tration of inulin in solution is shown in Table IX. The level of solubility at 20° was reached in four to five weeks.

TABLE IX

SEPARATION OF CHICORY INULIN FROM ITS SUPERSATURATED SOLUTION

| | | | | | | |
|---|---|---|---|---|---|---|
| Time, days | 0 | 5 | 12 | 23 | 28 | 36 |
| Inulin per 100 cc. of soln., g. | 5.83 | 3.97 | 2.18 | 1.65 | 1.49 | 1.34 |

## Summary

The solubility of dahlia inulin differs considerably from that of chicory inulin. Each of the two inulins exists in two modifications having different degrees of solubility. One of the modifications of chicory inulin is unstable, gradually changing into the less soluble form. Solubility was measured at different temperatures and in alcoholic solutions. The presence of levulose increases the solubility of dahlia inulin, but has no effect on the solubility of chicory inulin. Soluble inulin has no effect on the solubility of either dahlia or chicory inulin. Inulin is slowly deposited from its supersaturated solutions until normal solubility is reached.

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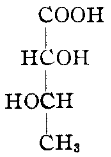
# The $C_4$-Saccharinic Acids. VII. The Preparation and Resolution of *dl-threo*-1,2-Dihydroxybutyric Acid[1]

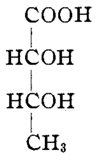
BY J. W. E. GLATTFELD AND JOHN W. CHITTUM

There are two theoretically possible *dl*-1,2-dihydroxybutyric acids. Both of these have recently been prepared in pure form and studied quite thoroughly.[2] One melts at 74–75° and the other at 81.5°. In still more recent work in this Laboratory[3] it has been shown that the acid of lower melting point probably has the *trans* configuration and the one of higher melting point the *cis* configuration. Braun has suggested the prefix *threo* for the *trans* acid and *erythro* for the *cis* acid. These suggestions are adopted in this paper.



$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{HCOH} \\ | \\ \mathrm{HOCH} \\ | \\ \mathrm{CH_3} \end{array}$$

*dl-threo*-1,2-Dihydroxybutyric acid, m. p. 74–75°



$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{HCOH} \\ | \\ \mathrm{HCOH} \\ | \\ \mathrm{CH_3} \end{array}$$

*dl-erythro*-1,2-Dihydroxybutyric acid, m. p. 81.5°

It is with the *dl-threo*-acid that this paper is concerned.

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[1] This article is largely from a dissertation presented by John W. Chittum in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Chicago.

[2] Glattfeld and Woodruff, THIS JOURNAL, **49**, 2309 (1927).

[3] Géza Braun, *ibid.*, **51**, 228 (1929).

*dl-threo*-1,2-Dihydroxybutyric acid was prepared by Glattfeld and Woodruff by the oxidation of crotonic acid of m. p. 72° by means of potassium chlorate in the presence of osmium tetroxide and also by means of barium permanganate. The work with potassium chlorate was repeated and the results verified but an additional fact was established that may affect seriously the yield of acid if ignored, namely, the fact that the free *dl-threo*-acid forms a compound with its own potassium salt that is comparatively insoluble in cold alcohol. The formation of this compound was observed about the same time by Braun, who analyzed it[4] and showed it to have the composition corresponding to the formula $C_4H_8O_4 \cdot C_4H_7O_4K$. We substantiated this formula further by preparing the compound from equal parts of the free acid and its potassium salt.

The chlorate method of preparation was greatly improved upon by Braun who used silver chlorate instead of potassium chlorate and thus avoided the complication due to the formation of the potassium double compound. We found this method to be by far the best one for the preparation of this acid.

The only report of work on the resolution of the *dl-threo*-acid is by Morrell and Hanson.[5] These workers prepared the acid by the oxidation of solid crotonic acid with barium permanganate. They failed to resolve the acid by the use of quinine, cinchonine, strychnine, morphine and brucine but reported partial success with quinidine. By the use of the last named alkaloid they obtained a *levo* acid whose specific rotation they report as $-13.51°$. Calculation of the specific rotation from the data they record, however, gives $-19.08°$ instead of $-13.51°$ and thus the correct rotation is left in doubt. Moreover, the free *dextro* acid was not obtained.

In the experimental work reported below the resolution of the acid was accomplished by means of brucine as well as quinidine. Both *dextro* and *levo* components were obtained in pure form in each case and found to have specific rotations of about $-15.1$ and $+15.1°$ in the experiments in which brucine was used and $-15.5$ and $+15.45°$ in those in which quinidine was used. The resolutions with the two alkaloids were made by different workers and at different times and the small differences in results are probably due to experimental error. It is probable that the true specific rotations at 20° lie somewhere between the figures recorded above.

## Experimental Part

**The Double Compound,** $C_4H_8O_4 \cdot C_4H_7O_4K$.—As the silver chlorate procedure has been found to be much more satisfactory than the one in which potassium chlorate is used, the latter will be discussed here only to record our work with the double compound formed by the acid and its potassium salt.

To a solution of 50 g. of crotonic acid (m. p. 72°) in 1 liter of water was added 95 g. of potassium chlorate and 20 cc. of a 0.3% solution of osmium tetroxide. After having stood for one week, the solution no longer decolorized bromine water. After extraction

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[4] Braun, This Journal, **51**, 244 (1929).

[5] Morrell and Hanson, *J. Chem. Soc.*, **85**, 197 (1904).

with benzene, it was concentrated at 60° at reduced pressure until the crystals which appeared caused bumping. The crystals (49 g. of practically pure potassium chlorate) were removed and the filtrate evaporated to dryness at reduced pressure and 60°. The residual sirup was dissolved in 150 cc. of absolute ethyl alcohol and the insoluble material separated by filtration while hot. As the filtrate cooled it deposited crystals. It was, therefore, thoroughly chilled and yielded 40 g. of white solid. This product was purified by solution in hot absolute alcohol, addition of ethyl acetate to turbidity, removal of turbidity with a little alcohol, and cooling of the solution. The crystals then deposited melted at 101–103° but still contained some chloride and chlorate.

These crystals were very soluble in water, almost insoluble in cold absolute alcohol, and insoluble in ethyl acetate and ether. The water solution was distinctly acid. With phenylhydrazine the substance gave a crystalline derivative of m. p. 132° and with brucine a salt of m. p. 229.5°. Authentic samples of the phenylhydrazide and the brucine salt of the *dl-threo*-acid melted at 130–131° and 232–234°, respectively, and mixtures of the corresponding compounds from the two sources melted over the same ranges as the pure individuals. These facts leave little doubt that the solid under discussion contained *dl-threo*-acid.

All doubt as to the identity of the compound was finally dispelled by its synthesis from its two constituents. Ten grams of crystalline *dl-threo*-acid was dissolved in 80 cc. of water. Half of this solution was carefully neutralized with a dilute solution of potassium hydroxide. The neutralized solution was then mixed with the untreated portion of the acid solution and the mixture evaporated to dryness at reduced pressure, water-bath at 70°. The sirup was dissolved in 25 cc. of hot absolute alcohol. The alcoholic solution yielded, on cooling, a quantity of fine white crystals which were collected on a filter, washed with ether and dried; yield 7.9 g., melting range 104–107°. A second crop of crystals was obtained by concentration at reduced pressure; weight 1.8 g.; melting range 95–106°. The total yield was, therefore, 9.7 g. or 83.6% of the theoretical amount.

**The Silver Chlorate Method of Preparation.**—Our procedure was practically that of Braun's second method,[6] except that we did not carry out the oxidation at zero degrees but at room temperature. To a solution of 100 g. of crotonic acid (m. p. 72°) in 5 liters of water which contained 0.25 g. of osmium tetroxide, was added 2.5 g. of silver chlorate twice daily until the reaction was complete (solution no longer turned brown even after standing for twenty-four hours); total amount of silver chlorate added 96 g., time required, three weeks. The solution was stored in the dark during the preparation. The silver chloride was then separated by filtration and washed with water, after which it was washed immediately with hydrochloric acid in order to destroy any silver oxalate that might have been present as this compound is explosive when dry. The water solution was extracted three times with 300 cc. of benzene to remove the osmium tetroxide and distilled to dryness at reduced pressure (bath at 60°). The residue was treated with sufficient ethyl acetate to dissolve the gum and the solution cooled. A small amount of material did not dissolve. Fresh ethyl acetate was then added to the solution until no more cloudiness was produced by further addition. The filtered solution was dried with sodium sulfate and then concentrated at reduced pressure to a small volume (150–200 cc.), transferred to a small flask and cooled in ice water for an hour. Crystallization was induced by scratching the walls of the flask with a glass rod. A crop of crystals which, after drying in a vacuum desiccator, weighed 80.5 g. was removed. The mother liquor was concentrated and two further crops of 7.5 g. and 4 g. obtained; total 92 g. of dry crystalline acid of m. p. 73.5–75.5° or 66%.

A repetition of this experiment with 80 g. of crotonic acid yielded 78 g. of crystalline acid or 70%.

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(6) Braun, THIS JOURNAL, **51**, 245 (1929).

The acid thus obtained is of a very much higher degree of purity than when either potassium or barium chlorate is used. The reaction proceeds more slowly than when either of these reagents is used but, once it is finished, the rest of the procedure is shorter and easier to carry out, and the yields by the silver chlorate method are much higher.

If it is desired to obtain acid of the highest purity, the crystals obtained as outlined above may be dissolved in two parts of ethyl acetate at 60°, followed by chilling of the solution to 0°. The crystals are washed on the suction filter first with a little cold ethyl acetate, then with ether, and dried in a vacuum desiccator over phosphorus pentoxide and paraffin. Crystals obtained by the barium chlorate method and purified in this manner melted at 73–74° and titrated correctly.

Neither the *dl*-acid nor either of the active acids is at all hygroscopic when pure. We have exposed all three to the laboratory atmosphere for days with no evidence of absorption of moisture.

**Resolution of the Acid with Brucine.**—Contrary to the experience of Morrell and Hanson, we found brucine to be an excellent resolving agent when water is used as the solvent.

The brucine salt was made in the usual way.[7] A mixture of twenty-five grams of recrystallized *dl-threo*-acid (m. p. 73–74°) in 800 cc. of water and 85 g. of anhydrous brucine was kept on the boiling water-bath until the solution was permanently alkaline (several hours). The solution was cooled, extracted twice with 100-cc. portions of benzene, and distilled to dryness at reduced pressure (water-bath at 70°); wt. of residue, 127 g. This was dissolved in 150 cc. of hot water, the solution cooled and allowed to stand first at room temperature for two hours and then for one hour in an ice-bath. The solid was then collected on a suction filter, pressed dry and kept in an oven at 70–75° until constant in weight; wt. 43.5 g. The mother liquor from Crop I was evaporated to dryness at reduced pressure as before. The residue, which weighed 60 g., was crystallized from 1 part of water. This process was repeated until four crops of crystals had been obtained. The residue from the mother liquor from Crop IV weighed 12 g. The solvent was changed at this point; the material was crystallized from 12 cc. of 50% ethyl alcohol. This yielded 2.8 g. of dry salt, Crop V. The residue from the filtrate from Crop V weighed 6.0 g. It was crystallized from 6 cc. of 50% ethyl alcohol and yielded 1.3 g. of dry material.

Five such experiments were made in each of which 25 g. of the *dl*-acid was used. Six crops of crystals were obtained in each case. The specific rotations of these (sodium light) are recorded below.

| Experiment | Crop I | Crop II | Crop III | Crop IV | Crop V | Crop VI |
|---|---|---|---|---|---|---|
| A | −32.5 | −24.5 | −21.0 | Lost | −21.8 | −22.5 |
| B | −33.5 | −21.2 | −21.3 | −22.2 | −20.5 | −22.0 |
| C | −32.9 | −21.2 | −20.6 | −21.9 | −21.0 | −18.6 |
| D | Lost | −21.7 | −24.5 | −23.7 | −21.5 | −23.0 |
| E | −32.8 | −21.4 | −21.0 | −23.0 | −21.2 | −19.6 |

It is apparent from these data that a partial resolution had been accomplished. Each Crop I was now recrystallized six times from water and from the results of these recrystallizations it is concluded that the pure anhydrous brucine salt of the levo acid has a specific rotation in water solution between −34.4° and −35.6°.

**Preparation of the Levo Acid from the Brucine Salt.**—To a solution of 40.5 g. of recrystallized brucine salt (−34.4 to −34.6°) in 200 cc. of water was added a hot solution of 12.5 g. of hydrated barium hydroxide in 200 cc. of water. The mixture was cooled, the brucine removed and the filtrate extracted five times with 75-cc. portions of

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(7) Glattfeld and Hanke, THIS JOURNAL, **40**, 976 (1918).

benzene. The barium was exactly precipitated with sulfuric acid, the barium sulfate removed and the filtrate evaporated to dryness at reduced pressure. The residual sirup weighed 9 g. Solution in a large volume (200–300 cc.) of ethyl acetate, filtration to remove gummy precipitate, and distillation of filtrate to dryness, gave 6 g. of gum which crystallized when seeded with racemic acid. The crystals were brought on a filter, washed with a little cold ethyl acetate and dried; m. p. 73.5–75°, $[\alpha]_D$ −15.0°.

A second portion of 75.2 g. of brucine salt (−35.1 to −35.7°) was treated in the manner outlined above. The rotation of the acid after three recrystallizations from ethyl acetate was −15.1°.

**Preparation of the Dextro Acid from the Brucine Salt.**—For the preparation of the dextro acid, various crops of brucine salt, −20.7 to −22.7°, were combined; weight 134.2 g. This salt was hydrolyzed in the manner outlined above for the levo acid and yielded 27 g. of crude crystalline acid; +11.3°. Fourteen grams of this material was subjected to five successive crystallizations from two parts of ethyl acetate and the specific rotation of the final product was found to be +15.1°.

**Resolution of the Acid with Quinidine.**—The work of Morrell and Hanson with quinidine was repeated. To a solution of 20 g. of the acid, m. p. 73.5–74.5°, in 400 cc. of hot water, quinidine was added until the solution was neutral (59 g. of alkaloid needed). The hot solution was filtered and deposited a crop of crystals which weighed 37.3 g. after three days in a vacuum desiccator over sulfuric acid; m. p. 117–117.5°; $[\alpha]_D$ +142.7°. Morrell and Hanson give 113–114° and +143.46° for the corresponding crop of crystals. They report the specific rotation as +142.2° after the material had been recrystallized six times. Our quinidine salt was recrystallized five times and then had a specific rotation of +147.5°. Further work with this salt showed it to be so much less soluble in water than the salt of the dextro acid that an almost complete separation of the two acids was found to be possible by the use of quinidine. The results recorded below support this statement.

A mixture of 60 g. of *dl* acid, m. p. 73.5–75°, in 2.5 liters of water, and 180 g. of quinidine was kept on the boiling water-bath for a half hour, cooled, filtered (2 g. of quinidine recovered) and the filtrate extracted three times with 500-cc. portions of ether. The solution was then concentrated at reduced pressure and brought to a weight of 1455 g. (1 part salt in 5 parts water), heated until all the solid was again in solution, then cooled rapidly and allowed to stand overnight. The crystals were then removed and dried in a vacuum desiccator over sulfuric acid for three days; wt. 90.3 g., $[\alpha]_D$ +147.5°; m. p. 116–122°.

It was found that it is the hydrated form of this salt which melts at 116–122° and that the m. p. must be taken rapidly to get this low value. If it is taken slowly, a very indefinite melting is observed with the last of the material liquefying at 159–162°. If the air-dry salt is extracted with boiling anhydrous ether (as is often done to avoid possible contamination with free alkaloid) it always melts at the higher value.

The filtrate from the first crop of crystals was concentrated and adjusted as before until it weighed 1395 g., cooled, seeded with crop 1 and allowed to stand for three days. The second crop was then removed; wt. 14 g., $[\alpha]_D$ +147.5°; m. p. (after ether treatment) 159–162°. A third crop of crystals was obtained by concentration of the filtrate to 1175 g. Crystals came very slowly this time even when the solution was stored for several days in the ice box; wt. crop 3, 6.8 g., $[\alpha]_D$ +149.5°; m. p. (after ether treatment) 159–162°.

The three crops of crystals were combined, wt. 106 g. (some material lost in tests of various sorts) and the filtrates and washings concentrated to dryness at reduced pressure, wt. residue 126 g. The acids were now set free from these two lots of material.

**Active Acids from Quinidine Salts.**—The two lots of salts were separately treated in 4–5 liters of hot water with an excess of barium hydroxide in hot solution, the mixtures cooled, the quinidine separated by filtration, the filtrates extracted with ether, the barium exactly removed as sulfate and the filtrates distilled to dryness at reduced pressure with water-bath finally at 100°; wts. of residues 24.5 g. from the crystalline salts, and 31 g. from the non-crystalline salts. Small samples of each were removed and the specific rotation determined. Then the residues were recrystallized from one and one-half parts of ethyl acetate and the specific rotation of the crystals obtained, again determined. This process was repeated five times with both levo and dextro acids. The results are recorded in the following table:

| | Levo acid | | | Dextro acid | | |
|---|---|---|---|---|---|---|
| | Weight, g. | $[\alpha]_D$ | | Weight, g. | $[\alpha]_D$ | |
| Residue | 24.5 | −13.55° | | 31 | +12.17° | |
| Crop 1 | 9 | −15.9° | Av. −15.5 | 15 | +13.4° | |
| Crop 2 | 7 | −15.6° | | 11 | +15.4° | Av. +15.45 |
| Crop 3 | 5.5 | −15.2° | | 10 | +15.5° | |
| Crop 4 | 4 | −15.1° | | 8 | +15.1° | |
| Crop 5 | 2 | −15.7° | | 6.5 | +15.8° | |

## Summary

It has been shown that in the preparation of *dl-threo*-1,2-dihydroxybutyric acid by the method of Glattfeld and Woodruff (oxidation of solid crotonic acid by means of potassium chlorate) a compound of formula $C_4H_8O_4 \cdot C_4H_7O_4K$ is formed which may lower the yield of acid. The method of Géza Braun (use of silver chlorate instead of potassium chlorate) avoids this difficulty and was found to be much superior.

The acid prepared by Braun's method was successfully and completely resolved with brucine and with quinidine. The specific rotations of the acids obtained when brucine was used were −15.0 and +15.1°, and when quinidine was used −15.5 and +15.45°. It is probable that the correct rotations at 20° lie somewhere between these two figures.

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