[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FORDHAM UNIVERSITY]

A New Synthesis of *l*-Galactose. The Structure of α- and β-Diacetone Dulcitol

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The natural occurrence of *l*-galactose, observed by Winterstein,[2] Oshima and Tollens,[3] and Lippmann[4] has been confirmed conclusively by Anderson[5] who succeeded in isolating *l*-galactose in appreciable quantities from the hydrolyzate of flaxseed mucilage.

Although no difficulties were encountered in repeating Anderson's procedure, the yields obtained in this Laboratory were considerably lower, due possibly to the grade of flaxseed on hand. We chose therefore, in order to procure more material, a synthetic way. Citrus pectic acid was converted to *d*-galacturonic acid,[6] which, upon reduction in alkaline medium, yielded *l*-galactonic acid lactone.[7] This, reduced in acidic medium until the reducing power as measured with Fehling's solution reaches a maximum, results in the desired *l*-galactose. This synthesis was carried out independently of the identical procedure of Fukunaga[8] and Iwadare and Kubota.[9] It has been included in this communication in order to serve as a confirmation of the results of the Japanese workers.

l-Galactose could also be prepared in a new way by oxidation of β-diacetone dulcitol (m. p. 112–113°) described by Fischer[10] which is formed together with α-diacetone dulcitol (m. p. 145–146°) in the acetonization of dulcitol. The latter is obtained in greater quantity when the condensation is conducted in the presence of 1–0.5% dry hydrochloric acid while the β-isomer prevails if 0.5% acid is used. As zinc chloride in combination with ortho and metaphosphoric acid[11] catalyzes the formation of the β-isomer, this acetonization was employed.

The oxidation at low temperature of β-diacetone dulcitol by means of potassium permanganate in alkaline solution yields the potassium salt of diacetone-*l*-galactonic acid. Its specific rotation is +51.3°, in agreement with other derivatives of *l*-galactonic acid which exhibit high dextro rotation. Treatment with an excess of normal sulfuric acid cleaves both isopropylidene groupings. After removal of the inorganic salts, *l*-galactonic acid was isolated and identified as its cadmium salt. The cadmium *l*-galactonate was then converted to the *l*-galactono lactone which was reduced with sodium amalgam in acidic medium. The resulting *l*-galactose was identified by its melting point and optical rotation (m. p. 164°; $[\alpha]^{23}D$ −79.6°). The yield calculated on β-diacetone dulcitol is only 5%.

This synthesis makes the structure of β-diacetone dulcitol probable. It could be established by oxidizing β-diacetone dulcitol in benzene solution with lead tetraacetate. The isolation of formaldehyde discloses a free glycol grouping in the terminal position. Therefore only two diacetone dulcitols of the nine possible isomers with a free terminal position remain. They are 3,4–5,6 diacetone dulcitol and 1,2–3,4 diacetone dulcitol. Of the two only the latter can be oxidized to *l*-galactonic acid or *l*-galactose, whereas the former, if oxidized under the same conditions, could yield *d*-galactonic acid and *d*-galactose only. Fischer's α-diacetone dulcitol was found to be 3,4–5,6-diacetone dulcitol. It also gave formaldehyde on lead tetraacetate oxidation and potassium diacetone *d*-galactonate ($[\alpha]D$ −51°), *d*-galactono lactone and *d*-galactose (m. p. 165–166°, $[\alpha]D$ +80.3°) when oxidized with permanganate as described above.

Experimental Part

β-Diacetone Dulcitol.—One hundred grams of finely powdered dulcitol was suspended in 2 liters of dry acetone to which was added in rapid succession 120 g. of fused zinc chloride and a homogeneous mixture of 20 g. of phosphorus pentoxide and 20 g. of phosphoric acid (85%). The whole was shaken mechanically for twenty-four hours. The insoluble material (17 g.) was then removed and the solution made alkaline by addition of aqueous sodium carbonate. The precipitated carbonates were filtered, washed with acetone and the combined filtrate and washings concentrated *in vacuo* until most of the acetone was removed. The resulting aqueous residue was extracted with ben-

(1) Due to the change in the activities of the senior author this problem cannot be continued further.

(2) Winterstein, *Ber.*, **31**, 1571 (1898).

(3) Oshima and Tollens, *ibid.*, **34**, 1422 (1901).

(4) Lippmann, *ibid.*, **55**, 3038 (1922).

(5) Anderson, *J. Biol. Chem.*, **100**, 249 (1933).

(6) Link and Nedden, *ibid.*, **94**, 307 (1931).

(7) Hoffmann-La Roche, German Patent 618,907 (1935).

(8) Fukunaga, *J. Chem. Soc. Japan*, **57**, 551 (1936).

(9) Iwadare and Kubota, *Inst. Phys. Chem. Res.*, Paper **754**, 183 (1938).

(10) Fischer, *Ber.*, **48**, 266 (1915).

(11) Grunenberg, Bredt and Freudenberg, THIS JOURNAL, **60**, 1507 (1938).

zene (four 100-cc. portions). After most of the solvent had been removed, the remaining solution was left to stand in the refrigerator; 45 g. of mixed diacetone dulcitols (m. p. 105–108°) separated which was dissolved in 100 cc. of acetone. One hundred cc. of petrolic ether was then added. After twenty-four hours colorless elongated plates separated. They were twice recrystallized from petrolic ether: yield, 7.5 g. (5.1%); m. p. 144–146°.[10] To isolate the beta modification the acetone–petrolic ether mother liquors were treated with an equal volume of petrolic ether and left to stand in the refrigerator for two days. After four recrystallizations from acetone–petrolic ether 35.5 g. (25%) of the beta isomer was obtained. This was in the form of small leaflets which melted at 112–114°. The compound is optically inactive ($CHCl_3$).

Lead Tetraacetate Oxidation

Isolation of Formaldehyde.—A solution of 5 g. of β-diacetone dulcitol in 100 cc. of dried benzene was allowed to react with 9 g. of lead tetraacetate at room temperature for six hours in a tightly stoppered flask. A condenser which led into a solution of 2,4-dinitrophenylhydrazine in sulfuric acid was then attached and the mixture heated on a steam-bath. A yellow crystalline precipitate was formed after a short time, which, after filtration and recrystallization from alcohol, melted at 165–167°.[12]

Anal. Calcd. for $C_7H_6O_4N_4$: N, 26.67. Found: N, 26.53.

A blank distillation with benzene and lead tetraacetate produced no precipitate. If, however, a few drops of formalin solution were added, the identical formal-2,4-dinitrophenylhydrazone was obtained, m. p. 166–168°.

Potassium Diacetone *l*-Galactonate.—For the preparation, Ohle's method[13] of oxidation with alkaline permanganate was used. Fifty grams of β-diacetone dulcitol was added with vigorous stirring to 5 liters of water at room temperature. After twenty minutes dissolution was complete and then 50 cc. of 40% potassium hydroxide and 60 g. of finely powdered potassium permanganate were added. The mixture was kept at room temperature and shaken continuously for twenty-four hours. After this time the manganese salts were filtered off and the clear filtrate neutralized with carbon dioxide. The solution was then concentrated *in vacuo* to a sirup which was extracted with four 50-cc. portions of ethyl alcohol. After removal of the excess alcohol a volume of 30 cc. remained. To this 60 cc. of acetone was added when fine white needles separated. The product, recrystallized from alcohol–acetone, weighed 22 g. The substance, dried *in vacuo* at 100° to a constant weight, decomposed at 195–200°.

Anal. Calcd. for $C_{12}H_{19}O_7K$: K, 12.42. Found: K, 12.40. Rotation: 0.5204 g. subst. in 5.0 g. H_2O; $l = 1$; $\alpha = +5.32$; $[\alpha]^{26}D$ +51.2.

Cadmium *l*-Galactonate.—Twenty grams of potassium diacetone *l*-galactonate was added to 150 cc. of *N* sulfuric acid and the mixture heated with vigorous stirring on the steam plate for one hour. The resulting solution was neutralized with cadmium hydroxide and then heated for one hour (70–80°) with excess cadmium carbonate. Any suspended cadmium carbonate was removed and the colorless filtrate concentrated *in vacuo* to half of its original volume. This solution deposited after forty-eight hours at 0° fine white needles. The salt, 3 times recrystallized from water, weighed 8.8 g. (28%) and decomposed at 197–201°.

Anal. Calcd. for $(C_6H_{11}O_7)_2Cd \cdot H_2O$: C, 27.69; H, 4.61; Cd, 21.54. Found: C, 27.69; H, 4.65; Cd, 21.42.

***l*-Galactose.**—Eight and one-half grams of cadmium *l*-galactonate was changed to the free acid by means of hydrogen sulfide, the solution concentrated under diminished pressure to a thick sirup, and then heated *in vacuo* for three hours in a boiling water-bath. The resulting *l*-galactono lactone was dissolved in 100 cc. of water and cooled to 0°. Then 25 g. of fresh 2.5% sodium amalgam was added, and the mixture stirred vigorously, keeping the reaction slightly acidic all the time and the temperature below 5°. During the course of two hours, 125 g. of amalgam had been added and the reduction appeared complete as estimated by the reduction of Fehling's solution. After separation of the mercury the solution was concentrated *in vacuo* to 50 cc. and poured into 500 cc. of alcohol with vigorous stirring. The separated inorganic salts were filtered off, dissolved in a small amount of water, and then reprecipitated by the addition of alcohol. The alcoholic extracts were combined and the solvent wholly evaporated under diminished pressure by adding water several times. The resulting solution was neutralized by warming with barium carbonate, and the filtrate from the precipitated barium sulfate was again evaporated to a sirup. Seven hundred cc. of ethyl alcohol was then added with vigorous stirring. In order to separate any sugar from the precipitated barium *l*-galactonate, it was dissolved in a small amount of water and reprecipitated with alcohol. The combined filtrates were evaporated and the remaining sirup taken up with 15 cc. of hot glacial acetic acid. This solution was cooled, seeded and left to stand in the ice-box. After a few days it became almost solid with crystals. They were filtered and washed with small amounts of cold alcohol. To purify the sugar it was dissolved in an equal weight of water and 3 times this volume of ethyl alcohol added. The twice recrystallized *l*-galactose weighed 1.8 g. and melted at 164°.

Anal. Calcd. for $C_6H_{12}O_6$: C, 40.00; H, 6.67. Found: C, 40.07; H, 6.87. Rotation: 0.3422 g. subst. in 5.0 g. H_2O + 1 drop NH_4OH; $l = 2$; $\alpha = -10.88$; $[\alpha]^{23}D$ −79.6.

α-Diacetone Dulcitol.—Forty-five grams of crude diacetone dulcitol was obtained when 50 g. of dulcitol was treated with 2 liters of dry acetone containing 1–0.5% hydrochloric acid. After 2 recrystallizations from petrolic ether they melted at 145°; yield 41 g. α-Diacetone dulcitol is optically inactive ($CHCl_3$).

Lead Tetraacetate Oxidation

Isolation of Formaldehyde.—A solution of 5 g. of α-diacetone dulcitol in 100 cc. of dried benzene was treated with 9 g. of lead tetraacetate as described previously. The isolated and recrystallized formal-2,4-dinitrophenylhydrazone melted at 165°.

Anal. Calcd. for $C_7H_6O_4N_4$: N, 26.67. Found: N, 26.48.

(12) Bryant, THIS JOURNAL, **54**, 3760 (1932).

(13) Ohle and Berend, *Ber.*, **58**, 2585 (1925).

A blank experiment with benzene and lead tetraacetate failed to give a precipitate with 2,4-dinitrophenylhydrazine.

Potassium Diacetone *d*-Galactonate.—Oxidation of 50 g. of α-diacetone dulcitol with alkaline permanganate as described for the preparation of the corresponding levo isomer gave 20 g. of a crystalline solid which after two recrystallizations from acetone–alcohol melted at 194–197°; yield 17 g.

Anal. Calcd. for $C_{12}H_{19}O_7K$: K, 12.42. Found: K, 12.42. Rotation: 0.4777 g. subst. in 5.0 g. H_2O; $l = 1$, $\alpha = -4.85$; $[\alpha]^{27}D$ -50.8.

Cadmium *d*-Galactonate.—Seventeen grams of potassium diacetone *d*-galactonate when treated as described for the levo isomer gave 7.0 g. of cadmium *d*-galactonate. Thrice recrystallized, it decomposed at 200–205°.

Anal. Calcd. for $(C_6H_{11}O_7)_2Cd \cdot H_2O$: C, 27.69; H, 4.61; Cd, 21.54. Found: C, 27.65; H, 4.82; Cd, 21.54.

***d*-Galactose.**—The *d*-galactose was prepared from the cadmium *d*-galactonate in the same manner as that described for the preparation of *l*-galactose. Seven grams of salt gave 1.4 g. of *d*-galactose which melted at 165–166° and had, in aqueous solution, a specific rotation of +80.3°.

Anal. Calcd. for $C_6H_{12}O_6$: C, 40.00; H, 6.67. Found: C, 40.07; H, 6.74.

The gift of a generous supply of dulcitol from the Atlas Powder Company is gratefully acknowledged. The microanalyses were carried out in this Laboratory by Mr. J. F. Alicino.

Summary

The constitution of the two isomeric α- and β-diacetone dulcitols has been investigated. Both compounds are believed to be chemical entities. They are optically inactive and contain, as seen by lead tetraacetate oxidation, two adjacent free hydroxyl groups in terminal position.

β-Diacetone dulcitol can be transformed by alkaline oxidation into diacetone *l*-galactonic acid and subsequently on acid hydrolysis into *l*-galactono lactone, which reduced with sodium amalgam is converted into *l*-galactose.

α-Diacetone dulcitol oxidized in the identical manner gave rise to diacetone *d*-galactonic acid, *d*-galactono lactone and *d*-galactose.

In the light of these experimental findings the conclusion seems to be justified that β-diacetone dulcitol is 1,2-3,4-diacetone dulcitol and the α-isomer 3,4-5,6-diacetone dulcitol. The two forms therefore would be enantiomorphic. This conclusion, however, is obviously conflicting with the fact that in the carbohydrate group the separation of enantiomorphs by direct crystallization has so far been found impossible.

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Organic Compounds in Chemotherapy. I. Derivatives of Sulfanilamide

BY HUGO BAUER

The following report deals with a series of derivatives of 4-aminobenzenesulfonamide (sulfanilamide) which were prepared in collaboration with Dr. S. M. Rosenthal for the purpose of chemotherapeutic studies. Comparative studies of sulfonamide compounds in experimental pneumococcus, streptococcus and meningococcus infections,[1] studies of the chemotherapy of choriomeningitis virus infection in mice with sulfonamide compounds,[2] and studies of some new sulfur compounds active against bacterial infections[3] have already been published.

Some of the compounds reported in this paper have been described also by other investigators working simultaneously in this field (see Table I). Their results in most cases agree with ours, although the methods of preparation differ in some respects.

Crossley, Northey and Hultquist[4] recently have suggested a system of terminology for these compounds. They have applied the name "sulfanilyl" to the radical $H_2NC_6H_4SO_2$-. We have adopted this terminology and have accordingly discarded the name "di-sulfanilamide" previously used by us for the compound $H_2NC_6H_4SO_2NHC_6H_4SO_2NH_2$. The name of this compound therefore becomes sulfanilyl sulfanilamide.

The general method of preparing the derivatives described herein consisted of condensation of amino compounds with acetanilide-4-sulfochloride, followed by deacetylation. The facility of the reaction is influenced by the more or less basic

(1) S. M. Rosenthal, H. Bauer and S. E. Branham, *Pub. Health Repts.*, **52**, 662 (May 21, 1937).

(2) S. M. Rosenthal, I. G. Wooley and H. Bauer, *ibid.*, **52**, 1211, Sept. 3, 1937.

(3) H. Bauer and S. M. Rosenthal, *ibid.*, **53**, 40 (Jan. 14, 1938).

(4) Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2217, 2222 (1938).