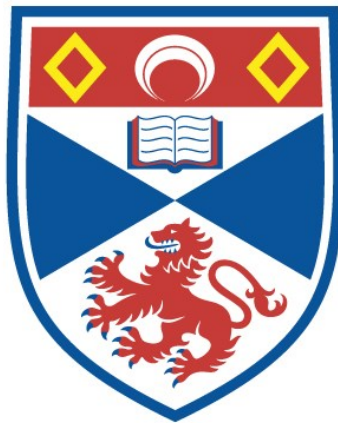


# **THE STRUCTURE OF MANNITOL**

**Ettie Stewart Steele**

**A Thesis Submitted for the Degree of PhD  
at the  
University of St Andrews**



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THE STRUCTURE  
OF  
MANNITOL



(8+A) Th. <sup>MS</sup> QD321, S8

AIEN ΔΡΙΣΤΕΥΕΙΝ.



Index as under:-

Ph.D. Thesis St. Andrews No. 1. 1919.

*A. J. J. J.*

THE STRUCTURE OF MANNITOL.

A Thesis presented for the Degree

of

DOCTOR OF PHILOSOPHY

of

THE UNIVERSITY OF ST ANDREWS.

By

Ettie Stewart Steele, M.A., B.Sc.



CERTIFICATE.

I certify that Miss E.S.Steele, M.A., B.Sc.,  
has spent nineteen Terms at Research Work under my  
direction and that she has fulfilled the conditions  
of Ordinance No 16 ( St Andrews ), <sup>and</sup> (so that she) is  
qualified to submit the accompanying Thesis in  
application for the Degree of Ph.D.

St. Andrews,

Dean of the Faculty of Science.

14th November, 1919.

D E C L A R A T I O N .

I hereby declare that the following Thesis is a record of the results of experiments carried out by me, and further, that the Thesis is my own composition and has not previously been presented for a Higher Degree.

The research was carried out in the Chemical Research Laboratory of the University of St Andrews, under the direction of Professor J.C.Irvine.

October 1919.

St Andrews.

### TRAINING AND EXPERIENCE IN RESEARCH.

I entered the University of St Andrews in October 1908, and graduated M.A. in 1912, and B.Sc. in 1914, obtaining Higher Standard in Botany, in Geology, and in Chemistry. In April 1914 I entered the Chemical Research Laboratory, and commenced a research on the configuration of alkylated sugars as determined by their conductivity in the presence of boric acid. During the winter session 1914-15, I continued this research, and acted at the same time as Lecture Assistant in the Department. In the following years, I held a Carnegie Research Scholarship in 1915-16 and 1916-17, and a Fellowship in 1917-18 and 1918-19.

Practically the whole of my time, from February 1915 to December 1918, was devoted to War Researches and War Preparations, a list of which is appended. In addition, however, I have completed a research on the structure of methylfructoside, which has been published, and for the purposes of this Thesis, have carried out experiments supplementary to my earlier work on mannitol.

I have been admitted by the Senatus Academicus as a Research Student of the University under Ordinance 61, my admission to date from 12th October, 1914.



PUBLISHED PAPERS.

1. Trans.Chem.Soc. 1915, 107, 1221.

"The influence of configuration on the condensation reactions of polyhydroxy-compounds. Part II. The effect of boric acid on the conductivity and specific rotation of methylated derivatives of mannitol " ( With J.C.Irvine )

2. Trans. Chem.Soc. 1915, 107, 1230.

"The mechanism of mutarotation in aqueous solution " ( With J.C.Irvine )

3. Trans.Chem.Soc. 1918, 113, 257.

"The structure of crystalline  $\beta$  -methyl-fructoside"

LIST OF WAR RESEARCHES.

1. Research on the removal of residual acetone from wood spirit. ( Candlemas Term 1916 )
2. Research on alternative methods of preparing " orthoform neu ". ( March 1916 )
3. Researches on the preparation of novocain from diethylamino-ethanol by four synthetical processes. ( June to September 1916 )
4. Research on the use of sulphuryl chloride and sulphur chloride as substitutes for thionyl chloride. ( September 1916 )
5. Research on the extraction of inulin from dahlia tubers. ( October to December 1916 )
6. Research on the preparation of fructose from inulin . ( Candlemas Term 1917 )
7. Research on the preparation of " mustard gas "
  - (1) preparation of thiodiglycol
  - (2) preparation of dichloroethyl sulphide
    - a by the action of hydrochloric acid
    - b by the action of thionyl chloride.( September 1917 to June 1918 )

8. Research on the Preparation of diallyl sulphate .  
( July and September 1918 )
9. Research on the preparation of diethylamine.  
( October 1918 )

LIST OF WAR PREPARATIONS.

1. Preparation of galactose by the hydrolysis of lactose . ( March to June 1915 )
2. Preparation of intermediate products for the preparation of novocain, including:
 

<ol style="list-style-type: none"> <li><u>a</u> Ethyl bromide</li> <li><u>b</u> Ethylene dibromide</li> <li><u>c</u> Glycol chlorhydrin</li> <li><u>d</u> Diethylamino-ethanol</li> </ol>	}	( July to October 1915 )
<ol style="list-style-type: none"> <li><u>e</u> Novocain .</li> </ol>		( September 1916 )
3. Recrystallisation of dulcitol.( Martinmas Term 1915 )
4. Preparation of " orthoform neu "
 

<ol style="list-style-type: none"> <li><u>a</u> Methyl ester of nitrobenzoic acid,</li> <li><u>b</u> Reduction of the methyl ester of nitrobenzoic acid to the methyl ester of amino-benzoic acid.</li> </ol>	( April to June 1916 )
---	------------------------
5. Preparation of fructose from inulin.  
( April to July 1917 )

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PART I.

REVIEW OF THE CHEMICAL EVIDENCE BEARING  
ON  
THE STRUCTURE OF MANNITOL.

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REVIEW OF THE CHEMICAL EVIDENCE BEARINGONTHE STRUCTURE OF MANNITOL.

The existence of the active polyhydric alcohols in nature and the fact that, in certain stages of plant life, they are found replacing the more commonly occurring glucose, has led workers in the carbohydrate field to examine these compounds and their derivatives, with a view to finding wherein they differ from or conform to the typical sugar structure, and to ascertain their relationship to the latter type of compound. Hitherto such work has been largely confined to an estimation of the hydroxyl content of the molecule, to a study of the optical activity, and to their synthetic production from known sugars by reduction. From such researches, the accepted constitution and configuration of these alcohols have been largely deduced.

A survey of the literature seems to leave little doubt that one may safely assign to mannitol a normal hexahydric structure, for numerous reactions provide products where all six hydroxyl groups of the parent alcohol have been replaced by substituent groups. One can record a whole series of these derivatives, prepared for the most part in standard reactions by reliable authorities, and all of which are well defined crystalline



compounds showing sharp melting points.

These are:-

Mannitol hexa-acetate - Schutzenberger, Annalen, 160, 94.\*

Mannitol hexa-chlorohydrin - Mourgues, Compt.rend. 1890,

Mannitol hexa-nitrate - Sobrero, Annalen, 64, 397. (111, 111

Mannitol hexa-sulphuric acid - Claesson, J.pr.Chem., (2), 20, 10.

Mannitol hexa-benzoate - Stohmann, Rodatz, Herzberg, J.pr.

Chem. (2), 36, 354.

Mannitol triacetone - Fischer, Ber., 1895, 28, 1167.

Mannitol triformal - Schulz & Tollens, Ber., 1894, 27, 1892.

Mannitol tribenzal - Meunier, Compt.rend. 1888, 106, 1425, 1732

Dichlorotetranitromannitol - Bouchardat, Compt.rend. 1873,

76, 1550.

Dibromotetranitromannitol - Bouchardat, Annales de Chim. &

Phys. 1875, (5), 6, 100.

Mannitol hexaphenylurethan - } Maquenne & Goodwin, Compt.

Mannitol hexaphenylcarbamate - } rend. 1904, 138, 633.

Moreover, the value for the magnetic rotation of mannitol has been shown to fall on a smooth curve with that of mono-, di-, tri-, tetra-, and penta-hydric alcohols ( Perkin, Trans.Chem.Soc., 1902, 81, 179 ) which seems good physical evidence that the alcohol is hexahydric. Further, such

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\* See also Bouchardat, Annales de Chim. & Phys. (5), 6, 107.  
and Franchimont, Ber., 1879, 12, 2059.

evidence as the oxidation of mannitol to mannosaccharic acid, and the action of hydriodic acid to give secondary hexyl iodide, would seem to justify the conclusion that the molecule is terminated symmetrically by two primary alcoholic groups. In addition, biological evidence in support of that afforded by chemical methods is to hand, for Hardeñ ( J.Chem.Soc., 1901, 79, 610) finds that the action of a specific bacillus is to produce twice as much alcohol from mannitol as from glucose, a difference which is attributed to the existence of the group  $\text{CH}_2\text{OH}\cdot\text{CHOH}\cdot$  two times in mannitol as contrasted with once in glucose.

A closer scrutiny, however, brings to light a number of unexpected irregularities in the properties of these alcohols. It has been stated that many definite hexa-derivatives of mannitol have been isolated, but it is remarkable that many experiments, which had as their object the preparation of these hexa-derivatives, yielded penta-derivatives, for the most part in better yield and under less severe conditions. The following examples may be quoted in support of this statement:-

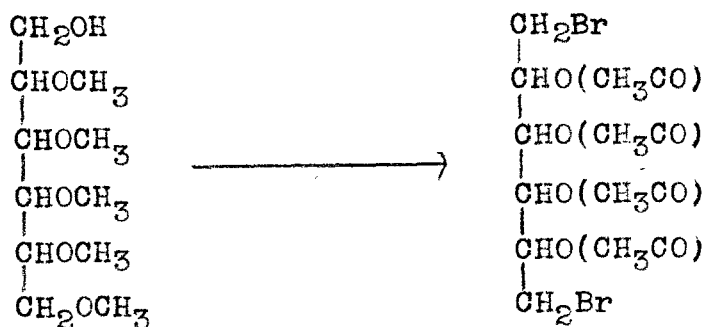
- Mannitol pentanitrate - Tichanowitsch, <sup>d.</sup>Jahr. Chem. 1864, 582.  
 Mannitol penta-benzoate - Skraup, Monatsh. 1889, 10, 389.  
 Mannitol pentaphenyl urethan - Tessmer, Ber., 1885, 18, 968.

One outstanding example is worthy of special mention. Mourgues ( loc.cit.), in a research in which he heated 300 grams of mannitol ( 1 mol.) with 7 mols. of phosphorus pentachloride, emphasises the great resistance of the compound to chlorination, and the extreme difficulty with which he obtained the hexa-chlorohydrin, recording a yield of only 0.1 per cent ( 1 - 1.5 grams ).

There is no doubt, however, that an excellent test case is provided in the preparation of alkylated derivatives of mannitol, and although it will be necessary subsequently to refer to this work in greater detail, it may now be mentioned that a number of striking results have been contributed in recent years by Irvine and Paterson ( Trans. Chem. Soc. 1914, 105, 915 ). In numerous attempts to prepare a hexa-methyl mannitol or a tetramethyl diethyl mannitol, they were confronted with a consistent resistance to complete substitution and found that the maximum number of hydroxyl groups which could be replaced was five.

The reaction, as carried out by these workers, was the standard one of heating either of the two known tetramethyl mannitols with the appropriate alkyl halide in presence of silver oxide, and in the course of a research carried out in this laboratory by a fellow worker and still unpublished, the above result has been corro-

borated. The investigation in question was on alkylation by the agency of methyl sulphate in alkaline solution, and a large number of experiments were performed on mannitol under conditions which were varied, not only as regards temperature and duration, but also the proportion of reacting materials. In no instance was a fully methylated mannitol forthcoming, whereas the penta-derivati~~ve~~<sup>ve</sup> was always produced in good yield. Further, the pentamethyl mannitol so isolated did not react with phosphorus pentabromide, and when subjected to drastic treatment with an acetic acid solution of hydrogen bromide, the whole of the methyl groups were swept out, and the resulting product was a symmetrical dibromotetracetyl mannitol.

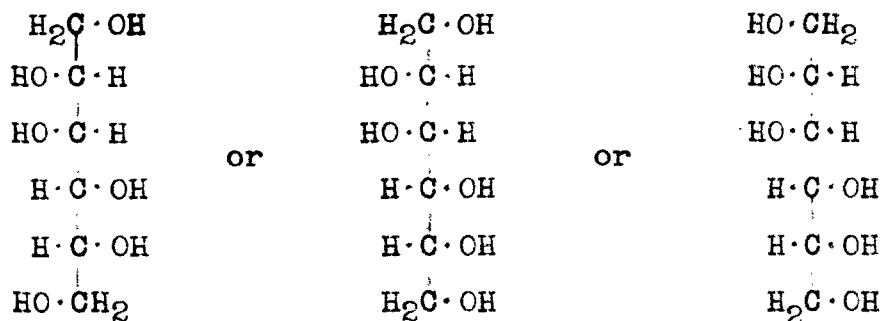


These results are significant, and the question whether the terminal groups in <sup>the</sup> mannitol molecule are identical or different is at once raised. It may be urged that no special significance need be attached to the individual reactions of any one hydroxyl group in a polyhydric

compound, but a closer scrutiny of the problem reveals its importance. For example, the union of monosaccharides to give disaccharides, or in turn, of disaccharides to give polysaccharides may be viewed broadly as condensations involving specific hydroxyl groups in the constituent molecules. This at once points to the desirability of studying the special properties of each hydroxyl group in a chain. In other words, critical research should be directed to the consideration of partially substituted sugars and alcohols.

It is only to be expected that, in a reducing sugar or a glucoside, the constituent hydroxyl groups should vary in character, but in the general case of polyhydric alcohols, and in the particular case of a symmetrical molecule such as mannitol, the suggestion that the terminal primary  $\text{CH}_2\text{OH}$  groups should differ widely in reactive powers must seem surprising. In addition to the evidence already submitted, fuller reference must, at this stage, be made to the two publications by Irvine and Paterson ( *loc.cit.* and *ibid.* 898.) which bear on this point, and have led up to the present research. No more than an outline of the work need be given here as the closely-sustained reasoning can be fully appreciated only by a study of the original papers.

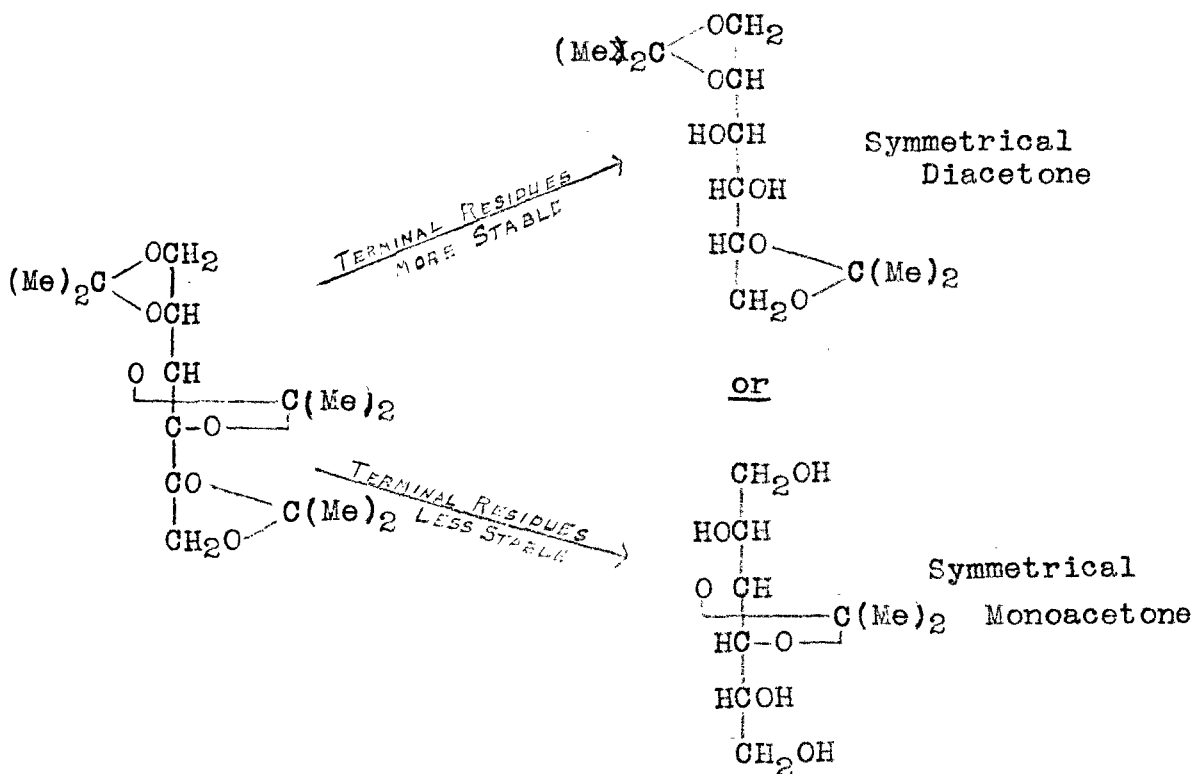
The problem in hand was the condensation of mannitol with acetone, and as a preliminary to further work, these acetone derivatives were carefully investigated. Applying the principle of graded hydrolysis to mannitol triacetone, it was found that mannitol diacetone was first obtained, followed by the monoacetone compound, and finally by mannitol itself, so that the acetone groups were eliminated one by one, and not two together followed by one as had been predicted. Hitherto, the conventional representation of the configuration of mannitol had been as a symmetrical molecule, in which the terminal  $\text{CH}_2\text{OH}$  groups were capable of free rotation giving:-



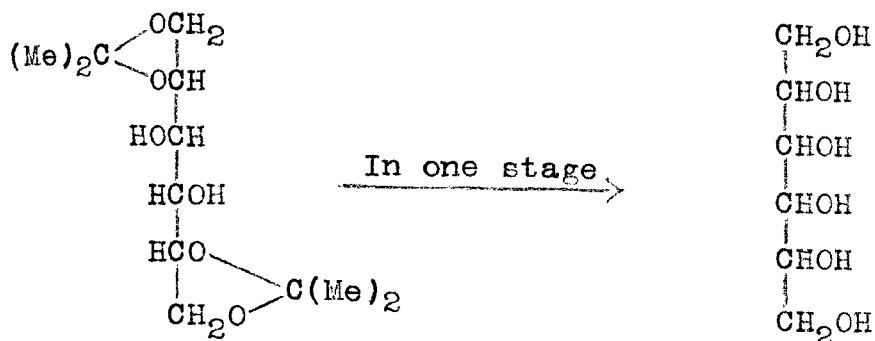
Apparently, in terms of the above structure, two out of the three acetone residues in mannitol triacetone would be identical, as each is coupled to one primary and one secondary alcoholic grouping, whereas the intermediate residue is linked to two secondary alcoholic groups and form, moreover, a trans-linking.



According, then, as one or other of the two types is less stable, a symmetrical diacetone or a monoacetone might be formed on graded hydrolysis. Formulae indicating the two possible routes of the hydrolysis are given below:

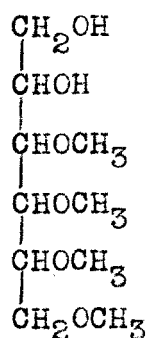


Further, in the event of a mannitol diacetone being formed as the initial hydrolytic product, this compound, owing to its symmetrical structure, ought to lose both acetone residues simultaneously on further hydrolysis.

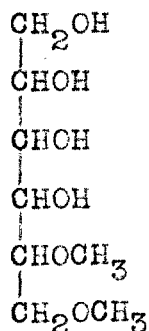


As stated, this expectation was not realised, and it was consequently necessary to subject each of the "mannitol acetones" to a constitutional study. They were accordingly methylated and the ketonic residues thereafter removed by hydrolysis, with the following results. Mannitol triacetone naturally remained unaffected by methylation, and mannitol was regenerated by the subsequent hydrolysis. Mannitol diacetone gave ultimately a dimethyl mannitol, and mannitol monoacetone a tetramethyl mannitol. The constitution assigned respectively to the tetramethyl and dimethyl mannitols are as shown below

Tetramethyl mannitol

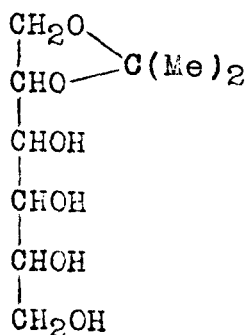


Dimethyl mannitol

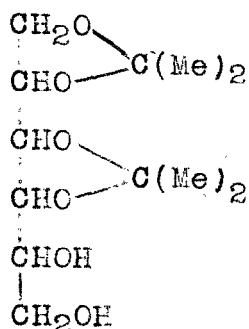


from which it follows that the parent compounds must be represented by

Mannitol monoacetone



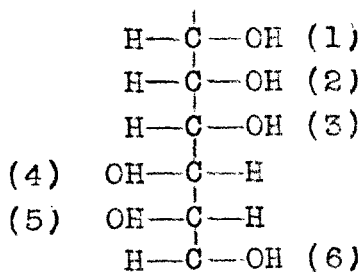
Mannitol diacetone



The dimethyl mannitol \* and tetramethyl mannitol obtained as above were both easily converted into a pentamethyl derivative but, on attempting to complete the alkylation, the sixth position remained resistant.

\*

In order to simplify reference to such derivatives in the course of the subsequent discussion, the positions of the hydroxyl groups have been indexed by numbers beginning from the position which displays steric hindrance to methylation thus:



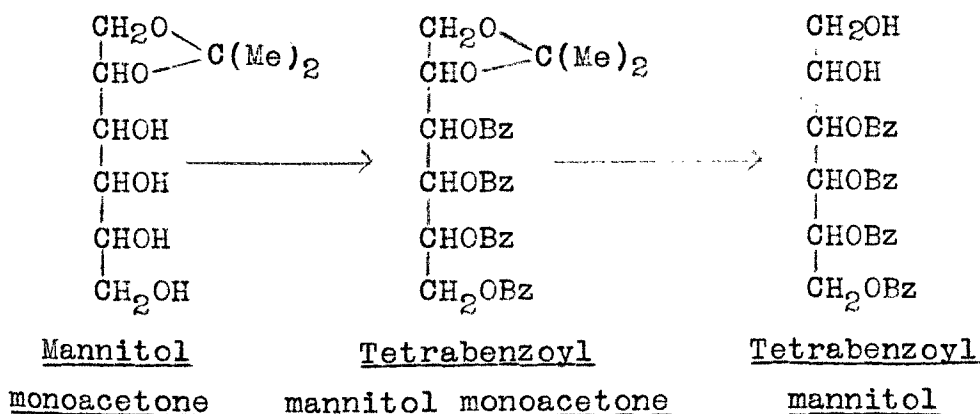
so that the dimethyl mannitol referred to will henceforth be described as 5,6- dimethyl mannitol.

Not only so, but the particular group incapable of further substitution was proved to be the terminal  $\text{CH}_2\text{OH}$  group. Consequently, the assumption that the primary alcoholic groups in mannitol are capable of free rotation is inadmissible, and the only alternative is that they can be locked in one position whereby the symmetry of the molecule is destroyed, three hydroxyl groups being thus attached to adjacent carbon atoms, and lying on the same side of the plane of the carbon chain. There are many examples throughout the literature where replacement of three hydroxyl groups so situated by methoxyl cannot be effected, and the present instance is one of the most striking. Hence, the explanation advanced to account for the steric hindrance is reasonable and justifiable, and there seems no doubt that the mannitol molecule has an unsymmetrical structure.

It has been shown that this resistance to substitution is not restricted to the introduction of methyl groups, but the possibility is still open that it may be due to the methyl groups already in the molecule, and that steric hindrance would no longer be encountered in attempts to introduce methyl groups into a molecule in which positions 3,4,5, and 6 are substituted by residues other than methyl groups. Further, the dimethyl mannitol described by Irvine and Paterson has  $\delta$  the methyl groups

in the 5,6, positions, and there seems no good reason why substitution should not be commenced from the other end of the molecule. Thus, a dimethyl derivative should be obtainable, in which the methyl groups occupy positions 1 and 2, and such a compound would be identical or isomeric with the 5,6-dimethyl mannitol already described, according as the two ends of the mannitol chain are the same or different.

A scheme to test these ideas was accordingly devised on the following lines. Mannitol monoacetone, prepared by the graded hydrolysis of mannitol triacetone as indicated by Irvine and Paterson ( loc. cit.) was converted into the tetrabenzoyl derivative according to Fischer's method ( Ber., 1915, 48, 266 ), and pure tetrabenzoyl mannitol monoacetone was thus obtained. The ketonic residue was thereafter removed by hydrolysis, with the ultimate formation of tetrabenzoyl mannitol in a pure state. The reactions involved are represented as under:-

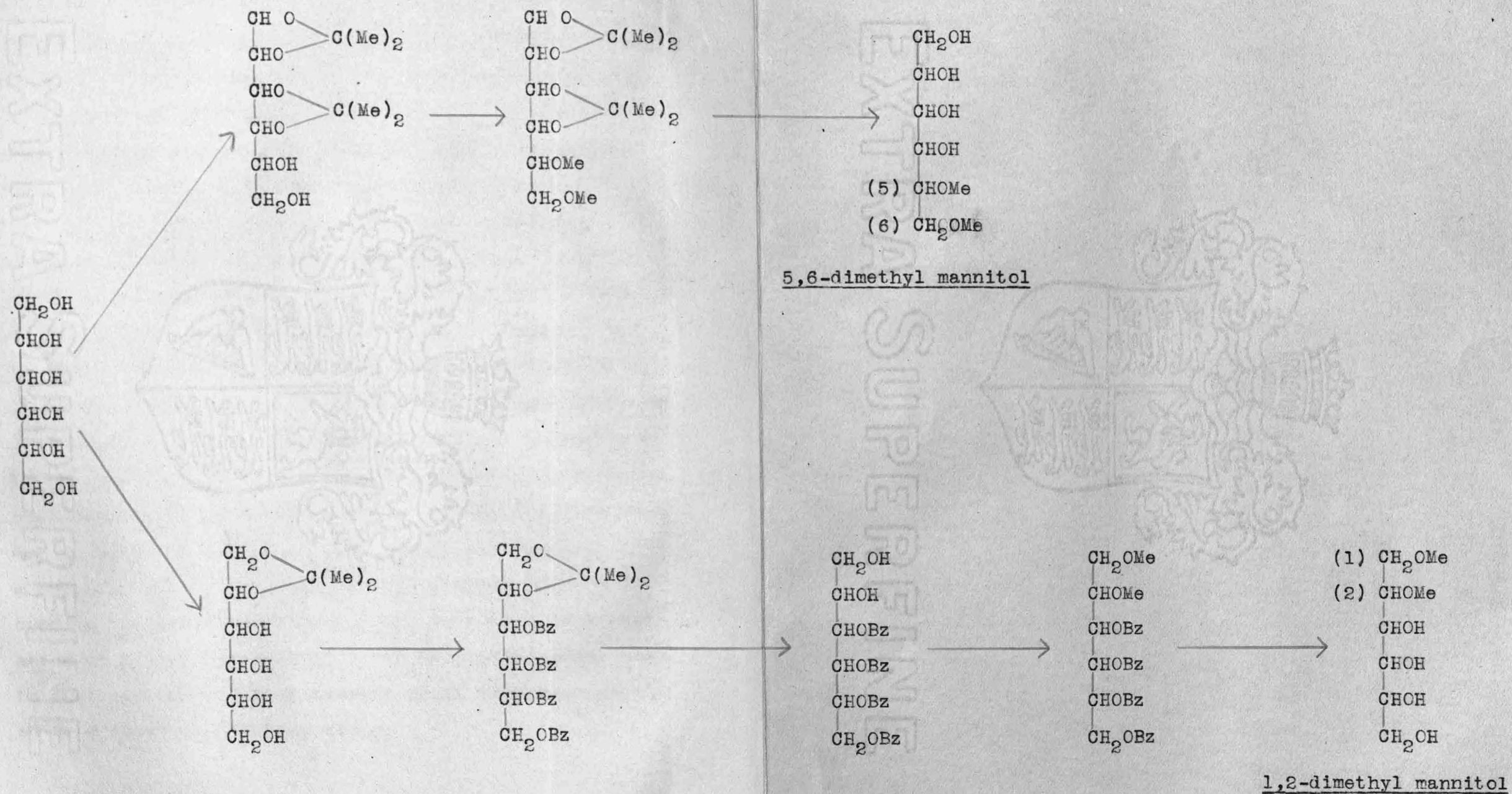


Inspection of the structural scheme above, will show that tetrabenzoyl mannitol is an excellent test substance for the particular enquiry in hand. Not only are the substituent groups already present other than methyl groups but, in addition, the only unsubstituted positions are Nos 1 and 2. In the event of normal methylation being possible in these positions, the 1,2-dimethyl mannitol obtainable on removal of the benzoyl groups would conform to the conditions already laid down. Unfortunately the desired result was not forthcoming for, on this occasion also, steric hindrance was encountered, and the product of the reaction with methyl iodide and silver oxide was a tetrabenzoyl monomethyl mannitol. Repeated treatment with the reagents named failed entirely to introduce a second methyl group, and the conclusion that the two ends of the mannitol molecule are not identical is thus strongly supported.

In order to provide a diagrammatic survey of the reactions contemplated, the following structural scheme is appended:



DIAGRAMMATIC SCHEME OF REACTIONS DESIGNED TO PRODUCE THE TWO ISOMERIC DIMETHYL MANNITOLS.



There is, however, one criticism of this view which may be offered viz: that the results on which the deduction is based, that the primary alcohol groups <sup>are</sup> in mannitol/different, are for the most part negative. In research of this kind, it is obvious that no further progress can be made on these lines, and another mode of attacking the problem must be sought.

The value of physical methods in testing chemical evidence is only now finding effective application in organic chemistry, and new experimental methods in this field are unfortunately limited in number and of recent development. That physical examination is in many ways preferable is undoubted. The changes involved in chemical reactions are very subtle, and specially so in the case of optically active substances. There is no guarantee that the constitution of a starting substance may be taken as a clue to that of the end product, and a critical reaction is frequently involved which may open up the possibility of optical inversion with formation of a stereoisomeride. It is only reasonable, then, to seek corroboration of results which have been obtained from chemical evidence alone.

PART II.

APPLICATION OF THE CONDUCTIVITY METHOD  
TO  
THE STRUCTURE OF MANNITOL AND OF ITS DERIVATIVES.

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APPLICATION OF THE CONDUCTIVITY METHOD  
TO  
THE STRUCTURE OF MANNITOL AND OF ITS DERIVATIVES.

For many years the only physical tests which have found wide application in investigations on sugars and related compounds have been the determination of optical rotations, of refractive indices, and of solubilities, but recently a new general principle has been introduced by Professor Boëseken of Delft. ~~As~~ The principle involved is novel, <sup>and</sup> an account may be given of the history of its development. As is well known, it has long been a practice when titrating boric acid to add a little mannitol or glycerol, as, without this addition, the titration is notoriously unreliable. On the other hand, in the presence of mannitol it is possible to titrate the acid as fully ionised. Another unexplained practice in analytical work was that of adding borax to solutions of substances of doubtful activity, in order to magnify the rotation and thus decide definitely as to whether the substance under examination was active or not. Correlating these factors, Boëseken estimated the conductivity and optical effects of adding boric acid to

a large number of hydroxy-compounds, and arrived at the generalisation that " polyhydroxy-compounds react with boric acid in solution, only when hydroxyl groups are on adjacent carbon atoms, and fall on the same side of the plane. " Thus, the system

$$\begin{array}{c} | \\ -\text{C}-\text{OH} \\ | \\ -\text{C}-\text{OH} \end{array}$$

would combine with boric acid, but the opposed configuration

$$\begin{array}{c} | \\ -\text{C}-\text{OH} \\ | \\ \text{OH}-\text{C}- \\ | \end{array}$$

would give no reaction.

If then, the polyhydroxy-compound is optically active, it is possible under the conditions stated to obtain exaltation of rotation in presence of boric acid, and concurrently, a corresponding change in the magnitude of the electrical conductivity of the solutions. The generalisation seems sound, and Boëseken has published a steady series of papers where his results are uniformly consistent and of wide application, not by any means confined to sugar derivatives.

In the light of the present discussion, the problem resolves itself into an examination of the effects, on rotation and conductivity, of adding boric acid to specific derivatives of mannitol, in which the hydroxyl groups exposed for reaction are occupying known positions in the chain. Such a study ought not only to throw some light on the comparative reactivity

of the two ends of the mannitol molecule, but also yield information as to which part of the molecule is mainly responsible for the change in the physical values. The methyl derivatives, although difficult of access, are definitely characterised, and accordingly were selected for this purpose along with the parent compounds, mannitol monoacetone and mannitol diacetone. The experimental methods followed were closely akin to those described by Boësen, and in order that the present results might be justifiably compared with his, a control standard was maintained throughout, which would ensure that the degree of accuracy of the determinations was similar.

In each case, a known weight of the substance to be examined was dissolved in (a) water, and (b) N/2 boric acid solution. Thereafter, in parallel experiments, a series of conductivity measurements was made in which the concentration of the compound was halved, in each succeeding determination, by the addition of an equal volume of water and N/2 boric acid solution respectively. That correlation of the ~~various~~ results might be possible, the ~~results~~ have been expressed under various headings thus:-

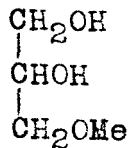
Columns I and II give the observed values for the conductivity in water and N/2 boric acid solution.



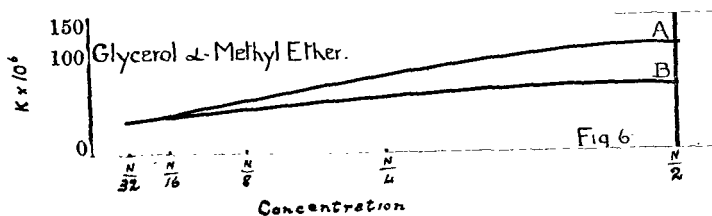
Column III indicates the magnitude of the change for each concentration, while in Column IV these figures are corrected for the conductivity of the boric acid used as solvent. A comparable factor is then found in the ratio of the two series of determinations, and these are given in Column V. Moreover, the changes have been recorded in the form of graphs, in which abscissa and ordinate represent concentration and magnitude of conductivity respectively; while, for each compound examined, two curves A and B are given, A being the conductivity in water, B that in N/2 boric acid solution.

Before embarking on the main research, however, one precaution had to be taken. It was necessary to justify the use of methylated derivatives in such work, and to show that the presence of the methyl group did not affect the reactions involved. Not only so, but it seemed desirable to examine the case of a simpler hydroxy-derivative than is afforded by the mannitol series, as, of necessity, special attention will be focussed on the behaviour of hydroxyl groups in the terminal positions. A suitable test substance for the purpose was obtainable in glycerol  $\alpha$ -methyl ether, where two hydroxyl positions are exposed to reaction, while the third is substituted by a methoxyl group:

# CONDUCTIVITY OF GLYCEROL $\alpha$ - METHYL ETHER.

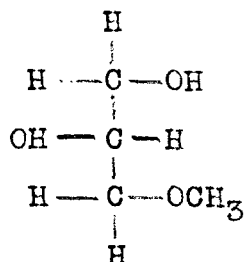


	I.	II.	III.	IV.	V.
	$K \times 10^6$	$K \times 10^6$			
Concentration.	in water.	in $N/2$ - boric acid.	Difference.	Exaltation.	Factor. $I \div II$ .
$N/2$	116.4	75.5	-40.9	-70.2	1.54
$N/4$	83.4	59.3	-24.1	-53.4	1.41
$N/8$	57.3	47.1	-10.2	-39.5	1.22
$N/16$	41.8	40.9	- 0.9	-30.2	1.02



A study of the figures and curve shows that the addition of boric acid to this compound diminishes the conductivity appreciably, and that therefore the boric acid seems to react to some extent. That the effect is a diminution which decreases with reduction of the concentration is noteworthy, as is also the fact that the ratios given in Column V are small numbers. The results

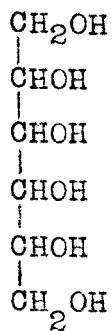
fall into line with those obtained by Boëseken himself for glycols, and in accordance with the views held by him, the configuration of glycerol  $\alpha$  -methyl ether is as represented below



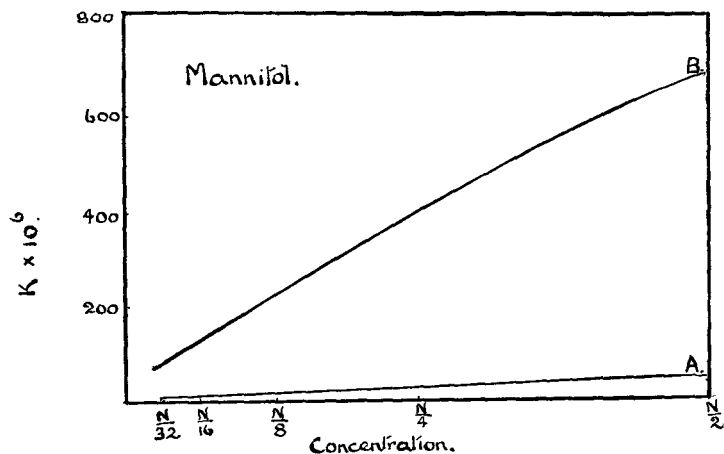
that is to say - the hydroxyl groups are repelled from one another and lie on opposite sides of the carbon chain. Apparently then, the presence of methyl groups does not vitiate the reaction with boric acid, and further investigation on the lines suggested was justified.

Obviously, a fundamental point in such work is the discrimination between a positive and <sup>a</sup>negative result, and mannitol and pentamethyl mannitol were selected as test substances which would indisputably provide the requisite types. In the former, six hydroxyl groups are exposed, any two of which may react, in contrast to the latter where only one hydroxyl position is unsubstituted, and the possibility of reaction is thus excluded.

# CONDUCTIVITY OF MANNITOL.

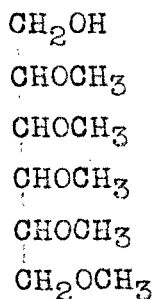


	I.	II.	III.	IV.	V.
Concentration.	$K \times 10^6$ in water.	$K \times 10^6$ in $N/2$ - boric acid.	Difference.	Exaltation.	Factor. $\text{II} \div \text{I}.$
$N$	92.9	1078	985.1	+955.8	11.6
$N/2$	61.6	704.2	642.6	613.3	11.4
$N/4$	36.9	407.5	370.6	341.3	11.0
$N/8$	22.4	223.3	200.9	171.6	9.9
$N/16$	15.0	123.7	108.7	79.4	8.2
$N/32$	11.0	73.6	62.6	33.3	6.7

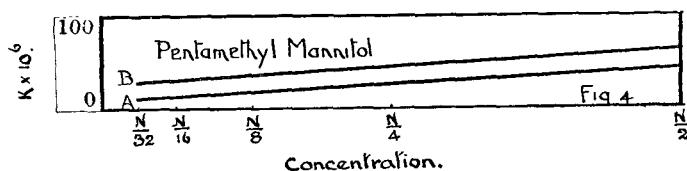


The increase in conductivity is great, diminishing with decrease in concentration, and the factors ( Column V ) are large, a fact which at once presents a sharp contrast to the case of pentamethyl mannitol, where the effect of the boric acid is slight.

CONDUCTIVITY OF PENTAMETHYL MANNITOL.



	I.	II.	III.	IV.	V.
Concentration.	$K \times 10^6$ in water.	$K \times 10^6$ in $N/2$ - boric acid.	Difference.	Exaltation.	Fact
$N/2$	44.2	54.2	10.0	-19.3	1.1
$N/4$	30.1	43.2	13.1	-16.2	1.4
$N/8$	20.5	37.1	16.6	-12.7	1.8
$N/16$	15.2	32.7	17.5	-11.8	2.1
$N/32$	14.0	30.6	16.6	-12.7	2.2

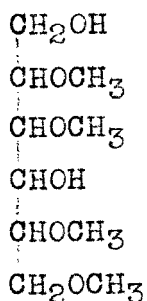


Here the values increase with dilution, and the factor is a small number.

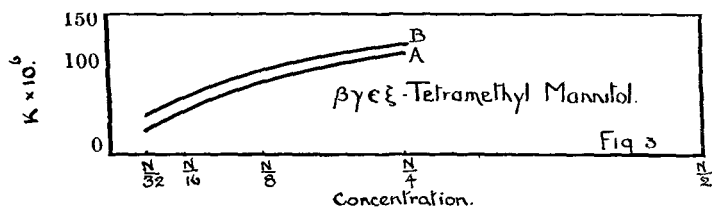
The two cases present definite features which may be used as standards, and alongside of which subsequent results may be ranged.

Following on the above, confirmation of Boësken's deduction that "only hydroxyl groups attached to adjacent carbon atoms can react", is readily obtainable from a study of this reaction, when applied to two isomeric tetramethyl mannitols viz: the 2,3,5,6- derivative and the 3,4,5,6- derivative. In the former, the unsubstituted positions are two places removed from one another, whereas in the latter, two hydroxyl groups are presented together in positions 1 and 2.

CONDUCTIVITY OF 2,3,5,6- TETRAMETHYL MANNITOL.

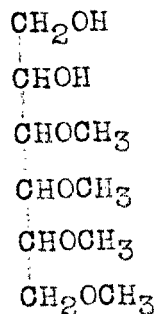


	I.	II.	III.	IV.	V.
Concentration.	$K \times 10^6$ in water.	$K \times 10^6$ in N/2- boric acid.	Difference.	Exaltation.	Factor.
N/4	110.7	120.0	9.3	-20.0	1.08
N/8	75.8	86.2	10.4	-18.9	1.14
N/16	48.6	60.4	11.8	-17.5	1.24
N/32	30.8	45.4	14.6	-14.7	1.47

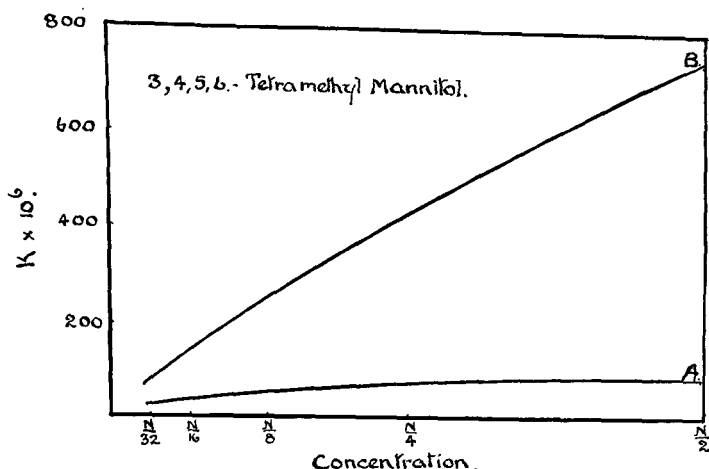


In this case it will be seen that the result is typically negative. The conductivity change is small, it decreases with decreasing concentration and, above all, the factor is small.

CONDUCTIVITY OF 3,4,5,6- TETRAMETHYL MANNITOL.



	I.	II.	III.	IV.	V.
Concentration.	$K \times 10^6$ in water.	$K \times 10^6$ in $N/2$ - boric acid.	Difference.	Exaltation.	Factor.
$N/2$	86.9	682.0	595.1	+565.8	7.8
$N/4$	64.7	410.6	345.9	316.6	6.3
$N/8$	42.8	229.6	186.8	157.5	5.4
$N/16$	27.3	126.9	99.6	70.3	4.6
$N/32$	19.6	73.1	53.5	24.2	3.7



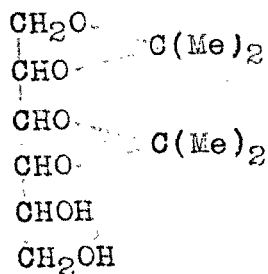
Here the reverse holds true. With this isomeride the conductivity shows a great increase, and the factor is a large number - clear proof that reaction with the boric acid has taken place, and substantial evidence that this is only so when hydroxyl groups are on neighbouring carbon atoms. A further interesting observation comes to light from a study of the curves. Those representing the changes in the case of 3,4,5,6-tetramethyl mannitol fall on the same points as those of mannitol itself for the same dilutions, showing that two hydroxyl groups exert the same influence as when all six are exposed, that is to say: an equal effect is produced by hydroxyl groups 1 and 2, and by 1,2,3,4,5, and 6. This is a highly unexpected and significant result, and it may be mentioned at this stage that Boësenken himself assumes its application in the striking paper (Ber., 1913, 46, 2612.) in which he allocates definite config-



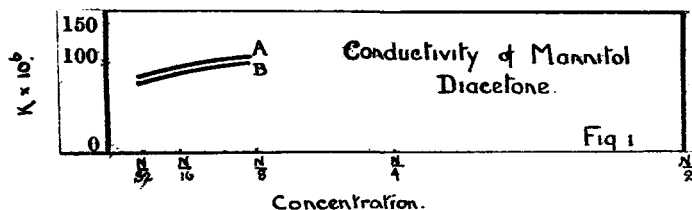
urations to  $\alpha$  - and  $\beta$  -glucose. It therefore seemed highly important to examine cases where alternative pairs of hydroxyl groups were exposed for reaction, and for this purpose, the compounds mannitol diacetone, mannitol monoacetone, and 5,6- dimethyl mannitol were considered appropriate. Inspection of the formulae for these derivatives shows that in mannitol diacetone there are two unsubstituted positions viz: 5 and 6 ; in mannitol monoacetone there are four 3,4,5, and 6 ; and in dimethyl mannitol also four - 1,2,3, and 4.

It may be remarked that, in the cases of both mannitol diacetone and mannitol monoacetone, the determinations were limited to three concentrations, on account of the inconstancy of the readings, an irregularity due to the hydrolytic effect of the boric acid present. Control solutions were, however, kept under polarimetric observation, and conductivity measurements were discontinued as soon as any change in specific rotation was apparent.

#### CONDUCTIVITY OF MANNITOL DIACETONE.

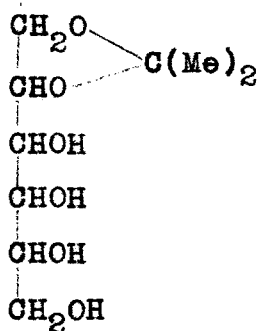


	I.	II.	III.	IV.	V.
Concentration.	$K \times 10^6$ in water.	$K \times 10^6$ in $N/2$ - boric acid.	Difference.	Exaltation.	Factor.
$N/8$	99.3	91.2	-8.1	+37.4	1.08
$N/16$	85.4	84.7	-0.7	-30.0	1.01
$N/32$	80.3	76.9	-3.4	-32.7	1.04

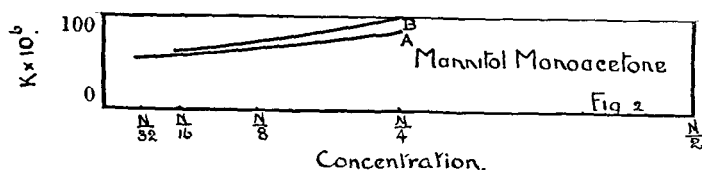


Here the only pair of hydroxyl groups which could contribute to reaction with boric acid occupy positions 5 and 6, but the result is in every sense negative, and may be compared with that for glycerol  $\alpha$ -methyl ether. The only reasonable conclusion is that these groups are opposed in space and lie on opposite sides of the carbon chain.

#### CONDUCTIVITY OF MANNITOL MONOACETONE.



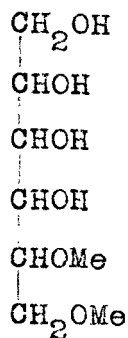
	I.	II.	III.	IV.	V.
Concentration.	$K \times 10^6$ in water.	$K \times 10^6$ in $N/2$ - boric acid.	Difference.	Exaltation.	Factor.
$N/4$	88.6	99.5	10.9	-18.4	1.12
$N/8$	66.8	71.4	4.6	-24.7	1.07
$N/16$	61.4	62.8	1.4	-27.9	1.02



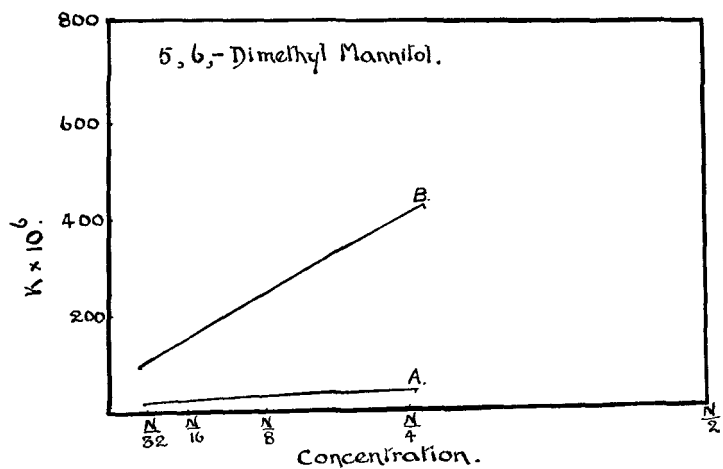
Mannitol monoacetone reacts similarly to mannitol diacetone, no increase in conductivity being occasioned on the addition of boric acid. The inclusion of another pair of hydroxyl groups thus brings about no change, so that confirmation of the deduction that hydroxyl groups 1 and 2 are mainly responsible for the reaction with boric acid is established.

Lastly the case of 5,6-dimethyl mannitol falls to be considered.

CONDUCTIVITY OF 5,6-DIMETHYL MANNITOL.



	I.	II.	III.	IV.	V.
	$K \times 10^6$	$K/10^6$			
Concentration.	in water.	in N/2- boric acid.	Difference.	Exaltation.	Factor.
N/4	33.6	405.9	372.3	+343.0	12.1
N/8	21.8	227.9	206.1	176.8	10.4
N/16	15.4	127.7	112.3	83.0	8.3
N/32	11.3	74.7	63.4	34.1	6.6

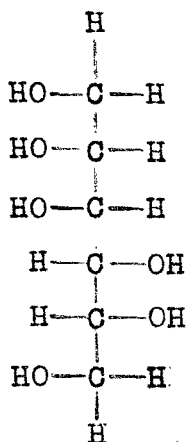


The increase in conductivity is considerable and the factor is large, diminishing with increasing dilution, so that the result is typically positive, and falls into line with the cases of mannitol itself and 3,4,5,6-dimethyl mannitol. The parallel is even more strongly emphasised by a study of the curves representing the change. The magnitude of the exaltation is identical for all three compounds, from which it follows that hydroxyl groups in positions 1,2,3, and 4 give the same reaction as when all six hydroxyl groups are free, and that the effect exerted by the hydroxyl groups in positions 5 and 6 is very small.

Now the only pair of hydroxyl groups common to mannitol, 3,4,5,6-tetramethyl mannitol and 5,6-dimethyl mannitol is situated in positions No. 1 and 2, and these three cases are the only ones where a positive result was obtained, so that little doubt remains that positions 1 and 2 are responsible for the change. Accepting Boeseken's generalisation, it follows that these hydroxyl groups are attached to adjacent carbon atoms, and are on the same side of the plane of the carbon chain.

Reviewing all the facts, it seems clear

that the two ends of the mannitol chain are not identical, that in positions 1 and 2 the hydroxyl groups are on the same side of the carbon plane whereas Nos. 5 and 6 are opposed as in  $\alpha$ -glycols. The configuration based on the chemical evidence is thereby confirmed, and the structure of mannitol, so far as has been ascertained, is



In concluding this section, it may be pointed out that, in the present thesis, discussion has been limited to the application of Boeseken's principles only so far as conductivity measurements are concerned. There still remains the supplementary aspect, that changes in conductivity on the addition of boric acid should be accompanied in the case of optically-active compounds by corresponding changes in specific rotation.

The obvious extension of the present in-

vestigation thus indicated has not been overlooked, and the results obtained are discussed in a paper published in the Journal of the Chemical Society, but detailed reference is omitted here, as it cannot be maintained that Boëseken's claims are fully justified so far as optical activity <sup>is</sup> are concerned.

On determining the specific rotation of each of the compounds now under discussion in pure water and in N/2 boric acid solution, the qualitative generalisation is confirmed that the specific rotation of an active compound is exalted in the presence of boric acid only when the latter reagent promotes an increase in conductivity. The changes thus occasioned are, however, frequently small, although widely different from those attributable to experimental error and this is shown in the following table in which some of the results are given:

Compound.	c.	Result of the conductivity test.	$[\alpha]_D^{20}$ in water.	$[\alpha]_D^{20}$ in N/2-boric acid.	Difference.
Mannitol .....		positive.	- 0.25°	+ 28.3°	+ 28.55°
$\epsilon\zeta$ -Dimethyl mannitol N/4		positive.	- 7.35	- 3.88	+ 3.47
$\gamma\delta\epsilon\zeta$ -Tetramethyl mannitol .....	N/8	positive.	- 13.02	- 6.72	+ 6.30
$\beta\gamma\epsilon\zeta$ -Tetramethyl mannitol .....	N/8	negative.	+ 38.54*	+ 40.64	+ 2.10
Pentamethyl mannitol N/2		negative.	+ 7.54	+ 8.25	+ 0.71
Mannitolmonoacetone N/4		negative.	+ 30.61	+ 29.50	- 1.11
Mannitoldiacetone ... N/8		negative.	+ 23.04	+ 22.43	- 0.61

Although it is possible to discriminate between a positive and negative result by the optical method, the distinction is by no means sharp and greater reliance has therefore to be attached to conductivity changes. This is not surprising in view of the fact that a conductivity determination is a simple measurement of ionic concentration, while the complex factors which govern the magnitudes of optical rotations in non-homogeneous systems are still obscure and largely unknown.



PART III.

EXPERIMENTAL.

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## EXPERIMENTAL.

### Preparation of Tetrabenzoyl Mannitol

Tetrabenzoyl mannitol monoacetone, prepared as described by Fischer, was hydrolysed, in accordance with the directions given by him (loc.cit.), by means of glacial acetic acid and hydrochloric acid. The method undoubtedly gives a pure product, but is scarcely practicable on the large scale, involving as it does large bulks of acid liquor, which require to be neutralised, and precipitation of the product as an emulsion which is not easy to extract.

The constants and properties of the product agreed closely with those quoted by Fischer, with one outstanding exception. The value for the specific rotation in tetrachloroethane, as given by Fischer, varies between  $+ 7.83$  and  $7.86$ , but, in the present work, the values ranged from  $+ 15.00$  to  $15.61$ . In order to ascertain which value is correct, three separate preparations of tetrabenzoyl mannitol were undertaken. The material was crystallised from a variety of solvents, including ethyl alcohol, a mixture of benzene and ligroin, and dry benzene, the last mentioned being that used by Fischer himself. In no case could any appreciable variation be de-

tected, and the above value of  $[\alpha]_D = +15.61$  was confirmed on each occasion. It is remarkable that this constant is exactly double that recorded by Fischer, and it is suggested that he may have been misled, in that the readings were taken in a 1 dcm. tube in place of a 2 dcm. tube.

#### Methylation of Tetrabenzoyl Mannitol.

Tetrabenzoyl mannitol ( 1 mol. ) was dissolved in methyl iodide ( 15 mols. ) by boiling under a condenser, and thereafter silver oxide (  $2\frac{1}{2}$  mols ) was gradually added. The alkylation was continued at the boiling point for eight hours, ether being used as the extracting agent. On removal of the solvent, a syrup remained, and this was subjected to a second methylation in which the same proportions of reagents were employed. The final product was a colourless syrup which failed to crystallise and could not be distilled. When boiled with water, the syrup was converted into an amorphous solid, which was not deliquescent and could be powdered in a mortar. In this condition it was further purified, by dissolving in a little dry ether and precipitating

with dry petroleum ether. On rubbing, the precipitate solidified to a white brittle amorphous powder. This purification was repeated a second time, the compound thereafter dried for 10 days in a vacuum desiccator, and finally for 1 hour at  $110^{\circ}\text{C}$ , followed by 30 minutes at  $120^{\circ}\text{C}$ .

Found: C = 68.35 , H = 5.10 per cent.

$\text{C}_{35}\text{H}_{32}\text{O}_{10}$  requires C = 68.62 , H = 5.23 per cent.

Found: OMe = 4.87, 6.00. Mean = 5.43 per cent

$\text{C}_{35}\text{H}_{32}\text{O}_{10}$  requires OMe = 5.06 per cent for one methoxyl group.

Found:  $(\text{C}_6\text{H}_5\text{CO}) = 64.6$  per cent.

$\text{C}_{35}\text{H}_{32}\text{O}_{10}$  requires  $(\text{C}_6\text{H}_5\text{CO}) = 68.6$  per cent for four benzoyl groups.

The compound was thus regarded as tetrabenzoyl monomethyl mannitol, and the various analytical results exclude entirely the possibility of a dimethyl derivative having been formed.

Repeated attempts were made to eliminate the benzoyl groups and thus obtain a monomethyl mannitol, but, as is frequently the case, hydrolysis proved to be imperfect and exceedingly slow, except when small quantities of material were employed, as for example, in the estimation of the benzoyl content.

Preparation of Test Substances required for the  
Determination of Conductivities.

As the compounds prepared specially for the present research have, by this time, been described fully in published papers, it is unnecessary to state more than the methods employed in each preparation, particularly as no irregularities were encountered.

Glycerol  $\alpha$  -methyl ether:

Glycerol was condensed with acetone by the agency of hydrogen chloride, and glycerol acetone isolated by fractionation. Thereafter, by methylation with silver oxide and methyl iodide, monomethyl glycerol monoacetone was obtained and from this glycerol  $\alpha$  -methyl ether by hydrolysis.

Liquid:- b.p.  $110^{\circ} / 13 \text{ mm.}$ ,  $n_D^{16}$  1.4432,  $D_4^{16}$  1.1192.

Mannitol triacetone:

This compound was prepared exactly as described by Fischer ( Ber., 1895, 28, 1167 ), the preparation presenting no special difficulty.

Colourless needles :- m.p.  $68^{\circ} - 70^{\circ}$ ,  $[\alpha]_D$  in alcohol +12.

Mannitol diacetone:

was obtained by the method devised by Irvine and Paterson ( loc.cit.), whereby mannitol triacetone

is subjected to graded hydrolysis. The process is reliable but tedious.

Colourless needles:- m.p.  $37^{\circ} - 39^{\circ}$ , b.p.  $172^{\circ}/11$  mm.

$[\alpha]_D$  in alcohol  $+ 15.7^{\circ}$

#### Mannitol monoacetone:

By extending the time over which mannitol triacetone is subjected to graded hydrolysis, the chief product is mannitol monoacetone, which was isolated as described by Irvine and Paterson.

Colourless plates:- m.p.  $85^{\circ}$

$[\alpha]_D$  in alcohol  $+ 23.2^{\circ}$

#### 5,6 - Dimethyl mannitol:

By alkylation, mannitol diacetone was converted into dimethyl mannitol diacetone ( b.p.  $140^{\circ}/13$  mm) and on careful hydrolysis the acetone groups were removed with the formation of dimethyl mannitol.

Colourless needles:- m.p.  $93^{\circ}$

$[\alpha]_D$  in alcohol  $- 8.85^{\circ}$

#### 3,4,5,6 - Tetramethyl mannitol:

On subjecting mannitol monoacetone to reactions parallel with those indicated above, the product finally obtained was tetramethyl mannitol, the constants for which agreed with those determined by

Irvine and Paterson.

Colourless liquid:- b.p. 167°/13 mm.

$[\alpha]_D$  in alcohol - 12.5°

2,3,5,6 - Tetramethyl mannitol:

The preparation of this isomeride involved a tedious series of processes.

Starting from vegetable ivory, the preparation of crystalline mannose was undertaken by the method recently described by Hudson, as, thanks to the courtesy of Dr Hudson, details of the process have been available in this laboratory for several years.

The mannose was converted into  $\alpha$ -methylmannoside by Fischer's method, and thereafter into tetramethyl methylmannoside. On hydrolysis, tetramethyl mannose was obtained, and from this, by reduction, the desired form of tetramethyl mannitol was isolated.

Colourless liquid:- b.p. 177°/11 mm.

$[\alpha]_D$  in alcohol + 39.8°

2,3,4,5,6 - Pentamethyl mannitol:

The particular method selected to produce the necessary pentamethyl mannitol was to methylate 3,4,5,6-

tetramethyl mannitol by the silver oxide reaction.

Colourless liquid:- b.p.  $142^{\circ}/12$  mm.

$[\alpha]_D$  in alcohol  $+ 8.9^{\circ}$ .

Each of the compounds used as test-substances in the conductivity derivatives thus displayed the standard physical constants, and may be regarded as pure.

It should also be mentioned that the boric acid required for the work was the purest obtainable, and was recrystallised several times before use. Before commencing the series of measurements which are embodied in the theoretical section of the Thesis, it was ascertained by means of blank experiments that the conditions employed permitted of a standard of accuracy at least equal to that adopted by Boeseken.



The work now described was commenced in April 1914 and has been carried out in the Chemical Research Laboratory of the University of St Andrews under the direction of Professor Irvine, for whose advice and help the author desires to express her grateful acknowledgement.



