[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEBRASKA]

THE ISOMERIC ALPHA,BETA-DIPHENYLGLUTARIC ACIDS[1]

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Part I. The Optically Inactive Acids

Introduction

An acid of this group was first synthesized by Avery and McDole[2] through the addition of benzyl cyanide to cinnamic ester and the hydrolysis of the product formed. The acid crystallized as needles. The corrected melting point was 226–228°. In this paper it will be referred to as "the higher-melting acid." The possibility of the presence of a lower-melting isomeric acid formed along with the higher-melting acid was considered by Avery and McDole in a discussion, of which the following is an abbreviation: "By working over the mother liquors a substance was obtained melting at 205° (uncorr.). However, careful work showed the presence of a small amount of nitrogen in the supposed isomeric acid and when this compound was placed in a sealed tube with hydrochloric acid and heated, the compound obtained in every case was the diphenylglutaric acid melting at 224° (uncorr.)." The nitrogen just referred to was actually due to a very minute trace of the monoamide of diphenylglutaric acid.[3] The 205° compound was in reality the nearly pure isomeric glutaric acid to be described in this paper as "the lower-melting acid," the melting point of which is 208–210° (corr.). It forms nearly square or oblong flat plates, beveled plates or prisms. The crystals formed under different conditions vary considerably in superficial appearance.

Substituting phenylacetic ester for phenylacetonitrile (benzyl cyanide), Borsche[4] effected the synthesis of the higher-melting acid. He describes a very satisfactory method for preparing the esters of this acid, and the acid itself, but makes no mention of the lower-melting acid which is formed in considerable quantity when the ester of the higher-melting acid is hydrolyzed by potassium hydroxide in the usual way.

By oxidizing 1,2-diphenylcyclopentene-3, Kishner[5] obtained a mixture of acids which he converted into their methyl esters and separated by fractional distillation. He thus obtained a methyl ester melting at 87° having the same percentage composition as the known methyl ester (143°) of α,β-diphenylgutaric acid. By saponifying this ester he obtained an

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[1] Read at the meeting of the Division of Organic Chemistry, American Chemical Society, Columbus, May 1, 1929.

[2] Avery and McDole, THIS JOURNAL, **30**, 596, 1423 (1908).

[3] Avery, *ibid.*, **50**, 2516 (1928).

[4] Borsche, *Ber.*, **42**, 4496 (1909).

[5] Kishner, *J. Russ. Phys.-Chem. Soc.*, **47**, 1819–1848 (1915).

acid in the form of needles melting at 200–201°, which he called the maleinoid form, designating the higher-melting acid as the fumaroid form.

By oxidizing β,γ-diphenylvalerolactone, Meerwein and Dott[6] obtained in the form of prisms an acid melting at 203–204°. It formed a methyl ester apparently identical with the "maleinoid" ester of Kishner. The acid, however, with its higher melting point and different crystalline form does not closely correspond to the latter's "maleinoid" acid.

The investigators referred to were in fairly close agreement in so far as the higher-melting acid is concerned. All reported needles melting above 220°, the exact temperature depending on the rapidity of heating. All reported a methyl ester melting sharply at about 143°. On the other hand, the only close agreement in regard to the lower-melting acid is the fact that two of the investigators report a methyl ester melting at 87°.

In view of the uncertainty in regard to the lower-melting acid, the authors of this paper regarded a thorough study of the subject as desirable.

Experimental Part

The Anhydride of the Lower-Melting Acid.—Five grams of the higher-melting acid was heated in a sealed tube with approximately 10 g. of acetyl chloride at 140° for four hours. The product of the reaction was treated with 50 cc. of petroleum ether. An oil separated out and became crystalline on stirring. After an hour the crystals were filtered off; yield, 4 g. The anhydride was purified by recrystallizing from hot tertiary amyl alcohol and gave plates, m. p. 124°, by dissolving in chloroform, adding absolute alcohol and condensing in a current of cold, dry air; by dissolving in chloroform and precipitating with petroleum ether, m. p. 126.5°.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.7; H, 5.3. Found: C, 76.6; H, 5.4.

That this body is the anhydride of the lower-melting acid is shown by its reacting readily to form this acid (and its esters), and not the higher-melting acid from which it was prepared. It also deports itself as an anhydride in forming the acid amide, the imide and the anilic acid.

This anhydride was formed almost quantitatively by treating the lower-melting acid with an excess of acetyl chloride, evaporating on the steam-bath and allowing the residue to crystallize.

The Lower-Melting α,β-Diphenylglutaric Acid.—This acid is gradually formed when the anhydride just described is treated with boiling water. It is formed more readily by dissolving the anhydride in an alkaline carbonate solution and precipitating with strong acid. It was first isolated in pure condition, however, by the following method: 30 g. of the methyl ester, m. p. 143°, was saponified by boiling with 15 g. of potassium hydroxide in 100 cc. of 95% alcohol. As the potassium salt precipitated out, water was added and the boiling continued for two hours. The solution was then evaporated to dryness, dissolved in water and added gradually to an excess of a 10% solution of hot hydrochloric acid. After cooling, the white crystalline mass was filtered off and washed well with water; yield, approximately 25 g. This was dissolved in hot 95% alcohol; boiling water was then added to incipient turbidity. On cooling, needles of the nearly pure higher-melting acid separated; yield, approximately 15 g. The filtrate was condensed to about one-third of its previous volume and cooled. The mix-

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[6] Meerwein and Dott, *J. prakt. Chem.*, 97, 264–268 (1918).

ture of the higher and lower acids formed was then filtered off; yield of mixed acids, approximately 10 g. The needles of the higher-melting acid and the beveled plates or short prisms of the lower-melting acid appeared to be present in about equal amounts when seen through the microscope. About 1 g. of the pure lower acid was obtained by repeated recrystallization from dilute acetic acid.

For practical purposes, however, the mixed acids are converted into the pure anhydride by heating with acetyl chloride at 140°. The anhydride in turn passes readily into the pure lower-melting acid as has just been stated.

The lower-melting acid formed by the oxidation of 1,2-diphenylcyclopentene-3 as described by Kishner, but purified by dissolving out the benzoic acid with benzene and recrystallizing the residue by dissolving in as small an amount of ethyl acetate as possible, adding benzene and condensing in a current of dry, cold air, is readily obtained in a pure condition.

The three samples just described have the same crystalline form, the same solubility relations and the same melting point, 208–210° (corr.). Melting points of mixed samples showed no variation.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.8; H, 5.7. Found: C, 71.6; H, 5.7. Titration: 0.1225 g. required 8.6 cc. of $N/10$ NaOH. Calcd.: 8.6 cc.

Except for the higher melting point obtained, the results just given are so closely in agreement with the conclusions of Meerwein and Dott that the synthesis of the acid by their method for the sake of comparison seemed unnecessary.

The Monoamide of α,β-Diphenylglutaric Acid.—Two grams of the anhydride dissolved in chloroform was treated for some time with dry ammonia gas. The white powder formed suspended in chloroform was shaken with concentrated ammonium hydroxide solution and evaporated to dryness. The residue recrystallized from 50% alcohol melted at 200–205° with decomposition and the evolution of ammonia. It was found to be identical with the monoamide of diphenylglutaric acid from β,γ-diphenyl-γ-cyanobutyric acid.[3] This fact is of interest as indicating that the cyano derivatives through which Avery and McDole first synthesized the higher-melting acid belong to the series of the lower-melting acid and that the series of the higher-melting acid is reached only in the final hydrolysis.

The Imide of the Lower-Melting α,β-Diphenylglutaric Acid.—The monoamide of the lower-melting acid on boiling with a mixture of 95% alcohol and concd. hydrochloric acid gives the corresponding imide as coarse, hair-like crystals; m. p. 225–229° without evolution of ammonia.

The imide may also be made as follows: β,γ-diphenyl-γ-cyanobutyric methyl ester is treated with strong alcoholic potash and evaporated almost to dryness over the open flame. Water is added and the process repeated. The mass is then dissolved in glacial acetic acid, concd. hydrochloric acid added and it is again evaporated over the open flame till a mass of coarse, hair-like crystals separate out. More hydrochloric acid is added, the mass again concentrated, then diluted with water, filtered and washed; yield, nearly quantitative. Recrystallized out of 80% alcohol it melts at 225–229°.

Anal. Calcd. for $C_{17}H_{15}O_2N$: C, 76.9; H, 5.7; N, 5.3. Found: C, 76.8; H, 5.6; N, 5.2.

The Anilic Acid.—2.26 g. of the anhydride of the lower-melting α,β-diphenylglutaric acid was dissolved in benzene, 0.93 g. of aniline in benzene was added and the solution warmed. A crystalline precipitate formed which after heating at about 80° for ten minutes was filtered off and washed with benzene; the yield of the crude product was nearly quantitative. Recrystallized three times from 50% alcohol, the anilic acid showed a constant melting point of 201–202°. The crystals appeared in the form of needles or rods.

Anal. Calcd. for $C_{23}H_{21}O_3N$: C, 76.8; H, 5.9; N, 3.9. Found: C, 76.5; H, 5.8; N, 3.8. Titration: 0.109 g. required 3.0 cc. of $N/10$ NaOH. Calcd.: 3.0 cc.

Transformation: The Higher Series $\rightleftarrows$ the Lower.—Concentrated hydrochloric acid diluted with an equal volume of water appears not to change compounds of the higher into those of the lower-melting series at any temperature.

Below 150° cyano derivatives are hydrolyzed by hydrochloric acid to a mixture of the amide and the lower-melting acid; at 150° to a mixture of the two acids, the higher-melting acid predominating as the temperature rises.

Below 180° the esters of the lower acid are hydrolyzed by hydrochloric acid with little transformation. Above 180° esters of the lower acid (and at 200° the acid itself) are transformed more or less completely into the higher-melting acid.

Saponification by alcoholic potassium hydroxide leads to the corresponding acid, mixed, however, with a varying amount of the isomeric compound. This action appears to explain why Kishner on saponifying the pure (87°) lower-melting methyl esters secured needles melting at 200–201°. He appears to have isolated a mixture of the acids.

As Kishner pointed out, the lower-melting acid is in part transformed into the higher by heating above its melting point.

The method of proceeding from the higher (or mixed acids) to the lower through the anhydride route has made it possible to prepare the lower-melting acid in quantity without excessive cost and effort.

Optical Properties.—Both acids are optically inactive.

Summary to Part I

The work previously published on the higher-melting acid, in so far as this paper relates to it, is confirmed in all essential points.

The lower-melting acid has been prepared in a pure condition by different methods, its crystalline habit noted and its melting point determined.

A mixture of the higher and lower-melting acids has been separated by fractional crystallization.

The higher-melting acid has been transformed into the anhydride of the lower. This anhydride has been isolated in pure form and used practically in preparing the lower acid.

The methyl ester (m. p. 143°), the ethyl ester (m. p. 93.3°) and the acid (m. p. 226–228°) belong to what we have termed the higher-melting series; the methyl ester (m. p. 87°), the ethyl ester 76° (as pointed out by Kishner) and the acid (m. p. 208–210°) belong to the lower-melting series.

The cyano and monoamide derivatives,[7] the imide (m. p. 225–229°) and the anilic acid (m. p. 201–202°) described in this paper, also appear to be members of the lower melting series.

To use the phraseology sometimes employed, but generally accepted with mental reservations when applied to saturated dibasic acids, the members of the higher-melting series might be termed "*trans*" or "fumaroid" compounds; while those of the lower-melting series would be designated as "*cis*" or "maleinoid" forms. Though these terms are freely used in the literature of the dimethyl- and diethylglutaric acids, they help to classify rather than to explain this and similar cases of stereoisomerism. Hence in

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[7] Avery, THIS JOURNAL, 50, 2515–2516 (1928).

the hope of throwing more light on the real difference in stereo structure between the two series, the authors next undertook to resolve each acid into its optical isomers.

Part II. The Optically Active Acids

Introduction

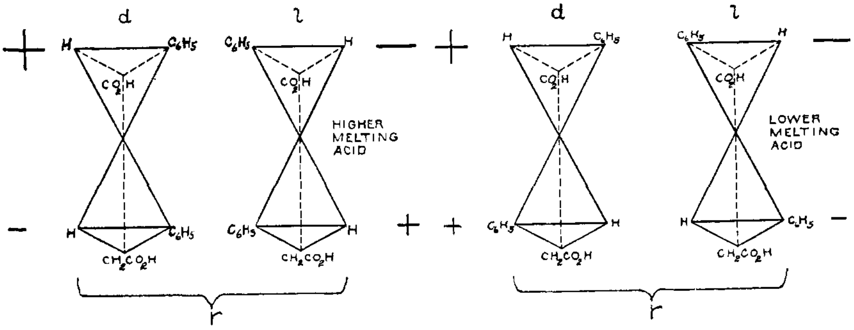
The general formula of all isomeric α,β-diphenylglutaric acids, $HOOCCH_2CH(C_6H_5)CH(C_6H_5)COOH$, shows two asymmetric carbon atoms of unequal effect on polarized light. The α-atom has without question the greater capacity for specific rotation.[8] Indicating this optical difference by the size of the signs employed, we have the following possibilities

$$HOOCCH_2CH(C_6H_5)CH(C_6H_5)COOH$$

$$\left.\begin{array}{lcc} d & \boldsymbol{\Large +} & - \\ l & \boldsymbol{\Large -} & + \end{array}\right\} r \qquad \left.\begin{array}{lcc} d & \boldsymbol{\Large +} & + \\ l & \boldsymbol{\Large -} & - \end{array}\right\} r$$

The higher-melting acid (m. p. 226–228°), as the experimental part of this paper will show, has been resolved, through fractional crystallization of the brucine salt, into isomers, one showing a *d*-rotation of 58.7°, and one showing a similar *l*-rotation.

The lower-melting acid (m. p. 208–210°) has also been resolved into isomers, one showing a *l*-rotation of 140.7°; the other showing a *d*-rotation of approximately the same amount. Hence it follows that the higher-melting acid (m. p. 226–228°) is a racemic form of the $\boldsymbol{\Large +}\ -;\ \boldsymbol{\Large -}\ +$ type. The lower 208–210° acid is a racemic acid of the $\boldsymbol{\Large +}\ +;\ \boldsymbol{\Large -}\ -$ type. The conclusion is then that there are in all six isomers, two inactive and four active. These may be expressed in another way, as indicated.



Experimental Part

Resolution of the Higher-Melting Acid.[9]—Thirty grams of finely powdered α,β-

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[8] Compare $C_6H_5CH(OH)COOH$, +157°, *Ber.*, **37**, 3176 (1904), with $C_6H_5CH(OH)CH_2COOH$, +19, *ibid.*, **39**, 790 (1906).

[9] Compare Wren and Still, *J. Chem. Soc.*, **107**, 444 (1915).

diphenylglutaric acid (226–228°) was thoroughly mixed with 82.8 g. of anhydrous brucine and stirred with 6000 cc. of water on a boiling water-bath until practically all of it had gone into solution. The temperature of the solution was kept below 80°. After filtration, the solution was allowed to cool. At the end of four days the crop was filtered and allowed to dry on a porous plate; yield, 67.5 g.

This material was recrystallized from hot water, 30 cc. of the solvent being used for each gram of the salt. The course of the resolution was followed by determining the specific rotation of the acid obtained from the successive filtrates. The values for the rotations of these filtrates made in acetone solution were as follows: −12.5°, −4.2°, +36.3°, +45.4°, +50.6°, +56.4°, +57.0°.

The crop from which the last filtrate was obtained, consisting of long well-defined prisms with pointed ends and weighing 5.5 g., was dissolved in hot water and decomposed with hydrochloric acid. 1.5 g. of *d*-α,β-diphenylglutaric acid was isolated, the specific rotation in acetone solution being as follows: $[\alpha]_D^{20}$, +58.7° (1 g. in 25 cc. of soln. gave, in a 1-dcm. tube, +2.35°). The rotation of this acid remained unchanged after further recrystallization.

d-α,β-Diphenylglutaric acid crystallizes from dilute ethyl alcohol in fine, hair-like crystals with a melting point of 224–226°. It is slightly soluble in hot water and benzene, and exceedingly soluble in ethyl alcohol, methyl alcohol, acetone and ethyl acetate. The solubilities shown by this acid are much greater than those of the inactive acid.

The brucine salt of the *l*-α,β-diphenylglutaric acid being more soluble than the salt of the *d*-α,β-diphenylglutaric acid, the usual difficulties were encountered in obtaining the acid in a pure form. However, a levorotatory acid that was practically pure was obtained in the following manner: the filtrate from the first crop of brucine salt was concentrated under reduced pressure to 3000 cc. and allowed to crystallize. The crop was filtered, the filtrate concentrated to 1000 cc. in the same way and again allowed to crystallize; 34 g. of the crude levorotatory brucine salt was thus obtained. This salt was recrystallized from hot water until when viewed through the microscope it was found to be uniform in crystalline structure. The crystals were short, well-formed prisms with beveled edges. The crop was dissolved in water and decomposed with hydrochloric acid. The acid was recrystallized from dilute ethyl alcohol and gave a specific rotation in acetone solution as follows: $[\alpha]_D^{20}$, −58.0° (0.172 g. in 25 cc. soln. gave in a 1-dcm. tube −0.40°). The rotation of this acid remained unaltered with further recrystallization.

l-α,β-Diphenylglutaric acid recrystallizes from dilute ethyl alcohol in fine hair-like crystals similar to those of the *d*-acid. It also exhibits solubility properties analogous to those of its antipode. The melting point of the *l*-acid was slightly lower than that of the *d*-acid.

Racemization of the Active Acids.—Equal quantities of the *d*- and *l*-α,β-diphenylglutaric acids were placed together and recrystallized several times from dilute ethyl alcohol. The acid crystallized in long needles with a melting point of 226–228°. It was optically inactive and exhibited all the properties of the acid from which its component parts were originally derived.

Resolution of the Lower-Melting Acid.—The procedure was in general similar to that employed in resolving the isomer. The brucine salt of the *l*-acid first separates out in the form of diamond-shaped plates. On condensing the mother liquor after the plates have been filtered off, the brucine salt of the *d*-acid appears in the form of prisms.

Twenty grams of the impure plates containing a small percentage of prisms and some coloring matter was dissolved in 5% alcohol, boiled with charcoal and filtered. On cooling, colorless plates nearly free from prisms separated out. These were dissolved again in hot dilute alcohol and permitted to crystallize. The process was repeated about twenty times from dilute alcohol and finally several times from water until samples of acid recovered from successive filtrates showed no change in rotation.

The acid was recovered from the filtrates by condensing to a small volume, acidifying with hydrochloric acid, extracting with ether and recrystallizing from very dilute alcohol slightly acidulated with acetic acid.

The samples of acid from the first few filtrates appeared as prisms, then as scales without definite form and later as flattened needles. The specific rotation passed rapidly with the successive recrystallizations from +12° to −130°, still more slowly to −140°, where it remained practically constant. There now remained 5 g. of the brucine salt, which was converted into the acid and recrystallized from dilute alcohol slighty acidulated with acetic acid.

l-α,β-Diphenylglutaric acid thus prepared gave a specific rotation in acetone as follows: $[\alpha]_D^{20}$, −140° (1.0 g. in 25 cc. of soln. gave in a 1-dcm. tube −5.63°). It crystallizes from hot dilute alcohol or acetic acid as long, flattened needles; m. p. 202°. The solubilities shown by this acid are much greater than those of the inactive acid from which it was resolved.

Titration of the *l*-acid: 0.1006 g. required 7 cc. of *N*/10 NaOH. Calcd.: 7.1 cc.

The corresponding *d*-acid was prepared as follows: 10 g. of the brucine salt, mostly prisms, previously mentioned as coming from the first filtrate after the first crop of diamond-like plates had been filtered off, was recrystallized from water until an admixture of diamond-shaped plates could no longer be detected by the microscope.

At this point the filtrates from the later recrystallizations were in turn decomposed and recrystallized as in the case of the *l*-acid. This process was repeated until a specific rotation of about +140° was observed in several successive samples. These latter samples were in turn recrystallized from dilute alcohol containing a drop of acetic acid. The *d*-acid thus obtained recrystallized in long flattened needles giving a melting point of 202°. *d*-α,β-Diphenylglutaric acid thus prepared gave a specific rotation in acetone as follows: $[\alpha]_D^{20}$ +140.6° (0.2188 g. in 25 cc. of solution gave in a 1-dcm. tube +1.23°).

Titration of the *d*-acid: 0.1848 g. required 12.9 cc. of *N*/10 NaOH. Calcd.: 13 cc.

The *l*-acid recrystallized with an equal weight of the *d*-acid showed all the properties of the 208–210° form from which the *l*- and the *d*-acid were resolved.

Acknowledgments.—To Dr. F. W. Upson we are especially indebted for suggesting the resolution, into their optical isomers, of the acids under consideration and for constructive criticism. Mr. R. M. Sandstedt has rendered us the favor of making the nitrogen determinations. Mr. Clifford Carr has greatly assisted in laboratory work generally and has made the combustions and titrations.

Summary of Part II

Both of the stereoisomeric acids considered in Part I have been resolved into optically active acids. Names for the six acids, now all definitely known, are suggested as follows.

Proposed Names

For the higher-melting acid (226–228°)		For the lower melting acid (208–210°)	
αd,βl − *αl,βd*-Diphenylglutaric acid (*i*), the r form of		*αl.βl* − *αd,βd*-Diphenylglutaric acid (*i*), the r form of	
αd,βl-Diphenylglutaric acid	(*d*) and	*αl,βl*-Diphenylglutaric acid	(*l*) and
αl,βd-Diphenylglutaric acid	(*l*)	*αd,βd*-Diphenylglutaric acid	(*d*)

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