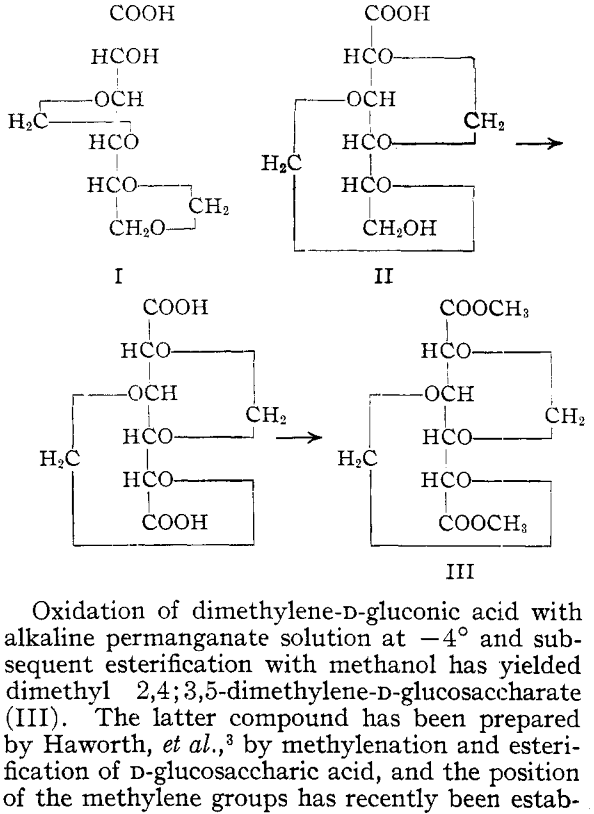
[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY, PEORIA, ILLINOIS[1]]

Dimethylene-D-gluconic Acid

BY C. L. MEHLTRETTER, R. L. MELLIES, C. E. RIST AND G. E. HILBERT

Dimethylene-D-gluconic acid was first prepared by Henneberg and Tollens[2] who suggested the most probable structure to be 3,4;5,6-dimethylenegluconic acid (I). No experimental proof for this configuration was given, however, and the possibility existed that the compound could have one of a number of other structures.



I II III

Oxidation of dimethylene-D-gluconic acid with alkaline permanganate solution at −4° and subsequent esterification with methanol has yielded dimethyl 2,4;3,5-dimethylene-D-glucosaccharate (III). The latter compound has been prepared by Haworth, *et al.*,[3] by methylenation and esterification of D-glucosaccharic acid, and the position of the methylene groups has recently been established by Jones and Wiggins.[4] On this basis it is concluded that dimethylene-D-gluconic acid contains one methylene group in acetal linkage with the hydroxyl groups at carbon atoms 2 and 4 and another with the hydroxyl groups at carbon atoms 3 and 5 (II).

Other evidence for the presence of a primary alcoholic group is the ready replacement of the tosyloxy group in tosylated methyl dimethylene-D-gluconate by iodine on treatment with sodium iodide in acetone solution.[5] The trityl derivative of methyl dimethylene-D-gluconate has also been prepared.

Methyl dimethylene-D-gluconate reacted readily with acetic anhydride and also benzoyl chloride in pyridine solution to form the corresponding crystalline acyl derivatives. A mixture of the methyl ester and 28% aqueous ammonia gave dimethylene-D-gluconamide in good yield. The acetyl and benzoyl derivatives of the latter compound were prepared with ease.

Experimental

Oxidation of Dimethylene-D-gluconic Acid.—Dimethylene-D-gluconic acid was prepared by the method of Henneberg and Tollens[2] which was modified by substituting D-glucono-δ-lactone for calcium D-gluconate. For the oxidation 22 g. (0.1 mole) of dimethylene-D-gluconic acid was dissolved in 100 ml. of water containing 12 g. (0.22 mole) of potassium hydroxide. The stirred solution was cooled to −4° by the addition of 200 g. of cracked ice, and 16.6 g. (0.11 mole) of finely powdered potassium permanganate introduced over a half-hour period. An additional 200 g. of ice was required to maintain the temperature of the solution at −4° for one hour more. The manganese dioxide was removed and the clear colorless filtrate neutralized to *p*H 8 with sulfuric acid. This solution was then evaporated to dryness *in vacuo* and esterified by refluxing for six hours with 600 ml. of methanol containing 20 g. of concentrated sulfuric acid. After removal of potassium sulfate by filtration, the solution was neutralized with excess barium carbonate. Barium sulfate and excess barium carbonate were centrifuged out and the clear supernatant liquor concentrated *in vacuo* to about half of its volume. The crystalline product which formed at this time weighed 6.4 g. and melted at 157°. On recrystallizing from methanol a m. p. of 157–157.5° was obtained. A mixture m. p. with authentic dimethyl 2,4;3,5-dimethylene-D-glucosaccharate was unchanged.

Anal. Calcd. for $C_{10}H_{14}O_8$: C, 45.8; H, 5.4; CH_3O, 23.6. Found: C, 46.0; H, 5.3; CH_3O, 23.6.

Upon further concentration of the mother liquor, 2.1 g. of the same product of m. p. 156–157° was obtained.

Methyl 2,4;3,5-dimethylene-D-gluconate.—A mixture of 400 g. (1.8 moles) of dimethylene-D-gluconic acid, 3.5 liters of methanol and 4 ml. of concentrated sulfuric acid was refluxed on a steam-bath for twenty-three hours. The product separated upon cooling the solution. Other crops were obtained by concentration of the mother liquors. When the crude product was recrystallized from methanol it melted at 151–152°; $[\alpha]^{25}D$ +13.3° (*c*, 3.75; methanol). The yield was 370 g. (87%).

Anal. Calcd. for $C_9H_{14}O_7$: C, 46.2; H, 6.0; CH_3O, 13.3. Found: C, 46.3; H, 5.9; CH_3O, 13.2.

The ethyl ester of dimethylene-D-gluconic acid was prepared on a small scale in an analogous manner. The product melted at 122–123.5° after recrystallization from ethanol. The yield was 34%; $[\alpha]^{25}D$ +22.0° (*c*, 1.23; methanol).

Anal. Calcd. for $C_{10}H_{16}O_7$: C, 48.4; H, 6.5; C_2H_5O, 18.2. Found: C, 48.3; H, 6.4; C_2H_5O, 18.2.

Methyl 6-Tosyl-2,4;3,5-dimethylene-D-gluconate.—To a solution of 11.7 g. (0.05 mole) of methyl dimethylene-D-gluconate in 80 ml. of dry pyridine at 25° was added dropwise a solution of 11 g. (0.058 mole) of *p*-toluenesulfonyl chloride in 20 ml. of pyridine. After three days at room temperature the solution was poured onto crushed ice with stirring. The compound obtained, after two recrystallizations of the crude product from methanol, melted at 101–102° and weighed 11.2 g. The yield was 58%; $[\alpha]^{25}D$ +20.6° (*c*, 1.65; acetone).

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[2] Henneberg and Tollens, *Ann.*, **292**, 34 (1896).

[3] Haworth, *et al.*, *J. Chem. Soc.*, 61 (1944).

[4] Jones and Wiggins, *ibid.*, 364 (1944).

[5] Oldham and Rutherford, THIS JOURNAL, **54**, 366 (1932).

Anal. Calcd. for $C_{16}H_{20}O_9S$: C, 49.5; H, 5.2; CH_3O, 8.0; S, 8.3. Found: C, 49.5; H, 5.3; CH_3O, 8.1; S, 8.1.

Methyl 6-Desoxy-6-iodo-2,4;3,5-dimethylene-D-gluconate.—A solution of 3.5 g. (0.009 mole) of methyl 6-tosyl-dimethylene-D-gluconate and 3.5 g. (0.023 mole) of sodium iodide in 40 ml. of acetone was heated in a sealed tube in an oil-bath at 100° for two and one-half hours. The contents of the tube were then transferred to a filter and washed with acetone. The filtrate and washings were concentrated to dryness *in vacuo*. The crude product (3 g.) obtained was washed with water, and the undissolved residue was recrystallized from benzene. The yield of product was 1.6 g. (53%); m. p. 153.5–154.5°; $[\alpha]^{25}D$ +20.8° (*c*, 2.46; acetone).

Anal. Calcd. for $C_9H_{13}O_6I$: C, 31.4; H, 3.8; I, 36.9; CH_3O, 9.0. Found: C, 31.6; H, 3.8; I, 36.8; CH_3O, 9.2.

Methyl 6-Trityl-2,4;3,5-dimethylene-D-gluconate.—Triphenylmethyl chloride, 5.1 g. (0.019 mole) was added in portions to a solution of 4.2 g. (0.018 mole) of methyl dimethylene-D-gluconate in 100 ml. of dry pyridine at 25°. The solution was poured onto crushed ice after standing seven days at room temperature. After three recrystallizations from ethanol, the product weighed 5.6 g. and melted at 141–142°. The last recrystallization did not raise the melting point. The yield was 66% of the theoretical amount; $[\alpha]^{25}D$ −8.8° (*c*, 2.13; acetone).

Anal. Calcd. for $C_{28}H_{28}C_7$: C, 70.6; H, 5.9; CH_3O, 6.5. Found: C, 70.7; H, 6.0; CH_3O, 6.7.

2,4;3,5-Dimethylene-D-gluconic Acid Phenylhydrazide.—Three grams (0.014 mole) of dimethylene-D-gluconic acid was heated with 12 ml. of phenylhydrazine in an oil-bath at 120–140°. After one-half hour, the clear, orange-red liquor above the precipitated gum was poured off and triturated with benzene. The solid product which resulted from this treatment was recrystallized three times from an ethanol–methanol mixture (3:1). The final product (0.8 g.; 18%) melted at 193–194°; $[\alpha]^{25}D$ +14.7° (*c*, 0.12; methanol).

Anal. Calcd. for $C_{14}H_{18}O_6N_2$: C, 54.2; H, 5.9; N, 9.0. Found: C, 53.8; H, 5.9; N, 9.0.

Methyl 6-Acetyl-2,4;3,5-dimethylene-D-gluconate.—To a solution of 9.4 g. (0.04 mole) of methyl dimethylene-D-gluconate in 80 ml. of dry pyridine at 0° was added dropwise 16 g. (0.16 mole) of acetic anhydride. After four days at room temperature, the solution was poured onto crushed ice. The solution from this treatment was concentrated *in vacuo* and allowed to stand. A white solid precipitated. A larger quantity of the product was isolated by chloroform extraction of the mother liquor. Recrystallization from methanol gave 10.1 g. of the pure product (90%), melting at 124–125°; $[\alpha]^{25}D$ +25.2° (*c*, 2.09; water).

Anal. Calcd. for $C_{11}H_{16}O_8$: C, 47.8; H, 5.8; CH_3O, 11.2; acetyl, 15.6. Found: C, 48.0; H, 5.7; CH_3O, 11.2; acetyl, 15.5.

Methyl 6-Benzoyl-2,4;3,5-dimethylene-D-gluconate.—To a solution of 23.4 g. (0.10 mole) of methyl dimethylene-D-gluconate in 160 ml. of dry pyridine was added 155 g. (0.11 mole) of benzoyl chloride. The mixture was cooled and after standing at room temperature for four days was concentrated *in vacuo* to a sirup. On mixing the sirup with 400 ml. of ice water, a gummy mass precipitated. This was separated by decantation and dissolved in 100 ml. of hot methanol from which it crystallized on cooling to 5°. The product was filtered, washed with cold methanol, and dried at 40°. Yield was 23.5 g. (70%); m. p. 95–96°. The melting point was not changed by another recrystallization from methanol. On concentrating the mother liquor, several grams more of product were obtained.

Anal. Calcd. for $C_{16}H_{18}O_8$: C, 56.8; H, 5.4; CH_3O, 9.2. Found: C, 57.0; H, 5.3; CH_3O, 9.2.

2,4,3,5-Dimethylene-D-gluconamide.—A solution of 117 g. (0.5 mole) of methyl dimethylene-D-gluconate in 1.5 liters of concentrated aqueous ammonia was allowed to stand at room temperature for forty hours. On concentrating *in vacuo* to dryness, a crude product was obtained which, when recrystallized from 90% ethanol, melted at 208–209°. Another recrystallization did not raise the melting point. The yield (90.3 g.) was 83% of the theoretical amount; $[\alpha]^{25}D$ +84.4° (*c*, 1.22; water).

Anal. Calcd. for $C_8H_{13}O_6N$: C, 43.8; H, 6.0; N, 6.4. Found: C, 43.8; H, 6.1; N, 6.5.

6-Acetyl 2,4;3,5-dimethylene-D-gluconamide.—To a solution of 11.0 g. (0.05 mole) of dimethylene-D-gluconamide in 150 ml. of dry pyridine was added 10.2 g. (0.10 mole) of acetic anhydride. On standing two days at room temperature a gelatinous precipitate formed. The mixture was concentrated *in vacuo* to near dryness, and the white residue recrystallized from methanol. The yield of product was 11.0 g. (85%); m. p. 198–199°. Another recrystallization from methanol did not raise the melting point: $[\alpha]^{25}D$ +65.7° (*c*, 1.43; water).

Anal. Calcd. for $C_{10}H_{15}O_7N$: C, 46.0; H, 5.8; N, 5.4; acetyl, 16.5. Found: C, 46.3; H, 5.9; N, 5.4; acetyl, 16.4.

6-Benzoyl 2,4;3,5-dimethylene-D-gluconamide.—A suspension of 65.8 g. (0.30 mole) of dimethylene-D-gluconamide in 500 ml. of dry pyridine was treated with 46.4 g. (0.33 mole) of benzoyl chloride. After two days the resulting solution was concentrated *in vacuo* to remove most of the pyridine. The residue was recrystallized from 300 ml. of 80% ethanol. The yield was 85 g. (88%); m. p. 202–203°. Another recrystallization from 80% ethanol did not raise the melting point, $[\alpha]^{25}D$ +67.2° (*c*, 1.05; 50% ethanol).

Anal. Calcd. for $C_{15}H_{17}O_7N$: C, 55.7; H, 5.3; N, 4.3. Found: C, 55.8; H, 5.3; N, 4.4.

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Summary

Dimethylene-D-gluconic acid has been shown to contain methylene groups in acetal linkage in the 2,4- and 3,5-positions by oxidation to 2,4;3,5-dimethylene-D-glucosaccharic acid and conversion to the known dimethyl ester.

The preparation of a number of new derivatives of 2,4;3,5-dimethylene-D-gluconic acid has been described.

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