Anal. Calcd. for $C_{15}H_{13}NO_3$: N, 5.49. Found: N, 5.38.

Oxime of II.—This was prepared in the usual way; yield 80%; colorless needles, m. p. 241–242°, crystallized from alcohol.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: N, 10.37. Found: N, 10.21.

3-Hydroxy-3-(nitromethyl)-beta-naphthoxindole (III).—A mixture, cooled in ice, was made of 1.0 g. of beta-naphthisatin, 0.35 g. of nitromethane, 3 drops of diethylamine, and 10 cc. of absolute ethyl alcohol. After twenty-four hours at room temperature white needles separated, which were purified by precipitation from acetone by slow addition of ligroin. III is unstable toward heat in solution, making purification by recrystallization difficult; yield, crude, 84%; m. p. 246–248°, with decomposition.

Anal. Calcd. for $C_{13}H_{10}N_2O_4$: N, 10.85. Found: N, 10.76.

Summary

Beta-naphthisatin reacts with acetone, acetophenone, and nitromethane to yield the corresponding aldol-like condensation products. The acetophenone product is dehydrated in the normal manner by treatment with mineral acid; further acid treatment causes the formation of beta-naphthcinchophen.

NEW YORK, N. Y. RECEIVED NOVEMBER 20, 1934

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

Isomeric α-Cyano-α-methyl-β-phenylglutaric Acids and their Derivatives

BY S. AVERY AND FRANK C. MCGREW

In the course of an investigation of substituted glutaric acids in general, with the aim of studying stereoisomerism in these and related compounds, Avery and Fossler[1] prepared α-methyl-β-phenylglutaric acid by Michael's reaction, linking methyl α-methylcinnamate with ethyl malonate in the presence of sodium ethoxide, subsequently saponifying, and decarboxylating the acid thus formed. The method, however, was unsatisfactory in that little of the pure product was obtained.

Carter and Lawrence[2] prepared this acid by a similar condensation using ethyl cinnamate and ethyl cyanoacetate, with subsequent methylation, hydrolysis and decarboxylation. Certain of the intermediate compounds were isolated and structures assigned to them; the isomerism noted was explained partly on stereochemical and partly on other structural grounds.

The present authors, in elaboration of the work of Carter and Lawrence, began with the same condensation. The product consisted of the two stereomeric esters, the initial substances which afford by hydrolysis under various conditions, two series of compounds, each member of which was found similar in constitution to the parallel substance of the other series, the only differences being those physical properties affected by different spatial configurations. In this communication the terms A and B series will be used instead of the α and β of Carter and Lawrence to avoid misunderstanding of the significance of the Greek letters. The conventional *trans* and *cis* terms are not used, since in the present work most of the spatial differences are not analogous to the type of isomerism exhibited by unsaturated compounds.

The A acid, prepared from the solid ethyl α-cyano-α-methyl-β-phenylglutarate by hydrolysis in absolute alcohol solution with potassium hydroxide, on treatment with acetyl chloride forms a compound melting at 111° which was shown by analysis to be not an acetylated imide, as supposed by Carter and Lawrence, but the anhydride of a dicarboxylic acid, stereomeric with the anhydride of the corresponding B cyano acid. From this fact and from the easy conversion of the A acid into the original 90° melting ester by esterification, it is established that the A acid is stereomeric with the B acid and has not the cyclic structure previously advanced.

The A and B cyano acids were subjected to resolution into their optically active enantiomorphs by fractional crystallization of the brucine salts. The A acid gave two isomers of melting point 185–187° (dec.) and $[\alpha]_D$ +7.4° and $[\alpha]_D$ −7.5°. The B acid was resolved into two isomers of melting point 164–165° (dec.) and $[\alpha]_D$ +32.4° and $[\alpha]_D$ −32.1°.

Efforts to prepare the tricarboxylic acid of Carter and Lawrence by alkaline hydrolysis gave only a tricarboxylic acid melting approximately at 188°, depending on the rate of heating,

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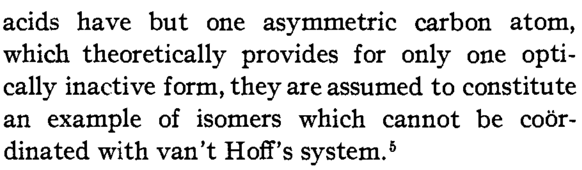
[1] Avery and Fossler, *Am. Chem. J.*, **20**, 516 (1898).

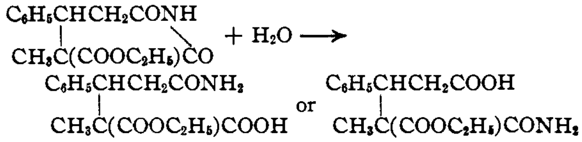
[2] Carter and Lawrence, *Proc. Chem. Soc.*, **16**, 178 (1900).

which is believed to be identical with the acid obtained by Michael and Ross.[3] By following the procedure of Dr. Ross,[4] but in the absence of detailed instructions, the unstable form melting at 148° could not be obtained. Since these two acids have but one asymmetric carbon atom, which theoretically provides for only one optically inactive form, they are assumed to constitute an example of isomers which cannot be coördinated with van't Hoff's system.[5]

By hydrolysis of the original A and B esters in acid solution new series of A and B compounds were formed. Each ester gave an ester-imide with a cyclic structure.



Homologous compounds were formed by the hydrolysis, under the same conditions, of the isomeric methyl esters. The same partial hydrolysis was attempted in the analogous series of α-cyano-α,β-dimethyl-, the α-cyano-α-benzyl-β-methyl-, and α-cyano-α-benzyl-β-phenylglutaric esters. Only the first of these three gave the ester-imide type of compound. The fact that the hydrolysis can be interrupted at this intermediate point indicates a steric effect of the α-methyl radical which other α-radicals do not have. Treatment of these ester-imides with potassium carbonate was found to open the ring giving the expected ester-amide-acids.



By the acid hydrolysis of either of the original condensation products or their derivatives, there was formed α-methyl-β-phenylglutaric acid, melting at 127°, along with an oil-like substance from which, by extraction with very dilute acetic acid, crystals melting at 115–117° were obtained. Titration of this 115–117° substance indicated that it was an isomer of the 127° acid or an isomeric mixture. Treatment of the 115–117° body with acetyl chloride at the temperature of the water-bath and subsequent hydrolysis yielded the original substance unchanged; however, by protracted heating in a sealed tube at 140° the greater portion was changed to the anhydride of the 127° acid. This deportment is similar to that observed in the case of the α,β-diphenylglutaric acids, the lower melting acid readily forming its anhydride, while the higher melting acid is changed to the anhydride of the lower melting one by heating with acetyl chloride at a higher temperature. If then we assume that the 127° acid is the "lower melting," "B," "*cis*," or "maleinoid" form, and the 115–117° body is a mixture of an unisolated "higher melting," "A," "*trans*," or "fumaroid" form with a small amount of the 127° acid, the properties and deportment of the 115–117° substance are exactly as might have been anticipated. Isomeric mixtures that melt fairly constantly, even after repeated recrystallization, at a temperature lower than the melting point of either constituent are by no means uncommon. The 115–117° substance mixed with an equal amount of the pure 127° acid melted at 108–110°, thus indicating that this body contained more of the unisolated isomer than of the 127° acid. Recrystallization of the brucine salt of the 127° acid did not resolve it into its optical isomers.

Repeated attempts to obtain the "double anhydride with acetic acid" of Carter and Lawrence gave negative results and it is apparent that, if this substance exists, it forms only when precisely the right conditions are achieved.

In an effort to discover compounds of the type under consideration but more readily separable into stereomers, the α-cyano derivatives of α,β-dimethyl-, α-ethyl-β-phenyl-, α-benzyl-β-methyl-, α-benzyl-β-phenyl-, α-isopropyl-β-phenyl-, α-methyl-β-*p*-tolyl-, and β-phenyl-γ-methylglutaric esters were prepared by methods similar to those previously used. In these cases, as well as the methyl, *n*-propyl and *n*-butyl esters of the A and B α-cyano-α-methyl-β-phenylglutaric acids, no crystalline ester could be isolated whose tendency to crystallize was as pronounced or whose melting point was as high, as that of the 90°A. ethyl α-cyano-α-methyl-β-phenylglutarate. Most of these condensations were carried out by Mr. Herman Koch. Since the data concerning the products are not complete at this time, they are not considered further in this communication.

Experimental Part

Isomeric Acid Potassium α-Cyano-α-methyl-β-phenylglutarates.—When the calculated amount of acetic acid

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(3) Michael and Ross, THIS JOURNAL, **52**, 4598 (1930).

(4) Ross, private communication.

(5) Michael and Ross, THIS JOURNAL, **55**, 1638 (1933).

was added to a concentrated aqueous solution of either the A or B normal potassium salt, the acid salt was precipitated. The solubilities of these salts are such that they can be purified readily by recrystallization from water.

Anal. Calcd. for $C_{13}H_{12}O_4NK$: K, 13.71. Found: (A) K, 13.56; (B) 13.75.

A α-Cyano-α-methyl-β-phenylglutaric Anhydride.—The A acid, on dissolving in acetyl chloride, evaporating nearly to dryness and crystallizing from isopropyl ether, gave a pure anhydride, m. p. 111°. When an aqueous solution of this substance was distilled, no acetic acid was detected in the distillate, although the A acid melting at 164° was obtained quantitatively from the residue.

Anal. Calcd. for $C_{13}H_{11}O_3N$: C, 68.09; H, 4.84; N, 6.12. Calcd. for $C_{15}H_{15}O_5N$: C, 62.26; H, 5.23; N, 4.85. Found: C, 67.97; H, 5.05; N, 6.12.

Esterification of A α-Cyano-α-methyl-β-phenylglutaric Acid.—Two grams of the 164° acid was suspended in 10 cc. of absolute ethyl alcohol and saturated with dry hydrogen chloride. After standing for fifteen hours, this mixture was poured into water and crystals separated out which melted at 90° and were identical with the original A ester. This reaction shows the constitution assigned to the 164° acid by Carter and Lawrence to be untenable.

Enantiomorphic A α-Cyano-α-methyl-β-phenylglutaric Acids.—The resolution was carried out by repeated fractional crystallization of the brucine salt from aqueous solution. The least soluble salt formed crystals of a pyramidal shape and gave the dextrorotatory acid, $[\alpha]_D$ +7.4°. The more soluble salt crystallized in hairy needles and afforded the levo acid, $[\alpha]_D$ −7.5°. Both optically active acids crystallized in rectangular blocks melting at 185–187° (dec.). When equal weights of the two were dissolved together and evaporated to dryness, the A acid, m. p. 164°, was formed.

Enantiomorphic B α-Cyano-α-methyl-β-phenylglutaric Acids.—The B acid, which crystallized readily from water, was difficult to resolve. The brucine salt gave two crystalline forms which were not easily distinguishable under the microscope. The less soluble salt crystallized in slender plates with beveled ends and gave the dextrorotatory acid, $[\alpha]_D$ +32.4°. The more soluble salt crystallized in needles and afforded the levo acid, $[\alpha]_D$ −32.1°. Both optically active acids crystallized in clusters of needles melting at 164–165° (dec.). When equal weights of the two were dissolved together and evaporated to dryness, the B acid, m. p. 194°, was formed.

α-Carboxy-α-methyl-β-phenylglutaric Acid.—By heating any of the cyano derivatives or "ester-imides" of either series with potassium hydroxide solution, and extracting with ether after acidification, the tricarboxylic acid was produced. From a mixture of acetone, chloroform and ligroin, or from benzene, the ether extract yielded crystals that could be further purified by recrystallizing from water. The acid melted with the evolution of carbon dioxide at approximately 188° (176–190°) depending on the rate of the rise of temperature. No crystalline product melting at approximately 148° could be isolated from any of the filtrates. Even when pure, however, the highest melting sample was found to be slowly decarboxylated when heated in a drying oven above 125°, yielding a gum-like mass from which α-methyl-β-phenylglutaric acid could be obtained. When heated in a sealed tube in water solution at 175°, α-methyl-β-phenylglutaric acid (m. p. 127°) was formed quantitatively.

Isomeric α-Carbethoxy-α-methyl-β-phenylglutarimides.—The A compound was prepared as follows. Five grams of the A ethyl α-cyano-α-methyl-β-phenylglutarate, 10 g. of glacial acetic acid and 25 g. of 18 normal sulfuric acid were refluxed for fifteen minutes. The solution was then poured into about 200 cc. of cold water with stirring and allowed to crystallize. After filtering and drying, the product weighed 2 g.; 28% of the starting material was recovered. Boiling for a longer time failed to increase the yield because of hydrolysis of this product. Crystallized from chloroform and isopropyl ether, it gave needles melting at 149° (corr.).

The corresponding B compound was prepared in exactly the same way from the liquid B ester. On crystallization from chloroform and isopropyl ether, it gave prisms melting at 128–129°.

Anal. Calcd. for $C_{16}H_{17}O_4N$: C, 65.42; H, 6.23; N, 5.09. Found: (A) C, 65.30; H, 6.24; N, 5.05; (B) C, 65.29; H, 6.22; N, 5.06.

Isomeric α-Carbomethoxy-α-methyl-β-phenylglutarimides were formed by this interrupted acid hydrolysis of the isomeric methyl esters. The A crystallized in needles; m. p. 172–173°. The B crystallized in plates melting at 167–169°.

Anal. Calcd. for $C_{14}H_{15}O_4N$: C, 64.34; H, 5.79; N, 5.36. Found: (A) C, 64.22; H, 5.81; N, 5.47; (B) C, 64.18; H, 5.79.

Isomeric α-Carbethoxy-α-methyl-β-phenylglutaramides.—Five-tenths gram of the A α-carbethoxy-α-methyl-β-phenylglutarimide was boiled with 0.3 g. of anhydrous potassium carbonate dissolved in very dilute alcohol. After boiling for half an hour, the alkaline solution was acidified with a slight excess of acetic acid and concentrated. On cooling, crystals in the form of prisms separated out, which melted at 163–164° after recrystallization from water. The B isomer was prepared in the same way from the **B** imide. It crystallized in long rod-like prisms and melted when pure at 168–170°. Each of these glutaramides, upon boiling for a few minutes with concentrated hydrochloric acid, formed again the imide from which it was prepared.

Anal. Calcd. for $C_{15}H_{19}O_5N$: C, 61.40; H, 6.53. Found: (A) C, 61.64; H, 6.62; (B) C, 61.54; H, 6.67.

Isomeric α-Methyl-β-phenylglutaric Acids.—Heating of the A or the B α-cyano-α-methyl-β-phenylglutaric ester, acid, or any of its derivatives and intermediate hydrolysis products, with acetic acid and hydrochloric acid to 150° in a sealed tube for several hours gave a product that on repeated recrystallization from benzene, and from water, melted at 127°, and was found to be identical with the acid previously prepared in less pure condition by Avery and Fossler, m. p. 122°, and Carter and Lawrence, m. p. 125°. From the filtrate an oil was obtained which was best crystallized from very dilute acetic acid. After numerous recrystallizations, needles were obtained melting at 115–117°.

Titrations. 127° acid: 0.0602 g. required 5.43 cc. of 0.1 *N* NaOH. Calcd.: 5.42 cc. 115–117° acid: 0.0992 g. required 8.95 cc. of 0.1 *N* NaOH. Calcd.: 8.93 cc.

Thirteen grams of the pure 127° acid was distilled in vacuum. The distillate upon hydrolysis and crystallization from water and from benzene yielded 10 g. of the original acid and about 3 g. of an oil-like substance from which the 115–117° body could be isolated.

The pure 127° acid was obtained in quantitative yield by the following procedure. One gram of α-carboxy-α-methyl-β-phenylglutaric acid was heated in a sealed tube in 30 cc. of water for one-half hour at 140–150°, the carbon dioxide removed, and the solution heated as above for two more hours at 175°. In the final product no trace of an oil was detected.

The authors are indebted to Mr. Hubert Liehe and especially to Mr. Herman Koch for assistance in the preparation and identification of certain of the compounds mentioned in this paper. To Dr. W. E. Craig is due the credit for checking and extending the work on the optically active compounds and the tricarboxylic acid.

Summary

1. The action of cold alcoholic potassium hydroxide on the stereomeric ethyl α-cyano-α-methyl-β-phenylglutarates is that of simple saponification leading to stereomeric acids. It does not in the case of the A (α or *trans*) series yield a salt of α-carboxy-α-methyl-β-phenylglutarimide as Carter and Lawrence believed. The derivatives formed by the action of acetyl chloride on the acids are true anhydrides. The A acid does not yield an acetylated imide.

2. The two racemic stereomeric α-cyano-α-methyl-β-phenylglutaric acids have been resolved into their optically active components.

3. The methyl group in the alpha position has been found to have an inhibiting effect on the hydrolysis in acid solution of substituted α-cyanoglutaric esters. Two stereomeric methyl and two ethyl esters of α-carboxy-α-methyl-β-phenlyglutarimide were formed by inhibited hydrolysis and from them the corresponding monoamides were obtained.

4. The compounds under consideration on complete saponification lead to α-methyl-β-phenylglutaric acid and an oil-like substance. From the latter a crystalline product believed to be a mixture of isomers has been obtained.

5. The mixture of esters originally synthesized by Carter and Lawrence and their derivatives were found more easily separable into stereomers than any of a number of similar esters containing other groups.

LINCOLN, NEBRASKA RECEIVED NOVEMBER 22, 1934

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BARNARD COLLEGE]

Addition Reactions of Unsaturated Alpha-Ketonic Acids. IV

BY MARIE REIMER, ELISE TOBIN AND MARGARET SCHAFFNER

In former papers of this series it has been shown that the behavior of benzalpyruvic acid and its bromination products is influenced to a marked degree by the introduction of a methoxyl group in different positions in the benzene ring. A recent study[1] of *m*-methoxybenzalpyruvic acid shows, for example, that it differs in many ways from its para isomer. *p*-Methoxybenzalpyruvic acid[2] is unaffected by light; it readily combines with solvents of crystallization, forms a fairly stable dibromide from which a hydrated, unsaturated bromo compound can be prepared; the acid and all its derivatives give brilliant color reactions with concentrated sulfuric acid. *m*-Methoxybenzalpyruvic acid, on the other hand, is sensitive to light; its dibromo addition product is relatively unstable; the acid and its bromination products are not hydrated in solution and the latter form no brilliantly colored complexes with concentrated sulfuric acid. Because of these differences, the behavior of the ketonic acid with both a meta and a para methoxyl group in the same molecule becomes of interest. Since the 3,4-dimethoxyphenyl group is a common one in many natural products[3] a study of the influence of methoxyl groups in these positions may not be without wider significance. The present paper describes results obtained with 3,4-dimethoxybenzalpyruvic acid.

In earlier work, methoxycinnamic acids corresponding to the ketonic acids under observation have been prepared for purposes of identification

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[1] Reimer and Kamerling, THIS JOURNAL, **55**, 4643 (1933).

[2] Reimer, *ibid.*, **48**, 2454 (1926).

[3] R Robinson, *J. Chem. Soc.*, **111**, 894 (1917); Schoepf and Bayerle, *Ann.*, **513**, 190 (1934).