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THE METHYLATION

OF

BENZYLATED GlUCOSE MERCAPTALS.
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INTRODUCTION.

HISTORICAL DEVELOPMENT OF MONOSACCHARIDE STRUCTURE.

The central compound of the carbohydrates is glucose and it is around this substance that the chemistry of the carbohydrates and their molecular structure has been developed.

The empirical formula was early established as CH₂O and on the development of the Beckmann apparatus the true formula was shown to be C₆H₁₂O₆ by Tollens and Mayer.

Meanwhile, Kiliand (1886) had demonstrated the presence of an aldehyde group by forming the cyanhydrin, which on hydrolysis and reduction gave D-glucose. The formation of this acid also indicated that the six carbons were arranged in a straight chain.

The next major development was the introduction by Fischer of the "Fischer Projection Formula."

```
H
\|_\|\|\|\|\|\|
C = O H-C-OH H-C-OH H-C-OH H-C-OH
| | | | | |
H-C-H H-C-H H-C-H
| | | |
H-C-H H-C-H
| | |
H-C-H
| |
CH₂OH.
```

\( \text{D - glucose} \) (Fischer Projection Formula.)
This structure with four asymmetric carbon atoms and hence allowing for 2^5 or 16 optical isomers (Van't Hoff - Le Bel Theory,) accounted for the numerous optical isomers of glucose that were being reported at the time, e.g. galactose by Pasteur as early as 1856.

Development of Ring Structure:

Fischer, on treating glucose with 0.5% methyl alcohol hydrogen chloride at 30°, found that, instead of obtaining a true acetal, only one methyl group entered the molecule and hence a methyl glucoside was obtained. A year later Alberda van Ekenstein isolated a second isomeric glucoside and to explain these two glucosides Fischer adopted a ring structure that had first been suggested by Tolleens in 1883, for glucose itself. Fischer did not however extend the ring structure to glucose and for the glucoside strongly assumed a 1:4 butylene oxide ring to be present.

In 1903 E. V. Armstrong was able to show the presence of both α and β-glucose by following the enzymatic hydrolysis of α and β-methyl glucosides by polarimetric analysis.

The point of ring closure was finally established by First who studied the products of oxidation of tetramethylglucose. By means of their crystalline dioxides he identified dimethoxy succinic acid and xylo-trimethoxycotutaric acid, the presence of the latter compound indicating that the ring closure was on carbon 5 of tetramethyl glucose.
The term pyranose ring for this 1:5 ring closure was suggested in 1926 by Haworth and has been generally adopted. The pyranose ring was represented by a hexagonal formula and X-ray evidence in support of such a ring has later been obtained by Mark.\(^8\)

![Pyranose Ring]

\(\alpha\)-d-glucopyranose

In 1932, Haworth\(^9\) reported a third methyl glucoside which he showed to have a 1:4 or butylene oxide ring. For this he suggested the term furanose ring. Since then, other furanose sugars have been prepared. In general, these furanoses or \(\gamma\)-sugars are relatively unstable and can revert to the pyranose form in solution. They are represented thus:

![Furanose Ring]

\(\alpha\)-d-glucofuranose

These sugars, e.g. fructose, occur naturally in the furanose form.
Open Chain or Acyclic Sugars.

The structure of monosaccharides is not limited to the pyranose and furanose rings. Prior to 1926 acyclic sugars had not been characterised but in that year Levine and Meyer obtained a pentamethyl glucose which contained no ring in its structure. In 1929 Wolfrom obtained a crystalline aldehyde pentacetate of \( \delta \)-glucose and since then numerous other acyclic sugar derivatives have been obtained. See Page 6.

It is apparent from the following evidence that the unsubstituted sugars themselves can exist in the acyclic state:

(a). The phenomenon of mutarotation is most easily explained by consideration of an intermediate acyclic form

\[
\begin{align*}
\text{OH} & \quad \text{+H} \quad \text{HOH} \\
\text{C} & \quad \leftrightarrow & \quad \text{H} \quad \text{C} \\
\text{OH} & \quad \text{+H} \quad \text{HOH} \\
\end{align*}
\]

(b). Sarchiewski showed that a carbonyl absorption band appeared immediately on the addition of alkali to glucose and disappeared when the alkali was neutralised. It was thus postulated that the acyclic form was the intermediate in the resynthesis of sugars by alkali.
(c) Solutions of reducing sugars that are normally cyclic show the presence of potential carbonyl groups by their capacity for forming amino condensation compounds such as phenylhydrazones, oximes and semi-carbazones.

(d) A slight alkalinity is necessary for the cyanhydrin reaction and it appears from this that the acyclic form of the sugar is an intermediate compound.

(e) Aqueous solutions of the ketoses (sorbose and fructose) give absorption spectra which indicate the presence of small amounts of the acyclic form. However with aldoses the results are negative but it has been shown that the aldoses are reducible at the dropping mercury cathode. This fact has been used for the determination of the amount of aldehyde-sugar present by the method of polarographic analysis.\textsuperscript{13}

Summarising, it may be said that the free aldehyde form of glucose may be considered to be one of the important tautomeric phases of the compound. The lactal structure may be considered as a passive tautomeric phase, opening when required, to form the more reactive free aldehyde phase. The so-called \textgamma-ring forms which are best characterised in the sugar acetate series, are known to possess the property of ease of lactal rupture. Their sensitivity to reagents may then be due to the ease of formation of the open chain forms, the latter being the true reactive phases.\textsuperscript{14}
Acyl Derivatives of the Acyclic Sugars.

Numerous acyl and alkyl derivatives of the sugars have been studied through the open chain forms of the monosaccharides, two main methods of preparation being available.

(a). Oximes.

\[
\begin{align*}
\text{H}_2\text{O} & \quad \text{H-C=CH} \\
\text{H-C} & \quad \text{H-C-CH} \\
\text{HO-C-H} & \quad \text{HO-C-H} \\
\text{H-C-OH} & \quad \text{H-C-OH} \\
\text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH}
\end{align*}
\]

(d-glucose) \quad (d-glucose oxime)

Glucose oxime was first prepared by Wohl\textsuperscript{15} and this substance was later methylated by Irvine and Moodie\textsuperscript{16} to give the methyl ether of 2:3:4:6-tetramethyl-d-glucose oxime.

The acetyl derivatives were later studied by Wolf from\textsuperscript{17,18}. who found that on acetylation of galactose oxime a mixture of galactononitrile pentaacetate, aldehyde galactose oxime hexaacetate and an isomeride of the latter were obtained. On hydrolysis the aldehyde pentaacetate of galactose could be obtained.

Apart from these cases the oximes have not been used very extensively for the preparation of the acyclic sugars.
(b). Mercaptals.

\[
\text{HO-C-H} \quad \text{H-C-CH} \quad \text{C}_2\text{H}_5\text{S} \quad \text{SC}_2\text{H}_5
\]

\[
\text{H-C-OH} \quad \text{H-C-OH} \quad \text{H-C-OH} \quad \text{H-C-OH}
\]

\[
\text{CH}_2\text{OH} \quad \text{CH}_2\text{OH}
\]

(\(\alpha\)-glucose) \hspace{1cm} (\(\alpha\)-glucose diethyl mercaptal)

\(\alpha\)-glucose diethyl mercaptal was first prepared by Fischer\(^1\) and derivatives of this substance have since been used extensively for the study of straight chain sugar compounds.

In 1926 Levine and Meyer\(^10\) prepared 2;3;4;5;6 - penta-methyl-\(\alpha\)-glucose by the methylation of glucose diethyl mercaptal followed by demercaptalation. By a similar method the di-methyl acetal of 2;3;4;5;6 - pentabenzoyl-\(\alpha\)-glucose has recently been prepared in this laboratory\(^20\).

In general the acetates and benzoates of glucose diethyl mercaptal have been better characterised than the methyl derivatives and Wolfrom and coworkers have extensively studied the acetates and related compounds\(^21\). Working with keto-
fructose-1,6-bisphosphate, to from has clearly demonstrated the existence of the open chain structure in this series of compounds.\textsuperscript{22}

The benzoates have been studied by Arigl and coworkers. In 1930 Arigl and Nuhschigel\textsuperscript{23} prepared 2:3:4:5:6-penta-benzoyl glucose diethyl mercaptal by benzoylation of glucose diethyl mercaptal with benzoyl chloride in the presence of pyridine. With benzoyl chloride in the presence of sodium hydroxide (c.f. Schotten - Baumann reaction) the tetra-benzoyl compound was obtained.

\[
\begin{array}{c}
\text{I.} \\
\text{(glucose diethyl mercaptal)}
\end{array}
\]

Methylation of II followed by debenzoylation and demercaptaion produced 2-methyl glucose\textsuperscript{24} in small yield.

Arigl and Schimal\textsuperscript{25} also mercaptalated 2:3:4:5 - tetra-benzoyl-d-glucose using ethyl mercaptan and hydrochloric acid. They claimed to have obtained a mixture of three products, (1) a compound containing three mercaptal groups,
(i) a diethyl mercaptal with a free hydroxyl group on carbon atom 2 and (ii) a chlorhydrin diethylmercaptal in which the hydrochloric acid instead of the ethyl mercaptan had reacted with the free -CH group.

**Chart I**  The mercaptalation of 2,3,4,6-tetra-tert-butyld-glucose.
The formation of compound (I) is difficult to understand as in the preparation of glucose diethyl mercaptoaldehyde the mercaptalization of d-glucose only the reducing carbon atom is substituted while the remaining five free -OH groups (including carbon atom 2) remain unaffected.

Acyl Migration:

Helferich and Klein first reported the occurrence of acyl migration when acetylation of 1:2:3:6-tetraacetyl-d-glucose with Purdie's reagents they obtained 2:3:4:6-tetraacetyl-α-methyl glucoside instead of the expected 1:2:3:6-tetraacetyl-4-methyl-α-d-glucose:

Early attempts to prepare α-methyl glucose from the carboxylic esters of acetone glucose were also frustrated by the occurrence of acetyl migration.

Acetyl migration in acyclic derivatives also has been shown to take place by Wolfrom and co-workers.
They obtained the same product from the mercurialation of 2:3:4:6-tetrasacetyl d-glucose as from the detritylation of 2:3:4:5-tetrasacetyl 6-trityl glucose diethyl mercaptoethyl. Obviously a migration had occurred in one of these reactions but they were unable to determine whether the product was the 2:3:4:5- or 2:3:4:6- acetate.

There appears to be less likelihood of migration occurring when benzoyl derivatives instead of acetyl derivatives are used:

(a) Robertson and Gall found that there was no evidence of benzoyl migration during the methylation of 5-benzoyl- methylglucofuranoside.

(b) Newall, Hirst and Tesce found that on methylation of 2:3:4-triacetyl a-methyl glucose they obtained 3:4:5-triacetyl 2-methyl a-methyl glucose, i.e. an acetyl migration had occurred from carbon atom 2 to 6.

However on methylating the corresponding 2:3:4-tribenzoyl glucose, followed by hydrolysis of the benzoyl groups, the expected a methyl glucose was obtained.

However the migration of benzoyl derivatives has been reported, as has already been indicated during the mercurialation in strongly acid medium of 2:3:4:6-tetra-benzoyl d-glucose. (Brigl and Schinle, see Chart F.)
Robertson\textsuperscript{32} states that the migration is catalysed by traces of alkali. This is supported by the fact that many of the reported instances of migration appear to occur during methylation with Purdie's reagents where there are liable to be traces of free alkali associated with the silver oxide. Grigl claims that the migration also occurs in a strongly acid medium.
PRESENT INVESTIGATION

In a previous work an attempt to synthesise 5-methyl glucose had been made as follows.
Carbon atoms 2, 3, 4 and 6 of the glucose chain were blocked with acetyl groups while carbon atom 5 remained blocked by the pyranose ring. On formation of the acyclic a-mercapto carbon atom 5 was freed. Hence on methylation, followed by subsequent hydrolysis of the a-mercapto and acetyl groups, 5-methyl glucose should have been obtained provided no acetyl migration had taken place.

However it was found on methylation of the tetraacetyl glucose a-mercapto that all the acetyl groups were gradually replaced by methyl groups - an unusual and unexpected result.

In this work it was planned to investigate this phenomenon further:—

(a) By the use of benzoyl instead of acetyl derivatives, these being more stable and less liable to acyl migration.

(b) By forming the acyclic sugar through the oxime as well as the mercaptal.

(c) By the use of silver oxide, specially prepared by a modified method, for all methylations, in order to avoid any possibility of debenzylation by this reagent.
(4) By the methylation of various other related benzoyl derivatives in order to try and ascertain the cause of replacement, if any, of benzoyl groups.

Finally it was hoped, if replacement could be avoided, to prepare a monomethyl glucose and to establish its identity.

For an outline of the proposed synthesis of the monomethyl glucose see Chart II.
Proposed Synthesis of 5-methyl glucose. (Chart II.)

\[ \begin{align*}
\text{H} - \text{C} - \text{OH} \\
\text{H} - \text{C} - \text{OH} \\
\text{NO}_2 - \text{C} - \text{H} \\
\text{H} - \text{C} - \text{OH} \\
\text{H} - \text{C} - \text{H}
\end{align*} \]

\[ \begin{align*}
\text{\textit{a-}\text{d-glucose}}.
\end{align*} \]

\[ \begin{align*}
\text{Benzoyl Chloride} \\
\text{in pyridine at 0°C.}
\end{align*} \]

\[ \begin{align*}
\text{N} - \text{C} - \text{OBz} \\
\text{H} - \text{C} - \text{OBz} \\
\text{BzO} - \text{C} - \text{H} \\
\text{N} - \text{C} - \text{OBz} \\
\text{H} - \text{C} - \text{OBz}
\end{align*} \]

\[ \begin{align*}
\text{1:2:3:4:6 pentabenzoyl d-glucose} \\
\text{(mixture of \textit{a-} and \textit{b-} forms.)}
\end{align*} \]

\[ \begin{align*}
\text{Rz} = -\text{CO.C}_6\text{H}_5
\end{align*} \]

\[ \begin{align*}
\text{HBr in glacial acetic acid}
\end{align*} \]

\[ \begin{align*}
\text{N} - \text{C} - \text{Br} \\
\text{H} - \text{C} - \text{OBz} \\
\text{BzO} - \text{C} - \text{H} \\
\text{N} - \text{C} - \text{OBz} \\
\text{H} - \text{C} - \text{OBz}
\end{align*} \]

\[ \begin{align*}
\text{\textit{b-}2:3:4:6 tetra benzoyl d-glucose} \\
\text{pyranosyl bromide.}
\end{align*} \]

\[ \begin{align*}
\text{\textit{b-}2:3:4:6 -tetra benzoyl -d-glucose}
\end{align*} \]

\[ \begin{align*}
\text{\textit{b-}2:3:4:6 -tetra benzoyl -d-glucose}
\end{align*} \]

\[ \begin{align*}
\text{EtSH + HCl}_2
\end{align*} \]
\[
\text{\textit{2:3:4:6 -tetra benzoyl d-glucose - diethyl mercapto\,\,}}
\]
\[
\text{\textit{d-glucose diethyl mercapto}}
\]
\[
\text{\textit{2:3:4:6 -tetra benzoyl 5-methyl\,\,}}
\]
\[
\text{\textit{d-glucose diethyl mercapto}}
\]
\[
\text{\textit{2:3:4:6 -tetra benzoyl -}}
\]
\[
\text{\textit{5-methyl d-glucose -}}
\]
\[
\text{\textit{dimethyl acetal}}
\]
\[
\text{\textit{or}}
\]
\[
\text{\textit{2:3:4:6 -tetra benzoyl -}}
\]
\[
\text{\textit{5-methyl d-glucose}}
\]
\[
\text{\textit{dimethyl acetal}}
\]
\[
\text{\textit{2:3:4:6 -tetra benzoyl -}}
\]
\[
\text{\textit{5-methyl d-glucose}}
\]
\[
\text{\textit{d-glucose}}
\]
\[
\text{\textit{5-methyl d-glucose}}
\]
Discussion of Results.

Benzoylation of d-glucose with benzoyl chloride and pyridine gave a mixture of α- and β-1:2:3:4:6 pentabenzoyl d-glucose (I). Some of the α-form was re-crystallised from alcohol and gave m.p. 187 - 188°; [α]D^18 = 132.0 °. Levine and Meyer [J. Biol. Chem. 76, 513 (1928)] report m.p. 187° and [α]D^20 = 138.5°.

Treatment of (I) with acetic acid saturated with hydrogen bromide gave β-2:3:4:6 tetra-benzoyl d-glucose pyrrocolyl bromide (II) which crystallised from petroleum ether (b.p. 100-120°) and gave m.p. 128 - 130° and [α]D^20 = 147.5°. Fischer and Helferich [Ann. 383, 89 (1911)] report m.p. 125 - 128°, [α]D^20 = 144.0°.

This product was unstable in the crystalline state and the physical constants of a small sample had changed considerably after one month.

On shaking an acetone solution of (II) with silver carbonate in the presence of a little water β-2:3:4:6 tetra-benzoyl d-glucose (III) was formed as a glassy mass when the solvent was removed. This gave [α]D^20 = 70.2° - no. mutarotation was observed. Fischer and Noth [Ber. 51, 332 (1918)] report [α]D^20 = 70.6° for the crystalline product but for the amorphous product report a mutarotation of [α]D^20 = 40.17° → 63.29° after two hours.
For the crystalline product Fischer and Nolth report m.p. 119°, the crystals having been obtained with some difficulty from ligroin solution. Their method was applied unsuccessfully in this case but a sample of the amorphous mass had begun to crystallise after several weeks. Attempts to recrystallise this crude product were not successful except by the use of methanol from which white crystals separated out and gave m.p. 103 - 104°. Recrystallisation from the same solvent did not raise the melting point. The above authors report that there is danger of both pyridine and methanol forming compounds with tetrabenzyol glucose and it is suggested that this may have occurred to a certain extent here and hence given rise to the low melting point.

This compound, $\beta$-2:3:4:6 tetrabenzyol d-glucose, was now used as a starting material for three different approaches to the problem:

(a) Formation of the mercaptal followed by methylation.
(b) Formation of the oxime followed by methylation.
(c) Methylation of tetrabenzyol glucose itself.
(a) Formation of the Mercaptal.

Sulphuration of tetrabenzoyl d-glucose (III) by the method of Wulff gave a pale yellow syrup which crystallised from ether or methyl iodide. This product, on re-crystallisation from ether was obtained as white flakes and gave m.p. 86 - 87°, \([\alpha]_D^{15} = 643 (\text{CHCl}_3)\) and contained 62.5% benzoyl \((-\text{CO-C}_6\text{H}_5\)%). It is calculated that tetrabenzoyl d-glucose diethyl mercaptal contains 59.8% benzoyl. The product obtained (IV) was concluded to be this compound.

There appears to be no reference to this compound (IV) in the literature.

It will be noted on Page 8 that Brigg and Schinle\(^{25}\) mercaptolated the same tetrabenzoyl d-glucose using hydrochloric acid instead of zinc chloride and obtained a mixture of three compounds the most interesting of which is 3:4:5:6'-tetrabenzoyl d-glucose diethyl mercaptal in which a migration of a benzoyl group from carbon atom 2 to carbon atom 5 has taken place. This migration may have occurred under the influence of the strongly acid conditions. In the present work no such migration has apparently occurred as will subsequently be shown.

Methylation of (IV) was carried out with silver oxide and methyl iodide, the silver oxide being very carefully prepared to avoid the possibility of any moisture or free
alkali being present. Methylation of similar types of acetyl derivatives had previously resulted in replacement of the acetyl groups and it was hoped to avoid this phenomenon.

The product obtained after methylation was first isolated as a syrup and this gave on analysis, 11.85% methoxyl and 49.4% benzoyl, whereas it is calculated that tetrabenzyll monomethyl glucose diethyl mercaptaol should contain 1.3% methoxyl and 59.3% benzoyl. Apparently, in spite of the precautions taken, some replacement of benzoyl groups had taken place.

However on taking this syrup up in a small quantity of dry ether, a crystalline product was obtained in small yield and gave m.p. 155 - 156.5°, $[\alpha]_D^{14} = 35.6$ (CHCl$_3$) and methoxyl 5.65%. Hence it appears that although replacement of benzoyl groups was tending to occur it was possible to obtain a monomethyl fraction from the reaction product. This product (V) is apparently a new compound and is thought to be 2:3:4:6-tetrabenzyll 5-methyl glucose diethyl mercaptaol.

Brigl and Schinle$^{25}$ on methylation of their mercaptol-ated tetrabenzyll glucose obtained what they showed to be 3:4:5:6-tetrabenzyll 2-methyl glucose diethyl mercaptaol and this gave m.p. 98 - 89° and $[\alpha]_D^{20} = 64.33$ (acetone). This is therefore obviously not the same compound as (V) which shows that migration of a benzoyl group from carbon atom 2 to carbon atom 5 has not occurred in this case.
A sample of (V) was methylated a second time and the methoxyl on the syrup rose about 1.5% indicating that replacement was still occurring but not nearly so readily as had been reported when acetyl derivatives were used.

Demercaptalation of (V) by the method of Bascu presented some difficulty owing to the insolubility of (V) in methanol. To effect solution it was necessary to add some acetone and it was feared that this may inhibit the formation of the acetal and hence lead to polymerisation of the product.

The product crystallised from methanol and recrystallisation produced small fine needles which gave m.p. 133.5 - 134°C \([\alpha]_D^2 = 29.2\) (CHCl₃) and methoxyl 5.51%. It is calculated that tetrabenzoyle monomethyl glucose diethyl acetal contains 14.2% methoxyl while tetrabenzoyle monomethyl glucose contains 5.1%. It is apparent therefore that the acetal was not formed but at the same time polymerisation had not occurred - as indicated by the crystalline product.

This compound (VI), 2:3:4:5-tetraenzoyle 5-methyl glucose has previously not been reported.

Hydrolysis of (VI) with sodium ethoxide followed by neutralisation, evaporation and extraction of the residue with dry acetone produced an almost colourless syrup which partially crystallised spontaneously on cooling, but which crystallised more extensively when ether was added.
This product (VIII) gave m.p. 98 - 102°, and methoxyl 14.7%. It is calculated that monomethyl glucose contains 15.96% methoxyl and it was apparent therefore that a monomethyl glucose had been obtained in very small yield.

There was not enough material available for further purification save through washing with warm ether, or for a measurement of the specific rotation. Hence it is not possible to say definitely that the product is 5-methyl glucose as the possibility of benzoyl migration having taken place cannot be overlooked. If it can be assumed that migration can occur from any carbon atom to any other carbon atom in the chain, then all five monomethyl glucoses are possible products. However the following facts should be noted:-

2-methyl glucose

m.p. 157 - 158, [α] = +12 → 65.3 (H₂O)

It has been shown on Page 20 that at least up until the demercaptalation step no migration had occurred from carbon atom 2 to carbon atom 5, so it is unlikely that the product is 2-methyl glucose. There is also a large discrepancy in the melting points of (VIII) and 2-methyl glucose although recrystallisation of (VIII) would possibly elevate the m.p. to a certain amount.

3-methyl glucose

α: m.p. 160 - 161°, [α] = +104 → 55.3° (H₂O)
β: m.p. 139 - 132°, [α] = +31.9 → 55.7° (H₂O)

4-methyl glucose

5-methyl glucose

6-methyl glucose

m.p. 143 - 144° [α] = +104.5 - 58° (H₂O)

Have not been previously crystallised.
It will be noted that acyl migration is catalysed by alkali\(^{32}\) while Brígj\(^{24}\) has reported migration in a strongly acid medium. These conditions have been carefully avoided in this work by ensuring, especially during methylation and debenzoylation, that the reactants are completely dry. It is during methylation processes that most cases of acyl migration appear to have taken place.

From the above observations it appears that the final product is possibly crystalline 5-methyl glucose but confirmatory evidence is lacking and there is no evidence as to the nature of the structure, i.e. whether it is a straight chain or a furanose sugar.

(b) Formation of the oxime of tetrabenzoyl d-glucose.

The preparation of the oxime by the method of Sohl was not successful probably owing to the rather rigorous conditions under which it is carried out. It is also apparent, as is explained on page 32, that the optimum pH for oxime formation is in the region of 5.7 whereas in this preparation it was approximately 6.7. The evolution of appreciable quantities of hydrogen cyanide indicated that considerable degradation had occurred.

The method of Wolfson\(^{17}\) which was modified considerably for use with a sugar derivative which is insoluble in water was found to be quite satisfactory.
The method has the advantage that the nature of the reactants in the reaction mixture ensures that the pH will be buffered to approximately the optimum value.

The oxime (IX) obtained by this latter method gave m.p. 58 - 59°, \( [\alpha]_D^{14} = 49.5 \text{ (CHCl}_3 \text{) and benzoyl ( -CO.C}_6\text{H}_5 \text{)} 70.4° \). It is calculated that 2:3:4:6-tetra benzoyl d-glucose oxime contains 68.7% benzoyl.

No reference to this compound (IX) could be found in the literature.

Methylation of (IX) resulted in a viscous syrup which on analysis gave methoxyl 7.62%. It is calculated that 2:3:4:6-tetra benzoyl 5-methyl d-glucose oxime contains 9.70%. Apparently methylation was not complete and a further methylation raised the methoxyl to 10.91%.

It will be noticed that replacement of the benzoyl by methoxyl groups does not appear to proceed so readily in the case of the oxime as in the corresponding diethyl mercaptal.

This product (X) was taken over at this stage by a coworker for further investigation similar to that already described for the mercaptal.
(c). The methylation of 2;3;4;6 -tetrabenzyll d-glucose.

This methylation was carried out for the purpose of investigating whether any replacement of benzoyl groups would occur when a normal cyclic benzoyl derivative is methylated under similar conditions to those already used for the acyclic compounds, i.e. the mercapto and oxime.

The product obtained crystallised readily from methanol in good yield and this product (XI) on recrystallisation gave m.p. 135 - 136°, \([\alpha]_{D}^{14} = +48.6^\circ (\text{CHCl}_3)\) and methoxyl 5.65%. It is calculated that 2;3;4;6 -tetrabenzyll methyl d-glucoside contains 5.75% methoxyl; hence it is apparent that no replacement has occurred.

Fischer and Helferich [Ann. 383. 90. (1911)] report that \(\beta\)-2;3;4;6 -tetrabenzyll methyl d-glucoside gives m.p. 160 - 162° and \([\alpha]_{D}^{20} = +31 (\text{CHCl}_3)\). Recrystallisation of (XI) did not raise the melting point and two possible suggestions are offered for the discrepancy in the physical constants:

(1) (XI) may be the \(\alpha\)-glucoside as it was prepared in a very different manner to the \(\beta\)-compound of Fischer and Helferich who treated 2;3;4;6 tetrabenzyll d-glucose pyranosyl bromide (II) with methanolic hydrochloric acid.
(11) Purdie and Irvine \textsuperscript{35} state that the methyl
iodide - silver oxide method of methylation cannot be used
when the glycosidic carbon atom is unsubstituted as there
is danger of partial oxidation to the carboxylic acid.
This may have occurred to some extent here.

However the important point for the present work is
that in this type of benzoylated sugar, replacement of benzoyl
groups has not occurred on methylation with Purdie's Reagents.

\textbf{Methylation of 2\textsuperscript{3}:3\textsuperscript{4}:4\textsuperscript{5}:5\textsuperscript{6} -pentabenzoyl glucose dimethyl acetal.}

This work was carried out by a coworker (R.J. McIlroy)
to investigate the possibility of replacement on methylation
with Purdie's reagents of a fully substituted benzoyl de-
rivatives of glucose having a straight chain structure.

A crystalline product was obtained in good yield which,
on recrystallisation from ethyl acetate, gave a m.p.
79.5 - 80.5\textdegree C which was not depressed by mixing with penta-
benzoyl glucose dimethyl acetal. This indicated that the
compound is stable to methylation with Purdie's reagents.

\textbf{Methylation of 2\textsuperscript{3}:3\textsuperscript{4}:4\textsuperscript{5}:5\textsuperscript{6} Pentabenzoyl d-glucose diethyl acetal.}

Methylation of this fully substituted compound with Purdie's
reagents gave a syrup on which all attempts at crystallisation
failed. The carefully dried syrup on analysis gave methoxyl
13.1\%.
There being no free groups in the above compound the methoxyl should have been nil. Replacement had apparently taken place.

The effect on benzoyl groups when various compounds, as described above, are methylated can be tabulated as follows:

<table>
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<td>cyclic derivative (1 free -OH group)</td>
<td>no replacement</td>
</tr>
<tr>
<td>cyclic</td>
<td>(no free -OH group)</td>
</tr>
<tr>
<td>mercaptalated cyclic derivative (1 free -OH group)</td>
<td>some replacement</td>
</tr>
<tr>
<td>mercaptalated cyclic derivative (fully subst.)</td>
<td>some replacement</td>
</tr>
<tr>
<td>oxime cyclic derivative (1 free -OH group)</td>
<td>slight (if any) replacement</td>
</tr>
</tbody>
</table>

Combustion analyses were carried out on the compounds that had not previously been reported in the literature, i.e. compounds IV, V, VI, VIII and IX.

The results of these analyses are set out and discussed on Page 71.
Summary.

1. Bongobromoglucose, obtained by treating pentabenzoyl d-glucose with hydrogen bromide, was converted to β-2:3:4:6 tetrabenzoyl d-glucose by the action of silver carbonate and a little water.

2. Treatment of tetrabenzoyl d-glucose with hydroxylamine hydrochloride and potassium acetate in alcohol produced a new compound, 2:3:4:6-tetrabenzoyl d-glucose oxime. Then this compound was methylated with Purdie's reagents no. or very little, replacement of benzoyl groups by methoxy groups took place.

3. Treatment of tetrabenzoyl d-glucose with zinc chloride and ethyl mercaptan produced a new compound, 2:3:4:6-tetrabenzoyl d-glucose diethyl mercaptal. Although methylation of this produced some replacement of benzoyl groups, a crystalline fraction of tetrabenzoyl monomethyl d-glucose diethyl mercaptal was separated which on demercaptalization and debenzoylation produced a crystalline monomethyl glucose which, providing no benzoyl migration has occurred, is 5-methyl glucose.
4. Methylation, under constant conditions, of several benzoylated glucose derivatives of various types indicated that replacement of benzoyl groups by methoxyl groups occurs only in the presence of the mercaptal group or possibly in the presence of the oxime group. The presence of the acyclic structure alone does not cause replacement to occur and it appears that the sulphur atom has an activating influence on the sugar molecule.
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Discussion of Various Reactions Involved.

Reaction I. Benzoylation.

The benzoyl derivatives of the sugars were first prepared by the application of the Schotten-Baumann reaction, using sodium hydroxide and benzoyl chloride. However this does not give complete benzoylation. (Brigl and Kuhlschlegel)\textsuperscript{27}

Complete benzoylation was obtained by Fischer\textsuperscript{39} who substituted quinoline for sodium hydroxide and later improved this by the use of pyridine.

In this preparation benzoyl chloride and pyridine were used according to the directions of Levene and Meyer.\textsuperscript{40}

A mixture of the \( \alpha \)- and \( \beta \)-forms of penta benzoyl glucose is obtained but this does not interfere with later stages of the synthesis.

Reaction II. Treatment with acetic acid saturated with Hydrogen Bromide.

In this reaction the glucosidic benzoyl group is replaced with a bromine atom to give \( \beta \)-glucosyl bromide. Both the \( \alpha \)- and the \( \beta \)-penta benzoyl derivatives give the \( \beta \)-bromo compound.

The bromo and iodo acyl sugar derivatives are unstable at room temperature in the dry state and the crystals are
hence not separated from the mother liquor till just prior to commencing the next reaction.

This type of compound was originally prepared by the action of acyl bromide on glucose (Koenigs and Knorr) but the method was later improved by Fischer who treated the hexose pentabenzozate with a glacial acetic acid solution of the halogen acid. This method was used in the present work.

Reaction III. Hydrolysis of bromo compound.

The historical work on the replacement of the halogen atom by a hydroxyl group in this type of compound has mostly been carried out on the acetyl derivatives for which two methods have been commonly used.

1. An acetone solution of the tetracyl bromo compound is shaken for several days with an aqueous solution of sodium nitrite when the tetracyl sugar is obtained in 70% yield.

The overall reaction is:

\[ R.Br + NaNO_2 + H_2O \rightarrow NaBr + HNO_2 + R.OH. \]

(2) Fischer (1912) showed that if an acetone solution of acetylbromo glucose was shaken with silver carbonate in the presence of a little water, tetracycl glu-
cose was obtained.
He later applied this method to the formation of 2:3:4:6-tetra-O-benzoyl glucose with good results.

Of the two methods available, the second appears to be the more satisfactory and was chosen in this case.


Various methods have been used for the formation of sugar oximes, all of which depend on the condensation of hydroxylamine with the reducing group of the sugar. The hydroxylamine is obtained from hydroxylamine hydrochloride by treating the latter substance with such reagents as sodium ethoxide, sodium acetate, sodium hydroxide etc.

\[ \text{NH}_2\text{CH}_2\text{HCl} + \text{CH}_3\text{COONa} \rightarrow \text{NH}_2\text{OH} + \text{NaCl} + \text{CH}_3\text{COONa}. \]

Wohl originally synthesised glucose oxime by refluxing glucose with an alcoholic hydroxylamine solution prepared by the action of sodium ethoxide in isopropanol and excess hydroxylamine hydrochloride.

Fructose oxime has been prepared (Wolfson and Thompson) in aqueous solution, using hydroxylamine hydrochloride and potassium acetate for the reaction.

It has been pointed out by Mucho and Sacks that the optimum pH for the formation of oximes is in the
region of 4.7 and that the reaction proceeds with far greater speed at this temperature. This pH is readily attained by use of the sodium acetate-acetic acid buffer. It will be noticed in the second method of preparation described above that, if the potassium acetate is kept in excess, both acetic acid and potassium acetate will appear in the reaction mixture and hence the optimum pH conditions should be attained.

It is therefore apparent that the method of Wolfrom and Thompson is the more satisfactory. In this work however certain modifications were necessary due to the insolubility of acyl derivatives in water, but it was found possible to use 95% ethyl alcohol as a solvent for all the reactants.

Reaction V. Mercaptalation.

The mercaptal of d-glucose was prepared by Fischer\(^{47}\) (1894) by the reaction of ethyl mercaptan and d-glucose in the presence of concentrated hydrochloric acid as the condensing agent.

It has later been shown that zinc chlorides can also be used as a condensing agent and provided a dehydrating agent is present the method can be used successfully in the presence of acid sensitive groups. This method was
developed by Wolfson\textsuperscript{48} for use with acylated sugars and has proved very suitable in the present investigation.

**Reaction VI: Methylation.**

Various methods have been used for introducing alkyl groups into molecules having free hydroxyl groups.

Haworth\textsuperscript{50} has used dimethyl sulphate and sodium hydroxide and this method was later improved (West and Holden\textsuperscript{51}) by the use of stronger alkali and carbon tetrachloride as a solvent. The general method, however, is unsuitable in the presence of acyl groups as under the strong alkaline conditions the acyl groups are completely replaced by methoxyl groups.

Muskat\textsuperscript{52} has developed a new method of alkylation that has been used with considerable success. The compound is dissolved in liquid ammonia and metallic potassium is added. This leads to the formation of the potassium salt of the carbohydrate which on treating with excess alkyl halide yields the alkylated carbohydrate. The reaction is rapid and the yield good and this appears to be a sound method of methylation if anhydrous liquid ammonia is readily available.

The most common and probably most generally useful
method of methylation is that due to Purdie and Irvine\textsuperscript{38} using silver oxide and methyl iodide. Apparently the silver oxide forms an intermediate silver alcoloholate group with each hydroxyl and on further reaction with methyl iodide this is replaced by the methoxyl \((-\text{O}.\text{CH}_3\)) group. This method has the advantage of apparently not affecting the acyl groups although it has been found during the current work that special precautions must be taken during the preparation of the silver oxide to ensure that the oxide is free from both water and traces of alkali, otherwise replacement is liable to occur.

**Reaction VII:** Demercaptalation.

Fischer\textsuperscript{47} when preparing the mercaptal (thioacetal) of glucose showed that the two thioacetal groups could be removed with mercuric chloride (2 mols).

Schneider and Sepp\textsuperscript{49} later removed only one of the thioacetal groups by using exactly 1 mol of mercuric chloride. Normal sodium hydroxide solution was added from time to time to neutralise the hydrochloric acid formed during the reaction.

It is now known that the demercaptalation reaction occurs in two stages, e.g. for glucose diethyl mercaptal:
(a) $C_6H_{12}O_5(\text{SET})_2 + \text{HgCl}_2 \rightarrow \text{Cl}-\text{Hg-S-ET} + \alpha$-ethyl thio glucoside + $\text{HCl}$

(b) $\alpha$-ethyl thioglucoside $+$ $\text{HgCl}_2 \rightarrow \text{Cl}$$-$Hg-S-ET $+$ $\text{HCl} + \text{glucose}$.

In the case of glucose derivatives, the difference in reaction velocities is considerable and by choice of suitable times and temperatures the reaction can be carried to the thioglucoside stage or to completion.

When demercaptalating acylated sugars it is necessary to maintain neutrality throughout the reaction to protect the acyl groups from the liberated hydrochloric acid. Cadmium carbonate was used for this purpose by Wolfson\textsuperscript{21}, while Pascu and Green\textsuperscript{34} later used yellow mercuric oxide.

In earlier methods of demercaptalation the yields were considerably reduced by the occurrence of polymerisation through the free aldehyde group. Pascu in his method, has overcome this by carrying out the reaction in absolutesmethanol solution at a temperature of 50$^\circ$C. Under these conditions the dimethyl acetal is formed in good yield.

In this work the method of Pascu and Green has been followed.
Reaction VIII: Debenzoylation or hydrolysis of benzoylated sugar.

Benzoyl groups are more difficult to remove than the corresponding acetyl groups and cannot be removed by means of alcoholic ammonia solution.

A convenient method due to Brigl and Schinle\textsuperscript{24} is to treat the benzoylated sugar with approximately $\frac{N}{2}$ sodium ethoxide in dry alcohol for 48 hours at room temperature. The solution is then neutralised with sulphuric acid, evaporated in vacuo, and the sugar residue extracted with a suitable solvent.
Purification of Reagents and Solvents.

Ether.

Diethyl Ether (B.P.) where required dry was stood, first over calcium chloride, and after filtering, over sodium wire in a dark bottle.

Methyl Alcohol.

"Absolute" methanol (500 c.c.) was added to magnesium turnings (15 gms.) in a three litre bolthead flask fitted with a double surface reflux condenser. Iodine (5 gms.) was dissolved in 30 C.C. of methanol and carefully added to the flask which was cooled by a stream of water to control the vigorous reaction.

When this initial activity had subsided the flask was heated on a water bath till all the magnesium had been converted to the methylate. A further 2 litres of methanol were then added.

The mixture was refluxed for six hours after which period the reflux condenser was replaced with a long fractionating column and the pure methanol distilled over. The initial distillate was returned to the still and the main fraction distilling at 64.8° was collected.

\[
\begin{align*}
\text{B.P.} & = 64.8^\circ \\
\eta^D_{20} & = 1.3293. \\
c.f. \eta^D_{20} & = 1.3290, \text{ Landolt - Bornstein.}
\end{align*}
\]

"Physikalisch - Chemische - Tabellen."
Acetone.

Acetone was dried over anhydrous potassium carbonate which had previously been dried for two days in an air oven at 100 - 110°C. The dried acetone was thus stored in a dark bottle and filtered when required.

\[ \rho_\text{D}^2 = 1.3590 \]

C.f. \[ \rho_\text{D}^2 = 1.3590 \] (International Critical Tables, VII, 12).

Chloroform:

Chloroform was dried over anhydrous sodium sulphate and filtered when required.

\[ \rho_\text{D}^2 = 1.4465 \]

C.f. \[ \rho_\text{D}^2 = 1.4460 \] (International Critical Tables.)

Preparation of Various Reagents.

Methyl Iodide

Methyl alcohol (540 c.c. dry absolute) and red phosphorous (120 gms.) were mixed together in a two litre bolthead flask fitted with a reflex condenser. Iodine (1200 gms.) was added in small portions over a period of one hour, the flask being kept in a cold water bath in order to control the vigorous reaction.
When all the iodine had been added, the water bath was heated to 50°C. and the mixture refluxed gently for one hour. After standing overnight, the crude methyl iodide was distilled off and washed successively with 10% aqueous sodium hydroxide, 10% aqueous sodium thiosulphate and distilled water.

The thus purified methyl iodide was dried over calcium chloride overnight and then slowly redistilled. The product was stored in a dark bottle which was tightly stoppered and waxed.

Yield: 1055 grams. i.e. 78% Theoretical.

b.p. 41-41.5°C. \( \eta^2_\text{P} = 1.5296. \)

c.f. \( \eta^2_\text{P} = 1.5293 \)

\[ \text{Gladstone J.C.S. 59, 293. (1879)} \]

Silver Carbonate.

Silver nitrate (85 gms. 0.5 moles) was dissolved in a minimum amount of water and to this was added potassium carbonate (33 grams, 0.244 moles) dissolved in 250 c.c. of water, i.e. the silver nitrate was in slight excess of the theoretical amount. After thorough stirring the white precipitate of silver carbonate was filtered at the pump and well washed with cold water. The precipitate rapidly
turned yellow and was kept as much as possible from the light.

After thorough drying in an air oven at a temperature of 100 - 110°C, the product was stored in a glass stoppered dark bottle.

**Silver Oxide.**

Silver oxide is usually prepared by precipitating the oxide from a hot silver nitrate solution by means of a slight excess of barium hydroxide solution. However it has been found that even after extensive washing of the oxide with boiling water a positive flame test for barium can still be obtained on the dried product. Consequently the following method of preparation has been used for the present work to ensure that a thoroughly dry and alkali free oxide is obtained.

Silver nitrate (56 grams, 0.33 moles) was dissolved in 250°C.C. of hot distilled water and added to potassium hydroxide (18 grams, 0.32 moles) in 100 C.C. of hot distilled water. The precipitated silver oxide was filtered at the pump and washed with numerous portions (3 litres in all) of boiling distilled water. The precipitate was then washed once with acetone and then with either and dried on a porous plate in a vacuum oven at 80°C. for ten hours. The dry
oxide was then stored in a glass stoppered brown bottle.

Saturation of Glacial Acetic Acid
with Hydrogen Bromide at 0°C. 55

Red phosphorous (24 grams) was mixed to a sludge with
60 C.C. of water in a distilling flask fitted with a drop-
pling funnel having a long stem.

Bromine (80 C.C., 240 grams) was slowly added from the
dropping funnel and hydrogen bromide was rapidly evolved.
The gas, contaminated with bromine vapour, was passed
through a U-tube containing glass beads coated with moist
red phosphorous which absorbed the bromine. Moisture was
removed by passing the hydrogen bromide through two U-tubes
containing calcium chloride.

The hydrogen bromide was then absorbed in glacial
acetic acid (170 grams 180 C.C.). Moisture was excluded
from the absorption flask by a calcium chloride tube. A
three way tap was fitted between the absorption bottle and
the rest of the apparatus to allow the atmosphere to be
admitted to the flask should there be a tendency to "suck
back."

The absorption bottle was not surrounded by ice for
the first hour to avoid the solidification of the glacial
acetic acid. After three to four hours the acid had be-
come saturated with hydrogen bromide and was a very light yellow in colour.

A difficulty of the preparation was the slowness with which the gas first began to come over from the distilling flask after the first of the bromine had been added. This was thought to be due to the water in the flask which utilised a fair amount of hydrogen bromide in becoming saturated before any could pass over into the rest of the apparatus. In a subsequent preparation the red phosphorus was mixed with half the volume of water and the preparation was consequently carried out far more rapidly and with greater ease.

**Ethyl Bromide**

50% Hydrobromic acid (520 gms. 3.2 moles, 340 c.c.) and concentrated sulphuric acid (80 c.c.) were mixed in a one litre two necked flask fitted with a dropping funnel and double surface reflux condenser. A condenser and thermometer were fitted to the top of the reflux condenser.

95% ethyl alcohol (160 c.c.) was added and the mixture heated on a water bath till refluxing commenced. Further concentrated sulphuric acid (140 c.c.) was then added slowly through the dropping funnel.
After refluxing for two hours the water was removed from the cooling jacket of the reflux condenser and distillation of the ethyl bromide commenced through the condenser fitted to the top of the reflux.

The fraction distilling at 38 - 39° was collected in a receiver packed in ice. This distillate was washed in turn with cold concentrated sulphuric acid, sodium carbonate solution and distilled water. The resulting alcohol free ethyl bromide was dried over calcium chloride and stored in a dark bottle.

Yield: 260 grams. i.e. 72% of theoretical.

**Ethyl Mercaptan.**

The apparatus was similar to that used for the preparation of ethyl bromide. Absolute ethyl alcohol (162 C.C.) was added to a solution of thiourea (166 gms. 2.18 moles) in ethyl bromide (238 grams, 162 C.C, 2.18 moles) in the 1 litre flask. This mixture was refluxed gently on a water bath for five hours by which time the following reaction had gone to completion.

\[
\text{C}_2\text{H}_5\text{Br} + \text{NH}_2\text{C} \rightarrow \text{S} \rightarrow \text{NH}_2\text{C} - \text{S} \cdot \text{C}_2\text{H}_5\cdot\text{HBr.}
\]

(thiocuronium salt.)
The clear amber-coloured mixture obtained as above was then refluxed for a further five hours with slightly more than two equivalents of sodium hydroxide solution (90 grams in 200 C.C. of water). Hydrolysis of the thiouronium salt took place as follows:

\[
2 \text{NH}_2\text{C}_3\text{C}_2\text{H}_5\text{HBr} + 2 \text{NaOH} \rightarrow 2\text{C}_3\text{H}_5\text{SH} \\
+ \text{NH}_2\text{C}-\text{NH.CH}_2\text{OH} + 2\text{NaBr}.
\]

Ethyl mercaptan was produced as a yellow oil immiscible with the bulk of the reaction mixture. This was distilled off in similar fashion to that described for ethyl bromide, the fraction distilling at 33-34° C. being collected in a receiver surrounded by crushed ice. A trap containing alkaline potassium permanganate was attached to the apparatus to prevent the escape of the offensive odour.

The distillate was dried over anhydrous sodium sulphate. The dry ethyl mercaptan so obtained was colourless and was stored in glass stoppered bottle, the stopper being wired on and waxed.

Yield: 126 grams, i.e. 95% of Theoretical.
Experimental.

The starting material was A.R. d-glucose which, after drying in a vacuum oven at 30°-35°C, gave:

\[ \text{m.p.} = 145^\circ \]
\[ [\alpha]_D^{18} = +52.9^\circ \text{ (water, } C = 1.0 \text{ after 24 hours).} \]

c.f. d-glucose, m.p. 146°C, \([\alpha]_D^{20} = 52.7 \text{ (water, } C = 4)\)


Benzoylation: \(^\text{(18)}\)

Powdered anhydrous d-glucose (20 grams, 0.111 moles) was added to a solution of benzoyl chloride (152 grms. 1.09 moles), pyridine (84 C.C.) and chloroform (140 C.C.). The solution of benzoyl chloride was prepared by cooling each reagent to -10°C, dissolving the benzoyl chloride in an equal volume of chloroform and adding this to a solution of pyridine in 70 C.C. of chloroform.

On adding the glucose to this solution reaction set in immediately and was controlled by cooling in ice water. The sugar slowly dissolved and a deep orange solution resulted which was allowed to stand in the refrigerator for eighteen hours.

A further 70 C.C. of chloroform was then added and the solution washed successively with two portions of dilute sulphuric acid, sodium bicarbonate solution and distilled
water each of these reagents being previously cooled to 0°C. This treatment removed much of the orange colour.

The chloroform solution was dried overnight over anhydrous sodium sulphate and the chloroform then removed under reduced pressure at a temperature of 35 - 40°C. The thick syrup remaining was evaporated three times with 20 c.c. portions of alcohol under reduced pressure. The final thick syrup remaining was taken up with 100 c.c. of alcohol containing 10% pyridine and crystallisation commenced almost immediately. After standing overnight in the refrigerator a large mass of white crystals had separated out. These were recrystallised first from alcohol containing 5% pyridine and then from alcohol. The product was filtered at the pump, washed with ice cold alcohol and dried in the vacuum oven at 35°C for four hours.

Yield: 45.0 grams, i.e. 58% of theoretical. m.p. of crude material, i.e. mixture of α- and β- forms, 153 - 156°C.

A small portion of the above was further recrystallised from warm alcohol in which the β-form is fairly insoluble and hence could be removed by filtration. This recrystallised product gave:

m.p. 187 - 188°C.

\[ \alpha_d^{18} = +132.0^\circ \] (Chloroform, C = 4.65)

Cf. \( \alpha = 1:2:3:4:6 \); pentabenzyl-d-glucose; m.p. 187°C;

\[ \alpha_d^{20} = +138.5^\circ \] (Chloroform) Levene and Bever [J. Biol. Chem. 76, 513] (1928)
Preparation of \( \beta-2:3:4:6 \) tetrabenzo\( \beta \) d-glucopyranosyl bromide. (Benzobromoglucone).\(^{42} \)

40 grams. (0.057 moles) of \( \alpha-1:2:3:4:6 \) pentabenzoyl d-glucose were dissolved in 550 C.C. of glacial acetic acid. Solution took place slowly on heating on a water bath but on cooling, the pentabenzoyl glucose separated out. Glacial acetic acid, saturated with dry hydrogen bromide at 0° C. (450 gms.) was then added and, even after prolonged shaking, solution of the pentabenzoyl glucose did not take place. Hence 20 C.C. of chloroform were added and solution took place immediately. After standing for one hour the solution had turned a light yellow colour.

The mixture was then poured into a large quantity (4 litres) of ice cold water. The reaction flask was washed out with chloroform and the washings added to the water. After stirring well the chloroform layer was separated and the aqueous layer extracted in three portions with chloroform, each portion being extracted once with 20 C.C. and twice with 10 C.C. of chloroform.

The combined chloroform extracts were washed with three 100 C.C. portions of distilled water and then dried over anhydrous sodium sulphate till the solution was clear.
The resulting pale yellow solution was evaporated under much reduced pressure, and a temperature not above 25°C (on account of the instability of bromo compound), to a thick syrup.

This syrup was taken up with 30 CC of petroleum ether (b.p. 100 - 120°C) and the product crystallised in a few hours.

Enough of this product for identification purposes (about 1.5 gms.) was removed and dried in a vacuum desiccator on a porous plate.

\[
\text{m.p. } 128 - 130^\circ, [\alpha]_D^{20} = +147.5^\circ (\text{toluene, } C = 0.48)
\]

\[
\text{c.f. } \beta-2:3:4:6 \text{ tetrabenzoyl-d-glucopyranosyl bromide;}
\]

\[
\text{m.p. } 125 - 128^\circ, [\alpha]_D^{20} = +144.7^\circ (\text{chloroform}).
\]

E. Fischer and B. Helferich, [Ann. 383.88(1911)]

The mother liquor was poured off the remainder of the crystals which were washed with ice cold petroleum ether, the washings being added to the mother liquor which was then evaporated under reduced pressure till a mass of crystals separated out of the small portion of liquor remaining. The two lots of crystals were combined and immediately dissolved in dry acetone in preparation for the next reaction.

No attempt was made to dry the main mass of crystals on account of the reported instability of bromo-sugar com-
pounds\textsuperscript{58} in the dry state. This precaution was well justified when a small sample of the product was examined after being kept in the crystalline state for one month and was found, then to melt at \textit{106 - 108}^\circ\textit{C}. Some decomposition had undoubtedly occurred.

The acetone solution of bromobenzoglucose was diluted to 130 C.C. with dry acetone and to this solution was added silver carbonate (25 gms, 0.091 moles), freshly prepared and dried in an air oven at 100 - 105°C, followed by 1.5 C.C. of distilled water added slowly from a burette while the mixture was shaken. Carbon dioxide was rapidly evolved for the first few minutes and until this evolution had nearly ceased, about 30 minutes later, shaking was continued by hand. The shaking was then continued for a further 4½ hours on a shaking machine, the mixture being examined periodically for the evolution of carbon dioxide.

The halogen free, colourless solution, after shaking for a few minutes with a little animal charcoal was filtered through on fine filter paper. This removed most of the silver but a further filtration was necessary to remove the last traces. The silver residues were washed thoroughly with warm acetone and the filtered washings added to the original filtrate.

After evaporation under reduced pressure a glassy viscous amorphous mass remained.
Yield = 32 gms. i.e. 95% of theoretical for two reactions pentabenzoyl glucose $\rightarrow$ bromobenzoglucose $\rightarrow$ tetrabenzoyl glucose.

$$\left[\alpha\right]_{D}^{20} = +70.2^\circ \text{ (alcohol, } \rho = 0.46)$$
c.f. $\beta$-2:3:4:6-tetrabenzoyl-d-glucose; $\left[\alpha\right]_{D}^{21} = +70.6^\circ \text{ (alcohol)}$
for crystalline product.

E. Fischer and H. Noth, [Ber., 51, 332 (1918)]

These workers observed a mutarotation of $\left[\alpha\right]_{D}^{17} = +48.17^\circ$ after 10 minutes to $\left[\alpha\right]_{D}^{17} = +63.29^\circ$ after three hours but observed no mutarotation of the crystalline product, the value $\left[\alpha\right]_{D}^{21}$ remaining constant.

In the present instance the value of $\left[\alpha\right]_{D}^{20}$ was attained immediately with the amorphous product and no mutarotation occurred.

Attempts to crystallise the amorphous product from petroleum ether (B.P. 100 - 120°C), as described by Fischer and Noth, were unsuccessful, but on keeping a sample for two months crystallisation slowly occurred. This crystalline product was recrystallised twice from methyl alcohol and gave:

m.p. 103 - 104°C.
Mercaptalation of \( \text{2,3,4,6-tetrabenzoyl-6-glucose} \). moles

Tetrabenzoyl glucose (6gms, 0.01) was dissolved in 27 c.c. of dry chloroform in a 150 c.c. glass stoppered reagent bottle. To this solution was then added anhydrous sodium sulphate (3.0 grams, previously dried at 100°C) and zinc chloride (1.7 gms, quickly ground and weighed in a stoppered weighing bottle). After cooling this solution in ice, dry ethyl mercaptan (12 c.c., 10 grams, 0.16 moles) was added and the stopper of the reagent bottle wired on and weighed. This mixture was held at approximately 4°C in a refrigerator for six days, the contents however being brought up to room temperature daily to ensure thorough mixing of the ingredients.

At the end of this period the mixture was poured into 60 c.c. of saturated sodium bicarbonate solution and the white precipitate formed filtered off at the pump. The residue and filtrate were extracted six times with small portions (5-10c.c.) of chloroform and the total chloroform extract so obtained dried overnight over anhydrous sodium sulphate. The then clear solution was evaporated under reduced pressure at 35°C to a light yellow syrup.

This syrup was soluble in warm ether and, on cooling in ice, crystallisation into white flakes took place.
rapidly. Crystallisation also took place when methyl iodide was added to the syrup at room temperature.

Yield of crystalline product, 4.6 gms.

A portion of the product recrystallised twice from ether gave:

m.p. 86 - 87° C.                         173 - 174°

\[ [\alpha]_{D}^{15} = +69.3^\circ \text{ (chloroform C = 1.01).} \]

Benzoyl (-CO.C6H5): Found : 62.5%

Calculated for C_{38}H_{35}O_{2}S_{2}: 59.8%
Preparation of \( \beta-2:3:4:6 \)-tetrabenzyol-\( d \)-glucose oxime.

\( \beta-2:3:4:6 \) tetrabenzyol-\( d \)-glucose (21 gms. 0.035 moles) was dissolved in a solution of hydroxylamine prepared as follows according to directions of Wohl.\(^{15} \)

Freshly cut metallic sodium (1.8 gms, 0.078 moles) was weighed in a stoppered weighing bottle to avoid the formation of sodium hydroxide. This was then added to 25 c.c. of dry absolute ethanol. The solution of sodium ethoxide so obtained was added to a solution of hydroxylamine hydrochloride (6 gms. 0.085 moles) dissolved in 10 c.c. of dry absolute ethanol (10 c.c.). Sodium chloride was precipitated and filtered off and the residue washed well with absolute alcohol. The resultant ethanolic solution of hydroxylamine had a volume of 50 c.c.

This mixture of tetrabenzyol-\( d \)-glucose and hydroxylamine was then refluxed for two hours during which period the solution turned a deep red colour. The alcohol was removed under reduced pressure and this precipitated out a small amount of sodium chloride which is soluble to a small extent in alcohol. The thick syrup remaining was hence extracted with chloroform, filtered and again distilled under reduced pressure to remove the chloroform. A viscous, deep red syrup remained.
During the removal of the alcohol the odour of cyanide was detected and a sample of the distillate gave a positive test for cyanide. Hence it was believed that some degradation had occurred during the reaction owing perhaps to the rather severe conditions under which it is carried out.

Hence the following method of preparation was investigated, it being a modification of the method of Wolfson and Thompson17 for the preparation of mannose oxime.

Tetraacetyl-d-glucose (2.3 grams 0.0039 moles) was dissolved in 50 C.C. of alcohol – heating on a water bath to 40°C was necessary to effect solution. Potassium acetate (1.5 gms. 0.015 moles) was dissolved in 25 C.C. of alcohol and added to hydroxylamine hydrochloride (0.75 grams, 0.011 moles) dissolved in 10 C.C. of distilled water. This solution was added to the tetraacetyl-d-glucose solution and the mixture gently heated on the water bath for 15 minutes and then allowed to stand with occasional shaking for a further two hours.

The solution was then evaporated under reduced pressure at 35°C till a mobile syrup separated out beneath the water-alcohol layer. The potassium chloride, excess potassium acetate and excess hydroxylamine which are all
readily soluble in water would be retained in the water-
 alcohol layer. The syrup was extracted with chloroform, 
and the water-alcohol layer was also twice extracted with 
small portions of chloroform. The combined extracts were 
washed with saturated sodium bicarbonate to remove acetic 
acid and then with distilled water. The chloroform so-
lution was then dried overnight over anhydrous sodium 
sulphate. The resulting clear, pale yellow coloured so-
lution was evaporated under reduced pressure to a thick 
syrup which immediately changed on cooling to a hard 
glassy crystalline mass.

Yield: 1.7 grams, i.e. 74% of theoretical for 
\( \beta-2:3:4:6 \) tetrabenzyol-\( \delta \)-glucose oxime.

\[ \text{m.p. 56 - 58}^\circ \]

After recrystallising from ether m.p. 58 - 59\( ^\circ \)
\[ [\alpha]_D^\circ +49.5\( ^\circ \) (chloroform, C = 1.04). \]

Benzyol (-CO.C_6H_5) : Found : 70.4%
Calculated for C_{54}H_{29}O_{10}N : 68.7%

**pH Measurement:**

The pH measurements were made with a pH meter using 
a glass electrode.

pH of reaction mixture (Wohl preparation) = 6.7.
pH of reaction mixture (modified Wolf from preparation) = 5.0

The mercaptal (5.18 grams, 0.0074 moles) was dissolved in methyl iodide (30 C.C.) and 3 C.C. of dry acetone added to assist solution. This solution was contained in a 150 C.C. round bottomed flask attached to a reflux condenser by a ground glass joint. Moisture was excluded from the system by a calcium chloride tube attached to the top of the condenser. Finely powdered dry silver oxide (14 grams) was added hourly in 1.5 gram portions over a period of nine hours and during this time the mixture was refluxed gently at 40 - 45°. The silver oxide was occasionally shaken up to facilitate the reaction.

After refluxing for 9 hours the methyl iodide solution was filtered off and the silver residues refluxed with two portions of dry chloroform to ensure thorough extraction. The combined chloroform extracts and methyl iodide solution were then evaporated under reduced pressure to an orange red syrup. This was taken up and evaporated again twice with dry absolute alcohol to ensure the removal of last traces of methyl iodide which would affect subsequent methoxyl determinations on the syrup.
Yield of syrup = 4.18 grams.

Methoxyl (-O.CH₃) Found: 11.85%
Calculated for C₃₉H₄₀O₉S₂: 4.33%

Benzoyl (-CO.C₆H₅) Found: 49.4%
Calculated for C₃₉H₄₀O₉S₂: 59.0%

These results did not indicate any definite compound and it was apparent that in spite of the precautions for keeping the reactants dry, a certain small amount of replacement of benzoyl groups by methoxyl groups had taken place.

The syrup was taken up in a few C.C. of ether and after two days a considerable amount of crystallisation had taken place. These crystals were separated from the mother liquor, washed with ice cold ether and dried in a vacuum desiccator.

Yield: 0.85 grams.

m.p. of crude product = 150 - 152°C.

A sample of this was recrystallised from ether for the purposes of analysis and gave:

m.p. 155 - 156.5°C \[\alpha\]₀D = +35.6 ° (CHCl₃, \(C = 2.12\))

Methoxyl (-O.CH₃) Found: 5.64%
Calculated for C₃₉H₄₀O₉S₂: 4.33%
A further sample of the mercaptal was methylated in the same manner as above and analysis of the syrup after one methylation gave:

methoxyl (-O.CH₃) = 12.4%

After a further methylation:

methoxyl (-O.CH₃) = 13.65%

Apparently replacement of the benzyl groups by methoxyl groups was occurring slowly.

After several days crystals separated out and these on recrystallisation from ether and mixing with the product described above did not depress the melting point.
Demercaptalation of tetrabenzoyl 
-\(\text{d-glucose diethyl mercaptal}\).

Tetrabenzoyl monomethyl \(\text{d-glucose diethyl mercaptal}\) (0.7 grams, 0.00098 moles) was dissolved in dry methanol (50 c.c.) and dry acetone (150 c.c.) at 50\(^\circ\)C, the latter solvent being necessary to effect complete solution. Yellow mercuric oxide (0.5 grams) and anhydrous sodium sulphate (0.5 grams) were added and to this mechanically stirred mixture was added a solution of mercuric chloride (6.5 grams, 2 mols) in absolute methanol (10 c.c.) over a period of 30 minutes. Stirring at 50\(^\circ\)C was continued for five hours after which the mixture was filtered and the methanol removed at 35\(^\circ\)C under reduced pressure. The residue was taken up in chloroform and filtered. The mercuric oxide residue was also thoroughly extracted with warm chloroform and the combined chloroform extracts evaporated at 35\(^\circ\)C to a yellow viscous mass. On adding methanol to this, yellow crystals separated out which were well washed with methanol.

Yield: 0.55 grams; i.e. 92\% theoretical for tetrabenzoyl monomethyl \(\text{d-glucose}\).
The colour of the crystals appeared to be due to slight contamination by very fine mercuric oxide which had not been removed by filtration. Hence the crystals were redissolved in chloroform and centrifuged. This removed the majority of the oxide. The chloroform was removed in vacuo and the product, on recrystallisation from methanol, gave small colourless masses of needles:

- m.p. 133.5 - 134° \([\alpha]_D^{17.5} = +29.2° \text{ (CHCl}_3, c = 1.45\).
- Methoxyl (\(\text{OCH}_3\)) Found: 5.51%

Calculated for (a) Tetrabenzoyl methyl (dimethyl) glucose acetal (\(C_{37}H_{56}O_{11}\)) 14.5%

(b) Tetrabenzoyl monomethyl glucose, (\(C_{35}H_{30}O_{10}\)) 5.1%
Hydrolysis of tetrabenzoylemonomethyl α-glucose.

Tetrabenzoylemonomethyl α-glucose (0.37 grams 0.0006 moles) was dissolved in dry acetone (10 c.c.) and to this was added freshly prepared approximately $\frac{N}{3}$ sodium ethoxide (10 c.c.). This mixture was stood at room temperature for 56 hours, when a considerable amount of sodium benzoate had precipitated out. The latter was removed by filtration and the residue well washed with warm dry acetone.

The combined filtrate and washings were neutralised to phenolphthalein with $\frac{N}{2}$ hydrochloric acid and the solution evaporated to dryness under vacuum at 35° C. The residue remaining was extracted repeatedly with hot dry acetone and filtered. The resulting clear solution was evaporated in vacuo to a clear slightly yellow syrup. On cooling this partial crystallisation occurred. Analysis of the syrup fraction gave:

- Methoxyl (-OH) 4.84 %
- Found: 4.84
- Calculated for $C_7H_{14}O_6$ 15.96%

A small quantity of ether was added and this caused more of the product to crystallise. These probably rather impure crystals were well washed with ether and analysis
after drying in a vacuum dessicator gave:

\[
\text{Methoxyl (CH}_3\text{)} \quad \text{Found: 14.7}\% \\
\text{Calculated for C}_7\text{H}_4\text{O}_6 \quad 15.95\%
\]

The small amount of crystals remaining were warmed with ether but only partial recrystallisation was possible. The few crystals obtained appeared to be purer and gave m.p. 98 - 102° after softening had occurred at 90°. Insufficient product was available to attempt a rotation.
Methylation of Tetrabenzoyle d-glucose oxime.

Tetrabenzoyle d-glucose oxime (0.8 grams, 0.00135 moles) was methylated in a similar fashion to that already described. Evaporation of the chloroform extracts at 35° gave a straw coloured viscous syrup. Attempts to crystallise this were not successful.

Yield of Syrup = 0.81 grams.

Methoxyl (-O.CH₃) Found : 7.02%
Calculated for C₅₆H₆₆O₁₀N : 9.70%

Apparently methylation had not been complete so a further similar methylation was carried out and analysis gave:

Methoxyl (-O.CH₃) Found : 10.91.

This product was subsequently taken over by a coworker for further investigation of the product obtained after removal of the oxime and benzoyle groups. The product however was insufficient for characterisation.
Methylation of 2:3:4:6 tetrabenzoyl d-glucose.

Tetrabenzoyl d-glucose (2 grams, 0.0034 moles) was methylated as previously described and on evaporating the chloroform extracts a pale yellow syrup remained. On treatment with methanol this crystallised readily. The crystals were filtered off and recrystallised from methanol.

m.p. 135 - 136°. After further recrystallisation from methanol m.p. 136°.

\[ [\alpha]_{D}^{14} = +48.6\,^\circ\quad (\text{CHCl}_3\quad c = 1.2) \]

C.f. \( \beta-2:3:4:6 \) tetrabenzoyl methyl glucoside; m.p. 160 - 162°. \( [\alpha]_{D}^{20} = +31\,^\circ\quad (\text{CHCl}_3) \); Fischer and Helferich. [Ann. 383, 90 (1911)]

Methoxyl \((-\text{O.CH}_3)\) Found: 5.65%

Calculated for \( C_{35}H_{37}O_{10} \) 5.75%

A further methylation did not affect the methoxyl value.
Methylation of 2:3:4:5:6 pentabenzoyl d-glucose diethyl mercaptal.

The pentabenzoyl glucose mercaptal was prepared in this laboratory (R. J. McIlroy) and gave:

m.p. 97.5°  \([\alpha]_D^{19} = +54° \) (CHCl₃).

c.f. C. Brigi and Muschlschege [Ber. 63, B. 1551 (1930)].
m.p. 97 - 98°  \([\alpha]_D^{19} = +49.6 \) (CHCl₃);

This mercaptal (0.86 grams, 0.001 moles) was methylated with methyl iodide (10 c.c.) and silver oxide (5 grams) by the same procedure as carried out for previous methylations. After removal of the solvent in vacuo all attempts to crystallise the remaining syrup with alcohol, ether and alcohol-ether mixtures failed. Finally the syrup was taken up and evaporated several times with absolute alcohol to remove any traces of the remaining methyl iodide.

Yield of carefully dried syrup = 0.68 grams.

Methoxyl (-O.CH₃)  Found : 13.1%

Theoretically the methoxyl should be nil as there are initially no free groups in the mercaptal molecule to methylate.
Analytical Methods.

Semi-Micro Benzoyl Determination.

Considerable difficulty was experienced in determining these groups on account of the fact that they are far less readily hydrolysed than acetyl groups and when stronger hydrolysing agents are used there is danger of the sugar being enolised and hence high results obtained. The following methods were investigated:

(a) The procedure of R. Clarke and E. Christensen\textsuperscript{59} for the determination of acetyl groups in sugars was applied to benzoylated sugars as follows. Hydrolysis was carried out with 0.05 N carbonate free sodium hydroxide at room temperature for 24 hours, the solution being occasionally shaken. The excess alkali was then titrated with standard \( \frac{N}{20} \) hydrochloric acid using phenolphthalein as indicator.

In general the results were low and it was apparent that hydrolysis was not complete. When stronger alkali was used the results were high, indicating that enolisation as well as hydrolysis was occurring. Hence this method was considered unsuitable for the determination of benzoyl groups in sugars.
(b). The improved method of Pregl using the apparatus originally designed by Kuhn and Roth⁶⁰, was investigated using certain modifications on account of the large size of the only apparatus available.

In this method the sample is hydrolysed by refluxing with either acid or alkali and on completion of hydrolysis the solution is made 10% acid and the benzoic acid so formed distilled off in an atmosphere of steam and titrated with standard alkali.

Both acid hydrolysis and alkali hydrolysis were attempted. Acid hydrolysis was carried out with Wenzel's sulphuric acid, prepared by adding 100 C.C. of sulphuric acid (S.G. 1.85) to 200 C.C. of water, at 100°C. Considerable charring of the sugar took place and the results were too high. Alkali hydrolysis was carried out with a 50% solution of potassium hydroxide in methanol. It was necessary to reflux the mixture for 3 - 4 hours to complete hydrolysis and the results so obtained were only satisfactory when fairly large blanks were subtracted.
(c) The method used by Brigl and Schinle was found the most satisfactory and gave reasonable results on the semi-micro scale as follows:

15 - 20 mgms. of the benzoyl derivative were weighed out in a glass capsule and introduced into a 50 C.C. stoppered flask. The sample was dissolved in 5 C.C. of absolute alcohol and 5 C.C. of 0.5 N sodium ethylate solution were added. The stoppered flask was then stood at room temperature for 48 hours, and then titrated with standard \( \frac{5}{1} \) hydrochloric acid, the titre being subtracted from a similar blank titration. From the volume of standard acid so obtained the benzoyl content could be readily calculated.
Semi-Micro Methoxyl Determination.

The determination was carried out according to the procedure of Zeisel, the apparatus being a modification of the usual Zeisel apparatus.

The sample is treated with hydriodic acid at a temperature of 130 - 135°C, when the alkoxy group \((-\text{OCH}_3\) or \(-\text{OC}_2\text{H}_5\)) is replaced with hydrogen and the alkyl iodide is formed. This is carried by a stream of carbon dioxide through a trap containing an aqueous suspension of red phosphorous in order to remove any traces of hydriodic acid. The alkyl iodide is then passed into a solution of 2% ammoniacal silver nitrate where the iodide is precipitated as silver iodide. The silver iodide is dried and weighed and when multiplied by the appropriate factor the weight of alkoxy in the sample can be determined.

Semi-Micro Sulphur Determination.

The usual semi-micro Carius method was attempted in which the sulphur is converted to sulphuric acid by heating in a sealed Carius tube with fuming nitric acid. The sulphate is then estimated as the insoluble barium salt.

Although this method was found accurate for estimating the sulphur in xylose mannitol derivatives completely.
negative results were obtained on the benzoyleted glucose mercaptal derivatives, even though positive qualitative tests for sulphur had been obtained.

Similar negative, or almost negative, results were obtained when the sulphur analyses were repeated in conjunction with the carbon-hydrogen analyses.

**Micro Combustion Analyses.**

These analyses were carried out by Messrs. Weiler and Strauss, Oxford.


**C₃₄H₂₉O₁₀N** Requires: C 66.8, H 4.75, N 2.3.

Found: 64.8, 4.60, 2.0

The synthesis of this previously unreported compound is thus confirmed.


**C₃₈H₄₈O₉S₂** Requires: C 64.9, H 5.41, S 9.12.

Found: 63.1, 5.60, 0.50.

(c). 2:3:4:6-tetrabenzoyl 5-methyl d-glucose diethyl mercaptal.

**C₃₉H₄₀O₉S₂** Requires: C 65.3, H 5.58, S 8.96

Found: 68.3, 5.09, 0.94.

The low sulphur values cannot be accounted for — see p. 70.
(d). 2:3:4:6-tetrabenzoyl 5-methyl glucose.

\[ C_{35}H_{30}O_{10} \]

Requires: C 68.9, H 4.92

Found: 68.8 5.94

The synthesis of tetrabenzoyl monomethyl glucose, previously unreported, is thus confirmed. As compounds (b), (c) and (d) are successive steps in the synthesis, the confirmation of compound (d) must, to a large extent, confirm the presence of compounds (b) and (c) in spite of the very low values obtained for sulphur and somewhat poor agreement between the observed and calculated values for carbon and hydrogen.

(e). Monomethyl d-glucose (possibly 5-methyl d-glucose).

\[ C_{7}H_{14}O_{6} \]

Requires: C 43.2, H 7.20.

Found: 40.4 7.41

As this sample was not able to be recrystallised the above results fairly well indicate the presence of monomethyl glucose.
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