JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

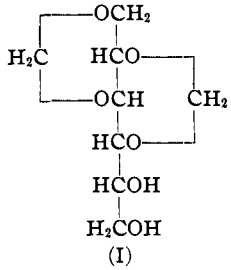
VOLUME 66 AUGUST 5, 1944 NUMBER 8

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

1,3:2,4-Dimethylene-D-epirhamnitol and 2,4-Methylene-D-epirhamnitol

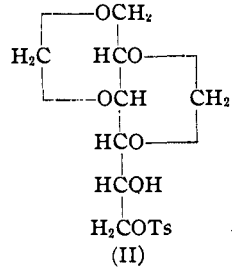
BY A. T. NESS, RAYMOND M. HANN AND C. S. HUDSON

In a recent communication[1] we reported the isolation and proof of structure of 1,3:2,4-dimethylene-D-sorbitol (I). Further study of the



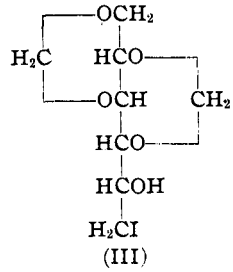
(I)

1,3:2,4-Dimethylene-D-sorbitol



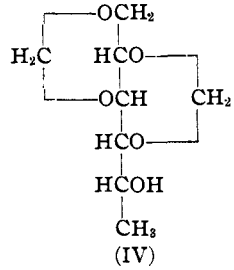
(II)

1,3:2,4-Dimethylene-6-tosyl-D-sorbitol



(III)

1,3:2,4-Dimethylene-6-iodo-D-sorbitol



(IV)

1,3:2,4-Dimethylene-D-epirhamnitol (*syn.* 1,3:2,4-Dimethylene-6-desoxy-D-sorbitol)

diacetal has shown that it is converted upon treatment in pyridine solution with one molecular equivalent of *p*-toluenesulfonyl chloride to a crystalline monotosyl ester melting at 160–161° and rotating $[\alpha]^{20}D$ −10.0° in chloroform. In view of the well-known tendency[2] of this arylating reagent to react preferentially with primary hydroxyl groups it seemed probable that the tosyl derivative is 1,3:2,4-dimethylene-6-tosyl-D-sorbitol (II); in support of this view it was found that the tosyl group of the substance could be replaced by iodine through the action of a solution of sodium iodide in acetone at 100° for two hours; according to the Oldham–Rutherford rule[3] this replacement is to be expected only if the tosyl group be attached to a primary hydroxyl group. A conclusive proof of the structure was obtained when it was found that upon reduction of the iodo derivative (III) with hydrogen and Raney nickel there was formed a desoxy-dimethylene-D-sorbitol (IV) which is identical with the diacetal that is obtained by condensing D-epirhamnitol with formaldehyde. Since D-epirhamnitol is 6-desoxy-D-sorbitol[4] and the acetal linkages of the dimethylene-D-sorbitol are known to be at positions 1,3 and 2,4, the structure of the desoxy-diacetal must be that of 1,3:2,4-dimethylene-6-desoxy-D-sorbitol (IV), the intermediate (II) must be 1,3:2,4-dimethylene-6-tosyl-D-sorbitol and (III) must be 1,3:2,4-dimethylene-6-iodo-D-sorbitol. The reactions represent a relatively simple conversion of a compound of the D-glucose series to one of the D-epirhamnose series.

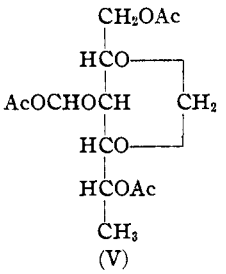
Although we were unable to isolate a monomethylene-D-epirhamnitol as a product of the condensation of D-epirhamnitol and formaldehyde, it has been possible to obtain such an acetal in an indirect manner, namely, by limited acetolysis of 1,3:2,4-dimethylene-D-epirhamnitol (IV) to 1,5-diacetyl-3-acetoxymethyl-2,4-methylene-D-epirhamnitol (V), which upon saponification yielded 2,4-monomethylene-D-epirhamnitol (VI). The last named substance is not oxidized by aqueous per-iodic acid, a fact which constitutes de-

(1) Ness, Hann and Hudson, THIS JOURNAL, **66**, 665 (1944).

(2) Ohle and Dickhäuser, *Ber.*, **58**, 2593 (1925); Levene and Raymond, *J. Biol. Chem.*, **102**, 317 (1933).

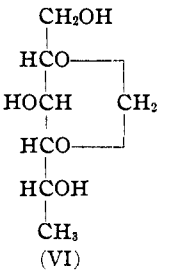
(3) Oldham and Rutherford, THIS JOURNAL, **54**, 366 (1932); *cf.* Oldham, *J. Chem. Soc.*, **127**, 2840 (1925).

(4) The parent aldose of D-epirhamnitol has been designated at various times by the names D-epirhamnose, D-isorhamnose, D-isorhodeose, D-chinovose, D-glucomethylose, and 6-desoxy-D-glucose.



(V)

1,5-Diacetyl-3-acetoxymethyl-2,4-methylene-D-epirhamnitol



(VI)

2,4-Methylene-D-epirhamnitol

finitive proof of the assigned structure (VI). The isolation of this 2,4-monomethylene acetal and particularly the formation of its precursor, compound (V), as a product of the acetolysis of 1,3:2,4-dimethylene-D-epirhamnitol in the high yield of 88%, is evidence supporting cur previously expressed views[5] regarding the limited acetolysis of methylene sugar alcohol acetals.

Experimental

1,3:2,4-Dimethylene-6-tosyl-D-sorbitol (II) from 1,3:2,4-Dimethylene-D-sorbitol (I).—To an ice-cold solution of 5.0 g. of 1,3:2,4-dimethylene-D-sorbitol[5b] in 50 cc. of pyridine was added dropwise an ice-cold solution of 4.6 g. (one molecular equivalent) of *p*-toluenesulfonyl chloride in 10 cc. of pyridine; the reaction mixture was allowed to stand at room temperature (23°) for four hours and then poured into 600 cc. of ice water and kept at 0° overnight; the precipitated tosyl derivative (5.8 g.; 67%) was separated by filtration and the filtrate on extraction with chloroform yielded a further 1.3 g. of the same substance to make the over-all yield 7.1 g. or 82%. The compound was recrystallized from 15 parts of alcohol in the form of rods which melted at 160–161° and rotated $[\alpha]^{20}D$ −10.0° in chloroform (*c*, 1.17)[6]; it is soluble in warm methyl alcohol, ethyl acetate and acetone and practically insoluble in cold ether, benzene and water.

Anal. Calcd. for $C_{15}H_{20}O_8S$: C, 49.99; H, 5.59; S, 8.90. Found: C, 49.90; H, 5.72; S, 8.81.

1,3:2,4-Dimethylene-6-iodo-D-sorbitol (III) from 1,3:2,4-Dimethylene-6-tosyl-D-sorbitol (II).—A solution of 4.0 g. of 1,3:2,4-dimethylene-6-tosyl-D-sorbitol and 4.0 g. of sodium iodide in 100 cc. of acetone was heated in a pressure bottle at 100° for two hours. The precipitate of sodium *p*-toluenesulfonate was separated by filtration and the filtrate was evaporated to dryness by an air current; the crystalline residue was suspended in 50 cc. of water to dissolve the inorganic salts, and the iodo-diacetal (2.5 g.) was separated by filtration; an additional 0.65 g. was obtained by extracting the aqueous solution with chloroform, the over-all yield being 90%. The substitution of acetonyl acetone as a solvent caused a reduction in the yield to 40–45%; an increase in the time of heating to three hours caused a reduction in yield to 60%. The 1,3:2,4-dimethylene-6-iodo-D-sorbitol was recrystallized from 10 parts of alcohol as needles which decomposed at 177–179° and rotated $[\alpha]^{20}D$ −21.7° in chloroform (*c*, 1.0). The compound is readily soluble in cold acetone and pyridine, warm methyl alcohol, benzene and ethyl acetate; it is slightly soluble in ether and cold water.

Anal. Calcd. for $C_8H_{13}O_5I$: C, 30.40; H, 4.14; I, 40.15. Found: C, 30.45; H, 4.17; I, 39.92.

1,3:2,4-Dimethylene-D-epirhamnitol (IV) from 1,3:2,4-Dimethylene-6-iodo-D-sorbitol (III).—A suspension of 3.0 g. of 1,3:2,4-dimethylene-6-iodo-D-sorbitol in a mixture of 50 cc. of water and 10 cc. of *N* sodium hydroxide (1.05 molecular equivalents) was agitated with hydrogen and Raney nickel under slight positive pressure; after one hour the absorption of hydrogen, measured at 30° and 758 mm., was 232 cc. (theory 237 cc.) and only 2 cc. more was absorbed in the next hour. The catalyst was separated by filtration and the filtrate was concentrated *in vacuo* to dryness; the crystalline residue was extracted with five 25 cc. portions of warm chloroform, the solvent was evaporated, and the crystals which remained (1.6 g.; 89%) were recrystallized from 20 parts of chloroform. The 1,3:2,4-dimethylene-D-epirhamnitol formed fine needles which melted at 182–183° and rotated $[\alpha]^{20}D$ −40.9° in water (*c*, 1.06); it is readily soluble in acetone, methyl and ethyl alcohols, ethyl acetate and dioxane and only slightly soluble in benzene, ether and heptane.

Anal. Calcd. for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.58; H, 7.36.

D-Epirhamnitol from Methyl-β-D-epirhamnoside.—Fifteen grams of methyl-β-D-epirhamnoside[7] ($[\alpha]^{20}D$ −54.6° in water) was dissolved in sufficient *N* hydrochloric acid to give a total volume of 100 cc. and the solution was refluxed for two hours; the rotation of the solution, based upon its presumed sugar content, was then $[\alpha]^{20}D$ +31.3° and this value, which agreed with the equilibrium rotation of +31.5° recorded by Votoček[8] for isorhodeose (D-epirhamnose), was unchanged upon refluxing the solution for a further thirty minutes. The cooled solution was agitated with 20 g. of silver carbonate and the precipitate of silver salts was separated by filtration. The filtrate was transferred to a bomb and agitated with Raney nickel and hydrogen under a pressure of 133 atmospheres at 100° for six hours; the catalyst was filtered off and the filtrate, which was not reducing to Fehling solution, showed a specific rotation $[\alpha]^{20}D$ of −10.1° in agreement with the value of −10.0° and −9.7° reported by Votoček and Rác[9] and Votoček and Valentin,[10] respectively, for D-epirhamnitol. The aqueous solution was concentrated *in vacuo* to a sirup which could not be crystallized; no one has yet crystallized D-epirhamnitol and accordingly the sirupy alcohol was employed directly in the acetal condensation which is described in the following paragraph.

1,3:2,4-Dimethylene-D-epirhamnitol (IV) from D-Epirhamnitol, Formaldehyde and Hydrochloric Acid.—A solution of 2.5 g. of sirupy D-epirhamnitol in a mixture of 4 cc. of concentrated hydrochloric acid and 4 cc. of 37% aqueous formaldehyde was placed in an evacuated desiccator containing moist sodium hydroxide and small beakers of concentrated sulfuric acid. After four days the gummy solid which had formed was extracted with three 10-cc. portions of hot absolute alcohol; the extract was concentrated *in vacuo* to dryness and the crystalline reaction product (2.5 g.) which deposited was recrystallized twice from 75 cc. of a mixture of equal parts of dioxane, benzene and heptane, yielding 1.0 g. of diacetal (m. p. 177–181°) which was contaminated by a small amount of trioxymethylene; the product was purified by extraction with 25 parts of hot acetone, the acetone solution was allowed to stand at 5° overnight, a small amount of precipitated trioxymethylene was separated by filtration, and the filtrate, upon dilution with an equal volume of heptane, deposited fine needles melting at 182–183° and rotating $[\alpha]^{20}D$ −40.6° in aqueous solution (*c*, 0.80). The product analyzed correctly for a dimethylene-desoxyhexitol (found: C, 50.62; H, 7.37) and it did not depress the melting point of the 1,3:2,4-dimethylene-D-epirhamnitol prepared by the

(5) (a) Ness, Hann and Hudson, THIS JOURNAL, **65**, 2215 (1943); (b) **66**, 665 (1944); (c) Hann, Ness and Hudson, *ibid.*, **66**, 670 (1944).

(6) All crystalline compounds described in the experimental part were recrystallized to constant melting point and specific rotation; *c* is the concentration in grams in 100 cc. of solution; the tube length was 4 dm.; all melting points were determined with the stem of the calibrated thermometer immersed in the rapidly stirred bath.

(7) Fischer and Zach, *Ber.*, **45**, 3761 (1912). We are indebted to Dr. A. E. Knauf for this material, which he prepared several years ago in this Laboratory.

(8) Votoček, *ibid.*, **44**, 823 (1911).

(9) Votoček and Rác, *Coll. Czechoslov. Chem. Commun.*, 1, 244 (1929).

(10) Votoček and Valentin, *Bull. soc. chim.*, [4] **43**, 219 (1928).

reduction of 1,3:2,4-dimethylene-6-iodo-D-sorbitol. The yield was 0.75 g.

1,5-Diacetyl-3-acetoxymethyl-2,4-methylene-D-epirhamnitol (V) from 1,3:2,4-Dimethylene-D-epirhamnitol (IV).—Three grams of 1,3:2,4-dimethylene-D-epirhamnitol was dissolved in 15 cc. of an ice-cold acetylating mixture prepared by adding 1 cc. of concentrated sulfuric acid dropwise to an ice-cold mixture of 70 cc. of acetic anhydride and 30 cc. of glacial acetic acid. The solution was shaken in a bath at 0° and after about ten minutes it set to a magma of fine needles. The reaction mixture was diluted with 200 cc. of ice-water and, after, two hours, the precipitate (3.9 g.) was separated by filtration; the filtrate was extracted with chloroform and upon evaporation of the extract an additional 0.7 g. of product was recovered, the total yield of 4.6 g. being 87%. The compound was recrystallized from 8 parts of alcohol as long, fine needles which melted at 116–117° and rotated $[\alpha]^{20}D$ +5.3° in chloroform (*c*, 0.90). It is soluble in benzene, ethyl acetate, acetone and pyridine and practically insoluble in water, cold alcohol and ether.

Anal. Calcd. for $C_{14}H_{22}O_9$: C, 50.29; H, 6.63; saponification, 100 mg. substance requires 8.97 cc. 0.1 *N* alkali. Found: C, 50.30; H, 6.62; saponification, 100 mg. substance consumed 8.93 cc. 0.1 *N* alkali.

2,4-Methylene-D-epirhamnitol (VI) from 1,5-Diacetyl-3-acetoxymethyl-2,4-methylene-D-epirhamnitol (V).—An ice-cold solution of 2.0 g. of 1,5-diacetyl-3-acetoxymethyl-2,4-methylene-D-epirhamnitol in 10 cc. of chloroform was mixed with 2 cc. of 0.2 *N* sodium methylate and the reaction mixture was allowed to stand at 5° for two days; the crystalline precipitate of 2,4-methylene-D-epirhamnitol which had deposited was separated by filtration and upon recrystallization from 15 parts of alcohol it formed prismatic needles melting at 176–177° and rotating $[\alpha]^{20}D$ −20.2° in water (*c*, 0.90). The yield was 1.1 g. (quantitative). The acetal is soluble in cold water and hot methyl and ethyl alcohols, moderately soluble in pyridine and practically insoluble in cold alcohol, chloroform, dioxane and hot or cold benzene or ethyl acetate.

Anal. Calcd. for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C 47.35; H, 7.88.

Stability of 2,4-Methylene-D-epirhamnitol (VI) against Oxidation by Per-iodic Acid.—To a solution of 0.1016 g. of 2,4-methylene-D-epirhamnitol in 15 cc. of water at 25°, 2.50 cc. (3 molecular equivalents) of 0.675 *M* periodic acid was added and the volume was adjusted to 25 cc. with water. Analysis of 5-cc. subsamples at the expiration of two, five and seventy hours showed that none of the oxidant had been consumed. The methylene-D-epirhamnitol therefore does not contain a glycol grouping as a part of its structure. The only possible structure for a monoacetal of a 6-desoxy-hexitol which conforms with this limitation is that of a 2,4-acetal; methylene-D-epirhamnitol is therefore 2,4-methylene-D-epirhamnitol.

1,3,5-Triacetyl-2,4-methylene-D-epirhamnitol.—A solution of 0.6 g. of 2,4-methylene-D-epirhamnitol in a mixture of 5 cc. of pyridine and 6 cc. of acetic anhydride was allowed to stand at 25° for three days, during which time some precipitation of needles occurred. The reaction mixture was poured into 150 cc. of ice water and the precipitated triacetyl derivative (1.0 g.; quantitative) was collected and recrystallized from 10 parts of alcohol. It formed needles which melted at 149–150° and rotated $[\alpha]^{20}D$ −0.6° in chloroform (*c*, 1.24) and −1.8° in acetone (*c*, 0.96). The compound is also soluble in ether, benzene and ethyl acetate; it is practically insoluble in cold methyl and ethyl alcohols, petroleum ether and water.

Anal. Calcd. for $C_{13}H_{20}O_8$: C, 51.31; H, 6.62; CH_3CO, 42.4. Found: C, 51.29; H, 6.63; CH_3CO, 42.1.

Summary

The conversion of 1,3:2,4-dimethylene-D-sorbitol to 1,3:2,4-dimethylene-D-epirhamnitol has been described. The first named diacetal, upon treatment in pyridine solution with one molecular equivalent of *p*-toluenesulfonyl chloride, forms a monotosyl compound which can be converted to an iodo-1,3:2,4-dimethylene-D-sorbitol that is reduced by hydrogen and Raney nickel to a desoxy-1,3:2,4-dimethylene-D-sorbitol; the latter substance is identical with a diacetal that is obtained by the condensation of D-epirhamnitol and formaldehyde and hence it can be only 6-desoxy-1,3:2,4-dimethylene-D-sorbitol (*syn.*, 1,3:2,4-dimethylene-D-epirhamnitol).

The 1,3:2,4-dimethylene-D-epirhamnitol has been subjected to limited acetolysis and the acetolysis product has been saponified to a monomethylene-D-epirhamnitol which is not oxidized by aqueous per-iodic acid, a fact which limits its structure to that of 2,4-methylene-D-epirhamnitol.

BETHESDA, MARYLAND RECEIVED APRIL 22, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF POLYTECHNIC INSTITUTE OF BROOKLYN]

The Preparation of Homophthalyl Cyclic Hydrazide and 4-Aminohomophthalyl Cyclic Hydrazide

BY WILLET F. WHITMORE AND ROBERT C. COONEY[1]

This paper describes the preparation of some homophthalyl cyclic hydrazides, homologous to the phthalyl cyclic hydrazides. The investigation was undertaken in order to study the effect of the substitution of the asymmetrical 7-membered cyclic hydrazide ring of the former type for the symmetrical 6-membered cyclic hydrazide ring of the latter type on the property of chemiluminescence.

Most of the conventional methods that could be used for the preparation of these new compounds would utilize homophthalic acid or one of its derivatives as the starting substance. Homophthalic acid was prepared by an extremely facile method,[2] which appears to have been overlooked by more recent investigators[3,4] studying homophthalic acid derivatives. In this method, a chromic acid oxidation of indene produces homophthalic acid directly in yields of 58%.

(1) An abstract of a dissertation presented in May, 1943, to the Graduate Faculty of Polytechnic Institute of Brooklyn by Robert C. Cooney in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Meyer and Vittenet, *Ann. Chim.*, [10] **17**, 271 (1932).

(3) Price, Lewis and Meister, THIS JOURNAL, **61**, 2762 (1939).

(4) Price, *Org. Syn.*, **22**, 30, 61 (1942).