hour. The dark solution was concentrated to a volume of 30 ml. after addition of 40 ml. of dioxane and the insoluble triethylammonium chloride (1.14 g., 83%) was separated by filtration. The filtrate was evaporated under reduced pressure to a dark brown oil which was triturated with 100 ml. of anhydrous ether and dissolved in 15 ml. of chloroform. The chloroform solution was treated with 15 ml. of carbon tetrachloride and allowed to stand. After two hours there was obtained from the ether and chloroform–carbon tetrachloride solutions 1.12 g. and 0.150 g., respectively, of impure product. Recrystallization of the combined, crude fractions from chloroform–carbon tetrachloride yielded 0.650 g. (15.85%) of the lactam XI as fine, yellow needles, m.p. 247–248°. A second recrystallization from the same solvent furnished analytically pure material, m.p. 248.0–249.3°.

Anal. Calcd. for $C_{25}H_{18}N_2O_4$: C, 73.16; H, 4.42; N, 6.83. Found: C, 73.27; H, 4.57; N, 6.80.

When treated with two equivalents of benzylamine the lactam XI reacted sluggishly, yielding a mixture from which only 15% of the theoretical amount of N,N′-dibenzyloxamide was isolated.

B.—To a solution of 0.150 g. (0.423 millimole) of 1,4-diphenyl-3-phenylacetylamino-2-azetidinone[7] in 10 ml. of dry dioxane was added 2 ml. of oxalyl chloride. After standing at room temperature for four hours, the solution was concentrated to an orange oil which was taken up in 25 ml. of methylene chloride and washed with 20 ml. of 5% sodium bicarbonate solution. The clear, yellow solution was dried by filtration, evaporated to a volume of 5 ml., treated with 10 ml. of carbon tetrachloride and allowed to stand in a loosely stoppered flask for two days. The yellow precipitate (0.040 g.) which had appeared was collected by filtration and was recrystallized from methylene chloride–carbon tetrachloride. The yield of XI as fine, yellow needles was 0.030 g. (17.4%), m.p. 246–247°, undepressed upon admixture with a sample prepared by method A.

CAMBRIDGE 39, MASSACHUSETTS RECEIVED MAY 10, 1951

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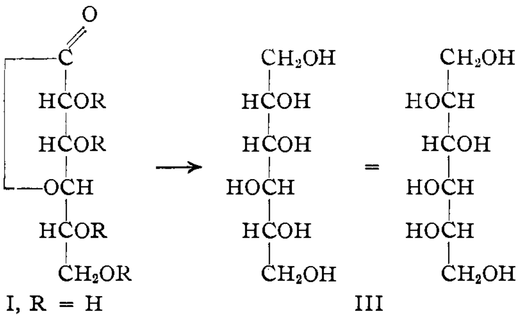
The Reduction of Various Sugar Acids to Glycitols with Lithium Aluminum Hydride

BY ROBERT K. NESS,[1] HEWITT G. FLETCHER, JR., AND C. S. HUDSON

Reduction of tetraacetyl-D-gulono-γ-lactone with an excess of lithium aluminum hydride has given L-glucitol (= D-gulitol) in 47% yield. In a similar fashion diacetyl-L-threaric anhydride has been reduced to L-threitol in 18% yield, dibenzoylerythraric acid to erythritol in 27% yield and erythraric acid to erythritol in 18% yield. The compound recorded in the literature as dibenzoylerythraric anhydride has been shown to be dibenzoylerythraric acid; authentic dibenzoylerythraric anhydride has been prepared and characterized.

In the course of recent investigations in this Laboratory need arose for a small quantity of L-glucitol (III). The logical starting point in the synthesis of this hexitol is D-gulono-γ-lactone (I) which may readily be prepared through the application of the Kiliani synthesis to D-xylose.[2] While the reduction of D-gulono-γ-lactone (I) to D-gulose has been extensively studied[3,4,5] and sirupy D-gulose reduced both with sodium amalgam[3,6] and through the use of hydrogen in the presence of a nickel catalyst,[7] previous work in this Laboratory on the reduction of sugar derivatives with lithium aluminum hydride[8] influenced us to investigate the application of this reducing agent in the direct reduction of D-gulono-γ-lactone (I) to L-glucitol (III) (= D-gulitol).[9,9a]

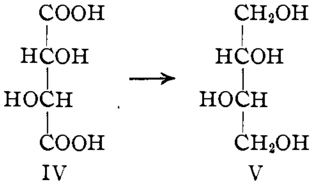


I, R = H

II, R = Ac

III

L-Glucitol (= D-Gulitol)

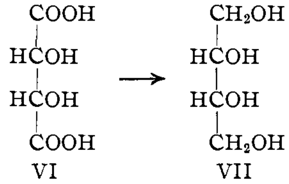


IV

L-Threaric acid

V

L-Threitol



VI

Erythraric acid

VII

Erythritol

The very low solubility of D-gulono-γ-lactone in ether and in tetrahydrofuran necessitated conversion of the substance to a more soluble derivative, its readily crystallizable tetraacetate (II).[10] Treatment of tetraacetyl-D-gulono-γ-lactone (II),

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[1] Senior Research Fellow, National Institutes of Health, 1948–1950.

[2] C. S. Hudson, O. Hartley and C. B. Purves, THIS JOURNAL, **56**, 1248 (1934).

[3] E. Fischer and R. Stahel, *Ber.*, **24**, 528 (1891).

[4] H. S. Isbell, *Bur. Standards J. Research*, **5**, 741 (1930).

[5] F. J. Bates and Associates, "Polarimetry, Saccharimetry and the Sugars," U. S. Govt. Printing Office, Washington, 1941, p. 465.

[6] E. Fischer and R. Stahel, *Ber.*, **24**, 2144 (1891).

[7] M. L. Wolfrom, B. W. Lew, R. A. Hales and R. M. Goepp, Jr., THIS JOURNAL, **68**, 2342 (1946).

[8] (a) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **72**, 4547 (1950); (b) **73**, 3742 (1951).

[9] Catalytic hydrogenation affords an equally attractive approach to this reaction since E. Baer and H. O. L. Fischer [*ibid.*, **61**, 761 (1939)] found that L-mannonic acid was converted to L-mannitol in 65% yield when its aqueous solution, containing a platinum oxide–iron oxide catalyst, was held for several days under 80 atmospheres of hydrogen.

[9a] NOTE ADDED SEPTEMBER 13, 1951.—In a paper which appeared while the present one was in press, M. L. Wolfrom and H. B. Wood [THIS JOURNAL, **73**, 2933 (1951)] have shown that D-gluco-D-*gulo*-heptonic γ-lactone may be reduced to either the corresponding aldose or glycitol in *ca.* 65% yields through the action of sodium borohydride. Since this reducing agent may be used in aqueous solution it is expected that it will prove superior to lithium aluminum hydride for reductions of the type described here.

[10] F. W. Upson, J. M. Brackenbury and C. Linn, *ibid.*, **58**, 2549 (1936).

dissolved in a mixture of ether and tetrahydrofuran, with an excess of lithium aluminum hydride gave, after hydrolysis with water and after deionization, L-glucitol, isolated as its sparingly soluble pyridine complex in 47% yield. From the recorded yields of D-gulose from the sodium amalgam reduction of D-gulono-γ-lactone[4,5] and assuming quantitative reduction of D-gulose to L-glucitol, it seems unlikely that the two-stage reduction of the lactone to the hexitol by the older methods would result in yields higher than this.

The L-glucitol (III) was identified through its rotation in aqueous ammonium molybdate and acid ammonium molybdate[11] and through the preparation from it of L-glucitol hexaacetate, D,L-glucitol and D,L-glucitol hexaacetate.

Attention was then turned to the relatively old problem of the reduction of L-threaric (IV) and erythraric (VI) acids[12] to the corresponding tetritols, L-threitol and erythritol.

Earlier attempts to reduce L-erythraric acid derivatives have been reviewed by Lucas and Baumgarten[13] who, starting with diacetyl-L-threaric anhydride, and, passing through a number of intermediate compounds, succeeded in obtaining L-threitol. More recently Trenner and Bacher[14] have carefully studied the catalytic reduction of esters of L-threaric and erythraric acids. These authors have found that esters of erythraric acid and L-threaric acid in alcoholic solution and in the presence of copper–chromium oxide could be reduced when heated at 165° under 5000 p.s.i. of hydrogen for five to six hours. While erythritol was thus obtained in 70% yield from dimethyl erythrarate, other tetritols were formed and it was shown that erythritol itself was partially isomerized under the relatively drastic conditions of the reduction.

It was of interest, therefore, to ascertain whether the tetraric acids and their derivatives could conveniently be reduced to the tetritols with lithium aluminum hydride. The readily preparable diacetyl-L-threaric anhydride[15] was treated in a mixture of ether and tetrahydrofuran with lithium aluminum hydride and, after deionization, L-threitol was obtained in a yield of 18%. No evidence was found for the presence of other tetritols in the negligible quantity of non-ionic material remaining in the mother liquor. The low yield in this and other such reductions is quite probably due to the removal of the starting material or some intermediate from the sphere of reaction as an insoluble inorganic complex. The L-threitol (V) was identified through the formation of its dibenzylidene derivative and through the preparation from the latter of dibenzylidene-D,L-threitol by combination with authentic dibenzylidene-D-threitol.

Attempts to prepare diacetylerythraric anhydride in crystalline form were unsuccessful and so attention was turned to dibenzoylerythraric anhydride. Brigl and Grüner[16] described a treatment of erythraric acid with an excess of benzoyl chloride as giving a product which, recrystallized from water, melted at 207–208° and showed correct analytical values for dibenzoylerythraric anhydride. These authors also stated that attempts to hydrolyze their so-called anhydride to dibenzoylerythraric acid were unsuccessful. Repetition (with minor modifications) of Brigl and Grüner's procedure has now been found to give a substance melting at 208–212°; while this is apparently identical with the product of the earlier authors, its analysis clearly shows it to be dibenzoylerythraric acid. Treatment of the acid in tetrahydrofuran solution with thionyl chloride readily converted it to the true anhydride (m.p. 139–142°) as was evident from elementary analysis. Since the anhydride was hydrolyzed with great ease, the relatively stable dibenzoylerythraric acid was used for reduction studies and there was obtained from it, through the action of lithium aluminum hydride, erythritol in 27% yield. The identity of the product was established through comparison with authentic material.

Since anhydrous erythraric acid was found to have an appreciable solubility in tetrahydrofuran, an attempt was made to reduce it directly in this solvent using lithium aluminum hydride. Erythritol in a yield of 18% was obtained.

Experimental[17]

L-Glucitol (III) from Tetraacetyl-D-gulono-γ-lactone (II).—Acetylation of D-gulono-γ-lactone with acetic anhydride in pyridine solution furnished a tetraacetate which melted at 103–104° and showed a rotation of −30.3° in U.S.P. chloroform (*c*, 0.65) and −34.3° in 4:1 acetone–water (v/v) (*c*, 0.95), no mutarotation being observed in either determination. Upson, Brackenbury and Linn[10] reported tetraacetyl-D-gulono-γ-lactone as melting at 103–104° and mutarotating from −37° (5 min.) to −35.5° (5 days) in 4:1 acetone–water at 25°.

Twenty grams of tetraacetyl-D-gulono-γ-lactone (0.0578 mole), dissolved in a mixture of 40 ml. of tetrahydrofuran and 40 ml. of ether, was added over the course of 35 minutes to 200 ml. of 1.39 *M* ethereal lithium aluminum hydride (0.278 mole), kept well stirred and protected from atmospheric moisture. After having been stirred for one hour at room temperature, the reaction mixture was diluted with 200 ml. of ether, cooled in an ice-bath, and the excess hydride decomposed by the gradual addition of 200 ml. of water. The ether was then removed by evaporation and the aqueous solution filtered from the precipitate which was then repeatedly washed with water. After deionization by passage through columns of Amberlite IR-120[18] and Duolite A-3,[19] the combined filtrate and washings were concentrated *in vacuo* to a clear colorless sirup. Repeated evaporation *in vacuo* of absolute alcohol from this residue, followed by solution in 2 ml. of pyridine, led to the isolation of L-glucitol as its pyridine addition compound (7.15 g., 47%). Heating *in vacuo* at 80° removed the major part of the pyridine of crystallization; recrystallization of the residue from ten parts of 90% alcohol afforded pure L-glucitol, melting at

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[11] *Cf.* N. K. Richtmyer and C. S. Hudson, *ibid.*, **73**, 2249 (1951).

[12] In conformity with modern practice [*Chem. Eng. News*, **26**, 1623 (1948)] the term L-threaric acid will be used for the common *dextro*-tartaric acid, IV, while erythraric acid will refer to *meso*-tartaric acid, VI. L-Threitol (V) and erythritol (VII), respectively, will be used to denote the corresponding tetritols.

[13] H. J. Lucas and W. Baumgarten, THIS JOURNAL, **63**, 1653 (1941).

[14] N. R. Trenner and F. A. Bacher, *ibid.*, **71**, 2352 (1949).

[15] H. J. Lucas and D. Pressman, "Principles and Practice in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 275.

[16] P. Brigl and H. Grüner, *Ber.*, **65**, 641 (1932).

[17] Melting points were measured with a calibrated Anschütz-type thermometer completely immersed in the bath liquid. Rotations are specific rotations for the D line of sodium at 20°; concentration is expressed in g. of substance per 100 ml. of solution.

[18] A product of the Resinous Products and Chemical Co., Washington Square, Philadelphia 5, Pa.

[19] A product of the Chemical Process Co., 901 Spring St., Redwood City, Cal.

91–93°. The rotation of this material, both in 5% ammonium molybdate (−25.9°, *c*, 0.43) and in a mixture of 20 ml. 5% ammonium molybdate and 5 ml. of 5% sulfuric acid (−103°, *c*, 0.40) is in agreement with the corresponding values obtained with D-glucitol purified in a similar manner (+26.4°, *c*, 0.42; +103°, *c*, 0.42).[11] Recrystallization from aqueous dioxane of a portion of the L-glucitol mixed with an equal weight of authentic D-glucitol gave D,L-glucitol, m.p. 136–138°. Wolfrom, Lew, Hales and Goepp[7] have reported a value of 135–137° for the melting point of D,L-glucitol. L-Glucitol hexaacetate, m.p. 99–101°, $[\alpha]^{20}\mathrm{D}$ −11.2° ($CHCl_3$, *c*, 0.73), and D,L-glucitol hexaacetate, m.p. 117–118°, were also prepared to confirm the identity of the L-glucitol. L-Glucitol hexaacetate has been recorded[7] as melting at 98–99° and rotating $[\alpha]^{27}\mathrm{D}$ −10°, while D,L-glucitol hexaacetate has been reported[7] to melt at 116–117°.

L-Threitol (V) from Diacetyl-L-threaric Anhydride.—Twelve grams (0.0555 mole) of diacetyl-L-threaric anhydride (m.p. 132–135°), prepared according to the procedure of Lucas and Pressman,[15] was dissolved in 30 ml. of pure, anhydrous tetrahydrofuran and gradually added, over the course of 30 minutes, to 260 ml. of *ca.* 0.4 *M* lithium aluminum hydride (0.104 mole) in ether.[20] After standing for one hour at room temperature the mixture was cooled and the excess reductant decomposed by the cautious addition of 100 ml. of water.[21] The gelatinous precipitate was removed by filtration and washed thoroughly with water. The combined filtrate and washings, freed of ether and tetrahydrofuran, were deionized by successive passage through columns of Amberlite IR-120[18] and Duolite A-4.[19] Concentration of the resulting solution *in vacuo* (60° bath) gave a sirup which was freed of water by solution in absolute ethanol and reconcentration *in vacuo*. From its solution in 15 ml. of absolute ethanol, the residue gave 1.21 g. (18%) of crude L-threitol as thin prisms melting at 83–86°.[22] Recrystallization from 5 ml. of absolute ethanol afforded pure L-threitol melting at 87–88° and rotating in ethanol +11.1° (*c*, 4.7). Maquenne and Bertrand[23] reported the melting point of L-threitol as 88–89° and its specific rotation in alcohol as +11.0° (*c*, 5).

Further evidence for the identity of the substance was obtained through the preparation of dibenzylidene-L-threitol by the method which Hockett[24] used for its enantiomorph. The dibenzylidene-L-threitol was found to melt at 219–223°; Hockett[24] reported a melting point of 218–222° for the D-isomer. When recrystallized with an equal quantity of authentic dibenzylidene-D-threitol, the product was obtained as a racemic mixture melting at 220–223°; Maquenne and Bertrand[25] reported a melting point of 220° for dibenzylidene-D,L-threitol.

Dibenzoylerythraric Acid.—Following the procedure which Brigl and Grüner[16] described for the preparation of what they believed to be dibenzoylerythraric anhydride, 10 g. of anhydrous erythraric acid (m.p. 160–161°) was heated with 27 ml. of benzoyl chloride at 120–125° for three hours. On cooling, the product crystallized from the reaction mixture; after being washed with absolute ether it weighed 20.5 g. (90%) and melted, after sintering slightly at 109°, at 138–142°. This crude dibenzoylerythraric anhydride was hydrolyzed by crystallization from aqueous acetone and was then recrystallized successively from methylene dichloride, carbon tetrachloride, 1:1 ether–pentane, benzene and finally again from 1:1 ether–pentane. Thus purified, the dibenzoylerythraric acid melted with decomposition at 208–212°. Brigl and Grüner[16] reported a melting point of 207–208° for the dibenzoylerythraric acid which they erroneously believed to be the anhydride.

Anal. Calcd. for $C_{18}H_{14}O_8$: C, 60.34; H, 3.94. Found: C, 60.47; H, 4.09.

The acid is soluble in tetrahydrofuran, sparingly soluble in ether and benzene; it is insoluble in carbon tetrachloride and pentane.

Dibenzoylerythraric Anhydride.—Repetition of the preparation described above but with omission of the crystallization from aqueous acetone afforded material melting at 141–144°. While this product probably represented fairly pure dibenzoylerythraric anhydride, analysis for carbon consistently gave values approximately 0.5% above that required by theory. The desired product was therefore prepared from dibenzoylerythraric acid by the method which Lucas and Baumgarten[13] used for dibenzoyl-L-threaric acid. Five grams of the dibenzoylerythraric acid, dissolved in 2 ml. of tetrahydrofuran, was treated with 6 ml. of thionyl chloride. Upon removal of solvent and excess reagent, there was obtained 3.61 g. (76%) of product melting at 134–135° after sintering at 111°. After treatment with decolorizing carbon, two recrystallizations from a dry, 1:1 mixture of acetone and pentane and two recrystallizations from a dry mixture of tetrahydrofuran and pentane, the pure dibenzoylerythraric anhydride was obtained in the form of clusters of clear, elongated prisms sintering at 111° and melting, with slight decomposition, at 139–142°. When a sample was rapidly heated to 125°, it liquefied and then immediately resolidified. The sintering at 111° may, therefore, represent conversion of the material to a higher-melting form. Crystals of a sample dried *in vacuo* at 100° for 2.5 hours had a milky appearance and melted at 139–142°.

Anal. Calcd. for $C_{18}H_{12}O_7$: C, 63.53; H, 3.56. Found: C, 63.48; H, 3.40.

The anhydride is soluble in tetrahydrofuran, warm acetone and warm benzene; it is slightly soluble in ether and insoluble in pentane. The anhydride hydrolyzes with extreme ease and solvents used for its recrystallization must be strictly anhydrous. A sample of the anhydride kept in a closed vial for three months was found to be largely converted to the corresponding acid.

Erythritol (VII) (a) from Dibenzoylerythraric Acid.—A solution of 3.5 g. (0.0098 mole) of dibenzoylerythraric acid in 15 ml. of anhydrous tetrahydrofuran was gradually added to 18 ml. of a solution of lithium aluminum hydride in tetrahydrofuran (*ca.* 2.4 *M*; 0.043 mole). The reaction mixture was boiled under reflux for one hour and the excess reductant then decomposed with water. The precipitate was removed by filtration and the filtrate extracted with ether to remove benzyl alcohol. After deionization and concentration, a sirup was obtained which, dissolved in a little absolute alcohol, afforded 317 mg. (27%) of crystalline product melting at 117–120° either alone or in admixture with authentic erythritol.

(b) **From Erythraric Acid (VI).**—A solution of 4.0 g. (0.0266 mole) of pure, anhydrous erythraric acid in 40 ml. of dry tetrahydrofuran was added over the course of 14 minutes to 32 ml. of an approximately 2.4 *M* solution of lithium aluminum hydride in tetrahydrofuran (0.0768 mole). The reaction mixture was boiled under reflux for 100 minutes, cooled, diluted with ether and cautiously treated with 75 ml. of water. After filtration, deionization and concentration, as in the preparation of L-threitol described above, there was obtained a sirup which, dissolved in 10 ml. of absolute alcohol, afforded 575 mg. (18%) of erythritol melting at 117–120°. The melting point of the preparation was not depressed upon admixture with authentic erythritol.

Acknowledgment.—The assistance of Mr. Harry W. Diehl in several of the preparations is gratefully acknowledged. The authors also wish to thank Dr. William C. Alford, Mrs. Evelyn G. Peake and Miss Paula M. Parisius for analytical determinations incident to this research.

Bethesda, Maryland Received April 19, 1951

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(20) Use of double this quantity of reducing agent failed to increase the yield of L-threitol significantly.

(21) In a similar experiment, ethanol was used to decompose the excess hydride. Sulfuric acid was then added to dissolve the precipitate which was formed and, after evaporation of the organic solvents, the solution was deionized with ion-exchange resins. After concentration, there was obtained 2.19 g. (32%) of crude L-threitol melting at 81–83°. Purification of this crude product proved difficult and entailed large losses.

(22) The material remaining in the mother liquor amounted to 540 mg.; when treated with benzaldehyde it yielded 400 mg. of dibenzylidene-L-threitol, melting at 218–219° and rotating in chloroform +76.8° (*c*, 0.80). R. C. Hockett [This Journal, **57**, 2260 (1935)] reported a value of −78.3° for the rotation of dibenzylidene-D-threitol in chloroform.

(23) L. Maquenne and G. Bertrand, *Compt. rend.*, **132**, 1419 (1901).

(24) R. C. Hockett, This Journal, **57**, 2260 (1935).

(25) L. Maquenne and G. Bertrand, *Compt. rend.*, **132**, 1565 (1901).