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Reduction of the Products of Periodate Oxidation of Carbohydrates. I. Hydrogenation with Raney Nickel of the Dialdehydes from the Methyl Glycopyranosides[1]

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It has been shown that the dialdehydes obtained from sugar glycosides by oxidation with periodic acid can be reduced readily to the corresponding alcohols, the structures of which have been proved. Since this treatment results in the elimination of all dissymmetry except that at C_1, an examination of these new alcohols provides a simple way of correlating the structure of glycosides.

The application of the Malaprade[3,4] periodate reaction to the elucidation of the structure of the alkyl glycosides of the aldohexoses and aldopentoses was examined first by Fleury[5] and co-workers, and later, in more rigorous fashion, by Jackson and Hudson[6,7] who used this reaction to effect a correlation of the structure of the glycosides; these workers demonstrated that, on oxidation with periodic acid, all methyl α-D-hexopyranosides yield a common dialdehyde I and all methyl β-D-hexopyranosides yield another common dialdehyde II. Similarly, all methyl α-D-pentopyranosides yield a common dialdehyde III and all methyl β-D-pentopyranosides yield another common dialdehyde IV. By means of bromine oxidation dialdehydes I–IV were converted to the corresponding dicarboxylic acids which were isolated as their crystalline barium or strontium salts.

It is apparent that if the dialdehydes I–IV are reduced, the corresponding alcohols should be obtained. This reaction has been achieved by hydrogenating under pressure (1000–2000 pounds per square inch) at 120° in the presence of a Raney nickel catalyst and by the action of sodium borohydride in aqueous solution.[8,9]

From an examination of formulas I–VIII the following stereochemical relationships are apparent. Dialdehydes I and II are diastereoisomers as are the respective salts of the dicarboxylic acids derived from them due to the retention of asymmetry at carbon atoms 1 and 5 in each case. However, dialdehydes III and IV are optical antipodes as are the salts of the respective dicarboxylic acids derived from them. Reduction of dialdehydes I and II to yield alcohols V and VI, respectively, should destroy, in each case, the asymmetry of carbon atom 5 but the asymmetry of carbon atom 1 should be retained. Thus alcohols V and VI, which differ only with respect to the configuration of carbon atom 1, should be optical antipodes. Alcohols VII and VIII, produced by reduction of dialdehydes III and IV, respectively, should also form a pair of optical antipodes.

The enantiomorphism of alcohols V and VI and of alcohols VII and VIII has been verified experimentally. Six methyl D-hexosides were prepared corresponding to the anomeric pairs of the methyl glycosides of D-glucose, D-mannose and D-galactose. Four methyl pentosides were prepared corresponding to the pair of anomeric methyl glycosides of D-xylose and the anomeric pair of glycosides of L-arabinose. The carefully purified glycosides were oxidized with periodic acid in aqueous solution at 20°, according to the procedure of Jackson and Hudson,[6] and the sirupy dialdehyde obtained in each case was hydrogenated in the presence of Raney nickel catalyst at 120° and at a pressure of 1000–2000 pounds per square inch. All the methyl α-D-hexosides yielded D′-methoxy-hydroxymethyldiethylene glycol (V) and all the methyl β-D-hexosides yielded L′-methoxy-hydroxymethyldiethylene glycol (VI). In the pentose series both methyl β-D-xyloside and methyl α-L-arabinoside yielded L′-methoxydiethylene glycol (VIII) and methyl α-D-xyloside and methyl β-L-arabinoside both yielded D′-methoxydiethylene glycol (VII).

It is apparent, therefore, that relating all methyl α-D-hexosides to a common alcohol (V) and all methyl β-D-hexosides to a common alcohol (VI) affords a new method of correlating the methyl hexosides. Similarly in the pentose series the derivation from all methyl α-D-pentosides and from all methyl β-L-pentosides of a common alcohol (VII) and the derivation from all methyl β-D-pentosides and from all methyl α-L-pentosides of a common alcohol (VIII) constitutes a new method of correlating the methyl pentosides. Thus in the pentose series of sugars it has been possible to achieve experimentally not only a correlation of all methyl α-D-pentosides with all methyl β-D-pentosides and a correlation of all methyl α-L-pentosides with all methyl β-L-pentosides, but also a correlation of the D- and L-series of the sugars.

The method of correlating the glycosides described herein possesses certain advantages over Jackson and Hudson's method of correlation. For example, the alcohols V, VI, VII and VIII, which distil *in vacuo* without decomposition, are obtained easily in high yield from the corresponding dialdehydes (I, II, III and IV, respectively). By comparison the crystalline salts of the dibasic acids produced from the dialdehydes I–IV by bromine oxidation are not so readily accessible. In the method of Jackson and Hudson the dibasic acids (in the form

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[2] From a thesis submitted to the graduate faculty of the University of Minnesota, January, 1951, in partial fulfillment of the requirements for the degree of Doctor of Philosophy by J. W. Van Cleve.

[3] L. Malaprade, *Bull. soc. chim.*, [4] **43**, 683 (1928).

[4] L. Malaprade, *Compt. rend.*, **186**, 382 (1928).

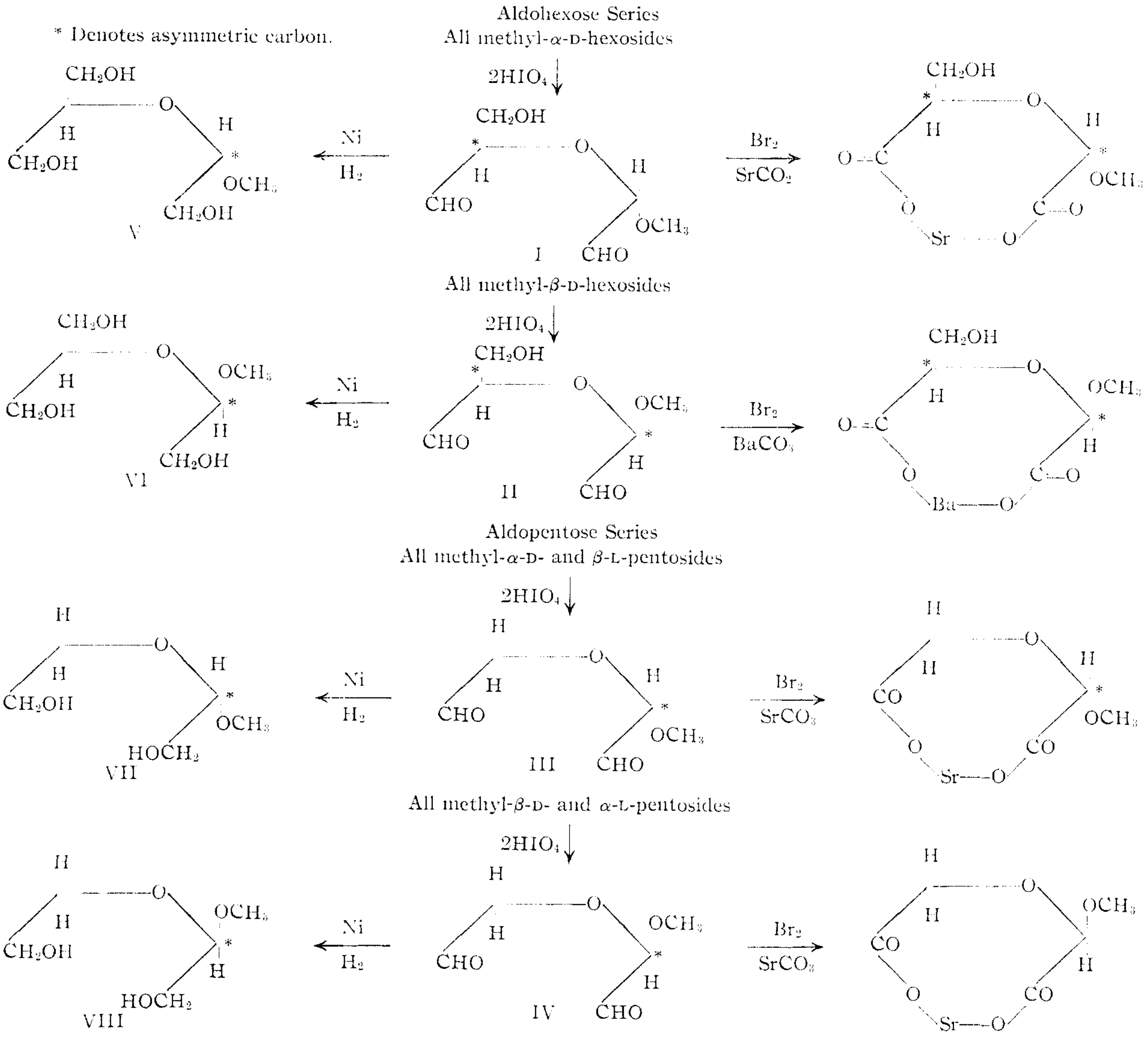
[5] H. Hérissey, P. Fleury and M. Joly, *J. pharm chim.*, [8] **20**, 149 (1934).

[6] E. L. Jackson and C. S. Hudson, THIS JOURNAL, **59**, 994 (1937).

[7] E. L. Jackson and C. S. Hudson, *ibid.*, **58**, 378 (1936).

[8] M. Abdel-Akher, J. E. Cadotte, Bertha Lewis, R. Montgomery, F. Smith and J. W. Van Cleve, *Nature*, **171**, 474 (1953).

[9] M. Abdel-Akher, J. K. Hamilton and F. Smith, THIS JOURNAL, **73**, 4691 (1951).



of their salts) derived from the methyl hexosides are diastereoisomers and hence do not possess the value as reference compounds as the alcohols V and VI (and their crystalline esters) which are enantiomorphs.

Each of the alcohols (V, VI, VII and VIII) obtained by reduction of the corresponding dialdehyde depends for its optical activity solely upon the asymmetry of the glycosidic number 1 carbon atom. It is of interest to note that alcohols V and VII, derived from the methyl α-D-(or methyl β-L-) glycosides were found to have a negative rotation whereas alcohols VI and VIII, derived from the methyl β-D-(or methyl α-L-) glycosides showed a positive rotation. At first glance these results appear to be contradictory to the rules of isorotation as applied to sugars according to which (in the D series of sugars) an α-glycosidic configuration for carbon atom 1 contributes a positive value to the optical rotation of a sugar molecule and a β-configuration a negative contribution. The reason for this apparent anomaly is not obvious, but it may be pointed out that the optical activity of a sugar molecule results not only from the contribution of each asymmetric center but also from the effect and stereochemical conformation of the sugar ring.

The trihydric alcohols V and VI derived from the methyl D-hexosides were characterized by the formation of crystalline tris-O-benzoates and tris-O-*p*-nitrobenzoates, while the dihydric alcohols VII and VIII derived from the methyl pentosides were characterized by the formation of crystalline bis-O-*p*-nitrobenzoates (see Table I).

Proof of Structure of Alcohols V, VI, VII and VIII.—The structure of the two hitherto unknown enantiomorphic alcohols (V or IX, R = H) and VI or X (R = H), derived from the methyl hexopyranosides is based upon the following experimental facts. Hydrolysis of the acetal linkages of these two alcohols (1 *N* hydrochloric acid at 20°) proceeded easily and yielded in each case one molecule of glycerol (XII, R = H), one of glycolic aldehyde (XI, R = H) and one of methanol. In each case the glycerol was identified as the tris-O-*p*-nitrobenzoate. The other products of hydrolysis, methanol (removed by evaporation) and glycolic aldehyde, did not interfere in the isolation of this ester which was identified by elementary analysis and by its

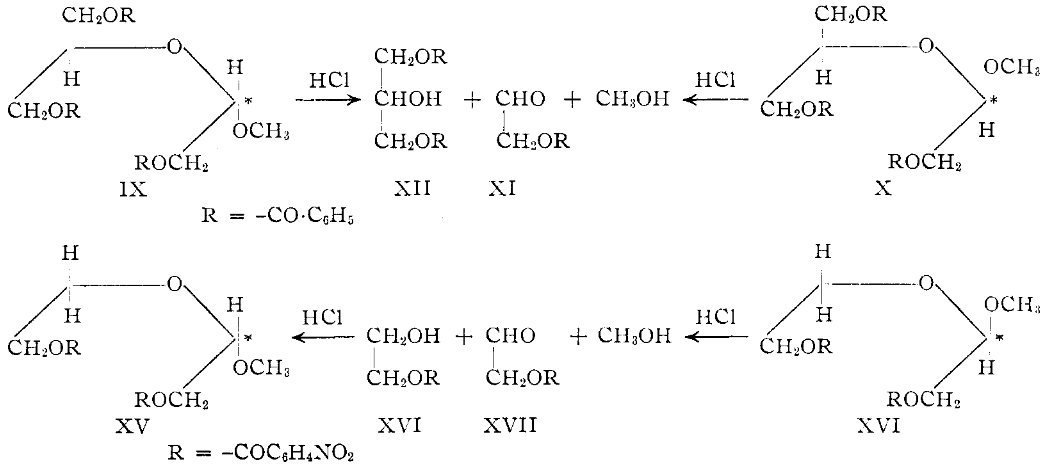
TABLE I

SPECIFIC ROTATIONS OF THE PRODUCTS OF THE PERIODIC ACID OXIDATION OF THE METHYL HEXOPYRANOSIDES AND METHYL PENTOPYRANOSIDES, OF THE ALCOHOLS OBTAINED BY HYDROGENATION AND OF THEIR DERIVATIVES

			Alcohol			
Methyl pyranoside	Methyl glycoside $[\alpha]^{20}_D$ (H_2O)	Dialdehyde $[\alpha]^{20}_D$ (H_2O)	$[\alpha]^{20}_D$ (EtOH)	Refractive index (20°)	O-Benzoate $[\alpha]^{20}_D$ (EtOH)	O-*p*-Nitrobenzoate $[\alpha]^{20}_D$ ($CHCl_3$)
-α-D-Gluco-[10]	+155.4°	+121.1°	− 9.9°	1.4660	−21.6°	−23.5°
-β-D-Gluco-[11]	− 30.3	−141.1	+11.4	1.4650	+21.8	+24.2
-α-D-Manno-[12]	+ 79.0	+121.5	− 8.6	1.4655	−20.2	−24.6
-β-D-Manno- isopropyl alcoholate[13]	− 51.1	−145.9	+10.7	1.4648	+22.4	+25.0
-α-D-Galacto- monohydrate[14]	+172.8	+118.4	−10.3	1.4652	−21.3	−24.3
-β-D-Galacto-[15]	± 0.0	−144.1	+10.8	1.4650	+21.1	+24.2
-α-D-Xylo-[16]	+149.4	+122.6	− 6.9	1.4410	.....	−10.0
-β-D-Xylo-[16]	− 63.0	−122.0	+ 7.5	1.4410	.....	+11.4
-α-L-Arabino-[15]	+ 19.7	−122.4	+ 6.8	1.4418	.....	+10.8
-β-L-Arabino-[12]	+235	+122.7	− 6.9	1.4421	.....	−10.2

melting point and mixed melting point with an authentic specimen prepared from glycerol.[17,18]

The identification of glycolic aldehyde as such, in small amounts, presents difficulties. The usual aldehyde reagents such as phenylhydrazine yield an osazone, the diphenylhydrazone of glyoxal. On the other hand, in the case of the tris-O-benzoates of alcohols IX and X (R = $-COC_6H_5$) the primary alcohol group of the glycolic aldehyde moiety is esterified. Consequently, one would deduce that hydrolysis of these tris-O-benzoates (IX and X, R = $-COC_6H_5$) would yield in each case the benzoate ester of glycolic aldehyde (XI, R = $-COC_6H_5$) which should give rise to a hydrazone. This proved to be the case. Esters IX and X were hydrolyzed with ease at room temperature in aqueous acetic acid which was 1 *N* with respect to hydrochloric acid. From the hydrolysate of each ester, glycolic aldehyde benzoate (XI, R = $-COC_6H_5$) was obtained as the crystalline 2,4-dinitrophenylhydrazone. The identity of this 2,4-dinitrophenylhydrazone was established by elementary analysis and by comparison with an authentic specimen prepared from erythritol.[19]



The structure of the two hitherto unknown enantiomorphic alcohols (VII or XV (R = H) and VIII or XIV (R = H)) derived from the pentose glycosides was proved in a similar manner as follows. Hydrolysis of the acetal linkages of these alcohols proceeded with ease (1 *N* hydrochloric acid at 20°) yielding in each case one molecule of ethylene glycol (XVI, R = H), one of glycolic aldehyde (XVII, R = H) and one of methanol. In the hydrolysate from each alcohol ethylene glycol was characterized as the bis-O-*p*-nitrobenzoate.[16,17]

As in the case of the trihydric alcohols V or IX (R = H) and VI or X (R = H), it was found advantageous to establish the identity of the glycolic aldehyde moiety in the alcohols VII or XV (R = H) and VIII or XIV (R = H), by hydrolysis of their esters, the bis-O-*p*-nitrobenzoates XV (R = $COC_6H_4NO_2$) and XIV(R = $COC_6H_4NO_2$). The O-*p*-nitrobenzoate of glycolic aldehyde (XVII, R = $-COC_6H_4NO_2$) so formed was isolated as the 2,4-dinitrophenylhydrazone which proved to be identical with an authentic specimen of the 2,4-dinitrophenylhydrazone of glycolic aldehyde O-*p*-nitrobenzoate prepared from erythritol.[20]

Experimental

A. Oxidation of the Methyl Hexopyranosides with Periodic Acid.—To a solution of methyl hexoside (2.5 g.) in

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[10] T. S. Patterson and J. Robertson, *J. Chem. Soc.*, 300 (1929).

[11] F. Smith and J. W. Van Cleve, THIS JOURNAL, **77**, 3159 (1955).

[12] F. Smith, *J. Chem. Soc.*, 1989 (1948).

[13] H. S. Isbell and Harriet L. Frush, *J. Research Natl. Bur. Standards*, **24**, 125 (1940).

[14] J. K. Dale and C. S. Hudson, THIS JOURNAL, **52**, 2534 (1930).

[15] W. Koenigs and E. Knorr, *Ber.*, 34, 957 (1901).

[16] C. S. Hudson, THIS JOURNAL, **47**, 265 (1925).

[17] R. Jaquemain and A. Muskovits, *Compt. rend.*, **202**, 497 (1936).

[18] J. U. Nef, *Ann.*, **335**, 284 (1904).

[19] H. Ohle and G. A. Melkonian, *Ber.*, **74**, 291 (1941).

[20] F. Smith and J. W. Van Cleve, THIS JOURNAL, **77**, July (1955).

water (150 ml.) was added 1 *N* periodic acid (70 ml.). The mixture was diluted quickly to 250 ml., shaken to uniformity and allowed to stand at room temperature. Part of the reaction mixture was poured into a 4-dm. polarimeter tube and the changes in optical rotation were observed. When the rotation had assumed a constant value (2–4 hours) an aliquot of the reaction mixture was titrated with standard sodium arsenite solution according to the method of Fleury and Lange.[21] In each case the titration revealed that two moles of periodic acid had been consumed per mole of glycoside.[6]

Isolation of the Dialdehyde D-Hydroxymethyl-D′-(I)- and -L′-(II)-Methoxydiglycolic Aldehyde.—The aqueous reaction mixture from above, which contained excess periodic acid, iodic acid and the dialdehyde, was neutralized with a saturated solution (20°) of barium hydroxide using a slight excess (tested with phenolphthalein), the excess being neutralized with a piece of solid carbon dioxide (Dry Ice). The precipitated barium salts were filtered off, washed with water, and the filtrate was evaporated *in vacuo* (bath, 40–45° at first, 35° in final stage of evaporation[22]) to dryness. Extraction of the residue with liberal quantities of absolute alcohol at room temperature gave a solution which was clarified with activated charcoal (the barium periodate and barium iodate were removed quantitatively in order to avoid possible interference at the elevated temperature of the subsequent catalytic hydrogenation). The clear solution was evaporated *in vacuo* (bath, 35–40° at first, 35° in final stage of evaporation[22]) to a clear sirupy residue. This sirup gave a rather weak and slowly developing Schiff test and a negative Fehling test.[23]

Catalytic Hydrogenation of the Dialdehydes I and II to the Corresponding Alcohols, D-Hydroxymethyl-D′-(V)- and -L′-(VI)-Methoxydiethylene Glycol.—The sirupy dialdehyde, obtained as described above, was transferred with the aid of 70 ml. of absolute ethanol to the stainless steel container of the hydrogenation bomb, 1.5–2 g. of Raney nickel catalyst was added, and the bomb was sealed. Hydrogenation was allowed to proceed at 1000–2000 pounds per square inch pressure at a temperature of 110–120°, with mechanical shaking, for 5–6 hours.

The reduced solution from the cooled bomb was treated with a little activated charcoal and filtered. The filtrate was evaporated to dryness *in vacuo* (bath, 35–40°) and the residue[24] (which gave no appreciable Schiff test) was transferred, with the aid of methanol, to a small flask for distillation in high vacuum. The main fraction, methoxyhydroxymethyldiethylene glycol, was obtained as a clear, viscous, colorless sirup which distilled without decomposition b.p. (bath temp.) 170–180° (0.001 mm.), yield 80% or better.

Reduction of D-Hydroxymethyl-D′-methoxydiglycolic Aldehyde (I) with Sodium Borohydride.—To a solution of the dialdehyde (1.45 g.), obtained from methyl α-D-glucopyranoside, in water (50 ml.), sodium borohydride (0.4 g.) was added in portions during 1 hour. The following changes in rotation were observed: (1 dm. tube) +2.45° (after 5 min.), −1.25° (15 min.), +0.5° (20 min.), +0.06° (30 min.), −0.06° (60 min.), −0.36° (2 hours) constant value. After keeping a further 1 hour at room temperature the solution was neutralized with carbon dioxide (tested with phenolphthalein) and evaporated (bath temp. 35–40°) *in vacuo* to dryness. The residue was extracted with hot ethanol giving a turbid solution which was cooled and centrifuged. The clear solution thus obtained was evaporated to dryness *in vacuo* giving D′-methoxyhydroxymethyldiethylene glycol (V) as a clear colorless liquid (1.1 g.), b.p. (bath temp.) 175° (0.001 mm.), n^{22}_D 1.4650, $[\alpha]^{20}_D$ −10° in water (*c* 2.2). *Anal.* Calcd. for $C_6H_{14}O_5$; C, 43.4; H, 8.4; OCH_3, 18.7 Found: C, 43.5; H, 8.4; OCH_3, 35.8. This high methoxyl value is believed to be due to the fact that cleavage of the molecule by hydriodic acid is accompanied by reduction so that the $CH_2OH{\cdot}CHO$ derived from C_1 and C_2 of the parent glycoside affords the extra molecule of alkyl halide; this would require OCH_3 (total), 37.35.[25]

Benzoylation of Methoxyhydroxymethyldiethylene Glycol (V and VI).—To a solution of the sirup (0.15–0.20 g.) in anhydrous pyridine (5 ml.) was added benzoyl chloride (0.5 ml.) and the mixture was heated on the water-bath at 80–90° for 30 minutes. The reaction mixture was allowed to cool to the temperature at which crystallization of the benzoyl chloride–pyridine complex commenced and was then poured into 20 ml. of saturated sodium bicarbonate solution. After a few minutes standing, the aqueous mixture, which contained oily droplets of the tribenzoate ester, was extracted twice with 20-ml. portions of chloroform. The combined chloroform extracts were washed three times with copious amounts of water, dried over anydrous calcium chloride, and evaporated under diminished pressure. Residual pyridine was removed by evacuating for an extended period (bath, 60–80°). To the pyridine-free residue was added a little petroleum ether and a seed crystal. Crystallization, which commenced immediately, was allowed to go to completion overnight. The crude product (*ca.* 0.5 g.) was recrystallized two or three times from chloroform–petroleum ether to give the pure tris-O-benzoate, m.p. 66–67° (IX and X, R = $-COC_6H_5$).

***p*-Nitrobenzoylation of Methoxyhydroxymethyldiethylene Glycol (V and VI).**—To a solution of the sirup (0.16 g.) in anhydrous pyridine (5 ml.) was added *p*-nitrobenzoyl chloride (0.80 g., or 150% of the theoretical amount) and the mixture was heated on the water-bath at 80–90° for 30 minutes. The reaction mixture was treated as in the benzoylation experiment above. The crude product (yield 0.35 g.), recrystallized from chloroform–petroleum ether afforded the tris-O-*p*-nitrobenzoate (R = $-COC_6H_4NO_2$), m.p. 110°.

The elementary analyses of the esters (tri-O-benzoates and tris-O-*p*-nitrobenzoates) of the enantiomorphic forms of methoxyhydroxymethyldiethylene glycol are recorded in Table II. The specific rotations are given in Table I.

Proof of Structure of D′-(V)- and of L′-(VI)-Methoxyhydroxymethyldiethylene Glycol. (a) Identification of the Glycerol Moiety Obtained by Acid Hydrolysis.—D′-(V)-or L′-(VI)-methoxyhydroxymethyldiethylene glycol (0.15 g.) was dissolved in 3 ml. of aqueous 1 *N* hydrochloric acid. After standing for 15 minutes the solution showed no optical activity and was neutralized with sodium bicarbonate. It was evaporated to dryness under diminished pressure and the residue was extracted with absolute alcohol. The alcoholic extract was evaporated to dryness *in vacuo* and the resulting residue was dissolved in 5 ml. of anhydrous pyridine. To the solution was added *p*-nitrobenzoyl chloride (0.76 g., or 150% of the theoretical amount) and the mixture was heated on the water-bath at 80–90° for 20 minutes. The cooled reaction mixture was poured into 20 ml. of saturated aqueous sodium bicarbonate solution. An oil separated which soon solidified. The solid material was filtered off, washed with water, and dissolved in 100 ml. of chloroform. The chloroform solution was dried over anhydrous calcium chloride, decolorized with a little activated charcoal and concentrated to a small volume. Petroleum ether was added to turbidity and the addition of a seed crystal caused the slow crystallization of 0.31 g. of the product. Recrystallization, once from chloroform–petroleum ether and once from hot ethyl acetate, gave glycerol tris-O-*p*-nitrobenzoate, m.p. 197.5° alone or in admixture with an authentic specimen.[17,18]

Anal. Calcd. for $C_{24}H_{17}O_{12}N_3$: C, 53.4; H, 3.2; N, 7.8. Found: for glycerol tris-O-*p*-nitrobenzoate obtained: (a) from D′-methoxyhydroxymethyldiethylene glycol (V or IX, R = H): C, 53.4; H, 3.1; N, 7.6, and (b) from L′-methoxyhydroxymethyldiethylene glycol (VI or X, R = H): C, 53.6; H, 3.6; N, 7.5.

(b) Identification of the Glycolic Aldehyde Moiety Obtained by Acid Hydrolysis.—To a solution of the tri-O-benzoate of D′-IX (R = COC_6H_5)- and of L′-X (R = COC_6H_5)-methoxyhydroxymethyldiethylene glycol (0.09 g.) in glacial acetic acid (2.75 ml.) was added concentrated hydrochloric acid (0.25 ml.). The resulting solution became optically inactive in a few minutes and to it was then added 2,4-dinitrophenylhydrazine (0.05 g.). In a few seconds, crystal-

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(21) P. Fleury and J. Lange, *J. pharm. chim.*, [8] **17**, 107 (1933).

(22) It was found important to keep the bath temperature strictly within these limits.

(23) To avoid deterioration in aqueous solution of this sensitive dialdehyde, it was found desirable to isolate and transfer it to the anhydrous ethanol solution (for subsequent hydrogenation) all in the same day.

(24) Occasionally this residue was slightly acid to litmus. Consequently, *just before distillation under high vacuum* a small amount of finely divided barium carbonate was added to the product in order to protect the acetal from cleavage.

(25) This material was prepared by Drs. J. K. Hamilton and M. Abdel-Akher.

TABLE II

ELEMENTARY ANALYSES OF THE ESTERS OF THE ENANTIOMORPHIC ALCOHOLS DERIVED FROM THE METHYL GLYCOSIDES

Parent methyl glycoside	Diethylene glycol	O-Benzoate[26]		O-*p*-Nitrobenzoate[27a,b]		
		Carbon	Hydrogen	Carbon	Hydrogen	Nitrogen
α-D-Glucopyranoside	D′-Methoxyhydroxymethyl-	67.5	5.5	52.8	3.9	7.0
α-D-Mannopyranoside	D′-Methoxyhydroxymethyl-	67.5	5.9	52.8	3.9	7.1
α-D-Galactopyranoside	D′-Methoxyhydroxymethyl-	67.9	5.9	52.9	3.9	7.2
β-D-Glucopyranoside	L′-Methoxyhydroxymethyl-	67.5	5.5	52.8	4.1	7.1
β-D-Mannopyranoside	L′-Methoxyhydroxymethyl-	67.8	5.6	52.7	3.6	6.95
β-D-Galactopyranoside	L′-Methoxyhydroxymethyl-	67.6	5.5	52.7	3.9	7.2
α-D-Xylopyranoside	D′-Methoxy-	..	..	52.6	4.5	6.2
β-L-Arabinopyranoside	D′-Methoxy-	..	..	52.7	4.6	6.3
β-D-Xylopyranoside	L′-Methoxy-	..	..	52.6	4.2	6.4
α-L-Arabinopyranoside	L′-Methoxy-	..	..	52.5	4.4	6.4

lization of the deep yellow hydrazone commenced and proceeded rapidly to completion. The product (0.05 g.) was recrystallized from chloroform–petroleum ether, m.p. 188.5°. A mixed melting point with an authentic specimen of O-benzoylglycolic aldehyde 2,4-dinitrophenylhydrazone[19] gave no depression.

Anal. Calcd. for $C_{15}H_{12}O_6N_4$: C, 52.3; H, 3.5; N, 16.3. Found: For the hydrazone obtained from: (a) the tris-O-benzoate of D′-methoxyhydroxymethyldiethylene glycol: C, 52.1; H, 3.7; N, 16.5, and (b) the tris-O-benzoate of L′-methoxyhydroxymethyldiethylene glycol: C, 52.4; H, 3.6; N, 16.0.

B. Oxidation of the Methyl Pentopyranosides with Periodic Acid.—The carefully purified crystalline methyl pentoside was oxidized in aqueous solution with periodic acid in the manner described for the methyl hexosides. After standing for a period of time, beyond which no further change in rotation was observed, the reaction mixture was shown by titration of an aliquot with standard sodium arsenite solution[21] to have consumed two moles of periodic acid per mole of glycoside.

Isolation of the Dialdehydes D′-Methoxydiglycolic Aldehyde (III) and L′-Methoxydiglycolic Aldehyde (IV).—This was effected in the manner described for the isolation of the dialdehydes from the methyl hexosides. The materials, colorless thin liquids, gave a negative Fehling test but a strong Schiff test.

Catalytic Hydrogenation of the Dialdehydes and Formation of D′-(VII)- and L′-(VIII)-Methoxydiethylene Glycol.—The dialdehyde, dissolved in absolute ethanol, was hydrogenated in the presence of Raney nickel in the same manner as described above for the dialdehydes obtained from the methyl hexosides. The products, D′- and L′-methoxydiethylene glycol, obtained in good yield (80% or better) distilled without decomposition (b.p. (bath temp.) 110–120° (0.01 mm.)) (see Table I).

Reduction of the Dialdehyde III with Sodium Borohydride.—When the dialdehyde obtained from methyl α-D-xylopyranoside (10 g.) in water (600 ml.) was treated with sodium borohydride (2.4 g.), the rotation (1-dm. tube) changed from +1.60° to −0.05°. The excess of sodium borohydride was decomposed with carbon dioxide and the solution was concentrated *in vacuo* to a sirup. The latter was extracted with ethanol and the solvent distilled *in vacuo*. Methanol was added and distilled *in vacuo* to remove borates. The process was repeated four times. The sirupy product was finally distilled *in vacuo* giving D′-methoxydiethylene glycol (VII) as a colorless liquid b.p. (bath temp.) 130–140° (0.001 mm.), n^{24}D 1.4443, $[\alpha]^{20}$D −6.9° in ethanol (*c* 0.6) (yield 5.5 g.).

Anal. Calcd. for $C_5H_{12}O_4$: C, 44.1; H, 8.8; OCH_3, 22.8. Found: C, 44.2; H, 9.6; OCH_3, 41.3.

The high methoxyl value is presumably due to the formation of an extra mole of alkyl halide produced from the two-carbon fragment that is derived from C_1 and C_2 of the original sugar molecule: this would require OCH_3, 45.6.[28]

Acetylation of the dihydric alcohol (pyridine and acetic anhydride) provided an almost quantitative yield of the corresponding di-O-acetate as a colorless liquid b.p. (bath temp.) 105–107° (0.001 mm.), n^{25}D 1.4286, $[\alpha]$D ±0° in chloroform.

Anal. Calcd. for $C_9H_{16}O_6$: C, 49.1; H, 7.3. Found: C, 49.0; H, 7.7.

The alcohol regenerated from this di-O-acetyl derivative by treatment with sodium methoxide[29] had b.p. 112–114° (bath temp.) (0.005 mm.), n^{26}D 1.4432 and showed $[\alpha]^{23}$D −7.5° in ethanol (*c*, 2.0).

***p*-Nitrobenzoylation of D′- and L′-Methoxydiethylene Glycol (VII and VIII).**—To a solution of the sirup (0.16 g.) in anhydrous pyridine (5 ml.) was added *p*-nitrobenzoyl chloride (0.60 g., or 150% of the theoretical amount) and the mixture was heated on the water-bath at 80–90° for 45 minutes. The cooled reaction mixture was poured into 20 ml. of saturated sodium bicarbonate solution. Almost immediately the oil, which separated, crystallized out to form a flocculent precipitate. The precipitate was filtered, washed well with water and dried on the funnel by aspirating air through it. When twice recrystallized from chloroform–petroleum ether the product melted at 112–113°.

The elementary analyses of the bis-O-*p*-nitrobenzoates (XIV and XV, R = $-COC_6H_4NO_2$) of the enantiomorphic forms of methoxydiethylene glycol are recorded in Table II. The specific rotations are given in Table I.

Proof of Structure of D′-(VII)- and of L′-(VIII)-Methoxydiethylene Glycol. (a) Identification of the Glycol Moiety Obtained by Acid Hydrolysis.—A solution of D′- or (L′)-methoxydiethylene glycol (0.15 g.) in 3 ml. of 1 *N* aqueous hydrochloric acid was allowed to stand for about 15 minutes whereupon it became optically inactive. The inactive solution was neutralized with sodium bicarbonate solution and evaporated to dryness *in vacuo* (bath, 40–45°). The residue was dissolved in anhydrous pyridine (5 ml.) and *p*-nitrobenzoyl chloride (0.61 g., or 150% of the theoretical amount) was added. The mixture was heated on the water-bath at 80–90° for about 15 minutes. The cooled reaction mixture was poured, with stirring, into 40 ml. of saturated sodium bicarbonate solution. The flocculent precipitate was filtered, washed well with water and dried. The crude product was dissolved in a rather large volume of chloroform and the resulting brownish solution was decolorized with activated charcoal. The clarified solution was evaporated to dryness *in vacuo* and the residue was dissolved in hot ethyl acetate. To the resulting solution, concentrated to a small volume, ether was added causing the rapid formation of large flaky, lustrous crystals of ethylene glycol-bis-O-*p*-nitrobenzoate, m.p. 146° alone or in admixture with an authentic specimen of ethylene glycol-bis-O-*p*-nitrobenzoate.[17,18]

Anal. Calcd. for $C_{16}H_{12}O_8N_2$: C, 53.4; H, 3.4; N, 7.8. Found: for ethylene glycol bis-O-*p*-nitrobenzoate obtained from: (a) D′-methoxydiethylene glycol: C, 53.8; H, 3.7; N, 7.8, and (b) L′-methoxydiethylene glycol: C, 53.2; H, 3.6; N, 8.1.

(b) Identification of the Glycolic Aldehyde Moiety Obtained by Acid Hydrolysis.—To a solution of the bis-O-*p*-nitrobenzoate ester of D′-(XV)- and of L′-(XIV)-methoxydiethylene glycol (0.08 g.) in 2.75 ml. of glacial acetic acid was added concentrated hydrochloric acid (0.25 ml.). To the optically inactive solution, which gave a weak Schiff test, was added 2,4-dinitrophenylhydrazine (0.55 g.,

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(26) Calcd. for the tris-O-benzoate of the methoxyhydroxymethyldiethylene glycols, $C_{27}H_{26}O_8$: C, 67.8; H, 5.5.

(27) (a) Calcd. for the tris-O-*p*-nitrobenzoate of methoxyhydroxymethyldiethylene glycol, $C_{27}H_{23}O_{14}N_3$: C, 52.9; H, 3.8; N, 6.9. (b) Calcd. for the bis-O-*p*-nitrobenzoate of methoxy-diethylene glycol, $C_{19}H_{18}O_{10}N_2$: C, 52.5; H, 4.2; N, 6.5.

(28) This material was prepared by Mr. G. W. Huffman.

(29) G. Zemplén, *Ber.*, **59**, 1254 (1926); **60**, 1555 (1927).

or 150% of the theoretical amount). The canary-yellow crystalline hydrazone formed immediately. It was filtered off, washed with a little glacial acetic acid, then with ether. Recrystallized from chloroform–petroleum ether, the hydrazone melted at 189–190°. A mixed melting point with an authentic specimen of O-*p*-nitrobenzoylglycolic aldehyde 2,4-dinitrophenylhydrazone[20] gave no depression.

Anal. Calcd. for $C_{15}H_{11}O_8N_5$: C, 46.3; H, 2.9; N, 18.0. Found for the hydrazone obtained from the bis-O-*p*-nitrobenzoate ester of: (a) D'-methoxydiethylene glycol: C, 46.3; H, 3.2; N, 17.7, and of (b) L'-methoxydiethylene glycol: C, 46.5; H, 3.1; N, 18.1.

ST. PAUL, MINNESOTA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Two 3-Epimeric Ketononoses[1]

BY M. L. WOLFROM AND HARRY B. WOOD, JR.

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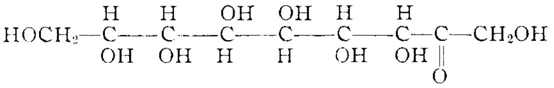
The synthesis of D-*erythro*-L-*manno*-nonulose (D-*arabino*-L-*tagato*-nonose, I) and of D-*erythro*-L-*gluco*-nonulose (D-*arabino*-L-*sorbo*-nonose, II), the first known ketononoses, is described. They were prepared by acetylation of the corresponding 2-epimeric aldoöctonic acids to give the fully acetylated acids which were converted to their acyl chlorides and these with diazomethane yielded the diazomethyl ketones. The latter were transformed into the *keto*-acetates which on deacetylation yielded the ketononoses (amorphous). These sugars were non-fermentable by yeast (*Saccharomyces*).

In continuation of our work on the preparation of higher ketoses, we report herein the synthesis of two sugars, the first known ketononoses, designated D-*erythro*-L-*manno*-nonulose (D-*arabino*-L-*tagato*-nonose, I) and D-*erythro*-L-*gluco*-nonulose (D-*arabino*-L-*sorbo*-nonose, II) from D-*erythro*-L-*manno*-octonic acid and D-*erythro*-L-*gluco*-octonic acid, respectively. The reaction sequence employed was

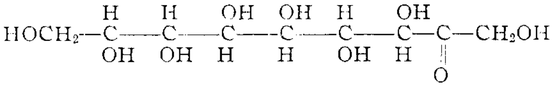
$$\mathrm{R{-}CO_2H \xrightarrow{SOCl_2} RCOCl \xrightarrow{CH_2N_2}}$$
$$\mathrm{R{-}CO{-}CHN_2 \xrightarrow{HOAc\ +\ Cu^{++}}}$$
$$\mathrm{R{-}CO{-}CH_2OAc \xrightarrow{Ba(OH)_2} CH_2OH{-}(CHOH)_6{-}CO{-}CH_2OH}$$

wherein R = $\mathrm{CH_2OCOCH_3{-}(CHOCOCH_3)_6{-}}$.



$$\mathrm{HOCH_2{-}\underset{OH}{\overset{H}{C}}{-}\underset{OH}{\overset{H}{C}}{-}\underset{H}{\overset{OH}{C}}{-}\underset{H}{\overset{OH}{C}}{-}\underset{OH}{\overset{H}{C}}{-}\underset{OH}{\overset{H}{C}}{-}\underset{\overset{\|}{O}}{C}{-}CH_2OH}$$

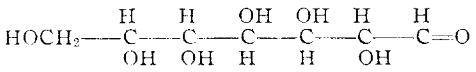
I, D-*erythro*-L-*manno*-Nonulose (D-*arabino*-L-*tagato*-nonose)



$$\mathrm{HOCH_2{-}\underset{OH}{\overset{H}{C}}{-}\underset{OH}{\overset{H}{C}}{-}\underset{H}{\overset{OH}{C}}{-}\underset{H}{\overset{OH}{C}}{-}\underset{OH}{\overset{H}{C}}{-}\underset{H}{\overset{OH}{C}}{-}\underset{\overset{\|}{O}}{C}{-}CH_2OH}$$

II, D-*erythro*-L-*gluco*-Nonulose (D-*arabino*-L-*sorbo*-nonose)

The starting point of our synthesis was D-mannose, which was converted to D-*glycero*-D-*galacto*-heptose



$$\mathrm{HOCH_2{-}\underset{OH}{\overset{H}{C}}{-}\underset{OH}{\overset{H}{C}}{-}\underset{H}{\overset{OH}{C}}{-}\underset{H}{\overset{OH}{C}}{-}\underset{OH}{\overset{H}{C}}{-}\overset{H}{C}{=}O}$$

either through the cyanohydrin reaction[2] with subsequent reduction of the aldonolactone to the aldose stage,[3] or, more directly, through the nitromethane procedure.[4] The configuration of D-*glycero*-D-*galacto*-heptose was established by Peirce[5] and the sugar was characterized further by Montgomery and Hudson.[6] One of the two possible aldoöctonic acids (D-*erythro*-L-*manno*-octonic acid), obtainable through the cyanohydrin reaction on D-*glycero*-D-*galacto*-heptose, was isolated by Fischer and Passmore.[3] Its configuration was established by Peirce[5] and confirmed by Hudson and co-workers.[7] The 2-epimer of this acid (D-*erythro*-L-*gluco*-octonic acid) was described first by Karabinos, Hann and Hudson,[8] who further characterized these 2-epimeric aldoöctonic acids and described the crystalline heptaacetate of D-*erythro*-L-*manno*-octonic acid.

In the D-*erythro*-L-*manno*-nonulose series, all of the intermediates in our synthetic scheme, except the *keto*-octaacetate, were obtained in crystalline form. In the D-*erythro*-L-*gluco*-nonulose structure, the acyl halide and the *keto*-acetate were not crystallized. Unfortunately, the two final products, the unsubstituted ketononoses I and II, resisted crystallization. The molecular rotations of the ketononoses are those predictable from their structures[9]; that of D-*erythro*-L-*gluco*-nonulose (270 × −47.2° = −12,700) falls between the values −14,100 and −10,800 established for L-*gluco*-heptulose[10] and D-*glycero*-L-*gluco*-octulose,[11] respectively, of like top structure, while that of D-*erythro*-L-*manno*-nonulose (270 × −20° = −5,400) compares favorably with those, −6,100 and −4,100, of the ketoheptose[9,12] and ketoöctose,[11] respectively, of like structure.

The diazomethyl ketones were obtained in pure form only by the application of chromatographic techniques, utilizing silicate columns. Their contaminants were probably the methyl esters of the acetylated octonic acids, the syntheses of which are described. The infrared spectra of the diazomethyl ketones were determined. The bands characteristic

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(1) Paper No. 15 in the series entitled "The Action of Diazomethane upon Acylic Sugar Derivatives"; previous communication, M. L. Wolfrom, J. M. Berkebile and A. Thompson, THIS JOURNAL, **74**, 2197 (1952).

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