zoic acid from a series of para substituted *syn*-benzaldoxime benzoates in the presence of triethylamine and pyridine has been determined.

2. The mechanism of the elimination reaction is discussed.

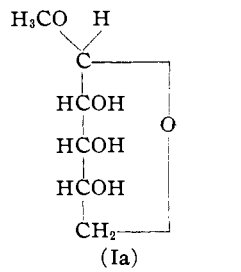
DURHAM, N. C. RECEIVED JANUARY 13, 1941

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

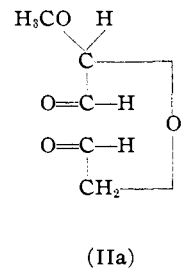
Crystalline β-Methyl-D-ribopyranoside[1]

BY ERNEST L. JACKSON AND C. S. HUDSON

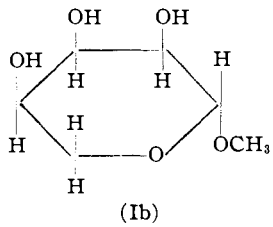
The isolation of a crystalline methyl-D-riboside by J. Minsaas[2] in 1934 made available for structural study a pure isomer of this methylpentoside. Levene and Tipson[3] had obtained evidence for the pyranoside ring structure of "normal methyl-riboside" through methylation of a sirup, which was presumably a mixture of isomeric methyl-D-ribosides. Although Minsaas made no study of the ring structure of his crystalline riboside, he inferred it to be a beta form because of the pronounced levorotation ($[\alpha]^{20}D$ $-113.6°$ in water) as compared with the rotation of the sirupy portion of his product, which he presumed to contain a large proportion of the alpha form. With the aid of seed crystals, kindly supplied by Dr. Minsaas, we have prepared the riboside in pure crystalline condition, with melting point 83° and $[\alpha]^{20}D$ $-105.0°$ in water, and by oxidation with periodic acid have proved it to be β-methyl-D-ribopyranoside (Ia or Ib).



(Ia)

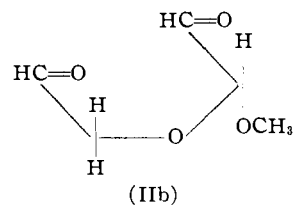


(IIa)



(Ib)

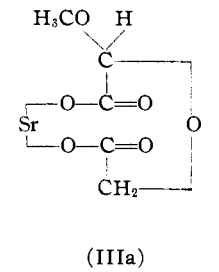
β-Methyl-D-ribopyranoside



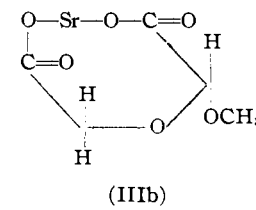
(IIb)

L′-Methoxy-diglycolic aldehyde

The crystalline riboside, upon oxidation by periodic acid or sodium metaperiodate, consumed two moles of the oxidant and produced one mole of formic acid. These data have been shown by us[4] to be typical of the oxidation of the methyl-aldopentopyranosides with periodic acid, and accordingly are in agreement with the oxidation of the ribopyranoside (Ia or Ib) to L′-methoxydiglycolic aldehyde (IIa or IIb). The final proof is based upon the oxidation of the product from the periodic acid reaction with bromine water kept neutral with strontium carbonate to produce in good yield the same crystalline strontium L′-methoxydiglycolate (IIIa or IIIb), which we had obtained in a similar way from β-methyl-D-arabinopyranoside and β-methyl-D-xylopyranoside.[4] These oxidation results not only prove the pyranoside ring structure and the beta classification of the crystalline riboside, but also show it to be substantially homogeneous[5] since the end rotation of the periodic acid oxidation solution, as indicated in Table I, was in agreement with the rotation of L′-methoxydiglycolic aldehyde derived from β-methyl-D-arabinopyranoside, β-methyl-D-xylopyranoside and β-methyl-D-lyxopyranoside.[6]



(IIIa)



(IIIb)

Strontium L′-methoxy-diglycolate

Experimental

Preparation of β-Methyl-D-ribopyranoside.—The procedure of Minsaas[2] was modified, principally by shortening

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

(2) J. Minsaas, *Ann.*, **512**, 286 (1934).

(3) Levene and Tipson, *J. Biol. Chem.*, **93**, 623 (1931); **92**, 109 (1931).

(4) Jackson and Hudson, THIS JOURNAL, **59**, 994 (1937); **61**, 1530 (1939).

(5) Jackson and Hudson, *ibid.*, **61**, 959 (1939).

(6) Isbell and Frush, *J. Research Natl. Bur. Standards*, **24**, 125 (1940).

TABLE I

ROTATIONS OF THE OXIDATION PRODUCTS OF THE β-METHYL-D-PENTOPYRANOSIDES

Substance	Methyl glycoside $[\alpha]^{20}D$	Dialdehyde[a] $[\alpha]^{20}D$	Dibasic acid[b] $[\alpha]^{20}D$	Strontium salt[c] $[\alpha]^{20}D$
β-Methyl-D-ribopyranoside	−105	−123.4	+12.2	+55.7
β-Methyl-D-arabinopyranoside[4]	−245	−123.7	+12.5	+55.7
β-Methyl-D-xylopyranoside[4]	− 65	−124.3	+12.2	+55.3
β-Methyl-D-lyxopyranoside[4]	−128	−125.5	....	....

[a] L′-Methoxydiglycolic aldehyde. Specific rotations calculated from the final $[M]D$ values of the periodic acid oxidation solutions. [b] Determined by liberating the acid (*c*, 1.2–1.6) from its pure anhydrous strontium salt with an equivalent of hydrochloric acid. [c] *c*, 1.07–1.15 in water.

the time for methylation of ribose through the increase in the concentration of hydrogen chloride in methyl alcohol from 0.25% to 1.0% and by omitting the distillation of the crude methyl-riboside. A solution of 10 g. of crystalline D-ribose,[7] rotating[8] −19.7° in water, in 100 ml. of a 1.0% absolute methyl alcoholic solution of hydrogen chloride was refluxed for six hours, then shaken for one hour with excess silver carbonate, and filtered after the addition of a small amount of activated carbon. The solution was concentrated *in vacuo* at room temperature to a thick, colorless sirup, which was thinned with 4 ml. of ethyl acetate, then seeded[9] with crystals of β-methyl-D-ribopyranoside and allowed to crystallize during several days at refrigerator temperature. The liquid was decanted from the crystals, which were washed with a little ice-cold ethyl acetate and dried at 25° *in vacuo* over calcium chloride. A second crop was obtained by concentration of the solution *in vacuo* (bath 40–45°) to a thick sirup and crystallization from a little ethyl acetate as just described; the yield was 3.6 g., or 33%. After one recrystallization from ethyl acetate the crystals, which resembled those described in detail by Minsaas,[2,10] rotated −103.3° in water. Following the fourth and fifth recrystallizations from the same solvent, the specific rotation was, respectively, −105.2 and −105.0° in water (*c*, 0.47; *l*, 4); m. p. 83° (uncor.).

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.90; H, 7.37; OCH_3, 18.90. Found: C, 44.02; H, 7.35; OCH_3, 18.69.

Oxidation of β-Methyl-D-ribopyranoside with Periodic Acid.—A solution of 0.5184 g. of pure β-methyl-D-ribopyranoside in water was added to 12.5 ml. of 0.5305 *M* aqueous periodic acid solution (2.1 molecular equivalents). The solution, after being diluted with water to 25 ml. at 20° and kept in a 20° room for twenty hours, showed $[M]^{20}D \times 10^{-2} = -163.1°$. This value corresponds to a specific rotation of −123.4° for L′-methoxydiglycolic aldehyde. An analysis of 5 ml. of the solution at the end of twenty hours showed an excess of 0.08 molecular equivalent of periodic acid, or the consumption of 2.02 molecular equivalents of the oxidant.

Strontium L′-Methoxydiglycolate from β-Methyl-D-ribopyranoside.—The oxidation of 1.55 g. of pure β-methyl-D-ribopyranoside by 75 ml. of 0.2652 *M* aqueous periodic acid solution was carried out at 20° during sixteen hours. After the solution had been neutralized to phenolphthalein with strontium hydroxide, L′-methoxydiglycolic aldehyde was isolated as a sirup by the procedure described in a previous paper[4] for the methoxy-diglycolic aldehydes from the methyl-pentopyranosides. To a solution of the dialdehyde in 400 ml. of water were added 30 g. of strontium carbonate and 2.4 ml. of bromine. After being shaken until the bromine had dissolved, the mixture was kept in the dark at room temperature for sixteen hours with frequent shaking during the first hour. Excess bromine was removed by aeration, excess strontium carbonate by filtration, bromine ions with silver carbonate and excess silver with hydrogen sulfide. The solution was concentrated *in vacuo* (bath, 50–55°) to 50 ml., filtered and the concentration continued to about 10 ml. After completion of crystallization in the refrigerator and filtration, a second crop was obtained by concentration of the solution *in vacuo* and addition of ethanol; the yield of needles of strontium L′-methoxy-diglycolate trihydrate was 2.1 g., or 72%. Purified by recrystallization from water and dried at 100° *in vacuo*, the anhydrous salt rotated +55.7° in water (*c*, 1.1; *l*, 4). The specific rotation of L′-methoxydiglycolic acid, obtained by liberation from the pure anhydrous strontium salt in aqueous solution with an equivalent of hydrochloric acid, was +12.2° (*c*, 1.2; *l*, 4).

Anal. Calcd. for $C_5H_6O_6Sr \cdot 3H_2O$: H_2O, 17.79; OCH_3, 10.21; Sr, 28.85. Found: H_2O, 17.75, 18.01; OCH_3, 10.14, 10.24; Sr, 28.62, 28.45.

Oxidation of β-Methyl-D-ribopyranoside with Sodium Metaperiodate.—An aqueous solution of 0.5376 g. of pure β-methyl-D-ribopyranoside was mixed with 15 ml. of 0.4585 *M* aqueous sodium metaperiodate solution (2.1 molecular equivalents). The solution, diluted with water to 25 ml. at 20° and kept in a 20° room for twenty hours, showed $[M]^{20}D \times 10^{-2} = -163.2$, which corresponds to a specific rotation of −123.5° for L′-methoxydiglycolic aldehyde. This value is in good agreement with the specific rotation of −123.4° calculated from the end rotation of the periodic acid oxidation solution. After twenty hours an analysis of 5 ml. of the solution showed an excess of 0.08 molecular equivalent of sodium metaperiodate, the consumption of the oxidant thus being 2.02 molecular equivalents. The acidity of the reaction solution at the end of twenty hours indicated the production of 1.00 molecular equivalent of formic acid (5 ml., diluted with 300 ml. of water and neutralized to methyl red, required 6.60 ml. of 0.1 *N* sodium hydroxide; calcd. 6.55 ml.).

We express our thanks to Dr. W. T. Haskins for carrying out the microanalyses.

Summary

The crystalline methyl-D-riboside described by Minsaas has been purified to a constant rotation, $[\alpha]^{20}D$ −105.0° in water, and melting point 83°. Upon oxidation with periodic acid or sodium

(7) D-Ribose was prepared from yeast nucleic acid by the procedure of F. P. Phelps, U. S. Patent 2,152,662 (1939).

(8) Except where otherwise stated, all rotations in this article are specific rotations at 20° for sodium light; *c* = g. per 100 ml. of solution; *l* = length in dm.

(9) A sirup of methyl-riboside, prepared by Minsaas' procedure, failed to crystallize during three months, but upon nucleation with crystals of the riboside, supplied by Dr. Minsaas, crystallization started promptly.

(10) Crystallographic measurements are reported by Haakon Braekken (*Kgl. Norske Videnskab. Selskabs. Forh.*, **9**, 184 (1936); *C. A.*, **31**, 7308 (1937)).

metaperiodate, followed by bromine water kept neutral with strontium carbonate, the riboside is converted to the same strontium L′-methoxydiglycolate which had been obtained previously from β-methyl-D-arabinopyranoside and β-methyl-D-xylopyranoside. This riboside is thus proved to be β-methyl-D-ribopyranoside.

WASHINGTON, D. C. RECEIVED FEBRUARY 20, 1941

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

2-Methyl-1,4-naphthohydroquinone Di-β-D-glucoside

BY BYRON RIEGEL, PERRIN G. SMITH[1] AND CARL E. SCHWEITZER[2]

The search for water-soluble compounds with antihemorrhagic activity suitable for parenteral administration in small volumes suggested the preparation of a glucoside. Contemporary with this work on water-soluble substances has been that of several other research groups. This has been described in the review on vitamins K.[3]

The octaacetate of the diglucoside was first prepared, and this on deacetylation gave the desired compound. Helferich[4] had prepared aryl glucosides by fusing glucose pentaacetate with various phenols in the presence of suitable catalysts. When zinc chloride was used as the catalyst, α-glucosides were obtained, but *p*-toluenesulfonic acid caused the formation of β-glucosides. On fusing the latter catalyst with 2-methyl-1,4-naphthohydroquinone and glucose pentaacetate, a rather unsatisfactory yield of 2-methyl-1,4-naphthohydroquinone bis-(tetraacetyl-β-D-glucopyranoside) was obtained. Michael's method,[5] which has been widely employed for the preparation of glucosides, proved to be much more satisfactory. The dipotassium salt of 2-methyl-1,4-naphthohydroquinone was condensed with 2,3,4,6-tetraacetyl-α-D-glucosyl bromide in a dilute acetone solution. Deacetylation of the octaacetate was first accomplished by a saturated aqueous solution of barium hydroxide, but subsequent experiments showed that aqueous methanolic ammonia gave almost quantitative yields. The 2-methyl-1,4-naphthohydroquinone di-β-D-glucoside monohydrate melted with decomposition at 275° and gave a specific rotation of −61°.

The solubility of the diglucoside, which could also be named 2-methyl-1,4-di-β-D-glucosidonaphthalene, was eventually shown to be 0.1–0.2 mg. per ml. This very low solubility obviously rendered the compound unsuitable for its intended use. However, this fact was overlooked in our earlier work, due to the ready formation of rather stable supersaturated solutions, and it was not until larger quantities of material had been prepared and checked both for rotation and bioassay that this unfortunate property was discovered.

Preliminary bioassay by Mrs. Flemintine Peirce Dann of the Abbott Laboratories on supersaturated solutions of the diglucoside indicated an activity of about one-third that of 2-methyl-1,4-naphthoquinone. This was the expected value because the diglucoside has a molecular weight about three times that of the naphthoquinone.

Attempts were made to prepare other glycosides. Pacsu's method[6] for converting β-alkyl glucosides to their α-isomers, which consists of treating the acetylated glucoside with titanium tetrachloride in chloroform, proved unsuccessful when applied to our aryl derivative. Since there are some indications in the literature that mannosides may be more soluble than glucosides, an attempt was made to prepare the dimannoside. Apparently, the 2,3,4,6-tetraacetyl-α-D-mannosyl bromide hydrolyzed so rapidly that it failed to condense to give the desired product.

The authors wish to thank the Abbott Laboratories for generously aiding this research and Professor Charles D. Hurd for his helpful suggestions on nomenclature.

Experimental[7]

2-Methyl-1,4-naphthohydroquionone Bis-(tetraacetyl-β-D-glucopyranoside).—(a) A melt of 3 g. (0.0172 mole) of 2-methyl-1,4-naphthohydroquinone, 13.4 g. (0.0344 mole) of β-D-glucose pentaacetate and 0.15 g. of *p*-toluenesulfonic acid was heated with stirring at 130° for thirty minutes, acetic acid being evolved. The products, which

(1) Abbott Research Associate, 1938–1940.

(2) Abbott Research Fellow, 1940–1941.

(3) Riegel, *Ergeb. Physiol. biol. Chem. exptl. Pharmakol.*, **43**, 133 (1940).

(4) Helferich and Schmitz-Hillebrecht, *Ber.*, **66**, 378 (1933).

(5) Michael, *ibid.*, **12**, 2260 (1879).

(6) Pacsu, THIS JOURNAL, **52**, 2563 (1930).

(7) All analyses by Mr. E. Shelberg, microanalyst for the Abbott Laboratories.