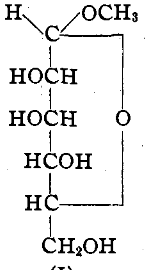
[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Studies on the Cleavage of the Carbon Chain of Glycosides by Oxidation. A New Method for Determining Ring Structures and Alpha and Beta Configurations of Glycosides[1]

BY ERNEST L. JACKSON AND C. S. HUDSON

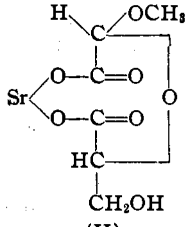
The oxidation of alpha-methyl-*d*-mannopyranoside (I) with barium hypobromite has been shown by us[2] to remove carbon atom 3 and to oxidize the alcohol groups at carbon atoms 2 and 4 to carboxyl groups, producing a dibasic acid which was isolated as the crystalline strontium salt (II). This salt could be prepared also through oxidation of the mannoside with periodic acid followed by oxidation of the product, the dialdehyde (III), with bromine water kept neutral with strontium carbonate. Inasmuch as this cleavage type of oxidation should be applicable to a large number of glycosides, it offered a new method for the proof of ring structures, provided the products from the various glycosides could be obtained in crystalline condition suitable for structural studies. The present article reports our progress in the development of the method as pertains to the methylaldohexosides and the methylaldopentosides.

The method consists in the oxidation of the glycoside with periodic acid in aqueous solution at 20° followed by the oxidation of the dialdehyde, after isolation, with bromine water in the presence of a metallic carbonate selected to yield a crystalline salt of the dibasic acid, the proof of the structure of which, in the case of the glycosides here studied, discloses the ring structure of the parent glycoside.[3] Important confirmatory evidence in the case of some structures is obtained by the measurement of the quantity of periodic acid consumed, as will be illustrated later.



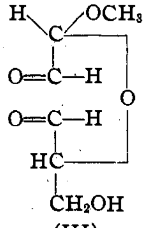
(I)

α-Methyl-*d*-mannopyranoside



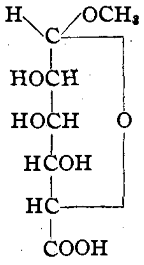
(II)

Strontium D′-methoxy-D-hydroxymethyl-diglycolate



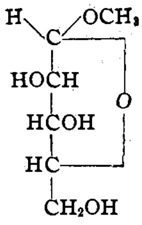
(III)

D′-methoxy-D-hydroxy-methyl-diglycolic aldehyde



(IV)

α-Methyl-*d*-mannuronide(1,5)



(V)

α-Methyl-*d*-arabinofuranoside

Inspection of the formulas shows that the same dialdehyde (III) and strontium salt (II) should be expected from all the eight possible alpha-methyl-*d*-aldohexopyranosides. The production of the same dialdehyde in the oxidation of four of these (the alpha-methyl-pyranosides of *d*-mannose, *d*-galactose, *d*-glucose and *d*-gulose) is apparent from the rotations recorded in Table I and the curves shown in Fig. 1. The dialdehyde from each of the four sources, isolated as a sirup and oxidized in the usual way, produced in yields of 65–70% the same crystalline strontium salt (II). The structure[4] of the strontium salt, particularly the presence of the *d*-glyceric acid moiety in the molecule, limits the ring of each of the four alpha-methyl-*d*-hexosides to the pyranoside(1,5) or septanoside(1,6) structure. In addition to the usually accepted evidence, two independent proofs, which exclude the septanoside ring structure and thereby

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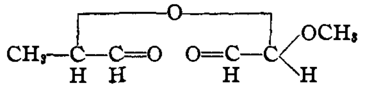
(1) Publication authorized by the Surgeon General, U. S. Public Health Service.

(2) Jackson and Hudson, THIS JOURNAL, **58**, 378 (1936); *Science*, **85**, 51 (1937).

(3) The proof of the structure might be accomplished also through the dialdehyde or a suitable derivative. By the periodic acid oxidation of alpha-methyl-*l*-rhamnoside of specific rotation −62.8° we have obtained, at the dialdehyde stage, a crystalline compound melting at 101–102° and showing $[\alpha]^{20}_{D}$ −143° in water. Analyses for carbon, hydrogen and methoxyl show its empirical formula to be $C_6H_{12}O_5$, corresponding to the monohydrate of the expected dialdehyde



$$CH_3-\underset{H}{C}-\underset{H}{C}=O \quad O=\underset{H}{C}-C\langle^{OCH_3}_{H}$$

(4) The experimental details, omitted in ref. 2, for the preparation of oxalic and *d*-glyceric acids from the strontium salt are given in the experimental part of this article.

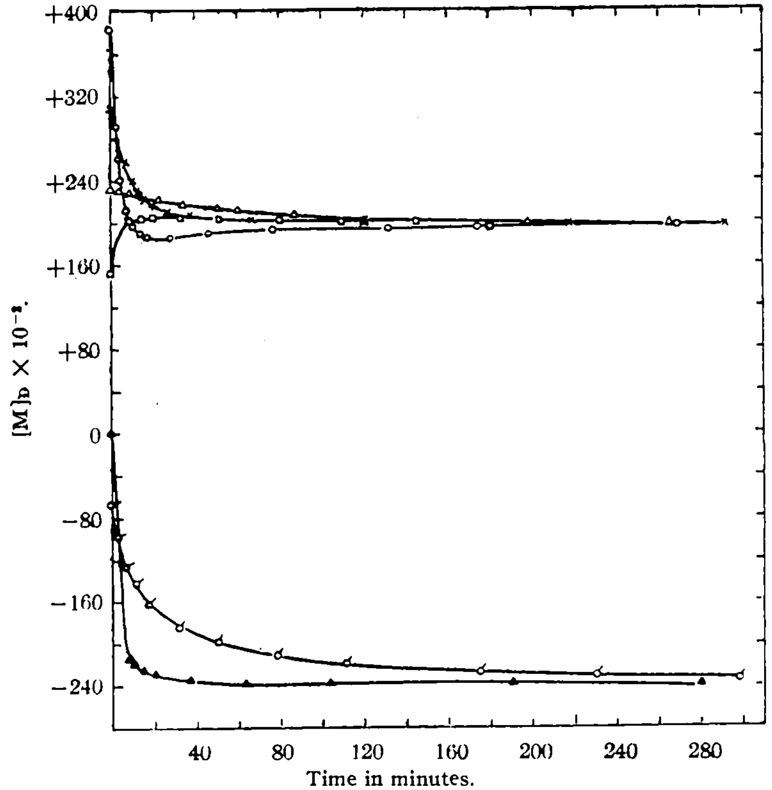


Fig. 1.—Rotatory changes during the oxidation of the methyl hexosides: ○, *α*-methyl-*d*-galactoside; ×, *α*-methyl-*d*-glucoside; △, *α*-methyl-*d*-guloside; □, *α*-methyl-*d*-mannoside; ơ, *β*-methyl-*d*-glucoside; ▲, *β*-methyl-*d*-galactoside.

limit the ring to that of a pyranoside, are provided by the present investigation. From the products of the oxidation of alpha-methyl-*d*-mannopyranoside with barium hypobromite we have prepared a crystalline brucine salt (m. p. 232°) which has been proved to be the brucine salt of alpha-methyl-*d*-mannuronide (IV). The formation of the methyl *d*-mannuronide through the oxidation of the primary alcohol group at carbon atom 6 to a carboxyl group obviously is incompatible with the 1,6-ring structure. The second proof is furnished by the preparation, through the usual oxidation reactions, of the strontium salt (II) from a new crystalline methyl-*d*-arabinofuranoside[5] (V); this proof will be presented when the oxidation of the methyl pentosides is discussed. The conclusion that the strontium salt (II) has the indicated structure is further supported by the known reactions of periodic acid;[6] the septanoside structure for an alpha-methyl-*d*-aldohexoside would be expected to consume three moles of periodic acid and yield the dialdehyde (X) (a substance which we have obtained from the alpha-methyl-*d*-pentopyranosides), whereas the alpha-methyl-*d*-aldohexosides that have been studied consume two moles of periodic acid and yield the dialdehyde (III).

The beta-methyl-*d*-aldohexopyranosides react with periodic acid in the same manner as the alpha forms, but the product (VI) is of course different since the dialdehydes from an alpha-beta pair retain the difference in configuration of carbon atom 1 that existed in the parent glycosides. Although the strontium salt in the beta series was not a crystalline compound, the barium salt (VII) crystallized quite readily and in high yield when prepared from beta-methyl-*d*-glucoside. By the same reactions as applied to the strontium salt from alpha-methyl-*d*-mannopyranoside, oxalic and *d*-glyceric acids were prepared from the barium salt; this limits the

TABLE I

PRODUCTS OF THE OXIDATION OF THE METHYL PENTOSIDES AND THE METHYL HEXOSIDES

Substance	Methyl glycoside $[\alpha]^{20}_{D}$	Dialdehyde[a] $[\alpha]^{20}_{D}$	Dibasic acid[b] $[\alpha]^{20}_{D}$	Strontium salt[c] $[\alpha]^{20}_{D}$
α-Methyl-*d*-arabinoside	− 17	+124.2	−12.7	−55.5
α-Methyl-*d*-xyloside	+154	+125.2	−12.1	−55.5
β-Methyl-*d*-arabinoside	−245	−123.7	+12.5	+55.7
β-Methyl-*d*-xyloside	− 65	−124.3	+12.2	+55.3
α-Methyl-*d*-arabinofuranoside	+123	+117.3[d]	+26.1	−53.3
α-Methyl-*d*-galactoside	+196	+120.7	+25.4	−53.5
α-Methyl-*d*-glucoside	+159	+121.1	+26.0	−52.9
α-Methyl-*d*-guloside	+120	+120.5	+25.4	−52.7
α-Methyl-*d*-mannoside	+ 79	+119.5	+26.3	−53.0
β-Methyl-*d*-galactoside	+ 1	−148.1	....	....
β-Methyl-*d*-glucoside	− 34	−150.6	+45.0	+35.9[e]

[a] D′ and L′-methoxy-diglycolic aldehydes from the methyl pentopyranosides; D′ and L′-methoxy-D-hydroxymethyl-diglycolic aldehydes from *α*-methyl-*d*-arabinofuranoside and the methyl hexosides. Specific rotations calculated from the final $[M]_D$ values of the oxidation solutions (Tables II and V). [b] Determined by liberating the acid (*c*, 1.2–1.6) from its pure, anhydrous strontium salt (barium salt for *β*-methylglucoside) with an equivalent of hydrochloric acid. [c] See Table IV, note (b) and Table VII, note (b). [d] See note (19). [e] Barium salt (*c*, 3.4).

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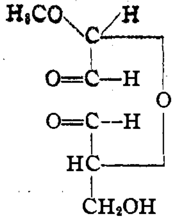
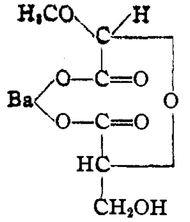
(5) Montgomery and Hudson, THIS JOURNAL, **59**, 992 (1937).

(6) Malaprade, *Bull. soc. chim.*, [5] **1**, 833 (1934); Clutterbuck and Reuter, *J. Chem. Soc.*, 1467 (1935); Fleury and Bon-Bernatets, *J. pharm. chim.*, [8] **23**, 85 (1936); Hérissey, Fleury and Joly, *ibid.*, [8] **20**, 149 (1934).

ring of beta-methyl-*d*-glucoside to the pyranoside or septanoside structure. In addition to the known evidence to exclude the septanoside structure, the dialdehyde that is produced and the quantity of periodic acid consumed are not those expected from beta-methyl-*d*-glucoseptanoside, which would doubtless consume three moles of periodic acid and generate the enantiomorph of the dialdehyde (X). The rotation of the dialdehyde from beta-methyl-*d*-galactoside (Table I and Fig. 1) indicates it to be the same compound as (VI) from beta-methyl-*d*-glucoside; this as well as the dialdehyde from all other beta-methyl-*d*-aldohexopyranosides will doubtless yield the crystalline barium salt (VII).

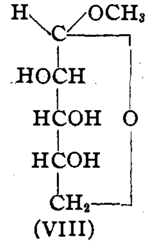


(VI)
L′-methoxy-D-hydroxy-methyl-diglycolic aldehyde

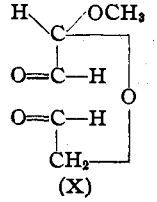


(VII)
Barium L′-methoxy-D-hydroxymethyl-diglycolate

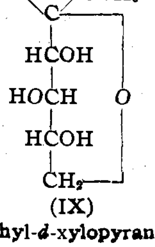
The oxidation products are named as derivatives of diglycolic aldehyde or acid; the prefixes D′ and L′ distinguish the configurations of carbon atom 1 in the products from the alpha- and beta-methyl glycosides, D′ signifying the configuration of carbon atom 1 as in alpha-methyl-*d*-mannopyranoside. The dibasic acid of specific rotation +26° from the alpha-methyl-*d*-aldohexopyranosides is named D′-methoxy-D-hydroxymethyl-diglycolic acid and that from beta-methyl-*d*-glucopyranoside, of specific rotation +45°, is named L′-methoxy-D-hydroxymethyl-diglycolic acid. The D and L symbols conform to the usual Fischer nomenclature for carbon 5 of the aldohexosides.



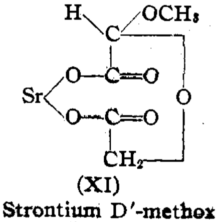
(VIII)
α-Methyl-*d*-arabinopyranoside



(X)
D′-methoxy-diglycolic aldehyde



(IX)
α-Methyl-*d*-xylopyranoside



(XI)
Strontium D′-methoxy-diglycolate

The oxidation of alpha-methyl-*d*-arabinopyranoside (VIII) and alpha-methyl-*d*-xylopyranoside (IX) with periodic acid should yield one and the same substance, namely, D′-methoxy-diglycolic aldehyde (X), and a similar oxidation of the beta forms likewise should be expected to produce a common dialdehyde, L′-methoxy-diglycolic aldehyde, the optical antipode of (X). The specific rotations listed in Table I and the curves in Fig. 2 show that the two pairs of methyl-*d*-pentopyranosides do indeed produce antipodal dialdehydes, the one from the alpha forms rotating +124° and that from the beta forms −124°. The dialdehyde from each of the four *d*-pentopyranosides produced, upon oxidation with bromine water and strontium carbonate, a crystalline strontium salt in about 80% yield; the salt (XI) from the two alpha forms rotated −56° while the salt from the two beta forms rotated +56°; these two salts are thus enantiomorphic forms. The methoxy-diglycolic acids from the methyl pentopyranosides, like the methoxy-D-hydroxymethyl-diglycolic acids from the methyl-aldohexopyranosides, are hydrolyzed readily in aqueous solution because of their acetal structure. The acid from the strontium salt (strontium L′-methoxy-diglycolate) prepared from beta-methyl-*d*-arabinopyranoside, when hydrolyzed and oxidized with bromine water yielded oxalic and glycolic acids, the latter identified through three crystalline derivatives (calcium glycolate, S-benzylthiuronium glycolate and *p*-bromophenacyl glycolate). Since glycolic acid contains only one alcoholic hydroxyl group, the oxygen linkage in the strontium salt must be as indicated, which proves the four parent methylpentosides to be of the pyranoside type and correlates the alpha and beta forms. Since the application of the usual oxidation reactions to a third crystalline methyl-*d*-arabinoside[5] (V) of specific rotation +123° yields a different strontium salt (II) (the one from the alpha-methyl-*d*-aldohexopyranosides, containing the *d*-glyceric acid grouping), the third methyl-*d*-arabinoside must have the furanoside structure (V) and be of the alpha configuration for carbon 1. This is the second

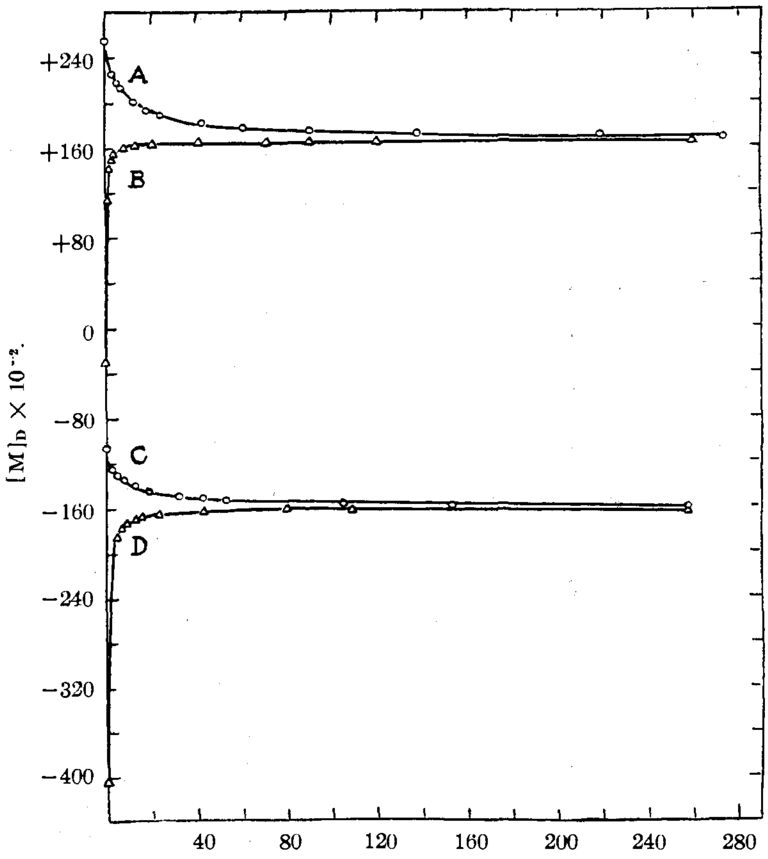
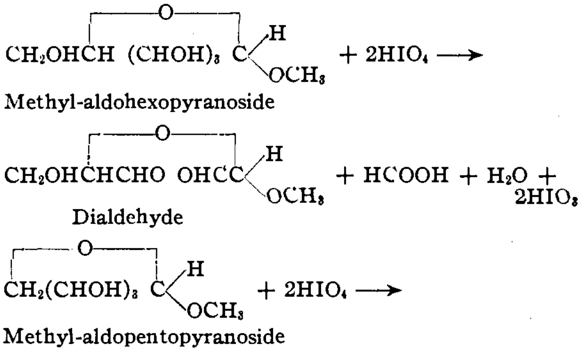


Fig. 2.—Rotatory changes during the oxidation of the methyl-pentopyranosides: (A), α-methyl-*d*-xylopyranoside; (B), α-methyl-*d*-arabinopyranoside; (C), β-methyl-*d*-xylopyranoside; (D), β-methyl-*d*-arabinopyranoside.

proof, mentioned previously, for the structure of (II), (III) and (I). One observes that these oxidation results correlate the configuration of a pentofuranoside (V) and a hexopyranoside (I).

The ring structures which have been shown by these oxidation results confirm the pyranoside structures that are now accepted from methylation data; in the case of alpha - methyl - *d* - gulopyranoside and alpha-methyl-*d*-arabinofuranoside, where methylation data are lacking, the new method supplies conclusive proof for ring structures and alpha classification.

The preparation of *d*-glyceric acid from the methyl *d*-aldohexosides through either strontium D′-methoxy - D - hydroxymethyl - diglycolate or barium L′-methoxy-D - hydroxymethyl - diglycolate provides the most direct correlation of the configuration of the sugars with glyceric acid.[7] The present type of oxidation offers the possibility of improved methods for the preparation in pure condition of stereoisomers, such as *d*- and *l*-glyceric and lactic aldehydes and the corresponding acids, and of many mixed acetals for which no methods of synthesis have been known. These oxidation reactions, with periodic acid as the oxidant, appear to proceed practically quantitatively according to the following typical equations, the first of which has been proposed by Hérissey, Fleury and Joly.[6]



$\mathrm{CH_2OHCH\,(CHOH)_3\,C{<}^{H}_{OCH_3} + 2HIO_4 \longrightarrow}$

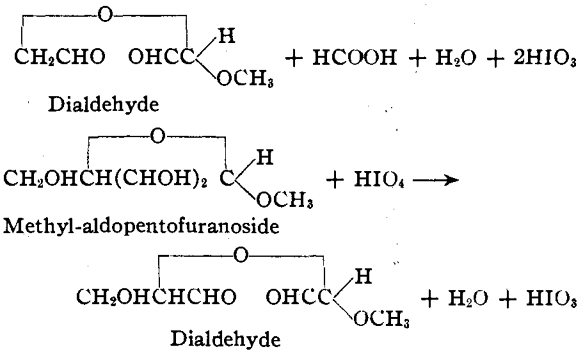
Methyl-aldohexopyranoside

$\mathrm{CH_2OHCHCHO\;\; OHCC{<}^{H}_{OCH_3} + HCOOH + H_2O + 2HIO_3}$

Dialdehyde

$\mathrm{CH_2(CHOH)_3\,C{<}^{H}_{OCH_3} + 2HIO_4 \longrightarrow}$

Methyl-aldopentopyranoside



$\mathrm{CH_2CHO\;\; OHCC{<}^{H}_{OCH_3} + HCOOH + H_2O + 2HIO_3}$

Dialdehyde

$\mathrm{CH_2OHCH(CHOH)_2\,C{<}^{H}_{OCH_3} + HIO_4 \longrightarrow}$

Methyl-aldopentofuranoside

$\mathrm{CH_2OHCHCHO\;\; OHCC{<}^{H}_{OCH_3} + H_2O + HIO_3}$

Dialdehyde

Experimental

Oxidation of Alpha-Methyl-*d*-mannopyranoside with Barium Hypobromite.—To a solution of 420 g. of barium hydroxide octahydrate and 166 g. of bromine in 12 liters of distilled water at 3° was added 100 g. of pure alpha-methyl-*d*-mannopyranoside. The solution, kept in the dark at 3 – 7° with occasional shaking, was free from hypobromite after eight to ten days as shown by starch–potassium iodide paper. The reaction of a second portion of the same amounts of barium hydroxide and bromine was complete after about eight days. The insoluble material (70–

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[7] *Cf.* Wohl and Momber, *Ber.*, **47**, 3346 (1914); **50**, 455 (1917); Wohl and Schellenberg, *ibid.*, **55**, 1404 (1922); Freudenberg and Brauns, *ibid.*, **55**, 1339 (1922).

75 g.), apparently barium carbonate, was removed by filtration and the neutral solution was concentrated *in vacuo* to 500 ml. About 325 g. of crystalline barium bromide was separated in two crops through filtration and concentration of the filtrate *in vacuo* to 250–300 ml. The solution then was evaporated *in vacuo* to dryness; a solution of the residue in 75 ml. of warm water was poured into 2 liters of hot methanol and stirred until the precipitated gum solidified. After being refluxed for an hour and cooled, the barium salts were filtered off and washed with hot methanol. The amount of contaminating barium bromide may be reduced by concentrating the aqueous solution of the crude product *in vacuo* to a thin sirup and repeating the precipitation and extraction with methanol. The yield of the amorphous, hygroscopic product, dried at 25° *in vacuo* over calcium chloride, was 100 g. containing 15–20% barium bromide and a little barium bromate. From the methanol solutions was recovered 25–30 g. of crystalline alpha-methyl-mannoside. A solution of 250 g. of barium salts in water was freed from bromine ions with silver carbonate, from excess silver with hydrogen sulfide and then from barium with sulfuric acid. The solution of organic acids was dextrorotatory and reduced Fehling's solution only slightly. After neutralization to phenolphthalein with strontium hydroxide solution, it was concentrated *in vacuo* to a thin colorless sirup to which was added 15 ml. of ethanol. Strontium D′-methoxy-D-hydroxymethyl-diglycolate dihydrate crystallized at 5° as fine needles; yield, 80 g. or 25% on the alpha-methyl-mannoside that reacted with the hypobromite. Recrystallized twice from water to which 10–15% of ethanol was added and dried to constant weight at 105° *in vacuo*, the pure anhydrous salt showed a specific rotation[8] of −53.0° in water (*c*, 0.6).

Anal. Calcd. for $C_6H_8O_7Sr$: C, 25.74; H, 2.88; OCH_3, 11.1; Sr, 31.33. Found:[9] C, 25.74, 25.54; H, 2.93, 3.04; OCH_3, 10.9, 10.8; Sr, 31.47, 31.49.

The specific rotation of D′-methoxy-D-hydroxymethyl-diglycolic acid in water, obtained by liberating it from the pure anhydrous strontium salt with an equivalent of hydrochloric acid, was +25.5° (*c*, 1.6).

Brucine alpha-methyl-*d*-mannuronide was prepared from 16 g. of crude barium salts. After removal of the bromine ions and the barium, the aqueous solution of the organic acids was heated on the steam-bath for three hours with excess of brucine; the excess was removed by filtration followed by extraction with chloroform, and the solution was concentrated *in vacuo* to a dry sirup. The sirup was crystallized from absolute ethanol and the product, which appeared to be a mixture of several brucine salts, yielded on fractionation from 95% ethanol about 4.5 g. (12%) of nearly pure brucine alpha-methyl-*d*-mannuronide. This was recrystallized to the constant melting point of 232° (dec.) from 95% ethanol, in which it is difficultly soluble. The pure compound lost 6.1% in weight upon being dried at 105° *in vacuo* and then showed a specific rotation of −2.5° in water (*c*, 2).

Anal. Calcd. for $C_{30}H_{38}O_{11}N_2$: C, 59.77; H, 6.36; OCH_3, 15.45; N, 4.65. Found (dried at 105° *in vacuo*): C, 59.70, 59.73; H, 6.26, 6.31; OCH_3, 15.4, 15.4; N, 4.70, 4.72.

This identification of the brucine salt was confirmed by the preparation from it of crystalline potassium alpha-methyl-*d*-mannuronide.[10] The calculated potassium hydroxide was added to a solution of 10 g. of pure brucine salt in 200 ml. of water, the brucine was removed and the solution was concentrated *in vacuo* to a thin sirup, which was crystallized with the aid of ethanol. The potassium salt showed $[\alpha]^{20}\text{D}$ + 45.2° in water (*c*, 1.5), from which is calculated $[\alpha]^{20}_{5780}$ +47.1° using the dispersion coefficient[11] 1.042. Ault, Haworth and Hirst reported $[\alpha]^{17}_{5780}$ +48° in water.

Anal. Calcd. for $C_7H_{11}O_7K\cdot{}^1/_2C_2H_5OH$: K, 14.5; OR (as OCH_3), 17.3. Found: K, 14.5, 14.4; OR (calcd. as OCH_3), 16.4.

Periodic Acid.—The subsequent oxidation reactions were carried out with solutions of pure periodic acid. In some preliminary experiments in which certain alpha-methyl-hexosides were oxidized by periodic acid prepared in aqueous solution from potassium periodate and an equivalent of sulfuric acid, the yield of strontium D′-methoxy-D-hydroxymethyl-diglycolate was low, probably due to the difficulty of complete removal of potassium ions which would interfere with the crystallization of the strontium salt. Crystalline periodic acid[12] (H_5IO_6) was found more satisfactory. To avoid interference with polarimetric observations by a small precipitate which separates in oxidations with fresh solutions of the product which we used, the solutions were kept overnight or longer at 20° and filtered prior to analysis[13] and use in oxidation experiments. Suitable solutions of periodic acid in water may also be prepared from barium periodate ($Ba_2I_2O_9$). A solution of 75 g. of potassium periodate in 2500 ml. of hot distilled water was cooled cautiously to the beginning of crystallization (about 65°); to this was added a solution of 89.2 g. of pure barium acetate monohydrate in 500 ml. of cold water. It was shaken thoroughly while cooling in ice-water and then kept at 5° for about six hours. The barium periodate was filtered off, washed free from acetic acid with cold water, air-dried for two days and then at 25° *in vacuo* over calcium chloride; yield 115–120 g., containing 37.6% barium. A solution of periodic acid was prepared by shaking mechanically for one and one-half hours a suspension of 20.6 g. of powdered barium periodate in 45 ml. of distilled water to which was added *N* sulfuric acid exactly equivalent to the barium found by analysis; the filtered solution was made to 200 ml. with water.

Oxidation of the Methyl-pentopyranosides.—To 98 ml. of 0.2693 *M* aqueous periodic acid (HIO_4) solution at 20° in a 100-ml. volumetric flask was added 2.0568 g. of the pure, powdered methyl-pentopyranoside crystals. The crystals were dissolved as quickly as possible, and the solution was kept in a 20° room while the rotatory changes recorded in Table II were observed. When the rotation

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[8] Throughout the article the rotations are for sodium light and all specific rotations are at 20°.

[9] All methoxyl analyses were carried out by E. P. Clark's modified Zeisel method [*J. Assoc. Official Agr. Chem.*, **15**, 136 (1932)].

[10] Ault, Haworth and Hirst, *J. Chem. Soc.*, 517 (1935).

[11] Phelps and Hudson, THIS JOURNAL, **48**, 505 (1926).

[12] Obtained from G. Frederick Smith Chemical Co., Columbus, Ohio.

[13] All analyses for periodic acid were carried out by the arsenite method for the determination of periodic acid in the presence of iodic acid [Fleury and Lange, *J. pharm. chim.*, [8] **17**, 107 (1933)].

TABLE II

ROTATORY CHANGES DURING THE OXIDATION OF THE METHYL-PENTOPYRANOSIDES TO DIALDEHYDES[a]

2.0568 g. of methyl-pentopyranoside and 98 ml.[b] of 0.2693 *M* HIO_4 solution[c]

α-Methyl-*d*-arabino-pyranoside		β-Methyl-*d*-arabino-pyranoside		α-Methyl-*d*-xylo-pyranoside		β-Methyl-*d*-xylo-pyranoside	
Time after soln., min.	$[M]_D \times 10^{-2}$	Time after soln., min.	$[M]_D \times 10^{-2}$	Time after soln., min.	$[M]_D \times 10^{-2}$	Time after soln., min.	$[M]_D \times 10^{-2}$
0	− 28.4[d]	0	−402.9[d]	0	+252.6[d]	0	−107.5[d]
1.33	+113.0	4.42	−185.4	3.2	+224.7	2.9	−124.5
1.92	+140.6	6.83	−178.5	5.1	+218.1	5.3	−130.5
2.9	+150.2	9.3	−173.7	7	+213.0	8.1	−135.2
4	+154.4	13.1	−168.8	13	+200.3	13.4	−139.9
8	+160.2	15.4	−168.2	18	+195.4	19.1	−143.6
12.9	+162.4	23	−165.4	24.1	+190.2	31.9	−149.1
21.1	+163.1	43.1	−163.3	42.2	+182.1	42.4	−151.2
41.2	+164.0	80	−162.6	60.7	+177.8	52.8	−152.2
71	+164.0	109	−162.6	90.2	+174.4	104.6	−156.7
90	+164.0	258	−163.3	137.9	+171.6	152.8	−158.8
120	+164.0			219	+168.8	258	−160.4
260	+164.0			274	+167.6	16 hrs.	−164.2
				557	+165.4		

[a] See Fig. 2. [b] The volume of the solution, measured at 20° after completion of the reaction, was 99.8 ml. [c] Although the reaction solution was kept in a 20° room, its temperature did not remain constant, due to the heat evolved in each of the oxidation reactions. *Cf.* α-methyl-galactoside, Table V, note *c*. [d] Calcd. from the usually accepted specific rotations in water of the methyl-pentopyranosides, which are in the order listed: −17.3, −245.5, +153.9, −65.5.

ceased to change, 5 ml. of the solution was analyzed for periodic acid at the time specified in Table III; the amount found in each case corresponded approximately to the excess (5%) over two molecular equivalents added at the start. The remainder of the solution was neutralized to phenolphthalein with hot strontium hydroxide solution with care to avoid any excess. The precipitate (strontium iodate and a little strontium periodate) was filtered off and washed with cold distilled water. After the addition of 1 g. of strontium carbonate the solution[14] was concentrated *in vacuo* (bath, 50°) to about 25 ml., filtered and the concentration (bath, 40°) continued to dryness. The residue was extracted thrice with 25-ml. portions of cold absolute ethanol and thrice with 10-ml. portions. An aqueous extract (35 ml.) of the crystals insoluble in ethanol showed no optical activity, indicating the complete solution of the dialdehyde in the ethanol. The dialdehyde was recovered from the ethanol solution as a colorless sirup by distillation of the solvent *in vacuo* (bath, 40–45°); its rotation in 250 ml. of solution in water is shown in Table III. The solution then was diluted with water to 500 ml.; 38 g. of strontium carbonate and 3 ml. of bromine were added and the mixture shaken until the bromine dissolved. The mixture was kept in the dark at room temperature for about eighteen hours with frequent shaking during the first hour. Excess bromine was removed by aeration and excess strontium carbonate by filtration. The rotation of the filtrate, containing principally strontium methoxy-diglycolate and strontium bromide, is given in Table III. After the strontium carbonate was washed with cold water, the combined solution and washings were shaken with silver carbonate (about 25 g.) until free from bromine ions, and the solids were filtered off and washed with cold water. The silver was removed from the filtrate as silver sulfide, excess hydrogen sulfide was expelled by aeration and the solution was concentrated *in vacuo* (bath, 50–60°) to about 50 ml., filtered and the concentration continued to 10–15 ml., when crystals of strontium methoxy-diglycolate began to separate. After completion of crystallization in the refrigerator the crystals were filtered off and washed with about 2 ml. of cold water. A second crop was obtained by evaporating the filtrate *in vacuo* to dryness and crystallizing the sirup from about 5 ml. of water to which ethanol was added to saturation. The yield of strontium methoxy-diglycolate trihydrate (air-dried, or dried at 25° *in vacuo* over calcium chloride) was the same from each of the four methyl-pentopyranosides, 3 g. or 79%. The crude trihydrate derived from the two alpha-methyl-*d*-pentopyranosides showed a specific rotation of about −43° in water (*c*, 0.6); the trihydrate from the two beta forms rotated about +43°. The strontium salt from each of the four sources was recrystallized thrice from eight parts of distilled water, yielding needles of the trihydrate; the rotation of the anhydrous salt, dried to constant weight at 100° *in vacuo*, was then constant. The rotations and

TABLE III

CONSUMPTION OF PERIODIC ACID. ROTATIONS BEFORE AND AFTER BROMINE OXIDATION OF THE DIALDEHYDES

Methyl-pentoside	HIO_4 analysis Time, hrs.	HIO_4 analysis Excess, %	Rotation[a] of sirupy dialdehyde α_D	Rotation[b] after bromine oxidation α_D
α - Methyl - *d* - arabino-pyranoside	3	4.8	+1.63	−0.65
β - Methyl - *d* - arabino-pyranoside	4	4.9	−1.64	+ .66
α - Methyl - *d* - xylo-pyranoside	8	6.1	+1.64	− .61
β - Methyl - *d* - xylo-pyranoside	16	5.3	−1.63	+ .66

[a] In aqueous solution (250 ml.); 2-dm. tube. [b] In aqueous solution (500 ml.); 2-dm. tube.

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(14) The neutral solution usually was kept overnight at 20–25° before distillation.

TABLE IV

ROTATIONS AND ANALYSES OF THE STRONTIUM SALTS FROM THE PENTOPYRANOSIDES

	$C_5H_6O_6Sr \cdot 3H_2O$ Found,[a] %		$C_5H_6O_6Sr$[a]			
Methyl-pentoside	H_2O	$[\alpha]^{20}_D$ in water[b]	C	H	OCH_3	Sr
Calculated values, %	17.80		24.03	2.42	12.42	35.10
α-Methyl-*d*-arabino-pyranoside	17.78	−55.5°	24.04	2.68	12.22	34.97
β-Methyl-*d*-arabino-pyranoside	17.82	+55.7°	23.92	2.56	12.20	34.91
α-Methyl-*d*-xylo-pyranoside	17.73	−55.5°	24.06	2.68	12.17	35.01
β-Methyl-*d*-xylo-pyranoside	17.79	+55.3°	23.94	2.69	12.16	35.07

[a] Dried to constant weight at 100° *in vacuo*. The anhydrous salts are quite hygroscopic. [b] C = 1.07–1.15 g. per 100 ml. of solution. At concentrations of 0.6–1.2 g. per 100 ml. the rotation, which varies with the concentration, may be expressed by the equation: $[\alpha]^{20}_D = \pm 48.5° \pm 6.33\ C$, the positive sign pertaining to the salt from the β-methyl *d*-pentopyranosides.

analyses are shown in Table IV. The rotation of the dibasic acid from each of the strontium salts is recorded in Table I.

Proof of Structure.—To a solution of 15.0 g. of pure strontium salt ($C_5H_6O_6Sr \cdot 3H_2O$), derived from beta-methyl-*d*-arabinopyranoside, in 250 ml. of water, was added 98.8 ml. of *N* sulfuric acid and 350 ml. of 95% ethanol; after fifteen hours the strontium sulfate was filtered off and washed with cold 50% ethanol. The filtrate was concentrated *in vacuo* to about 50 ml., the solution was diluted with 50 ml. of ethanol, filtered and the concentration continued to a colorless sirup, which was taken up in water and again concentrated *in vacuo* (bath, 50°) to a thick sirup. The dextrorotatory solution of the sirup in 100 ml. of water was heated on the steam-bath for two hours; it then showed no rotation[15] in a 4-dm. tube. After dilution of the solution with water to 200 ml., 4 ml. of bromine was dissolved in it and the mixture kept in the dark at room temperature for forty-five hours. Excess bromine was removed by aeration, and the solution was neutralized to phenolphthalein with barium hydroxide solution. The precipitated barium oxalate was filtered off, washed and dried at 25° *in vacuo* over calcium chloride; yield, 6.1 g. From the barium oxalate was prepared oxalic acid dihydrate which was identified by its melting point of 99.5–101° and by titration with solutions of sodium hydroxide and potassium permanganate.

To the filtrate from the crude barium oxalate was added sufficient sulfuric acid to precipitate the barium exactly. The filtered solution was freed from bromine ions by shaking with 25 g. of silver carbonate, after which excess silver was removed as sulfide and the solution concentrated *in vacuo* to about 50 ml., filtered and the concentration continued to make exactly 25 ml. of solution, aliquots of which were used for the preparation of derivatives of glycolic acid. Calcium glycolate was prepared by neutralizing 11.5 ml. to phenolphthalein with pure calcium hydroxide solution and concentrating; fine needles; air-dried; yield 2.5 g. or 83%, containing 28.6% of combined water. One recrystallization from water gave the pure compound.

Anal. Calcd. for $C_4H_6O_6Ca$: Ca, 21.08. Found (dried at 115° *in vacuo*): Ca, 21.09, 21.11.

S-Benzylthiuronium glycolate was prepared from 5 ml. of the glycolic acid solution; after neutralization with 5 *N* sodium hydroxide and evaporation nearly to dryness, a solution of the sodium glycolate in 3–4 ml. of hot water was added to a hot solution of 2.18 g. of S-benzylthiuronium chloride in 14 ml. of 95% ethanol. The product, isolated according to Donleavy,[16] was purified by recrystallization from 95% ethanol; m. p. 143° (corr.) alone or mixed with the salt prepared from authentic glycolic acid. *p*-Bromophenacyl glycolate, prepared from 8.5 ml. of the glycolic acid solution by the usual procedure[17] and recrystallized several times from aqueous ethanol, melted at 142° (corr.) and showed no depression when mixed with the ester from authentic glycolic acid.

Anal. Calcd. for $C_{10}H_9O_4Br$: Br, 29.3. Found: Br, 29.6.

Oxidation of Alpha-Methyl-*d*-arabinofuranoside.[18]—The furanoside (1.8300 g.), dried to constant weight in an evacuated desiccator over phosphorus pentoxide, was made up to 25 ml. of solution in water at 20°; its specific rotation was +120.5°, the solution rotating 17.64° to the right in a 2-dm. tube. Exactly 24 ml., containing 1.7568 g. of the furanoside, was added to 25 ml. of 0.5365 *M* periodic acid solution (1.25 molecular equivalents) in a 50-ml. volumetric flask; the solution, made up to 50 ml. at 20° with water and kept in a 20° room, showed $[M]_D \times 10^{-2}$: +196.9 (five minutes); +194.8 (twenty minutes); +193.5 (thirty-five minutes); +191.2 (eighty minutes); +189.2 (three hours); +188.4 (five hours); +186.4, constant (twenty-four hours). After twenty-three hours an analysis of 5 ml. of the solution showed 12.6% excess periodic acid, or the reaction of 1.09 molecular equivalents.[19]

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(15) L'-methoxy-diglycolic acid, because of its acetal structure, should be expected to undergo hydrolysis readily; apparently the acetal is hydrolyzed nearly completely during the heating and the subsequent bromine oxidation by which hydrobromic acid is generated. It is noteworthy that the parent methyl-aldopentopyranoside is much more resistant to acid hydrolysis than the derived acetal; the cleavage of the carbon chain of the pyranoside ring increases the ease of hydrolysis.

(16) Donleavy, THIS JOURNAL, **58**, 1004 (1936).

(17) Judefind and Reid, *ibid.*, **42**, 1043 (1920); Hann, Reid and Jamieson, *ibid.*, **52**, 819 (1930).

(18) Supplied by Miss Edna Montgomery. The properties of the furanoside, particularly pertinent being its hygroscopicity, are described by Montgomery and Hudson.[5]

(19) From the difficulty experienced in obtaining sufficiently large samples of the furanoside in the anhydrous condition, it seems probable that the discrepancy between the rotation of +120.5° of the sample oxidized and the value +123° assigned to the pure compound[5] is due to moisture. Calculated on this assumption the sample (1.7210 g.) reacted with 1.12 molecular equivalents of periodic acid and the final $[M]_D \times 10^{-2}$ was +190.2 (twenty-four hours) corresponding to a specific rotation of +117.3° for the dialdehyde. The reaction of the excess of one molecular equivalent of periodic acid

TABLE V

ROTATORY CHANGES DURING THE OXIDATION OF THE METHYL HEXOSIDES TO DIALDEHYDES[a]

2.4296 g. of anhydrous methyl hexoside or the equivalent as hydrate[20] and 98 ml.[b] of 0.2689 *M* HIO_4 solution[c]

α-Methyl-*d*-galactoside		α-Methyl-*d*-glucoside		α-Methyl-*d*-guloside		α-Methyl-*d*-mannoside		β-Methyl-*d*-galactoside		β-Methyl-*d*-glucoside	
Time after soln., min.	$[M]_D \times 10^{-2}$	Time after soln., min.	$[M]_D \times 10^{-2}$	Time after soln., min.	$[M]_D \times 10^{-2}$	Time after soln., min.	$[M]_D \times 10^{-2}$	Time after soln., min.	$[M]_D \times 10^{-2}$	Time after soln., min.	$[M]_D \times 10^{-2}$
0	+380.7[d]	0	+308.4[d]	0	+232.1[d]	0	+153.3[d]	0	+ 1.4[d]	0	− 66.4[d]
2.9	+291.5	6.5	+256.0	3.5	+231.0	9	+199.9	8	−212.6	3.1	− 97.9
4.2	+260.1	10	+239.8	8.4	+229.3	14	+202.9	10	−217.4	7.3	−126.0
5.2	+240.9	13	+230.4	22.1	+221.7	20	+204.4	14.5	−224.9	11	−142.2
7.6	+212.1	16	+223.4	34	+217.8	33	+204.3	20.3	−228.6	16.6	−162.5
10.1	+198.5	20.5	+216.8	49.9	+214.6	51	+202.7	37.3	−233.3	31.6	−182.8
14	+189.5	26.5	+211.1	60	+212.7	80	+201.1	63	−237.0	50.2	−197.8
18	+186.2	37.5	+206.9	87	+207.2	110	+198.8	103	−238.0	77.8	−209.8
28	+187.6	66.5	+203.3	120	+202.3	145	+197.4	190	−239.3	111.4	−218.5
46	+190.5	120	+200.1	198	+198.5	180	+196.1	280	−240.0	175.3	−227.2
77	+193.1	218	+197.8	265	+197.1	265	+194.6	458	−240.0	230	−230.7
132	+194.5	293	+197.0	24 hrs.	+195.3	420	+193.7			298	−234.4
174	+195.0	413	+196.2							25 hrs.	−244.1
269	+195.7										
374	+195.7										

[a] See Fig. 1. [b] The volume of the solution, measured at 20° after completion of the reaction, was practically 100 ml. [c] The solutions were prepared at 20° and kept thereafter in a 20° room, but the temperature was variable due to the heat evolved in each of the oxidation reactions, the increase being 10° for α-methyl-*d*-galactoside. [d] Calcd. from the usually accepted specific rotations in water of the methyl-hexosides which are in the order listed: +196.1, +158.9, +109.4, +79, +0.7, −34.2. The value for α-methyl-guloside refers to its monohydrate.

Strontium D′-methoxy-D-hydroxymethyl-diglycolate in a yield of about 60% was prepared from the oxidation solution by the general directions given under the methyl-pentopyranosides. Recrystallized twice as fine needles from fifteen parts of water to which 10–15% of ethanol was added, and dried to constant weight at 105° *in vacuo* the anhydrous salt showed a specific rotation of −53.3° in water (*c*, 0.6).

Anal. Calcd. for $C_6H_8O_7Sr$: C, 25.74; H, 2.88; OCH_3, 11.1; Sr, 31.33. Found: C, 25.74, 25.80; H, 3.16, 3.12; OCH_3, 11.0, 10.9; Sr, 31.29, 31.36.

The identification of the strontium salt as a derivative of D′-methoxy-D-hydroxymethyl-diglycolic acid is confirmed by the specific rotation +26.1° (*c*, 1.4) of the dibasic acid obtained by liberating it from its pure strontium salt with an equivalent of hydrochloric acid (*cf.* Table I).

Oxidation of the Methyl-hexosides.—The procedure was the same as described for the methyl-pentopyranosides, using 98 ml. of 0.2689 *M* periodic acid solution and 2.4296 g. of pure anhydrous methyl-hexoside,[20] or a multiple of these quantities. The rotatory changes are shown in Table V; the results of analyses for periodic acid, carried out with 5 ml. of the solutions at specified times, are recorded in Table VI and show for each methyl-hexoside about the excess (5%) over two molecular equivalents added at the start. After completion of the oxidation reaction the solution from each alpha-methyl-hexoside was neutralized with strontium hydroxide solution and treated as outlined for the methyl-pentopyranosides. In Table VI is recorded the rotation of the sirupy D′-methoxy-D-hydroxymethyl-diglycolic aldehyde, isolated from each alpha-methyl-hexoside, and also the rotation after oxidation with bromine water in the presence of strontium carbonate. The yield of the crystalline hydrate of strontium D′-methoxy-D-hydroxymethyl-diglycolate, dried at 25° *in vacuo* over calcium chloride, was 65–70% from each alpha-methyl-hexoside; at this stage it usually showed a specific rotation in water of about −47° (*c*, 0.7). The strontium salt was recrystallized from fifteen parts of water, to which 10–15% ethanol was added, until the rotation of the anhydrous salt was constant. It crystallizes readily as fine needles which, after being dried in an evacuated desiccator over calcium chloride, contain two moles of combined water. Calcd. for $C_6H_8O_7Sr \cdot 2H_2O$: H_2O, 11.41. Found H_2O (dried at 105° *in vacuo*): 11.66. The identity of the strontium salt from the four alpha-

TABLE VI

CONSUMPTION OF PERIODIC ACID. ROTATIONS BEFORE AND AFTER BROMINE OXIDATION OF THE DIALDEHYDES

Methyl hexoside	HIO_4 Analysis Time, hrs.	HIO_4 Analysis Excess, %	Rotation[a] of sirupy dialdehyde α_D	Rotation[b] after bromine oxidation α_D
α-Methyl-*d*-galactoside	5	5.2	+2.00	−0.73
α-Methyl-*d*-glucoside	6	6.9	+1.99	− .68
α-Methyl-*d*-guloside	24	4.7	+1.98	− .69
α-Methyl-*d*-mannoside	6	6.1	+1.92	− .69
β-Methyl-*d*-galactoside	6	5.8	−2.25	+ .48
β-Methyl-*d*-glucoside	25	5.2	−2.24	+ .49[c]

[a] In aqueous solution (250 ml.); 2-dm. tube. [b] In aqueous solution (500 ml.); 2-dm. tube. [c] Barium L′-methoxy-D-hydroxymethyl-diglycolate.

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could be caused by slight hydrolysis of the glycoside during the oxidation reaction, or a slight contamination of the sample by a pyranoside form.

[20] In the case of alpha-methyl-*d*-guloside its crystalline monohydrate (2.6552 g.), and of beta-methyl-*d*-glucoside its hemihydrate (2.5425 g.), was used. The carefully purified alpha-methyl-*d*-guloside monohydrate melted at 76–77° and showed a specific rotation of +109.4° in water (*c*, 2.2) in agreement with the values of Isbell [*J. Research Nat. Bur. Standards*, **8**, 6 (1932)].

TABLE VII

ROTATIONS AND ANALYSES OF STRONTIUM D′-METHOXY-D-HYDROXYMETHYL-DIGLYCOLATE FROM THE ALPHA-METHYL-HEXOSIDES

Methyl-hexoside	$[\alpha]^{20}_D$ in water[b]	$C_6H_8O_7Sr$[a] Found, % C	H	OCH_3	Sr	
Calculated values		25.74	2.88	11.1	31.33	
α-Methyl-*d*-galactoside	−53.5°				31.25	
α-Methyl-*d*-glucoside	−52.9°				31.25	31.17
α-Methyl-*d*-guloside	−52.7°	25.71	2.86	10.9	31.23	31.16
		25.80	3.12	10.9		
α-Methyl-*d*-mannoside	−53.0°				31.27	31.13

[a] Dried to constant weight at 105° *in vacuo*. The anhydrous salt is quite hygroscopic. [b] C = 0.58–0.65 g. per 100 ml. of solution. At concentrations of 0.6–1.2 g. per 100 ml. the rotation, which varies with the concentration, may be expressed by the equation: $[\alpha]^{20}D = -48.6° - 7.36\ C$.

methyl-hexosides is shown by the rotations and analyses given in Table VII. A confirmation of this identification is afforded by the agreeing values of the specific rotation of D′-methoxy-D-hydroxymethyl-diglycolic acid, obtained by liberating it with an equivalent of hydrochloric acid from the pure strontium salt derived from each of the four alpha-methyl-hexosides (*cf.* Table I).

Barium L′-Methoxy-D-hydroxymethyl-diglycolate from Beta-methyl-*d*-glucoside.—The strontium salt prepared from beta-methyl-*d*-galactoside by the usual procedure unfortunately was not crystalline. The galactoside as shown by the data in Tables V and VI utilizes two moles of periodic acid in the manner typical of the hexopyranoside structure and yields a dialdehyde rotating about the same as that from beta-methyl-*d*-glucoside. This amorphous strontium salt appeared therefore to be the normal product from the beta-methyl-*d*-aldohexopyranosides, but its amorphous nature caused us to change to the barium salt, which crystallized quite readily when prepared from beta-methyl-*d*-glucoside.

After completion of the oxidation of beta-methyl-*d*-glucoside, the solution was neutralized with barium hydroxide solution and the procedure for the methyl-pentopyranosides was followed with the substitution of barium carbonate for strontium carbonate. The yield of crystalline barium salt, dried in an evacuated desiccator over calcium chloride and showing a specific rotation of +34 to +35° in water (*c*, 1.5), was 15 g. from 12.2 g. of beta-methyl-*d*-glucoside hemihydrate. Recrystallized twice from water as fine needles of the dihydrate (air-dried), the barium salt after being dried at 100° *in vacuo* showed the specific rotation[21] +35.9° in water (*c*, 3.4) which was unchanged by another recrystallization. The anhydrous salt is quite hygroscopic.

Anal. Calcd. for $C_6H_8O_7Ba \cdot 2H_2O$: H_2O, 9.86. Found (dried at 100° *in vacuo*): H_2O, 9.92, 9.97. Calcd. for $C_6H_8O_7Ba$: C, 21.86; H, 2.45; OCH_3, 9.4; Ba, 41.70. Found: C, 21.84, 21.91; H, 2.58, 2.67; OCH_3, 9.3, 9.2; Ba, 41.72, 41.66.

The rotation of L′-methoxy-D-hydroxymethyl-diglycolic acid in water, from the barium salt and an equivalent of hydrochloric acid, is recorded in Table I.

Proof of Structure of the Strontium and Barium Salts from the Methyl-hexosides.—D′-Methoxy-D-hydroxymethyl-diglycolic acid, prepared from 15 g. of pure hydrated strontium salt,[22] was hydrolyzed in aqueous solution; the hydrolyzed acid was oxidized with bromine water and neutralized with barium hydroxide solution, all as described for the structure of strontium L′-methoxy-diglycolate. From the barium oxalate (5.7 g.) was prepared oxalic acid dihydrate of m. p. 99.5–101° which, after dehydration at 100°, melted at 189–190°; it was characterized further by the previously mentioned analyses.

The filtrate from the barium oxalate, freed from barium with sulfuric acid, from bromine ions with silver carbonate and from excess silver with hydrogen sulfide, was concentrated *in vacuo* to about 200 ml., filtered and neutralized to phenolphthalein with pure calcium hydroxide solution. The solution was concentrated *in vacuo* to a sirup which crystallized readily, yielding about 6 g. of crude calcium *d*-glycerate. After two recrystallizations from water and drying in the air, the calcium *d*-glycerate dihydrate melted at 141–142° (uncorr.) and showed a specific rotation in water of +14.6 ± 0.5° compared with m. p. 138° and specific rotation +14.07° found by Anderson.[23]

After the exact removal of the barium with sulfuric acid from 250 ml. of an aqueous solution containing 19.4 g. of pure anhydrous barium salt (barium L′-methoxy-D-hydroxymethyl-diglycolate) prepared from beta-methyl-*d*-glucoside, the solution was concentrated *in vacuo* to 200 ml., the organic acid was hydrolyzed by heating and treated thereafter by the above procedure for the preparation of barium oxalate (6.9 g.) and calcium *d*-glycerate (8.5 g. of crude). The oxalic acid dihydrate from the barium oxalate melted at 99.5–101°, and was characterized further as previously described. The calcium *d*-glycerate dihydrate after three recrystallizations from water showed m. p. 141–142° (incorr.) and specific rotation +14.9 ± 0.5° in water.

Anal. Calcd. for $C_6H_{10}O_8Ca \cdot 2H_2O$: H_2O, 12.59; Ca, 14.00. Found (from the strontium salt): H_2O, 12.78; Ca, 13.95, 13.78; (from the barium salt) H_2O, 12.61; Ca, 13.91, 13.86.

We express our thanks to Dr. R. M. Hann for a supply of galactose and S-benzylthiuronium

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(21) Variation of the rotation with the concentration should be anticipated from the close relationship to the strontium salts.

(22) The sample of strontium salt was prepared by the oxidation of alpha-methyl-*d*-mannoside with barium hypobromite.

(23) Anderson, *Am. Chem. J.*, **42**, 421 (1909); *cf.* Nef, Hedenburg and Glattfeld, THIS JOURNAL, **39**, 1650 (1917); Fischer and Jacobs, *Ber.*, **40**, 1069 (1907).

chloride, to Dr. Alice T. Merrill for the methyl-guloside, to Miss Edna M. Montgomery for the methyl-arabinosides and to Mr. C. G. Remsburg for carrying out some of the analyses.

Summary

The oxidation of alpha-methyl-*d*-mannopyranoside with barium hypobromite was shown[2] to produce a dibasic acid which was isolated as its crystalline strontium salt and was proved to be a derivative of diglycolic acid (D′-methoxy-D-hydroxymethyl-diglycolic acid). The same strontium salt has been prepared in yields of 65–70% through oxidation of four alpha-methyl-hexosides (alpha-methyl-*d*-mannoside, *d*-glucoside, *d*-galactoside and *d*-guloside) with periodic acid followed by oxidation of the resulting dialdehyde with bromine water kept neutral with strontium carbonate. The structure of the strontium salt, particularly the presence of the *d*-glyceric acid moiety in its molecule, proves each of the four alpha-methyl-hexosides to be of the pyranoside type, this being the first proof for alpha-methyl-*d*-guloside. Beta-methyl-*d*-glucoside produces by way of these oxidation reactions a crystalline barium salt which also has the *d*-glyceric acid grouping in its molecule; evidence is presented that this salt is barium L′-methoxy-D-hydroxymethyl-diglycolate from which follows the pyranoside structure for beta-methyl-*d*-glucoside.

The alpha forms of methyl-*d*-arabinoside (−17°) and methyl-*d*-xyloside (+154°) yield another crystalline strontium salt (strontium D′-methoxy-diglycolate) and the beta forms of these two glycosides −245 and −65°, respectively) produce strontium L′-methoxy-diglycolate, the optical antipode of the salt from the alpha forms. Since the latter two strontium salts contains the glycolic acid structure in their molecules the four parent methyl-pentosides must have the pyranoside structure. A third crystalline methyl-*d*-arabinoside (+123°) yields the strontium salt with the *d*-glyceric acid grouping (the one from the alpha-methyl-*d*-aldohexopyranosides); this new methyl-arabinoside must therefore possess the furanoside structure and the alpha configuration.

The cleavage type of oxidation, having wide application among the glycosides, thus provides a new method for the determination of ring structures and for the correlation of the configuration of carbon atom 1 of glycosides. It also affords the most direct way of correlating the configuration of the sugars with glyceric acid.

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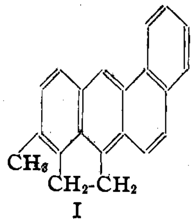
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

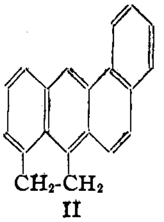
The Synthesis of 1,2-Benzanthracene Derivatives Related to 3,4-Benzpyrene

BY MELVIN S. NEWMAN

In seeking to account for the carcinogenic activity of methylcholanthrene, I, and cholanthrene, II, in terms of chemical constitution,[1] Fieser and the author[2] prepared 5,10-dimethyl-1,2-benzanthracene, III, and 10-methyl-1,2-benzanthracene, IV. In that publication it was reported that III is comparable in rapidity of action to I and II. The results of further biological tests[3] indicate that IV has approximately the same activity as I, II and III. Thus, in viewing the structures of these four compounds, the conclusion is to be drawn that the structural feature necessary for strongly developed cancer-producing properties in hydrocarbons of the 1,2-benzanthracene series is substitution at position 10.



I



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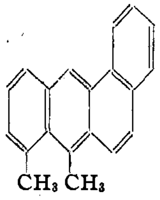
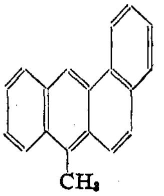


III



IV

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(1) For a more complete discussion of the carcinogenic activity of 1,2-benzanthracene derivatives see Fieser, *et al.*, *Am. J. Cancer*, **29**, 260 (1937).

(2) Fieser and Newman, THIS JOURNAL, **58**, 2376 (1936).

(3) Private communication from Dr. M. J. Shear. See also Fieser and Hershberg, *ibid.*, **59**, 394 (1937).