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

ISOMERIC ALPHA,BETA-DIPHENYL-DELTA-KETONIC ACIDS. I[1]

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Introduction

α,β-Diphenylglutaric acids, the isomerism of which has been explained by Avery and Maclay,[2] have, in so far as their asymmetric carbon atoms are concerned, a structure similar to α,β-diphenyl-δ-ketonic acids, as the following comparison shows.

Glutaric acids $CO(OH)CH_2CH(C_6H_5)CH(C_6H_5)CO_2H$
Ketonic acids $CO(R)CH_2CH(C_6H_5)CH(C_6H_5)CO_2H$

It is to be anticipated, therefore, that a careful study of isomeric δ-ketonic acids will disclose many points of similarity between these compounds and the corresponding δ-carboxylic or glutaric acids. By analogy it should be possible to synthesize two optically inactive stereoisomers in the case of each ketonic acid. These acids should form two definite series of isomeric derivatives, as nitriles and esters. The preparation of such compounds would add convincing evidence of the correctness of the explanation of stereoisomerism in the glutaric series. Finally, as in the glutaric series, it should be possible to resolve each inactive acid into its optical isomers. The present paper, however, deals with inactive isomers only.

The study just outlined would naturally begin with isomeric α,β-diphenyl-γ-acetylbutyric acids, but inasmuch as efforts to prepare acids of this composition were unsuccessful, owing to the active hydrogen atoms of the acetyl group, attention was turned to other derivatives.

By combining benzyl cyanide or an ester of phenylacetic acid with benzalpinacolone, one might expect to synthesize derivatives of isomeric α,β-diphenyl-γ-trimethylacetylbutyric acids. The experimental part of the paper will show that such compounds were easily formed in so far as the higher-melting series is concerned. Lower-melting isomers, however, were formed in small quantities. It was, moreover, not found possible to secure them free from isomeric admixture. The higher-melting series is as follows

Methyl ester 175° ⇄
Acid 235–236°
Nitrile 86° →

The lower-melting series will be discussed in the experimental part of this paper.

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[1] Read at the Atlanta meeting, Organic Section, American Chemical Society, April 8, 1930.

[2] Avery and Maclay, THIS JOURNAL, 51, 2833 (1929).

Owing to the poor yield and the doubtful purity of the lower-melting isomers, the authors of this paper decided to turn their attention to the corresponding benzoyl derivatives, which had already found a place in chemical literature.

The Isomeric α,β-Diphenyl-γ-benzoylbutyric Acids.—Borsche,[3] by combining ethyl phenylacetate with benzalacetophenone, obtained an ethyl ester of this series melting at 153–154° which hydrolyzed in alkaline solution to the salt of an acid melting at about 240°. He designated it as α,β-diphenyl-γ-benzoylbutyric acid.

By the oxidation of α,β,δ-triphenyl-δ-hydroxyvaleric acid, Meerwein[4] obtained an acid of the same composition melting at 186–187°. By combining methyl phenylacetate with benzalacetophenone, he obtained a mixture of isomeric esters. The esters yielded two acids, one melting at 186–187°, identical with the oxidation product previously obtained, and an isomer melting at 260–261°. These formed methyl esters melting at 157–158° and 177–178°, respectively. Meerwein's work indicates that the 240° acid of Borsche was a mixture of isomers.

By combining benzyl cyanide with benzalacetophenone, Kohler and Allen[5] obtained a nitrile melting at 118° and an isomer melting at 109°. The higher-melting nitrile gave a methyl ester melting at 150°, the lower nitrile a methyl ester melting at 139°. Both esters gave on saponification an acid melting at 239°. This acid on esterification with methanol and hydrogen chloride gave a product melting at 150°, identical with the ester (150°) obtained directly from the higher-melting nitrile.

Owing to the lack of close agreement in certain parts of the work of previous investigators, the authors of this paper have attempted to clarify the subject by repeating (with some modifications) and extending the work of their predecessors. They have made free from isomeric admixture the ethyl ester (156° corr.) of Borsche, (1) by direct synthesis, (2) by esterification of the 260–261° acid of Meerwein and (3) by treating the 118° nitrile of Kohler and Allen with ethanol and hydrogen chloride. The methyl ester 177–178° of Meerwein has been prepared (1) by direct synthesis, (2) by treating the 118° nitrile with methanol and hydrogen chloride, and (3) by esterification of the 260–261° acid. The 260–261° acid of Meerwein has been prepared (1) by hydrolyzing the 156° ethyl ester, also the 177–178° methyl ester, (2) by hydrolyzing the 118° nitrile, and (3) by hydrolyzing a lactone not found in the literature of the subject.

The 186–187° acid of Meerwein has been prepared (1) by fractional crystallization from a mixture of the acids resulting from the hydrolysis of the mixed esters or of the mixed nitriles, (2) by hydrolysis of the pure

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[3] Borsche, *Ber.*, **42,** 4497 (1909).

[4] Meerwein, *J. prakt. Chem.*, **97,** 272 (1918).

[5] Kohler and Allen, THIS JOURNAL, **46,** 1522 (1924).

esters (ethyl 100–101°, methyl 155°), and (3) by the hydrolysis of a lactone. The following list shows the members of both series that the authors of the present paper have prepared free from any isomeric admixture.

The higher-melting series

Methyl ester	177–178°	⇄	Acid 260–261°
Ethyl ester	156°	⇄	
Lactone	220–222°	⇄	
Nitrile	118°	→	

The lower-melting series

Methyl ester	155°	⇄	Acid 186–187°
Ethyl ester	100–101°	⇄	
Lactone	136°	⇄	

The ready formation of distinct lactones from both acids and the hydrolysis of these lactones into the original acids is evidence against the assumption of a "*trans*" or "fumaroid" form for the 260–261° acid and the "*cis*" or "maleinoid" form for the 186–187° acid.

Experimental Part

The Trimethylacetyl Derivatives

The Nitrile of α,β-Diphenyl-γ-trimethylacetylbutyric Acid.—Benzalpinacolone condenses with benzyl cyanide readily under a variety of conditions. The details of the procedure employed will be given under the description of the condensation of benzyl cyanide with benzalacetophenone. No trimolecular body is formed. On recrystallizing from light gasoline, crystals superficially reminding one of quartz are obtained, melting point 86° (corr.), yield about 90% of the theoretical.

Anal. Calcd. for $C_{21}H_{23}NO$: C, 82.57; H, 7.60; N, 4.62. Found: C, 82.57; H, 7.84; N, 4.50.

The 86° nitrile hydrolyzed (in acid solution) to an acid melting at 236°, while a less pure sample, of slightly lower and less definite melting point, not only gave the 236° acid but also a small percentage of an acid melting between 189 and 190°.

The Methyl Ester of α,β-Diphenyl-γ-trimethylacetylbutyric Acid.—A crystalline mass is formed by the reaction of benzalpinacolone with methyl phenylacetate in the presence of sodium methylate. The yield of the impure ester was nearly quantitative. Repeated recrystallizations from methanol gave a product forming long slender needles melting at 175°, soluble in chloroform and benzene.

Anal. Calcd. for $C_{22}H_{26}O_3$: C, 78.06; H, 7.75. Found: C, 77.97; H, 7.78.

The ester saponified (in acid solution) to an acid identical with the 236° acid obtained from the nitrile. The 236° acid with methanol and hydrogen chloride again formed the 175° ester.

The filtrates from the above were condensed and again recrystallized from methanol. By repeated fractional crystallizations a small amount of a product forming long, slender rods, m. p. 110–115°, was obtained. It was found impossible to obtain a product with a sharp melting point.

Anal. Calcd. for $C_{22}H_{26}O_3$: C, 78.06; H, 7.75. Found: C, 77.64; H, 7.70.

This 110–115° ester saponified in acid solution to a 189–190° melting acid.

The α,β-Diphenyl-γ-trimethylacetylbutyric Acid.—As previously stated, a sharply melting acid may be prepared from the 86° nitrile or the 175° methyl ester by hydrolysis in acid solution. This 236° acid crystallizes from 95% ethyl alcohol in flattened needles or long plates.

Titration. 0.3211 g. required 19.72 cc. of $N/10$ NaOH. Calcd.: 19.82 cc. *Anal.* Calcd. for $C_{21}H_{24}O_3$: C, 77.73; H, 7.46. Found: C, 77.76; H, 7.43.

The evidently impure 110–115° ester saponified to an acid melting at 189–190°. A sharp melting point could not be obtained after repeated recrystallizations of the small amount available. It appeared to be identical with the acid obtained from the fraction of the nitrile melting below 86°.

Titration. 0.3904 g. required 24.16 cc. of $N/20$ NaOH. Calcd.: 24.10 cc. *Anal.* Calcd. for $C_{21}H_{24}O_3$: C, 77.73; H, 7.46. Found: C, 77.63; H, 7.46.

In spite of the analytical data, the presence of the lower-melting isomers is not definitely established. The quantities were minute in comparison with the well-defined bodies of a higher-melting series. Sharp melting points and clearly defined crystal forms are lacking. The most probable conclusion is that the 110–115° ester and the 189–190° acid, though members of a lower-melting series, contain also a small admixture of the higher isomers and possible traces of some unidentified compound.

The above view is further strengthened by the fact that when the pure 175° ester is saponified in alkaline solution, the salts of mixed acids are formed. From this mixture the pure 236° acid, and an acid or acid mixture melting at 189–190° can be separated by fractional crystallization. The change from the pure ester to a mixture of isomeric acid salts by hydrolysis in alkaline solution will be dealt with later in this paper.

An attempt was made to obtain the lower-melting acid in pure condition by proceeding in the following manner. Phenylacetaldehyde was united to benzalpinacolone in the presence of sodium methylate. A product melting sharply at 158°, of very definite crystalline character was obtained. The composition is that of a direct addition product, $C_{21}H_{24}O_2$. This substance proved to be highly stable, thus differing in behavior from the α,β,δ-triphenylvalerolactone of Meerwein.

The Benzoyl Derivatives

Preparation of the 118° Nitrile of α,β-Diphenyl-γ-benzoylbutyric Acid.—A yield of nearly 90% of this compound (melting at 116–118°) was obtained by slightly modifying the procedure of Kohler and Allen. On the basis of the benzalacetophenone employed, about a 10% excess of benzyl cyanide was used and less than one mole of sodium methylate in a methanol solution. The mixture was stirred for half an hour at the temperature of the ice-bath, then at room temperature. After seeding with nitrile previously prepared, a crystalline mass separated out which soon became too thick to stir conveniently. Ligroin was then added and stirring continued. After two hours of vigorous stirring, glacial acetic acid in slight excess in proportion to the sodium methylate was added and the mass filtered off, washed with ligroin, dried and recrystallized. Made in this way it is nearly free from the trimolecular body and from the lower-melting nitrile of Kohler and Allen. This last named compound, thoroughly investigated by these authors, was prepared in this Laboratory in quantity and purity sufficient only to show its relation to the 186–187° acid.

Hydrolysis of the Nitriles.—The nitrile is dissolved in boiling acetic acid in a flask fitted with a return flow condenser. To the boiling solution, drop by drop, a mixture of equal volumes of sulfuric acid and water is added. Separation of oily drops of the unchanged nitrile indicates that the strong aqueous sulfuric acid solution is being added too rapidly. After some time crystals begin to appear in the boiling solution. During a period of about six hours, the original acetic acid solution is diluted to about two volumes with the sulfuric acid solution.

The content of the flask is now poured into cold water and filtered. The crystalline substance retained by the filter is treated in a large beaker with potassium carbonate, in slight excess, dissolved in enough boiling water to hold in solution the difficultly soluble potassium salt formed. The undissolved portion is unchanged nitrile and a small amount of an unidentified cleavage product. This is filtered off and rejected. The filtrate contains the acid sought in the form of the potassium salt, which being difficultly soluble in water may partially separate out on cooling. The filtrate is acidified, the precipitated acid filtered off, dried and recrystallized using methods described under the next sub-heading.

Hydrolyzed in the above manner, the 118° nitrile yields the 260–261° acid. The lower-melting nitrile gives the 186–187° acid. Hydrolyzing in acid solution is of importance inasmuch as many nitriles cannot be successfully saponified by sodium or potassium hydroxides and, further, as previously pointed out by Avery and Maclay for the glutaric series, hydrolyzing in an acid medium at moderate temperature does not effect a transformation of the lower $\rightleftharpoons$ higher series, while the sodium or potassium hydroxides often cause such transformation.

Preparation of the Mixed (260–261° and 186–187°) α,β-Diphenyl-γ-benzoylbutyric Acids.—Ten and four-tenths grams of benzalacetophenone and 7.5 g. of methyl phenylacetate were dissolved in 25 cc. of absolute methanol. To the solution, cooled in an ice-bath, 1.15 g. of sodium dissolved in absolute methanol was added. The mixture was stirred for half an hour in the ice-bath and then at room temperature until it was too thick to stir well. Ligroin was added as a diluent and stirring continued for several hours; 5 cc. of glacial acetic acid was added and the stirring continued for half an hour. The crystalline mass was filtered, washed with ligroin and dried. The mixed esters were then hydrolyzed in acid solution and the mixed acids separated as follows. The 260–261° acid separated out on cooling from a hot glacial acetic solution of the two acids and is obtained in a pure condition by further recrystallization from this solvent. The acetic acid filtrates are brought together, heated and water added until a crystallizing precipitate forms at the boiling temperature. On cooling, nearly all of the 186–187° acid separates out. By fractional recrystallization from hot benzene, rejecting the small portion of the 260–261° acid that first separates out on cooling, the acid is obtained in a nearly pure condition. Recrystallization again from benzene gives the pure 186–187° acid. This is an adaptation of the procedure of Borsche and of Meerwein.

The Ethyl Ester of the 186–187° Acid.—To complete the series of methyl and ethyl esters (for both isomers) the ethyl ester of the lower-melting acid was prepared with ethyl alcohol and hydrochloric acid. It is readily soluble in the usual organic solvents, crystallizes in long, slender plates or needles and melts at 100.5°.

The Lactones of the α,β-Diphenyl-γ-benzoylbutyric Acids.—The 186–187° acid dissolves readily in acetyl chloride at the temperature of the steam-bath. The concentrated solution is treated with ligroin and the precipitate formed recrystallized from tertiary amyl alcohol. It separates from this solvent as needles or long prisms, soluble in acetic acid, chloroform and benzene, m. p. 136°. On heating the solution in acetic acid to boiling, adding 50% sulfuric acid and continuing the boiling for a few minutes, the 186–187° acid is regenerated.

The 260–261° acid is less readily soluble in acetyl chloride. The lactone begins to separate out before the acid is completely dissolved. After protracted boiling, ligroin is added to the flask containing the products of the reaction and the mass is filtered off and recrystallized out of a mixture of tertiary amyl alcohol and chloroform. It forms needles or rods, more difficultly soluble in the ordinary solvents than its isomer, m. p. 220–222°. It hydrolyzes to the 260–261° acid.

Anal. Calcd. for $C_{23}H_{18}O_2$: C, 84.62; H, 5.56. Found for the 136° lactone: C, 84.30; H, 5.60. Found for the 220–222° lactone: C, 84.48; H, 5.64.

Transformation: The Higher Series $\rightleftarrows$ the Lower.—Saponification by alcoholic potassium or sodium hydroxide of the esters of either series leads to the corresponding acid, mixed, however, with a certain amount of the isomer. The action appears to explain why in some previous investigations an acid melting at 239–240° was obtained.

Summary

The points of analogy between the corresponding δ-ketonic and δ-carboxylic acids are considered.

α,β-Diphenyl-γ-trimethylacetylbutyric acid has been synthesized and possible isomeric forms are discussed.

The work of previous investigators on α,β-diphenyl-γ-benzoylbutyric acid is reviewed. Discrepancies in the literature are found to have resulted mainly from the hydrolysis of pure esters by sodium or potassium hydroxide, thus forming isomeric mixtures. Through the preparation of new compounds, both series of the isomeric benzoyl derivatives are now fairly complete. Resolution of both isomeric acids into optical isomers may be anticipated.

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ACTION OF METALLIC SODIUM ON DIPHENYL- AND DITOLYLTRICHLORO-ETHANES[1]

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In a former report[2] the author stated that when diphenetyltrichloroethane was treated wuth sodium in benzene a good yield of p,p'-diethoxystilbene was obtained. He was unable at the time to account for the mechanism of the reaction although similar products had been reported from the reaction of the same compound with zinc.[3] This investigation was undertaken to determine the course of the reaction and the nature of the products formed.

It was found that the presence of moisture is essential to the reaction in benzene, as in its absence no p,p'-diethoxystilbene could be isolated and most of the starting product was recovered unchanged. The reaction apparently takes the course

$$(C_2H_5OC_6H_4)_2CHCCl_3 + 4Na + H_2O \longrightarrow C_2H_5OC_6H_4CH{=}CHC_6H_4OC_2H_5 + 3NaCl + NaOH$$

Fritsch[4] found that heating the compound with sodium alcoholate in a

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[1] The author was assisted in this work by Irma Magnusson, graduate assistant in chemistry at the University of North Dakota.

[2] Harris and Frankforter, THIS JOURNAL, **48**, 3144 (1926).

[3] Goldschmidt, *Ber.*, **6**, 990 (1874); Elbs and Foster, *J. prakt. Chem.*, **39**, 298 (1882).

[4] Fritsch and Feldmann, *Ann.*, **306**, 72 (1899).