Potential antiviral agents: synthesis and conformational studies in the sugar series

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POTENTIAL ANTIVIRAL AGENTS.
SYNTHESIS AND CONFORMATIONAL STUDIES
IN THE SUGAR SERIES.

By Bernard Scanlon

Supervisor: Dr. J.B. Lee

A thesis submitted for the degree of
Doctor of Philosophy
of
Loughborough University of Technology

May, 1968
To my wife Anne

and to my parents.
FOREWORD

I wish to express my gratitude to Dr. J.B. Lee for his guidance and encouragement throughout this work.

I would also like to thank my wife, Anne, for her help in preparing the manuscript for this thesis; the staff of the Chemistry Department for their assistance during this work; Allen and Hanburys Limited and I.C.I. Pharmaceutical Division for carrying out microbiological tests.

Financial assistance from Loughborough University of Technology is gratefully acknowledged.
SUMMARY

The structure of sugar oximes has been examined by nuclear magnetic resonance spectroscopy (n.m.r.). There appears to be no simple relationship between the structure of the oxime and the ratio, on acetylation, of acetylated nitrile to acetylated oxime. The synthesis of thiazines, from thioamides and vinyl ketones, appears to have limited scope and was unsuccessful when applied to aldono-thioamides. The synthesis of several 2-aldono-1,3-thiazoles is recorded. Other routes to nitrogen and sulphur-containing ring systems with sugar side chains have been investigated. Some of these compounds have been tested for microbiological activity. The structure of sugar imidazolines has been examined by n.m.r. spectroscopy.

The conformation of straight chain acetylated sugars is explained in terms of a simple model. The n.m.r. measurements on several acyclic sugars are in accordance with this model. The method developed by Whiffen, relating conformation to optical rotation, has been extended to acetylated pyranoses by determining new values for Whiffen's rotation parameters. New parameters have been evaluated which make it possible to treat acyclic sugars by this method. Although the assumptions made in this treatment limit the accuracy, it seems that optical rotation provides useful supporting evidence for conformation.

In the final chapter, the results of a preliminary investigation into the reactions of organo lithium compounds with carbohydrates are reported.
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INTRODUCTION
1. a) The Viruses.

At the present time, molecular processes within the cell and the interaction between virus and host are insufficiently elucidated to allow the rational design of an antiviral agent. However, a study of the virus, its host, and the mechanism of its replication, indicates the stages of viral-host interaction that are likely to be susceptible to drug action.

The viruses\textsuperscript{1,2} are a diverse group of parasitic micro-organisms ranging in size from the tobacco necrosis virus, with a diameter of 16\textmu m, to the psittacosis virus, with a diameter of 270 \textmu m. There is a parallel diversity in composition and structure. The small plant viruses consist of ribonucleic acid (RNA) and protein only, whereas the psittacosis vaccinia virus\textsuperscript{3} contains protein (89\%), deoxy-ribonucleic acid (DNA 5.6\%), cholesterol (1.4\%), phospholipid (2.2\%) and neutral fat (2.2\%). The two virus types described below illustrate this diversity.

The Maus-Elberfeld (ME)\textsuperscript{4,5} virus is a small RNA containing virus belonging to the picornavirus group. Crystallised preparations of the virus contain more than 20\% RNA. Electron microscopy shows the virus particles to be 24 \textmu m in diameter, but under high resolution (using negative staining techniques) the virus appears as a polyhedron. (I)
The RNA can be extracted with phenol and its rate of sedimentation indicates a molecular weight of about 2,000,000. This RNA, in the absence of its capsid, is still infective, therefore the RNA must carry the genetic information for the virus. The protein coat carries the virus antigenic character but is not infective. The protein is not, as was originally thought, homogeneous, but consists of two or possibly three major polypeptides.

The Newcastle Disease Virus (NDV) is larger and more complex in structure and composition than the MEvirus and belongs to the myxovirus group. It has a diameter of 120-180μm. The RNA is contained inside a long hollow tube of protein which is known variously as the NP, G, and internal-g-protein. This protein is specific for the serological type of virus. The tube of nucleoprotein is coiled up inside a protein envelope. The outer protein envelope contains lipid and carbohydrate. The capsid contains the serological sub-group specific antigen and also the haemagglutinating and enzyme activity. As shown in the diagram (II) the virus is spherical in shape with spikes projecting from the surface. The spikes may contain the haemagglutinin and the enzyme but this is not certain.

![Diagram of Newcastle Disease Virus (II)](image-url)
The protein fractions showing these activities have been separated. The myxoviruses bind themselves to receptor sites on the cell surface. Erythrocytes, from several animals, although not susceptible to infection by these viruses, possess the receptor sites. The bonding between the cells and the viruses causes agglutination. On incubation, the virus is set free. The erythrocytes cannot be re-agglutinated and they have presumably lost the receptor sites. The viruses, on the other hand, are unchanged and can agglutinate further erythrocytes. During incubation a further product is produced and this has been characterised as N-acetyllneuraminic acid.

\[
\text{(III)}
\]

\[
\text{CH}_2\text{OH}
\]
\[
\text{HO}
\]
\[
\text{HO}
\]
\[
\text{AENH} - \text{O} - \text{CO}_2\text{H}
\]
\[
\text{OH}
\]
\[
\text{OH}
\]

(III)

The virus enzyme which breaks the cell-virus bond, setting free the neuraminic acid, is called a neuraminidase. Neither the structure of the enzyme, nor of the haemagglutin is known.

1. b) **The Host.**

Only those cell processes which are of immediate importance to the virus will be considered.

The cell or plasma membrane is about 80 Å thick and consists of a bimolecular layer of polar lipids coated on both sides with protein. The surface is very complex in structure and, as yet, far from understood. It is on this protein layer that the virus
finds a receptor and in some way modifies the membrane, which controls the cell's permeability, and allows the virus to enter after shedding its own capsid.

The intracellular functions of most interest to the virus are the synthesis of nucleic acid and protein.

The cell's genetic information is carried by the nucleotide sequence in the DNA. Almost all the cell's DNA is contained in the nucleus. There is a considerable amount of evidence to show that DNA acts as a template for messenger (m) RNA synthesis, which in turn controls the amino acid sequence in the cell's protein.

In the nucleus, the DNA is made up of two strands, with complementary base sequence, in the form of a double helix around a common axis. The two strands are held together by hydrogen bonding as shown in diagram (IV).

Hydrogen bonding between strands.  Hydrogen bonding between T-Thymine, A-adenine, P-phosphate.  guanine (G) and cytosine (C)
In some bacteria, a single duplex of DNA carries all the genetic information; in more complex animals, several strands of DNA are required. During replication, the DNA duplex breaks open and a complementary strand is built up with triphosphate (pyrophosphate) esters of the nucleotides on each parent strand, to give two identical duplexes. The two new strands are synthesised from the same starting point, unidirectionally and simultaneously. Two enzyme types involved in the synthesis have been characterised; DNA polymerase and DNA nucleotide transferase. The latter enzyme controls the transfer of the nucleotides to the parent DNA and the former the polymerisation of the nucleotides. The polymerisation requires the enzyme, primer DNA, Mn$^{2+}$ ions and the nucleotide triphosphate esters. The enzyme is not necessarily peculiar to a single type of primer DNA. The synthesis of mRNA follows a similar pattern and is catalysed by DNA-dependent RNA polymerase. In vitro both strands of the primer DNA are copied; the resulting RNA molecules are complementary and can be annealed. In vivo it appears that only one strand of the DNA is copied and it seems likely that the DNA duplex is not completely separated during this synthesis. In the bacteriophages $\phi$ and SP8, which have double stranded DNA, one strand is rich in pyrimidine bases and, having a much higher molecular weight, can be separated from its complementary strand by centrifugation. Only the pyrimidine-rich DNA can be annealed with the natural mRNA.

Although the synthesis of neither DNA nor mRNA is completely understood, a little is known of the mechanism and the enzymes associated with it.

Outlined below are the essential steps in protein synthesis. The amino acid is activated by reaction with adenosine triphosphate, giving the amino-acyl-adenylate.
This amino-acyl-adenylate enzyme complex then reacts with transfer (t) RNA to give amino-acyl-t-RNA. A different enzyme is required for each amino acid. The reaction is highly specific; even the structurally similar leucine, isoleucine and valine are substituted for each other less than once in 10,000 times.\(^3\)

![Chemical structures of leucine, isoleucine, and valine](attachment:image.png)

Protein synthesis takes place at the ribosomes, which line up on the mRNA to form polysomes and these travel in one direction along the mRNA. As the ribosomes move along, the amino-acyl-t-RNA attached to them recognise the codons on the mRNA, move into place and bond. The process is shown schematically below. (V)
The interaction of the ribosomes and the polynucleotides is independent of their cellular origin. The incorporation of amino acids by the ribosomes, is stimulated by both synthetic and natural polynucleotides. Transfer RNA is bound to the ribosome, irrespective of whether it is carrying its amino acid or not. Cysteine specific tRNA can be induced to carry alanine, but with mRNA, its reaction is as if it were cysteine-acyl-tRNA. Thus all the evidence indicates that the base sequence in the polypeptide chains is determined by the mRNA.

1. c) Antibiotics That Interfere With Nucleic Acid and Protein Synthesis.

Several drugs are known which disrupt nucleic acid and protein synthesis and these should have a marked effect on the virus.

The mitomycins (VI) block the synthesis of DNA, while RNA and protein synthesis continue for a limited period. This is illustrated by the growth of RNA virus in mitomycin treated cells.
Mitomycin C (VI)

The DNA from mitomycin treated cells behaves as though the two strands were cross linked which would prevent DNA synthesis. RNA synthesis can continue because it does not require its DNA primer to separate into strands. Mitomycin might be expected to be effective against DNA virus, as their replication rate is much higher than a normal cell's, but in practice it is found that virostatic doses kill mammalian cells.

Actinomycin (VII) strongly inhibits DNA dependent RNA polymerase.

Actinomycin D (VII)

It forms a reversible complex with DNA, inhibiting DNA dependent RNA polymerase, by blocking the primer DNA. There is a good correlation between the strength of the DNA complex and the degree of RNA inhibition. The DNA complex alters the physical properties of the DNA. The duplex conformation is stabilised; therefore the separation of the two strands
for DNA synthesis requires more energy.\textsuperscript{46,47} It is not surprising therefore that at higher concentrations, actinomycin D blocks DNA synthesis.

Actinomycin D is too toxic to mammalian cells to be used against viruses generally. Many RNA viruses, which in replication do not use a DNA template, are completely insensitive to Actinomycin.\textsuperscript{48} DNA viruses, on the other hand, are sensitive to a varying degree.\textsuperscript{48} Herpes simplex virus, grown in HeLa cell culture, is far more sensitive to actinomycin than the host cell.\textsuperscript{49} At dose levels that only temporarily depress cell RNA and DNA synthesis, actinomycin completely inhibits viral DNA synthesis. It is known that actinomycin requires guanine nucleotides for its complex formation\textsuperscript{50} and viral DNA is particularly rich in guanine residues.\textsuperscript{51}

The synthesis of protein, in mammalian cells and bacteria, does not look an attractive centre for selective drug action, as the processes seem to be essentially the same. However, the ribosomes of mammalian cells and bacteria are different\textsuperscript{52,53} and many useful antibiotics, which selectively interfere with bacteria protein synthesis, have been developed. Streptomycin prevents the transfer of the amino acids from t RNA to the growing polypeptide chain.\textsuperscript{54} Puromycin and chloramphenicol\textsuperscript{56} also selectively disrupt bacterial protein synthesis. These antibiotics are not selective in their action as far as viral protein synthesis is concerned.

1.d d) Replication of RNA Viruses\textsuperscript{57}

Small RNA viruses are able to replicate quite independently of DNA. Their growth is unaffected by DNA inhibitive drugs such as actinomycin D\textsuperscript{58} or thymidine analogues.\textsuperscript{59} The virus replication is carried out in the absence of the otherwise universal genetic material DNA. As the RNA, in the absence of the capsid, is still infective, all the genetic information must be carried by the RNA.
Viral protein is synthesised on host cell ribosomes as is normal protein. In infected cells, several types of protein are synthesised, many of which are not involved in the viral capsid or in the host cell's normal synthesis. The function of some of these proteins has been determined. One of these extra proteins is an inhibitor of DNA-dependent RNA polymerase. This inhibitor is supported by another, which inhibits protein synthesis by modifying the ribosomes. The size and shape of the ribosome aggregate changes from being characteristic of the host to being characteristic of the virus.

A second group of proteins coded for by the viral RNA is the RNA-dependent RNA polymerases.

The polysomes from infected cells contain RNA, which is identical in molecular weight and base composition to the viral RNA. When these polysomes are isolated and incubated in vitro, they synthesise protein, which is immunologically related to the
capsid proteins. The messenger function of viral RNA, is further demonstrated by the addition of viral RNA, from a bacteriophage, to an in vitro protein synthesis system, which results in phage protein being synthesised.

The location of virus RNA synthesis is not known specifically, but it does take place in the large particle (quickly sedimenting) part of the cytoplasm. This fraction includes the polysomes responsible for viral protein and polymerase synthesis. The close juxtaposition of viral RNA and protein synthesis has led to the suggestion that these syntheses form an integrated system. The bulk of the RNA formed during the period of rapid synthesis, has all the properties of single stranded viral RNA. A small proportion (2-5%) has physical properties which suggest that it is double stranded. The double stranded material consists of a positive and negative strand as required by the Watson-Crick model. Two mechanisms have been suggested for viral RNA synthesis. Both models build a complementary strand as the first stage.

\[ \text{polymerase} \]
\[ \text{nucleotide triphosphates} \]

\[ + \]

\[ U \]
\[ C \]
\[ G \]

\[ A \]

\[ + \]

\[ U \]
\[ C \]
\[ G \]

\[ A \]
\[ C \]
\[ G \]

\[ A \]
\[ U \]

\[ + \]

(IX)
The semi-conservative mechanism\textsuperscript{79,80} then suggests that the parent strand peels away as a new positive strand is formed on the negative template.

![Diagrams](image)

\( (X) \)

This mechanism explains most of the kinetic data, but not why none of the parental RNA appears in the progeny,\textsuperscript{81,82} or the high incidence of labelled parental RNA that occurs in the double stranded material.\textsuperscript{83} The alternative mechanism,\textsuperscript{84} the so-called "conservative mechanism", accounts for these anomalies. The original parental positive strand and complementary negative strand never become completely separated.

![Diagrams](image)

\( (Xa) \)

\( (XI) \)

-12-
It is thought that two enzymes are used in both mechanisms; one to form the original duplex, and a second to form the progeny nucleic acid. The mechanism is not resolved, and some recently obtained results have been interpreted as indicating that only one enzyme is involved, and that the complementary strand of RNA plays no part in the replication process.

Maturation of the virus is probably a spontaneous process and no energy is required. Mature viruses do not appear until the RNA and protein synthesis are well under way. Once the process starts it is quite rapid. It takes about one minute to synthesise the RNA and two or three minutes later it is encapsulated.

1. e) Antiviral Agents.

It is not proposed to consider antibodies, interferon, statolon, helenine, or other natural products that have prophylactic or therapeutic properties against viral diseases, but are of unknown structure. Nor is it proposed to consider broad range antibiotics that are active against the more complex virus of the psittacosis group.

Amantadine (XII) - This compound inhibits the multiplication of several myxoviruses. To be effective, it must be added to the culture very soon after infection. It is not virucidal at the concentrations used and does not affect the absorption of the virus onto the cell surface.
It is thought that amantadine affects the virus's penetration into
the cell. Trials of this drug against influenza virus in man, show
that it has prophylactic properties but no therapeutic ones. 95,96.

Guanidine and Hydroxybenzylbenzimidazole (H.B.B.) (XIII)-
These compounds, which have similar antiviral characteristics,
inhibit the growth of many picornaviruses. 97 They have no virucidal
action and do not interfere with the viruses' adsorption or
penetration into the cell. 97,98

Their action appears to start about two hours after the infection
of the virus, and finish when maturation begins to take place. 97,98,99
It is thought that both inhibit the formation of RNA polymerase, 100
or alternatively, interfere with the messenger function of the
viral RNA. 101 Neither drug has any toxic effect on the host cell
at the concentrations used, but they are of little value as
prophylactic or therapeutic agents as resistant mutants develop
very quickly. 102

Pyrimidines - Iododeoxyuridine (XIV) was developed as
an anti-tumour agent 103 but its ability to inhibit viral RNA
synthesis was soon recognised. 104
It does not affect RNA viruses, with the possible exception of Rous sarcoma virus. This drug, and its variants, behave as thymidine analogues in the cell. They are converted to the triphosphate and incorporated in the DNA. This DNA, however, cannot fulfill its normal role and cell replication ceases. The nature of the malfunctioning, caused by the abnormal DNA, is not known. The drugs attack mammalian cells and cannot be used systematically except as a last resort. Patients with malignant diseases, given intravenous injections of IUDR were found to be resistant to vaccinia virus. Used topically, IUDR shows therapeutic properties against herpetic keratitis in man. Against herpes infections of the skin, the results have been variable.

**Thiosemicarbazones** - These compounds inhibit some of the poxviruses but not other viruses, and are completely non-toxic to the host cell. The first active compound found was p-aminobenzaldehyde semicarbazone but more active compounds, such as isatin \( \beta \)-thiosemicarbazone (IBT) and its \( N \)-methyl and \( N \)-ethyl derivatives have been developed.
IBR does not affect viral DNA synthesis or the related enzyme synthesis.\textsuperscript{115, 116} Viral m RNA, formed late in the cycle, becomes unstable,\textsuperscript{117} and prevents the synthesis of some of the viral antigens.\textsuperscript{118} The chemical reactions involved are unknown. Numerous experiments with animals have shown that IBR has prophylactic and chemotherapeutic properties. Treatment must be started at the same time or soon after infection, as the semicarbazones do not affect established disease.

N-methyl isatin-$\beta$-thiosemicarbazone (methisazone) has been used as a prophylactic against smallpox. Close contacts of smallpox in Madras\textsuperscript{119, 120, 121} were divided into two groups. Of 2,842 people in the control group, 114 contracted smallpox and 20 died; of the 2,297 people taking oral doses of methisazone, 6 contracted smallpox and only 2 died.

The thiosemicarbazones are the most useful anti-viral agents developed to date.

Thiourea\textsuperscript{121} and Dithiobiuret\textsuperscript{122} - These compounds and several of their derivatives show antiviral activity. In both cases the NH-C-NH group appears to be essential to activity. The dithiobiuret (XVI) has been used with limited success against poliomyelitis in man.\textsuperscript{123} The source of their activity is not known.
I. 2-(dimethyl carbamoyl) phenyl-2,4-dithiobiuret (XVI)

Urethan,\(^{124}\) \(\alpha\)-hydroxy and \(\alpha\)-keto-aldehydes,\(^{125,126}\) biguanides,\(^{127}\) triazines,\(^{128}\) and some steroids\(^{129}\) have also shown varying degrees of activity but, in general, little is known of the mechanisms involved.

Atebrine\(^{130}\) (XVII) and Caprochlorone\(^{131}\) (XVIII) have also been shown to possess antiviral activity.

(XVII)  \hspace{1cm} (XVIII)

Folic acid analogues\(^{132}\) inhibit viral DNA synthesis but have no effect on RNA viruses.\(^{133}\)

Amino acid analogues - These have been found to have antiviral activity. \(L\)-threo-3-phenyl serine\(^{134}\) (XIX) and \(3\)-(p-fluorophenyl)alanine\(^{135}\) inhibit influenza virus. In both cases, the addition of phenylalanine reverses the inhibition, and the analogues are thought to interfere with the process of protein synthesis. These compounds are toxic to mammalian cells.
In principle, the vulnerable points for attack in virus replication are those where its biochemical processes can be differentiated easily from those of the host cell. Actinomycin D is effective because of the high guanine content in the viral DNA; guanidine and benzimidazole possibly attack the unique virus RNA-dependant RNA polymerase, and amantadine interferes with the penetration of the virus into the cell. The cytoplasmic replication of viral DNA and RNA, and the numerous inhibitor proteins required in virus replication, should yield to drug action.

The therapeutic problems will remain even when these drugs are found. In many viral diseases such as influenza, yellow fever and haemorrhagic smallpox, it seems likely that, by the time the symptoms are apparent, the viral level is already on the decrease. In these cases, agents such as serosin, which modify the tissue response, are more useful. Nevertheless, those viral diseases that develop more slowly, such as measles, poliomyelitis and vaccina gangrenosa, should respond to antiviral agents.
THE SYNTHESIS OF FIVE AND SIX MEMBERED RINGS CONTAINING NITROGEN AND SULPHUR

The 'N-C-S' fragment occurs in very many biologically active systems; in penicillin in the thiazole ring; in cephalosporin in the thiazine ring; in thioureas and thiosemicarbazones. Heterocyclic systems containing this fragment and having a sugar side chain, have been synthesised and their biological activity measured. The conformer distribution of the compounds has been determined approximately by n.m.r.

Aldonic acid nitriles and thioamides have previously been synthesised but only two reports of the synthesis of heterocyclics, from aldonic acid thioamides, have appeared. Beyer\textsuperscript{136} prepared 2-[penta-0-acetyl -D-glucopentahydroxypentyl]-4-phenyl-1,3-thiazole from penta-0-acetyl-D-glucondthioamide and -ω-phenacyl bromide, and Cañas Rodriguez and Aparicio\textsuperscript{137} prepared the corresponding 4-methyl thiazole by a modified method.

Aromatic and aliphatic nitriles and thioamides have been used as starting materials for the synthesis of thiazine and thiazole heterocyclics. Some of the synthetic routes used are outlined below. An investigation of the suitability of these routes for the synthesis of thiazole and thiazine derivatives of the sugars is reported here.

Condo\textsuperscript{138} and his co-workers described the condensation of aromatic and aliphatic nitriles with thioglycollic acid to give the α-imino-aryl (or alkyl)-mercaptoacetic acid hydrochloride (I).

\[
\text{RCN} + \text{CH}_2(\text{SH})\text{CO}_2\text{H} \rightarrow \text{RO}^\text{S-CH}_2\text{CO}_2\text{H} + \text{HCl}
\]
In view of the isolation of this compound (I) by Chabrier and Renard$^{139}$ as an intermediate in the synthesis of thiazoline-4-ones from a thioamide and chloroacetic acid, this reaction could offer a route to the 2-[polyhydroxyalkyl]-thiazoline-4-ones.

In their search for a synthetic route to cephalosporin C, Barrat$^{140}$ and his co-workers synthesised a number of 5,6-dihydro-4-hydroxy-4H-1,3-thiazines (II) by condensing thioamides with vinyl ketones.

\[
\text{C-C}^\text{SH} + \text{CH}_2\text{CH}-\text{C}-\text{CH}_3 \rightarrow \text{C-C}^\text{N}^\text{OH} \text{CH}_3
\]  

(II)

The same ring system was prepared by Pinkus$^{141}$ who synthesised 2-phenyl-5,6-dihydro-4H-1,3-thiazine (III) from thiobenzamide and 1-bromo-3-chloro-propane.

\[
\text{C-C}^\text{SH} + \text{Br.CH}_2\text{CH}_2\text{CH}_2\text{Cl} \rightarrow \text{C-C}^\text{N}
\]  

(III)

Manni, Reckendorf and Bonner$^{142}$ synthesised the 2-[polyhydroxyalkyl]-tetrahydrothiazines (IV) from 3-mercaptopropylamine hydrochloride and the corresponding aldose.

\[
\text{CHO} \quad \begin{array}{c}
\text{CH}_2\text{SH} \\
\text{H}
\end{array} \quad \text{triethylamine} \quad \begin{array}{c}
\text{H} \\
\text{H}
\end{array}
\]  

(IV)

The conversion of thioamides to thiazoles by the condensation of the thioamide with α-halo-ketones or aldehydes, (the Hantzsch$^{143}$ synthesis) has a wide application and, as previously noted, has been used in the sugar series.
A number of sugar derivatives with a nitrogen and sulphur containing five membered ring, have been synthesised. Bonner and Reckendorf prepared the 2-polyhydroxyalkyl-thiazolidines (V) by condensing aldoses (glucose, galactose and mannose) with 2-mercaptop-ethylamine-hydrochloride.

\[
\text{CHO} + \text{H}_2\text{N}-\text{CH}_2 \rightarrow \text{CH}_2\text{N} \text{H} \\
(\text{CHOH})_5 \quad \text{HS-CH}_2 \quad (\text{CHOH})_5 \\
\quad \text{H} \quad \text{H}
\]

(V)

Schubert investigated the condensation of monosaccharides with cysteine, and suggested the products were 2-polyhydroxyalkyl-thiazolidines (VI).

\[
\text{CHO} \quad \text{CH}_2\text{-CH}_2\text{CO}_2\text{H} \\
(\text{CHOH})_5 \quad \text{SH} \quad \text{NH}_2 \quad \text{OH} \quad \text{CH}_2\text{CO}_2\text{H} \\
\quad \text{H} \quad \text{H} \quad \text{H} \\
\quad \text{CH}_2\text{N} \text{H} \\
(\text{CHOH})_5 \\
\quad \text{H}
\]

(VI)

Vadopalaite and Karabinos treated Schubert's 2-galacto- and 2-manno-thiazolidines with Ranay nickel under de-sulphurisation conditions and isolated galactitol and mannitol. Therefore, either hydrolysis of the carbon-nitrogen bond is taking place, or the original structure is incorrect.

Christensen and Goodman, in search of an anti-radiation drug, synthesised 4'-6'-benzylidene-1'-O-methyl-a-D-allopyranos-[2;3':4,5]-2-thiazoline (VII) by the route outlined below.
Hoffmann and Gabriel\textsuperscript{148,149} studied the oxidation of thiobenzamide to give 3,5-diphenyl-1,2,4-thiodiazol (VIII). The same compound (VIII) was isolated by Ishikawa\textsuperscript{150,151} by condensing thiobenzamide with benzonitrile and oxidising the resulting benziminoisothiobenzamide (IX) with iodine.

\[
\begin{align*}
\text{Me-S=C=S} & \\
\text{Al/Hg} & \\
\text{Me-S-C=C} & \\
\end{align*}
\]

\textbf{II.b) Condensation of Thioglycollic Acid with Schiff's Bases.}

Surrey\textsuperscript{152} reported the condensation of thioglycollic acid with Schiff's bases to yield the corresponding thiazolidones (X).

\[
\begin{align*}
\text{RCH=NR'} + \text{CH}_2(\text{SH})\text{CO}_2\text{H} & \rightarrow \text{RCH}_2\text{SCH}_2\text{NHR'} \quad \text{H}_2\text{O} \\
\text{RCH=NR'} & \quad \text{RCH}_2\text{SCH}_2\text{NHR'} \\
\end{align*}
\]
A number of Schiff's base derivatives of amino sugars have been prepared, for example, Jolles and Morgan\textsuperscript{153} prepared the Schiff's base from glucosamine and 2-hydroxy-naphthaldehyde. Glucosylamines are considered to exist predominantly in the ring form (XI) and periodic acid oxidation and the observed mutorotation\textsuperscript{155} support this assumption. There is spectroscopic evidence\textsuperscript{156} that at least some glucosylamines, for example, N-o-tolyl-glucosylamine, exist in the Schiff's base form (XII) since they absorb in the infra-red at 1660 cm\textsuperscript{-1}, a region associated with C=N absorption.

\begin{align*}
\text{CHOH} & \quad \text{CHOH} \\
\text{H} & \quad \text{H} \\
\text{H-C=N-R} & \quad \text{H-C=N-R'} \\
\text{(CHOH)}_{5} & \quad \text{(CHOH)}_{5} \\
\text{H} & \quad \text{H}
\end{align*}

Furthermore, Miller and Pöckl\textsuperscript{157} showed that even glucosylamines normally considered to be in the ring form, add hydrogen cyanide as though they existed in the Schiff's base form.

\begin{align*}
\text{CN} & \quad \text{CN} \\
\text{H} & \quad \text{H} \\
\text{H-C=N-R} & \quad \text{H-C=N-R'} \\
\text{(CHOH)}_{5} & \quad \text{(CHOH)}_{5} \\
\text{H} & \quad \text{H}
\end{align*}

Consequently, the reaction of a number of true-Schiff's base sugar derivatives and glucosylamines with thioglycollic acid were investigated.

II.c) The Structure of Sugar Imidazolidines

In attempting to elucidate the basis of certain colour reactions used in the micro-analysis of amino sugars, Scott\textsuperscript{158} initially
suggested that the amino sugars condensed with phenylisothiocyanate to give 1-phenyl-2-thiol-4-[D-arabino-tetrahydroxybutyl]-imidazole (XIII), but he later suggested\textsuperscript{159} that the compound was 4-hydroxy-3-phenyl-5-[D-arabino-tetrahydroxybutyl]-imidazolidine-2-thione(XV). Nueberg and Wolf\textsuperscript{160} had previously investigated this reaction and concluded that the product was the imidazole (XIII) or the corresponding thione (XIV).

\[
\text{HCNH}_2 + \phi-N=C=S \rightarrow \begin{array}{c}
\text{(CHOH)}_4 \\
\text{H}
\end{array} \quad \begin{array}{c}
\phi \text{N} \text{-SH} \\
\text{(CHOH)}_4 \\
\text{H}
\end{array}
\]

(XIII) \quad (XIV)

\[
\begin{array}{c}
\text{OH} \\
\text{N} \text{=} S \\
\text{(CHOH)}_4 \\
\text{H}
\end{array}
\]

(XV)

Fernandez-Bolahos and his co-workers\textsuperscript{161} also investigated the reaction and concluded that the product was 1-phenyl-4,5-[\text{p-glucopyran}]-imidazolidine-2-thione(XVI).

\[
\begin{array}{c}
\text{CH}_2\text{OH} \\
\text{OH} \\
\text{O} \\
\text{N} \phi \\
\text{S} \\
\text{N} \\
\text{H}
\end{array}
\]

(XVI)

This synthesis has been repeated and the n.m.r. spectra of the product and its acetylated derivatives examined to provide further evidence of the structure of the compound.
III.a) Importance of Stereochemistry and Conformation in Drug Action.

The most widely accepted theory of drug action is the receptor theory. Ariens outlines the theory in the following way. "The interaction of receptor and drug must be seen as a mutual moulding of drug and receptor. There is a mutual adaptation as far as shape and charge are concerned."

The interaction of a drug with an enzyme is shown schematically below. (I).

\[ \text{Enzyme} + \text{Substrate} \rightarrow \text{Enzyme-substrate} \]

\[ \text{Enzyme} + \text{Products} \]

Competitive Inhibitor (blocks enzyme active site).

\[ \text{Non-competitive inhibitors} \]

If this moulding of drug and receptor takes place, then the structure...
stereochemistry and conformation of the drug must be important. The following examples illustrate that this is the case.

Antigens can be formed by linking carbohydrates to proteins. Injection of these antigens into test animals produces antibodies which can be isolated. The antibody-antigen reaction shows stereoselectivity. The amount of precipitate, using homologous and heterologous antibody-antigen mixtures, is shown in Table (1) below.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Antigens</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\alpha$-Glucoside</td>
<td>$\beta$-Glucoside</td>
<td>$\beta$-Galactoside</td>
<td></td>
</tr>
<tr>
<td>$\alpha$-Glucoside</td>
<td>+ + +</td>
<td>+ +</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>$\beta$-Glucoside</td>
<td>+ +</td>
<td>++++</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>$\beta$-Galactoside</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td></td>
</tr>
</tbody>
</table>

(+ indicates relative amounts of precipitate formed.)

Table (1)

The four stereoisomers (IIa, b, c, d) of chloramphenicol are shown below.
The D(-)threo compound is a highly active antibiotic. Changing the stereochemistry at C₁ [L(+)-threo and D(-)erythro] reduces the activity virtually to zero. Changing the stereochemistry at C₂[L(+)-erythro] reduces the activity considerably. If these compounds exist in the fully extended zig-zag chain, then the active groups seen by a flat enzyme surface are as shown below (III). In each case, the groups in the 2 and 3 positions are

\[
\begin{array}{c}
\text{D(-) threo} \\
\text{(l-p-nitrophenyl-2-dichloroacetamido-1,3-propanediol)}
\end{array}
\]
closer to the enzyme surface. Therefore the C₃ hydroxy group
would be expected to be very important in forming the drug-receptor
complex. This would explain the lack of activity shown by the
L(+)-threo and D(-)-erythro compounds. The L(+)-erythro compound
should bind to the enzyme and its activity could be due to
distortion of the dichloroacetamido group. This explanation of the
relative activity of the isomers is purely speculative, as the
shape of the enzyme and the conformation adopted by the drug on
its surface are unknown.

There are several examples of small changes in a drug structure,
enhancing, or completely destroying its activity. In the benzimide
azoles, the 2-hydroxybenzyl substituent is essential for anti-viral
activity.¹⁶⁹ Alkylation of one of the imidazole nitrogen atoms
enhances activity as the homologous series is ascended as far as
propyl, but has little effect thereafter.¹⁶⁹

III b) The Conformation of Straight Chain Sugars.

It is generally assumed that straight chain sugars exist
in the fully extended zig-zag chain. This assumption is supported
by the work of Barker, Bourne and Whiffen¹⁷º,¹⁷¹ on the formation
of cyclic acetals by polyhydric alcohols. For example:
1,5-dibenzyl-D-arabitol could form an αT, an αC or a βT cyclic
acetal. (Using the above authors' nomenclature - C and T refer
to cis and trans on the Fischer Projection (IVa) and α and β denote the relative positions of the carbon atoms carrying the oxygens involved in acetal formation).

\[ \text{CH}_2\text{OBz} \]
\[ \text{HO} \]
\[ \text{OH} \]
\[ \text{CHO} \]
\[ \text{CH}_2\text{OBz} \]  

(a)  

(b)  

(IV)

If the zig-zag conformation (IVb) is adopted, then the distance between the oxygen atoms \( O_2 \) and \( O_3 \) is 2.83 Å, \( O_3 \) and \( O_4 \) is 3.68 Å, and \( O_2 \) and \( O_4 \) is 3.43 Å. The optimum oxygen-oxygen distance for acetal formation is 2.34 Å and therefore the α T acetal should be formed. Haskins, Hann and Hudson\(^{172}\) isolated the α T acetal, 1,5-dibenzoyl-2,3-benzylidene-D-arabitol, in high yield (73%). Barker, Bourne and Whiffen considered several cyclic acetals and were thus able to rationalise the Hann-Hudson rules.\(^{173}\)

Schwarz\(^{174}\) found that adjacent hydroxyls in a threo relationship in hexitols, are preferentially oxidised by periodate. It is generally thought that periodate oxidation involves the formation of a five membered ring complex, in the first instance, and it preferentially attacks glycols where the dihedral angle between the hydroxyl groups is small. If the hexitols exist in the fully extended chain, then the threo hydroxyls will have a dihedral angle of 60° and the erythro of 180° and therefore the threo arrangement should be attacked preferentially by periodate.
Nuclear magnetic resonance spectroscopy has been used extensively in conformational analysis of simple acyclic compounds and of pyranose sugars. Stevenson and Lemieux studied the acetylated pyranose sugars, and the coupling constants they observed give a useful starting point for studies of acetylated acyclic sugars. All the above analyses are based on the Karplus Equation (V) or some modification of this equation.

\[ J_{HH} = A + B \cos \theta + C \cos 2\theta \]  

where \( J_{HH} \) is the coupling constant between vicinal protons, \( \theta \) is the dihedral angle and \( A, B \) and \( C \) are constants.

Karplus derived the equation from a quantum mechanical analysis of the six electron system \( H \cdot C \cdot C \cdot H \). The values of the constants \( A, B \) and \( C \) are modified to suit the observed values in different types of compounds.

Optical rotation has been used as an indication of the configuration of the \( \alpha \) and \( \beta \) hydroxy groups in sugars. The nitrile rule, the benzimidazole rule, and the phenylosotriazole rule all relate the sign of the rotation to the configuration at \( C_2 \).

More general approaches to optical rotation-structure relationships are outlined by Whiffen and Brewster. They both conclude that the Van't Hoff Principle of superposition is invalid. Whiffen, who considers ring sugars, in particular containing only oxygen, carbon and hydrogen, ignores the optical rotation terms associated with the individual asymmetric centres, and considers only terms arising from vicinal arrangements. The essential steps in Whiffen's method are outlined below. In a four atom fragment(VIa) the contribution to the optical rotation is dependent on the sine of the dihedral angle (\( \theta \)), therefore when \( \theta = 0^\circ \) or \( 180^\circ \) the contribution is zero,
When $\phi > 0 < 180^\circ$ the contribution is positive, and when $\phi > 180^\circ < 360^\circ$ the contribution is negative. The proportionality constant is not evaluated, but by considering pyranose sugars of known conformation, Whiffen was able to assign values to groups of contributions, e.g.

$0/0-20/H+H/H = 45^\circ$

Where $0/0$ symbolises two oxygen atoms and $0/H$ an oxygen atom and a hydrogen atom with a gauche arrangement as in (VIb and c). A positive sign indicates an angle of $+60^\circ$ and a negative sign indicates an angle of $300^\circ$ both measured in a clockwise direction.

The sugar being examined is broken down into the individual vicinal contributions and these are rearranged to fit Whiffen's group rotation parameters. The observed rotation is compared to the calculated rotation. The agreement between observed and calculated values, within the range of compounds considered, is very good. In Whiffen's calculations, the following assumptions are made:

1) The contribution from asymmetric centres in compounds containing only carbon, hydrogen and oxygen and no multiple links, is small, and can be ignored to a first approximation.

2) Only staggered conformers need be considered.

3) The attachment atom, and not the attached group, governs the contribution; therefore $\text{CH}_3$ and $\text{CH}_2\text{OH}$ are not differentiated.
This restriction is relaxed for ring oxygens which are differentiated from alcoholic oxygens.

iv) That each vicinal increment is unaffected by the rest of the compound and that the vicinal increments may be added algebraically.

Brewster's treatment is more general. The direction of rotation is governed by the difference in the polarisability of the groups attached to the asymmetric centre. In (VII), if the polarisability is in the order $A > B > C > D$ then dextro rotation takes place. By considering compounds with pure asymmetric centres, Brewster draws up a table of rotational rank which shows that atomic refraction can be used as a measure of polarisability. The contribution of a fragment such as (VIa) is given by equation (VIII)

$$[M] = 160 R_A^{\frac{1}{2}} \times R_{A'}^{\frac{1}{2}}$$

where $R_A$ is the atomic refraction of atom A and M is the contribution to the observed rotation. Brewster calculates the optical rotation for some optically active paraffins and gets very good agreement with observed values.

Neither Whiffen's nor Brewster's method has been applied to acyclic sugars.
ORGANO LITHIUM REACTIONS

Relatively little work has been reported on the reaction of organo-lithium compounds with sugars. Hurd and Holszekt examined the reaction of phenyl and butyl lithium with acetylated halo-
sugars. From the reaction of phenyl lithium with tetra-O-acetyl-
-D-glucopyranosyl chloride, they isolated D-glucopyranosyl benzene (10%) and a second major product (30%, A) with the same analysis, which was not the a-anomer. They supposed that the
configuration of one or more of the asymmetric centres had altered
during the cleavage of the acetyl groups by the phenyl lithium.

In a reaction of tetra-O-acetyl-\(\alpha\)-D-glucopyranosyl bromide and phenyl lithium, only the unidentified sugar (A) was isolated.

English and Levy studied the reaction of phenyl lithium
and methyl lithium with 1,2-\(\alpha\)-isopropylidene-3-\(\alpha\)-benzyl-5.6-
anhydro-\(\alpha\)-glucose (I). Phenyl lithium with (I) gave the expected 1,2-isopropylidene-3-benzyl-\(\alpha\)-glucofuranosyl-6-benzene. Methyl
lithium reacted with (I) to give 1,2-\(\alpha\)-isopropylidene-3-\(\alpha\)-benzyl-
5-deoxy-5,6-\(\alpha\)-glucose (II).

\[
\begin{align*}
\text{(I)} & \quad \quad \text{(II)}
\end{align*}
\]

The work described here concerns the use of suitably protected
sugars in reaction with organo-lithium compounds.
RESULTS AND DISCUSSION
THE SYNTHESIS OF FIVE AND SIX MEMBERED RINGS CONTAINING NITROGEN AND SULPHUR,

1. a) **Synthesis of Sugar Nitriles.**

Aldoses readily condense with hydroxylamine hydrochloride, in buffered solution, to form the corresponding oximes.\(^{194,195}\)

The structure of sugar oximes is not well characterised. Both syn-anti isomerisation and cyclo-acylo tautomerisation are possible (Ia, b, c and d) and this is reflected in their reactions. Thus, glucose oxime, on acetylation, gives a mixture of the acetylated nitrile (II) and the hexa-2-acetyl oxime (III) which differs from the hexa-2-acetyl oxime prepared from 2,3,4,5,6-penta-2-acetyl-aldehyde-D-glucose.

![Chemical structures](image)

The oximes mutarotate in aqueous solution\(^{196}\) and this is generally accepted as resulting from the establishment of equilibrium between the \(\alpha\) and \(\beta\) forms (Ic, Id). In contrast, it has been...
assumed that the oximes exist preferentially in the straight chain form, since acetylation usually gives the corresponding nitrile as the major product. Deulofeu and Labriole De Restelli studied the acetylation of several sugar oximes but were unable to explain their results in terms of the structure of the oxime. They suggested that the ratio of acetylated nitrile to straight chain acetylated oxime was related to the ratio of anti to syn oxime. The percentage of acetylated nitrile, acetylated straight chain oxime and acetylated cyclic oxime, calculated from reports in the literature are shown in Table (i).

No work has been reported of attempts to measure the ratio of syn to anti oxime in the sugar series but Karabatos, Taller and Vane studied the syn-anti isomer distribution of aliphatic oximes by n.m.r. They based their assignment on the assumption that a: R (in IV) changes from methyl, to ethyl, to isopropyl, to tertiary butyl, the ratio of IV/V will increase.

\[
\begin{align*}
\text{R} & \overset{C = \text{N}}{\text{Ha}} \text{OH} \\
\text{IV} & \overset{\text{R}}{\text{C = N}} \text{OH} \\
\text{V} & \overset{\text{Ha}}{\text{R}}
\end{align*}
\]

The proton Ha in the syn isomer occurs at ca. 0.7 \text{ppm} lower field than the corresponding proton in the anti isomer. Recently, Kleinspehn and his co-workers have examined n.m.r. spectra of several oximes, using dimethyl sulphoxide as a solvent. Dimethyl sulphoxide strongly hydrogen bonds to the oxime hydroxy group. This results in the hydroxy proton appearing as a sharp peak at a constant chemical shift over a wide range of concentration.
<table>
<thead>
<tr>
<th>Sugar</th>
<th>Conditions</th>
<th>Total Yield</th>
<th>Acetylated Nitrile</th>
<th>Acetylated Acyclic Oxime</th>
<th>Acetylated Cyclic Oxime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arabinose</td>
<td>Pyridine/Ac$_2$O:3/2</td>
<td>56%</td>
<td>100%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oxime$^*$</td>
<td>0°C.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xylose</td>
<td>As above</td>
<td>14%</td>
<td>100%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oxime$^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhamnose</td>
<td>As above</td>
<td>19%</td>
<td>100%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oxime$^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhamnose</td>
<td>As above</td>
<td>49%</td>
<td>40%</td>
<td>-</td>
<td>60%</td>
</tr>
<tr>
<td>Oxime$^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ribose</td>
<td>As above</td>
<td>25%</td>
<td>100%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oxime$^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>As above</td>
<td>57%</td>
<td>-</td>
<td>-</td>
<td>100%</td>
</tr>
<tr>
<td>Oxime$^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannose</td>
<td>As above</td>
<td>65%</td>
<td>-</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>Oxime$^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Deoxy-</td>
<td>As above</td>
<td>34%</td>
<td>100%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>glucose$^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galactose</td>
<td>As above</td>
<td>-</td>
<td>50%</td>
<td>50%</td>
<td>-</td>
</tr>
<tr>
<td>Oxime$^*$</td>
<td>25°C</td>
<td>63%</td>
<td>34%</td>
<td>34%</td>
<td>32%</td>
</tr>
<tr>
<td>Galactose</td>
<td>Na Ac$_2$/Ac$_2$O</td>
<td>32%</td>
<td>57%</td>
<td>-</td>
<td>43%</td>
</tr>
<tr>
<td>Oxime$^*$</td>
<td>(High temp.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galactose</td>
<td>Pyridine/Ac$_2$O:1/1</td>
<td>72%</td>
<td>-</td>
<td>-</td>
<td>100%</td>
</tr>
<tr>
<td>Oxime$^*$</td>
<td>0°C.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galactose</td>
<td></td>
<td>74%</td>
<td>39%</td>
<td>-</td>
<td>61%</td>
</tr>
<tr>
<td>Oxime$^*$</td>
<td>15°C.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galactose</td>
<td></td>
<td>71%</td>
<td>62%</td>
<td>-</td>
<td>38%</td>
</tr>
<tr>
<td>Oxime$^*$</td>
<td>100°C.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucosamine</td>
<td>As above</td>
<td>107%</td>
<td>100%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oxime$^*$</td>
<td>0°C.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Our results only quoted where they are substantially different from the literature values or where no values could be found.

Table (i).
They found that the chemical shift difference between the \(=\text{CH}\) proton and the \(=\text{N-OH}\) proton was ca. \(3.7\) for syn-isomers and \(4.7\) for anti-isomers. Tabulated below, Table (ii), are the syn-anti distributions of some sugar oximes. As it is generally unnecessary to purify the oxime prior to synthesising the nitrile, these results are recorded on the crude dried oxime, no attempt at crystallisation being made. The concentration of oxime in dimethyl sulphoxide (DMSO) was 10% or less.

<table>
<thead>
<tr>
<th>Sugar Oxime</th>
<th>(% \text{ Syn})</th>
<th>(% \text{ Anti})</th>
<th>(\gamma \text{ (CH-NOH) Syn})</th>
<th>(\gamma \text{ (CH-NOH) Anti})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arabinose</td>
<td>75</td>
<td>25</td>
<td>3.15</td>
<td>4.0</td>
</tr>
<tr>
<td>Xyllose</td>
<td>80</td>
<td>20</td>
<td>3.2</td>
<td>4.1</td>
</tr>
<tr>
<td>Ribose</td>
<td>0</td>
<td>100</td>
<td>-</td>
<td>4.1</td>
</tr>
<tr>
<td>Rhammose</td>
<td>100</td>
<td>-</td>
<td>3.2</td>
<td>-</td>
</tr>
<tr>
<td>Glucose</td>
<td>62</td>
<td>38</td>
<td>3.35</td>
<td>4.3</td>
</tr>
<tr>
<td>Galactose</td>
<td>37</td>
<td>63</td>
<td>3.15</td>
<td>4.0</td>
</tr>
<tr>
<td>Mannose</td>
<td>100</td>
<td>-</td>
<td>3.15</td>
<td>-</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>-</td>
<td>100</td>
<td>-</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Table (ii)

There appears to be no simple relationship between the structure of the sugar and the type of oxime formed. There is evidence to show that oximes undergo trans elimination\(^{203}\) and one might expect that predominantly syn-oximes would give high yields of acetylated oxime, while the predominantly anti-isomeric sugars would yield the nitrile. This, however, does not appear to be the case. Comparisons are difficult to make because the total yields in these reactions are very variable. The conformer distribution in the reaction mixture.
(pyridine/acetic anhydride) may well be different from that in DMSO. The n.m.r. spectra of xylose, arabinose, ribose, glucose, galactose, mannose, rhamnose and glucosamine oximes, did not change over short periods in DMSO, even after the addition of small amounts of water. The complete absence of the NH proton (ca. 4 ppm) showed that these sugars exist in the acyclic form. The n.m.r. spectra of mannose and xylose oximes were also examined in DMSO (d_6) and the overall integration confirmed that these sugar oximes were in the acyclic form. The spectrum of galactose oxime is shown in Plate Ia. Recrystallization of arabinose oxime from aqueous alcohol gives the β-anomer (VIb) of the pyranose form of the oxime.

![Diagram of sugar structures](image)

The n.m.r. spectra of the acyclic, β, and a mixture of the α and β forms of arabinose oxime are shown in Plates Ib, IIa, and IIb respectively. The dihedral angle between the anomeric proton and the C2 proton in the β form is 60° and therefore, a coupling constant of 2.4 Hz/s should be observed. The quartet, for the anomeric proton, at 5.1 ppm has coupling constants of 2.4 Hz/s and 5.1 Hz/s. The NH proton at 3.95 ppm has a coupling constant of 5.1 Hz/s with the anomeric proton. The DMSO (d_6), in which this experiment was carried out, contained sufficient water to cause mutarotation.
D-Galactose oxime

anti OH

Plate I a

6 c./sec./unit.

L-Arabinose oxime

syn OH

anti OH

Plate I b
$\beta$-Arabinose oxime

Plate II a

Plate II b
After fifteen hours, a second quartet at 4.9 \gamma was present in the spectrum with $J_{\text{H}_1\text{NH}} = 5.10/s$ and $J_{\text{H}_1\text{H}_2} = 6.70/s$, which is consistent with the coupling expected for the \( \alpha \) anomer. Only the cyclic oxime of arabinose shows appreciable mutorotation, as would be expected from the n.m.r. spectra. The specific rotations are listed in Table (iii).

<table>
<thead>
<tr>
<th>Sugar</th>
<th>([\alpha]_D) DMSO</th>
<th>([\alpha]_D) DMSO + H(_2)O</th>
<th>Lit. Value* [(\alpha)] D H(_2)O</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-Xylose oxime</td>
<td>7.6°</td>
<td>5.6°</td>
<td>-</td>
</tr>
<tr>
<td>D-Mannose oxime</td>
<td>-7.0°</td>
<td>-7.0° to -8.1°</td>
<td>+3.8°</td>
</tr>
<tr>
<td>L-Arabinose oxime (acyclic)</td>
<td>42.1°</td>
<td>42.1° to 31.0°</td>
<td>+12.3°</td>
</tr>
<tr>
<td>L-Arabinose oxime (cyclic)</td>
<td>101.9°</td>
<td>101.9° to 33.2°</td>
<td>+12.3°</td>
</tr>
</tbody>
</table>

Table (iii)


The mutorotation is shown to be first order by a straight line plot (VII) of $\log_{10}$ concentration of the \( \beta \) anomer (observed rotation-mutorotation) against time.
It appears that in DMSO, the cyclic and acyclic forms are not in equilibrium. In the case of xylose oxime, the n.m.r. spectrum, in deuterium oxide, shows two low field doublets at 1.77 and 2.35, which integrate overall for one proton. The spectrum is therefore consistent with that expected for a mixture of syn and anti isomers only, and does not change with time. Therefore, either the equilibrium between cyclic and acyclic must strongly favour the latter, or cyclic and acyclic forms are not in equilibrium in this solvent.

There is no evidence to show that the isomeric distribution of oxime controls the relative yield of acetylated nitrile, acyclic oxime and cyclic oxime.

I.b) Condensation of Thioglycollic Acid with Nitriles.

Using the method described by Condo, a-aminomethylmercaptoacetic acid hydrochloride (VIII) was prepared. This salt was treated with aqueous sodium bicarbonate but chloroform extraction gave only negligible yields of 2-methyl-thiazoline-4-one (IX). Improved yields (20%) of the thiazoline were achieved if an alcoholic solution of the iminomercapto acetic acid hydrochloride was heated under reflux with a weakly basic resin. The yield of the thiazoline was further improved (43%) by reaction under reflux with sodium bicarbonate in absolute ethanol. During this latter reaction, some ammonium chloride was deposited onto the walls of the condenser. The residue from the cold reaction mixture was separated, and ammonium chloride
isolated by sublimation (yield 25%, based on nitrogen). A high boiling fraction which collected during the distillation of the 2-methyl-thiazoline-4-one was shown to be acetamide (yield 27%) by spectral and elemental analysis.

Attempts to condense penta-O-acetyl-D-glucononitrile with thioglycollic acid were unsuccessful. The sugar nitrile is not very soluble in ether at 0°C and saturation of the ether with hydrogen chloride reduces the solubility still further. After several days at 0°C the starting material was largely recovered. Starting materials were the only isolated product when the reaction was carried out at 25°C, even after several days. Experiments were made using dry dioxan or diglyme as solvent, in both of which the sugar nitrile is very soluble. The sugar nitrile was still recovered largely unchanged but small amounts of the corresponding sugar amide were also isolated. When reaction was attempted using ethyl thioglycollate in place of the free acid, again no condensation products were obtained. It appears that sugar nitriles do not readily form α-iminomercapto acetic acid derivatives.

I.c) Synthesis of Thioamides.

A somewhat improved method has been developed for the synthesis of the fully acetylated sugar thioamides. The acetylated sugar nitrile was dissolved in pyridine, and hydrogen sulphide passed into the solution, triethylamine having been added as a catalyst. This has the advantage over previous methods\textsuperscript{136,137} that the reaction mixture is homogeneous. In most cases, high yields were recorded. It was observed, however, that the presence of even small amounts of acetylated oxime in the acetylated sugar nitrile
strongly interfered in the reaction and resulted in no thioamide being obtained. The thioamides are crystalline solids, with the exception of D-mannono-thioamide which failed to crystallise even after preparative layer chromatography (P.L.C.). The physical properties of the thioamides are recorded below. (Table iv).

<table>
<thead>
<tr>
<th>Fully acetylated Aldono-Thioamide</th>
<th>M.Pt.°C.</th>
<th>Yield</th>
<th>UV (MeOH)</th>
<th>I.R. Spectra (Nujol) cm.⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>D- Glucono</td>
<td>147-8</td>
<td>94%</td>
<td>272</td>
<td>9500 3420, 3310, 3200, 1625</td>
</tr>
<tr>
<td>D-Galactono</td>
<td>131-3</td>
<td>64%</td>
<td>272</td>
<td>8000 3400, 3350, 3230, 1630</td>
</tr>
<tr>
<td>2-Amino-D-glucono</td>
<td>148-50</td>
<td>74%</td>
<td>272</td>
<td>9400 3450, 3320, 3200, 1650</td>
</tr>
<tr>
<td>D-Ribono</td>
<td>119-121</td>
<td>67%</td>
<td>272</td>
<td>8000 3360, 3280, 3180, 1630</td>
</tr>
<tr>
<td>D-Xyloho</td>
<td>138-40</td>
<td>90%</td>
<td>272</td>
<td>9600 3450, 3400, 3300, 1640</td>
</tr>
<tr>
<td>L-Arabinono</td>
<td>196-8</td>
<td>89%</td>
<td>272</td>
<td>9800 3410, 3350, 3300, 1640</td>
</tr>
<tr>
<td>D-Mannono</td>
<td>-</td>
<td>15%</td>
<td>259</td>
<td>7300 3380, 3300, 3190, 1620</td>
</tr>
</tbody>
</table>

Table (iv)

Tetra-O-acetyl-2-deoxy-D-glucononitrile failed to give a thioamide by this method.

The n.m.r. spectra, which are discussed in more detail in the next section, show two very broad low field peaks which suggest the protons are attached to nitrogen. It might be expected, by analogy with the amides, that thioamides exist in the thione form. The N-H stretching frequencies in amides and thioamides are similar. (Table v).
<table>
<thead>
<tr>
<th>N-H Stretching Frequencies in $R - \text{CONH}_2$</th>
<th>N-H Stretching Frequencies in $R - \text{CSNH}_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3500 cm$^{-1}$</td>
<td>3400 cm$^{-1}$</td>
</tr>
<tr>
<td>3400 cm$^{-1}$</td>
<td>3400 cm$^{-1}$</td>
</tr>
<tr>
<td>3350 cm$^{-1}$</td>
<td>3300 cm$^{-1}$</td>
</tr>
<tr>
<td>3180 cm$^{-1}$</td>
<td>3200 cm$^{-1}$</td>
</tr>
</tbody>
</table>

Table (v)

Acetamide absorbs at 214 nm and a large bathochromic shift is expected when C=O is replaced by C=S.$^{204}$ Replacing C=O by C=N (as in oxime) does not give rise to a bathochromic shift. The U.V. spectra indicate that the sugar thioamides exist in the thione form.

1.d) Synthesis of Thiazines from Thioamides.

The condensation of thiobenzamide with methyl vinyl ketone, catalysed by boron trifluoride etherate, to give 2-phenyl-4-methyl-4-hydroxy-5,6-dihydro-4$H$-1,3-thiazine (X) has previously been reported.$^{140}$

$$\phi - \text{C}\text{S}\text{NH}_2 + \text{CH}_2\text{CH}_3\text{O}_\text{BF}_3 \xrightarrow{60\%} \phi\text{C}\text{N}\text{S}\text{OH}\text{CH}_3$$

(X)

We found the scope of the reaction to be very limited. No thiazine was isolated when thioacetamide or aldonothioamides were used in place of thiobenzamide. Even with thiobenzamide itself, substitution of mesityl oxide or benzilacetophenone for methyl vinyl ketone, reduced the yield considerably. No thiazine was isolated when
crotonaldehyde methyl benzalpyruvate or ethyl cinnamalpyruvate were reacted with thiobenzamide.

A yellow crystalline solid separated from a solution of mesityl oxide, thiobenzamide and boron trifluoride on standing. Shaking a chloroform solution of these crystals with aqueous sodium bicarbonate, gave 2-phenyl-4,6,6-trimethyl-4-hydroxy-5,6-dihydro-1,3-thiazine. The physical properties of the thiazine are recorded in Table (vi). The n.m.r. spectrum showed five aromatic protons at 2.4 \( \gamma \); a hydroxy proton at 6.4 \( \gamma \); which readily exchanged with deuterium oxide; the methylene protons at 7.95 \( \gamma \) and 8.25 \( \gamma \) with a geminal coupling constant of 14c/s; one methyl group at 8.50 \( \gamma \) and two methyl groups at 8.55 \( \gamma \). The elemental analysis gave the required empirical formula. After three days, a further crop of crystals were separated from the reaction mixture and after purification were shown to be 3,5-diphenyl-1,2,4-thiodiazol (XI). This compound was characterised by comparing it with a genuine sample of the thiodiazol, prepared by oxidising thiobenzamide with iodine as described by Hoffmann.

\[
\begin{align*}
2\phi - C \left\langle \begin{array}{c}
\text{NH}_2 \\
S
\end{array} \right\rangle + I_2 & \rightarrow \phi - C \left\langle \begin{array}{c}
N-C-\phi \\
S-N
\end{array} \right\rangle + H_2S + 2HI \\
\text{(XI)}
\end{align*}
\]

The condensation of thiobenzamide with benzalacetophenone gave variable results. In the initial experiment, an oil separated from the reaction mixture, which, on neutralisation, was shown by thin layer chromatography (T.L.C.) to contain starting materials and three other components. The major component was isolated in 15% yield and shown to be 3-\( \phi \)-benzoyl-1,3-diphenyl-propan-1-one(XII).
The I.R. spectrum showed the presence of \( \text{S} - \text{C} = \text{O} \) (1665 cm\(^{-1}\)) and \( \text{C} = \text{O} \) (1685 cm\(^{-1}\)) groups and a typical mono-substituted benzene pattern. Elemental analysis gave the required empirical formula. The n.m.r. spectrum showed fifteen aromatic protons, a methine proton at 4.80 \( \gamma \) and the methylene protons at 6.20 \( \gamma \). The coupling between the methine and methylene protons appear as an \( A_2X \) system with a coupling constant of 7.60 Hz, rather than an \( ABX \) system. The possible fully staggered arrangements around these carbon atoms are shown below. (XIII)

The most likely explanation for the simple spectrum is that conformers (a) and (b) are nearly equally populated, with negligible population of (c), and that the average shielding experienced by the protons \( H_3 \) and \( H_3' \) is the same.

A small amount (15 mg) of a second component was isolated and this gave the correct elemental analysis for the sulphone (XIV).
There was insufficient material to confirm the structure and attempts to oxidise 4-methyl-4-hydroxy-1,3-thiazine to the sulphone, by standard methods, were unsuccessful.

\[ \text{(XIV)} \]

In a further experiment, the 2,4,6-triphenyl-4-hydroxy-5,6-dihydro-1,3-thiazine (XV) was isolated and its physical properties are recorded in Table (vi). The elemental analysis gave the required empirical formula.

\[ \text{(XV)} \]

The n.m.r. spectrum showed fifteen protons at the low field; a methine proton at 5.6\( \tau \); the methylene protons at 6.3\( \tau \) and a singlet at 8.3\( \tau \) which exchanged with deuterium oxide.

<table>
<thead>
<tr>
<th>Thiazine</th>
<th>M.Pt</th>
<th>Yield</th>
<th>( \lambda_{\text{max}} )</th>
<th>( \epsilon_{\text{max}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-phenyl-4-methyl-4-hydroxy-5,6-dihydro-1,3-thiazine.</td>
<td>133-134( ^\circ )C</td>
<td>60%</td>
<td>240 m( \mu )</td>
<td>15,200</td>
</tr>
<tr>
<td>2-phenyl-4,6,6-trimethyl-4-hydroxy-5,6-dihydro-1,3-thiazine.</td>
<td>105-106( ^\circ )C</td>
<td>21%</td>
<td>239 m( \mu )</td>
<td>16,600</td>
</tr>
<tr>
<td>2,4,6-triphenyl-4-hydroxy-5,6-dihydro-1,3-thiazine.</td>
<td>115.5-116.5( ^\circ )C</td>
<td>15%</td>
<td>243 m( \mu )</td>
<td>36,000</td>
</tr>
</tbody>
</table>

Table (vi)
In attempted condensation using aldonothioamides and thiacetamide, only unreacted thioamide was recovered. The reaction of thiobenzamide with crotonaldehyde gave a small amount of a black viscous syrup which showed a continuous band from Rf 1.0 to Rf 0.0 on T.L.C.

An attempt to condense $\beta$-bromo-tetra-O-acetyl-D-glucopyranose with 2-phenyl-4-methyl-4-hydroxy-1,3-thiazine to obtain the thiazine glycoside was unsuccessful. The solvent used in this reaction was t-butanol and this preferentially reacted with the bromoacetylglucose, giving $\beta$-t-butyl-2,3,4,6-tetra-O-acetyl-D-glucanopyranose. The hydroxyl group in the 4-position in the thiazine is, therefore, less reactive than a normal tertiary carbinol.

The condensation of an $\alpha,\beta$-dibromoketone, with a thioamide, was examined. This could theoretically give rise to a thiazine or a thiazol. The reaction was first attempted with thiobenzamide and dibromobenzal-acetophenone. These were reacted under reflux in absolute alcohol with sodium carbonate (to remove any hydrogen bromide formed.) Dehydrobromination occurred, giving a high yield of the $\alpha$-bromobenzal acetophenone. The experiment was repeated with no added sodium carbonate. Starting materials, $\alpha$-bromobenzal acetophenone (16%), 3,5-diphenyl-1,2,4-thiodiazol (6%), 3,2-benzoyl-1,3-diphenylpropen-1-one (5%) and one uncharacterised component (2%), were isolated by column chromatography. The production of the thiodiazol implies oxidation of the thiobenzamide under these conditions, which is surprising. This oxidation has been accomplished with thionyl chloride and benzensulphonyl chloride $^{205,206}$ but no mechanism was reported. 3-$\beta$-Benzoyl-1,3-diphenylpropan-1-one must be the product of a reduction process,
but we have no evidence that a linked oxido-reduction process is occurring. The reaction shows little promise as a route to thiazines.

The reaction of a $\beta$-halo ester with a thioamide was examined. An alcoholic solution of thiobenzamide was heated under reflux with ethyl $\beta$-iodopropionate, the expected product being 2-phenyl-4-hydroxy-5H-1,3-thiazine. (XVI) The major product was benzamide.

$$\phi - C \iff S \quad O E t$$

(XVI)

The reaction was repeated using sodium acetate as a buffer, but this caused the elimination of hydriodic acid from the $\beta$-iodo-ester, giving ethyl acrylate. The reaction was also tried using pyridine as a solvent but although no pyridine salt was formed at room temperature, it is formed at higher temperatures and the only product isolated was the $\beta$-carboxylethyl pyridinium iodide. Finally, thiobenzamide was reacted under reflux in anhydrous acetone with barium carbonate as added base. After five days, the reaction mixture was examined by T.L.C. which showed that only minor changes had occurred. A small amount of a product was isolated which was insufficient for characterisation, although its U.V. spectrum $\lambda_{\max}$ 270, $\epsilon_{\max}$ ca. 40,000, was consistent with that of the expected thiazine. The reaction was repeated using gluconothioamide, but no condensation took place.

Pinkus$^{141}$ reported the condensation of thiobenzamide with 1-bromo-3-chloropropane. This reaction was repeated and 2-phenyl-
-5,6-dihydro-4H-1,3-thiazine was isolated in good yield (77%). However, when the reaction was attempted with gluconothioamide, no hydrogen bromide was evolved. The reaction mixture darkened and the resulting tar could not be resolved.

I. e) Synthesis of Thiazoles from Thioamides.

Beyer and Schultz\(^{136}\) isolated 2-[\(\beta\)-gluco-penta-O-acetyl-pentyl]-4-phenyl thiazole from the condensation of gluconothioamide with \(\omega\)-phenacyl bromide. We were unable to repeat their work using their reaction conditions. Chromatography of the reaction mixture gave, as the major fraction, material which appeared by T.L.C. to be largely homogeneous, contaminated only with small amounts of starting material. However, examination showed that this was not the expected thiazole. The n.m.r. spectrum, for example, indicated that the product was a mixture which contained no thiazole. The U.V. spectra showed an absorption band at 310 m\(\mu\) (\(\epsilon\) ca. 13,000) which is inconsistent with a thiazole structure. An absorption in the I.R. at 1690 cm\(^{-1}\) and at 7.2 \(\tau\) in the n.m.r. spectra, indicated that \(\text{\(S\)}\)-acetylation might have occurred, but attempts to prepare \(\text{\(S\)}\)-acetyl-penta-\(\text{\(O\)}\)-acetyl-\(\text{\(D\)}\)-gluconothioamide were unsuccessful. It was found that the thioamide and \(\omega\)-phenacyl bromide could be successfully condensed by reaction together under reflux in dry acetone, in the presence of sodium hydrogen carbonate. A number of other halo-compounds were examined. No thiazole was isolated in attempted condensations of penta-\(\text{\(O\)}\)-acetyl-\(\text{\(D\)}\)-gluconothioamide with chloroacetone, bromoacetone, ethyl chloroacetate or ethyl bromoacetate, although a variety of products were obtained from phenacyl halides. The physical properties of the 2-aldono-thiazoles, prepared by this method are recorded in Table (vii) below.

---

\(^{136}\)Beyer and Schultz.
The reaction of penta-O-acetyl-D-gluconothioamide with D-bromo-phenacyl bromide was followed by U.V. spectroscopy. Samples were withdrawn from the reaction mixture, suitably diluted and their U.V. spectra examined. A plot of the change in extinction coefficient against time, at two wavelengths where maxima occurred, is shown below. (Diagram XVII). Glucono thioamide, D-bromo-phenacyl bromide and 2-gluco-4-phenyl-1,3-thiazole, all absorb strongly at 260 μμ and to a lesser extent at 219 μμ.

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>M.Pt.</th>
<th>Yield</th>
<th>λ&lt;sub&gt;max&lt;/sub&gt;</th>
<th>ε&lt;sub&gt;max&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-gluco-penta-O-acetyl pentyl-</td>
<td>-</td>
<td>120-3°C</td>
<td>42%</td>
<td>255</td>
<td>16,200</td>
</tr>
<tr>
<td>D-gluco-penta-O-acetyl pentyl-</td>
<td>Br</td>
<td>126-128°C</td>
<td>82%</td>
<td>260</td>
<td>17,800</td>
</tr>
<tr>
<td>D-gluco-penta-O-acetyl pentyl-</td>
<td>Me</td>
<td>80-81.5°C</td>
<td>90%</td>
<td>255</td>
<td>16,600</td>
</tr>
<tr>
<td>D-gluco-penta-hydroxy pentyln-o2</td>
<td>-</td>
<td>180°C</td>
<td>56%</td>
<td>315</td>
<td>12,000</td>
</tr>
<tr>
<td>D-galacto-penta-O-acetyl pentyl-</td>
<td>-</td>
<td>120.5°C</td>
<td>96%</td>
<td>253</td>
<td>16,200</td>
</tr>
<tr>
<td>D-galacto-penta-O-acetyl pentyl-</td>
<td>Br</td>
<td>syrup</td>
<td>47%</td>
<td>260</td>
<td>16,200</td>
</tr>
<tr>
<td>L-arabo-tetra-O-acetyl butyl-</td>
<td>Br</td>
<td>91-94°C</td>
<td>55%</td>
<td>263</td>
<td>16,500</td>
</tr>
<tr>
<td>D-xylo-tetra-O-acetyl butyl-</td>
<td>-</td>
<td>syrup</td>
<td>70%</td>
<td>262</td>
<td>12,000</td>
</tr>
<tr>
<td>D-xylo-tetra-O-acetyl butyl-</td>
<td>Br</td>
<td>syrup</td>
<td>81%</td>
<td>254</td>
<td>13,000</td>
</tr>
</tbody>
</table>

Table (vii)

-50-
A possible reaction scheme is outlined below. (XVIII).

\[
\begin{align*}
\text{CH}_2\text{Br} + \text{C}(\text{CHOAc})_5 & \rightarrow \text{[intermediate]} \rightarrow \text{C}(\text{CHOAc})_5 \\
\end{align*}
\]

(XVIII)

It is supposed that the intermediate absorbs strongly at 219 \(\mu\) and weakly or not at all at 260 \(\mu\). Initially, the starting materials are used up, forming the intermediate, thus the absorption at 219 \(\mu\) increases, and that at 260 \(\mu\) decreases. As the concentration of the intermediate increases, the rate of the second reaction will increase, and the intermediate will finally break down to give the product faster than it is formed. During this stage of the reaction, the absorption at 219 \(\mu\) decreases and that at 260 \(\mu\) increases. The U.V. spectra indicate that the intermediate is fairly stable.

Unfortunately, the intermediate was not isolatable and the overlapping of the absorptions from the starting materials and product, prevented any quantitative analysis. The n.m.r. absorption for the proton in the 5-position in the thiazole ring
is markedly solvent-dependent in the case of 2-arabino- and 2-glucop-β-bromo-phenyl thiazoles. The chemical shift of some 2,4-disubstituted thiazoles in chloroform and DMSO were examined and are collected in Table (viii).

![Thiazole structure]

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>1 CDCl₃</th>
<th>2 DMSO</th>
<th>1 - 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-glucop-penta-O-acetyl pentyl-</td>
<td>2.39</td>
<td>1.79</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>L-arabo-tetra-O-acetyl butyl-</td>
<td>2.57</td>
<td>1.85</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>Ø</td>
<td>2.4</td>
<td>1.87</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Ø</td>
<td>2.28</td>
<td>1.73</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>CH₃</td>
<td>Ø</td>
<td>1.98</td>
<td>1.93</td>
<td>0.05</td>
</tr>
<tr>
<td>CH₃</td>
<td>(insoluble)</td>
<td>1.97</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>CH₃</td>
<td>3.08</td>
<td>2.70</td>
<td>0.38</td>
</tr>
<tr>
<td>Ø</td>
<td>CH₃</td>
<td>3.15</td>
<td>2.70</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Table (viii)

Both the 2- and 5- hydrogens in the thiazole ring are "acidic" and can be replaced by lithium. These protons might, therefore, hydrogen bond with DMSO, thus showing a shift to lower field. Considerable shifts to lower fields are recorded for all but 2-methyl-4-phenyl-1,3-thiazole. We are unable to explain this anomalous result.
I.f) The Reaction of Thioglycollic Acid with Schiff's Bases. \(^{152}\)

The condensation of thioglycollic acid with a Schiff's base gives a thiazolidine-4-one. (XIX).

\[
R - C = N - R' + CH_2SH \overset{\text{condensation}}{\longrightarrow} R - C
\]

(XIX)

\(N\)-phenyl-\(D\)-glucosylamine, \(N\)-p-tolyl-\(D\)-glucosylamine and \(N\)-o-tolyl-\(D\)-glucosylamine were synthesised and reacted with thioglycollic acid, using azeotropic distillation to remove any water formed. In each case a brown-thick tar resulted from which only small amounts of the starting material could be isolated. Considerably more than an equimolar amount of water was eliminated. Even if the reaction was stopped, after one mole equivalent of water had been collected, a complex mixture resulted. From this mixture, only starting material could be separated. The sugar was clearly dehydrating under these conditions. It was considered that acetylation might stabilise the hydroxyl groups. When \(N\)-o-tolyl-\(D\)-glucosylamine was acetylated, a tetra-\(O\)-acetyl derivative was obtained, the n.m.r. spectrum of which showed it to be in the glucosylamine rather than the Schiff's base form.

No condensation took place when ethyl thioglycollate was reacted with \(N\)-o-tolyl-\(D\)-glucosylamine. Troutman and Long\(^{207}\) found that \(N\)-alkyl Schiff's bases condense readily with ethyl thioglycollate to give the thiazolidine-one but where the \(N\)-substituent is aryl, the condensation does not really occur. The same authors point out that alkyl amines more readily form amides with esters than do aryl amines. They also found that benzylidene aniline failed to
condense with ethyl thioglycollate and we have found only very low yields of thiazolidine-one even when using p-toluenesulphonic acid as a catalyst. Both Surrey\textsuperscript{203} and Troutman\textsuperscript{207} suggest that the first step in the synthesis is nucleophilic attack by the sulphur. This attack should be enhanced by the addition of a Lewis acid which should polarise the C=N bond as shown below.(XX).

\[
\begin{array}{c}
\text{C} = N - R' \\
\text{R}
\end{array}
\quad \xrightarrow{\text{BF}_3} 
\quad \begin{array}{c}
\delta^+ \\
\text{C} = N - \text{R}
\end{array}
\]

(XX)

The addition of boron trifluoride etherate to the Schiff's base and ethyl thioglycollate in benzene solution led to the separation of a yellow crystalline material which contained boron. On neutralisation of a solution of this boron complex in alcohol with a basic resin, the original Schiff's base and some benzaldehyde were recovered. The Schiff's base by itself forms an identical crystalline boron trifluoride complex. Therefore the reaction is not facilitated by addition of boron trifluoride. This may be merely a consequence of the removal of the Schiff's base as its boron trifluoride complex. The mechanism (XXI) suggested by Troutman and Long and an alternative mechanism (XXII) are shown below.

\[
\begin{array}{c}
\text{H} \\
\text{R - C = N - R'} \\
\text{S} \\
\text{CH}_2\text{CO}_2\text{Et}
\end{array}
\quad \xrightarrow{\text{H}} 
\quad \begin{array}{c}
\text{H} \\
\text{R - C = NHR'} \\
\text{S} \\
\text{CH}_2\text{CO}_2\text{Et}
\end{array}
\]

-54-
Since protonation can take place both on the nitrogen and the oxygen of the ester group, either mechanism could show acid catalysis. Formation of the boron trifluoride complex would be expected to block mechanism (XXI) as the nitrogen lone pair would not be available to attack the ester group. Since the nitrogen lone pair is not involved in the concerted mechanism, boron trifluoride might possibly catalyse the reaction. Mechanism (XXI) best explains the available evidence.

There is no report of any Schiff's bases of the type \( R - CH = N - R' \), where \( R \) is alkyl, undergoing this condensation. Furthermore, there is doubt whether glucosylamines exist in the Schiff's base form, so an examination of a genuine sugar-Schiff's base was made. The condensation of \( N \)-anisylidene-tetra-O-acetyl-D-glucosamine (where \( R \) is aryl and there is no doubt that the sugar is a Schiff's base) with thioglycollic acid and ethyl thioglycollate, was attempted. Unreacted Schiff's base only, was recovered from these reactions. A possible explanation of the lack of reactivity is that the sugar imposes a large steric barrier to the reaction.
1. f) The Structure of Sugar Imidazolidines

Scott\textsuperscript{159} considered the U.V. spectrum ($\lambda_{\text{max}}$ 240 m$\mu$ and $\varepsilon_{\text{max}}$ 20,000) of the product, from the condensation of glucosamine with phenyl isothiocyanate, to be inconsistent with the imidazole structure (XXIII) first proposed by Nueberg and Wolff.\textsuperscript{160} He considered that the product's ionophoretic behaviour in borate solution indicated that the sugar was acyclic, thus ruling out the imidazolidine structure (XXIV). Scott proposed that the product was 3-phenyl-4-hydroxy-5-[\textit{d}-arabinotetrahydroxybutyl]-1,3-imidazolidine-2-thione (XXV).

Scott also prepared (XXV) by the route shown below and found it to have an identical U.V. spectrum and ionophoretic mobility with the glucosamine-phenylisothiocyanate product.

Fernandez-Bolanos and his co-workers\textsuperscript{161} also investigated the reaction and considered the product (which had an almost identical U.V. spectrum with Scott's product) to be
I-phenyl-4,5-[D-glucopyran]-imidazolidine-2-thione (XXIV).

The following evidence was presented for this structure.

The product, after desulphurisation, absorbed only 1-mole of periodate, indicating only two adjacent hydroxyl groups.

Unfortunately, the expected dialdehyde (XXVI) could not be isolated.

On mild acetylation, the imidazolidine gave a triacetate and under more forcing conditions gave a tetra-acetate for which the structures (XXVII) and (XXVIII) respectively were proposed.

The I.R. spectrum of I-N-p-tolyl-2-acetylthio-(4,5:2',1')-[3',4',6'-tri-O-acetyl-D-glucopyran]-imidazole (XXVIII) shows a band at 1690 cm\(^{-1}\) which is ca. 50 cm\(^{-1}\) lower than an O-ester band and agrees well with the value predicted by Baker and Harris\(^ {209} \) for S-esters.

Further evidence for the cyclic structure of sugar imidazolidines comes from the synthesis of the acyclic tautomers (XXIII) by Huber and his co-workers,\(^ {210} \) from N-arylamino-1-deoxy-D-fructoses and ammonium thiocyanate in the presence of acetic acid. The acyclic tautomers, after desulphurisation, absorb 3 moles of periodate, indicating four adjacent hydroxyl groups, and the 4-formyl-imidazoline was isolated and characterised. These compounds
readily form a tetra-acetyl derivative which shows no
$\alpha$-ester absorption in the I.R.

Using the method outlined by Scott, glucosamine was
condensed with phenylisothiocyanate. The product was almost
identical in U.V. spectrum ($\lambda_{\text{max}} 242 \text{ m}\mu$, $\epsilon_{\text{max}} 19,500$) with
Scott's material ($\lambda_{\text{max}} 240 \text{ m}\mu$, $\epsilon_{\text{max}} 20,000$); its melting
point (206-209°C), and elemental analyses were close to those
recorded for Bolaños' compound (208°C). The elemental analysis
rules out the 4-hydroxy imidazolidine structure suggested by
Scott. On acetylation with pyridine/acetic anhydride (3:1 mixture)
the tri-$\beta$-acetyl derivative was isolated. Using acetic anhydride/
perchloric acid as the acetylating agent, the $\alpha$-acetyl-tri-$\beta$-
acetyl derivative was isolated. The tri-$\beta$-acetyl derivatives of
the imidazolidines (XXVII) ($R=\alpha$-nitrophenyl, $\beta$-nitrophenyl and
p-tolyl) and the corresponding $\alpha$-acetyl-tri-$\beta$-acetyl derivatives
($R=p$-tolyl, $p$-methoxyphenyl and $p$-ethoxyphenyl) have been
previously reported. The main bands in the I.R. spectra of the
imidazolidine and its acetylated derivatives are given in Table (ix).

<table>
<thead>
<tr>
<th>[D-Glucopyranose]</th>
<th>Tri-$\beta$-acetyl</th>
<th>$\alpha$-acetyl-tri-$\beta$-acetyl</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imidazolidine ($R=\beta$)</td>
<td>derivative</td>
<td>derivative</td>
<td></td>
</tr>
<tr>
<td>$3440 \text{cm}^{-1}$ and $3200 \text{cm}^{-1}$</td>
<td>3370cm$^{-1}$</td>
<td></td>
<td>OH and NH</td>
</tr>
<tr>
<td>$1720 \text{cm}^{-1}$</td>
<td>1735cm$^{-1}$</td>
<td>C=O in $\text{O-CH}_3$</td>
<td></td>
</tr>
<tr>
<td>$1695 \text{cm}^{-1}$</td>
<td>C=O in $\text{O-S-CH}_3$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$1605 \text{cm}^{-1}$ and $1590 \text{cm}^{-1}$</td>
<td>1600cm$^{-1}$ +1585cm$^{-1}$</td>
<td>1600cm$^{-1}$ + 1595cm$^{-1}$</td>
<td>C=C aromatic</td>
</tr>
<tr>
<td>$770 \text{cm}^{-1}$ and $700 \text{cm}^{-1}$</td>
<td>765cm$^{-1}$ +700cm$^{-1}$</td>
<td>765cm$^{-1}$ +700cm$^{-1}$</td>
<td>C-H mono subst. aromatic</td>
</tr>
<tr>
<td>$785 \text{cm}^{-1}$</td>
<td>785cm$^{-1}$</td>
<td>785cm$^{-1}$</td>
<td>Pyranose ring (sym.)</td>
</tr>
<tr>
<td>$920 \text{cm}^{-1}$</td>
<td>915cm$^{-1}$</td>
<td>915cm$^{-1}$</td>
<td>Pyranose ring (assym.)</td>
</tr>
</tbody>
</table>

Table (ix)
The assignment of the pyranose ring breathing vibrations is within the range given by Spedding but in the presence of an aromatic group, these are not unambiguous. The n.m.r. spectra of N-phenyl [D-glucopyranose]-imidazolidine and its acetylated derivatives are shown on plates (III, IV and V). The n.m.r. spectrum of the imidazolidine in dimethyl sulphoxide (d6), shows three hydroxyl protons, two of which are secondary (they appear as doublets) and one primary (it appears as a triplet); a doublet at 4.07 (one proton); a singlet at 0.90 (one proton) and five aromatic protons centred at 2.5. The remaining part of the spectrum which is too complex for first order analysis, contains six protons. On treatment with deuterium oxide, the peak at 0.90 and the three hydroxyl peaks disappear and a waterpeak at 6.10 appears which integrates for four protons.

The n.m.r. spectrum of the triacetyl derivative shows two O-Ac peaks, one integrating for six protons at 7.94 and the other for three protons at 7.99; two doublets at 4.04 and 4.68 respectively; each integrate for one proton and it is assumed that the lower field doublet (J = 7.50/s) arises from the anomeric proton; a low field proton (2.24) which exchanges with deuterium oxide, is assigned to N-H (or possibly S-H) and with the exception of the aromatic protons, the remaining signals cannot be assigned.

The n.m.r. spectrum shows a considerable change in the S-acetyl-tri-O-acetyl derivative. The acetyl protons absorb at 7.92 (six protons), 8.00 (three protons) and 7.10 (three protons). One of the acetyl groups obviously differs from the rest, and considered together with the I.R. spectra, this is indisputable.
1-Phenyl-4,5:2,1-[D-glucopyranosyl]-imidazolidine-2-thione

(Inset: D$_2$O exchange)

Plate III

$NH$ (or $SH$)

$6 \text{ c/sec/unit}$
1-Phenyl-4,5:2′,1′-[3′,4′,6′-tri-O-acetyl-β-D-glucopyranosyl]-imidazolidine-2-thione

(Inset: D$_2$O exchange)
1-Phenyl-2-\(\delta\)-acetyl-4,5:2',1'-[3',4',6'-tri-\(\alpha\)-acetyl-D-glucopyranosyl]-imidazoline

Plate \(\mathbf{V}\)

\(6\, \text{c./sec/unit}\)
evidence for an $\alpha$-acetyl group. The anomeric proton gives a signal at $4.05\gamma$ ($J_{H_1H_2} = 7.5\text{c/s}$) and the signal from the $C_2$ proton has moved downfield to $5.10\gamma$. The $C_3$ proton has also moved downfield to $4.25\gamma$ and appears as a doublet ($J_{H_3H_4} = 3\text{c/s}$), while the $C_5$ proton gives rise to an octet at $4.8\gamma$. The protons at $C_4$ and $C_6$ appear in the same region and are not readily analysable. On treatment with deuterium oxide, no exchange takes place. The n.m.r. evidence supports the [D-glucopyranosylimidazolidine] structure (XXIV) proposed by Bolaños.

The five and six membered ring fusion may be either diequatorial or equatorial-axial, assuming the C-N (equatorial) bond in glucosamine is not broken. The diequatorial fused system (XXIX) could result from an internal $S_N2$ reaction on the $\alpha$ anomer. Models show that this ring system is very strained, as expected for a trans fusion of five and six membered rings and the coupling constant between $H_2$ and $H_3$ would be expected to be of the order of $8\text{c/s}$ whereas the observed coupling is zero. The $\alpha$ fused system could arise from an internal $S_N2$ reaction on the more stable $\beta$ anomer as shown below:
The conformations which show least bond angle strain are the half chair, (XXX) the boat, and the skew boat forms. The boat and the skew boat forms both require that the coupling between H₂ and H₃ should be of the order of 8c/s, and as the coupling constant is zero, these conformations can only make a very minor contribution. In both these conformations, the non-bonded interactions are quite large. A model shows that in the half chair form, the dihedral angle subtended by H₂ and H₃ is approximately 90° and this would account for no coupling being observed between these protons. The dihedral angle between H₁(α) and H₂(α), which in the chair form is 60°, is approximately 10°, thus accounting for the high observed coupling constant (J₁ H₂ = 7.5c/s.). Further, the O-acetyl groups in 6-D-glucopyranose normally appear as one peak in the n.m.r, since they are all disposed equatorially. However, in the half chair form, the C₂O-acetyl group adopts a position which approaches axial and this accounts for the observed second O-acetyl peak. Normally, the separation of axial and equatorial O-acetyl groups in the pyranose sugars is around 14c/s and in this case the separation of the C₂O-acetyl group
from the $C_4$ and $C_6$ $Q$-acetyl groups is $8\text{c/s}$. Barton and his co-workers\textsuperscript{213} noted that the axial and equatorial groups at $C_3$ and $C_6$ in the half chair form of cyclohexene are differently disposed to normal axial and equatorial groups; they called these groups pseudoequatorial and pseudoaxial.

It is considered that the n.m.r. spectra of the imidazolidine and its tri-acetyl derivative supports the thione structure. The radical change in the n.m.r. spectrum on going from the tri-acetyl to the tetra-acetyl derivative is most simply explained by a change in the ring structure from imidazolidine to imidazoline. In the imidazoline, the proton $H_3$ will fall in the deshielding cone of the $C=N$, and $H_2$ will experience a much stronger inductive effect, which accounts for the downfield shift of over $20\text{c/s}$ for both these protons.

The imidazoline (XXXI) was prepared using the method described by Huber and his co-workers.\textsuperscript{210} The compound absorbs in the U.V. at $\lambda_{max}$ $265$ m$\mu$, $\epsilon_{max}$ $8,500$ and readily forms a tetra-acetyl derivative.

\[ \text{CH.NH-OC(O)} \text{H} \text{I} \\
\text{CH_3} \text{I} \\
\text{C=O} \\
\text{((CHOH)_4)I} \\
\text{NH_4NCS \rightarrow} \\
\text{CH.N-} \text{C=O} \text{S} \\
\text{((CHOH)_4)I} \\
\text{H} \]

(XXXI)

The n.m.r. spectrum in DMSO, of the hydroxy alkyl imidazoline (XXXI) yielded only a limited amount of information but it showed a singlet at $3.0\tau$ (one proton) which would be expected
for the proton in the 5 position in the imidazoline ring. The n.m.r. spectrum (Plate VI) of the tetra-O-acetyl derivative shows twelve O-acetyl protons around 7.9 \( \gamma \); the methyl group attached to the aromatic ring at 7.60 \( \gamma \); multiplets at 5.8 \( \gamma \) (two protons) and 4.75 \( \gamma \) (one proton) which are typical values for \( H_6^1, H_6^2 \) and \( H_5^2 \), in straight chain acetylated sugars; a quartet at 4.45 \( \gamma \) (one proton) assigned to \( H_4 \), with \( J_{H_3^1, H_4^1} = 4c/s \) and \( J_{H_4^1, H_5^1} = 8.5c/s \); a slightly broadened doublet at 3.95 \( \gamma \) (one proton) assigned to \( H_2 \), with \( J_{H_2^1, H_4^1} = 4c/s \) and slightly broadened by allylic coupling with \( H_3 \); a slightly broadened singlet at 3.12 \( \gamma \) (one proton) assigned to \( H_2 \); the aromatic protons at 2.65 \( \gamma \) and a broad singlet at -2.0 \( \gamma \) which disappears on shaking with D\(_2\)O. The n.m.r. is in agreement with the structure postulated by Huber and his co-workers and with the conformation shown in (XXXII).

(XXXII)

As Scott pointed out, the U.V. spectrum of the glucosamine-phenylisothiocyanate condensation product, supports the imidazolidine structure and is in agreement with the values reported by Behringer and Meier\(^{21}\) for the imidazolidine-2-thione system.

Field displaced
200c/s downfield

NH (or SH)
If the model used by Foster for ionopheresis in borate buffered solution is correct, then a D-arabino-tetrahydroxybutyl side chain would not greatly enhance the mobility of the imidazolidine. Foster's model is analogous to that used by Barker, Bourne and Whiffen for the formation of cyclic acetals. Thus the D-arabino-tetrahydroxy-butyl side chain offers only one favourable site for borate complexing; this is a β' ring between C₄ and C₆ (XXXIII) and even this complex is not highly favourable.

Böseken used the conductivity increment $\Delta$, ($\Delta = \frac{\text{conductivity boric acid/polyol soln.} - (\text{conductivity of the boric acid soln.} + \text{the conductivity of the polyol soln.})}{10^6}$) as a measure of the complexing between the polyol and the boric acid. The conductivity increment for arabitol (β' ring complex) is only half that for xylitol (β'C ring complex) but, nevertheless, is three times higher than that for β-D-glucose. In the alternative half chair form of the ring structure (XXXIV) the hydroxyl at C₄ is only about 2.6 Å from the NH in the imidazolidine ring. As the NH proton is quite acidic, the complexing shown below should be fairly strong. It seems possible that complexing of this type could explain the anomalously high ionopheretic mobility observed by Scott.
(XXXIV)
CONFORMATIONAL ANALYSIS

lla) Nuclear Magnetic Resonance.

Many reports\textsuperscript{217, 218, 219, 220} of n.m.r. studies of sugars have appeared in the literature since the commencement of this work, but none of these deal with the conformer distribution in acyclic sugars. Some studies of conformer distribution in simple acyclic systems have been reported. Kingsbury and Best\textsuperscript{221} have studied the conformational preferences in diastereoisomers of the substituted diphenylhalopropane system (I) by n.m.r. Using a similar method, Whitesides, Sevenair and Goetz\textsuperscript{222} have determined the energy difference between the trans and gauche conformers in the 1-substituted 3,3-dimethyl butanes (II).

![Diagram](I)

![Diagram](II)

As mentioned in the introduction, Karplus\textsuperscript{184,185} derived an equation (III) relating the observed coupling constant ($J_{HH}'$) to the dihedral angle ($\phi$) subtended by vicinal protons. On the basis of the values which Karplus suggested for

$$J_{HH}' = A + B \cos \phi + C \cos 2 \phi$$  

(III)

A = 4.22 \hspace{1em} B = -0.5 \hspace{1em} C = 0.45

the constants $A$, $B$, and $C$, the coupling constant for protons with a dihedral angle of $60^\circ$, is $4.5c/s$, and with a dihedral angle of $180^\circ$ is $9.5c/s$. Karplus also indicated how the calculated
coupling constant could be corrected for the electronegativity of substituents. (IV)

\[ J_{HH}' = J_{HH}^u (1 - 0.07 \Delta X) \]  

(IV)

\( J_{HH}' \) is the corrected average coupling constant, and \( J_{HH}^u \) is the uncorrected average value from the Karplus Equation for a molecule such as \( \text{CH}_2\text{CH}_2X \). Applying this correction to the protons in an acetylated sugar, the coupling constants calculated on Pauling's electronegativity values, should be 9.2 Hz (\( \phi = 180^\circ \)) and 4.2 Hz (\( \phi = 60^\circ \)). Karplus also suggested some further corrections that could be applied, but these are relatively small and require a knowledge of the exact bond lengths and bond angles. This information is not available. The coupling constants from this form of the Karplus Equation (III) fit with coupling constants observed in acyclic sugars. However, there is a large variation in calculated coupling constants, depending on the form of the Karplus Equation used. The original Karplus Equation (V) and a modified form of it, derived by Williamson and Johnson (VI) are shown below, together with the coupling constants they predict for gauche and trans protons.

\begin{align*}
J &= 8.5 \cos^2 \phi - 0.28 \quad 0^\circ \leq \phi \leq 90^\circ \\
J &= 9.5 \cos^2 \phi - 0.28 \quad 90^\circ \leq \phi \leq 180^\circ \\
J &= 10 \cos^2 \phi \quad 0^\circ \leq \phi \leq 90^\circ \\
J &= 16 \cos^2 \phi \quad 90^\circ \leq \phi \leq 180^\circ
\end{align*}

(V)

(VI)
Coupling Constants for Gauche and Trans Vicinal Protons

<table>
<thead>
<tr>
<th>$\phi$</th>
<th>Eq (V)</th>
<th>Eq (VI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\phi = 180^\circ$</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>$\phi = 60^\circ$</td>
<td>1.8</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Table (1)

The coupling constants recorded by Lemieux and his co-workers\(^\text{225}\) in the acetylated pyranoses for diaxial protons ($\phi = 180^\circ$) were 5-8 c/s and equatorial-axial ($\phi=60^\circ$) or diequatorial ($\phi=60^\circ$) were 2-3.5 c/s. Cohen, Sheppard and Turner\(^\text{226}\) estimated that these coupling constants should be 9.4 c/s ($\phi=180^\circ$) and 2.7 c/s ($\phi=60^\circ$). It therefore seems reasonable to predict that, in the acetylated aldehydo sugars, a coupling constant around 9.5 c/s indicates a trans arrangement of vicinal protons (VIIa), and a coupling constant of around 2.0 c/s indicates a gauche arrangement. (VIIb and c)

(VII)
If the fractional populations of VIIa, b and c are $p_t$, $p_{g1}$ and $p_{g2}$ respectively, then, assuming that rate of rotation is much greater than the chemical shift differences between the protons in the different conformations, the observed coupling constant will be given by equation (VIII).

$$J_{obs.} = J_t p_t + J_g (p_{g1} + p_{g2})$$  \hspace{1cm} (VIII)

If $p_t = p_{g1} = p_{g2} = 1/3$, then equation (VIII) becomes

$$J_{obs.} = J_t + 2J_g$$  \hspace{1cm} \frac{3}{3}

and in the case of the acetylated sugars, using the predicted coupling constants for gauche and trans protons, the observed coupling constant should be 4.5c/s.

If the acetylated aldehydo sugars have highly favoured conformers, then coupling constants of the order of 2.0c/s and 9.5 c/s should be observed; on the other hand, if the population of all the available conformers is approximately equal, then coupling constants of 4.5c/s should be observed.

If one takes a fully extended zig-zag chain as a model (A), the n.m.r. spectrum (Plate VII) of tetra-O-acetyl-D-xylonothioamide (IX) can be predicted.

![Model A](image)

(IX) - Model A.
Tetra-$\alpha$-acetyl-$\alpha$-xylo-thioamide

Plate VII

![Diagram of molecular structure and spectra]
Predicted and Observed Coupling Constants for (IX)

<table>
<thead>
<tr>
<th>Coupling Constant</th>
<th>Dihedral Angle</th>
<th>Predicted J Value</th>
<th>Observed J Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$J_{H_2H_3}$</td>
<td>$\phi = 6^0$</td>
<td>2.0 c/s</td>
<td>3.0 c/s</td>
</tr>
<tr>
<td>$J_{H_3H_4}$</td>
<td>$\phi = 6^0$</td>
<td>2.0 c/s</td>
<td>7.0 c/s</td>
</tr>
<tr>
<td>$J_{H_4H_5}$</td>
<td>$\phi = 180^0$</td>
<td>9.5 c/s</td>
<td>6.0 c/s</td>
</tr>
<tr>
<td>$J_{H_4H_5'}$</td>
<td>$\phi = 6^0$</td>
<td>2.0 c/s</td>
<td>3.8 c/s</td>
</tr>
</tbody>
</table>

Table (11)

The observed $J_{H_2H_4}$ value is not compatible with the fully extended chain conformer. Rotating C$_3$-C$_4$ through 60$^0$ and 120$^0$ gives conformers (IX)B and (IX)C respectively.

In conformer B ($\phi_{H_2H_4} = 180^0$) the expected coupling constant for $H_2H_4$ is 9.5 c/s, in conformer C($\phi_{H_2H_4} = 60^0$) it is 2.0 c/s. Conformer B must be the most highly populated to give the observed coupling constants. The fractional population of

\[ R = CH_2OAc \]
conformer B, \( P_B \), can be calculated from equation (VIII).

\[
7.0 = 9.5 \ P_B + 2.0 \ (1 - P_B)
\]

\( P_B = 0.7 \)

The stability of conformer B can be explained in terms of non-bonded interactions. The values for these interactions (Table III) are those quoted by Eliel, Allinger Angyal and Morrison. 227

<table>
<thead>
<tr>
<th>Group</th>
<th>Vicinal Gauche Interaction</th>
<th>1,3 Eclipsed Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>k cal/mole</td>
<td>k cal/mole</td>
</tr>
<tr>
<td>RR, CH</td>
<td>0.35</td>
<td>3.7</td>
</tr>
<tr>
<td>OAc</td>
<td>0.35</td>
<td>2.2</td>
</tr>
<tr>
<td>H</td>
<td>0</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* This value has not been determined but is probably of the right order.

Table (III)

The following assumptions are made in this analysis:

a) In general, the attachment atom in a group dominates the group's steric interactions.

b) The 1,3 diaxial interactions in cyclohexane and the 1,3 eclipsed interactions in the zig-zag chain, are the same.

c) Axial-equatorial interactions in the cyclitols and 1,2 gauche interactions in the zig-zag chain are the same.

d) The entropy changes are small.

e) Interactions other than vicinal gauche and 1,3 eclipsed, can be ignored.
The Newman projections for C₃–C₄ in conformers A, B and C are shown below:

![Newman projections](image)

The vicinal interactions are 1.05 kcal/mole for A and C, and 0.7 kcal/mole for B. Assuming these vicinal interactions control the conformer distribution, the population of each conformer can be calculated as shown below. There is a double probability of finding the chain in a gauche conformation (A and C) and this is allowed for by an entropy factor R ln 2.

\[
\Delta g^0 = \Delta H^0 - T \Delta S
\]

\[
\Delta g^0 = -0.35 + 0.42
\]

\[
\Delta g^0 = +0.07 \text{ kcal/mole}
\]

\[
K = e^{-\Delta g^0/RT}
\]

\(G\) = Free Energy \hspace{1cm} \(S\) = Entropy

\(H\) = Enthalpy \hspace{1cm} \(K\) = Equilibrium Constant

This gives the population of the trans conformer (B) as 49% and this should give a coupling constant of 5.8 Hz. This is still considerably lower than the observed coupling constant.

The 1,3 eclipsed interactions between C₂ and C₄ for conformers A, B and C are given in Table (iv) below.
<table>
<thead>
<tr>
<th>Conformer</th>
<th>1,3 Interactions</th>
<th>Total Energy From 1,2 + 1,3 Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>H/H = 0</td>
<td>3.05 k cal/mole</td>
</tr>
<tr>
<td></td>
<td>OAc/OAc = 2.0 k cal/mole</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>C/H = 0.9 k cal/mole</td>
<td>2.05 k cal/mole</td>
</tr>
<tr>
<td></td>
<td>O/H = 0.45 k cal/mole</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>C/OAc = 2.2 k cal/mole</td>
<td>3.70 k cal/mole</td>
</tr>
<tr>
<td></td>
<td>OAc/H = 0.45 k cal/mole</td>
<td></td>
</tr>
</tbody>
</table>

Table (iv)

The ratio of the populations in each conformer can be calculated as before, since

\[ \frac{N_A}{N_B} = K = e^{-\Delta G(A-B) / RT} \]

and \( N_A + N_B + N_C = 1 \) where \( N_A, N_B \) and \( N_C \) are the mole fractions in conformers A, B and C respectively. Thus

\[ \frac{N_B}{N_A} = e^{-1000 / RT} \]

therefore \( \log \frac{N_B}{N_A} = \frac{1000}{2.3 \times 2 \times 298} = 0.73 \)

therefore \( \frac{N_B}{N_A} = 5.4 \)

Similarly \( \frac{N_B}{N_C} = 16.5 \)

and \( \frac{N_A}{N_C} = 3.1 \)

therefore \( \frac{N_B}{N_A} + \frac{N_B}{N_C} = 5.4 + 16.5 \)

\(-73-\)
\[
\frac{N_A + N_C}{N_B} = \frac{1}{0.25}
\]

therefore \(N_A + N_C = 0.2\)

and since \(N_A = 3.1 \times N_C\)

\(N_A = 0.15\) and \(N_C = 0.05\)

The calculated coupling constant \(J\) is given by

\[
J = 9.5 \times 0.8 + 2.0 \times 0.2 = 8.0 \text{ c/s}
\]

The calculated value compares with the observed value of 7 c/s.

The calculation is based on the premise that no rotation takes place around the \(\text{C}_2-\text{C}_3\) bond. In practice, the low \(J_{H_2H_3}\) value of 3 c/s indicates that this is true in a qualitative sense, but a correction can be applied. Rotation through 60° and 180° around \(\text{C}_2-\text{C}_3\) in (IX)A gives conformers (IX)D and (IX)E respectively.

Conformer D involves a 1,3 eclipsed interaction between the \(\text{C}_4\) acetyl group and the \(\text{C}_2\) thioamide group. Considering the sizes of these groups, the interaction should be large and this conformer will have negligible population. Conformer E requires \(J_{H_2H_3} = 9.5\text{ c/s}\) whereas conformers A, B and C require...
\( J_{H_2H} = 2.0 \text{c/s} \) and so the population of \( E \) can be calculated.

\[
J_{\text{obs.}} = P_E \times 9.5 + 2.0 \left( p_A + p_B + p_C \right)
\]

\( P_E = 0.13 \)

Correcting the calculated coupling constant, we have

\[
J_{\text{calc.}} = 0.87 \times 8.0 + 0.13 \times 2.0
\]

\( J_{\text{calc.}} = 7.2 \text{c/s} \)

This value is in good agreement with the observed coupling constant of 7.0c/s. If the total interactions for conformers B and E are calculated, the size of the 1,3 interaction between the thioamide group and hydrogen is found to be 2.2 k cal/mole.

(In this calculation, interactions involving \( C_5 \) in both the conformations, and the 1,2 gauche interactions between the thioamide group and the sugar chain, and between the thioamide group and oxygen, were considered to be equal.)

The conformer distribution calculated from the coupling constants and from non-bonded interactions are based on physical constants determined in different systems and must be subject to fairly large errors. However, this close agreement indicates that the calculated distribution is of the right order.

Since the 1,3 eclipsed interactions are large compared to vicinal gauche interactions, the former will have the major role in controlling the conformer distribution. Gauche interactions down the chain, excluding the terminal position, can have only two values; 0.7 or 1.05 k cal/mole, whilst the 1,3 interactions between two positions can vary from 0.9 to 5.7 k cal/mole.

The suggestion that 1,3 interactions control the conformer
distribution can be readily tested. Thus in tetra-O-acetyl-L-arabonothioamide (X) where there are no major 1,3 interactions in the fully extended chain, the coupling constants should be those predicted from the model and are shown in Table (v).

<table>
<thead>
<tr>
<th>Coupling constant</th>
<th>Predicted J value</th>
<th>Observed J value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$J_{H_2 H_3}$</td>
<td>2.0c/s</td>
<td>2.4c/s</td>
</tr>
<tr>
<td>$J_{H_3 H_4}$</td>
<td>9.5c/s</td>
<td>8.8c/s</td>
</tr>
<tr>
<td>$J_{H_4 H_5}$</td>
<td>9.5c/s</td>
<td>6.0c/s</td>
</tr>
<tr>
<td>$J_{H_2 H_5'}$</td>
<td>2.0c/s</td>
<td>3.0c/s</td>
</tr>
</tbody>
</table>

The couplings $J_{H_2 H_3}$ and $J_{H_3 H_4}$ are almost as predicted. The conformational distribution for the terminal group is different from that along the chain and this is reflected in the coupling constants. The possible staggered conformers (XI) and their relative populations, calculated from non-bonded interactions,
Tetra-\(\alpha\)-acetyl-\(L\)-arabonothioamide

Plate VIII

6 c./sec./unit
are shown in Table (vi) below.

![Chemical Structures](image)

**Table (vi)**

<table>
<thead>
<tr>
<th>Configuration</th>
<th>Conformer</th>
<th>1,2 Interactions k cal/mole</th>
<th>1,3 Interactions k cal/mole</th>
<th>Total Interactions k cal/mole</th>
<th>Conformer Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACO-</td>
<td>OAe</td>
<td>(XI)A</td>
<td>0.35</td>
<td>0.45</td>
<td>0.8</td>
</tr>
<tr>
<td>ACO-</td>
<td>CH2OAe</td>
<td>(XI)B</td>
<td>0.70</td>
<td>0.90</td>
<td>1.6</td>
</tr>
<tr>
<td>ACO-</td>
<td>CH2OAe</td>
<td>(XI)C</td>
<td>0.35</td>
<td>2.0</td>
<td>2.35</td>
</tr>
<tr>
<td>OR</td>
<td>OAe</td>
<td>(XI)A</td>
<td>0.35</td>
<td>0.45</td>
<td>0.8</td>
</tr>
<tr>
<td>OR</td>
<td>CH2OAe</td>
<td>(XI)B</td>
<td>0.70</td>
<td>2.0</td>
<td>2.70</td>
</tr>
<tr>
<td>OR</td>
<td>CH2OAe</td>
<td>(XI)C</td>
<td>0.35</td>
<td>0.90</td>
<td>1.25</td>
</tr>
</tbody>
</table>

In the first case, where the OAe groups are on the same side of the chain in the Fischer projection, the conformer distribution indicates that the coupling constants should be $J_{H_a H_b} = 7.6\text{c/s}$, $J_{H_a H_b} = 2.5\text{c/s}$; where the OAe groups are on opposite sides, the predicted coupling constants are $J_{H_a H_b} = 7.0\text{c/s}$, $J_{H_a H_b} = 4.3\text{c/s}$. 

-79-
The corrected values for $J_{H_4H_5}$ and $J_{H_4H_6}$ are in fair agreement with the observed coupling constants. The protons $H_4H_5H_6$, are treated as an isolated ABX system for purposes of analysis, the coupling between $H_4(X)$ and $H_5$ being treated as simple first order coupling. The calculated coupling constants are, in practice, quite close to the values obtained by direct reading from the spectrum. The chemical shift difference between $H_bH_b'$ is usually very small, and in several cases the analysis proved impossible because intensity data and line positions could not be measured. Typical analyses are shown in Appendix (I).

In tetra-$O$-acetyl-$D$-xylonothioamide, it was postulated that the size of the thioamide group prevented rotation around $C_2-C_3$. It would follow that, if this group is replaced by a smaller group, conformer (XIIA) should become the most populated.

![Diagram](A)

![Diagram](B)

(XII)

The corresponding nitrile (XII, $R = C\equiv N$) meets this requirement but the n.m.r. spectrum proved impossible to analyse by first order methods. If one considers the 4-phenyl-thiazole derivative (XII, $R = C_S^N$), the inclusion of the nitrogen and sulphur of the thioamide group, in a five membered ring, reduces the group's effective size considerably. Analysis of the spectrum
was possible in this case. The predicted and observed coupling constants are shown in Table (vii).

<table>
<thead>
<tr>
<th>Coupling Constant</th>
<th>Predicted J Value</th>
<th>Observed J Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$J_{H_2H_3}$</td>
<td>9.5c/s</td>
<td>6.8c/s</td>
</tr>
<tr>
<td>$J_{H_2H_4}$</td>
<td>2.0c/s</td>
<td>4.0c/s</td>
</tr>
<tr>
<td>$J_{H_4H_5}$</td>
<td>7.0c/s</td>
<td>6.5c/s</td>
</tr>
<tr>
<td>$J_{H_4H_5'}$</td>
<td>4.3c/s</td>
<td>5.1c/s</td>
</tr>
</tbody>
</table>

Table (vii)

The value of $J_{H_2H_3}$ indicates that the population of conformer (XIIA) is 66%. The value of $J_{H_2H_4}$ indicates that the population of conformer (XIIB) is 24%. All other conformations are relatively unfavourable and (XIIA) and (XIIB) would be expected to account for almost 100% of the compound, and the value of 90% calculated from the n.m.r. spectrum is of the right order.

Tabulated below are the coupling constants predicted from the major conformer, and the observed coupling constants for a number of acyclic sugar derivatives.
2-[[D-xylo-tetra-O-acetylbutyl]-4-phenyl-1,3-thiazole.

Plate IX
<table>
<thead>
<tr>
<th>Sugar-Major Conformer Predicted from Steric Interaction</th>
<th>Coupling Constant</th>
<th>Predicted J for Major Conformer</th>
<th>Observed J Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetra-O-acetyl-β-L-arabono-</td>
<td>$J_{H_2H_3}$ 2.0c/s</td>
<td>3.0c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{H_3H_4}$ 9.5c/s</td>
<td>7.8c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{H_4H_5}$ 2.5c/s</td>
<td>3.6c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{H_4H_5'}$ 7.6c/s</td>
<td>4.8c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{H_2H_3}$ 2.0c/s</td>
<td>2.4c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{H_3H_4}$ 9.5c/s</td>
<td>8.8c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{H_4H_5}$ 2.5c/s</td>
<td>3.0c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{H_4H_5'}$ 7.6c/s</td>
<td>6.0c/s</td>
<td></td>
</tr>
<tr>
<td>R=CSNH$_2$</td>
<td>$J_{H_2H_3}$ 2.0c/s</td>
<td>3.0c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{H_3H_4}$ 9.5c/s</td>
<td>8.6c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{H_4H_5}$ 2.5c/s</td>
<td>3.2c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{H_4H_5'}$ 7.6c/s</td>
<td>5.0c/s</td>
<td></td>
</tr>
<tr>
<td>R = –C=S –N(SH)Br (Plate X)</td>
<td>$J_{H_2H_3}$ 2.0c/s</td>
<td>4.0c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{H_3H_4}$ 9.5c/s</td>
<td>8.0c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{H_4H_5}$ 2.5c/s</td>
<td>3.0c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{H_4H_5'}$ 7.6c/s</td>
<td>5.0c/s</td>
<td></td>
</tr>
</tbody>
</table>
Table (viii) continued

<table>
<thead>
<tr>
<th>Sugar–Major Conformer Predicted from Steric Interaction</th>
<th>Coupling Constant</th>
<th>Predicted J for Major Conformer</th>
<th>Observed J Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teta-O-acetyl-D-xylanothioamide</td>
<td>( J_{H_2 H_3} ) 2.0c/s</td>
<td>3.0c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( J_{H_3 H_4} ) 9.5c/s</td>
<td>7c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( J_{H_4 H_5} ) 4c/s</td>
<td>3.8c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( J_{H_4 H_5'} ) 6c/s</td>
<td>6.8c/s</td>
<td></td>
</tr>
<tr>
<td>2-[D-xylo-tetra-O-acetylbutyl]-4-aryl-1,3-thiazole</td>
<td>( J_{H_2 H_3} ) 9.5c/s</td>
<td>6.8c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( J_{H_3 H_4} ) 2.5c/s</td>
<td>4.0c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( J_{H_4 H_5} ) 4.3c/s</td>
<td>5.1c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( J_{H_4 H_5'} ) 7.0c/s</td>
<td>6.5c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( J_{H_2 H_3} ) 9.5c/s</td>
<td>6.8c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( J_{H_3 H_4} ) 2.0c/s</td>
<td>4.0c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( J_{H_4 H_5} ) 4.3c/s</td>
<td>5.1c/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( J_{H_4 H_5'} ) 7.0c/s</td>
<td>6.5c/s</td>
<td></td>
</tr>
<tr>
<td>Sugar-Major Conformer Predicted from Steric Interaction</td>
<td>Coupling Constant</td>
<td>Predicted J for Major Conformer</td>
<td>Observed J Value</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>-------------------</td>
<td>--------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Penta-O-acetyl-D-gluco</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$J_{H_2 H_3}$</td>
<td>2.0c/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$J_{H_2 H_4}$</td>
<td>9.5c/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$J_{H_4 H_5}$</td>
<td>4.6c/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$J_{H_5 H_6}$</td>
<td>2.5c/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$J_{H_5 H_6'}$</td>
<td>7.6c/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$J_{H_5 H_6}$</td>
<td>6.0c/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$J_{H_5 H_6'}$</td>
<td>5.8c/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$J_{H_5 H_6}$</td>
<td>4.2c/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$J_{H_5 H_6'}$</td>
<td>4.3c/s</td>
</tr>
</tbody>
</table>
Table (viii) continued

<table>
<thead>
<tr>
<th>Sugar-Major Conformer Predicted from Steric Interaction</th>
<th>Coupling Constant</th>
<th>Predicted J for Major Conformer</th>
<th>Observed J Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penta-O-acetyl-D-galactono-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R=[OAc]</td>
<td>(J_{H_{2}H_{3}})</td>
<td>2.0c/s</td>
<td>2.0c/s</td>
</tr>
<tr>
<td>R=[OAc]</td>
<td>(J_{H_{2}H_{4}})</td>
<td>9.5c/s</td>
<td>9.4c/s</td>
</tr>
<tr>
<td>R=[OAc]</td>
<td>(J_{H_{2}H_{5}})</td>
<td>2.0c/s</td>
<td>-</td>
</tr>
<tr>
<td>R=[OAc]</td>
<td>(J_{H_{2}H_{6}})</td>
<td>4.3c/s</td>
<td>5.1c/s</td>
</tr>
<tr>
<td>R=[OAc]</td>
<td>(J_{H_{2}H_{6}'})</td>
<td>7.0c/s</td>
<td>6.8c/s</td>
</tr>
</tbody>
</table>

-83-
Table (viii) continued

<table>
<thead>
<tr>
<th>Sugar-Major Conformer Predicted from Steric Interaction</th>
<th>Coupling Constant</th>
<th>Predicted J for Major Conformer Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penta-O-acetyl-D-galactono</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{R} = \text{C} = \text{N} - \text{S}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}_2\text{H}_3}$</td>
<td>2.00/s</td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}_2\text{H}_4}$</td>
<td>9.50/s</td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}_2\text{H}_5}$</td>
<td>2.00/s</td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}_5\text{H}_6}$</td>
<td>4.30/s</td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}_5\text{H}_6'}$</td>
<td>7.00/s</td>
</tr>
<tr>
<td><strong>Plate (XII)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}_2\text{H}_3}$</td>
<td>2.00/s</td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}_2\text{H}_4}$</td>
<td>9.50/s</td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}_2\text{H}_5}$</td>
<td>2.00/s</td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}_5\text{H}_6}$</td>
<td>4.30/s</td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}_5\text{H}_6'}$</td>
<td>7.00/s</td>
</tr>
<tr>
<td><strong>N-acetyl-tetra-O-acetyl-D-glucosaminothioamide</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}_2\text{H}_3}$</td>
<td>2.00/s</td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}_2\text{H}_4}$</td>
<td>9.50/s</td>
</tr>
<tr>
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<td>$J_{\text{H}_2\text{H}_5}$</td>
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</tr>
<tr>
<td></td>
<td>$J_{\text{H}_5\text{H}_6}$</td>
<td>4.30/s</td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}_5\text{H}_6'}$</td>
<td>7.00/s</td>
</tr>
<tr>
<td>Sugar-Major Conformer Predicted from Steric Interaction</td>
<td>Coupling Constant</td>
<td>Predicted J for Major Conformer</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td>-------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Tetra-O-acetyl-D-ribonitrile</td>
<td>$J_{\text{H}<em>{2}\text{H}</em>{3}}$</td>
<td>2.0 c/s</td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}<em>{2}\text{H}</em>{4}}$</td>
<td>9.5 c/s</td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}<em>{4}\text{H}</em>{5}}$</td>
<td>2.5 c/s</td>
</tr>
<tr>
<td></td>
<td>$J_{\text{H}<em>{5}\text{H}</em>{5}'}$</td>
<td>7.6 c/s</td>
</tr>
</tbody>
</table>

In the following tables (ix) and (x), are collected the n.m.r. spectral parameters, for two acyclic sugar derivatives, at temperatures from -60°C to +150°C. At -60°C, the coupling constants approach 2.0 c/s and 9.5 c/s. At +150°C, when all the conformers tend to be equally populated, the coupling constants approach 4.5 c/s. This spectral data supports the assumed values for the coupling constants between vicinal protons with a gauche and trans arrangement.
2-[[\(\text{L-}\)-arabino-tetra-O-acetylbutyl]-4-\(\text{p-}\)-bromophenyl]-1,3-thiazole.

Plate X
2-[D-glucopenta-O-acetylpenyl]-4-p-bromophenyl-1,3-thiazole.
2-[(D-galacto-penta-O-acetylpentyl)-4-p-bromophenyl-1,3-thiazol]-

Plate XII

6 c/sec/unit
2-[(2-glucopenta-0-acetylpentyl)-4-p-bromophenyl-1,3-thiazole

<table>
<thead>
<tr>
<th></th>
<th>TEMPERATURE</th>
<th>CHLOROFORM (d₁)</th>
<th>DMBO (d₆)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-60°C</td>
<td>-10°C</td>
<td>+30°C</td>
</tr>
<tr>
<td>J₃H₂H₃</td>
<td>7.40 s</td>
<td>7.20 s</td>
<td>7.00 s</td>
</tr>
<tr>
<td>H₂</td>
<td>3.73 γ</td>
<td>3.73 γ</td>
<td>3.74 γ</td>
</tr>
<tr>
<td>J₃H₂H₄</td>
<td>3.00 s</td>
<td>3.40 s</td>
<td>3.30 s</td>
</tr>
<tr>
<td>H₃</td>
<td>4.10 γ</td>
<td>4.10 γ</td>
<td>4.11 γ</td>
</tr>
<tr>
<td>J₃H₄H₅</td>
<td>8.00 s</td>
<td>7.50 s</td>
<td>7.00 s</td>
</tr>
<tr>
<td>H₄</td>
<td>4.61 γ</td>
<td>4.56 γ</td>
<td>4.54 γ</td>
</tr>
<tr>
<td>J₄H₅H₆</td>
<td>-</td>
<td>3.50 s</td>
<td>3.70 s</td>
</tr>
<tr>
<td>J₅H₆</td>
<td>-</td>
<td>5.50 s</td>
<td>5.50 s</td>
</tr>
<tr>
<td>OAc</td>
<td>8.97 γ</td>
<td>8.00 γ</td>
<td>8.04 γ</td>
</tr>
<tr>
<td>7.89 γ (2)</td>
<td>7.93 γ (2)</td>
<td>7.96 γ (2)</td>
<td>8.00 γ (2)</td>
</tr>
<tr>
<td>7.82 γ</td>
<td>7.84 γ (2)</td>
<td>7.91 γ</td>
<td>7.94 γ</td>
</tr>
<tr>
<td>7.79 γ</td>
<td></td>
<td></td>
<td>7.88 γ</td>
</tr>
</tbody>
</table>

Table (ix)
2-[L-arabino-tetra-O-acetylbutyl]-4-p-bromophenyl-1,3-thiazole.

<table>
<thead>
<tr>
<th></th>
<th>TEMPERATURE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHLOROFORM (d₁)</td>
</tr>
<tr>
<td></td>
<td>-60°C</td>
</tr>
<tr>
<td>J₉H₂H₃</td>
<td>2.1c/s</td>
</tr>
<tr>
<td>H₂</td>
<td>3.5γ</td>
</tr>
<tr>
<td>J₉H₂H₄</td>
<td>9.5c/s</td>
</tr>
<tr>
<td>H₃</td>
<td>4.15γ</td>
</tr>
<tr>
<td>J₄H₄H₅</td>
<td>-</td>
</tr>
<tr>
<td>J₄H₄H₅'</td>
<td>-</td>
</tr>
<tr>
<td>OAc</td>
<td>7.96γ</td>
</tr>
<tr>
<td></td>
<td>7.88γ</td>
</tr>
<tr>
<td></td>
<td>7.82γ</td>
</tr>
<tr>
<td></td>
<td>7.74γ</td>
</tr>
</tbody>
</table>

Table (x)
II.b) Optical Rotation

It should be possible to relate the conformational distribution of acetylated sugars to their molecular rotations. The methods of Whiffen\textsuperscript{190} and Brewster\textsuperscript{191} for predicting molecular rotations, differ considerably. Whiffen, for instance, defined a parameter $0/0 = 20/H + H/H$ as $F$, having a value of $+45^\circ$; using the formula $\Delta M = 160 R_A^2 R_A^{1/2} F$ should have a molecular contribution of $+11$. In the sugar series, better agreement with observed rotations is obtained by using Whiffen's values than by using Brewster's more general method. Since only polyhydroxy compounds are to be considered here, Whiffen's approach is used. Calculation of the predicted molecular rotation for acetylated sugars will only be simple if the OA\textsuperscript{c} group shows no conformational preference; that is, if the populations of conformers a, b and c are equal (XIII). Whiffen assumed that there was no conformational preference for the hydroxy group, which therefore makes no contribution to the observed rotation, and the agreement between observed and calculated values justifies this assumption. It might be expected that the rotation of propionyl and acetyl esters would be the same if the ester group makes no contribution to the molecular rotation. Table (xi) shows those molecular rotations of the propionyl and acetyl esters of the aldonic acid nitriles that are recorded in the literature.

\[\text{C} \quad \text{Ac} \quad \text{C} \quad \text{C} \quad \text{Ac} \quad \text{C} \quad \text{C} \quad \text{C}
\]

\[\text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \]

\[\text{a} \quad \text{b} \quad \text{c} \quad \text{c} \quad \text{c} \quad \text{c} \quad \text{c} \quad \text{c} \]

(XIII)
Sugar | $\left[M\right]_{D}\left(CHCl_3\right)$ Fully Acetylated Derivative | $\left[M\right]_{D}\left(CHCl_3\right)$ Fully Propionated Derivative
---|---|---
D-Galactonitrile | 167.5 | 167.7
D-Glucononitrile | 186 | 183.3
L-Rhammonitrile | -15.5 | -27.4
D-Mannnonitrile | -6.9 | +25.6

Table (xi)

With the exception of mannononitrile, agreement is reasonably good, and since penta-O-propionyl-D-mannnonitrile has been isolated only as a syrup, the recorded rotation could be in error.

Whiffen based his parameters upon rotation values for the polyhydroxy compounds determined in aqueous solution, and these values are unsuitable for acetylated compounds where the rotation is determined in chloroform. New values for these parameters have to be calculated. The supposition, that the acetyl group does not contribute to the molecular rotation, is tested by predicting the rotations of some acetylated compounds of known conformation, and comparing these values with the observed rotational values. It is unlikely that self-consistent values for these parameters can be determined if the acetyl group makes a major contribution to the observed rotation.

Acetylated-polyhydroxy-cyclohexanes can all be described by one rotation parameter, $F_\omega (0/0 - 20/H + H/H)$. MacCasland has determined the conformer distribution for the quercitols and the following calculations assume these distributions. A typical calculation is shown below.
Penta-O-acetyl-124/35-quercitol exists in the alternative chair form (ca. 100%). Newman projections and vicinal interactions for each C-C bond are shown below.

The predicted rotation is \(-90^0\) (using Whiffen's value for F).

Table (xii) shows the observed and calculated values (using \(F = 45^0\)) of the molecular rotations for some acetylated polyhydroxy-cyclohexanes.
<table>
<thead>
<tr>
<th>Polyol</th>
<th>Conformation</th>
<th>Rotation Parameter</th>
<th>Calculated [M] CHCl₃</th>
<th>Observed [M] CHCl₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penta-O-acetyl-125/34-quercitol</td>
<td>20</td>
<td>80</td>
<td>-1.8F</td>
<td>-81</td>
</tr>
<tr>
<td>Penta-O-acetyl-124/35-quercitol</td>
<td>-</td>
<td>100</td>
<td>-2F</td>
<td>-90</td>
</tr>
<tr>
<td>Penta-O-acetyl-123/45-quercitol</td>
<td>20</td>
<td>80</td>
<td>1.4F</td>
<td>63</td>
</tr>
<tr>
<td>Monoacetyl cyclohexane-1/2-diol</td>
<td>100</td>
<td>-</td>
<td>F</td>
<td>45</td>
</tr>
</tbody>
</table>

Table (xii)

The agreement between observed and calculated values is good, with the exception of penta-O-acetyl-123/45-quercitol, and the error here is unlikely to be related to the acetyl groups as the error for the parent hydroxy compound is of the same order (37°).

The calculation of the molecular rotation of the acetylated pyranoses is more complicated, and the following parameters are required:

\[
\begin{align*}
0/0 - 20/H + 0/0 &= F \\
0_g/0 - 0_g/H - 0/H + H/H &= G \\
0/C - C/H - 0/H + H/H &= H \\
0_r/O - C_r/O - C_r/H + C_r/H &= I \\
\bar{0}_r/O_g + \bar{0}_r/H - C_r/O_g - H/H &= J
\end{align*}
\]

\(O_g = \) glycosidic oxygen
\(O_r = \) ring oxygen
\(C_r = \) ring carbon
\(\bar{C}_r = \) ring carbon attached to ring oxygen; i.e. \(C_1\) and \(C_5\).

Although it has been assumed that the potential minima around the O-Ac bond are the same, this assumption is not valid for the anomeric position. Whiffen solved the analogous problem for the
methyl glycosides by noting the difference between the \( \alpha \)-hydroxy and the \( \beta \)-\( \alpha \)-methyl pyranoses, and an identical procedure is used here. Hudson\(^{229}\) noted that the configuration of the second carbon atom had a pronounced effect on anomeric contribution to the molecular rotation. In Table (xiii) are listed the molecular rotations of some partially acetylated sugars with a free anomeric position, and the corresponding fully acetylated derivative.

<table>
<thead>
<tr>
<th>2,3,4,6-tetra-( \alpha )-acetyl Pyranose</th>
<th>Anomeric Substituent</th>
<th>Molecular Rotation (CHCl₃)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )-D-glucopyranose</td>
<td>OH</td>
<td>493</td>
</tr>
<tr>
<td>( \alpha )-D-glucopyranose</td>
<td>OAc</td>
<td>395</td>
</tr>
<tr>
<td>( \beta )-D-glucopyranose</td>
<td>OH</td>
<td>8</td>
</tr>
<tr>
<td>( \beta )-D-glucopyranose</td>
<td>OAc</td>
<td>15</td>
</tr>
<tr>
<td>( \alpha )-D-galactopyranose</td>
<td>OH</td>
<td>501</td>
</tr>
<tr>
<td>( \alpha )-D-galactopyranose</td>
<td>OAc</td>
<td>416</td>
</tr>
<tr>
<td>( \beta )-D-galactopyranose</td>
<td>OH</td>
<td>108</td>
</tr>
<tr>
<td>( \beta )-D-galactopyranose</td>
<td>OAc</td>
<td>98</td>
</tr>
<tr>
<td>( \alpha )-D-mannopyranose</td>
<td>OH</td>
<td>92</td>
</tr>
<tr>
<td>( \alpha )-D-mannopyranose</td>
<td>OAc</td>
<td>214</td>
</tr>
<tr>
<td>( \beta )-D-mannopyranose</td>
<td>OH</td>
<td>-47</td>
</tr>
<tr>
<td>( \beta )-D-mannopyranose</td>
<td>OAc</td>
<td>-99</td>
</tr>
</tbody>
</table>

Table (xiii)

Table (xiii) indicates that a correction for an \( \alpha \)-anomeric OAc group where the C₂OAc is equatorial, is ca-95° (glucose and galactose) and +120° when the C₂ group is axial (mannose).
The correction for a $\beta$ (C$_2$ equatorial OAc) anomeric group is relatively small and is taken as 0°; the correction for a $\beta$(C$_2$ axial OAc) is -52° (mannose). Only pyranoses, which can be expected to be almost exclusively in either the normal (N) or alternate (A) chair form, are considered. Only arabinose, of the pyranoses considered, exists in the A chair conformation.

Stanek noted that arabinose, which has the L configuration at C$_2$, had an anomeric contribution (Hudson's 2A value) which was typical of a sugar with a D-configuration at C$_2$. In $\beta$-D-arabinose (XVa), the relationship between the anomeric OAc and the C$_2$OAc is similar to, but the mirror image of, that of $\alpha$-D-glucose (XVb, D-configuration at C$_2$) rather than that of $\alpha$-D-mannose (XVc, L-configuration at C$_2$).

![Diagrams](image)

C$_1$-C$_2$-\(\beta\)-D-
arabinose
C$_1$-C$_2$-\(\alpha\)-D-
-glucose
C$_1$-C$_2$-\(\alpha\)-D-
mannose

(a) (b) (c)

(XV)

The same anomeric correction is therefore used for $\beta$-D-arabinose and $\alpha$-D-glucose, only the sign being changed.

For the hexoses, a correction for the C$_5$-C$_6$ bond must also be made. Whiffen used a correction factor of +30° for the D-series and this value is used here. The values of Whiffen's parameters which give the best fit for the sugars considered, are given in Table (xiv).

-93-
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rotation Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F = 0/0 - 20/H + H/H</td>
<td>+45</td>
</tr>
<tr>
<td>G = 0/0 - 00/H - 0/H + H/H</td>
<td>+110</td>
</tr>
<tr>
<td>H = 0/C - C/H - 0/H + H/H</td>
<td>+105</td>
</tr>
<tr>
<td>I = 0/0 - C/C - 0/H + Cr/H</td>
<td>+180</td>
</tr>
<tr>
<td>J = γ/0 + γ/H - C/C + γ/H + Cg/H</td>
<td>+220</td>
</tr>
</tbody>
</table>

Table (xiv)

A typical calculation is shown below.

\[ \text{a-D-Galactose} \]

\[ [M]_D = 416 \]

Free hemiacetal \( \text{OH}[M]_D = 50 \)

Newman projections along vicinal carbon-carbon bonds.

\[ C_1-C_2(1) \quad C_2-C_3(2) \quad C_3-C_4(3) \quad C_4-C_5(4) \quad C_5-O_r(5) \quad O_r-C_1(6) \]
(1) \[ \text{g-D-galactose} = \text{30+0+J+2F+I-H+g}=525^\circ \]

The table (xv) below shows predicted and observed rotation for several pyranoses.
<table>
<thead>
<tr>
<th>Sugar</th>
<th>Anomeric Substituent</th>
<th>Rotational Parameter</th>
<th>Predicted $[\text{M}]_D$</th>
<th>Observed $[\text{M}]_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,3,4,6-tetra-O-acetyl-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-D-glucose</td>
<td>OH</td>
<td>30+G+J+H</td>
<td>465</td>
<td>495</td>
</tr>
<tr>
<td>α-D-glucose</td>
<td>OAc</td>
<td>30+G+J+H</td>
<td>370</td>
<td>395</td>
</tr>
<tr>
<td>β-D-glucose</td>
<td>OH</td>
<td>30+H-G</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>β-D-glucose</td>
<td>OAc</td>
<td>30+H-G+β</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>α-D-galactose</td>
<td>OH</td>
<td>30+G+J+2F+I-H</td>
<td>525</td>
<td>501</td>
</tr>
<tr>
<td>α-D-galactose</td>
<td>OAc</td>
<td>30+G+J+2F+I</td>
<td>430</td>
<td>416</td>
</tr>
<tr>
<td>β-D-galactose</td>
<td>OH</td>
<td>30+2F+I-G-H</td>
<td>85</td>
<td>108</td>
</tr>
<tr>
<td>β-D-galactose</td>
<td>OAc</td>
<td>30+2F+I-G+H+β</td>
<td>85</td>
<td>95</td>
</tr>
<tr>
<td>α-D-mannose</td>
<td>OH</td>
<td>30+J+H-2F-I</td>
<td>85</td>
<td>92</td>
</tr>
<tr>
<td>α-D-mannose</td>
<td>OAc</td>
<td>30+J+H-2F-I+α</td>
<td>205</td>
<td>214</td>
</tr>
<tr>
<td>β-D-mannose</td>
<td>OAc</td>
<td>30+G+H-2F-I+β</td>
<td>-77</td>
<td>-94</td>
</tr>
<tr>
<td>β-D-allopyranose</td>
<td>OAc</td>
<td>30+H-G+β</td>
<td>25</td>
<td>-57</td>
</tr>
<tr>
<td>2,3,4-tri-O-acetyl-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-D-xylene</td>
<td>OH</td>
<td>∗ 0</td>
<td>-110</td>
<td>-52</td>
</tr>
<tr>
<td>β-D-xylene</td>
<td>OAc</td>
<td>-G+β</td>
<td>-110</td>
<td>-79</td>
</tr>
<tr>
<td>α-D-xylene</td>
<td>OH</td>
<td>G+J</td>
<td>330</td>
<td>182</td>
</tr>
<tr>
<td>α-D-xylene</td>
<td>OAc</td>
<td>G+J+α</td>
<td>235</td>
<td>284</td>
</tr>
<tr>
<td>α-D-arabinose</td>
<td>OAc</td>
<td>-2F+G-I-β</td>
<td>-160</td>
<td>-140</td>
</tr>
<tr>
<td>β-D-arabinose</td>
<td>OAc</td>
<td>-2F+G-I-J-α</td>
<td>-505</td>
<td>-468</td>
</tr>
<tr>
<td>β-D-ribose</td>
<td>OAc</td>
<td>-G+β</td>
<td>-110</td>
<td>-169</td>
</tr>
</tbody>
</table>

Table (xv)

In general there is a fair measure of agreement between predicted and observed values. $\beta$-D-Allopyranose and $\beta$-D-ribofuranose both
have an axial OA\textsuperscript{c} group in the C\textsubscript{3} position and this will have an effect on the anomeric contribution. Using the mean deviation between observed and calculated values (-70) for these sugars, and correcting the calculated values we get -45° (observed -57°) for $\beta$-D-allopyranose and -180° (observed -169°) for $\beta$-D-ribopyranose.

There seems to be no obvious explanation why the values for $\alpha$ and $\beta$-D-xylopyranose, with the free hemiacetal hydroxyl group, should be so much in error. The value of the molecular rotation used for $\alpha$-D-xylopyranose is that quoted by Hudson and Dale.\textsuperscript{231} Anita\textsuperscript{232} examined this material and found it to be a mixture of the $\alpha$ and $\beta$ forms. Nevertheless, the value Anita quotes for pure $\alpha$-D-xylopyranose (127°) is lower than the value quoted by Hudson and Dale. The literature values are therefore suspect. The agreement between the observed and predicted values indicates that the OA\textsuperscript{c} groups make little or no contribution to the observed rotation.

The conformation of straight chain sugars can be predicted from the non-bonded interactions, and their molecular rotations calculated in an analogous manner to that of the pyranoses. Unfortunately, only two straight chain acetylated sugars (arabitol and mannitol) are completely described by the parameters derived by Whiffen. Brewster's method, using atomic refractions, can be applied and a typical example is shown below.

Brewster showed that the rotation contribution ($\Delta M$) of two vicinal (XVI) groups with a gauche relationship, is given by,

$$\Delta M = 160 R_A^{\frac{1}{2}} R_B^{\frac{3}{2}}$$

where $R_A$ and $R_B$ are the atomic refractions.
of A and B respectively. (If A or B is unsaturated, then the refraction of the unsaturated group is used). In Table (xvi) below, the products of the atomic refractions (due to Vogel) of various atoms, are summarised.

<table>
<thead>
<tr>
<th>Atom/Group</th>
<th>Atomic Refraction</th>
<th>Atom/Group</th>
<th>Atomic Refraction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\frac{1}{2} R_A \frac{1}{2} R_B$</td>
<td></td>
<td>$\frac{1}{2} R_A \frac{1}{2} R_B$</td>
</tr>
<tr>
<td>Carbon</td>
<td>Carbon</td>
<td>2.59</td>
<td>Nitrile</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>Hydrogen</td>
<td>1.03</td>
<td>Nitrile</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Oxygen</td>
<td>1.52</td>
<td>Carbon</td>
</tr>
<tr>
<td>Nitrile</td>
<td>Nitrile</td>
<td>5.46</td>
<td>Carbon</td>
</tr>
<tr>
<td>Nitrile</td>
<td>Carbon</td>
<td>3.77</td>
<td>Hydrogen</td>
</tr>
</tbody>
</table>

Table (xvi)

Consider as an example, penta-O-acetyl-D-arabitol: -(XVII)
The distribution between conformer (a) and (b) is 75:20. (See Conformational Analysis p.77) $\Delta M(C_1-C_2) = +4$

$\Delta M = 160 (R_O \frac{2}{3} R_O \frac{1}{3} R_O \frac{2}{3} R_H \frac{1}{3})$

$\Delta M = 11$

$\Delta M = -22$

The distribution between conformer (a) and (b) is 75:20. (See Conformational Analysis p.77) $\Delta M(C_1-C_2) = +4$

$\Delta M = 160 (R_O \frac{2}{3} R_H \frac{2}{3} R_O \frac{1}{3} R_H \frac{2}{3} R_O \frac{1}{3} R_C \frac{1}{3} R_O \frac{1}{3} R_H \frac{1}{3})$

$\Delta M = -34$

$\Delta M = 160 (R_C \frac{2}{3} R_O \frac{1}{3} R_C \frac{1}{3} R_O \frac{2}{3} R_C \frac{1}{3} R_O \frac{1}{3} R_C \frac{1}{3} R_C \frac{1}{3} R_O \frac{1}{3} R_H \frac{1}{3})$

$\Delta M = 11$

$\Delta M = 160 (R_C \frac{2}{3} R_O \frac{1}{3} R_C \frac{1}{3} R_O \frac{2}{3} R_C \frac{1}{3} R_O \frac{1}{3} R_C \frac{1}{3} R_O \frac{1}{3} R_H \frac{1}{3})$

$\Delta M = 11$

$\Delta M = -99$
The distribution between conformer (a) and (b) is 70:30. The predicted molecular rotation for penta-ß-acetyl-ß-arabitol is therefore -19°.

In Table (xvii) below, the observed and predicted molecular rotations of some sugars are given. In the case of the nitriles, the assumption that the molecular rotation is due entirely to the vicinal interactions is not valid. The carbon atom to which the nitrile is attached, might well make a contribution as it is asymmetric with respect to the polarisability of the attached groups. (Atomic refraction is used as a measure of polarisability). It is not possible to calculate this "pure" asymmetric contribution. However, if this contribution is ignored, it should give rise to a constant error.

<table>
<thead>
<tr>
<th>Fully Acetylated Sugar</th>
<th>Observed ([M]_{DCHCl}\text{]})</th>
<th>Brewster's Method Predicted</th>
<th>Error</th>
<th>Whiffen's Method Orig. Parameters</th>
<th>Modified Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-Arabitol</td>
<td>130.6</td>
<td>-19</td>
<td>-</td>
<td>+45</td>
<td>-79</td>
</tr>
<tr>
<td>D-Mannitol</td>
<td>108.5</td>
<td>-12</td>
<td>-</td>
<td>+33</td>
<td>-65</td>
</tr>
<tr>
<td>D-Sorbitol</td>
<td>29.5</td>
<td>-74</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>D-Iditol</td>
<td>111.2</td>
<td>160</td>
<td>+5</td>
<td>+12.7</td>
<td></td>
</tr>
<tr>
<td>D-Mannnonitrile</td>
<td>-7.7</td>
<td>+ 5</td>
<td>+12.7</td>
<td>+12.7</td>
<td></td>
</tr>
<tr>
<td>D-Ribononitrile</td>
<td>108.7</td>
<td>-76</td>
<td>-134.7</td>
<td>-89.6</td>
<td></td>
</tr>
<tr>
<td>D-Arabononitrile</td>
<td>-10.4</td>
<td>-60</td>
<td>-49.6</td>
<td>-136</td>
<td></td>
</tr>
<tr>
<td>D-Galactononitrile</td>
<td>167.2</td>
<td>+31</td>
<td>-136</td>
<td>-136</td>
<td></td>
</tr>
<tr>
<td>D-Glucononitrile</td>
<td>186</td>
<td>-141</td>
<td>-32.7</td>
<td>-32.7</td>
<td></td>
</tr>
<tr>
<td>D-Xylononitrile</td>
<td>172.5</td>
<td>-148</td>
<td>-320.5</td>
<td>-320.5</td>
<td></td>
</tr>
</tbody>
</table>

Table (xvii)
There is no correlation between predicted and observed values, indicating either that the conformational analysis is in error or that this simplified modification of Brewster's method is not applicable to these compounds. The values predicted by Whiffen's method for the alditols indicate that, neither the parameters derived for the pyranoses, nor their acetylated derivatives, can be used for the straight chain sugars. New values for the parameters must therefore be determined.

In order to determine rotational parameters for the acyclic sugars, their conformer distribution must be known or assumed. For an analysis to be manageable, only a small number of conformers can be considered. The predicted values for the parameters are large, and even relatively small changes in conformer distribution can have a considerable effect on the molecular rotation. In the aldehydo sugars and the nitriles, the asymmetric contribution of $C_2$ could be large, but the agreement between predicted and observed values of the molecular rotations for these sugars indicates that it is small. The possible conformations of the $C_1$ group must also be considered. All these factors limit the accuracy and generality of the method.

The values of the rotational parameters are listed in Table (xviii) below.
The conformations considered are indicated by the rotational parameters and are selected by the following rules.

1) In the absence of any large 1,3 interactions the fully extended chain conformation is adopted.

2) Where large 1,3 interactions occur, rotation takes place to relieve the interaction in such a way that the major part of the chain retains the fully extended zig-zag conformation.

3) The conformation at the terminal position is as predicted previously.

4) For the aldehydo sugars it is assumed that the conformation shown below (XVIII) is adopted and the contribution this makes to the molecular rotation is accounted for in the A and B parameters.

![Diagram](image)
The predicted and observed molecular rotations for some straight chain sugars are shown in the following table (xix).

Table (xix)

<table>
<thead>
<tr>
<th>Fully Acetylated Sugar</th>
<th>Rotational Parameters</th>
<th>Predicted $[\text{M}]_D$</th>
<th>Observed $[\text{M}]_D^{(\text{CHCl}_3)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-Arabitol</td>
<td>$\text{C}_1\text{-C}_2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a) $0/0+H/H-20/H=F(0.75)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) $C/H-C/O+0/H-H/H=-H(0.2)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{C}_2\text{-C}_3$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$2C/H=2C/0+0/0-H/H=F - 2H$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{C}_3\text{-C}_4 = 0$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{C}_4\text{-C}_5$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a) $0/0+H/H-20/H=F(0.7)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) $C/O-C/H+H/H=0=H-F(0.3)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total: $2.15F - 1.9H$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-Mannitol</td>
<td>$\text{C}_1\text{-C}_2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a) $0/0+H/H-20/H=F(0.7)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) $C/O-C/H+H/H=0=H-F(0.3)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{C}_2\text{-C}_3 = 0$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{C}_3\text{-C}_4$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$2C/H=2C/0+0/0-H/H=F - 2H$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{C}_4\text{-C}_5 = 0$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{C}_5\text{-C}_6$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a) $0/0+H/H-20/H=F(0.7)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) $C/O-C/H+H/H=0=H-F(0.3)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total: $1.8F - 1.4H$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-Iditol</td>
<td>$\text{C}_1\text{-C}_2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a) $C/H-0/C+0/H-H/H=-H(0.5)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) $H/H+0/O-20/H=F(0.5)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{C}_2\text{-C}_3$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C/C=2C/H+2C/H-O/O = Z$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{C}_3\text{-C}_4$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$2C/O=2C/H-O/O=H/H=2H = F$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

continued
Table (xix) continued

<table>
<thead>
<tr>
<th>Fully Acetylated Sugar</th>
<th>Rotational Parameters</th>
<th>Predicted $[\text{M}]^\circ_D$</th>
<th>Observed $[\text{M}]^\circ_D(\text{CHCl}_3)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-Iditol (cont.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_4$-C$_5$</td>
<td>C/C-2C/H+20/H-0/0=Z</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_5$-C$_6$</td>
<td>a) H/H+0/0-20/H=F(x0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) C/H-C/0-H/H+0/H=-H(x0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total: 2 Z + H</td>
<td>90</td>
<td>111.2</td>
</tr>
<tr>
<td>D-Sorbitol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_1$-C$_2$</td>
<td>a) -0/0+20/H-H/H=-F(x0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) C/0-C/H-0/HI/HI=H(x0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_2$-C$_3$</td>
<td>2C/H-20/H-C/C+0/0= - Z</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_3$-C$_4$</td>
<td>2C/H-20/C-0/H+0/0=F - 2H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_4$-C$_5$</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_5$-C$_6$</td>
<td>a) 0/0+H/H-20/H=F (x0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) C/0+H-C/H+0/H=H-F(x0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total: 0.9 F - 1.2 H - Z</td>
<td>16</td>
<td>29.5</td>
<td></td>
</tr>
<tr>
<td>D-Xylononitrile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_2$-C$_3$</td>
<td>CN/H-CN/C+0/0+C/H</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20/H=X+Y+2F+H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_3$-C$_4$</td>
<td>2C/H-20/C+0/0-H/H=F - 2H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_4$-C$_5$</td>
<td>a) 0/0+H/H-20/H=F(x0.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) C/0+H-C/H+0/H=H=- H(x0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total: X + Y + 3.75 F - 3.2 H</td>
<td>181</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>D-Ribononitrile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_2$-C$_3$</td>
<td>CN/0-CN/C+0/H=0/0+C/H-H-Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_3$-C$_4$</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_4$-C$_5$</td>
<td>a) 0/0+H/H-20/H=F(x0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) C/0+H-C/H+0/H=H=- H(x0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total: 0.7 F - 0.3 H + Y</td>
<td>89</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>D-Arabononitrile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_2$-C$_3$</td>
<td>CN/H-CN/0+C/H-H+0/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0/C=X+F - 2H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_3$-C$_4$</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-104-  
continued
<table>
<thead>
<tr>
<th>Fully Acetylated Sugar</th>
<th>Rotational Parameters</th>
<th>Predicted $[M]_D^\circ$</th>
<th>Observed $[M]_D^\circ$(CHCl$_3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-Arabonitrile (cont.)</td>
<td>$C_4^\circ-C_5^\circ$ a) $0/0+H/H-20/H=F(x0.7)$ b) $C/0-C/H+0/H-0/0=H = F(x0.3)$ Total: $X + 1.4F - 1.7 H$</td>
<td>-34</td>
<td>-10</td>
</tr>
<tr>
<td>d-Gluconitrile</td>
<td>$C_2^\circ-C_3^\circ$ CN/H-CN/C+O/O-O/H/C/H -O/H=X+Y+2F - H</td>
<td>196</td>
<td>186</td>
</tr>
<tr>
<td></td>
<td>$C_3^\circ-C_4^\circ$ 2C/H-2C/0-H+0/0=F -2H</td>
<td>169</td>
<td>168</td>
</tr>
<tr>
<td></td>
<td>$C_4^\circ-C_5^\circ = 0$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_5^\circ-C_6^\circ$ a) $0/0+H/H-20/H=F(x0.7)$ b) $C/0-C/H+0/H-0/0=H = F(x0.3)$ Total: $X+Y+3.4 F - 2.7 H$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d-Galactono-</td>
<td>$C_2^\circ-C_3^\circ$ CN/O-CN/H+O/C-0/H/H -C/H= - X - F + 2H</td>
<td>169</td>
<td>168</td>
</tr>
<tr>
<td>nitrile</td>
<td>$C_3^\circ-C_4^\circ$ 2C/H-2C/0-H+0/0=F -2H</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_4^\circ-C_5^\circ = 0$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_5^\circ-C_6^\circ$ a) $0/0+H/H-20/H=F(x0.75)$ b) $C/0-C/H+0/H-0/0=H = F(x0.2)$ Total: $0.55 F + 0.2 H - X$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d-Mannonitrile</td>
<td>$C_2^\circ-C_3^\circ$ CN/O-CN/H+C/H-0/C=-X</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_3^\circ-C_4^\circ$ 2C/H-2C/0+0/O-H/H=F -2H</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_4^\circ-C_5^\circ = 0$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$C_5^\circ-C_6^\circ$ a) $0/0+H/H-20/H=F(x0.70)$ b) $C/0-C/H+0/H-0/0=H = F(x0.3)$ Total: $1.4 F - 1.7 H - X$</td>
<td>16</td>
<td>-7.7</td>
</tr>
</tbody>
</table>

continued
<table>
<thead>
<tr>
<th>Fully Acetylated Sugar</th>
<th>Rotational Parameters</th>
<th>Predicted $[\text{M}]_D^0$</th>
<th>Observed $[\text{M}]_D^0(\text{CHCl}_3)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-Rhamnononitrile</td>
<td>As for D-mannono-nitrile but with no C₅-C₆ contribution.</td>
<td>-115</td>
<td>13.2</td>
</tr>
<tr>
<td>D-Fucononitrile</td>
<td>As for D-galactono-nitrile but with no C₅-C₆ contribution.</td>
<td>25</td>
<td>74.2</td>
</tr>
<tr>
<td>Aldehydo-D-arabinose</td>
<td>The conformation for the aldehydes is the same as that for the nitriles; X is replaced by A and Y is replaced by B.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldehydo-D-xylose</td>
<td>Total: $A+1.4F - 1.7H$</td>
<td>191</td>
<td>190.8</td>
</tr>
<tr>
<td>Aldehydo-D-ribose</td>
<td>Total: $A+B+3.75F - 3.2H$</td>
<td>-46</td>
<td>-50.5</td>
</tr>
<tr>
<td>Aldehydo-D-glucose</td>
<td>Total: $0.7F - 0.3H + B$</td>
<td>-361</td>
<td>-121</td>
</tr>
<tr>
<td>Aldehydo-D-galactose</td>
<td>Total: $A+B+3.4F - 2.7H$</td>
<td>-29</td>
<td>-15.9</td>
</tr>
<tr>
<td>Aldehydo-D-fucose</td>
<td>Total: $0.55F + 0.2H - A$</td>
<td>-56</td>
<td>-95</td>
</tr>
<tr>
<td>Fully Propionylated Sugars</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-Galactononitrile</td>
<td>As for acetylated esters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total: $0.55F + 0.2H - X$</td>
<td>169</td>
<td>168</td>
<td></td>
</tr>
<tr>
<td>D-Glucononitrile</td>
<td>Total: $X + Y + 3.4F - 2.7H$</td>
<td>196</td>
<td>183</td>
</tr>
<tr>
<td>D-Mannnononitrile</td>
<td>Total: $1.4F - 1.7H - X$</td>
<td>16</td>
<td>25.6</td>
</tr>
<tr>
<td>D-Rhammononitrile</td>
<td>Total: $-X + F - 2H$</td>
<td>-115</td>
<td>27.4</td>
</tr>
</tbody>
</table>

The overall agreement between predicted and observed values supports the assigned conformational distribution. Notable exceptions to the overall pattern of agreement are tetra-$\text{O}$-acetyl...
(and propionyl)-D-rhamnononitrile and tetra-O-acetyl-aldehydo-D-ribose. The errors may be partly due to the difficulty in optimising the values of the rotational parameters but the error of ca 140° for the rhamnose derivatives is too large to be accounted for in this way. The predicted value of -115° is calculated from conformer (XIXa) but a second conformer (XIXb) may well make some contribution as it involves no large 1,3-interactions.

Tetra-O-acetyl-D-rhammonitriile (XIX)

The Newman projections for conformer (b) together with vicinal interactions are shown below.

The distribution at C₄-C₅ presents a problem; models indicate...
that when either the O-acetyl or methyl group lies close to the sugar chain as in \(\text{C}_4\)-\(\text{C}_5\)(b)] a large steric interaction occurs, and therefore only conformer \(\text{C}_4\)-\(\text{C}_5\)(a)] is considered. Any contribution from conformer (XIXb) would tend to close the gap between predicted and observed values for the rotation. If the same procedure is repeated for tetra-O-acetyl-D-fucononitrile (XXa), we get conformer (XXb).

![Diagram of conformers](image)

Tetra-O-acetyl-D-fucononitrile (XX)

The predicted rotation from conformer (a) is \(+25^\circ\), from (b) is \(-125^\circ\) and the observed value is \(+74^\circ\). In this case, any contribution from conformer (b) will increase the disparity between the observed and predicted values. The only essential energy difference between the fucono and rhamnono compounds in conformer (b) is in the 1,2 interactions around \(\text{C}_3\)-\(\text{C}_4\) (XXI) and this will be of the order of 500 cals. greater for fucononitrile.

![Diagram of 1,2 interactions](image)

\(\text{C}_3\)-\(\text{C}_4\) Rhamnononitrile

\(\text{C}_3\)-\(\text{C}_4\) Fucononitrile (XXI)

Assuming that the contribution from conformer (b) in fucononitrile
is negligible, its population in rhamnonitrile cannot be greater than 30%. Taking conformer (XIXb, 30%) into account, the predicted value for rhamnonitrile is \(-35^\circ\), which compares better with the observed value of \(+13.3^\circ\).

The even larger error of \(240^\circ\) for the ribose derivative, indicates that here too, the conformational analysis is inaccurate. Conformer (XXIIa) was used to determine the molecular rotation but conformer (b) is also possible. In the case of the sugar thioamides, conformers of the type (b) are shown by examination of n.m.r. spectra to be highly populated (as discussed earlier).

\[
\begin{align*}
\text{(a)} & \quad \text{(b)} \\
\end{align*}
\]

Conformer (XXIIb) gives the following rotational parameters.

\[
\begin{align*}
C_2-C_3 & \quad \text{CHO/H-CHO/O+O/C-C/H} = A \\
C_3-C_4 & \quad \text{C/C-C/H+O/O-C+H/H-O/H} = Z + 2F - H \\
C_4-C_5(a) & \quad \text{H/H-20/H+0/O} = 0.5 F \\
C_4-C_5(b) & \quad \text{C/H-C/O+O/H-H/H} = -0.5 H \\
\text{Total} & \quad A + Z + 2.5F - 1.5H = +405
\end{align*}
\]

(At \(C_4-C_5\) the conformation where the OA\(\bar{E}\) interacts most strongly with the sugar chain is considered to have a negligible population). If the distribution between conformer (a) and conformer (b) is 7:3, then the predicted rotation is \(-127^\circ\) (observed \([M]_D\ -121^\circ\)). However, if this is the conformer distribution for tetra-O-acetyl-aldehydo-D-

-109-
-ribose, a similar distribution must occur for xylose. The molecular rotation for the xylose conformer, where the aldehydo-group stays in the plane of the chain, and the C₅ group twists out of plane, is -85°. Assuming the same relative conformer distribution as for ribose, the recalculated molecular rotation is -57° which agrees well with the observed value of -50.5°. The nitrile group is smaller than the aldehydo-group and therefore type (b) conformer would not be expected to be as important as for the aldehydo-sugars, but as Table (xx) below shows, the agreement between observed and predicted rotations improves if (b) makes a contribution.

<table>
<thead>
<tr>
<th>Fully Acetylated Nitrile</th>
<th>[M]°D Conformer(a)</th>
<th>[M]°D Conformer(b)</th>
<th>Observed [M]°D CHCl₃</th>
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<tbody>
<tr>
<td>D-Xylose</td>
<td>181</td>
<td>140</td>
<td>160</td>
</tr>
<tr>
<td>D-Ribose</td>
<td>89</td>
<td>130</td>
<td>109</td>
</tr>
</tbody>
</table>

Table (xx)

The above results show that molecular rotation can provide useful supporting evidence for conformational distribution. The method could be used quite generally for series of acyclic compounds if the "pure" asymmetric contribution for systems were known.
In the initial experiment, the reaction of pentachlorophenyl lithium(I) with methyl-2,3-anhydro-4,6-0-benzylidene-a-D-allopyranosid(II) was examined. Compound (II) is only slightly soluble in most solvents, and was added to the pentachlorophenyl lithium solution as a suspension in benzene. Attack upon the epoxide ring in the sugar is rather hindered sterically, and for this reason an excess of (I) was used. Mills\(^{234}\) has postulated that 4,6-benzylidene sugars, where ring inversion is unlikely, will obey the Fürst and Plattner's rule\(^{235}\) and show diaxial opening of the epoxide ring. In general, this appears to be the case, but there are some examples\(^{236}\) of diequatorial ring opening of (II). The products from diequatorial and diaxial ring opening are shown below. (The epoxide ring bonds are shown as equatorial and axial for clarity).

Diequatorial Ring Opening

\(\text{(D-gluco)}\)

\((\text{III})\)

Diaxial Ring Opening

\(\text{(D-altro)}\)

\((\text{IV})\)
Neither of these products was isolated from the reaction mixture. The use of a large excess of butyl lithium and hexachlorobenzene complicated the reaction. On chromatography, a fraction containing hexachlorobenzene and a small amount of pentachlorobenzene was isolated. The second major fraction isolated was 3,4,5,6-tetrachlorotricyclo-[6,2,2,0^{2,7}]-dodeca-2(7),3,5,9,11-pentaene (v-28% based on reacted hexachlorobenzene). This product results from elimination of lithium chloride, and attack by the tetrachlorobenzyne on the solvent (v).\textsuperscript{237}

![Diagram]

The adduct was identified by the comparison of spectra and melting point with an authentic sample of the adduct kindly provided by Dr. H. Heaney and Mr. J. M. Jablonski. The only other major fraction was a mixture of at least six components, and attempted separation of these by P.L.C. was only partially successful. The metallation of hexachlorobenzene by butyl lithium in benzene, is obviously far from complete as ca 85% of unreacted hexachlorobenzene was recovered. The excess butyl lithium attacked the sugar, making the mixture of products even more complicated. One of the fractions (F4) isolated, contained a benzylidene group, an \textit{n}-butyl group and two hydroxyl groups by n.m.r., but T.L.C. showed this fraction to be a mixture of three components running closely.
together. The major fraction \( (F_3) \) which was contaminated with a second component containing an \( n \)-butyl side chain, was shown by n.m.r. to contain a low field proton and no methoxyl group. The I.R. showed an absorption peak at 1645 cm\(^{-1} \) which is typical of an \( \alpha, \beta \)-unsaturated ether.

The reaction was repeated using a much smaller excess of lithium butyl. The fraction soluble in petroleum-ether was chromatographed and three major fractions isolated. The first fraction was a mixture of hexa- and pentachlorobenzene, a partial separation of which was achieved by recrystallisation. The second fraction was the tetrachlorobenzene-benzene adduct (17%). The remaining fraction contained all the reacted sugar. This fraction was shown by T.L.C. to consist of essentially two components. These components were separated by P.L.C. and recrystallised from methanol. The major product (ca 50% of this fraction) formed a mono-acetyl derivative and had an elemental analysis, I.R. and n.m.r. spectra consistent with ring opening of the epoxide with pentachlorophenyl lithium. The only proton expected to show as a doublet, in the n.m.r. (Plate XIII), is the anomeric proton. In both the diaxial (VI) and diequatorial (VII) ring-opened products, this doublet should have a coupling constant of around 30 Hz (assuming the chair conformation is adopted).

![Diagram](image-url)
Methyl-4, 6-O-benzylidene-2-deoxy-2-pentachlorophenyl-\(\alpha\)-D-altroside.

(Inset: \(\mathrm{D}_2\mathrm{O}\) exchange)
The observed coupling constant for the low field doublet is 7c/s. Coxon has studied the n.m.r. spectra of 4,6-benzylidene hexosides, and in the altrose compounds which he examined, the anomeric proton had a coupling constant consistent with the chair conformation (VI). However, the axial pentachlorophenyl group may be large enough to force the altrose into the boat form. Two boat forms (VIII) and (IX) are shown below.

(VIII)  (IX)

Both boat forms would give rise to a large coupling constant for the anomeric proton. The only other resolved resonance is a low field quartet. This is assigned to $H_2$ as this proton is deshielded by the aromatic ring. The coupling constants for the quartet are 7c/s and 9c/s which is consistent only with conformer (IX). This conformer has the three large groups, pentachlorophenyl, hydroxyl and methoxyl, in pseudo equatorial positions. The assignment of structure assumes that neither the benzylidene nor the methoxyl group has migrated.

The second product was characterised as 4,6-D-benzylidene-2-pentachlorophenyl-D-altal (X).
The corresponding compound where R = phenyl, was isolated by Overend, Feast and Williams,\textsuperscript{239} as the only product from the attack of phenyl lithium on the methyl-4,6-O-benzylidene-2,3-anhydro-\alpha-D-alloside. The n.m.r. spectrum of (X) is shown in Plate (XIV). The main features of the spectrum are the low field singlet at 3.58 ppm and the absence of the methoxyl protons. The I.R. spectrum indicates an \(\alpha,\beta\)-unsaturated ether. The loss of methanol was not expected as the methoxyl and C\textsubscript{2} hydrogen cannot attain the diaxial orientation which would favour elimination. The steric interactions in the allal (X) are obviously less than those in the altrose (VI) and this would provide the driving force for the reaction. In the original allose (XI), the methoxyl and C\textsubscript{2} hydrogen are diaxially orientated and a possible mechanism is shown below.
4,6-O-Benzylidene-2-deoxy-2-pentachlorophenyl-D-allal

Plate XIV
The reaction was repeated using methyl-4,6-O-benzylidene-2,3-
anhydro-\(\alpha\)-D-mannoside. This sugar epoxide is much more soluble in ether than the corresponding alloside. An ether solution was therefore used as there is no possibility of benzyne attack on the solvent and the metallation of hexachlorobenzene goes in higher yield in ether than in benzene. Diastereomeric epoxide ring opening requires attack at C\(_3\) and attack in this position is sterically hindered. Unreacted epoxide (31\%) was recovered.

Chromatography of the petroleum ether-soluble material gave two major fractions. The first fraction was a mixture of hexa- and pentachlorobenzene (ca 35\% of original hexachlorobenzene). The second fraction was characterised as methyl-4,6-O-benzylidene-\(\alpha\)-D-altropyranoside (IV, R=OH), presumably arising from attack by lithium hydroxide on the epoxide. This is somewhat surprising as Robertson and Griffith\(^{240}\) found it necessary to heat the mannoside at 100°C, in a sealed tube, with 5\% sodium methoxide, for twenty hours to get complete hydrolysis.

An attempted reaction between lithium tetrachloropyridine and methyl-4,6-O-benzylidene-2,3-anhydro-\(\alpha\)-D-mannopyranose, was unsuccessful. The unreacted epoxide was largely recovered. Similarly, an attempted reaction between 4-methyl-lithium thiazyl and methyl-4,6-O-benzylidene-2,3-anhydro-\(\alpha\)-D-allopyranose, led to the recovery, in high yield, of the unreacted epoxide. Beroud and Metzger\(^{241}\) have shown that lithium thiazyls readily attack less sterically hindered epoxides.

Only one reaction between a halo-sugar (di-O-isopropylidene-
\(\alpha\)-D-mannosyl chloride) and pentachlorophenyl lithium, was examined. The first product to separate from petroleum ether...
was a slightly syrupy solid. After two recrystallisations this material was still not highly crystalline. The n.m.r. spectrum (Plate XV) showed a low field doublet (one proton), one hydroxyl group and only one isopropylidene group. The I.R. spectrum showed hydroxyl and an absorption at 1660 cm\(^{-1}\) which is assigned to an \(\alpha,\beta\)-unsaturated ether. This evidence is consistent with the compound being 5,6-\(\alpha\)-isopropylidene-\(\beta\)-pentachlorophenyl-1,2-dideoxy-\(\alpha\) arabo-furanose-1-ene. (XII).

![Chemical Structure](image)

(XII)

A model shows the expected coupling constants to be \(J_{H_2H_3} \simeq 4\,\text{c/s}\) (\(\varphi_{H_2H_3} \simeq 50^\circ\)) and \(J_{H_3H_4} \simeq 8\,\text{c/s}\) (\(\varphi_{H_3H_4} \simeq 10^\circ\)). The observed values are \(J_{H_2H_3} = 3\,\text{c/s}\) and \(J_{H_3H_4} = 6\,\text{c/s}\). The addition of D\(_2\)O causes the \(H_3\) multiplet to sharpen, indicating that the hydroxyl group is at \(C_3\). The compound decomposed on attempted purification by chromatography. Three main fractions were isolated. The first fraction was a mixture of hexa- and pentachlorobenzene. The second fraction, a pale yellow syrup, which rapidly darkened in colour on standing, was not identified. T.L.C. showed two major spots running closely together (Rf 0.56 and Rf 0.53, 5\% methanol/benzene). The I.R. spectrum showed a strong OH and
5,6-o-Isopropylidene-1-pentachlorophenyl-1,2-dideoxy-D-arabino-furanose-1-ene.

(Inset: D₂O exchange)
aliphatic C-H absorption and an unassigned absorption at 1720 cm\(^{-1}\). The n.m.r. spectrum showed two isopropylidene groups, one butyl group and five sugar-chain protons. The third fraction was identified as 2,3:5,6-di-O-isopropylidene-\(\alpha\)-D-mannofuranose.

Only one other 1,2-unsaturated furanose derivative has been reported. Ness and Fletcher\(^{242}\) synthesised 3,5-di-O-benzoyl-1,2-dideoxy-\(\beta\)-erythro-pent-1-enofuranose (XIII) as shown below.

\[
\begin{align*}
\text{(XIII)} & & \text{(XIV)} & & \text{(XV)} & \\
\text{The compound decomposed on standing and reacted with methanol or water to give (XIV) a and b respectively. The reaction with water also gave furfural benzoate (XV).}
\end{align*}
\]

Stacey and his co-workers\(^{243}\) have used dimethyl sulfoxide/acetic anhydride as an oxidising agent in the sugar series with considerable success. The product from the oxidation of 1,2:3,4-di-O-isopropylidene-\(\alpha\)-D-galactopyranose (XVI) was considered to be 1,2:3,4-di-O-isopropylidene-\(\alpha\)-D-galacto-hexodialdo-1,5-pyranose from its B.pt and I.R. spectrum. (XVII)
However, the major product from two organo-lithium reactions, with this compound, was identified as 1,2:3,4-di-0-isopropylidene-α-D-galactopyranose. Re-examination of the starting material showed that acetylation, not oxidation, had taken place in the initial reaction giving 1,2:3,4-di-0-isopropylidene-6-0-acetyl-α-D-galactopyranose. Acetyl groups are readily cleaved by organo-lithium compounds. Albright and Goldmann have previously reported acetylation occurring when using DMSO/acetic anhydride as an oxidant.
MICROBIOLOGICAL TESTS

2-Phenyl-4-methyl-4-hydroxy-5,6-dihydro-4H-1,3-thiazine was tested for antimicrobial, antifugal, neurological and cardiovascular activity. Gram positive bacteria are usually susceptible to antibiotics; gram negative bacteria are much less so. Fungal diseases appear to be of increasing importance both in humans and in agriculture and, in general, do not respond to treatment with antibiotics. The biological tests reflect the need for chemotherapeutic agents in these areas. Some sugar thiazoles were tested as antibiotics and 2-\([\text{D-glucopenta-0-acetylpentyl}]\)-4-phenyl-1,3-thiazole was also tested as an anthelmintic. Short explanatory notes on the cultures used are given below.

**Staphylococcus aureas** - Gram positive bacteria which are pathogenic and are resistant to antibiotics in many cases.

**Escherichia coli** - Gram negative bacteria which are not usually pathogenic; occasionally they cause infection of the genito-urinary tract, but are resistant to antibiotics.

**Proteus vulgaris** - Gram negative bacteria which are generally non-pathogenic but may be encountered in cystitis, infantile diarrhoea and suppurative lesions. Treatment with antibiotics is not always successful.

**Pseudomonas pyocyanea** - Gram negative bacteria which are not pathogenic to man but cause a considerable amount of food spoilage. The bacteria are resistant to antibiotics.
Salmonella typhi - Gram negative bacteria which are often responsible for food poisoning and a close relative to the causative agent (S. typhosa) of typhoid fever. Some strains are resistant to antibiotics.

Candida albicans - A yeast-like fungi which grow in mucous membranes and skin lesions and generally do not respond to treatment with antibiotics.

Haemophilus influenzae - Gram negative bacteria which cause acute respiratory illness, pus-type meningitis in children and acute conjunctivitis.

Brucella abortus - Gram positive bacteria which are not usually pathogenic to man. They cause abortion in female cattle and also sterility and lameness. Auromycin and chloromycetin have been used with some success against the disease.

Microsporum canis - A dermatophyte which usually attacks only cats and dogs. When they are transmitted to humans, the reaction can be severe. Thorough scrubbing with soap and water eliminates the fungi.

Trichophyton mentagrophytes and T. rubrum are causative agents of "athletes foot".

Heterakis and Nippostrongylus are round worms of the class Nematoda.

Heterakis is found mainly in chickens and Nippostrongylus in horses.
## PRIMARY PARASITOLOGICAL TEST REPORT

**ALLEN AND HANBURY LTD. WARE**

**A.H. Number 1824**  |  **Originator Index JBL 1**  |  **Date 6.7.64.**
---|---|---

**Formula** $C_{11}H_{13}NOS$  |  **Name** 5,6-Dihydro-4-methyl-2-phenyl-4H-1,3-thiazin-4-ol

### Tests for Antimicrobial Activity

<table>
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<th>Culture Media</th>
<th>24 hours</th>
<th>5 days</th>
<th>Antagonists</th>
<th>24 hours</th>
<th>5 days</th>
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<table>
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<tr>
<th>TEST</th>
<th>RESULT/REMARKS</th>
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</thead>
<tbody>
<tr>
<td>Acute oral LD₅₀ (Mouse)</td>
<td>800 mg./kg.</td>
</tr>
<tr>
<td>Effects on behaviour in the mouse</td>
<td>Transient sedation following 400 mg./kg. orally. Slight passivity, ptosis and reduced grip strength. Onset 15 min., peak effects 15-30 min., duration 60 min.</td>
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<tr>
<td>Climbing test</td>
<td>Slight inhibition of climbing behaviour following 200 mg./kg. orally.</td>
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<td>Effects on body temperature in the mouse</td>
<td>No effects at 2 hr. following 200 mg./kg orally. Reduced mortality 200 mg./kg.S.C.; -ve 100 mg./kg.S.C.; -ve 200 mg./kg.orally.</td>
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<td>Anticonvulsant 1. Leptazol 2. M.E.S.</td>
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<td>Anti-tremorine</td>
<td>-ve 200 mg./kg.orally</td>
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<td>Anti-amphetamine</td>
<td>-ve 200 mg./kg.orally</td>
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<td>Anti-reserpine</td>
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<tr>
<td>Analgesic 1. Hot-plate 2. Phenyl quinone 3. Tail-clip</td>
<td>-ve 200 mg./kg. orally and S.C. Negligible activity 200 mg./kg. orally Negligible activity 200 mg./kg. orally</td>
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**PRIMARY PHARMACOLOGICAL REPORT (CARDIOVASCULAR/SMOOTH MUSCLE)**

Compound Number AH.1824.

**EFFECT ON PERIPHERAL NORADRENALINE (NA) LEVELS IN THE MOUSE**

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**CONSCIOUS CAT: Effects on normal behaviour (Grades response ++++ maximal)**

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<th>Restlessness</th>
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<th>Pupil</th>
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**ANAESTHETISED CAT: Wt. Sex Anaesthesia.**

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**ANAESTHETISED GUINEA-PIG.**

(0,0-10% reduction; + 10-50% reduction; ++ 50-75% reduction; +++ 75-100% reduction)

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<th>Anti-ACH.</th>
<th>Anti-5HT</th>
<th>Anti-bradykinin</th>
<th>Anti-histamine</th>
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<td>ANTIBACTERIAL (In Vivo)</td>
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</tr>
<tr>
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<tr>
<td></td>
<td>Gram +ve</td>
<td>Gram -ve</td>
<td>Gram +ve</td>
<td>Gram -ve</td>
</tr>
<tr>
<td>61</td>
<td>58,849</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>N.A.</td>
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<tr>
<td>62</td>
<td>58,850</td>
<td>&gt;1,000</td>
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<td>N.A.</td>
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<tr>
<td>63</td>
<td>58,851</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>N.A.</td>
</tr>
<tr>
<td>65</td>
<td>58,853</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>N.A.</td>
</tr>
</tbody>
</table>

*Minimum inhibitory concentration in p.p.m.

N.A. = not active.

\[
\begin{align*}
R' & \quad R'' \\
61 & \text{penta-\(O\)-acetyl-\(D\)-glucopentyl} \quad H \\
62 & \text{pentahydroxy-\(D\)-glucopentyl} \quad \text{NO}_2 \\
63 & \text{penta-\(O\)-acetyl-\(D\)-glucopentyl} \quad \text{Br} \\
64 & \text{tetra-\(O\)-acetyl-\(D\)-arabinoctyl} \quad \text{Br} \\
65 & \text{penta-\(O\)-acetyl-\(D\)-glucopentyl} \quad \text{Me}
\end{align*}
\]

Compound 61 showed no activity against *Heterakis* or *Nippostrongylus.*
EXPERIMENTAL

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Experiments</th>
</tr>
</thead>
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<td>The synthesis of five and six membered rings containing nitrogen and sulphur.</td>
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<td>Aldononitriles.......................... 1 - 9</td>
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<td>2-Substituted thiazol-4-ones...........10 - 15</td>
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<td>Aldonothioamides.........................16 - 24</td>
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<td>Thiazoles..................................44 - 68</td>
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<td>Thiazolidine-4-ones......................69 - 80</td>
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<td>II</td>
<td>Organo lithium reactions................1 - 7</td>
</tr>
</tbody>
</table>
EXPERIMENTAL

Micro analyses were carried out by Mr. P. Borda, Mr. R. White, Mr. K. Scott or Drs. G. Weiler and F.B. Strauss.

Melting points and boiling points are uncorrected.

Infrared spectra were recorded on a Unicam SP 200, a Perkin Elmer 237 or 257 spectrophotometer. Solids were examined using the nujol mull technique and liquids as thin films. The following abbreviations are used in recording I.R. spectra: - s. - strong; m. - medium; w. - weak and b. - broad.

Ultraviolet spectra were recorded on an SP 800 spectrophotometer using matched 10mm. cells unless otherwise stated, and methanol as the solvent.

Nuclear magnetic resonance spectra were recorded by Mr. M. Jiggins or Mr. R. Chabbra on a Perkin Elmer R 10 (60M. c/sec.) spectrometer using tetramethylsilane as an internal standard unless otherwise stated. The following abbreviations are used in recording these spectra: - b. - broad; s. - singlet; d. - doublet; t. - triplet; q. - quartet; qn. - quintet; sx. - sextet; sp. - septet; o. - octet and m. - multiplet.

Optical rotations were measured using a Bendix NFL Automatic Polarimeter 143C.

Column chromatography was on B.D.H., M.F.C. grade silica. Thin layer chromatography was on Keiselgel H.F.254. Preparative layer chromatography was on Keiselgel P.F.254.
Spots were detected by U.V. light, iodine vapour or by charring with sulphuric acid.

Vapour phase chromatography employed a Pye series 104 Chromatograph fitted with a flame ionisation detector.

Petroleum ether refers to the 60-80°C. boiling range and solvents were dried by standard methods.

Literature melting points are those quoted by J.R.A. Pollock and R. Stevens in the Dictionary of Organic Compounds unless another reference is given.

1.) 2,3,4,5,6-Penta-O-acetyl-D-glucononitrile
   Method (I) as described by H.T. Clarke and S.M. Nagy.245

Sodium (20g.) was added to methanol (350ml.) in a round-bottomed flask fitted with a reflux condenser. Initially, the reaction was controlled by cooling the flask in an ice bath. This solution of sodium methoxide was carefully added to a solution of hydroxylamine hydrochloride (61g., 0.88M.) in water (20ml.). After twenty minutes, the solution was cooled to 0°C. and the sodium chloride removed by filtration and washed with cold methanol (350ml.). The combined filtrate and washings were warmed to 65°C. and a solution of D-glucose (90g., 0.5M) in 25% aqueous methanol (200ml.) added slowly whilst stirring. The resulting solution was held at 65°C. for a further two hours. The solvent was removed using a rotary evaporator. Absolute alcohol (100ml.) was added and the solution again evaporated to dryness. This last stage was repeated in order to remove all the water.
A sample of the oxime, which was a syrup, was taken and its n.m.r. spectrum examined in DMSO.

A solution of the oxime, in glacial acetic acid (50ml.) and acetic anhydride (100ml.), was slowly added to a stirred suspension of finely powdered, anhydrous sodium acetate (100g.) in hot acetic anhydride (650ml.). After the addition was complete, the reaction mixture was heated for one hour on a water bath. The acetic acid and unreacted anhydride were distilled off under reduced pressure. The residue was poured into an ice/water mixture (2,000ml.) and allowed to stand overnight. After chilling to 0°C., the brown solid which had separated was filtered, dissolved in hot absolute alcohol, decolourised with charcoal and recrystallised from alcohol.

Yield : 91g. (47%)
M.pt. : 79.5 - 81°C. (Lit. M.pt. 82.5 - 83.5°C.)
I.R.spectrum (cm⁻¹) : 1760s. (OAc⁻), C=N not assignable.
n.m.r. Spectrum (CD₂COCD₂) : 
H₂, H₃ and H₄ m., 4.4 (3 protons); H₅ m., 4.9 (1 proton); H₆, H₇ m., 5.8 (2 protons); OAc s., 7.85 (9 protons) and OAc s., 8.0 (6 protons).

2.) 2,3,4,5,6-Penta-O-acetyl-β-D-galactonitrile

a) The title compound was prepared by the method (I) described above (0.25 H. scale).

β-D-Galactose oxime (not recrystallised)
Yield : 21g. (86%)
The n.m.r. spectrum was examined in DMSO. The nitrile did not separate as a solid on pouring onto ice. The almost black
syrup which was isolated did not decolourise on treatment with charcoal. Repeated crystallisations from absolute alcohol gave a white solid.

**Yield : 3.8g. (4% as nitrile).**

The n.m.r. spectrum showed that the material contained approximately 20% of the hexa-O-acetyl-\(\beta\)-galactose oxime (doublet at 2.57, \(J=50/s\)).

b) **Method (II).** \(\Delta\)-Galactose oxime (10g.) in pyridine (30ml.) and acetic anhydride (30ml.) was heated at 110\(^\circ\)C. for three hours. The solution was cooled and poured into iced water. The solid which separated was filtered off, decolourised with charcoal and after five crystallisations from alcohol, a white crystalline solid collected.

**Yield : 7g. (34%)**


**I.R. spectrum (cm\(^{-1}\)) : 1740 s. and 1720 s. (\(\text{C}=\text{N}\)), \(\text{C}=\text{N}\) not assignable.**

c) **As for (b) above except pyridine (30ml.) and acetic anhydride (20ml.) and heated at 110\(^\circ\)C. for one hour. The work up was much easier but the yield of the nitrile lower.**

**Yield : 2g. (10%)**


**n.m.r. Spectrum (CDCl\(_3\)) : \(H_2, H_3, H_4\) and \(H_5\) m., 4.6 (4 protons); \(H_6, H_6'\) two quartets, 5.6 (2 protons); \(\text{OAc} s., 7.85\) (3 protons), 7.9 (9 protons) and 8.0 (3 protons).**
3) 2,3,4,5-Tetra-O-acetyl-D-xylonitrite

As for glucononitrile method (I), 0.125 M. scale.

A sample of the oxime, a syrup, in DMSO, was examined by n.m.r.

\[ [\alpha]_D^{2} = 7.6^\circ \text{(DMSO, c=3.1)} \] No mutarotation observed over twenty-three hours.

\[ [\alpha]_D^{2} = 5.6^\circ \text{(DMSO/H}_2\text{O (9/1) c 3.1)} \] No mutarotation observed over seven hours.

The nitrile was recrystallised from absolute alcohol.

Yield : 14g. (37%)

M.pt. : 80-82°C. (Lit.M.pt. 81-82°C)

n.m.r. Spectrum (CD_3COCD_3) γ : H_2H_3, H_4m., 4.4 (3 protons);
H_5H_6m., 5.8 (2 protons); OAc s., 7.8 (6 protons), 7.9
(3 protons) and 8.0 (3 protons).

I.R. Spectrum (cm\(^{-1}\)) : 1740 s. (OAc), C\=N not assignable.

4) 2,3,4,5-Tetra-O-acetyl-L-arabonitrile

As for glucononitrile method (I), 0.125 M. scale.

Crude arabinose oxime, in DMSO, was examined by n.m.r.

\[ [\alpha]_D^{2} = 42.1^\circ \text{(DMSO, c 0.27)} \] Time : zero

\[ [\alpha]_D^{2} = 34.7^\circ \text{(DMSO, c 0.27)} \] Time : 60mins.

\[ [\alpha]_D^{2} = 31.0^\circ \text{(DMSO, c 0.27)} \] Time : 3,600mins.


The n.m.r. spectrum of the recrystallised material was also examined in DMSO.

\[ [\alpha]_D^{2} = 101.9^\circ \text{(Initial)} \]

\[ [\alpha]_D^{2} = 33.2^\circ \text{(Final)} \]
L-Arabinose oxime (0.0889g.) in DMSO/H₂O (5ml./0.194g.)

The variation of rotation with time is shown in Table (i) below.

<table>
<thead>
<tr>
<th>Time (mins.)</th>
<th>Rotation Reading (a)</th>
<th>a - Nutorotation Reading (x)</th>
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Table (i)
Arabinose nitrile was recrystallised from absolute alcohol.

Yield : 14.5g. (39%)

M.pt. : 116-118°C. (Lit. M.pt. 120-121°C.)

I.R. spectrum (cm⁻¹) : 1750 s. and 1730 s. (OAc),

C₂N not assignable.

n.m.r. Spectrum (CD₃COCD₃) : H₂d., 4.18 (1 proton);
H₃q., 4.38 (1 proton); H₄sp., 4.74 (1 proton); H₅H₆₁m.,
5.8 (2 protons); OAc s., 7.83 (6 protons), 7.96 (3 protons)
and 7.98 (3 protons).

5.) 2,3,4,5-Tetra-O-acetyl-D-ribonitrile

D-Ribose oxime was prepared by method (I) using 3g.
of D-ribose.

Yield : 3g. (90%)

The n.m.r. spectrum was examined in DMSO.

The oxime (3g.) was added to pyridine (6ml.) and acetic anhydride (4ml.)
at 0°C. and left in the refrigerator overnight. The nitrile
was recrystallised from alcohol.

Yield : 1.4g. (25%)

M.pt. : 70-71°C (Lit. M.pt. 71-72°C.)

I.R. spectrum (cm⁻¹) : 1750 s. and 1730 s. (OAc),

C₂N not assignable.

n.m.r. Spectrum (CDCl₃) : H₂d., 4.22 (1 proton);
H₃ and H₄m., 4.6 (2 protons); H₅H₆₁m., 5.7 (2 protons);
OAc s., 7.83 (9 protons) and 7.91 (3 protons).
6.) 2,3,4,5-Tetra-O-acetyl-D-rhamnononitrile

The oxime was prepared by method (I) using D-rhamnose (10g.).

Yield : 9.5g. (87%)
The n.m.r. spectrum was examined in DMSO.

The nitrile was prepared by method (II). D-Rhamnose oxime (6g.) was added to pyridine (25ml.) and acetic anhydride (20ml.) at room temperature and left overnight.

On work up, a syrup was isolated.

T.L.C.     10% EtOH/benzene     Rf 0.7

Benzene     Rf 0.5

The syrup was chromatographed on a silica column (100g.) the eluent being changed gradually from 50/50, petroleum ether/benzene to benzene. The major product, eluted over seven 100ml. fractions, weighed 5.4g. (49% based on nitrile) and consisted of a single component by T.L.C.

n.m.r. Spectrum (CDCl₃) ′: m. (assigned to CHNOAc mixture of isomers), 2.4 (0.75 protons); m., 4.6 (4 protons); OAc s., 7.82, 7.88 and 7.96 (≈15 protons) and CH₃ d., 8.8 (J=6c/s, 3 protons).

The mixture of nitrile and acetylated oxime (5.4g) was dissolved in dry pyridine (20ml.) and heated on a water bath for four hours. The reaction mixture was cooled, poured into iced water, the syrup separated, dissolved in alcohol and decolourised with charcoal. The resulting syrup failed to crystallise.

Yield : 1g. (18%)
The n.m.r. spectrum was almost identical with that of starting
7.) 2,3,4,5,6-Penta-O-acetyl-D-mannono- 

D-mannose (20g., 1/9 H.) and potassium acetate (30g., 1/3 m.) were dissolved in water (30ml.) and hydroxylamine hydrochloride (14g., 1/5 M.) added. The solution was warmed for a few minutes and then cooled in an ice/water bath. The solid which separated was filtered and dried under vacuum.

Yield: 20g. (97%)


The n.m.r. spectrum of the oxime was examined in DMSO.

Penta-O-acetyl-D-mannononitrile was prepared by method (I) except that after the addition of the oxime (10g.) the reaction mixture was heated for one minute only.

After two crystallisations from alcohol, the n.m.r. spectrum of the product was examined and showed the presence of hexa-O-acetyl mannose oxime.

n.m.r. Spectrum (CDCl₃) 7: m. (assigned to acetylated oxime), 2.4 (0.6 protons); H₆H₃H₄m., 4.5 (3 protons); H₅m., 4.8 (1 proton); H₆H₆'m., 5.8 (2 protons); OAc s., 7.85, 7.91 and 7.93 (17-18 protons). After four further recrystallisations, penta-O-acetyl-D-mannononitrile, free from the acetylated oxime, was isolated.

Yield : 5.2g. (25%)

M.pt. : 90.5 - 92.5°C (Lit. M.pt. 92-93°C.)

I.R. spectrum (cm⁻¹) : 1750 s. (OAc), C=O not assignable.

n.m.r. Spectrum (CDCl₃) 7: H₂H₃H₄m., 4.5 (3 protons); H₅ex., 4.9 (1 proton); H₆H₆'m., 5.8 (2 protons); OAc s.,

-135-
7.85 (9 protons) and 7.95 (6 protons).

8.) 3,4,5,6-Tetra-O-acetyl-N-acetyl-D-glucosaminonitrile

D-glucosamine oxime hydrochloride was synthesised by method (I) except that the oxime separated on standing for two days. Glucosamine hydrochloride (20g.) was used. The oxime was not recrystallised.

Yield : 15g. (70%)
M.pt. : 159-162°C. (Lit. M.pt. 166°C.)

The n.m.r. spectrum was examined in DMSO.

The nitrile was synthesised by method (II) using glucosamine oxime hydrochloride (15g.), pyridine (30ml.) and acetic anhydride (30ml.). The nitrilo was recrystallised from alcohol.

Yield : 23.5g. (91%)

I.R. spectrum (cm\(^{-1}\)) : 3220 m. (NH amide); 1750 s. (OAc); 1650 s. (NAc); CHN not assignable.

n.m.r. Spectrum (CD\(_3\)COCD\(_3\)) \(\gamma\) : NH b.d., 2.2 (1 proton, exchanges with D\(_2\)O); H\(_2\)H\(_3\)H\(_4\)H\(_5\)m., 4.6 (4 protons); H\(_6\)H\(_6\)m., 5.8 (2 protons); \(\delta\) s., 7.78 (3 protons), 7.83 (3 protons) and 8.02 (9 protons).

9.) 3,4,5,6-Tetra-O-acetyl-2-deoxy-D-glucononitrile

2-Deoxy-D-glucose oxime was prepared by method (I) from 2-deoxy-D-glucose (5.5g.). The oxime was recrystallised from aqueous alcohol.

Yield : 5g. (83%)
M.pt. : 162-164°C.
The nitrile was synthesised using method (II) and recrystallised from alcohol.

Yield : 3.1g. (34%)

M. Pt. : 154-156°C.

I.R. spectrum (cm⁻¹) : 2250 m. (C=O) and 1740 s. (OAc).

n.m.r. Spectrum (CDCl₃) 7 : H₃C=H₂ m., 4.7 (3 protons);
H₆H₆ m., 5.8 (2 protons); H₂H₂ 'two q., 7.3 (2 protons);
OAc s., 7.80 (3 protons), 7.88 (3 protons) and 7.93 (6 protons).

Elemental Analysis

Required for C₁₄H₁₉N

<p>| | | |</p>
<table>
<thead>
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<th></th>
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<td>N</td>
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<td>4.03</td>
</tr>
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</table>

The method is as described by Condo et al.¹³⁸

A solution of methyl cyanide (4.1g., 1/10 M.) and thioglycollic acid (9.2g., 1/10 M.) in sodium-dried diethyl ether (30ml.) was saturated with dry hydrogen chloride at 0°C. and left overnight in the refrigerator. The crystals which had separated were filtered, washed with dry ether and dried in a vacuum oven over phosphorous pentoxide.

Yield : 13.4g. (78%)

Decomposition pt. : 95°C. (Lit. value 115°C.)

An aqueous solution of the hydrochloride was titrated against standard caustic soda using methyl orange as an indicator. The titration indicated that the hydrochloride was 88% pure.
11. **Neutralisation of α-iminomethylmercaptoacetic acid hydrochloride (I)**

a) Compound I (5g.) was shaken with aqueous sodium bicarbonate and extracted with chloroform. The organic layer was separated, washed with water and dried over anhydrous sodium sulphate. The chloroform was evaporated off and the residue (100mg., 6%) was found to have an identical I.R. spectrum with that of 2-methyl-thiazol-4-one.

b) The above neutralisation was repeated using a weakly basic resin (Amberlite IR45B).

Compound I (5g., 3/100 M.) and the resin (15g., approximately a five-fold excess) in ethanol, were shaken for 24 hours. G.L.C. (10% silicone oil, 50°C.) showed that no thiazolone had been formed. The mixture was heated under reflux for three hours and after cooling, the resin was filtered off. The ethanol solution was distilled and the fraction boiling between 122-123°C. collected (0.8g., 24%). During the distillation, a white solid was deposited on the walls of the condenser. This material gave positive tests for ammonium and chlorido ion.

c) Compound I (5g., 3/100 M.) and anhydrous sodium acetate (2.5g., 3/100M.) were heated under reflux for six hours in absolute ethanol. On cooling, the solution was filtered and distilled. The fraction boiling between 122-124°C. (1g., 30%) was collected. This fraction had an identical I.R. spectrum with that of 2-methyl-thiazol-4-one.

d) Compound I (7.5g., 9/200 M.) and sodium bicarbonate (4.5g.) were heated under reflux in absolute ethanol for four hours. The solution was cooled and filtered.
The ethanol solution was distilled and 2-methyl-thiazol-4-one (2.2g., 43%) collected between 120-128°C. A second high boiling fraction (0.7g., 27%) was collected at 130-133°C.

This fraction crystallised on cooling and was re-crystallised from chloroform/ether 50/50 and was identified as acotamide.

Elemental Analysis

\[
\begin{align*}
\text{C} & \quad \text{H} & \quad \text{N} \\
\text{Required for C}_2\text{H}_5\text{NO} & \quad 40.67 & \quad 8.47 & \quad 23.73 \\
\text{Found} & \quad 40.32 & \quad 8.94 & \quad 24.41 \\
\text{M.pt.} & \quad 78-79^\circ \text{C.} \quad (\text{Lit M.pt. 82-83}^\circ \text{C.})
\end{align*}
\]

The I.R. spectrum was identical with that of an authentic sample of acotamide.

The filtrate was heated under reduced pressure in a sublimator.

A white material sublimated at a bath temperature of 130°C at 5mm. Hg. This material gave positive ammonium and chloride ion tests. The yield of ammonium chloride (0.6g.) represents a 25% yield based on the imino compound.

12.) 2-Methyl-thiazol-4-one.

Thiaacetamide (3.7g.) and chloroacetic acid (4.7g) were heated in acetic acid for ten minutes. The reaction mixture was poured into water, neutralised with sodium carbonate, extracted with benzene and distilled.

Yield : 0.8g. (14%)

B.pt. : 120-123°C. (Lit B.pt. 120-122°C.)
13.) Attempted preparation of \( \alpha \)-imino-(D-gluc-o-penta-O-acetyl-pentyl)-mercaptoacetic acid hydrochloride.

a) A suspension of penta-O-acetyl-D-glucononitrile (4.2g., 1/100 M.) and thioglycollic acid (1g., a slight excess) in dry ether (100ml.) was saturated with dry hydrogen chloride at 0°C. and left for 72 hours in the refrigerator. The suspension was filtered, washed with dry ether and recrystallised from ethanol. The sugar nitrilo was recovered almost quantitatively.

b) The experiment was repeated using dry diglyme saturated with hydrogen chloride at 0°C. and penta-O-acetyl-D-glucononitrile (8.2g., 1/50 M.). After standing overnight at 0°C., no precipitate had separated and dry ether (100ml.) was added. The material which separated was recrystallised from alcohol and identified as penta-O-acetyl-D-glucamide. Yield: 0.8g. (9%)  


I.R. spectrum (cm\(^{-1}\)) : 3440, 3300, 3260 and 3180 m.

(NH, amide); 1750 s. (OAc), 1680 s. (C = O, amide) and 1605 m. (NH\(_2\) deformation band).

n.m.r. Spectrum (CD\(_3\)COCD\(_3\))\(\gamma\): NH\(_2\) b.s., 3.3 (2 protons, exchange with D\(_2\)O); H\(_3\)H\(_4\)m., 4.5 (2 protons); H\(_2\)d., 4.75 (1 proton); H\(_5\)m., 5.0 (1 proton); H\(_6\)H\(_6\)m., 5.8 (2 protons); OAc s., 7.85, 7.93 and 8.00 (15 protons).

Elemental Analysis  

C \quad H \quad N  

Required for C\(_{16}\)H\(_{23}\)NO\(_{11}\) 47.4 \quad 5.81 \quad 3.46  

Found 47.5 \quad 5.87 \quad 4.10
The diglyme and ether were evaporated under reduced pressure and methanol added and penta-O-acetyl-D-glucononitrile separated (2.8 g).

14) Ethyl thioglycollate

Thioglycollic acid (18.4 g. 1/5 M.) and acetyl chloride (4 g.) were heated under reflux for four hours in absolute alcohol. Ethyl thioglycollate was distilled and the fraction boiling between 56° and 58°C. /14 mm. Hg. collected. (Lit B.pt. 55° C/17 mm. Hg.)

Yield: 13.5 g. (50%) 

15.) Condensation of penta-O-acetyl-D-glucononitrile with ethyl thioglycollate.

Penta-O-acetyl-D-glucononitrile (1.9 g., 1/200 M.) and ethyl thioglycollate (0.65 g., >1/200 M.) were dissolved in dry diglyme (8 ml.) and dry ether (20 ml.) and saturated with dry hydrogen chloride at 0°C. The reaction mixture was held at 0°C for forty-eight hours. The solvent was evaporated at reduced pressure and methanol added. The methanol solution was shaken with sodium bicarbonate, filtered and evaporated. The residue was column chromatographed on silica gel (200 g.). The column was eluted with 20% diethyl ether/petroleum ether changing to 60% diethyl ether/petroleum ether, 50 ml. fractions being taken. Three major fractions were isolated and identified as ethyl thioglycollate, penta-O-acetyl-D-glucononitrile (42% recovery) and the corresponding amide (17%).
16.) **2,3,4,5,6-Penta-O-acetyl-D-gluconothioamide.**

Penta-O-acetyl-D-glucononitrile (3g.) was dissolved in pyridine (3ml.) and triethylamine (1ml.) and hydrogen sulphide bubbled through the solution for three hours. The solution was poured onto ice/water (100ml.) and after standing, a solid separated. The solid was filtered off and recrystallised from alcohol.

Yield : 94%


n.m.r. Spectrum (CDCl₃): NH₂ two s., 2.1 and 2.4 (2 protons, exchange with D₂O); H₃q., 4.18 (1 proton); H₂d., 4.34 (1 proton); H₄t., 4.58 (1 proton); H₅q., 4.59 (1 proton); H₆H₆' sp., 5.77 (2 protons); OAc s., 7.78 (3 protons), 7.89, 7.93, and 7.97 (12 protons).

Elemental Analysis | C | H | N | S
--- | --- | --- | --- | ---
Required for C₁₆H₂₃NO₁₀S | 45.9 | 5.17 | 3.42 | 7.74
Found | 45.6 | 5.45 | 3.32 | 7.60

17.) **2,3,4,5-Tetra-O-acetyl-L-arabonothioamide.**

The title compound was prepared from the corresponding nitrile using the conditions described in experiment (16) and recrystallised from alcohol.

Yield : 89%


n.m.r. Spectrum (CD₃COCD₃): NH₂ b.s., 1.2 (2 protons, exchange with D₂O); H₃q., 4.10 (1 proton); H₂d., 4.35 (1 proton); H₄sp., 4.81 (1 proton); H₅H₅' sp., 5.80 (2 protons); OAc s., 7.85 (3 protons), 7.96 and 8.01 (12 protons).
Elemental Analysis

Required for $\text{C}_{13}\text{H}_{19}\text{NO}_3\text{S}$  

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<tr>
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<tr>
<td>Found</td>
<td>3.81</td>
<td>9.39</td>
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2,3,4,5-Tetra-O-acetyl-D-xylonothioamide.

The title compound was prepared from the corresponding nitrile using the conditions described in experiment (16) and recrystallised from alcohol.

Yield : 90%

M.pt. : 138-140°C. (hot stage) (Lit. M.pt. 132.5-133.5°C.)

n.m.r. Spectrum (CD$_3$COCD$_3$)$_2$: NH$_2$ b.s., 1.2 (2 protons, exchange with D$_2$O); H$_3$q., 4.18 (1 proton); H$_2$d., 4.43 (1 proton); H$_4$sx., 4.68 (1 proton); H$_5$H$_5$' sp., 5.8 (2 protons); OAc s., 7.82 (3 protons), 7.98 and 8.00 (9 protons).

Elemental Analysis

Required for $\text{C}_{13}\text{H}_{19}\text{NO}_3\text{S}$  

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<tr>
<th></th>
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<tr>
<td>Found</td>
<td>3.92</td>
<td>9.40</td>
</tr>
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</table>
19.) **Tetra-O-acetyl-D-ribonothioamide.**

The title compound was prepared from the corresponding nitrile using the conditions described in experiment (16) and recrystallised from alcohol.

Yield : 67%

M.pt. : 119-121°C.

n.m.r. Spectrum (CDCl₃): \( \text{NH}_2 \) two s., 1.0 and 1.3 (2 protons, exchange with D₂O); \( \text{H}_2\text{H}_3\text{m} \), 4.2 (2 protons); \( \text{H}_4\text{m} \), 4.6 (1 proton); \( \text{H}_5\text{H}_5' \) two q., 5.7 (2 protons);

OAc s., 7.80 (3 protons), 7.93 and 7.94 (9 protons).

Elemental Analysis

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<td>4.01</td>
<td>9.17</td>
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Found

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<tr>
<td>44.46</td>
<td>5.54</td>
<td>3.78</td>
<td>8.82</td>
</tr>
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</table>

20.) **3,4,5,6-Tetra-O-acetyl-N-acety1-D-glucosaminothioamide**

The title compound was prepared from the corresponding nitrile using the conditions described in experiment (16) and recrystallised from alcohol.

Yield : 74%


n.m.r. Spectrum (CD₃COCD₃): \( \text{GSH}_2\text{b.s.} \), 1.1 (2 protons); \( \text{NH} \) \( \text{b.s.} \), 2.8 (1 proton, exchanges with D₂O); \( \text{H}_3\text{q} \), 4.15 (1 proton); \( \text{H}_4\text{q} \), 4.60 (1 proton); \( \text{H}_2\text{H}_2\text{m} \), 4.9 (2 protons);

\( \text{H}_6\text{H}_6'\text{m} \), 5.8 (2 protons); \( \text{A\partial s.} \), 7.9 (3 protons) and 8.0 (12 protons).
21. 2,3,4,5,6-Penta-O-acetyl-D-galactonothioamide

The title compound was prepared from the corresponding nitrile using the conditions described in experiment (16) and recrystallised from alcohol.

Yield : 64%

M.pt. : 131-133°C. (Lit. M.pt. 132-133°C.\textsuperscript{137})
n.m.r. Spectrum (CD\textsubscript{3}COCD\textsubscript{3}): \textit{NH} b.s., 1.1 (2 protons, exchange with D\textsubscript{2}O); H\textsubscript{3}q., 4.08 (1 proton); H\textsubscript{2}d., 4.49 (1 proton); H\textsubscript{4}q., 4.58 (1 proton); H\textsubscript{5}m, 4.75 (1 proton); H\textsubscript{6}H\textsubscript{6}'tw o q., 5.9 (2 protons); OAc s., 7.85 (3 protons), 7.90 (3 protons), 7.98 (3 protons) and 8.02 (6 protons).

No galactonothioamide could be isolated when galactononitrile containing some acetylated oxime was used as the starting material.

22. 2,3,4,5,6-Penta-O-acetyl-D-mannonothioamide

The title compound was prepared from the corresponding nitrile using the conditions described in experiment (16). The product failed to crystallise. The syrup was chromatographed on a silica column (100g.) using petroleum ether/benzene (50/50) changing gradually to diethyl ether/benzene (30/70) as the eluent. The major fraction (0.5g., 15%) had an I.R. spectrum typical of an aldono-thioamide but failed to crystallise. A fraction of the syrup was re-chromatographed by P.L.C. The resulting product still failed to crystallise and although the spectral evidence shows that the product is the thioamide, the elemental analysis indicates that it is impure.
Yield: 15% 
n.m.r. Spectrum (CDCl$_3$): GSNH$_2$ two s., 1.5 and 2.0 (2 protons, exchange with D$_2$O); H$_2$H$_3$H$_4$ s., 4.4 (3 protons); H$_5$ m., 4.8 (1 proton); H$_6$ b.s., 5.8 (2 protons); OAc s., 7.82, 7.85 and 7.92 (15 protons).

Elemental Analysis

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<td>Required for C$<em>{16}$H$</em>{23}$NO$_{10}$S</td>
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<td>5.17</td>
<td>3.42</td>
<td>7.74</td>
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<tr>
<td>Found</td>
<td>47.9</td>
<td>5.60</td>
<td>2.91</td>
<td>5.9</td>
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23.) Attempted preparation of tetra-O-acetyl-2-deoxy-D-
gluconothioamide.

The conditions described in experiment (16) were used but only unreacted nitrile (35%) was recovered.

24.) Thiobenzamide.

Thiobenzamide was prepared using the conditions described in experiment (16).

Yield: 24g. (90%)


I.R. spectrum (cm$^{-1}$): 3400, 3350 and 3200 s. (NH$_2$), 1630 s. and 780 s. and 690 s. (CH deformation).

n.m.r. Spectrum (CDCl$_3$): GSNH$_2$ b.s., 1 (2 protons) and aromatic protons as multiplets at 2.1 and 2.6 (5 protons).

25.) 2-Phenyl-4-methyl-5,6-dihydro-4-hydroxy-4H-1,3-thiazine.

Boron trifluoride etherate (0.5ml.) was added dropwise to a stirred solution of thiobenzamide (1.37g., 1/100 M.) and methyl vinyl ketone (0.89 g., 1/100 M.) in dry ether (25ml.). After fifteen minutes, the solid which had separated was filtered off and washed with a small quantity of dry ether.
and then taken up in solution with chloroform. The chloroform solution was shaken with aqueous sodium bicarbonate, washed with water and then dried over magnesium sulphate. After filtering off the drying agent, the chloroform was evaporated and the residue crystallised from petroleum ether (80-100) to give pale yellow crystals.

Yield : 60%
I.R. spectrum (cm⁻¹) : 3250 s. (OH); 1590 s. and 1580 s. (C=N and C=C aromatic); 760 s. and 690 s. (C-H deformation).

n.m.r. Spectrum (CDCl₃): aromatic protons m., 2.2 and 2.6 (5 protons); H₆H₆ OH m., 6.8 (3 protons, 1 proton, exchanges with D₂O); H₅H₅ m., 8.1 (2 protons) and CH₃s., 8.58 (3 protons).

26.) 2-Phenyl-4,6,6-trimethyl-5,6-dihydro-4-hydroxy-1,3-thiazine.

Experiment (25) was repeated using thiobenzamide (3.9g., 3/100 M.) and mesityl oxide (9ml., a large excess).

The product was recrystallised from petroleum ether (80-100).

Yield : 1.4g. (21%)
M.pt. : 105-106°C.
I.R. spectrum (cm⁻¹): 3250 s. (OH) 1590 s. (C=N and C=C aromatic); 760 s. and 700 s. (CH deformation).

n.m.r. Spectrum (CDCl₃): m., 2.4 (5 protons); s., 6.4 (1 proton); d., 7.95 (1 proton); d., 8.25 (1 proton);
s., 8.50 (3 protons) and s., 8.55 (6 protons).

Elemental Analysis

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<td>Found</td>
<td>66.84</td>
<td>7.60</td>
<td>5.78</td>
<td>13.40</td>
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The reaction mixture was allowed to stand for a further three days and the oil which had separated was worked up as previously described. The product was recrystallised from alcohol and identified as 2,5-diphenyl-1,2,4-thiadiazol by comparison with an authentic sample.

Yield : 0.2g. (6%)


Mixed M.pt. : 88-91°C.

n.m.r. Spectrum (CDCl\(_3\))\(\gamma\): aromatic protons m., 1.6, 1.9 and 2.5.

27.) 2,4,6-Triphenyl-5,6-dihydro-4-hydroxy-1,3-thiazine.

a) The condensation was carried out as described in experiment (25), using 1/20 M. quantities. The resulting syrup was examined by T.L.C. 10% diethyl ether/petroleum ether: Rf 0.9, Rf 0.8, Rf 0.5, Rf 0.3 and Rf 0.0.

Thiobenzamide : Rf 0.0  Benzylideneacetophenone : Rf 0.5.

The syrup was chromatographed on silica (250g.) but only the component at Rf 0.3 and starting materials were isolated pure. After recrystallisation from petroleum ether/diethyl ether, this component was identified as 3-\(S\)-benzoyl-1,3-diphenyl-propan-1-one.

Yield : 2.4g. (15%)

M.pt. : 114°-116°C.
I.R. spectrum (cm⁻¹) : 1680 s. (φ-C), 1660 s., (φ-φ - S), 1600 m. and 1580 m. (C=C aromatic)

n.m.r. Spectrum (CDCl₃): m., 1.9-2.8 (15 protons); t., 4.48 (1 proton); d., 6.20 (2 protons).

Elemental Analysis

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<tr>
<td>Fnd</td>
<td>75.50</td>
<td>5.56</td>
<td>8.96</td>
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</table>

b) This experiment was repeated on 1/100 M. scale and in this reaction a solid separated which on work up gave 2,4,6-triphenyl-5,6-dihydro-4-hydroxy-1,3-thiazine on recrystallisation from petroleum ether (80-100⁰).

Yield : 0.5g. (15%)  
M.pt. : 115.5-116.5⁰C.

I.R. spectrum (cm⁻¹) : 3250 s. (OH); 1590 s. and 1570 s. (C=N and C=C aromatic), 960 s. and 600 s. (CH deformation).

n.m.r. Spectrum (CDCl₃): m., 1.9-2.8 (15 protons); q., 5.6 (1 proton);m., 6.3 (2 protons) and s., 8.34 (1 proton, exchanges with D₂O).

Elemental Analysis

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<td>Req</td>
<td>76.50</td>
<td>5.51</td>
<td>4.05</td>
<td>9.29</td>
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<tr>
<td>Fnd</td>
<td>76.35</td>
<td>6.00</td>
<td>4.35</td>
<td>9.17</td>
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</table>

On standing, a viscous oil separated from the reaction mixture. After work up, a white crystalline solid separated from alcohol. The first crop of crystals gave the correct analysis for the sulphone of the triphenyl thiazine. The second crop of crystals were identified as the 3-φ-benzoyl-1,3-diphenyl-propan-1-one.
Elemental Analysis

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<tr>
<td>Required for C\textsubscript{22}H\textsubscript{19}N\textsubscript{3}O\textsubscript{3}S</td>
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<td>5.05</td>
<td>3.71</td>
<td>8.62</td>
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<tr>
<td>Found</td>
<td>69.70</td>
<td>4.96</td>
<td>3.79</td>
<td>8.60</td>
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</table>

28.) Attempted oxidation of 2-phenyl-4-methyl-4-hydroxy-5,6-dihydro-4H-1,3-thiazine.

The title compound (1g., 1/200 M.) in glacial acetic acid (10ml.) was added slowly to a solution of potassium permanganate (0.32g., 3/200 M.) in water (150ml.). When the addition was complete, sulphur dioxide was passed through the solution to remove excess potassium permanganate. Ice was added to the solution but no precipitation took place. The aqueous solution was extracted with chloroform but only starting material (50mg.) was isolated. M.pt. 128-130°C. The I.R. spectrum was identical with that of the title compound.

29.) Attempted condensation of thiobenzamide with crotonaldehyde.

The condensation was carried out as described in experiment (25) using thiobenzamide (2.8g., 1/50 M.) crotonaldehyde (3ml., an excess) and boron trifluoride therate (1.5ml.) in dry ether. After twelve days the small amount of an almost black oil which had separated was worked up. The resulting oil was shown to be a complex mixture and no attempt was made to isolate any of the components.

T.L.C. 10% diethyl ether/petrolaum ether showed a continuous streak from Rf 0.0 to Rf 1.0.
30.) Methyl-4-phenyl-2-oxo-3-ene-butyrate (methyl benzalpyruvate).

To a stirred solution of pyruvic acid (17.6g., 1/5 M.) and benzaldehyde (21.2g., 1/5 M.) in methanol (10g.) was added a solution of potassium hydroxide (16.8g.) in methanol (50ml.). The first portion (35ml.) of the potassium hydroxide solution was added dropwise and the reaction mixture held at 0°C; the remainder of the solution (15ml.) was added quickly after removing the ice bath. The reaction mixture was left at 25°C. overnight and the solid which separated was filtered off. The solid was added to hydrochloric acid (50ml. 5N HCl + 75ml. of H₂O). The oil which separated was dried by azeotropic distillation with benzene.

A portion of the benzalpyruvic acid (9.5g.) was heated under reflux with methanol saturated with hydrogen chloride. On cooling, a yellow crystalline solid separated, which was filtered off and recrystallised from methanol.

Yield : 6.5g. (63%)
M.pt. : 69-71.5°C. (Lit. M.pt. 73.5-74.5°C.)

31.) Ethyl-6-phenyl-2-oxo-3,5-diene-hexyrate (Ethyl cinnamal pyruvate.)

The title compound was prepared by the method described in experiment (30).

Yield : 55%

32.) Condensation of thioacetamide (I) with methyl benzalpyruvate (II).

Compound I (0.75g., 1/100 M.) and II (1.9g., 1/100 M.)
were dissolved in n-butanol (50ml.). T.L.C. showed that no reaction had taken place after thirty hours. Boron trifluoride etherate (1ml.) was added to the reaction mixture but no precipitation took place and after five hours, the T.L.C. showed no change.

33.) Attempted condensation of penta-O-acetyl-D-gluconothioamide (I) and methyl vinyl ketone (II).

a) To a suspension of I (2g.) and II (2ml., an excess), in dry ether (100ml.) was added boron trifluoride etherate (2ml.). The suspension was shaken for twelve hours, and then shaken with an aqueous solution of sodium bicarbonate. The solid was separated by filtration and the ether solution dried (Na₂SO₄) and evaporated under reduced pressure. The filtrate and residue were crystallised from alcohol. The crystallised material (2g.) was shown to be (I) by comparison of M.pt. and 1'R. spectrum with an authentic sample.

b) The above reaction was repeated using butanol as a solvent, but once again, starting material only was recovered.

c) The first reaction was repeated, heating under reflux for three hours. After neutralisation, gluconothioamide (65%) was isolated by chromatography.

34.) Attempted condensation of penta-O-acetyl-D-gluconothioamide (I) with mesityl oxide (II).

a) Compound I (2g.) and II (2ml., an excess) were dissolved in dry diglyme (20ml.) and boron trifluoride etherate (0.5ml.) added. After twelve hours the reaction mixture was poured into iced water, neutralised with sodium bicarbonate and extracted.
with chloroform. The chloroform was evaporated and the residue recrystallised from alcohol. The product was shown to be (I) by comparison of M pt. and I.R. spectrum with an authentic sample.

b) The reaction was repeated using hydrobromic acid (2ml., 47%) as a catalyst. Unreacted sugar thioamide (60%) was recovered.

35.) Attempted condensation of penta-O-acetyl-D-gluconothioamide (I) and methyl benzalpyruvate (II).

a) Compound I (2.1g., 1/200 M.), II (0.95g., 1/200 M.) and boron trifluoride etherate (1.5ml.) in dry dioxan (50ml.) were left at room temperature for four days. No precipitation took place and the T.L.C. showed no change.

b) The above experiment was repeated except that the solution was saturated with dry hydrogen chloride at 0°C. and no boron trifluoride etherate was used. After eighteen hours T.L.C. showed some reaction had taken place. On evaporating the solvent and neutralising, a solid which was soluble in chloroform and water, and smelt strongly of hydrogen sulphide, was isolated. On T.L.C. considerable smearing took place and no definite spots could be seen. Chromatography was not attempted.

36.) Attempted condensation of penta-O-acetyl-D-gluconothioamide (I) and ethyl cinnamalpyruvate (II)

Compound I (2.1g., 1/200 M.) and II (1.1g., 1/200 M.) were dissolved in n-butanol and allowed to stand for one week. The solvent was evaporated off under reduced pressure leaving
a dark viscous oil. No distinct spots were evident on T.L.C., only a continuous smear.

Chromatography was not attempted.

37.) Attempted condensation of 1-bromo-tetra-O-acetyl-α-D-glucopyranose (I) with 2-phenyl-4-methyl-5,6-dihydro-4-hydroxy-1,3-thiazine (II).

Compound II (2.1g.), activated silver carbonate (4g.) and anhydrous calcium sulphate in t-butanol (100ml.) and acetone (50ml.) were shaken together for half an hour in darkness. Compound I (3.5g.) was added and the reaction mixture shaken for a further twenty-four hours. The solvent was evaporated under reduced pressure and the residuo crystallised from diethyl ether. The crystalline material (1.4g., 66%) was identical to compound (II). The residual material was shown by T.L.C. to be essentially a mixture of compound (II) and one unknown material. This material was chromatographed on silica (eluent- petroleum ether changing to 50% diethyl ether/petroleum ether). The major component, a white crystalline solid, was identified as O-t-butyl-tetra-O-acetyl-β-D-glucopyranose.

Yield : 1.2g. (32%)


I.R. spectrum (cm⁻¹) : 1750 s., (OAc)

n.m.r. Spectrum (CDCl₃)T: H₁H₂H₃H₄m., 5 (4 protons); H₆H₆’m., 5.85 (2 protons); H₇m., 6.3 (1 proton); OAc s., 8.0 (12 protons) and t-butyl s., 8.78 (9 protons).
38. Condensation of thiobenzamide (I) with $\alpha,\beta$-dibromobenzalacetophenone (II).

a) Compound I (1.37 g., 1/100 M.), II (3.58 g., 1/100 M.) and sodium carbonate (2 g.) in ethanol (50 ml.) were heated under reflux for two hours. After cooling, chloroform (10 ml.) was added and the solution filtered. The filtrate was dissolved in dilute nitric acid and on addition of silver nitrate solution, silver bromide precipitates. The chloroform-soluble fraction was chromatographed on silica (100 g.). $\alpha$-Bromo-benzalacetophenone (2.5 g., 87%), M.pt. 40-42°C. (Lit M.pt. 42-44°C.), was isolated.

b) Compound I (2 g., 40% excess) and II (3.6 g., 1/100 M.) were heated under reflux in absolute ethanol (50 ml.) for four hours. T.L.C. showed that not all the thiobenzamide had reacted. The reaction mixture was chromatographed on silica (200 g.) using 5% (increasing to 30%) diethyl ether/petroleum ether as eluent. A partial separation of the mixture of products was achieved. The yields quoted are those of pure material isolated and no attempt to estimate the composition of mixed fractions was made.

The first fraction isolated was identified as 3,5-diphenyl-1,2,4-thiodiazole. The I.R. and n.m.r. spectra were identical with those of an authentic sample.

Yield : 6%


U.V. spectrum $\lambda_{max}$ 256 m$\mu$, $\varepsilon_{max}$ 66,500
Elemental Analysis

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<td>70.85</td>
<td>4.84</td>
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The second fraction isolated was identified as α-bromobenzalacetophenone by comparison of its T.L.C. behaviour and I.R. spectrum with that of an authentic sample.

Yield : 16%

The third fraction was identified as 3-β-benzoyl-1,3-diphenyl-propan-1-one by comparison of its I.R. and n.m.r. spectra with those of the material isolated from experiment (27a).

Yield : 5%
M.pt. : 111-112°C.

Elemental Analysis

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<tr>
<td>Found</td>
<td>76.36</td>
<td>5.16</td>
</tr>
</tbody>
</table>

The fourth fraction isolated has not been identified.

Yield : 2%
Decomposition pt. : 136°C.

I.R. spectrum (cm\textsuperscript{-1}) : 3500 s. (OH), 1680 s., 1590 m. and 1580 m.

U.V. spectrum : λ\textsubscript{max} 291 m\textsubscript{μ}, ε\textsubscript{max} 9600 (based on M.wt. of 320).

Elemental Analysis

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required for C\textsubscript{24}H\textsubscript{22}S\textsubscript{2}O\textsubscript{3}</td>
<td>68.25</td>
<td>5.21</td>
<td>15.17</td>
</tr>
<tr>
<td>Found</td>
<td>69.05</td>
<td>5.28</td>
<td>14.91</td>
</tr>
</tbody>
</table>

The last pure fraction isolated was thiobenzamide.
Recovery : 48%

39.) 3,5-Diphenyl-1,2,4-thiadiazol.

A solution of thiobenzamide (2.8g., 1/50 M.) and
iodine (2.52g., 1/50 M.) in absolute alcohol (100ml.) was
allowed to stand at 25°C. for three hours and then heated
under reflux for a further hour. The excess iodine was
reduced with sodium thiosulphate and the solution
neutralised with sodium bicarbonate. The solution was
filtered and the ethanol evaporated off under reduced
pressure. The residue was extracted with chloroform.
The chloroform layer was washed with water, dried over
magnesium sulphate and the solvent was evaporated. The
residue was recrystallised from diethyl ether/petroleum
ether. The first material to crystallise (1.8g., 64%) was
identified by its T.I.C. and I.R. spectrum as
thiobenzamide. On standing, a second fraction
crystallised out and was identified as 3,5-diphenyl-1,2,4-
thiadiazol.

Yield : 0.6g. 25%

40.) Condensation of thiobenzamide with ethyl-\(\beta\)-iodopropionate.
a) Thiobenzamide (2.6g.) and ethyl-\(\beta\)-iodopropionate (46g.)
were refluxed in ethanol for eight hours. The ethanol was
removed on a rotary evaporator and chloroform added to the
resulting material. A white crystalline solid separated
which gave a positive test for halogen. This solid was
neutralised by treatment with aqueous sodium bicarbonate and then extracted with chloroform. The chloroform layer was washed with water, dried over magnesium sulphate and the solvent evaporated. The residue (benzamido) was recrystallised from petroleum ether (60-80).

Yield : 78%
Mixed M.pt. with benzamide : 123-127°C.

Elemental Analysis

Required for C₇H₇NO

<table>
<thead>
<tr>
<th>Element</th>
<th>Found</th>
<th>Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>11.95</td>
<td>11.56</td>
</tr>
</tbody>
</table>

b) The experiment was repeated using pyridine as a solvent and heating for three hours. The solvent was removed on a rotary evaporator. T.L.C. (diethyl ether/petroleum ether); Reaction mixture Rf 0.5 (with tailing) and Rf 0.0; thiobenzamide Rf 0.5; ethyl-A-iodopropionate Rf 0.9.

The thiobenzamido was separated by column chromatography on silica using diethyl ether/petroleum ether (50/50) as the eluent. The material at Rf 0.0 was then eluted with absolute alcohol. This material was a reddish oil which gave a positive nitrogen and halogen, and a negative sulphur test. Analysis is in approximate agreement with the product being A-carboxyethyl pyridinium iodido.

I.R. spectrum (cm⁻¹): 3450 s., (OH), 3050 s., (C-H in pyridine), 2980 s., (C-H aliphatic), 1730 s., (C=O in CO₂H) and 1630 s.
Elemental Analysis

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required for $C_8H_{10}INO_2$</td>
<td>34.4</td>
<td>3.58</td>
<td>5.02</td>
</tr>
<tr>
<td>Found</td>
<td>34.4</td>
<td>4.96</td>
<td>4.88</td>
</tr>
</tbody>
</table>

(In an initial experiment, pyridine and ethyl-\(\beta\)-iodopropionate had been allowed to stand at room temperature and no pyridinium compound was formed.)

c) The experiment was repeated on 1/100M. scale. In this experiment ethanol was used as the solvent and sodium acetate (4.2g., 5/100M.) was added to neutralise any hydriodic acid formed in the reaction. The reaction mixture was heated under reflux for twelve hours. T.L.C. showed that thiobenzamide was still present. The solvent was removed by distillation and it was noted that the distillate smelt strongly of ethyl acrylate. G.L.C. on silicone oil at 80°C confirmed the presence of ethyl acrylate. The solid that remained after removing the solvent was extracted with chloroform. The residue was dissolved in nitric acid and silver nitrate added. The silver iodide which precipitated was filtered and weighed. Wt. of AgI = 160 mg. (Theoretical yield of AgI for 100% reaction = 215mg.) (Silver acetate is relatively soluble in water—Ag\(\text{Ac}\) = 0.72g/100ml. H\(_2\)O; AgI = 3 x 10\(^{-7}\) /100ml. H\(_2\).)

d) The experiment was repeated on 1/100M. scale, dry acetone (50 ml) was used as the solvent and dry barium carbonate (1.97 g. 1/100M.) added to neutralise any hydriodic acid formed. After heating under reflux for five days, T.L.C. (30% diethyl ether/petroleum ether) showed a trace of a new material. The barium carbonate was separated and the solvent removed, leaving a pale yellow solid, which was crystallised from methanol.
Yield: 15 mg.

I.R. spectrum (cm\(^{-1}\)):
- 3060 w (C-H aromatic, 1600 m.
- and 1590 m. (C=O aromatic), and 745 s. and 695 s. (mono-subst. aromatic C-H deformation.)

U.V. spectrum: \( \lambda \max \) 270 mfl. \( \epsilon \max \approx 40000 \)

41. Attempted condensation of penta-O-acetyl-D-glucosethiocamide (I) with ethyl-\( \beta \)-iodopropionate (II)

The condensation between I (2.1g., 1/200M.) and II (1.1g., 1/200 M.) was attempted using the conditions described in experiment (40d). The mixture was heated for six hours under reflux; T.L.C. showed no change in the reaction mixture and compound (I) was recovered in good yield.

42. 2-Phonyl-5,6-dihydro-4H-1,3-thiazine.

Thiobenzamide (2g.) and 1-bromo-3-chloropropane (20g.) were heated under reflux for three hours. More than a mole-equivalent of hydrogen chloride was evolved during this time. The solution was allowed to cool and extracted with water. The aqueous extract was made alkaline (sodium hydroxide) and extracted with ether. The other was evaporated and the residue recrystallised from aqueous alcohol.

Yield: 1.85g. (72%)


I.R. spectrum (cm\(^{-1}\)). 3060 w. and 3010 w (C-H aromatic)
- 1615 m., 1605 m. and 1580 m. (C=N and C=C aromatic).

n.m.r. Spectrum (CDCl\(_3\))\( _7 \): aromatic protons m., 2.2 and 2.6 (5 protons); H\(_4\)H\(_4\)t., 6.13 (2 protons); H\(_5\)H\(_6\)t.,
6.95 (2 protons) and H$_2$H$_2$'q., 8.20 (2 protons).

43.) Attempted condensation of penta-O-acetyl-D-
     gluconothioamide (I) with 1-bromo-3-chloropropane. (II).

Compound I (2g.) and II (10g.) were heated under reflux
but no HCl was evolved. The reaction mixture was worked
up as described in experiment (42). Only a black intractable
solid was isolated.

44.) Attempted condensation of tetra-O-acetyl-L-
     arabonothioamide (I) with ω-phonacyl bromide (II).

To a stirred solution of I (1.7g., 1/200M.) and anhydrous
sodium acetate (3g.) in glacial acetic acid (25ml.) at 50°C.
was added, dropwise, compound II (1g., I/200M.) in glacial
acetic acid (5ml.). The reaction mixture was held at 50°C.
for one hour after the addition was complete, and then poured
into an ice/water mixture (150 ml.). The resulting syrup
failed to crystallise. T.L.C. showed the major spot at
Rf 0.85 and minor spots at Rf 0.90 (II) and Rf 0.55 (I).
The syrup (400mg.,) was chromatographed on silica. The
major fraction (350mg.) a syrup, was essentially the
component Rf 0.85 together with traces of (I) and (II).
I.R. spectrum (cm$^{-1}$) : 3470 w., 3090 w., 3070 w. and
3030 w. (C - H aromatic); 2970 w., 2930 w. (C - H aliphatic);
1750 s. (OAc); 1690 m., 1650 m. and 1600 w. (C= C aromatic).

n.m.r. Spectrum (CDCl$_3$): aromatic protons m., 2.2 and
2.6 (5 protons); d., 3.58 (0.3 protons); q., 4.15 (0.3 protons);
b.m., 5.8 (1.3 protons); b.m., 6.4 (0.7 protons); s., 7.35
(0.7 protons); and several s. around 7.9 (6 protons).
U.V. spectrum (methanol): $\lambda_{\text{max}}$ 265\(\text{nm}\), $\epsilon_{\text{max}}$ 13,000, and $\lambda_{\text{max}}$ 305\(\text{nm}\), $\epsilon_{\text{max}}$ 9,400 ($\epsilon_{\text{max}}$ based on mol.wt of 450).

Elemental Analysis

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required for C(<em>{21})H(</em>{23})NO(_3)S</td>
<td>56.12</td>
<td>5.16</td>
<td>3.12</td>
</tr>
<tr>
<td>Found</td>
<td>56.59</td>
<td>5.53</td>
<td>5.15</td>
</tr>
</tbody>
</table>

45.) Attempted condensation of penta-O-acetyl-D-gluconothioamide (I) with p-nitrophenacylbromide (II).

Compound I (2.1g., 1/200M.) and II (1.3g., 1/200M.) were reacted together under the conditions described in experiment (44). The resulting syrup was chromatographed on silica. The major component (Rf 0.70, 10% ethanol/benzene) was contaminated with a small amount of a second material (Rf 0.55) which was neither of the starting materials.

Yield : 1.8g.

I.R. spectrum (cm\(^{-1}\)): 3470 w.; 3090 w.; 3070 w. and 3040 w. (C - H aromatic); 2980 w. and 2930 w. (C - H aliphatic); 1750 s. (O\(_\text{Ar}\)); 1690 m., 1660 m. and 1600 m. (C - C aromatic).

n.m.r. Spectrum (CDCl\(_3\))

- Aromatic protons two d., 1.72 and 2.10 (4 protons, typical A\(_2\)B\(_2\) pattern); m., 2.75 (2 protons); m., 4.2 ($\frac{1}{2}$ proton); m., 4.7 ($\frac{1}{2}$ proton); m., 5.7 (2 protons); m., 6.4 ($\frac{1}{2}$ proton); s., 7.3 (2 protons); s., 7.83 and 7.95 (6 protons).

U.V. spectrum (methanol): $\lambda_{\text{max}}$ 265\(\text{nm}\), $\epsilon_{\text{max}}$ 16,000 and $\lambda_{\text{max}}$ 311m, $\epsilon_{\text{max}}$ 12,700 ($\epsilon_{\text{max}}$ based on mol.wt. of expected 2-aldono-thiazolo).
Elemental Analysis

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required for C_{24}H_{26}N_{2}O_{12}S</td>
<td>50.88</td>
<td>4.59</td>
<td>4.95</td>
<td>5.65</td>
</tr>
<tr>
<td>Found</td>
<td>53.01</td>
<td>5.19</td>
<td>5.42</td>
<td>4.48</td>
</tr>
</tbody>
</table>

46.) 2-(D-glucopyranosylpentyl)-4-p-bromophenyl-thiazole.

a) Penta-O-acetyl-D-glucopyranosamide (2.1g., 1/200M.) and anhydrous sodium bicarbonate (1g.) were heated under reflux in dry acetone (25ml.). To this stirred solution was added dropwise, 4'-bromophenacyl bromide (1.4g., 1/200M.) in dry acetone (10ml.). The reaction mixture was heated under reflux for twelve hours and then decolorised with charcoal and evaporated under reduced pressure to dryness. The residue was extracted with chloroform and filtered. The chloroform was removed and the residue recrystallised from alcohol.

Yield : 2.4g. (82%) 
M.pt. : 118-120°C.

I.R. spectrum (cm\(^{-1}\)) : 3110 w. (C - H aromatic) and 1750 s. (OAc).

n.m.r. Spectrum (CDCl\(_3\)) \(\delta\): aromatic protons two d., 2.25 and 2.40 (4 protons, \(J_{AB} = 9\text{c/s}\)); \(H_5\) s., 2.55 (1 proton); \(H_2\') d., 3.75 (1 proton); \(H_3\)' q., 4.10 (1 proton); \(H_4\)' q., 4.55 (1 proton); \(H_5\)' s., 4.85 (1 proton); \(H_6\)' s., sp., 5.8 (2 protons); \(OAc\)' s., 7.85 , 7.87 , 7.93 and 8.02 (15 protons). The n.m.r. spectrum was also examined in DMSO and at various temperatures.

U.V. spectrum (methanol) : \(\lambda_{\max} 260\text{m\(\mu\)}, \epsilon_{\max} 17,800\).
Elemental Analysis

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>Br</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required for C\textsubscript{24}H\textsubscript{26}BrNO\textsubscript{10}\textsubscript{S}</td>
<td>48.00</td>
<td>4.36</td>
<td>2.33</td>
<td>13.31</td>
</tr>
<tr>
<td>Found</td>
<td>47.79</td>
<td>3.94</td>
<td>2.13</td>
<td>11.23</td>
</tr>
</tbody>
</table>

b) Experiment (46a) was repeated using methanol as the solvent.

Yield: 48%  

c) Experiment (46b) was repeated on 1/200N. scale; samples (2ml.) were withdrawn, diluted (to 25ml.) and examined by U.V. spectroscopy, using a Unicam S.P. 800 and a Hilger Watts Uvispec. The data is summarised in Table ii.

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>Absorbance (260\textmu m)</th>
<th>Absorbance (219\textmu m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.326</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.130</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1.010</td>
<td>0.728</td>
</tr>
<tr>
<td>15</td>
<td>0.860</td>
<td>0.760</td>
</tr>
<tr>
<td>20</td>
<td>0.780</td>
<td>0.780</td>
</tr>
<tr>
<td>25</td>
<td>0.620</td>
<td>0.804</td>
</tr>
<tr>
<td>30</td>
<td>0.525</td>
<td>0.804</td>
</tr>
<tr>
<td>53</td>
<td>0.715</td>
<td>0.816</td>
</tr>
<tr>
<td>69</td>
<td>0.780</td>
<td>0.736</td>
</tr>
<tr>
<td>89</td>
<td>0.880</td>
<td>0.748</td>
</tr>
</tbody>
</table>

* Average of five determinations.

Table ii

47). 2-(D-gluco-penta-0-acetylpentyl)-4-phenyl-1,3-thiazole.

The title compound was prepared using the conditions described in experiment (46b) and recrystallised from aqueous alcohol.
Yield : 42%

I.R. spectrum (cm\(^{-1}\)) : 3100 w. and 3070 w. (C – H aromatic); 1750 s., (OAc); 1600 w. and 1580 w. (C = C aromatic).

n.m.r. Spectrum (CDCl\(_3\)) : aromatic protons m., 2.1 and 2.2 (5 protons); H\(_5\)' s., 2.50 (1 proton); H\(_2\)' d., 3.7 (1 proton); H\(_3\)' q., 4.05 (1 proton); H\(_4\)' q., 4.5 (1 proton); H\(_5\)' o., 4.8 (1 proton); H\(_6\)'H\(_6\)' sp., 5.8 (2 protons); OAc s., 7.84, 7.86, 7.92 and 8.00 (15 protons).

U.V. spectrum (methanol) : \(\lambda_{\text{max}}\) 255\(\mu\mu\), \(\epsilon_{\text{max}}\) 16,200

Elemental Analysis

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required for C(<em>{24})H(</em>{27})NO(_{10})S</td>
<td>55.28</td>
<td>5.22</td>
<td>2.69</td>
<td>6.15</td>
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<tr>
<td>Found</td>
<td>55.69</td>
<td>5.84</td>
<td>2.52</td>
<td>5.60</td>
</tr>
</tbody>
</table>

48. \(2-(\beta\text{-gluco-penta-0-acetylpentyl})-4-\beta\text{-methylphenyl-1,3-thiazol}\)

The title compound was prepared using the conditions outlined in experiment (46a) and recrystallised from aqueous alcohol.

Yield : 90%
M.pt. : 80-81.5°C.

I.R. spectrum (cm\(^{-1}\)) : 3100 w. (C – H aromatic); 1750 s. (OAc).

n.m.r. Spectrum (CDCl\(_3\)) : aromatic protons two d., 2.1 and 2.8 (4 protons); H\(_5\)' s., 2.60 (1 proton); H\(_2\)' d., 3.7 (1 proton); H\(_3\)' q., 4.05 (1 proton); H\(_4\)' q., 4.5 (1 proton); H\(_5\)' m., 4.8 (1 proton); H\(_6\)'H\(_6\)' q., 5.8 (2 protons); CH\(_3\)' s., 7.62 (3 protons); OAc s., 7.85, 7.87, 7.93 and 8.01 (15 protons).

U.V. spectrum (methanol) : \(\lambda_{\text{max}}\) 255\(\mu\mu\), \(\epsilon_{\text{max}}\) 16,600
Elemental Analysis

<table>
<thead>
<tr>
<th>Element</th>
<th>Required</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>56.12</td>
<td>56.21</td>
</tr>
<tr>
<td>H</td>
<td>5.45</td>
<td>5.30</td>
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<tr>
<td>N</td>
<td>2.61</td>
<td>2.76</td>
</tr>
<tr>
<td>S</td>
<td>5.97</td>
<td>5.65</td>
</tr>
</tbody>
</table>

49) \(\text{2-(D-gluco-penta-hydroxypentyl)-4-p-nitrophenyl-1,3-thiazole.}\)

The title compound was prepared using the conditions described in experiment (46b). In this reaction deacetylation took place. The reaction was repeated using the conditions described in experiment (46a) but deacetylation took place under these conditions also. The compound was recrystallised, with difficulty, from aqueous alcohol.

Yield : 56%

Decomposition pt. : 180°C.

I.R. spectrum (cm\(^{-1}\)) : 3350 s. (OH); 3120 w. (C - H aromatic) and 1665 m. (C = C aromatic).

n.m.r. Spectrum (DMSO \(d_6\)) : \(H_5\) s., 1.62 (1 proton); aromatic protons b.s., 1.7 (4 protons); \(H_2\) d., 4.95 (1 proton) OH b.s., 5.45 and 5.95 (5 protons; exchange with \(D_2O\)); \(H_3'H_4'H_5'H_6'H_6'\) b.s., 6.45 (5 protons)

U.V. spectrum (methanol) : \(\lambda_{\text{max}}\) 315 m\(\mu\), \(\epsilon_{\text{max}}\) 12,000

Elemental Analysis

<table>
<thead>
<tr>
<th>Element</th>
<th>Required</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>47.20</td>
<td>46.69</td>
</tr>
<tr>
<td>H</td>
<td>4.50</td>
<td>5.08</td>
</tr>
<tr>
<td>N</td>
<td>7.87</td>
<td>8.20</td>
</tr>
<tr>
<td>S</td>
<td>8.99</td>
<td>8.34</td>
</tr>
</tbody>
</table>

50.) \(\text{2-(D-galacto-penta-O-acetylpentyl)-4-phenyl-1,3-thiazole.}\)

The title compound was synthesised using the conditions described in experiment (46a) and recrystallised from aqueous alcohol.
Yield : 96%
M.pt. : 120.5-121.5°C.

I.R. spectrum (cm⁻¹) : 1740 s. (OAc).
n.m.r. spectrum (CDCl₃)γ: aromatic protons m., 2.15 and 2.65 (5 protons); H₅ s., 2.60 (1 proton); H₂' d., 3.65 (1 proton); H₃' q., 4.2 (1 proton); H₄' q., 4.5 (1 proton); H₅' m., 4.7 (1 proton); H₆'H₆'' two q., 5.9 (2 protons); OAc s., 7.82, 7.87, 7.95, 8.00 and 8.09 (15 protons).

U.V. spectrum (methanol): λ max 253μμ, ε max 16,200

Elemental Analysis

<table>
<thead>
<tr>
<th>C</th>
<th>H</th>
<th>N</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required for C₂₄H₂₇NO₁₀S 55.28</td>
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<td>2.69</td>
<td>6.14</td>
</tr>
<tr>
<td>Found 55.48</td>
<td>4.93</td>
<td>3.18</td>
<td>6.15</td>
</tr>
</tbody>
</table>

5l) 2-(D-galacto-penta-0-acetylpentyl)-4-p-bromophenyl-1,3-thiazole.

The title compound was synthesised using the conditions described in experiment (46a). The syrup isolated in this experiment was chromatographed on silica (100g.) using 10% (increasing gradually to 30%) diethyl ether/petroleum ether.

The major component, a syrup, (which showed some tailing on T.L.C.) failed to crystallise. A portion (100mg.) of the syrup was rechromatographed by P.L.C. but still failed to crystallise.

Yield : 47%

I.R. spectrum (cm⁻¹) : 3020 w. (C - H aromatic); 2970 m., 2940 w. and 2860 w. (C - H aliphatic); 1760 s. (OAc) and 1580 m. (C = C aromatic).

n.m.r. Spectrum (CDCl₃)γ: aromatic protons two d., 2.25 and 2.45 (4 protons); H₅ s., 2.55 (1 proton); H₂' d., 3.65 (1 proton)
H₃ 'q., 4.2 (1 proton); H₄ 'q., 4.45 (1 proton); H₅ 'm.,
4.65 (1 proton); H₆ 'H₆'' two q., 5.85 (2 protons); OAc s.,
7.80, 7.84, 7.93, 7.98 and 8.07 (15 protons).

Elemental Analysis
C     H     N     S
Required for C₂₄H₂₆BrNO₁₀S 48.00 4.33 2.33 5.33
Found  47.69 4.69 2.56 4.85

52.) 2-(1-arabino-tetra-O-acetylbuty1)-4-p-bromophenyl-
1,3-thiazole.

The title compound was synthesised using the conditions
described in experiment (46a) and recrystallised from aqueous
alcohol.

Yield: 55%
M.pt.: 91-94°C.
I.R. spectrum (cm⁻¹): 1760 s. (OAc).

n.m.r. Spectrum (CDCl₃) γ: aromatic protons two d., 2.25
and 2.5 (4 protons); H₅ s., 2.60 (1 proton); H₄' d., 3.6
(1 proton); H₃ ' q., 4.2 (1 proton); H₄' sp., 4.7 (1 proton);
H₅ 'H₅'' q., 5.75 (2 protons); OAc s., 7.83, 7.93, 7.95 and
8.03 (12 protons).
U.V. spectrum (methanol): λ max 263μμ, E max 16,500

Elemental Analysis
C     H     N     S     Br
Required for C₂₁H₂₂BrNO₈S 47.73 4.17 2.65 6.06 15.15
Found  47.25 4.21 3.00 5.58

53.) 2-(D-xylo-tetra-O-acetylbuty1)-4-phenyl-1,3-thiazole.

The title compound was synthesised using the conditions
described in experiment (46a). The product, a syrup, appeared
pure by T.L.C.

Yield : 81%

I.R. spectrum (cm\(^{-1}\)) : 3090 w. and 3030 w. (C – H aromatic) and 1750 s. (OA\(\delta\)).

n.m.r. Spectrum (CDCl\(_3\))\(\gamma\): aromatic protons m., 2.1 and 2.6 (5 protons); H\(_5\) s., 2.55 (1 proton); H\(_2\)' d., 3.65 (1 proton); H\(_3\)' q., 4.2 (1 proton); H\(_4\)' m., 4.7 (1 proton); H\(_5\)' H\(_5\)' two q., 5.7 and 5.85 (2 protons) and OA\(\delta\) s., 7.85, 7.9 and 7.95 (12 protons).

Elemental Analysis

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<td>S</td>
<td>7.32</td>
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54.) 2-(D-xylo-tetra-O-acetylbutyl)-4-p-bromophenyl-1,3-thiazole.

The title compound was synthesised using the conditions described in experiment (46a) and the product chromatographed on silica using 10% diethyl ether/benzene.

Yield : 70%

I.R. spectrum (cm\(^{-1}\)) : 3100 w. and 3020 w. (C – H aromatic); 2960 m. 2930 m. and 2850 m. (C – H aliphatic); 1750 s. (OA\(\delta\)) and 1590 w. (C\(=\)C aromatic).

n.m.r. Spectrum (CDCl\(_3\))\(\gamma\): aromatic proton two d., 2.3 and 2.45 (4 protons); H\(_5\) s., 2.4 (1 proton); H\(_3\)' d., 3.65 (1 proton); H\(_3\)' q., 4.2 (1 proton); H\(_4\)' m., 4.7 (1 proton); H\(_5\)' H\(_5\)' m., 5.7 (2 protons); OA\(\delta\) s., 7.8, 7.9 and 7.95 (12 protons).
Elemental Analysis

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<td>4.01</td>
<td>2.76</td>
<td>5.61</td>
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</table>

55.) Attempted condensation of penta-O-acetyl-D-gluconothioamide with chloroacetone.

The condensation was attempted using the conditions described in experiment (46a) but T.L.C. showed that no reaction had taken place after thirty hours.

56.) Attempted condensation of penta-O-acetyl-D-gluconothiamide (I) with bromoacetone.

Acetone (0.3g.) and compound I (2.1g.) were heated under reflux in chloroform/ethyl acetate (100ml. 50/50 mixture) and cupric bromide (2.2g.) added. After heating for eight hours, only 20% of the theoretical amount of hydrogen bromide had been evolved and no white cuprous bromide was evident. The solution was cooled and filtered. The black crystalline material gave a positive test for bromide and contained 22.67% copper by an iodometric titration. ($\text{CuBr}_2$ contains 26.08% Cu and $\text{Cu}_2\text{Br}_2$ contains 44.39% Cu.) The copper compound showed no strong absorption in the I.R. region; elemental analysis showed only a negligible amount of carbon and hydrogen.

The chloroform/ethyl acetate layer was washed with water, dried (sodium sulphate) and evaporated to dryness. The oily residue which remained was shown to be a complex mixture by T.L.C. containing some gluconothioamide. The I.R. spectrum showed a strong absorption in the hydroxyl region. Chromatography was not attempted.
57.) Attempted condensation of penta-O-acetyl-D-gluconothioamide (1) with chloroacetic acid.

a) A solution of I (0.5g, 1/800 H.) and chloroacetic acid (0.12g., 1/800 H.) in dry diglyme (25ml.) was warmed on a steam bath. After six hours, T.L.C. showed that no reaction had taken place. The reaction mixture was poured into ice/water and the solid which separated was recrystallised from alcohol. The recrystallised material was identical with compound I (70% recovery).

b) The reaction was repeated using alcohol as the solvent. T.L.C. showed that no reaction had taken place and compound I (55%) was recovered.

58.) Attempted condensation of penta-O-acetyl-D-gluconothioamide (1) with ethyl chloroacetate.

A stirred solution of compound I (2.1g., 1/200H.) and ethyl chloroacetate (0.6g., 1/200H.) in dry acetone (15ml.) and sodium bicarbonate (1g) were heated under reflux for thirty hours. T.L.C. showed that no reaction had occurred. The solution was filtered, evaporated to dryness and the residue recrystallised from alcohol. The recrystallised material was identical with compound I (86% recovery).

59.) Attempted condensation of penta-O-acetyl-D-gluconothioamide (1) with ethyl bromoacetate.

The condensation was carried out (1/200H.) using the conditions described in experiment (46a). T.L.C. showed that some reaction had taken place. (Product-major components Rf 0.3 and Rf 0.6, compound 1 Rf 0.3, 10%
ethanol/benzene). On chromatography (silica 5%, methanol/benzene eluent) a pale yellow syrup, Rf 0.6 (some tailing) was separated. This material (0.5g.) was not identified and may consist of more than one component but the n.m.r. and I.R. spectra are inconsistent with expected thiazol-4-one. I.R. spectrum (cm⁻¹): 3150 w; 2910 s. and 2850 s. (C-H aliphatic); 1750 s. (OAc). n.m.r. Spectrum (CDCl₃) γ: m, 4.5 (3 protons); m, 5.8 (5 protons); s., 6.45 (<1 proton); s., 6.65 (<1 proton); OAc s., 7.85 and 7.95 (15 protons) and t. (J=70/s.), 8.7 (3-4 protons).

60.) p-Methyl-β-naphacylbromide.

Carbon dioxide was bubbled through a solution of p-methylacetophenone (50g.) in glacial acetic acid (250g.) while bromine (60g.) was added dropwise. After the addition was complete, carbon dioxide was bubbled through the solution for a further twenty minutes. The reaction mixture was then warmed on a water bath for three hours. The acetic acid solution was poured into ice/water and the solid which separated was filtered, dried, distilled (88-98°C. at 1mm Hg) and recrystallised from alcohol.

Yield : 48g. (60%)

61.) Attempted acetylation of penta-O-acetyl-D-glucosothioamide (I).

a) To a stirred solution of compound I (1.6g.) and pyridine (1ml.) in dry acetone (15 ml.) was added acetyl chloride (0.5g.) in dry acetone (10ml.) After the addition was complete, the
solution was heated under reflux for thirty minutes. The reaction mixture was poured into ice/water. The syrup which separated was recrystallised from alcohol and identified as compound I (66% recovery).

b) The reaction was repeated using a longer reflux period. Only starting material was recovered.

c) To a cooled (0°C.) solution of compound I (4.1g., 1/100M.) in pyridine (10ml.) was slowly added acetic anhydride (10ml.). After sixteen hours at 0°C, a portion of the reaction mixture was poured into ice/water. The solid which separated was filtered and recrystallised from methanol/water. This material was identical with compound (I). The mother liquor was evaporated and the residue had an identical I.R. spectrum and T.L.C. behaviour with compound I (50% recovery).

After ten days the remainder of the reaction mixture was treated in the same way. The resulting syrup, which consisted of compound (I) and one other major component by T.L.C., was chromatographed on silica. The second component (50% of the mixture) was separated and recrystallised from ether. Its M.pt. (79-81°C.), I.R. and n.m.r. spectra were identical with those for penta-O-acetyl-D-glucono-nitrilo.

62.) 2,4-Diphenyl-1,3-thiazole.

A solution of thiobenzamide (2.8g., 1/50M.) and \( \text{\textalpha}\)-phenacyl bromide (4g., 1/50M.) in absolute alcohol was heated under reflux for two and a half hours and then allowed to cool after reducing the volume (25ml.). The title compound separated and was recrystallised from ethanol.
Yield : 4.1g. (80%)
M.pt. : 90-92°C (Lit M.pt. 248 91-92°C.)
The n.m.r. spectrum was examined in deuterio-chloroform and 
DMSO.
63.) 2-Phenyl-4-p-bromophenyl-1,3-thiazole.
The title compound was synthesised from thiobenzamide 
and p-bromophenacylbromide using the conditions described in 
experiment (62).
Yield : 65%
M.pt. : 121-122°C.
I.R. spectrum (cm⁻¹) : 3100 w. and 3040 w. (C - H aromatic). 
Elemental Analysis

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64.) 2-Methyl-4-phenyl-1,3-thiazole
The title compound was synthesised from thioacetamide 
and phenacylbromide using the conditions described in 
experiment (62).
Yield : 50%
B.pt. : 188-194°C / 15mm Hg. (Lit. B.pt 284°C.)
The n.m.r. spectrum was examined in deuterio-chloroform and DMSO.
65.) 2-Phenyl-4-methyl-1,3-thiazole.
The title compound was synthesised from thiobenzamide 
and chloroacetone using the conditions described in experiment 
(62). The compound distilled at a bath temperature of 190°C./ 
13mm Hg. (Lit. B.pt. 190-195°C. at 15mm Hg.).
Yield : 5%
The n.m.r. spectrum was examined in deuterio-chloroform and DMSO.
66.) 2-Methyl-4-p-bromophenyl-1,3-thiazole

The title compound was synthesised from thioacetamide and p-bromophenacylbromido using the conditions described in experiment (62).

Yield : 92%  

The n.m.r. spectrum was examined in deuterio-chloroform and DMSO.

67.) Bromoacetone

Bromo (400g., 2.5M) was added dropwise to a vigorously stirred solution of acetone (380g., 5M), water (625ml.) and potassium perchlorate (75g.). Once initiated, the reaction proceeded without external heating. After the addition was complete, the reaction mixture was allowed to stand for one hour and then the lower layer separated. This layer was shaken with magnesium oxide, washed with water, dried (calcium chloride) and distilled.

Yield : 150g. (22%)

B.pt. : 50-53°C./20mmHg (Lit. B.pt. 63.5-64°C./50mmHg.).

68.) 2-Methyl-1,3-thiazole

Formamide (66g., 1.47M.) was added to a cooled suspension of phosphorous pentasulphido (67.8 g., 0.32M.) in dry dioxan (100ml.). Bromoacetone (137g.) was then added at a rate which just held the reaction mixture at reflux. After the addition was complete, the solution was heated under reflux for a further hour. Hydrochloric acid (300ml., 5M.) was added and the reaction mixture was subjected to steam distillation. After one litre of distillate had been collected, the reaction
mixture was basified by adding sodium hydroxide pellets and
the thiazole was steam distilled. The distillate was
saturated with potassium carbonate and extracted with
diethyl ether. The thiazole was isolated by distillation.

Yield: 32%
B.pt.: 48-53°C./18mm Hg. (Lit B.pt. 70°C./90mm Hg.)
The n.m.r. spectrum was examined in deutero-chloroform and
DMSO.

69.) \( \text{\textit{N}} \)-phenyl-\( \text{\textit{D}} \)-glucosylamine.

D-Glucose (36g.) and redistilled aniline (18.6g.) in
absolute alcohol (300ml.) were heated under reflux for two
hours. On cooling, the title compound separated out,

Yield: 35g. (83%)
M.pt.: 132-136°C. (Lit M.pt. is reported between 110-150°C;
the solid is amorphous)

The I.R. spectrum showed no C=N absorption.

70.) \( \text{\textit{N}} \)-o-tolyl-\( \text{\textit{D}} \)-glucosylamine.

The title compound was synthesised from D-glucose and
\( \text{\textit{o}} \)-toluidine using the conditions described in experiment (69).

Yield: 57%
M.pt.: 87-90°C. (Lit values reported between 95-110°C).
I.R. spectrum (cm\(^{-1}\)) 3300 s., (OH); 1670 m., (possibly C=N)
and 1610 m. and 1595 m. (C=C aromatic).

The title compound (5g.) was added to pyridine (35ml.) and
acetic anhydride (35ml.) at 0°C. The reaction mixture was
set aside at 0°C. for forty-eight hours and then poured into
ice/water and the solid material was separated by filtration. 

N-o-tolyl-2,3,4,6-tetra-O-acetyl-\(\beta\)-D-glucosylamine was 
recrystallised from alcohol.

Yield : 98%

M.pt. : 108.5-109.5°C. (Lit. M.pt. 109°C)

I.R. spectrum (cm\(^{-1}\)) : 3400 w., 3420 m. (NH); 1750 s. (OAc); 
1670 w., 1610 w. and 1595 w. (\(C=O\) aromatic).

n.m.r. Spectrum (CDCl\(_3\)) \(\gamma\) : aromatic protons and NH m., 3.1 
(5 protons); \(\text{H}_1\text{H}_2\text{H}_3\text{H}_4\text{m.}, 4.8 (4 protons); \text{CH}_3\) two s., 5.20 
and 5.28 (2.5 protons (the integration error may be due to the 
proximity of other peaks) slightly broadened by allylic 
coupling); \(\text{H}_5\text{H}_6\) q., 5.8 (2 protons); \(\text{H}_5\text{m.}, 6.1 (1 proton) 
and OAc s., 7.94 (\(\approx 12\) protons).

Elemental Analysis

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<td>H</td>
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<td>N</td>
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The title compound was synthesised from \(\beta\)-glucose and 
\(\beta\)-toluidine using the conditions described in experiment (69).

Yield : 56%


I.R. spectrum (cm\(^{-1}\)) : 3300 s. (OH) and 1610 w. (\(C=O\) aromatic)

Benzylidene aniline.

The title compound was synthesised from benzene and 
aniline using the conditions described in experiment (69) 
and recrystallised from absolute alcohol.

Yield : 61%


I.R. spectrum (cm\(^{-1}\)) : 3070 w. (C - H aromatic), 1630 m. (C=\(N\)
and 1595 m. and 1580 m. (C=O).

73.) **Attempted condensation of N-phenyl-D-glucosylamine with thioglycollic acid.**

N-Phenyl-D-glucosylamine (30g., 1/9 M.) and thioglycollic acid (10.2g., 1/9 M.) were heated under reflux for four hours in benzene using an entrainment technique to remove the water formed. The theoretical yield of water is 2ml. but 13.5 ml. was collected. The benzene was evaporated under reduced pressure leaving a black intractable tar which failed to decolorise with charcoal.

74.) **Attempted condensation of N-o-tolyl-D-glucosylamine with thioglycollic acid.**

The reaction was carried out as described in experiment (73). Again several mole equivalents of water was eliminated and only a black intractable tar was isolated. The reaction was repeated using N-p-tolyl-β-D-glucosylamine with the same result.

75.) **Attempted condensation of N-o-tolyl-D-glucosylamine with ethyl thioglycollate.**

The reaction was carried out as described in experiment (73) except that ethyl thioglycollate was used in place of thioglycollic acid. Water was eliminated slowly and an oil began to separate out of the reaction mixture. A sample of the oil was taken, and had an identical I.R. spectrum with N-o-tolyl-D-glucosylamine. Alcohol was added to the benzene solution until the oily layer was redissolved and the reaction mixture was heated under reflux for six hours. The major
components appeared from T.L.C. to be the starting materials. The reaction mixture was evaporated under reduced pressure and acetylated using pyridine/$\text{Me}_2\text{O}$ at 0°C. After twenty-four hours the reaction mixture was poured into ice/water but the oil which separated could not be resolved by column chromatography.

76. Attempted condensation of benzylidene aniline with ethyl thioglycollate.

The condensation was attempted (1/50H.) using the conditions described in experiment (73). After heating under reflux for twelve hours, T.L.C. showed the presence of starting materials and a trace of $N$-phenyl-2-phenyl-1,3-thiazolidine-4-one.

A crystal of p-toluenesulphonic acid was added to the reaction mixture which was then heated under reflux for nine hours. T.L.C. analysis still showed only a trace of the thiazolidone.

Boron trifluoride etherate (2ml.) was added to the cooled reaction mixture and after standing, a total of 3.2g. of a yellow crystalline solid was isolated. This material contained boron (flame test) and had an I.R. spectrum which was similar to that of benzylidene aniline with additional absorption bands at 1250 cm$^{-1}$ m. (ether) and a strong broad absorption at ca 1050 cm$^{-1}$ (B–F).

The boron complex in chloroform was treated with aqueous sodium bicarbonate, washed with water and dried (magnesium sulphate). T.L.C. (in three solvent systems) showed the product to be benzylidene aniline together with a trace of
ethyl thioglycollate but no thiazolidone. The I.R. spectrum showed a weak absorption at 1/10cm\(^{-1}\) which was absent in the original benzylidene aniline. A portion of the neutralised material (1g.) was chromatographed and benzaldehyde (50mg.), identified by I.R. spectrum and G.L.C. (silicone oil), was isolated. The only other component isolated was benzylidene aniline.

The boron complex (0.2g.) in absolute alcohol (20ml.) was shaken for twelve hours with Dc-acidide FF resin (3g., in its hydroxy form). T.L.C. showed the product to be benzylidene aniline.

77.) **Boron trifluoride complex of benzylidene aniline.**

Boron trifluoride etherate was added to a solution of benzylidene aniline in dry ether. A cream coloured solid separated which contained boron and had an identical I.R. spectrum with the boron complex isolated in experiment (76).

78.) **Attempted condensation of the boron trifluoride-benzylidene aniline complex with ethyl thioglycollate.**

Benzylidene aniline complex (0.5g.) and ethyl thioglycollate (0.5g.) in dry pyridine (25ml.) were heated on a water bath for three hours. The reaction mixture was neutralised with sodium bicarbonate, washed with water and dried (sodium sulphate). T.L.C. analysis showed only benzylidene aniline and ethyl thioglycollate. G.L.C. (silicone oil) confirmed an almost quantitative recovery of ethyl thioglycollate.

79.) **N-Anisylidene-1,3,4,6-tetra-O-acetyl-\(\delta\)-D-glucosamine.**

Glucosamine hydrochloride (4.3g., 1/50M.) was dissolved in water (50ml.) and sodium acetate (5.4g., 1/25M.) and...
anisylidene (5.4g., 1/25M.) in methanol (20ml) added. After three hours the solvent was removed and the residue washed with ether, followed by ice-cold water. N-anisylidene-β-D-glucosamine was recrystallised from alcohol.

Yield: 4.5g (71%)
M.pt.: 164-167°C. (Lit. M.pt. 166°C.)

N-anisylidene-β-D-glucosamine (4.5g.) was acetylated using pyridine (20ml.) and acetic anhydride (20ml.) at 0°C. The title compound was recrystallised from alcohol.

Yield: 5.4g. (77%)
M.pt.: 182-184°C. (Lit. M.pt. 188°C.)
I.R. spectrum (cm⁻¹): 1750 s. (OAc); 1640 s. (C=N) and 1610 s. (C=C aromatic).

n.m.r. Spectrum (CDCl₃ 40Mc/s)γ: CH=N s., 1.65 (1 proton); aromatic protons two d., 2.2 and 3.0 (4 protons); H₁d., 3.95 (1 proton), JH₁H₂ ≈ 8.0c/s; H₂H₃ m., 4.6 (2 protons); H₆H₆' m., 5.7 (2 protons); OMe s., 6.1 (3 protons); H₅m., 6.5 (1 proton); OAc s., 7.95, 8.0 and 8.1 (12 protons).

80.) Attempted condensation of N-anisylidene-1,3,4,6-tetra-O-acetyl-β-D-glucosamine (I) with thioglycollic acid.

Compound I (2.25g., 1/200M.) and thioglycollic acid (0.46g., 1/200M.) in dry benzene (50ml.) were heated under reflux using a Dean and Stark apparatus. After sixty-five hours the reaction mixture was poured into ice/water. The solid which separated was recrystallised from alcohol (1.5g, 68%) and identified as compound (I) by T.L.C., M.pt. and I.R. spectrum.

The reaction was repeated using ethyl thioglycollate. Compound (I) was recovered in high yield.

-181-
81.) 1-Phenyl-4,5:2',1'-([D-glucopyranO]-imidazolidine-2-thione

To a solution of [D-glucosamine hydrochloride (4g.) in water (100ml.) was added phenyl isothiocyanate (5ml.) in pyridine (130ml.). The solution was warmed (35-40 °C.) for two hours and the volume reduced by evaporation under reduced pressure. The material which separated was recrystallised from alcohol and identified as the title compound. The n.m.r., I.R. and U.V. spectra were examined.

Yield : 4.5g. (84%)

The title compound (1.5g.) was treated with pyridine (25ml.) and acetic anhydride (25ml.). After forty-eight hours at 0°C. the solution was poured into water. The syrup which separated was recrystallised from alcohol. The n.m.r. and I.R. spectra showed the compound to be a tri-Q-acetyl derivative.

Yield : 1.3g. (61%)
M.pt. : 166-167°C.

The title compound (0.9g.) was treated with acetic anhydride (10ml.) and perchloric acid (0.5ml. 70%) the temperature being maintained at 30-40°C. for sixteen hours. The reaction mixture was poured into ice/water and the solid which separated recrystallised from alcohol. The I.R. spectrum showed the material to be a mixture of the tri- and tetra-acetyl compounds. Two further crystallisations gave 1-phenyl-2-S-acetyl-4,5:2',1'- (tri-Q-acetyl-[D-glucopyranO]-imidazoline which was identified by I.R. and n.m.r. spectra.

Yield : 0.5g. (35%)
M.pt. : 186-188°C.

-182 -
Elemental Analysis

Required for $C_{21}H_{24}N_2O_8S$ 54.3 5.18
Found 54.7 5.88

82.) 1-p-Toly1-4-(D-arabino-tetra-hydroxybutyl)-imidazoline-2-thione $^{210}$

To a solution of 1-deoxy-1-p-toluidino-D-fructose (8.4g., 1/25M.) in hydrochloric acid, was added potassium thiocyanate (4g., 1/25M.) and aqueous alcohol (40ml., 50/50) and the solution warmed for two hours. The hot aqueous alcohol layer was decanted and the material, which separated on cooling, was recrystallised from alcohol.

Yield : 1.2g. (10%)

The title compound (1g.) was treated with pyridine (10ml) and acetic anhydride (10ml) at 0°C. for twelve hours. The material which separated on pouring into ice/water proved difficult to recrystallise.

Yield : 0.8g. (52%)
M.pt. : 70-76°C. (Lit. M.pt. 79.5-80.5°C).
ORGANO LITHIUM REACTIONS

I.) Reaction of methyl-2,3-anhydro-4,6-benzylidene-α-D-alloside (I) with pentachlorophenyl lithium.

To a cooled (0°C.), stirred solution of hexachlorobenzene (7.1g., 1/40H.) in dry benzene, under a stream of nitrogen, was added slowly lithium butyl in hexane (10ml. 1/40H.) After half an hour, a suspension of compound I (1.3g., 1/200H.) in dry benzene (100ml.) was added and a clear solution resulted. The reaction mixture was held at 0°C. for eight hours and then allowed to stand at room temperature for twelve hours. The benzene solution was then shaken with water, separated and dried. The benzene was evaporated off and the residue extracted with petroleum ether. The petroleum ether insoluble fraction (5.2g.) on recrystallation from ethanol/chloroform, melted at 214-215°C. (hexachlorobenzene M.pt.) and had an identical I.R. spectrum with hexachlorobenzene. The petroleum ether soluble fraction (2.9g.) was chromatographed on a neutral alumina column (280g., Brockman Activity I). The solvent was gradually changed from petroleum ether to benzene to ether over 290 fractions (25ml.). The first component isolated was mainly hexachlorobenzene (920mg.) identified by its I.R. spectrum. This material appeared to contain a small amount of pentachlorobenzene (I.R. bands at 1165cm⁻¹, 1085cm⁻¹, 860cm⁻¹ and 820cm⁻¹). The second major fraction (296mg.) was identified as 3,4,5,6-tetrachlorotricyclo-[6,2,2,0²,7]-dodeca-2(7),3,5,9,11-pentaene. (M.pt. 123-125°C.). The structure was confirmed by comparison of n.m.r. and I.R. spectra with those of an authentic sample. The third major fraction (700mg.) was a mixture of what
appeared to be four major components.

T.L.C. (benzene); Rf 0.7, Rf 0.5, Rf 0.4 and Rf 0.3.
(2.5% ethanol/benzene); Rf 0.9, Rf 0.6, Rf 0.5 and Rf 0.4.

These three fractions account for 66% of the material placed on the column. The four components (F₁, F₂, F₃ and F₄) from the third fraction were separated by P.L.C. (three plates, eluting with benzene).

F₁ (15mg., 5% of the material placed on the plate) was a mixture of at least three components (by T.L.C.) and no attempt to separate these was made.

F₂ (49mg. 16%) was rechromatographed and the resulting material appeared to contain only trace impurities (by T.L.C.).

I.R. spectrum (cm⁻¹): 3400 s., (OH); 3060 m. and 3020 m. (C-H aromatic); 2950 s., 2920 s. and 2850 s. (C-H aliphatic); 1710 s., 1645 m. and 1605 m.

n.m.r. Spectrum (CCl₄): m., 2.75 (20); s., 3.35 (2.5); d., 4.35 (0.8.), J=1.5c/s); broad band ca 6.0 (3); b.s. 7.0 (5).

F₃ (88mg., 29%) was rechromatographed and the syrup which was isolated examined spectroscopically.

I.R. spectrum (cm⁻¹): 3450 s. (OH); 2950 s., 2920 s. and 2850 s. (CH aliphatic); 1705 w. and 1640 s.

n.m.r. Spectrum (CDCl₃): aromatic protons m., 2.5 (5 protons); H₁s., 3.56 (1 proton); βCH s., 4.28 (1 proton); H₃H₄H₅H₆ and H₆'m., 5.5 and 6.0 (5 protons); OH b.s. 7.65 (1 proton, exchanges with D₂O) and overlapping methyl and methylene protons at 8.3-9.1 (3-4 protons).

F₄ (82mg., 27%) was shown by T.L.C. to consist of three components running closely together. These were not separated.
n.m.r. Spectrum (CDCl₃): aromatic protons m., 2.6 (7.5); s., 3.52 (<0.5); unresolved m., 5.3 - 6.2 (4.5); b.s., 7.4 (3, exchange with D₂O) and overlapping methyl and methylene protons, 8-9.2 (12).

2.) Reaction of methyl-2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (I) with pentachlorophenyl lithium.

a) The reaction (1/200M., with respect to I) was carried out as described in experiment (I) except that only a half molar equivalent excess of hexachlorobenzene was used.

The petroleum ether insoluble fraction was identified as hexachlorobenzene (1g., 50% recovery).

The petroleum ether soluble material (2.4g.) was chromatographed as described in experiment (I) and the following fractions were isolated.

The first fraction (950mg.) was recrystallised from alcohol. The first crop of crystals (110mg.) was identified as hexachlorobenzene by I.R. spectroscopy. The second crop of crystals (440mg.) was a mixture of hexa and pentachlorobenzene (M.pt. 76-90°C.) The I.R. spectrum on halo carbon oil shows C - H aromatic absorptions at 3100 cm⁻¹ and 3060 cm⁻¹.

The second fraction (150mg.) was identified by M.pt. 123-125°C. and its I.R. and n.m.r. spectra as the tetrachlorobenzene adduct.

The remaining fraction (1040mg.) consisted of two major components (T.L.C., 5% methanol/benzene- Rf 0.78 and Rf 0.66) and several minor components. The major components were separated by P.L.C.

Component I (methyl-4,6-O-benzylidene-2-deoxy-2-pentachloro-phenyl-α-D-altroside).

Yield : 50% M.Pt. 181-182°C.
I.R. Spectrum (cm⁻¹) : 3500 s., (OH); 3010 m., (C-H aromatic) -186-
and 2920 m. and 2850 m., (C-H aliphatic).

n.m.r. Spectrum (CDCl₃): aromatic protons b.s., 2.55 (5 protons); ßCH s., 4.25 (1 proton); H₁ d., 4.75 and H₂ q., 4.9 (2 protons); H₃H₄H₅H₆H₄'=m., ca 5.8 (5 protons); ßMe s., 6.65 (3 protons) and OH b.s., 8.2 (exchanges with D₂O).

\([\alpha] = -34.1^\circ \text{(CHCl₃ c 0.4)}\)

Elemental Analysis

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
<th>Cl</th>
</tr>
</thead>
<tbody>
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<td>Required for C₁₂₀H₇₇Cl₅O₅</td>
<td>46.99</td>
<td>3.30</td>
<td></td>
</tr>
<tr>
<td>Found</td>
<td>47.27</td>
<td>3.69</td>
<td></td>
</tr>
</tbody>
</table>

Component II (4,6-Ç-benzylidene-2-pentachlorophenyl-D-allal).

Yield : \(\approx 30\%\)

H.pt. : 154-156°C.

I.R. spectrum (cm⁻¹) : 3550 m., (OH); 3010 s., (C - H aromatic); 2910 w.; and 2850 w., (C - H aliphatic) and 1640 s., (C=O).

n.m.r. Spectrum (CDCl₃): aromatic protons b.s., 2.55 (5 protons); H₁ s., 3.55 (1 proton); ßCH-s., 4.25 (1 proton); H₃H₄H₅H₆H₄'=m., ca 5.7 (5 protons) and OH b.s. 7.6 (1 proton, exchanges with D₂O).

\([\alpha] = +65.4^\circ \text{(CHCl₃, c.0.8)}\)

Elemental Analysis

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<tbody>
<tr>
<td>Required for C₁₉H₁₃Cl₅O₄</td>
<td>47.27</td>
<td>2.69</td>
<td>36.80</td>
</tr>
<tr>
<td>Found</td>
<td>47.39</td>
<td>2.87</td>
<td>36.88</td>
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</table>

b) A portion of the crude product (0.190g.) was acetylated by treatment with pyridine (2ml.) and acetic anhydride (2 ml.) at 0°C. for seventy-two hours. The syrup which was isolated consisted of at least eight components by T.L.C. The crude syrup (\(\approx\)100mg) was partially resolved by P.L.C. Three major components were isolated but only one was characterised.

Component I (25mg.) was recrystallised from methanol and was shown by n.m.r. to have lost the benzylidene group. It appeared to be a mixture of two sugars; one with an ßMe group and one with...
a 1,2-double bond.

Component II (45mg., methyl-4,6-0-benzylidene-3-0-acetyl-2-deoxy-2-pentachlorophenyl-\(\alpha\)-D-altrose) was recrystallised from methanol and characterised by elemental and spectral analysis.

M.pt. : 136 - 138°C.

n.m.r. Spectrum (CDCl\(_3\))\(\gamma\): aromatic protons b.s., 2.55 (5 protons); \(\text{OCH}_3\) s., 4.25 (1 proton); \(H_1\) d., 2.75 (1 proton); \(H_2\) m., 4.9 (1 proton); \(H_3-H_6\) m., ca 5.6 (5 protons); \(\text{OCH}_3\) s., 6.65 (3 protons); \(\text{OAc}\) s., 7.9 (3 protons). The spectrum also shows methanol (possibly from recrystallisation).

\[ [\alpha]_D^0 = -24.9^0 \text{ (CHCl}_3, c.0.46) \]

Elemental Analysis

\begin{tabular}{|c|c|c|c|}
\hline
& C & H & Cl \\
\hline
Required for C\(_{22}\)H\(_{19}\)Cl\(_5\)O\(_6\) & 47.43 & 3.41 & 31.89 \\
Found & 45.74 & 3.48 & 31.40 \\
\hline
\end{tabular}

Component III (12mg) was recrystallised from methanol.

The n.m.r. spectrum showed the presence of aromatic protons and an \(\text{\(\text{n}\)-butyl group}.\)

3.) Reaction of methyl-2,3-anhydro-4,6-0-benzylidene-\(\alpha\)-D-mannoside (I) with pentachlorophenyl lithium.

The reaction was carried out as described in experiment (2) using compound I (0.65g.). The petroleum ether insoluble fraction was extracted with hot petroleum ether which, on cooling, gave compound I (200mg., 31%). The petroleum ether soluble fraction (1.4g.) was chromatographed on alumina (80g., neutral activity 1, using petroleum ether changing to benzene to methanol/benzene.). The following major fractions were isolated.
Fraction I (360 mg.) was shown by I.R. to be hexachlorobenzene together with some pentachlorobenzene.

Fraction II (220 mg.) was not identified but its n.m.r. and I.R. spectra showed that it did not contain a sugar group.

Fraction III (190 mg. 28%) was shown by n.m.r. to be methyl-4,6-O-benzylidene-α-D-altroside.


n.m.r. Spectrum (CDCl₃)γ: aromatic protons m., 2.6 (5 protons); OCH s., 4.35 (1 proton); H₁ d., 5.35 (1 proton, J=10 c/s.); H₂,H₃,H₄,H₅,H₆ and H₆' b.m., ca 6 (6 protons); OMe s., 7.6 (3 protons) and OH two d., 7.0 and 7.4 (2 protons, exchange with D₂O.).

\[ \alpha \] = 111.2° (CHCl₃, c. 0.54) (Lit. value 115°)

Elemental Analysis

<table>
<thead>
<tr>
<th>Required for C₁₄H₁₈O₆</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C 59.6</td>
<td>58.7</td>
</tr>
<tr>
<td>H 6.39</td>
<td>6.47</td>
</tr>
</tbody>
</table>

4. Reaction of methyl-2,3-anhydro-4,6-O-benzylidene-α-D-mannoside (I) with tetrachloropyridyl lithium.

Butyl lithium in hexane (1.5 ml. of a 2.5 M. solution, 3/800M.) was added to a stirred solution of pentachloropyridine (1.0 g., 3/800M.) in dry ether (50 ml.) at -15°C., under an atmosphere of nitrogen. The solution was held at -15°C. for one hour and then allowed to warm up to room temperature and a solution of compound I (0.66 g., 1/200M.) in dry ether (50 ml.) was added. The reaction mixture was heated under reflux for three hours and worked up as described in experiment (1) except that the residue was extracted with diethyl ether. The diethyl ether soluble material (1.24 g.) was chromatographed on alumina (80 g., Brookman Activity 1, eluent 25% benzene/petroluem ether changing to benzene to 1% methanol in benzene). The following major fractions were isolated.
The first fraction (130 mg.) was identified by its IR spectrum and T.L.C. behaviour as pentachloropyridine.

The second fraction (330 mg.) was shown by its I.R. spectrum and T.L.C. behaviour to be a mixture of compound I and pentachloropyridine.

The last major fraction (470 mg. 71% recovery) was identified as compound I by its I.R. spectrum and T.L.C. behaviour.

5.) Reaction of methyl-2,3-anhydro-4,6-0-benzylidene-\(\alpha\)-D-alloside (I) with 4-methyl-lithium thiazyl.

A solution of 4-methyl-1,3-thiazole (1.0 g., 0.01 M.) in dry diethyl ether (20 ml.) was added to a stirred solution of lithium butyl in hexane (5 ml. of 2.57 M., 0.0128 M.) at -50°C. under a stream of nitrogen. After thirty minutes a suspension of compound I (2.6 g. 0.01 M.) in dry diglyme (150 ml.) was added. After four hours the reaction mixture was allowed to warm up to room temperature and water (5 ml.) was added. The solution was filtered and the filtrate recrystallised from chloroform/ether (80/20). The crystallised material (2.2 g.) was identified by its I.R. spectrum as compound (I). A further quantity (200 mg.) of compound (I) was isolated from the diglyme solution on partial evaporation giving a total recovery of 92%.

6.) Reaction of 2,3;5,6-di-O-isopropylidene-\(\alpha\)-D-mannosyl chloride (I) with pentachlorophenyl lithium.

Pentachlorophenyl lithium (3/800 M.) was generated as described in experiment (1) and a solution of compound I (0.66 g., 1/400 M.) in dry diethyl ether (20 ml.) was added. After eighteen hours at room temperature the reaction mixture was worked up as described in experiment (1). The petroleum ether soluble fraction was
reduced in volume and a crystalline material separated (0.5 g.) which was twice recrystallised from petrolatum ether to give a slightly syrupy solid.

I.R. spectrum (cm$^{-1}$): 3500 m. and 3400 m. (OH); 1660 m. (C$\equiv$C$-O$) and 720 s. (C-Cl)

n.m.r. Spectrum (CDCl$_3$): H$_2$d., 4.6 (1 proton); H$_3$q., 4.9 (1 proton); m., 5.5 (2 protons); m., 5.9 (2 protons); OH b.d., 7.9 (1 proton, exchanges with D$_2$O) and methyl protons two s., 8.55 and 8.65 (6 protons).

The crystalline material was shown by T.L.C. to be a major component of the petrolatum ether layer. The bulk of the petrolatum ether soluble material and the crystallised material were combined and chromatographed on alumina (eluting with benzene changing to methanol/benzene). The following major fractions were isolated.

The first fraction (500 mg.) was shown by its I.R. spectrum to be a mixture of hexa- and pentachlorobenzene.

The second fraction (185 mg.,) was a mixture of two components (T.L.C. 5% methanol/benzene, Rf 0.56 and Rf 0.53) which darkened in colour on standing.

I.R. spectrum (cm$^{-1}$): 3450 s. (OH); 2980 s., 2920 m. (CH aliphatic); 1710 w. and 1660 w. (On standing the peaks broadened considerably).

n.m.r. Spectrum (CDCl$_3$): b.m., 5.0 - 6.2 (5); s., 7.75 (5.5); methyl groups two s., 8.55 and 8.6 (±12) and a b.s., 8.7 (±13).

The third fraction (180 mg.) was identified as 1,2,5,6-di-O-isopropylidene-β-D-mannofuranosido.


I.R. spectrum (cm$^{-1}$): 3450 s. (OH)

n.m.r. Spectrum (CDCl$_3$): H b.s., 4.6 (1 proton); H$_2$t., 5.15 (1 proton, $J_{H_2H_3}$ = 6c/s., $J_{H_3H_4}$ = 3c/s.); H$_2$d., 5.4 (1 proton);
1,2:3,4-di-0-isopropylideno-\(\alpha\)-d-galacto-hexodialdo-1,5-pyranose.

This material was prepared using the conditions outlined by Stacey and his co-workers. The crude product was distilled and the fraction distilling at a bath temperature of 172-180° C./0.6 mm Hg.) was collected. (Lit.254 bath temperature 140° C./0.15 mm Hg.). The product showed a strong absorption at 1740 cm\(^{-1}\) and no absorption in the OH region of the infra-red.

This material was reacted with pentachlorophenyl lithium and 4-methyl-lithium-thiazyl using the conditions previously described. In each case a single major component was isolated from column chromatography. A sample of this syrup was further purified by P.L.C. Analysis showed it to be 1,2:3,4-di-0-isopropylidene-\(\alpha\)-d-galactoside.

I.R. spectrum (cm\(^{-1}\)) : 3500 s. (OH); 2980 s.
n.m.r. Spectrum (\(\text{CCl}_4\))\(^{7}\): H\(_1\)=, 4.5 (1 proton); q., 5.4 (1 proton); m., 5.75 (2 protons); m., 6.35 (3 protons);
OH b.s., 6.6 (1 proton, exchanges with \(\text{D}_2\)O) and methyl protons s., 8.45 , 8.55 and 8.65 (12 protons).

Elemental Analysis

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required for (\text{C}<em>{12}\text{H}</em>{20}\text{O}_6)</td>
<td>55.37</td>
<td>7.75</td>
</tr>
<tr>
<td>Found</td>
<td>55.46</td>
<td>7.69</td>
</tr>
</tbody>
</table>

The n.m.r. spectrum of the starting material was examined; it contained no low field proton (CHO occurs at 0.28\(^{\tau}\)) but it showed the presence of an acetyl group at (7.85\(^{\tau}\)) which indicates that the starting material was 1,2:3,4-di-0-isopropylidene-6-O-acetyl-\(\alpha\)-D-galactoside.
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Analysis of ABX Systems.


Shown below is a schematic representation of the n.m.r. spectrum for the $H_4H_5H_5'$ protons in tetra-$Q$-acetyl-$D$-xylonothioamide.$(I)$

There are two ways of assigning the $AB-$ and $AB+$ quartets. These are:

\[
\begin{align*}
\text{A} & : & a & c & e & g & 1 & 3 & 5 & 7 \\
& & b & d & f & h & 2 & 4 & 6 & 8 \\
\text{B} & : & a & b & c & d & 1 & 3 & 5 & 7 \\
& & e & f & g & h & 2 & 4 & 6 & 8 \\
\end{align*}
\]

Only A gives the required intensity pattern (weak-strong-strong-weak).

From A $\frac{1}{2}|J_{AX} + J_{BX}| = 5c/s$ (separation of the mid-points of the two quartets).

$|J_{AB}| = \text{separation } 1-3 = \text{sepn. } 2-4 = \text{sepn. } 5-7 = \text{sepn. } 6-8 = 12c/s.$

$2D_+ = \text{sepn. } 1-5 = \text{sepn. } 3-7 = 18c/s.$

$2D_- = \text{sepn. } 2-6 = \text{sepn. } 4-8 = 16c/s.$

$D_+ \sin 2\theta_+ = \frac{1}{2} J_{AB}$

whence $\sin 2\theta_+ = 0.66$ and $2\theta_+ = 41^048'$ or $138^012'$. and $\cos 2\theta_+ = 0.745$ or $\cos 2\theta_+ = -0.745$.
Similarly \( D_\sin 2\theta = \frac{1}{2} J_{AB} \)
whence \( \sin 2\theta = 0.75 \) and \( 2\theta = 48^\circ 30' \) or \( 131^\circ 30' \)
and \( \cos 2\theta = 0.66 \) or \( \cos 2\theta = -0.66 \).

It is generally possible to assess which combination of angles is correct from the X part of the spectrum. In this case, X is further coupled which complicates the analysis. However, if a first order approach is permissible, the X part of the spectrum is consistent with a four lined spectrum from the AB coupling, further split by \( H_2 \).

Therefore \( \theta_{+}=41^\circ 48' \) and \( \theta_{-}=48^\circ 30' \) and the following parameters can be calculated.

\[
J_{AX} = 6.4c/s \quad J_{BX} = 3.6c/s.
\]

\( \nu_A = 22.5c/s \) (from arbitrary zero) \( \nu_B = 10.5c/s \)

A similar calculation gives the following parameters for

\( H_2 H_6' \) in \( 2-[D-\text{galacto-penta-O-acetylpentyl}]4\)-phenyl-1,3-thiazole.(II)

\( J_{AB} = 11.5c/s \quad J_{AX} = 7.1c/s \quad J_{BX} = 4.9c/s \)

\( \nu_A = 33.5c/s \quad \nu_B = 10c/s \)

Line spectra, calculated from the above values, and the observed spectra are shown in plate (XVI). The energy and intensity values are tabulated below.

<table>
<thead>
<tr>
<th>Line No.</th>
<th>Xylonothioamide (I) Energy &amp; Intensity</th>
<th>2-Galacto-thiazole (II) Energy &amp; Intensity</th>
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<tbody>
<tr>
<td>1</td>
<td>0 &amp; 0.25</td>
<td>0 &amp; 0.55</td>
</tr>
<tr>
<td>2</td>
<td>4 &amp; 0.33</td>
<td>5 &amp; 0.58</td>
</tr>
<tr>
<td>3</td>
<td>12 &amp; 1.75</td>
<td>11.5 &amp; 1.45</td>
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<tr>
<td>4</td>
<td>16 &amp; 1.67</td>
<td>16.5 &amp; 1.42</td>
</tr>
<tr>
<td>5</td>
<td>16 &amp; 1.75</td>
<td>25.5 &amp; 1.45</td>
</tr>
<tr>
<td>6</td>
<td>22 &amp; 1.67</td>
<td>32.5 &amp; 1.42</td>
</tr>
<tr>
<td>7</td>
<td>28 &amp; 0.25</td>
<td>37.0 &amp; 0.55</td>
</tr>
<tr>
<td>8</td>
<td>34 &amp; 0.33</td>
<td>44 &amp; 0.58</td>
</tr>
</tbody>
</table>
H$_6$H$_6'$ Tetra-O-acetyl-D
xylanothiocamide

Plate XVI

H$_6$H$_6'$ 2-[D-galacto-penta-O-acetylpentyl]-
4-phenyl thiazole

3 c/sec/unit