ$, $[\alpha]_D^{25} +51^\circ$ (c 2 in CHCl_3) (Found: C, 54.6; H, 4.5; S, 7.9%, M^+ 394. $\text{C}_{18}\text{H}_{18}\text{O}_8\text{S}$ requires C, 54.8; H, 4.6; S, 8.1%, M^+ 394). T.l.c. investigation of the mother liquors after removal of the initial crystalline product, revealed several components with similar but different mobilities to those of products already isolated, and this mixture was not further investigated.

Phenyl tetra-O-benzoyl-1-thio- β -D-galactopyranoside (134). -

Phenyl 1-thio- β -D-galactopyranoside (171) (2.6 g) (see p. 90) was treated with pyridine (15 ml) and benzoyl chloride (15 ml), and the reaction mixture was processed in the usual way (p. 88) to yield a light yellow syrup which crystallised (3 crops) from ethanol-light petroleum as fine white needles of the β -thiogalactoside (134) (4.5 g, 69%). Recrystallised (x3) from ethanol it had m.p. $117-118^\circ$, $[\alpha]_D^{25} +91^\circ$ (Found: C, 70.1; H, 4.7; S, 4.7. $\text{C}_{40}\text{H}_{32}\text{O}_9\text{S}$ requires C, 69.8; H, 4.7; S, 4.7%). When this compound was being recrystallised from ethanol it initially separated as a syrup, but this gradually crystallised when the mixture was allowed to stand at room temperature.

Phenyl 2,4,6-tri-O-benzoyl-1-thio-D-threo-hex-1-enopyranosid-3-ulose (135). -

Phenyl tetra-O-benzoyl-1-thio- β -D-galactopyranoside (134) (1.7 g) and NBS (1.3 g, 3.0 mol. equiv.) were heated under reflux in carbon tetrachloride (70 ml) for 15 min. T.l.c. (solvent F) indicated that compound (134) (R_F 0.84) had been replaced by a single new carbohydrate component (R_F 0.67) which showed up as a bright yellow spot on spraying and heating. The mixture was processed (p. 115) to yield a light yellow syrup which crystallised from ethanol to give the tribenzoate (135) as a white solid (1.2 g, 83%). Recrystallised from ethanol it had m.p. $160-161^\circ$, $[\alpha]_D^{25} +37^\circ$ (c 1.5 in CHCl_3) (Found: C, 68.4; H, 4.3; S, 5.7. $\text{C}_{33}\text{H}_{24}\text{O}_8\text{S}$ requires C, 68.3; H, 4.2; S, 5.5%).

Reaction of methyl (phenyl tri-O-acetyl-1-thio- β -D-glucopyranosid)uronate (86) with NBS. - Compound (86) (1.0 g) and NBS (2.1 g, 5.0 mol. equiv.) were heated under reflux in carbon tetrachloride (70 ml) for 0.5h. T.l.c. (solvent F) indicated that compound (86) (R_F 0.54) had been completely replaced by two new carbohydrate components (R_F 0.48 and 0.76), the less mobile component being detected as a bright yellow spot on t.l.c. plates after spraying and heating. The mixture was processed (p.115) to yield a yellow syrup which was subjected to p.l.c. (solvent E) and gave two syrupy fractions A (0.38 g) and B (0.20 g).

Fraction A, the less mobile fraction, resisted crystallisation and was characterised as a crude sample of methyl (phenyl 2,4-di-O-acetyl-1-thio-D-erythro-hex-1-enopyranosid-3-ulos)uronate (155) by its n.m.r. spectrum, δ 7.2-7.7 (5H, m, aromatic), 5.55 (1H, d, $J_{4,5}$ 5.5Hz, H-4), 4.97 (1H, d, H-5), 3.71 (3H, s, OCH_3), 2.18 and 2.08 (2x 3H, s, acetyl). No attempt was made to further purify this product.

Fraction B, the more mobile fraction, crystallised from ethanol to yield methyl (phenyl tetra-O-acetyl-5-C-bromo-1-thio- β -D-glucopyranosid)uronate (156) as white needles (0.14 g, 12%). Recrystallised from ethanol it had m.p. 107-108°, $[\alpha]_D$ -81° (Found: C, 45.5; H, 4.5; S, 6.3; Br, 15.9. $C_{19}H_{21}BrO_9S$ requires C, 45.2; H, 4.2; S, 6.3; Br, 15.8%), δ 7.1-7.6 (5H, m, aromatic), 4.7-5.8 (4H, m, H-1,2,3,4), 3.80 (3H, s, OCH_3), 2.07, 2.02, and 1.94 (3 x 3H, s, acetyl).

Methyl (phenyl tri-O-acetyl- β -D-glucopyranosid)uronate (157). -

Methyl tetra-O-acetyl- β -D-glucopyranuronate (93) (5.0 g), phenol (1.37 g, 1.1 mol. equiv.) and boron trifluoride diethyletherate (9.4 g, 5.0 mol. equiv.) were dissolved in chloroform (70 ml) and the solution was allowed to stand at room temperature. After 47h, t.l.c. (solvent E) indicated that compound (93) had been largely replaced by a new, weakly u.v.-absorbing carbohydrate component of greater mobility, whereupon the mixture was processed (as described for thiolyse, p.107) to yield a colourless syrup. Although this initially resisted crystallisation, a sample which was purified by p.l.c. (solvent E) crystallised spontaneously on being taken to dryness, and the use of a seed crystal permitted the phenyl β -glucuronate (157) to be crystallised from propan-2-ol as fine white

needles (2.4 g, 44%). Recrystallised from propan-2-ol it had m.p. 119-120°, $[\alpha]_D -31^\circ$ [Lit., ²²³ m.p. 117-118° and 126.5-127.5 (two forms), $[\alpha]_D -35.6^\circ$] δ 2.05 (12H, s, acetyl), 3.72 (3H, s, OCH₃), 4.0-4.4 (1H, m, H-5), 4.9-5.5 (4H, m, H-1,2,3,4), and 6.8-7.5 (5H, m, Ph).

Methyl tetra-O-acetyl-5-C-bromo- β -D-glucopyranuronate (158). -

Methyl tetra-O-acetyl- β -D-glucopyranuronate (93) (5.0 g) and NBS (2.8 g, 1.2 mol. equiv.) were heated under reflux in carbon tetrachloride (200 ml) for 1³/₄h, by which time compound (93) had been replaced by a single more mobile component [t.l.c. (solvent E)]. The mixture was processed (p. 115) to yield a syrup which crystallised from ethanol (50 ml) to give methyl tetra-O-acetyl-5-C-bromo- β -D-glucopyranuronate (158) as white needles (4.1 g, 68%). Recrystallised (x2) from ethanol it had m.p. 159-161°, $[\alpha]_D -107^\circ$ (Found: C, 39.4; H, 4.1; Br, 17.8. C₁₅H₁₉BrO₁₁ requires C, 39.6; H, 4.2; Br, 17.6%) δ 6.25 (1H, d, J_{1,2} 7Hz H-1), 5.0-5.8 (3H, m, H-2,3,4), 3.82 (3H, s, OCH₃), 2.13, 2.08, 2.04 and 2.01 (4 x 3H, s, acetyl). This compound sublimed readily at temperatures just below its m.p., and after a sample had been sublimed at 0.2 mm Hg and 150-160° it was shown (n.m.r.) not to have undergone any chemical change, and recrystallised from ethanol it had m.p. 160-162°, $[\alpha]_D -107^\circ$.

When compound (93) (1.0 g) and NBS (1.2 mol. equiv.) were heated under reflux in carbon tetrachloride (70 ml) for 3.5h in the dark, the NBS appeared to remain unchanged and t.l.c. and n.m.r. studies indicated that the only carbohydrate present was the starting compound (93). When an analogous mixture containing in addition benzoyl peroxide (0.033 g, 0.05 mol. equiv.) was heated under reflux in the dark, however, t.l.c. indicated that the 5-C-bromo-derivative (158) was gradually formed, that after 3.5h it was the major component, and that a little of compound (93) remained unreacted.

Methyl tri-O-acetyl-2,6-anhydro-L-gulonate (163). - Methyl (phenyl tri-O-acetyl-1-thio- β -D-glucopyran)uronate (86) (9.0 g) was heated under reflux in ethanol (200 ml) with Raney Nickel W7²⁴⁷ (ca., 60 g). After 1h, compound (86) had been replaced largely by one new non-u.v.-absorbing less mobile component [t.l.c. (solvent E)]. The solution was filtered and then taken to dryness to yield a crude white solid*. Recrystallised

*The preparation was performed up to this stage by R. Blattner.

from ethanol it gave methyl tri-O-acetyl-2,6-anhydro-L-gulonate (163) (4.6 g, 68%). A sample of this, recrystallised from ethanol and then ethanol containing a little chloroform, had m.p. 116-117°, $[\alpha]_D +39^\circ$ (Found: C, 49.0; H, 5.8. $C_{13}H_{18}O_9$ requires C, 49.1; H, 5.7%) δ 4.6-5.3 (3H, m, H-3,4,5), 3.9-4.4 (2H, m, H-2,6e), 3.70 (3H, s, OCH_3), 3.45 (1H, q, $J_{5,6a}$ 7.5Hz, $J_{6a,6e}$ 10.5Hz, H-6a).

Methyl tri-O-acetyl-2-bromo-2-deoxy- α -L-xylo-hex-2-ulopyranosonate (164). - Methyl tri-O-acetyl-2,6-anhydro-L-gulonate (163) (2.0 g) and NBS (2.24 g, 2.0 mol. equiv.) were heated under reflux for 50 min, after which t.l.c. (solvent E) indicated that compound (163) had been replaced by a major and a minor new, more mobile, u.v.-absorbing carbohydrate component. The mixture was processed (p.115) to yield a colourless syrup which crystallised from ethanol (10 ml) at 0° to give the 2-bromo-derivative (164) as white crystals (1.2 g, 47%), $[\alpha]_D -124^\circ$. Recrystallised (x2) from ethanol it had m.p. 103-107°, $[\alpha]_D -132^\circ$ (Found: C, 39.3; H, 4.4; Br, 20.7. $C_{13}H_{17}BrO_9$ requires C, 39.3; H, 4.3; Br, 20.1%) [Lit.,¹⁹⁶ m.p. 107-109°, $[\alpha]_D -135^\circ$]. The 60MHz n.m.r. spectrum of this material [δ 4.75-5.6 (3H, m, H-3,4,5), 3.8-4.4 (2H, m, H-1,1'), 3.77 (3H, s, OCH_3), 1.99, 2.01 and 2.04 (3 x 3H, s, acetyl)] and the 100MHz n.m.r. spectrum reported by Goshima and Tokuyama²¹⁵ for compound (164) were compared in detail, and were found to be identical.

Compounds prepared, but not otherwise referred to. -

(a) Phenyl tri-O-benzoyl-1-thio- β -D-xylopyranoside (174). Phenyl 1-thio- β -D-xylopyranoside (175) was prepared by catalytic deacetylation of the tetraacetate (85), and recrystallised from ethanol it had m.p. 143-144° $[\alpha]_D -68^\circ$ (c 4 in H_2O) [Lit.,¹⁰⁴ m.p. 144°, $[\alpha]_D -71^\circ$ (c 1.4 in H_2O)]. Compound (175) (1.5 g) was treated with pyridine (10 ml) and benzoyl chloride (10 ml) and the reaction mixture was processed in the usual way (p. 88) to yield light yellow syrup which crystallised from ethanol as fine white needles of phenyl tri-O-benzoyl-1-thio- β -D-xylopyranoside (174) (3.1 g, 90%). Recrystallised from acetic acid it had m.p. 139-140°, $[\alpha]_D -28^\circ$ (Found: C, 68.7; H, 4.7; S, 6.1. $C_{32}H_{26}O_7S$ requires C, 69.3; H, 4.7;

S, 5.8%) δ 7.6-8.1 (6H, m, m-benzoyl), 7.0-7.6 (14H, m, o- and p-benzoyl and PhS), 5.0-5.9 (4H, m, H-1,2,3,4), 4.66 (1H, q, $J_{4,5e}$ 5Hz, $J_{5a,5e}$ 12Hz, H-5e), and 3.77 (1H, q, $J_{4,5a}$ 6Hz, H-5a).

(b) Phenyl 3,4,6-tri-O-acetyl-2-O-benzoyl-1-thio- β -D-glucopyranoside (176). - 1,3,4,6-Tetra-O-acetyl- α -D-glucopyranose (98) (10 g) was dissolved in pyridine (50 ml), and to this solution cooled in an ice-bath, benzoyl chloride (8 ml) was gradually added. The reaction mixture was processed in the usual way (p. 88) to yield a light yellow syrup, which was shown to be a single u.v.-absorbing carbohydrate component on t.l.c. and revealed a doublet δ 6.44 (J 3.5Hz) in its n.m.r. spectrum [c.f., compound (98) has a doublet at δ 6.20 (J 4Hz)]. A sample purified further by p.l.c. resisted crystallisation.

The crude syrup (12.1 g) was dissolved in chloroform (100 ml) and hydrogen bromide (30 ml, 45% w/v in glacial acetic acid) was added. After 7h at room temperature, the solution was washed with water (x2) and then added to a solution of potassium hydroxide (2.0 g) and thiophenol (4.2 g) in methanol, and was heated under reflux for 1h. T.l.c. (solvent E) indicated that a single new u.v.-absorbing carbohydrate component had been formed. The solution was washed with water (x2), dried, and reduced to a syrup which crystallised from ethanol (70 ml) at room temperature to give phenyl 3,4,6-tri-O-acetyl-2-O-benzoyl-1-thio- β -D-glucopyranoside (176) as fine white needles (7.4 g, 52%). Recrystallised from ethanol and then acetic acid it had m.p. 149-150°, $[\alpha]_D^{20} +28^\circ$, δ 7.8-8.2 (2H, m, o-PhCO₂), 7.1-7.6 (8H, m, m- and p-PhCO₂, and PhS), 4.6-5.6 (4H, m, H-1,2,3,4), 4.0-4.4 (2H, m, H-6,6'), 3.6-4.0 (1H, m, H-5), 1.87, 2.01, 2.08 (3 x 3H, s, acetyl).

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