

[CONTRIBUTION FROM THE SANDERS LABORATORY OF CHEMISTRY, VASSAR COLLEGE]

The α,β,γ -Triphenylbutyric Acids and Related Compounds¹BY H. MARJORIE CRAWFORD, JEAN CLARKE DAVIDSON AND MARY ALYS PLUNKETT²

In searching for a good method for the preparation of 2,3-diphenyltetralone-1 we encountered enough gaps and inconsistencies in the literature to make it seem worth while to investigate this whole series of compounds thoroughly.

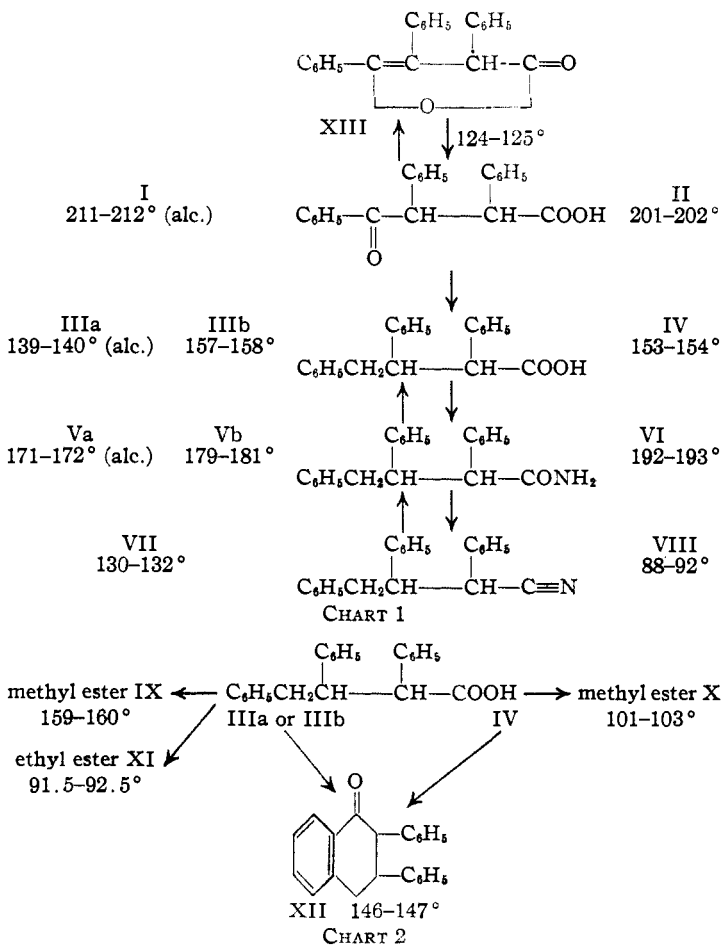
This paper reports the relationships between the stereoisomeric α,β,γ -triphenylbutyric acids, their methyl esters, ethyl esters, amides and nitriles and the α,β -diphenyl- β -benzoylpropionic acids. These relationships are shown in the following charts, the odd numbers (I, III, etc.) representing one series of corresponding racemic modifications and the even numbers (II, IV, etc.) representing the other series. Many reagents tend to give compounds of both series or to change one isomer into the other. The members of the odd series seem to be more stable, as they are the main products of the reactions of both series.

de Schutzenbach³ prepared the nitriles of α,β,γ -triphenylbutyric acid (recorded as melting at 129–131° and 193°) by the reaction of benzylmagnesium chloride on the nitrile of α -phenylcinamic acid and described the preparation of a mixture of the two stereoisomeric α,β,γ -triphenylbutyric acids by the alkaline hydrolysis of the 129° nitrile. The acids were separated by crystallization from alcohol and the less soluble one contained alcohol of crystallization and melted at 138°. The second isomeric acid was more soluble, crystallized without solvent and melted at 152–153°. She did not mention the hydrolysis of the 193° nitrile.

Bergmann, Schapiro and Eschinazi⁴ prepared α,β,γ -triphenylbutyric acid by another method, the final step of which was the catalytic reduction of α,β,γ -triphenylvinylacetic acid. They crystallized their acid from benzene–ligroin and reported a melting point of 158°, saying that only the higher melting form of the acid was isolated. They prepared the methyl ester, melting at 158°, by means of diazomethane. The amide was prepared by means of phosphorus pentachloride and ammonium hydroxide and melted at 168–169° when crystallized from ethanol.

We have shown that the acid described by Bergmann does not correspond to the 152° acid of de Schutzenbach, but is the solvent-free form (IIIb) of the acid which she described as melting at 138° (IIIa). The amide described by Bergmann contains alcohol of crystallization (Va) and when crystallized from solvents other than ethyl alcohol, melts at 179–181° (Vb). The amide Va and the acid IIIa each contain one molecule of ethyl alcohol of crystallization. Both the acid and the amide may be obtained either with or without alcohol of crystallization by a change of solvent and both forms give the same reactions. The keto acid I, which corresponds to this series, also contains alcohol of crystallization, but the nitrile VII does not. None of the compounds of the even series contain alcohol of crystallization.

In twenty-four preparations of the nitriles by the method of de Schutzen-



(1) Presented at the fall meeting of the American Chemical Society, New York City, September, 1944.

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(3) de Schutzenbach, *Ann. chim.*, **6**, 53–96 (1936).

(4) Bergmann, Schapiro and Eschinazi, *THIS JOURNAL*, **64**, 559–561 (1942).

bach, we have never isolated a nitrile melting at 193°, but always obtained one melting at 88–92° (VIII) in addition to the one melting at 130–132° (VII) which she described. We were never able to get both acids by hydrolyzing the 130° nitrile, but did get both from the 88° nitrile.

Hydrolysis of the high-melting nitrile, VII, gave acids and amides of the odd series (IIIa, IIIb, Va and Vb). Hydrolysis of the low-melting nitrile, VIII, gave acids and amides of both the odd and the even series (IIIa, IIIb, IV, Va, Vb and VI). Hydrolysis of the amides Va and Vb gave the acids of the odd series (IIIa and IIIb). Hydrolysis of the amide VI gave acids of both the odd and the even series (IIIa, IIIb and IV). The acid IIIb gave only one amide (Vb) while the acid IV gave both amides (Vb and VI). Dehydration of the amide VI gave only the nitrile VIII. Dehydration of the amide Va gave only the nitrile VII, while the amide Vb gave both nitriles (VII and VIII).

The two keto acids (I and II), their methyl and ethyl esters, the unsaturated lactone (XIII)⁵ and the reduction of II to IV⁶ have already been described. A similar reduction of the keto acid I gave the saturated acid IIIa. All attempts to make the amides of the keto acids failed, and any reaction which involved the use of phosphorus pentachloride or thionyl chloride resulted in the formation of the lactone (XIII).

Experimental

The α,β -diphenyl- β -benzoylpropionic acids (I and II) were prepared by the method described earlier.⁵ The reduction of the keto acid II to the α,β,γ -triphenylbutyric acid IV has been described⁶ and a similar Clemmensen reduction of the other keto acid (I) gave the other α,β,γ -triphenylbutyric acid (IIIa) which was identical with the acid prepared by the hydrolysis of the nitriles and amides as described later.

Attempts to prepare the amides of the keto acids by heating the ammonium salt to 175°, by refluxing the ethyl ester with concentrated ammonia and by treating the acid with phosphorus pentachloride, phosphorus trichloride or thionyl chloride followed by ammonia were all unsuccessful. Whenever either of the keto acids was treated with phosphorus pentachloride, phosphorus trichloride or thionyl chloride it was dehydrated to the unsaturated lactone XIII described before.⁵

Preparation of Nitriles VII and VIII.—The nitriles of α,β,γ -triphenylbutyric acid (VII and VIII) were made according to the directions of de Schutzenbach³ with slight modifications. The nitrile of α -phenylcinnamic acid (82 g., 0.4 mole) was placed in a Soxhlet and extracted by the ether from a boiling solution of 0.5 mole of benzylmagnesium chloride. The mixtures were allowed to stand several hours. Some of the mixtures became brown solids during the reaction and all were solids by the next morning. The reaction mixtures were then decomposed with ice and 60 ml. of 6 *N* hydrochloric acid. After one to two hours the brown color had all disappeared and there remained a clear water layer, a yellow ether layer and a white precipitate. The solid was separated and crystallized from ethyl acetate, and gave about 50 g. of the nitrile VII, m. p. 130–132°. The water layer was discarded and the ether layer was added to the remaining ethyl acetate solution. Slow evaporation of this solution usually gave more of VII. When it became obvious that a mixture was separating

from the solution, the solvent was evaporated and the residue was distilled under reduced pressure. The following fractions were obtained: (1) below 200° (40 mm.), dibenzyl; (2) 200–240° (30 mm.), nitrile of α -phenylcinnamic acid; (3) 240–265° (20 mm.), nitrile VII; (4) 265–280° (30 mm.), nitrile VIII. These fractions all solidified and were crystallized from alcohol. Average yields were 51% of VII and 25% of VIII, based on the nitrile of α -phenylcinnamic acid. The nitriles were only slightly soluble in ether, moderately soluble in alcohol and very soluble in ethyl acetate and acetone. VII separated from ethyl acetate in long, glistening needles and VIII, which was more soluble in all solvents, separated from ethyl alcohol in small, white grains.

Hydrolysis of Nitriles and Amides.—These reactions were carried out using the three methods described below, and the results are summarized in Table I.

Method 1.—Ten grams of the nitrile or amide, 30 ml. of glacial acetic acid, 3 ml. of concd. sulfuric acid and 2 ml. of water were heated on the steam-bath or refluxed for varying periods of time. The dark mixture was cooled, poured on ice and the resulting solid separated. The solid was ground up, boiled with 100 ml. of water and 2 g. of potassium hydroxide and filtered hot. The solution was acidified with hydrochloric acid, and the solid fractionally crystallized from alcohol or benzene-petroleum ether. The solid which was insoluble in the alkaline solution was recrystallized from ethyl acetate or benzene-petroleum ether. The various crops of crystals were identified by mixed melting points with known compounds.

Method 2.—Ten grams of the nitrile or amide, 5 g. of potassium hydroxide and 40 ml. of diethylene glycol were refluxed for about six hours, cooled and poured onto ice. If a precipitate formed, it was filtered and recrystallized from ethyl acetate or benzene-petroleum ether. The alkaline solution was acidified and gave a precipitate of acids which were separated by fractional crystallization from alcohol or benzene-petroleum ether.

Method 3.—Ten grams of the nitrile or amide, 4 g. of potassium hydroxide and 40 ml. of isoamyl alcohol were refluxed for three to four hours. About 400 ml. of water was then added and the isoamyl alcohol removed by steam distillation. The hot solution was filtered and the filtrate, on acidification, gave acids which were separated by fractional crystallization from alcohol. The solid which was insoluble in the alkaline solution was crystallized from benzene-petroleum ether or alcohol and gave the amides.

In one case 20 g. of the nitrile VIII was refluxed for six hours with 5 g. of potassium hydroxide and 150 ml. of 95% ethyl alcohol. After working up the reaction mixture according to Method 3, the products were 3.6 g. of recovered VIII, 3.7 g. of the other nitrile VII, 5.3 g. of the amide Vb and 3.2 g. of the amide Va.

The amide VI was the least soluble of the three amides and crystallized from alcohol-acetone as shining leaflets, m. p. 192–193°. It is only slightly soluble in petroleum ether and in ether, moderately soluble in alcohol and very soluble in ethyl acetate, benzene, chloroform and acetone. The amide Vb is obtained by crystallization from benzene-petroleum ether, chloroform, carbon tetrachloride, ethyl acetate or acetone as small, clear crystals, m. p. 179–181°. The amide Va separates from alcohol as shining needles, m. p. 171–172°. When 1.9214 g. of the amide Va was heated at 110° for five hours, it lost 0.2365 g. This corresponds to one molecule of alcohol of crystallization per molecule of the amide.

Preparation of Amides from Acids.—Bergmann⁴ prepared the amide Va from the acid IIIb by treating the acid with phosphorus pentachloride and concd. ammonia. Using the same procedure, we prepared Vb from IIIb. The only variation was to use a solvent other than alcohol in the crystallization. When this procedure was carried out with the acid IV, the tetralone XII resulted. The amide VI was prepared by refluxing 5 g. of the acid IV with 20 ml. of thionyl chloride for one hour, removing the excess thionyl chloride under reduced pressure and pouring the acid chloride into 50 ml. of concd. ammonia. The resulting solid, filtered and recrystallized from ethyl ace-

(5) Crawford, THIS JOURNAL, 60, 3078 (1938).

(6) Crawford, *ibid.*, 61, 608 (1939).

TABLE I
 HYDROLYSIS OF NITRILES AND AMIDES

Grams of compound hydrolyzed	Method	Conditions	Products in grams						Total yield in %	
			IIIa	Acids		IV	Amides			VI
				IIIb			Va	Vb		
60	VII	1	Reflux 32 hrs.	31.4			34.4			97
60	VII	2	Reflux 7 hrs.	3.7	42.5			10.6		89
60	VII	3	Reflux 6 hrs.	3.8	15.0			33.6		79
20	VIII	1	Steam-bath 48 hrs.		1.1	1.0		13.0	4.0	90
20	VIII	1	Reflux 47 hrs.		5.1	2.3	0.6	9.0		77
40	VIII	1	Steam-bath 43 hrs.		0.3			21.0	13.1	81
10	VIII	1	Reflux 45 hrs.		3.4			2.4	1.7	72
8	VIII	2	Reflux 6 hrs.		6.9					82
10	VIII	3	Reflux 6 hrs.	0.65	5.5			3.3		88
1	Va	3	Reflux 3 hrs.	0.3				0.7		91
20	Va	3	Reflux 5 hrs.	1.5	3.8			12.1		89
20	Vb	3	Reflux 5 hrs.		7.0			13.2		99
20	Vb	2	Reflux 7 hrs.		17.7			0.3		90
3	VI	2	Reflux 7 hrs.	0.4	2.2	0.5				100
3	VI	3	Reflux 9 hrs.	0.9	0.5		1.5			95
2	VI	1	Steam-bath 48 hrs.						1.5	75

tate, gave 3.1 g. of VI (62%) and 0.5 g. of the other amides, Va and Vb (10%).

Dehydration of Amides.—This reaction was carried out by the usual method of refluxing 5 g. of the amide with 5 g. of phosphorus pentachloride and 20 ml. of phosphorus oxychloride for forty minutes. The cooled mixture was poured onto ice, the resulting solid was dissolved in ether and this ether solution was washed twice with a solution of sodium bicarbonate and once with water. Evaporation of the ether and crystallization from alcohol gave the nitriles. The amide VI gave a 93% yield of the nitrile VIII. The amide Va gave an 83% yield of the nitrile VII. The amide Vb gave 20% of VII and 60% of VIII.

Preparation of Ethyl Esters.—Attempts to make the ethyl ester of the acid IV were all unsuccessful and gave oils which would not solidify. The methods used were treatment of the acid with thionyl chloride and absolute ethyl alcohol, boiling the acid with absolute ethyl alcohol and sulfuric acid, and refluxing the silver salt with ethyl bromide.

The same ethyl ester XI resulted from the acids IIIa and

IIIb, either by refluxing the acid with absolute ethyl alcohol and sulfuric acid or by treating the acid with thionyl chloride followed by absolute ethyl alcohol. Crystallization from ethyl alcohol gave clear, colorless needles melting at 91.5–92.5°.

Preparation of Methyl Esters.—The methyl ester IX, described by Bergmann,⁴ was obtained in 70% yield when 2 g. of the acid IIIa was refluxed with methyl alcohol and sulfuric acid. It was the only product isolated when acid IV was treated with thionyl chloride and methyl alcohol, and was obtained along with methyl ester X when acid IIIb was treated with thionyl chloride and methyl alcohol.

The methyl ester X was obtained in 90% yield by refluxing the acid IV with methyl alcohol and sulfuric acid. It was also obtained from acid IIIb along with methyl ester IX when thionyl chloride was used in the preparation. It was crystallized from methyl alcohol and separated as small, clear plates melting at 101–103°.

Preparation of 2,3-Diphenyltetralone-1.—This tetralone has been prepared by Crawford⁶ and by Bergmann.⁴ It

 TABLE II
 ANALYSES

	Temp.	Calculated		Found	
		C	H	C	H
$\begin{array}{c} \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \\ \quad \\ \text{C}_6\text{H}_5\text{CH}_2\text{CH} - \text{CH} - \text{COOH} \end{array}$	IIIa 139–140° (alc.)	79.52	7.23		
	IIIb 157–158°	83.54	6.33	83.33	6.88
	IV 153–154°	83.54	6.33	82.98	6.43
$\begin{array}{c} \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \\ \quad \\ \text{C}_6\text{H}_5\text{CH}_2\text{CH} - \text{CH} - \text{CONH}_2 \end{array}$	Va 171–172° (alc.)	79.74	7.53	79.31	7.63
	Vb 179–181° ^{ob}	83.77	6.71	79.78	7.64
	VI 192–193° ^{ob}	83.77	6.71	83.79	7.19
$\begin{array}{c} \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \\ \quad \\ \text{C}_6\text{H}_5\text{CH}_2\text{CH} - \text{CH} - \text{C}\equiv\text{N} \end{array}$	VII 130–132°	88.85	6.44	83.39	6.73
	VIII 88–92° ^{ob}	88.85	6.44	83.93	6.93
				88.89	6.29
$\begin{array}{c} \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \\ \quad \\ \text{C}_6\text{H}_5\text{CH}_2\text{CH} - \text{CH} - \text{COOCH}_3 \end{array}$	IX 159–160°	83.58	6.72	83.99	6.94
	X 101–103° ^{ob}	83.58	6.72	83.30	6.93
				83.50	6.71
$\begin{array}{c} \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \\ \quad \\ \text{C}_6\text{H}_5\text{CH}_2\text{CH} - \text{CH} - \text{COOC}_2\text{H}_5 \end{array}$	XI 91.5–92.5° ^{ob}	83.72	7.00	83.74	7.00
				83.95	7.12

* Analyzed by de Schutzenbach.³ ^b New compounds.

resulted unexpectedly in one case when the acid IV was treated with phosphorus pentachloride. It resulted in small yields when any of the acids (IIIa, IIIb or IV) was heated with concentrated sulfuric acid and glacial acetic acid, and in better yields when any of the acids was treated with thionyl chloride followed by anhydrous aluminum chloride.

Summary

1. Relationships are established between the

stereoisomeric α,β -diphenyl- β -benzoylpropionic acids and their saturated reduction products.

2. Relationships are established between the three stereoisomeric α,β,γ -triphenylbutyric acids and the corresponding two methyl esters, one ethyl ester, three amides and two nitriles.

3. Five new compounds are reported.

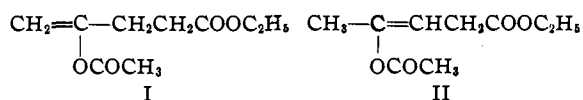
POUGHKEEPSIE, NEW YORK RECEIVED AUGUST 1, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Reaction of Ketene with Keto Esters and Diketones

BY CHARLES D. HURD, OLIVER E. EDWARDS¹ AND J. R. ROACH²

Gwynn and Degering³ have shown that methyl-
 $\text{CH}_3\text{C}=\text{CH}_2$
 vinyl acetate, OCOCH_3 may be prepared from acetone by interaction with ketene in the presence of sulfuric acid. If ethyl levulinate and ketene reacted comparably two possible compounds (I, II) might be formed.



In studying this reaction we found that a 50% yield of product was obtained by maintaining a reaction temperature of 115°. It readily absorbed one mole of bromine. Ozonolysis gave evidence for both I and II in about equal amounts because one mole of the enol acetate yielded 0.42 mole of succinic acid and 1.16 moles of acetic acid. The succinic acid obviously came from 0.42 mole of I, whereas the acetic acid points to 0.37 mole of II (*i. e.*, one-half of 1.16-0.42).

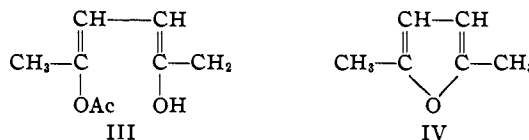
The terminal double bond of ethyl 4-acetoxy-4-pentenoate (I) suggests a polymerizable structure but the substance did not polymerize in four days at 90° in the presence of benzoyl peroxide.

Ethyl acetoacetate, when treated similarly with ketene, yielded the enol acetate, presumably ethyl 3-acetoxycrotonate.

Acetylacetone reacted exothermically with ketene and sulfuric acid catalyst. 1-Methyl-2-acetylvinyl acetate, $\text{CH}_3\text{COOC}(\text{CH}_3)=\text{CHCOCH}_3$, was formed in good yields. That the product was not triacetylmethane seems certain because of its boiling point (92° at 18 mm.) which is twelve degrees lower than that recorded⁴ for triacetylmethane (104° at 19 mm.) and because it resisted extraction from ether solution by aqueous sodium carbonate. The 1-methyl-2-acetylvinyl acetate displayed no tendency to poly-

merize during forty-eight hours at 70° in the presence of 2% of benzoyl peroxide, nor in another forty-eight-hour period with an additional 2% of benzoyl peroxide.

Acetylacetone, $\text{CH}_3\text{COCH}_2\text{CH}_2\text{COCH}_3$, also reacted vigorously with ketene and sulfuric acid but the product isolated in 65% yield was not an enol acetate (III) but was 2,5-dimethylfuran (IV). It is reasonable, however, to believe that the enol acetate was present in an intermediate step. Acetic anhydride was the other product of this reaction.



This reactivity of ketene toward the carbonyl group in β - and γ -keto esters and in β - and γ -diketones was not found in ketones which possessed an oxygen or nitrogen atom alpha to the carbonyl group. Thus, when acetyl acetate, $\text{CH}_3\text{COOCH}_2\text{COCH}_3$, was treated with ketene in the presence of a little sulfuric acid, there was no reaction either at 20° or 75°. (This experiment was performed by Arthur Berger.) Recovery of the acetyl acetate was practically quantitative. Much the same was true for biacetyl and pyruvonnitrile, CH_3COCN , but a slight amount of higher boiling reaction products were observed in these trials.

Recently the claim has been made⁵ for preparation of the enol acetate of pyruvonnitrile by reaction of ketene with hydrogen cyanide at 35°. In the present work we tried unsuccessfully to prepare pyruvonnitrile by addition of hydrogen cyanide to ketene but the only product which was definitely established was diketene. In one of the several experiments undertaken, one mole of ketene (42 g.) was dissolved in one mole of hydrogen cyanide at -78°. This was brought to room temperature during a period of forty hours. Distillation of the products under diminished pres-

(1) Holder of Weyerhaeuser Timber Company Fellowship, 1941-1943.

(2) Holder of Pittsburgh Plate Glass Company Fellowship, 1941-1943.

(3) Gwynn and Degering, *THIS JOURNAL*, **64**, 2218 (1942).

(4) Birckenbach, *Ber.*, **65**, 1071 (1932).

(5) Vollmann, Schloffer and Ostrowski, German Patent 736,504, May 13, 1943; *C. A.*, **38**, 2970 (1944).