

## Optically Active $\alpha,\alpha'$ -Diethylglutaric Acids and their Anhydrides

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The  $\alpha,\alpha'$ -diethylglutaric acid,  $\text{HOOC} \cdot \text{CH}(\text{C}_2\text{H}_5) \cdot \text{CH}_2 \cdot \text{CH}(\text{C}_2\text{H}_5) \cdot \text{COOH}$ , was first described by Dressel<sup>1</sup> who apparently had in hand a mixture only of the isomeric forms. Auwers<sup>2</sup> succeeded in isolating the high-melting acid in a pure state while the other was obtained as a low-melting mixture with the first one. Reformatsky<sup>3</sup> later prepared both acids in the pure state and found the melting points  $119.5\text{--}120^\circ$  and  $93.5\text{--}94.5^\circ$ , respectively. By treatment with acetyl chloride the high-melting acid was transformed into a liquid anhydride but no anhydride of the low-melting acid was described.

No report has been given of an optical resolution of any of the acids and it could not therefore be decided which was the meso- and which the racemic form. We have prepared both the inactive acids according to the method used by Auwers<sup>2</sup> and found the same melting points as given by Reformatsky. All attempts to resolve optically the high-melting acid by fractional crystallization of an alkaloid salt failed. On the other hand we were able by means of the brucine salt, and also the cinchonidine salt, to resolve the low-melting acid into active components having a specific rotation in ethanolic solution of about  $\pm 30.3^\circ$  and m.p.  $75.5\text{--}76.5^\circ$ . From the form of the melting point curve between the antipodes it can be concluded that the inactive acid is a true racemic form.

The active acids were easily converted into the corresponding active anhydrides without any racemization taking place. The sign of the rotation changed, however, when passing from an active acid into its anhydride and *vice versa*. The highest specific rotation found for an anhydride was  $-24.6^\circ$ . The anhydrides were obtained as liquids which could be distilled in a vacuum without diminishing their optical rotation.

### EXPERIMENTAL

#### Preparation of the inactive acids

The ethyl ester of propane-1,1,3,3-tetracarboxylic acid was prepared mainly according to Knoevenagel<sup>4</sup> by condensation of malonic ester and formaldehyde using diethylamine as a catalyst. The yield was about 50 %. The method used by Dressel<sup>1</sup> was also tried, *viz.* the reaction between sodium malonic ester and methylene iodide. The yield was about the same but as the first method was the easier to carry out it was preferred.

The ethylation of the propanetetracarboxylic ester was effected by treatment with sodium ethoxide and ethyl iodide as described by Auwers<sup>2</sup>. The crude reaction product was obtained in a yield of about 50 % as a colourless crystalline mass with m.p. 58–61° which was used directly for further reactions. If desirable it could be recrystallized from ether and was then obtained as clear crystals with m.p. 60–61°.

The hydrolysis of the ethyl-substituted tetracarboxylic ester and the subsequent decarboxylation to dicarboxylic acid were carried out in one operation, mostly in the following way. The ester (20 g) was dissolved in concentrated sulphuric acid (35 ml) and adding water (35 ml) most of the ester separated as a layer on top of the acid. The mixture was then refluxed until practically all ester had disappeared which took 25–30 hours. On cooling a mixture of the acids was obtained as a crystalline mass in a yield of 90–95 %.

The separation of the two inactive acids from the crystalline mass melting from 70° to 100° was a rather difficult and tedious process. Several methods were tried but the only useful one was repeated fractional crystallization alternately from water and benzene. As an example may serve the following. A solution of 10 g of the crystalline mass in 140 ml water was decolorized by boiling with charcoal. On cooling crystals rich in the high-melting form and having m.p. 113–117° soon separated and were filtered off the next day. The mother liquor left at room temperature for a couple of days gave a new fraction of crystals having the m.p. 85–90°. The mother liquor from these crystals was concentrated somewhat when more crystals rich in the high-melting acid were obtained. This process was continued until in all 4 g of an acid rich in the highmelting form and 4 g rich in the low-melting form had been obtained. The material from several experiments was collected and the further purification carried out by continued fractional crystallization either from water or from benzene. The purest high-melting acid had m.p. 119–120°.

0.2061 g required 21.92 ml 0.1 N NaOH, M 188.1; calc. M 188.2.

The isolation of the pure low-melting acid was successful only when the initial separation of the mixture of the acids resulted in a fraction sufficient rich in the low-melting acid. Then repeated crystallizations from water and benzene in the end led to an acid with m.p. 93.5–94.5°.

0.1740 g required 18.48 ml 0.1 N NaOH, M 188.2

Both acids were very soluble in ether, acetone, methanol, ethanol, chloroform and glacial acetic acid.

In the case of  $\alpha,\alpha'$ -dimethylglutaric acid Möller<sup>5</sup> found that the meso-form but not the racemic form gave an anhydride on treatment with acetyl chloride (quite unaccountably he at the same time found that both the active components of the racemic form were transformed into anhydrides under the same conditions). If the isomeric forms of the  $\alpha,\alpha'$ -diethylglutaric acid behaved in the same way it should be possible to separate the meso-form from the racemic form by means of acetyl chloride. It was, however, found that both the inactive isomerides of  $\alpha,\alpha'$ -diethylglutaric acid on heating with acetyl chloride easily gave the corresponding anhydrides. The anhydrides formed liquids which boiled at 154–155°, at 15 mm Hg. Starting with an acid-mixture having m.p. 88–91° the acid-mixture recovered from the distilled anhydrides had m.p. 90–91° which showed that no separation of the isomerides was effected in this way.

### Resolution of the racemic acid

In a warm solution of 10 g  $\alpha,\alpha'$ -diethylglutaric acid with the m.p. 93.5–94.5° in 240 ml water 21 g of brucine (a little less than 1 mole alkaloid to 1 mole acid) were dissolved in portions. Placing the solution in a refrigerator and inoculating with crystals from a preliminary experiment 10.4 g brucine salt of the (+)-acid crystallized in the course of two days. After recrystallizing once from water the salt was dissolved in hydrochloric acid and the active acid extracted with ether.

$$[\alpha]_D^{20} = +28.74^\circ \quad (p = 4.02 \text{ in abs. ethanol})$$

On concentrating the mother liquor some more salt of the (+)-acid was obtained. From the rest of the solution a levorotatory acid (3 g) was obtained having a specific rotation of  $-19.4^\circ$ .

In another case, starting with 14 g of racemic acid, the least soluble brucine salt was recrystallized 6 times from water. The acid isolated from this salt had the specific rotation  $+29.5^\circ$ . A new treatment with brucine did not lead to an increase of the rotation.

In the mean time it had been found that the cinchonidine salt (1 mole alkaloid to 1 mole acid) crystallized well from acetone. Also in this case the salt of the (+)-acid crystallized first. In a series of experiments in which the cinchonidine salt had been recrystallized 1, 3 and 6 times from acetone the following specific rotations for the acid were found:  $+29.03^\circ$ ,  $+29.65^\circ$  and  $+30.75^\circ$ . A final treatment of the acid  $+30.75^\circ$  with cinchonidine resulted in an acid with rotation  $+30.3^\circ$ . This active acid on recrystallization from water was obtained in well-developed flat prisms with m.p.  $75.5-76.5^\circ$ .

$$[\alpha]_D^{20} = +30.33^\circ \quad (p = 4.0 \text{ in abs. ethanol})$$

In order to determine the specific rotation at various concentrations it was necessary to measure the variation of the specific gravity with concentration. The results obtained, using the racemic acid, are given in Table 1 in which  $p$  denotes g acid in 100 g ethanolic solution.

Table 1. Specific gravity of solutions of racemic acid in ethanol.

$p$	$d_4^{20}$
0	0.791
3.94	0.801
10.21	0.816
13.52	0.824
21.17	0.843
39.15	0.889

According to these figures the relationship between specific gravity and percentage is practically linear.

The specific rotation of the (+)-acid at various concentrations will be found in Table 2.

Table 2. Specific rotation of (+)- $\alpha,\alpha'$ -diethylglutaric acid in abs. ethanol.

$p$	$d_4^{20}$	$l$	$\alpha_D^{20}$	$[\alpha]_D^{20}$
4.014	0.801	2	+ 1.95°	+ 30.33°
10.29	0.816	2	5.09	30.30
13.26	0.824	2	6.63	30.33
21.26	0.844	2	10.92	30.44
40.86	0.893	1	11.36	31.13
49.09	0.914	1	14.12	31.47
57.41	0.936	1	17.34	32.26

The isolation of pure levorotatory acid was successful only once. In that case 0.9 g of a levorotatory acid isolated from the light soluble cinchonidine salt was dissolved in 10 ml hot water and 1 ml 2 *N* hydrochloric acid added to the cooled solution. The next day a crystalline acid was filtered off consisting mostly of racemic acid (m.p.  $89-91^\circ$ ). When the filtered solution had been left for another day some rather big rhombic crystals had separated (0.2 g). Recrystallized from water the m.p. was  $75.5-76.5^\circ$ .

$$[\alpha]_D^{20} = -30.34^\circ \quad (p = 3.54 \text{ in abs. ethanol})$$

By other experiments the (-)-acid isolated always had a lower rotation ( $-20$  to  $-27^\circ$ ). As shown by the melting point curve in Fig. 1 the inactive acid is a true racemic form.

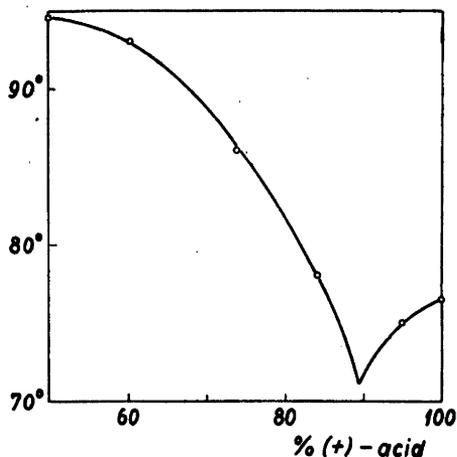


Fig. 1. Melting points of mixtures of (+)- and (-)-*a,a'*-diethylglutaric acids

### The optically active anhydrides

The active acid (0.5 g) to which had been added acetyl chloride (3 g) was heated to 50–60° for 2 hours. After removing excess of acetyl chloride the anhydride was distilled in a vacuum. None of the anhydrides would crystallize. Starting with pure (+)-acid a levorotatory anhydride with the following rotation was obtained:

$$[\alpha]_D^{20} = -24.64^\circ \quad (p = 4.975 \text{ in dioxan})$$

The specific rotation of the acid recovered from this anhydride was +30.56°, showing that no racemization had taken place during the preparation of the anhydride. From a (-)-acid with specific rotation -20.24° an anhydride was prepared having the rotation +13.75° ( $p = 4.36$  in abs. ethanol). The acid recovered from this anhydride had the specific rotation -19.91°.

### SUMMARY

Of the two inactive *a,a'*-diethylglutaric acids with m.p. 119–120° and 93.5–94.5°, respectively, the low-melting was found to be the racemic form. It was resolved into optically active components having the specific rotations  $\pm 30.3^\circ$ . The two inactive as well as the active acids were converted into the corresponding anhydrides. On preparing the anhydride of an active acid the sign of the rotation changed but no racemization took place. The highest specific rotation observed for an anhydride was -24.6°.

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