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New Derivatives of *d*-Erythronic and *l*-Erythronic Acid

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The preparation and properties of some hitherto unreported derivatives of *d*-erythronic and *l*-erythronic acids are described in this paper. The only record in the literature of an acetylated or benzoylated erythronic lactone is that described by Nef,[1] who obtained diacetyl-*dl*-erythronic lactone and dibenzoyl-*dl*-erythronic lactone. Nef described his acetylated *dl*-erythronic lactone as a fluid sirup which was very little soluble in water, properties which are in agreement with the characteristics found for the acetylated *d*-erythronic and *l*-erythronic lactones reported in this paper. Nef obtained dibenzoyl-*dl*-erythronic lactone as a crystalline material, and the dibenzoyl-*d*-erythronic lactone and the dibenzoyl-*l*-erythronic lactone which are described below were also found to be crystalline.

The rotations obtained for the *d*- and the *l*-erythronic amides agree in sign with Hudson's[2] rule for the rotation of amides of the α-hydroxy acids. The magnitudes of the specific rotations of the *d*- and the *l*-erythronic amides which were actually found and which were predicted by the values ascribed by Hudson[3] to the α- and β-asymmetric carbon atoms of the amides of the α-hydroxy acids of the sugar group, were in approximate agreement.

The starting material for this study of some of the derivatives of *d*- and *l*-erythronic acid was a sample of *dl*-erythronic lactone, m. p. 88–90° (uncorr.), furnished by Dr. J. W. E. Glattfeld of the Chemistry Laboratory of the University of Chicago. The resolution of the *dl*-erythronic lactone into the pure *d*-erythronic lactone and *l*-erythronic lactone was accomplished by the method of Glattfeld and Forbrich.[4] The *l*-erythronic lactone thus obtained and purified by recrystallization from ethyl acetate was in the form of long, glistening, white needles; m. p. 102° (uncorr.); $[\alpha]^{20}_{\mathrm{D}}$ +72.47°, in water, $c = 4.6\%$. These properties are in close agreement with those cited in the literature for *l*-erythronic lactone.[4–6] The *d*-erythronic lactone which was prepared also exhibited characteristics agreeing with the literature[4,5,7–10]: needles were obtained on recrystallization from ethyl acetate; m. p. 102–103° (uncorr.); $[\alpha]^{20}_{\mathrm{D}}$ −72.54°, in water, $c = 4.4\%$.

The rotations of the derivatives described were determined in a temperature controlled room varying from 24–25° by means of a Bates type saccharimeter.

Experimental

Diacetyl-*l*-erythronic Lactone.—Diacetyl-*l*-erythronic lactone was prepared by the method of Upson and Brackenbury.[11] Dry hydrogen chloride gas was bubbled into 25 cc. of acetic anhydride for several minutes. To this solution chilled to 0° was added 5 g. of pure *l*-erythronic lactone with constant stirring. The reaction mixture was allowed to stand at room temperature until the lactone had been in solution for twenty-four hours. The solution was then evaporated *in vacuo* from a water bath heated to 80°. The resulting sticky mass was transferred to a vacuum desiccator and kept over sodium hydroxide to remove any volatile acids.

All efforts to crystallize the diacetyl-*l*-erythronic lactone from various solvents failed. One sample on standing a year did not crystallize. The non-crystalline material was very soluble in benzene, chloroform, methyl alcohol, acetone, ethyl acetate, and ether. It was onyl slightly soluble in water, carbon tetrachloride, and petroleum ether; $[\alpha]^{25}_{\mathrm{D}}$ + 50.73, in 80% acetone, $c = 5.2\%$, rotation unchanged for three days. The yield of diacetyl-*l*-erythronic lactone was quantitative.

Anal. Calcd. for $C_8H_{10}O_6$: C, 47.51; H, 4.99. Found: C, 47.49; H, 5.07. Acetyl groups: Calcd. number of acetyl groups per molecule: 2.00. Found: 2.02. 0.09263 g. consumed 13.90 cc. 0.1 *N* NaOH. Calcd. for 0.09263 g.: 13.75 cc. 0.1 *N* NaOH.

Diacetyl-*d*-erythronic Lactone.—Except for a modification involving purification, the method of preparing diacetyl-*d*-erythronic lactone was the same as that which was used in the preparation of diacetyl-*l*-erythronic lactone. Five grams of the pure *d*-erythronic lactone was treated with 25 cc. of acetic anhydride and dry hydrogen chloride gas according to the method of Upson and Brackenbury.[11] Following the evaporation of the hydrogen chloride and acetic anhydride *in vacuo* at 80°, the resulting non-crystalline material was dissolved in chloroform. The chloroform solution was washed successively with ice water, iced sodium bicarbonate solution, and again with ice water. The chloroform in the washed solution was removed by evaporation in the air

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(1) Nef, *Ann.*, **357**, 214 (1907).

(2) Hudson, THIS JOURNAL, **40**, 813 (1918).

(3) Hudson and Komatsu, *ibid.*, **41**, 1141 (1919).

(4) Glattfeld and Forbrich, *ibid.*, **56**, 1209 (1934).

(5) Nef, Hedenburg and Glattfeld, *ibid.*, **39**, 1638 (1917).

(6) Ruff, *Ber.*, **34**, 1362 (1901).

(7) Erlbach, *ibid.*, **68**, 534 (1935).

(8) Glattfeld, *Am. Chem. J.*, **50**, 135 (1913).

(9) Ruff, *Ber.*, **32**, 3672 (1899).

(10) Jensen and Upson, THIS JOURNAL, **47**, 3019 (1925).

(11) Upson, Brackenbury and Linn, *ibid.*, **58**, 2549 (1936).

and in a vacuum desiccator. The diacetyl-*d*-erythronic lactone remained as a mobile, non-crystalline material; $[\alpha]^{25}\mathrm{D}$ $-50.64°$, in 80% acetone, $c = 4.9\%$, rotation unchanged for twenty-four hours.

Anal. Calcd. for $C_8H_{10}O_6$: C, 47.51; H, 4.99. Found: C, 47.09; H, 4.97. Acetyl groups: Calcd. number of acetyl groups per molecule: 2.00. Found: 2.04. 0.08285 g. consumed 12.53 cc. of 0.1 *N* NaOH. Calcd. for 0.08285 g.: 12.30 cc. of 0.1 *N* NaOH.

Although the acetyl derivatives of the *d*- and *l*-erythronic lactones were not obtained in crystalline form, nevertheless the analytical data and especially the specific rotations of the two forms indicate that they are true diacetyl derivatives.

Glattfeld and Kribben (private communication) report recently the preparation of *dl*-diacetylerythronic lactone in crystalline form; m. p. 52–53°.

***l*-Erythronic Amide.**—*l*-Erythronic amide was prepared in quantitative yield by a simple method suggested by the work of Glattfeld and Macmillan.[12] It is necessary to carry out this preparation in an efficient hood. To 2 g. of pure *l*-erythronic latone in a Petri dish was added liquid ammonia drop by drop obtained directly from an inverted cylinder through a glass delivery tube. On stirring the mixture, the lactone quickly dissolved. Most of the ammonia was removed by evaporation in the air and final traces of the ammonia were removed by placing the Petri dish over concentrated sulfuric acid in a vacuum desiccator at 30° for at least twenty-four hours. After a few hours in the vacuum desiccator, the *l*-erythronic amide crystallized in the form of white needles; m. p. 91–92° (uncorr.); $[\alpha]^{25}\mathrm{D}$ $-26.22°$, in water solution, $c = 4.9\%$.

Anal. Calcd. for $C_4H_9O_4N$: C, 35.53; H, 6.72; N, 10.37. Found: C, 34.69; H, 6.74; N, 10.41.

l-Erythronic amide was also prepared by the usual method of passing dry ammonia gas into a warm, saturated solution of pure *l*-erythronic lactone in absolute alcohol, but the resulting product was difficult to crystallize, was tan in color, and gave a low nitrogen value. Recrystallization from hot ethyl acetate resulted in the larger portion changing into a dark brown, sticky, insoluble mass, while the smaller part dissolved and separated as nearly white needles. Thus any heat treatment in the preparation of *l*-erythronic amide is to be avoided, and as a result, the treatment of *l*-erythronic lactone with liquid ammonia, in which the entire process is carried out at room temperature, is much to be preferred.

***d*-Erythronic Amide.**—The method of preparing *d*-erythronic amide was identical to that used in the preparation of *l*-erythronic amide. The *d*-erythronic amide was obtained as white needles; yield quantitative; m. p. 91–92° (uncorr.); $[\alpha]^{25}\mathrm{D}$ $+26.23°$, in water solution, $c = 4.1\%$.

Anal. Calcd. for $C_4H_9O_4N$: C, 35.53; H, 6.72; N, 10.37. Found: C, 35.44; H, 6.74; N, 10.41.

d-Erythronic amide, like the corresponding *l*-derivative, formed some needles on recrystallization from warm ethyl acetate, but the larger part of the material refused to dissolve and formed a brown, sticky mass. The preparation of an inferior, tan colored *d*-erythronic amide of low nitrogen content was accomplished by passing dry ammonia gas through a saturated, warm, alcoholic solution of *d*-erythronic lactone.

Acetylated *d*- and *l*-Erythronic Amides.—Both the *d*- and the *l*-erythronic amides were acetylated according to the method of Major and Cook,[13] and in spite of the elimination of heat treatment, the final product in both cases was a dark brown, sticky mass.

A different approach, that of treating the acetylated *d*-erythronic lactone and the acetylated *l*-erythronic lactone with liquid ammonia, also resulted in two dark brown, sticky products.

Dibenzoyl-*l*-erythronic Lactone.—Nef[1] reported the preparation of dibenzoyl-*dl*-erythronic lactone by heating the *dl*-erythronic lactone with benzoyl chloride to 100°, with the subsequent separation of the dibenzoyl derivative on the addition of 10 cc. of ether. This method was tried in the attempt to prepare the pure dibenzoyl-*d*- and *l*-erythronic lactone derivatives, varying the time of heating because of the omission of this detail in Nef's directions, but without success.

Dibenzoyl-*l*-erythronic lactone was successfully prepared by dissolving 1.5 g. of pure *l*-erythronic lactone in 5 cc. of pyridine, and adding 3 cc. of benzoyl chloride in three portions while cooling under the cold water tap. The reaction mixture, after standing for twenty-four hours at room temperature, was poured into ice water. An oil separated which was washed and rubbed up well in three changes of ice water. The addition of a small amount of 90% methyl alcohol to the drained oil caused it to solidify. The substance was recrystallized twice from 90% CH_3OH, filtered, washed with water, and dried at 50° *in vacuo*. The purified dibenzoyl-*l*-erythronic lactone was in the form of clear, glistening needles which melted at 110–111° (uncorr.). The crystals were very soluble in absolute ethyl and methyl alcohols and chloroform, quite soluble in ether, and nearly insoluble in water: $[\alpha]^{25}\mathrm{D}$ $+176.29°$, in dry chloroform, $c = 3.9\%$; yield 72% crude product before purification; 31% pure compound after two recrystallizations.

Anal. Calcd. for $C_{18}H_{14}O_6$: C, 66.24; H, 4.33. Found: C, 65.84; H, 4.37.

Dibenzoyl-*d*-erythronic Lactone.—The method of preparing dibenzoyl-*d*-erythronic lactone was identical to that used in the preparation of dibenzoyl-*l*-erythronic lactone. The clear, glistening needles of dibenzoyl-*d*-erythronic lactone melted at 110–111° (uncorr.); $[\alpha]^{25}\mathrm{D}$ $-176.86°$, in dry chloroform, $c = 3.5\%$.

Anal. Calcd. for $C_{18}H_{14}O_6$: C, 66.24; H, 4.33. Found: C, 66.15; H, 4.39.

Tribenzoyl-*d*-erythronic Amide.—Two grams of *d*-erythronic amide was dissolved in 15 cc. of pyridine and treated with 5 cc. of benzoyl chloride according to the method employed in benzoylating *l*-erythronic lactone. The sticky mass which separated on treatment with ice water crystallized either from 90% ethyl alcohol or 80% acetone. After three recrystallizations, the tribenzoyl-*d*-erythronic amide was obtained in the form of white needles; m. p. 201° (uncorr.). The specific rotation of

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[12] Glattfeld and Macmillan, THIS JOURNAL, **58**, 898 (1936).

[13] Major and Cook, *ibid*, **58**, 2474 (1936).

tribenzoyl-*d*-erythronic amide was obtained only approximately because of the slight solubility of the compound in chloroform; $[\alpha]^{25}_{\mathrm{D}}$ +9.64°, in chloroform, $c = 0.89\%$; $[\alpha]^{25}_{\mathrm{D}}$ +11.13°, in chloroform, $c = 0.70\%$ are two of the approximate values obtained.

Anal. Calcd. for $C_{25}H_{21}O_7N$: C, 67.09; H, 4.73; N, 3.13. Found: C, 65.79; H, 4.75; N, 3.28.

Tribenzoyl-*l*-erythronic Amide.—1.41 grams of *l*-erythronic amide was dissolved in 5 cc. of pyridine and treated with the calculated amount of benzoyl chloride using the same method employed in benzoylating *l*-erythronic lactone. The sticky mass which separated on treatment with ice water was dissolved in a small amount of hot 90% methyl alcohol from which it crystallized. On recrystallization twice from 80% acetone, filtering, washing with water, and drying at 50° *in vacuo*, the tribenzoyl-*l*-erythronic amide was obtained as white needles; m. p. 201° (uncorr.). $[\alpha]^{25}_{\mathrm{D}}$ −9.01°, in chloroform, $c = 0.19\%$, is only an approximate value because of the slight solubility of the tribenzoyl-*l*-erythronic amide in chloroform.

Free *dl*-Erythronic Acid.—*d*-, *l*- and *dl*-erythronic acids have never been prepared in pure form. Ruff[6,9] obtained solutions of *d*-erythronic acid and *l*-erythronic acid, and Börnstein and Herzfeld[14] obtained erythronic acid as a thick sirup which was neither titrated nor analyzed.

In this study an attempt to prepare free *dl*-erythronic acid by the method of Brackenbury and Upson[15] failed because the *dl*-erythronic acid was soluble in glacial acetic acid.

The method employed by Rehorst[16] to prepare arabonic acid was used in the attempt to prepare free *dl*-erythronic acid with only partial success, producing a non-crystalline material which contained 63% free acid according to titrations. The failure of the Rehorst method was believed to be due to the ease with which the free acid is converted into the lactone.

Conversion of *d*-Erythronic Lactone into *d*-Threonic Phenylhydrazide (Newer Nomenclature[17]).—Four and one-half grams of impure *d*-erythronic lactone was treated with 12.0 g. of $Ba(OH)_2 \cdot 8H_2O$ and 40 cc. of water for five days over a steam-bath according to the method of Upson and Bonnett.[18] The Ba^{++} was removed with the calculated amount of sulfuric acid, and an exact adjustment of Ba^{++} and $SO_4^{=}$ was obtained. The barium sulfate was removed by filtration, and the filtrate was evaporated to a thick sirup *in vacuo* below 60°. To the thick sirup was added 4.5 cc. of phenylhydrazine and 4.5 cc. of absolute ethyl alcohol, the mixture was warmed until homogeneous, and was set aside for twenty-four hours. A precipitate formed which, according to its m. p. 164–165°, was neither *d*-erythronic phenylhydrazide nor *d*-threonic phenylhydrazide. This product may have been *dl*-threonic phenylhydrazide which has a m. p. 167.5°.[19] The excess phenylhydrazine was removed in the following way: the alcohol was first removed by distillation *in vacuo;* the residue was dissolved in water, and the water solution was extracted with ether; the water of the phenylhydrazine-free solution was evaporated off *in vacuo*. The resulting solid was dissolved in eight parts of absolute ethyl alcohol and, after standing at room temperature for approximately two weeks, large plate crystals formed on the bottom of the container. Without recrystallization, for the quantity was too small, the crystals exhibited m. p. 154–155°; $[\alpha]^{25}_{\mathrm{D}}$ −25.76°, in water, $c = 0.74\%$. These properties agree with those in the literature for *d*-threonic phenylhydrazide.[5,8,10,20,21]

Summary

1. Diacetyl-*l*-erythronic lactone and diacetyl-*d*-erythronic lactone were prepared by acetylation of the corresponding lactones.

2. *d*-Erythronic amide and *l*-erythronic amide were prepared by treating *d*-erythronic lactone and *l*-erythronic lactone with liquid ammonia.

3. Dibenzoyl-*l*-erythronic lactone and dibenzoyl-*d*-erythronic lactone were prepared by benzoylation of the corresponding lactones.

4. Tribenzoyl-*l*-erythronic amide and tribenzoyl-*d*-erythronic amide were prepared.

5. *d*-Erythronic lactone was converted into *d*-threonic phenylhydrazide (newer nomenclature).

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(14) Börnstein and Herzfeld, *Ber.*, **18**, 3353 (1885).

(15) Brackenbury and Upson, THIS JOURNAL, **55**, 2512 (1933).

(16) Rehorst, *Ber.*, **63**, 2279 (1930).

(17) Hockett, THIS JOURNAL, **57**, 2260 (1935).

(18) Bonnett and Upson, *ibid.*, **55**, 1245 (1933).

(19) Glattfeld and Hoen, *ibid.*, **57**, 1405 (1935).

(20) Nef, *Ann.*, **403**, 204 (1914).

(21) Anderson, *Am. Chem. J.*, **42**, 401 (1909).