Advances in
Carbohydrate Chemistry

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CONTENTS

Psicose, Sorbose and Tagatose

By J. V. Karabinos, *Saint Procopius College, Lisle, Illinois*

Acetals and Ketals of the Tetritols, Pentitols and Hexitols

By S. A. Barker and E. J. Bourne, *The University, Birmingham, England*

The Glycals

By Burckhardt Helferich, *Chemisches Institut der Universität, Bonn, Germany*

The Chemistry of the 2-Amino Sugars (2-Amino-2-Deoxy-Sugars)

By A. B. Foster and M. Stacey, *Department of Chemistry, The University, Birmingham, England*

The Size and Shape of Some Polysaccharide Molecules

By C. T. Greenwood, *The University of Edinburgh, Scotland*

THE METHYL ETHERS OF THE ALDOPENTOSES AND OF RHAMNOSE AND FUCOSE

By R. A. Laidlaw and (the late) E. G. V. Percival

The University of Edinburgh, Scotland

Contents

I. Introduction

Apart from their intrinsic interest the methyl ethers of certain of the pentoses, especially those of L-arabinose and D-xylose, are of great importance in structural studies of the naturally occurring pentosans, and of plant gums and mucilages.[1] This also applies to the methyl ethers of L-rhamnose and L-fucose.

The general methods of synthesis and of derivations of structure which have been described in previous articles on the methyl ethers of D-glucose[2] and of D-galactose,[3] apply also in this series, so that it has been thought to be unnecessary to give full details in every case. The article has been compiled with the object of providing readily accessible data about the properties of the known methylated pentoses in the hope that it will be of assistance to workers interested in structural studies on polysaccharides containing pentose residues. Derivatives of rhamnose and fucose have also been included because of the importance of the former as a building unit in the plant gums and mucilages, and because fucose is a component of gum tragacanth, of the seaweed polysaccharide

(1) F. Smith and J. K. N. Jones, *Advances in Carbohydrate Chem.*, **4**, 243 (1949).
(2) E. J. Bourne and S. Peat, *Advances in Carbohydrate Chem.*, **5**, 145 (1950).
(3) D. J. Bell, *Advances in Carbohydrate Chem.*, **6**, 11 (1951).

sulfate fucoidin, of the jelly coat of sea urchin eggs, of blood-group polysaccharides and of frog-spawn mucin.

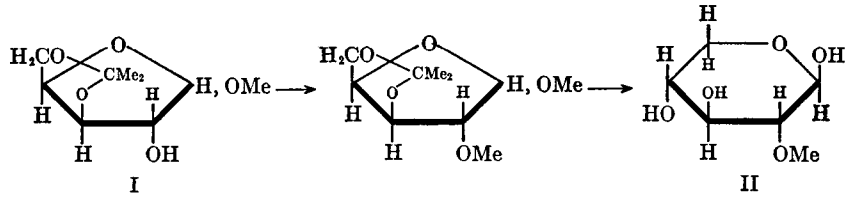
II. The Methyl Ethers of D-Xylose

With the exception of 4-methylxylose all the methyl ethers that are derivable theoretically from D-xylopyranose or D-xylofuranose are known. From the products of hydrolysis of methylated polysaccharides 2-methyl-, 3-methyl-, 2,3-dimethyl-, 2,4-dimethyl-, 3,4-dimethyl- and 2,3,4-trimethyl-D-xylose have been separated. No D-xylofuranose derivatives have been isolated from a natural source. Unknown at the present time are the 4-methyl-, 4,5-dimethyl-, 2,4,5- and 3,4,5-trimethyl- and 2,3,4,5-tetramethyl-D-xylose.

1. *2-Methyl-D-xylose*

2-Methyl-D-xylose has been isolated from the products of hydrolysis of methylated esparto xylan,[4] methylated pear cell-wall xylan[5] and from the methylated xylan of the red seaweed *Rhodymenia palmata.*[6] The methylated seed mucilages of *Plantago lanceolata,*[7] *Plantago arenaria*[8] and *Plantago ovata*[9] also yield 2-methyl-D-xylose on hydrolysis.

The synthesis of this sugar (II) has been achieved[10] from methyl 3,5-isopropylidene-D-xylofuranoside ($\alpha\beta$ mixture) (I) by methylation and



hydrolysis. 2-Methyl-D-xylose has also been prepared by the methylation and hydrolysis of methyl 3,5-ditrityl-D-xylofuranoside ($\alpha\beta$ mixture).[11] The location of the methyl group was proved by the formation of D-xylose phenylosazone on treatment with phenylhydrazine.

(4) (a) R. A. S. Bywater, W. N. Haworth, E. L. Hirst and S. Peat, *J. Chem. Soc.*, 1983 (1937); (b) S. K. Chanda, E. L. Hirst, J. K. N. Jones and E. G. V. Percival, *ibid.*, 1289 (1950).

(5) S. K. Chanda, E. L. Hirst and E. G. V. Percival, *J. Chem. Soc.*, 1240 (1951).

(6) S. K. Chanda and E. G. V. Percival, *Nature*, **166**, 787 (1950).

(7) E. G. V. Percival and I. C. Willox, *J. Chem. Soc.*, 1608 (1949).

(8) W. A. G. Nelson and E. G. V. Percival, *J. Chem. Soc.*, 58 (1942).

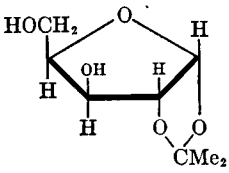
(9) R. A. Laidlaw and E. G. V. Percival, *J. Chem. Soc.*, 1600 (1949).

(10) G. J. Robertson and T. H. Speedie, *J. Chem. Soc.*, 824 (1934).

(11) R. J. McIlroy, *J. Chem. Soc.*, 100 (1946).

2. *3-Methyl-D-xylose*

3-Methyl-D-xylose has been isolated from the methylated seed mucilages of *Plantago lanceolata*[7] and *Plantago ovata*.[12] Synthesis[13] has been effected from 1,2-isopropylidene-D-xylofuranose (III) by conversion into 1,2-isopropylidene-5-trityl-D-xylofuranose (IV), methylation to the corresponding 3-methyl ether (V) followed by hydrolysis. The corresponding 5-benzoate was also used in a parallel synthesis. The constitution of the product was proved[13] by the fact that the monomethyl-xylose underwent both methyl furanoside and methyl pyranoside formation, showing



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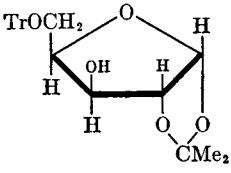

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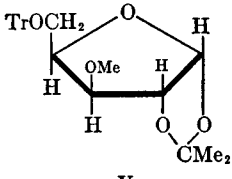


V

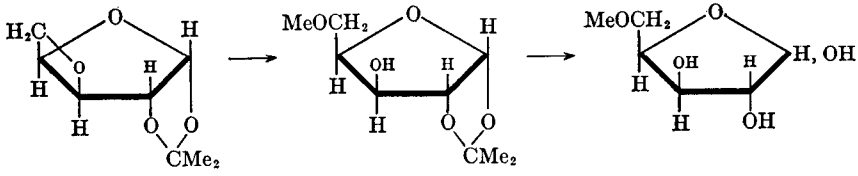
the absence of substitution on C4 and C5, and gave a *p*-bromophenylosazone which still contained a methoxyl residue, so that the substituent was clearly not on C2.

3. *4-Methyl-D-xylose*

No synthesis of 4-methyl-D-xylose has been reported. The osazone has been obtained from 2,4-dimethyl-D-xylose.[14]

4. *5-Methyl-D-xylose*

5-Methyl-D-xylose (VII) was synthesized by Levene and Raymond[13] from 1,2-isopropylidene-5-tosyl-D-xylofuranose by conversion into the corresponding 3,5-anhydride (VI) followed by heating with sodium



VI VII

methoxide in methanol, and hydrolysis with dilute acid. An alternative method avoids the isolation of the anhydride. The constitution of the product was decided from the method of preparation and because

(12) R. A. Laidlaw and E. G. V. Percival, *J. Chem. Soc.*, 528 (1950).
(13) P. A. Levene and A. L. Raymond, *J. Biol. Chem.*, **102**, 331 (1933).
(14) O. Wintersteiner and Anna Klingsberg, *J. Am. Chem. Soc.*, **71**, 939 (1949).

the derived *p*-bromophenylosazone differed from that prepared from 3-methyl-D-xylose.

5. *2,3-Dimethyl-D-xylose*

2,3-Dimethyl-D-xylose has been obtained by the hydrolysis of many methylated polysaccharides, especially the xylans,[4,5,6] although it has also been isolated from the hydrolysis products of methylated mucilages such as the one from *Plantago lanceolata*.[7] This important dimethylpentose was first isolated as a sirup by Hampton, Haworth and Hirst[15] by the hydrolysis of methylated esparto xylan. The constitution was established as follows. Methylation and hydrolysis gave 2,3,4-trimethyl-D-xylose, thus eliminating the possibility of substitution on C5. The corresponding dimethylxylonic acid gave a γ-lactone, showing that the hydroxyl group on C4 was unsubstituted. Failure to form an osazone was additional evidence for substitution on C2.

Originally obtained as a sirup, the carefully purified 2,3-dimethyl-D-xylose prepared from esparto xylan[4(b)] and pear cell-wall xylan[5] has now been obtained crystalline.[6,15a]

The synthesis of 2,3-dimethyl-D-xylose from methyl 5-benzoyl-D-xylofuranosides ($\alpha\beta$ mixture) by methylation, debenzoylation and hydrolysis has been reported.[16]

6. *2,4-Dimethyl-D-xylose*

2,4-Dimethyl-D-xylose has been isolated from the products of hydrolysis of the methylated seed mucilages of *Plantago lanceolata*[7] and *P. ovata*[12] and from the algal xylan of *Rhodymenia palmata*.[6]

The crystalline β-form of the sugar was first isolated[17] by the hydrolysis of the mixture of products obtained by the methylation with methyl iodide of the thallium derivatives of methyl xylopyranosides ($\alpha\beta$ mixture) in which the 2,4-dimethyl-D-xylose was the principal component. Since the corresponding acid gave a pyranolactone, the amide gave a negative Weerman test and the derivatives in question were different from those of 2,3-dimethyl-D-xylose, the constitution was established.

[In the Weerman reaction, treatment of an amide with sodium hypochlorite and alkali leads to the formation of a sugar lower in the series; in this way a hexonamide is converted into a pentose sugar. The first stage in this transformation is the formation of the corresponding iso-

(15) H. A. Hampton, W. N. Haworth and E. L. Hirst, *J. Chem. Soc.*, 1739 (1929).

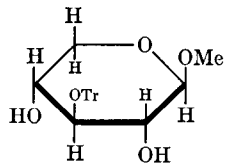
(15a) S. K. Chanda, Elizabeth E. Percival and (the late) E. G. V. Percival, *J. Chem. Soc.*, 260 (1952).

(16) G. J. Robertson and D. Gall, *J. Chem. Soc.*, 1600 (1937).

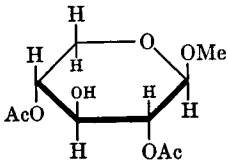
(17) C. C. Barker, E. L. Hirst and J. K. N. Jones, *J. Chem. Soc.*, 783 (1946).

cyanate. The isocyanate from an α-hydroxy amide decomposes with the liberation of sodium isocyanate, which may be identified and estimated as hydrazodicarbonamide.[17a] This technique is known as the "Weerman test." If, however, the α-position is methylated, no sodium isocyanate is formed, the degradation proceeding by a different route (see page 9). A negative Weerman test thus indicates that the α-hydroxyl group is substituted.]

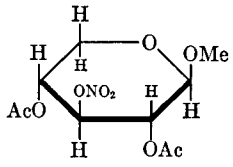
Derivatives of 2,4-dimethyl-D-xylose had been prepared twelve years previously by the following synthetic route.[10] Methyl β-D-xylopyranoside, on treatment with triphenylchloromethane in pyridine, gave methyl 3-trityl-β-D-xylopyranoside (VIII) as a sirup, the diacetyl derivative of which was allowed to react with hydrogen chloride in benzene to give methyl 2,4-diacetyl-β-D-xylopyranoside (IX). The conditions used were considered to preclude the possibility of an acyl rearrangement. Treatment with fuming nitric acid in chloroform gave crystalline methyl 2,4-diacetyl-β-D-xylopyranoside 3-nitrate (X). After deacetylation with dimethylamine, the crude methyl β-D-xylopyranoside 3-nitrate was methylated and the nitrate group removed by means of reduction with sodium amalgam to give crystalline methyl 2,4-dimethyl-β-D-xylopyranoside (XI).



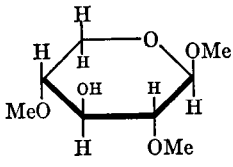
VIII



IX



X



XI

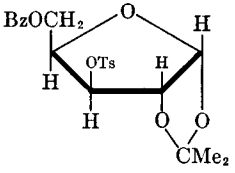
It is unfortunate that the free sugar itself was not isolated, for that would have enabled a comparison between the properties of the material synthesized by the above route and of the product obtained later by the thallium method.[17] The interpretation of the result of the above synthesis depends on the assumption that the trityl group substituted the hydroxyl residue on C3. Evidence in support of this was adduced by

(17a) R. A. Weerman, *Rec. trav. chim.*, **37**, 16 (1917).

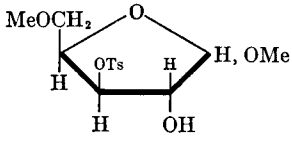
comparing the crystalline tosyl derivative (m. p. 88°) of XI with methyl 2,3-dimethyl-4-tosyl-β-D-xylopyranoside (m. p. 56°–59°) and methyl 3,4-dimethyl-2-tosyl-β-D-xylopyranoside (m. p. 105°) prepared from methyl 3,4-dimethyl-β-D-xyloside (see below). Obviously, however, this decision rests on the assumption that the 3,4-dimethyl-D-xylose synthesized by the same authors[10] has in fact the constitution assigned to it.

7. *2,5-Dimethyl-D-xylose*

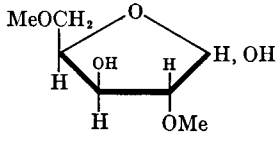
5-Benzoyl-1,2-isopropylidene-3-tosyl-D-xylofuranose[13] (XII) was treated with sodium methoxide to remove the benzoyl residue.[16] Methylation gave the corresponding 5-methyl ether which, on heating with methanolic hydrogen chloride, gave methyl 5-methyl-3-tosyl-D-xylofuranosides (XIII) (both α- and β-forms, the latter being isolated in the crystalline state). Methylation of XIII gave methyl 2,5-dimethyl-3-tosyl-D-xylofuranoside in which the tosyl group was removed by hydrolysis with alcoholic potassium hydroxide, and the glycoside methyl residue



XII



XIII



XIV

by acid hydrolysis, giving 2,5-dimethyl-D-xylose (XIV). The identity of the product was proved by conversion to the *p*-bromophenylosazone of 5-methyl-D-xylose.[13]

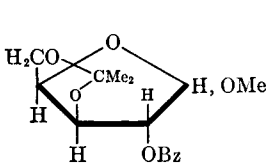
8. *3,4-Dimethyl-D-xylose*

The claim[8,18] that 3,4-dimethyl-D-xylose was a constituent of the products of hydrolyzed methylated plantain seed mucilages is now recognized to be of doubtful validity,[7] but evidence has been presented that this sugar occurs in the hydrolysis products of methylated gum tragacanth.[19] The sugar so obtained gave a crystalline pyranolactone and the derived amide gave a positive Weerman test.

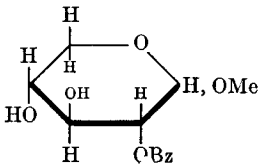
The synthesis of 3,4-dimethyl-D-xylose had previously been recorded[10] but no direct comparison of similar derivatives of the natural and synthetic product had been made. For the synthesis, methyl 3,5-isopropylidene-D-xyloside (αβ mixture) was converted into the 2-benzoate (XV) which with hot methanolic hydrogen chloride was transformed (presumably) into methyl 2-benzoyl-D-xylopyranosides (αβ mixture) (XVI)

(18) J. Mullan and E. G. V. Percival, *J. Chem. Soc.*, 1501 (1940).
(19) Sybil P. James and F. Smith, *J. Chem. Soc.*, 739 (1945).

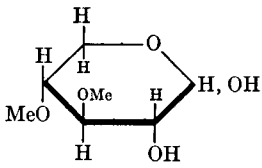
which after methylation, debenzoylation with sodium methoxide and hydrolysis gave 3,4-dimethyl-D-xylose (XVII).



XV



XVI



XVII

The product gave a sirupy dimethylxylose phenylosazone, and was recovered unchanged on standing for three days in cold methanolic hydrogen chloride, from which it was concluded that a free hydroxyl group was present on C2 and that furanoside formation was inhibited by the presence of a methoxyl residue on C4. Because of the possibility of the migration of the benzoyl group and for other reasons it is perhaps unfortunate that more rigid proofs of the structure of the synthetic material were not presented.

9. *3,5-Dimethyl-D-xylose*

The isolation of free 3,5-dimethyl-D-xylose has never been reported,[19a] but the corresponding furanolactone[13] has been synthesized by the methylation both of 1,2-isopropylidene-D-xylofuranose and of 1,2-isopropylidene-5-methyl-D-xylofuranose, followed by hydrolysis and oxidation. The facts that the lactone on methylation gave trimethyl-D-xylofuranolactone (isolated as the crystalline phenylhydrazide) and that the dimethyl xylonolactone had a slow rate of hydrolysis, agreed with the structure assigned.

10. *2,3,4-Trimethyl-D-xylose*

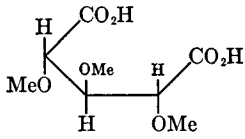
Trimethyl-D-xylopyranose has been isolated from the hydrolysis products of methylated xylans,[4,5,6] gums[20] and mucilages.[7–9,12,18] This crystalline sugar played an important part in the recognition of the fact that the pyranose ring structure was of prime importance in the sugar group. It was first prepared[21] by the methylation of D-xylose with dimethyl sulfate and sodium hydroxide followed by hydrolysis. Oxida-

(19a) A recent article by R. A. Laidlaw [*J. Chem. Soc.*, 2941 (1952)], reports the preparation of 3,5-dimethyl-D-xylose by the methylation of 1,2-isopropylidene-3-methyl-D-xylose, followed by hydrolysis. Its properties are shown in Table I, (page 29).

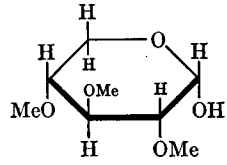
(20) E. L. Hirst and J. K. N. Jones, *J. Chem. Soc.*, 506 (1946).

(21) A. E. Carruthers and E. L. Hirst, *J. Chem. Soc.*, 2299 (1922).

tion with nitric acid[22] gave the meso*xylo*trimethoxyglutaric acid (XVIII), thus proving the constitution (XIX).



XVIII



XIX

11. *2,3,5-Trimethyl-*D*-xylose*

Trimethyl-D-xylofuranose was obtained by the methylation of the mixture of methyl xylofuranosides obtained by the condensation of D-xylose with methanolic hydrogen chloride at room temperature, followed by hydrolysis.[23]

The constitution of this substance was settled by oxidation with bromine to give a stable γ-lactone, and with nitric acid to give L(+)-dimethoxysuccinic acid.[24]

III. The Methyl Ethers of D-Arabinose

It is only comparatively recently that D-arabinose has been found to be a constituent of natural products in contrast to the frequent occurrence of its enantiomorph. Units of D-arabofuranose have been shown to form part of the molecules of the polysaccharides isolated from *Mycobacterium tuberculosis* (human strain),[25] being identified as methyl 3,5-dimethyl-D-arabofuranoside in the products of hydrolysis, after methylation, of the somatic polysaccharide, and as the above glycoside and the methyl trimethyl-D-arabofuranoside in the lipid-bound fraction. 2-Methyl-D-arabinose has been synthesized.

1. *2-Methyl-*D*-arabinose*

Three methods have been described for the synthesis of 2-methyl-D-arabinose.

The first method employs the Ruff degradation of 3-methyl-D-glucose.[26]

In the second, crystalline methyl β-D-arabopyranoside was converted into the 3,4-isopropylidene derivative (XX), which on methylation with silver oxide and methyl iodide and removal of the isopropylidene residue with methanolic hydrogen chloride, gave methyl 2-methyl-β-D-arabo-

(22) E. L. Hirst and C. B. Purves, *J. Chem. Soc.*, 1352 (1923).

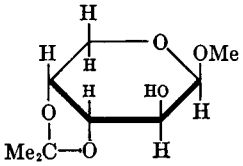
(23) W. N. Haworth and G. C. Westgarth, *J. Chem. Soc.*, 880 (1926).

(24) W. N. Haworth and C. R. Porter, *J. Chem. Soc.*, 611 (1928).

(25) (Sir) Norman Haworth, P. W. Kent and M. Stacey, *J. Chem. Soc.*, 1211, 1220 (1948).

(26) O. T. Schmidt and A. Simon, *J. prakt. Chem.*, **152**, 190 (1939).

pyranoside (XXI), from which the free sugar was isolated by hydrolysis with sulfuric acid in the usual way.[27]



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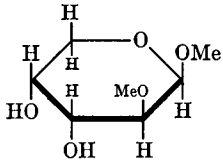
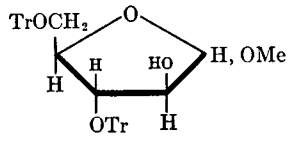


XXI



XXII

The third process consists of converting methyl D-arabofuranosides ($\alpha\beta$ mixture) into the 3,5-dityrityl ether (XXII) by treatment with trityl chloride in pyridine, from which by methylation and subsequent detritylation and hydrolysis, 2-methyl-D-arabinose was obtained.[28] The product gave D-arabinose phenylosazone on treatment with phenylhydrazine acetate.

2. *2,4-Dimethyl-D-arabinose*

2,4-Dimethyl-D-arabinose has been obtained[29] from 3-β-D-galactopyranosyl-D-arabopyranose, obtained by the Wohl-Zemplén degradation of lactose, by methylation and hydrolysis. Oxidation with nitric acid gave β-hydroxy-$\alpha\gamma$-dimethoxy-D-*arabo*-glutaric acid, the amide of which was the enantiomorph of the product obtained from 2,4-dimethyl-L-arabinose.

3. *3,5-Dimethyl-D-arabinose*

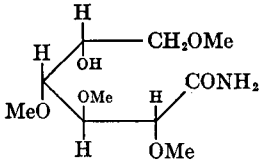
The structure of this substance isolated from the somatic specific polysaccharide of *M. tuberculosis*[25] was determined from the facts that the corresponding amide was the enantiomorph of 3,5-dimethyl-L-arabonamide (see below) and that by complete methylation followed by hydrolysis, oxidation and amide formation, 2,3,5-trimethyl-D-arabonamide was obtained.

4. *2,3,5-Trimethyl-D-arabinose*

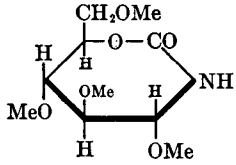
Trimethyl-D-arabofuranose (XXV) has been prepared by the degradation of 2,3,4,6-tetramethyl-D-gluconamide (XXIII) by the action of sodium hypochlorite (Weerman reaction), the cyclic urethane (XXIV) undergoing hydrolysis with dilute sodium hydroxide solution in the cold.[30]

The constitution of the product was indicated by the fact that its specific rotation was equal and of opposite sign to that of trimethyl-

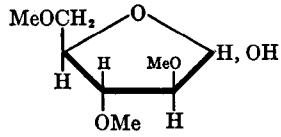
(27) J. K. N. Jones, P. W. Kent and M. Stacey, *J. Chem. Soc.*, 1341 (1947).
(28) G. J. Halliburton and R. J. McIlroy, *J. Chem. Soc.*, 299 (1949).
(29) F. Smith, *J. Chem. Soc.*, 744 (1939).
(30) W. N. Haworth, S. Peat and J. Whetstone, *J. Chem. Soc.*, 1975 (1938).



XXIII



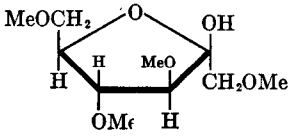
XXIV



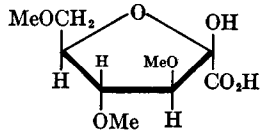
XXV

L-arabofuranose, that the methyl pentoside was readily hydrolyzed and that the corresponding lactone, which was only slowly hydrolyzed in aqueous solution, gave 2,3,5-trimethyl-D-arabonamide on treatment with ammonia.

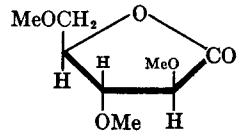
2,3,5-Trimethyl-D-arabonolactone (XXVIII) has also been prepared from tetramethyl-D-fructofuranose (XXVI) by oxidation with nitric acid to give 3,4,6-trimethyl-2-keto-D-gluconic acid (XXVII), followed



XXVI



XXVII



XXVIII

by oxidation with barium permanganate.[31] Oxidation of the product, 2,3,5-trimethyl-D-arabonolactone, with nitric acid, followed by esterification and amide formation, gave D(−)-dimethoxysuccinic acid.[32]

5. *2,4,5-Trimethyl-D-arabinose*

This compound, which restored the color to Schiff's reagent, has been isolated by the action of alkali on the cyclic urethane obtained from 2,3,5,6-tetramethyl-D-gluconamide.[30]

6. *3,4,5-Trimethyl-D-arabinose*

2,3,5,6,7-Pentamethyl-D-glucoascorbic acid on ozonolysis and hydrolysis gives 3,4,5-trimethyl-D-arabonic acid.[33] The ester and the amide are also described, the constitution of the latter following from the fact that it gave a positive Weerman test.

7. *2,3,4,5-Tetramethyl-D-arabinose*

By the methylation of 3,4,5-trimethyl-D-arabonic acid there was isolated methyl 2,3,4,5-tetramethyl-D-arabonate, from which the corresponding amide was prepared.[33]

(31) J. Avery, W. N. Haworth and E. L. Hirst, *J. Chem. Soc.*, 2317 (1927).
(32) W. N. Haworth, E. L. Hirst and A. Learner, *J. Chem. Soc.*, 2432 (1927).
(33) W. N. Haworth, E. L. Hirst and J. K. N. Jones, *J. Chem. Soc.*, 549 (1937).