2. The constituents present are: acids—stearic, oleic, gadoleic, erucic, $C_{24}H_{46}O_2$, $C_{26}H_{50}O_2$, an hydroxyoleic acid; alcohols—oleyl, tetradecyl, cetyl, octadecyl, cholesterol, glycerol: hydrocarbon—squalene.

3. The purgative properties of the oil have probably been over-emphasized, although there does seem to be a modicum of pharmacological action. This may be dependent on its content of esters of higher alcohols.

4. Extraction with liquid sulfur dioxide has been shown to be a satisfactory method for the separation of the saturated and unsaturated constituents of the unsaponifiable fraction.

BALTIMORE, MARYLAND

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

ISOMERIC ALPHA-PARA-NITROPHENYL-BETA-PHENYL-DELTA-KETONIC ACIDS

BY S. AVERY, C. B. BISWELL AND E. E. LISTON

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Attempts to resolve the inactive isomeric α,β-diphenyl-δ-ketonic acids, described in a previous paper,[1] into optically active forms were unsuccessful. It was accordingly decided to synthesize the acids named in the title of this paper in the expectation that these would more readily permit the formation of optical isomers. Although attempts along this line up to the present had not been successful, these inactive nitro acids and their derivatives show certain properties markedly different from all delta-ketonic acids previously studied.

The two isomeric nitriles of α-p-nitrophenyl-β-phenyl-γ-benzoylbutyric acid have been investigated by Allen.[2] He appears, however, not to have interested himself in preparing the acids themselves and no further reference appears in the literature. Further, no work has been found bearing on α-p-nitrophenyl-β-phenyl-γ-trimethylacetylbutyric acid or its derivatives.

In condensing benzalpinacolone with methyl p-nitrophenylacetate in the presence of sodium methoxide, a crystalline substance was formed, easily purified, and without evidence of isomeric admixture. When, however, benzalpinacolone was condensed with ethyl p-nitrophenylacetate in the presence of sodium ethoxide, a crystalline substance was formed which hydrolyzed to an isomer of the one obtained by the methyl condensation route. Though the isomers melted with decomposition at the same temperature, the crystalline forms were distinctly different and their derivatives showed marked variations. An entirely similar result was obtained when benzalacetophenone was condensed, first with methyl p-

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[1] Avery and Jorgensen, THIS JOURNAL, **52,** 3628 (1930).

[2] Allen, *ibid.*, **47,** 1733 (1925).

nitrophenylacetate in the presence of sodium methoxide, and later when ethyl *p*-nitrophenylacetate and sodium ethoxide were used. Isomeric, not identical, forms were obtained by the different routes. In the case of both series, those obtained by the methyl route crystallized, in general, as coarse needles or prisms; those by the ethyl route as fine needles or hairs. The derivatives of the acids obtained through the ethyl condensation, in general, melted higher than those obtained in a corresponding way through the methyl condensation. In order to distinguish between the two isomers, the authors will in this article designate the two series as the "E" series and the "M" series. Condensation of *n*-propyl and *n*-butyl esters in the presence of sodium dissolved in the corresponding alcohols, led to what we have termed the "E" series. Hydrolysis of the lower melting nitrile led to the "M" series; hydrolysis of the higher to the "E" series. The 126° ("M") nitrile described by Allen can, as he has pointed out, be transformed into the "E" or higher melting nitrile and, as the authors have found, the process can be in part reversed. The ethyl esters of the "M" series can be readily transformed into the corresponding esters of the "E" series by dissolving in ethyl alcohol and treating with sodium ethoxide. Both isomeric acids give distinct lactones which can be converted into their corresponding acids and esters.

In the benzoyl series, the amount of the nitriles formed is in the ratio of about 3 to 1 in favor of the "E" product while in the trimethylacetyl series the yield of the "E" nitrile is almost quantitative. While small amounts of the "E" derivative may be detected when the methyl route is followed in condensing the ester in the benzoyl series, it does not appear to be formed in the trimethylacetyl ester condensation.

Except for minor details the results obtained in both series show close analogy, and the distinction in the compounds formed in the methyl route from those formed in the ethyl route is equally characteristic in the case of the benzoyl and the trimethylacetyl derivatives.

The diagram represents in a graphic way the relations of the several compounds mentioned.

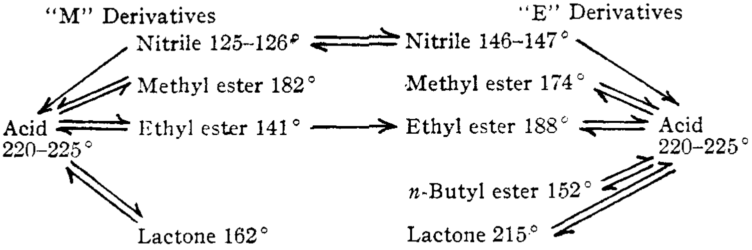
Experimental Part

The Benzoyl Series

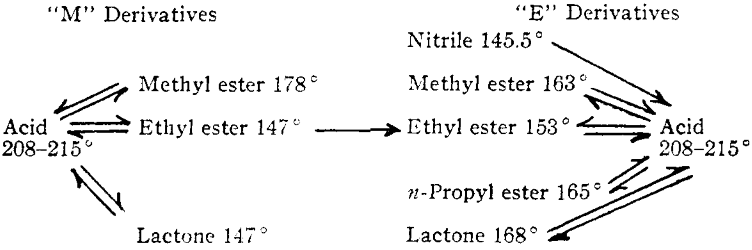
The "M" Methyl α-*p*-Nitrophenyl-β-phenyl-γ-benzoylbutyrate.—Ten grams of methyl *p*-nitrophenylacetate and 10.1 g. of benzalacetophenone were dissolved in warm absolute methanol. After cooling, a solution of 1.2 g. of sodium dissolved in 20 cc. of methanol was added. The flask containing the mixture was immediately plunged into ice water and the contents stirred for a few minutes during which time a crystalline deposit separated. After standing for several hours, acetic acid was added to discharge the color. The pasty mass was taken up with ligroin, filtered and washed with water. Recrystallized from *n*-butyl alcohol or a mixture of methanol and chloroform, the compound separated in the form of beveled plates melting at 182°; yield, about 95%.

Anal. Calcd. for $C_{24}H_{21}O_5N$: C, 71.44; H, 5.25. Found: C, 71.42; H, 5.38.

BENZOYL SERIES



TRIMETHYLACETYL SERIES



The "M" α-p-Nitrophenyl-β-phenyl-γ-benzoylbutyric Acid.—The ester just described was hydrolyzed by boiling in acetic acid solution with a mixture of equal parts of water and sulfuric acid added drop by drop over a considerable period of time. The product of hydrolysis was poured into water, filtered and washed, then dissolved in dilute ammonium hydroxide, filtered again and reprecipitated with hydrochloric acid. Recrystallized from acetic acid the acid separated in the form of pointed prisms melting with decomposition at 220–225°.

Anal. Calcd. for $C_{23}H_{19}O_5N$: C, 70.93; H, 4.92. Found: C, 70.57; H, 4.94.

Titration. 0.2116 g. required 5.17 cc. of $N/10$ NaOH. Calcd.: 5.15 cc.

The "M" Ethyl α-p-Nitrophenyl-β-phenyl-γ-benzoylbutyrate.—This ester was formed by the action of ethanol and hydrogen chloride on the acid just described. Recrystallized from alcohol, it separated in the form of prisms melting at 141°.

Anal. Calcd. for $C_{25}H_{23}O_5N$: C, 71.91; H, 5.55; N, 3.36. Found: C, 72.01; H, 5.66; N, 3.46.

The "M" α-p-Nitrophenyl-β-phenyl-γ-benzoylbutyrolactone.—A mixture of 2 g. of the "M" acid and 10 cc. of acetyl chloride was heated for fifteen hours in a sealed tube at a temperature of 60°. After evaporating off most of the acetyl chloride, the residue was taken up with a small amount of petroleum ether. On stirring, a crystalline mass formed which was further purified by recrystallizing from isobutyl alcohol, m. p. 162°.

Anal. Calcd. for $C_{23}H_{17}O_4N$: C, 74.37; H, 4.62. Found: C, 74.42; H, 4.68.

The "M" α-p-Nitrophenyl-β-phenyl-γ-benzoylbutyronitrile.—It is very difficult to obtain this nitrile so wholly free from the "E" isomer that the product of saponification is not contaminated with the "E" acid, showing marked drop in the melting point. The acid obtained by hydrolyzing the "M" nitrile is readily converted into the ethyl ester from which the traces of the "E" ethyl ester can be separated through the comparative insolubility of this ester in alcohol.

The "E" Ethyl α-p-Nitrophenyl-β-phenyl-γ-benzoylbutyrate.—Ethyl p-nitrophenylacetate was condensed with benzalacetophenone in ethanol solution with sodium ethoxide according to the directions given for the preparation of the "M" methyl α-p-

nitrophenyl-β-phenyl-γ-benzoylbutyrate. Twice recrystallized from a mixture of chloroform and ethanol, it melted at 188°.

Anal. Calcd. for $C_{25}H_{23}O_5N$: C, 71.91; H, 5.55; N, 3.36. Found: C, 71.72; H, 5.49; N, 3.36.

The "E" α-*p*-Nitrophenyl-β-phenyl-γ-benzoylbutyric Acid.—This acid was obtained by the hydrolysis in acid solution of the "E" ethyl ester just described. Recrystallized from a mixture of ethyl acetate and glacial acetic acid, it separated in the form of long hair-like crystals melting with decomposition at 220–225°.

Anal. Calcd. for $C_{23}H_{19}O_5N$: C, 70.93; H, 4.92. Found: C, 71.03; H, 4.99.

Titration. 0.2651 g. required 6.75 cc. of *N*/10 NaOH. Calcd.: 6.83 cc.

The "E" Methyl α-*p*-Nitrophenyl-β-phenyl-γ-benzoylbutyrate.—This ester was prepared from the "E" acid with methanol and hydrogen chloride. Recrystallized from methanol the compound melted at 174°.

Anal. Calcd. for $C_{24}H_{21}O_5N$: C, 71.44; H, 5.25. Found: C, 71.53; H, 5.29.

The "E" *n*-Butyl α-*p*-Nitrophenyl-β-phenyl-γ-benzoylbutyrate.—This compound was obtained by the direct condensation of *n*-butyl *p*-nitrophenylacetate with benzalacetophenone in the presence of sodium dissolved in *n*-butyl alcohol. Recrystallized from *n*-butyl alcohol the compound separated in the form of slender prisms or needles melting at 152°.

Anal. Calcd. for $C_{27}H_{27}O_5N$: C, 72.77; H, 6.11. Found: C, 73.14; H, 6.14.

The "E" α-*p*-Nitrophenyl-β-phenyl-γ-benzoylbutyrolactone.—A mixture of 1 g. of the "E" acid and 20 cc. of acetyl chloride was heated for five hours in a sealed tube at 110°. Petroleum ether was added, the product filtered, and recrystallized from tertiary amyl alcohol; yield, 85%, m. p. 215°.

Anal. Calcd. for $C_{23}H_{17}O_4N$: C, 74.37; H, 4.62. Found: C, 74.20; H, 4.63.

The "E" α-*p*-Nitrophenyl-β-phenyl-γ-benzoylbutyronitrile.—The hydrolysis of this nitrile in acid solution did not result in as pure a product as was obtained by the hydrolysis of the esters. However, the pure acid may be obtained by conversion of the impure acid into the 188° ethyl ester and hydrolysis of the same.

Transformation: "M" Derivatives $\rightleftharpoons$ "E" Derivatives.—Allen has shown that the "E" nitrile may be obtained from the "M" nitrile by treating the latter with alkali.

The authors found that when 1 g. of the "E" (147°) nitrile was added to 50 cc. of approximately 99% ethanol, 10 mg. of sodium carbonate added, and the mixture refluxed for some time, solution was gradually accomplished with the change to a deep red color. After two hours, a drop of glacial acetic acid was added to discharge the color. On cooling and condensing to two-thirds its volume, 0.5 g. of the "E" nitrile separated. Further condensing with subsequent cooling led to an additional small amount of the "E" isomer, the filtrate yielding 0.2 g. of the "M" nitrile, m. p. 124–126°. It is evident that whether one starts with the lower or with the higher melting nitrile, a condition of equilibrium is soon reached in alkaline solution.

The "M" ethyl ester is transformed into the "E" ethyl ester by sodium ethoxide in ethanol solution. The transformation appears to be nearly quantitative.

The Trimethylacetyl Series

The methods of preparation and purification of the members of this series of acids and derivatives were, in general, analogous to those described for the corresponding members of the benzoyl series. The "M" methyl ester, "E" ethyl ester, "E" *n*-propyl ester and the "E" nitrile were prepared by direct condensation of the corresponding ester or nitrile of *p*-nitrophenylacetic acid with benzalpinacolone. Hydrolysis of the "M" methyl ester led to the formation of the "M" acid while hydrolysis of the "E" ethyl ester, "E" *n*-propyl ester, and the "E" nitrile resulted in the formation of the "E" α-*p*-nitrophenyl-β-phenyl-γ-trimethylacetylbutyric acid. The lactones were prepared in the usual manner.

The following table contains a brief summary of the data concerning the two isomeric α-*p*-nitrophenyl-β-phenyl-γ-trimethylacetylbutyric acids and their derivatives.

			Analysis, %			
			Calcd.		Found	
Compound	Series	M. p., °C.	C	H	C	H
Acid	"M"	208–215	68.26	6.28	68.13	6.30
Methyl ester	"M"	178	68.89	6.58	68.84	6.63
Ethyl ester	"M"	147	69.48	6.85	69.30	6.85
Lactone	"M"	147	71.76	6.03	71.86	6.06
Acid	"E"	208–215	68.26	6.28	68.23	6.30
Nitrile	"E"	145.5	71.97	6.30	71.76	6.29
Methyl ester	"E"	163	68.89	6.58	68.90	6.61
Ethyl ester	"E"	153	69.48	6.85	69.50	7.03
n-Propyl ester	"E"	165	70.03	7.11	69.90	7.13
Lactone	"E"	168	71.76	6.03	71.62	5.96

The "M" ethyl ester of this series, like the corresponding ester in the benzoyl series, can be transformed into the "E" ethyl ester by dissolving in ethyl alcohol and treating with sodium ethoxide.

Efforts to transform derivatives of the "E" series into those of the "M" series were unsuccessful.

Comparison of the Trimethylacetyl Derivatives with the Benzoyl Derivatives.—In the case of the trimethylacetyl derivatives, no mixtures of isomers were evident in any of the condensations. All condensations led to members of the "E" series except the condensation of methyl *p*-nitrophenylacetate with benzalpinacolone in the presence of methanol and sodium methoxide. The trimethylacetyl derivatives crystallized more readily than the benzoyl derivatives and were more easily prepared in pure condition. Aside from these facts, the two series closely parallel each other.

The authors are indebted to Mr. J. M. Brackenbury, Mr. Kenneth Majors and Mr. Frank McGrew for assistance in preparing these compounds and in doing analytical work, and to Dr. W. D. Maclay for assisting in preparing the communication for publication.

Summary

Isomeric α-*p*-nitrophenyl-β-phenyl-γ-benzoylbutyric acids and a number of their derivatives have been prepared.

Isomeric α-*p*-nitrophenyl-β-phenyl-γ-trimethylacetylbutyric acids and their derivatives have also been prepared and compared with the preceding.

In preparing the nitriles of these acids through direct condensation, methanol and ethanol may be used interchangeably, or mixed, as a solvent without influencing the result.

In the condensation with methyl esters, sodium methoxide in the presence of methanol leads to one of the isomeric series ("M"); while in the case of the ethyl esters, sodium ethoxide in the presence of ethanol leads to the other series ("E"). *n*-Propyl esters in *n*-propyl alcohol, and *n*-butyl

esters in *n*-butyl alcohol lead to the same series ("E") as is obtained by the ethyl condensation. The "E" series is the more stable form. Through the selection of esters, condensing agents and solvents, either series may be made at pleasure.

LINCOLN, NEBRASKA

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

STUDY ON THE CONFIGURATION OF EPHEDRINE[1]

BY KARL FREUDENBERG,[2] EUGENE SCHOEFFEL AND EMIL BRAUN

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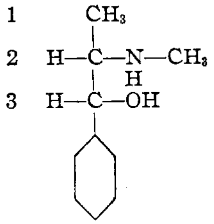
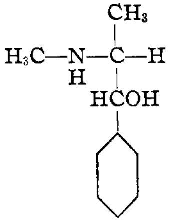
The configurational relationship of ephedrine and pseudoephedrine (I or II)[3] has been discussed by different investigators[4] from the viewpoint that in one of the two stereoisomers the OH group is located nearer to the $NHCH_3$ group than in the other.



I



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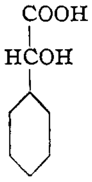
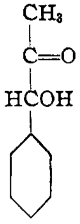


III



IV

Since the bond between carbon atoms 2 and 3 is free to rotate, the two groups can approach each other in the same way in both substances. We do not believe that any evidence with regard to the configuration can be given in this way.

The only possible way of solving the problem would be to bring the two asymmetric carbon atoms in steric correlation with substances of known configuration.

This has been carried out for carbon atom 3 in the following manner. The amide of *d*-mandelic acid (III) forms with methylmagnesium iodide the levorotatory phenylacetylcarbinol IV. This reaction was carried out with the inactive material by H. Wren,[5] whose method has been improved. The rotation of our carbinol IV is lower (about two-thirds)

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[1] Steric series No. 15; preceding communication, *Ber.*, **64**, 703 (1931).

[2] Carl Schurz Memorial Professor for 1931 at the University of Wisconsin.

[3] A report on the ephedrine alkaloids is given by K. K. Chen and C. H. Kao, *J. Am. Pharm. Assocn.*, **15**, 625 (1926); *cf.* K. K. Chen and C. F. Schmidt, *Medicine*, **9**, 1 (1930).

[4] E. Schmidt, *Arch.*, **252**, 89 (1914); E. Späth and R. Göhring, *Monatsh.*, **41**, 319 (1920); H. Emde, *Helv. Chim. Acta*, **12**, 365 (1929).

[5] Wren, *J. Chem. Soc.*, **95**, 1592 (1909).