together with bromine in the side chain, and blue and green with bromine also in the ring are the same and in the same order as the color changes brought about by increased numbers of systems of conjugated double linkages in unsaturated hydrocarbons when treated with concentrated sulfuric acid.[6] The accumulation of substituting groups in our compounds has, in the reaction with sulfuric acid, the same effect as an increase in the condition of unsaturation and of conjugation in these hydrocarbons.

After these experiments had been completed, a paper by Pfeiffer and Wizinger[7] appeared in which the color reactions of sulfuric acid with α, α-dianisylethylenes are described. It is striking that these substances give violet colors with sulfuric acid only when there is halogen in the side chain, as is the case with our compounds.

Summary

For the purpose of comparison with other unsaturated α-ketonic acids, *o*-methoxybenzalpyruvic acid and its reactions with bromine have been studied.

The color reactions of sulfuric acid with benzalpyruvic acid, *p*-methoxybenzalpyruvic acid and *o*-methoxybenzalpyruvic acid are described.

NEW YORK CITY

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

THE ACTION OF SODIUM BENZYL CYANIDE WITH CINNAMIC ESTER. II[1]

BY S. AVERY

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Introduction

In 1897, Walther and Schickler[2] brought together equal moles of sodium ethylate, benzyl cyanide and cinnamic ester in the presence of ether. From the products of the reaction they isolated a substance melting at 162–163°. This they believed to be cinnamylbenzyl cyanide, but as the analysis indicated the presence of one molecule more of water than this compound would call for, they regarded it as a hydrated derivative.

Three years later Erlenmeyer[3] isolated as a product resulting from the reaction of dry sodium ethylate, cinnamic ethyl ester and benzyl cyanide

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[6] Kuhn and Winterstein, *Helv. Chim. Acta*, **11**, 151 (1928).

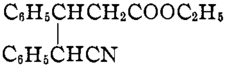
[7] Pfeiffer and Wizinger, *Ann.*, **461**, 132 (1928).

[1] Read at the meeting of the Division of Organic Chemistry, American Chemical Society, St. Louis, April 18, 1928.

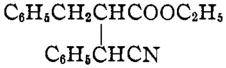
[2] Walther and Schickler, *J. prakt. Chem.*, [2] **55**, 347 (1897).

[3] E. Erlenmeyer, Jr., *Ber.*, **33**, 2006 (1900).

a substance melting at 99–100° having the composition $C_{29}H_{19}O_2N$. He suggested the following as structural possibilities.

I 

$$\begin{array}{l} C_6H_5CHCH_2COOC_2H_5 \\ \qquad | \\ C_6H_5CHCN \end{array}$$

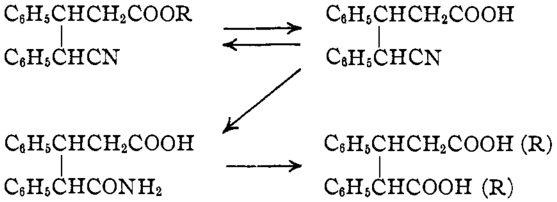
II 

$$\begin{array}{l} C_6H_5CH_2CHCOOC_2H_5 \\ \qquad\qquad | \\ \quad C_6H_5CHCN \end{array}$$

Erlenmeyer found, further, that this substance on saponification gave the "cinnamylbenzyl cyanide" (m. p. 162–163°) of Walther and Schickler. Hence the latter could not have the structure previously ascribed to it, and Erlenmeyer suggested that it was probably the imide of diphenylglutaric acid.

In 1908 Avery and McDole[4] showed that the substance melting at 162–163° was in reality β,γ-diphenyl-γ-cyanobutyric acid. This made it evident that Erlenmeyer's formula I was correct, and eliminated II as a possibility.

The preceding is a partial summary of the published researches relating to the compounds derived from the action of benzyl cyanide (1 molecule) with cinnamic ester (1 molecule). It is the hope of the author that the present paper will supply the most important gaps in our knowledge of these compounds and of their saponification products. The following compounds of this series have been studied



$$\begin{tikzcd}
\begin{array}{l} C_6H_5CHCH_2COOR \\ \qquad | \\ C_6H_5CHCN \end{array} \arrow[r, shift left] & \begin{array}{l} C_6H_5CHCH_2COOH \\ \qquad | \\ C_6H_5CHCN \end{array} \arrow[l, shift left] \arrow[dl] \\
\begin{array}{l} C_6H_5CHCH_2COOH \\ \qquad | \\ C_6H_5CHCONH_2 \end{array} \arrow[r] & \begin{array}{l} C_6H_5CHCH_2COOH\ (R) \\ \qquad | \\ C_6H_5CHCOOH\ (R) \end{array}
\end{tikzcd}$$

Of the compounds just outlined, β,γ-diphenyl-γ-monamide glutaric acid and β,γ-diphenyl-γ-cyanobutyric methyl ester have not been previously reported. α,β-Diphenylglutaric ethyl ester is of interest as it has been prepared by Borsche[5] through the action of phenyl acetic ester on cinnamic ester thus leading to the synthesis of the α,β-diphenylglutaric acid without the use of benzyl cyanide. Further, this glutaric acid, according to the researches of Kishner,[6] and Meerwein and Dott[7] is one of two stereoisomers, which are best distinguished through a comparison of the methyl with the ethyl esters.

Turning now to the possibility of the condensation of one molecule of benzyl cyanide with two molecules of cinnamic ester, we find that Erlen-

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[4] Avery and McDole, THIS JOURNAL, **30**, 596, 1423 (1908).

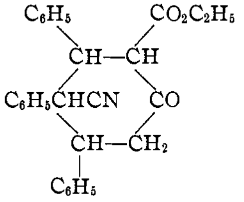
[5] Borsche, *Ber.*, **42**, 4496 (1909).

[6] Kishner, *J. Russ. Phys.-Chem. Soc.*, **47**, 1819–1848 (1915); *J. Chem. Soc.*, **110**, I, 292 (1916).

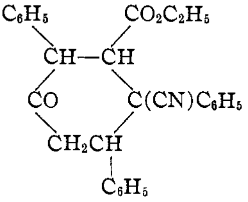
[7] Meerwein and Dott, *J. prakt. Chem.*, **97**, 264–268 (1918).

meyer,[8] at the temperature of the steam-bath, obtained a body melting at 206–207°, having the empirical formula $C_{28}H_{25}O_3N$, representing the direct union of benzyl cyanide with two molecules of cinnamic ester minus one molecule of the corresponding alcohol. For the structure of the substance, he suggests the following possibilities

I

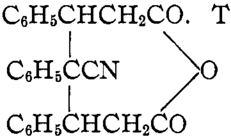


II

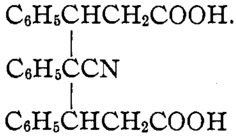


Formula I shows condensation as effected in the β-position in relation to the two carboxyl groups. Formula II shows condensation as effected in the α-position toward one and in the β-position toward the other carboxyl group. Both formulas show secondary ring formation. The experimental part of this paper shows that the substance under consideration may also be prepared by the action of sodium β,γ-diphenyl-γ-cyanobutyric ester on cinnamic ester. It is hardly probable that benzyl cyanide in condensing with first one and then with a second molecule of cinnamic ester should form first a β- and then an α-condensation product. Finally, the work of Dieckmann, referred to later, shows that ring formation in the case of dibasic esters takes place with elimination of alcohol in the α-position in relation to the unchanged ester group. For these reasons we may regard Formula II as excluded. This confirms Formula I excepting only the typographical error of one excess H atom.

Using methods similar to those employed by Erlenmeyer, Avery and McDole isolated a substance melting at 231–232° (uncorr.) for which they suggested "only tentatively" the formula $C_6H_5CHCH_2CO$. The experimental part of this communication shows this to have been incorrect, and that the substance was really 2-keto-4,5,6-triphenyl-5-cyanohexahydrobenzoic methyl ester. They gave, however, to the acid obtained by hydrolyzing this product the correct formula, namely,



$$\begin{array}{l} C_6H_5CHCH_2COOH \\ \quad\quad\; | \\ C_6H_5CCN \\ \quad\quad\; | \\ C_6H_5CHCH_2COOH \end{array}$$



The course of the reactions when one molecule of benzyl cyanide reacts with two of cinnamic ester is as follows.

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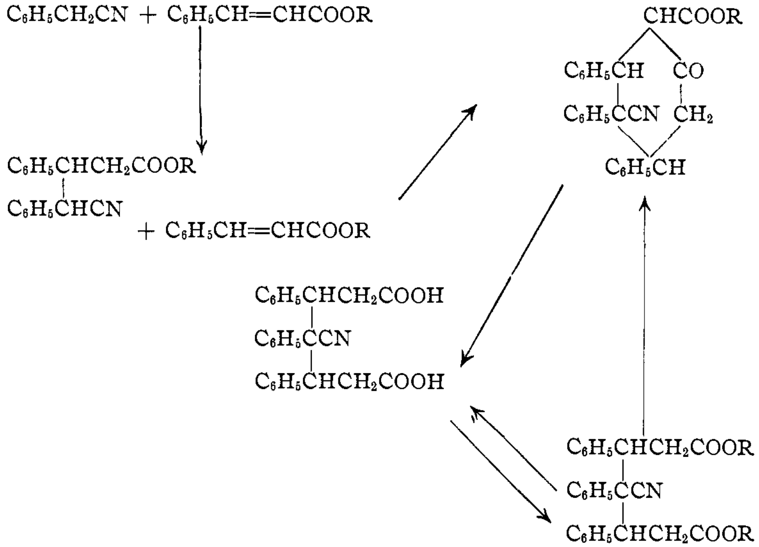
[8] E. Erlenmeyer, Jr., *Ber.*, **33**, 2009–2010 (1900).



The reactions just outlined may be explained by assuming that the β,γ-diphenyl-γ-cyanobutyric ester first formed reacts further with cinnamic ester to form an ester of the pimelic series, but that in the presence of the condensing agent it immediately gives off alcohol, forming an ester of the hexahydrobenzoic series. This latter reaction is to be expected in the light of Dieckmann's[9] investigations on ring formation with dibasic esters. As in the case of less complex 2-keto-hydrobenzoic esters, this ester hydrolyzes to an acid of the pimelic series from which the pimelic esters may be obtained.

Experimental Part

β,γ-Diphenyl-γ-cyanobutyric Methyl Ester.—Five g. of sodium dissolved with heating in a small excess of methyl alcohol was added to 25.5 g. of benzyl cyanide and the mixture was cooled to approximately 20°; 35.7 g. of melted methyl cinnamate was then added, the mixture well shaken and placed in a bath at 0° for approximately five hours, then allowed to stand at 20 to 25° for several days. A crystalline mass gradually formed. This was macerated with a strong aqueous solution of ammonium chloride, filtered and washed. The yield including the substance recovered from filtrates after twice crystallizing amounted to 41–42 g. or 67% of the theoretical. The crystals are long, transparent needles, soluble in benzene, chloroform, acetic ether and hot alcohol, difficultly soluble in petroleum ether. A sample recrystallized to constant melting point melted sharply at 106.5° (corr.).

Anal. Calcd. for $C_{18}H_{17}O_2N$: C, 77.4; H, 6.1; N, 5. Found: C, 77.7; H, 6.1; N, 5.

This compound is also formed when benzyl cyanide is condensed with ethyl cinnamate using sodium methylate as a condensing agent; also when β,γ-diphenyl-γ-cyanobutyric acid is treated with methyl alcohol and hydrogen chloride gas. The latter

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[9] Dieckmann, *Ber.*, **27,** 103 (1894); *Ann.*, **317,** 100 (1901).

reaction shows it as the methyl ester of an acid, the structure of which was previously determined by Avery and McDole. The procedure just described is similar to that followed by Erlenmeyer in working with the corresponding ethyl compounds.

β,γ-Diphenyl-γ-cyanobutyric Ethyl Ester.—The synthesis of this compound corresponds exactly to that of the methyl ester, except that ethyl derivatives are used throughout. A 50% yield was obtained; melting point, 101.5° (corr.); crystalline form and solubility similar to the methyl ester.

Anal. Calcd. for $C_{19}H_{19}O_2N$: C, 77.8; H, 6.5; N, 4.8. Found: C, 77.9; H, 6.6; N, 4.8.

The sharp melting point (slightly higher than found by previous investigators) and the closely checking analysis indicate a high degree of purity in the preparation. On saponification it gives the corresponding acid, thus clearly indicating its composition.

β,γ-Diphenyl-γ-cyanobutyric Acid.—Some difficulty is encountered in preparing this compound in a pure condition. Contamination with the ester resulting from incomplete saponification, and contamination with the corresponding monamide acid due to the saponification proceeding too far, are equally to be avoided.

Five g. of the pure ester (methyl or ethyl) was dissolved in 50 cc. of 95% ethyl alcohol, 1.5 g. of potassium hydroxide in solution added, and the solution digested on the steam-bath. Water was added from time to time until the total volume equaled about 80 cc. Heating was continued for about fifteen minutes after a drop no longer became turbid with water. Then strong acetic acid was added in excess. On cooling and diluting little by little a granular precipitate formed. Care is to be taken not to cool and dilute so rapidly as to form a milky emulsion. Ultimately a large excess of water is added. The yield is about 90% of the theoretical.

The ester may also be saponified by dissolving in strong acetic acid and boiling, while gradually diluting with hydrochloric acid; melting point, 163.5–165° (corr.) according to rate of temperature increase. It partially decomposes on melting. Benzene was found to be the best solvent for separating the acid in a pure condition from the more soluble esters and from the less soluble monamide glutaric acid.

β,γ-Diphenyl-γ-monamide Glutaric Acid.—A compound melting from 200–205° had been noted in previous investigations but no definite suggestions were made in regard to its composition or structure. It is readily formed when β,γ-diphenyl-γ-cyanobutyric acid or a corresponding ester is boiled with strong alcoholic potash, evaporated with the addition of small amounts of water and finally brought to a temperature of 100°. On dissolving the salt-like mass and acidifying, a milky or resinous substance forms which becomes crystalline on standing. Recrystallized from alcohol or, better, from acetic acid it forms glistening, transparent flakes. It melts at 200–205° with the evolution of ammonia. It is nearly insoluble in ligroin, difficultly soluble in benzene or chloroform and readily in hot alcohol or acetic acid.

Anal. Calcd. for $C_{17}H_{17}O_3N$: C, 72.0; H, 6.05; N, 4.9. Found: C, 71.8; H, 6.05; N, 4.9. Titration: 6.85 cc. of $N/10$ NaOH neutralized 0.1928 g. Calcd.: 6.8 cc.

α,β-Diphenylglutaric Acid and Esters.—The acid may be prepared by hydrolyzing β,γ-diphenyl-γ-monamide glutaric acid, β,γ-diphenyl-γ-cyanobutyric acid, or its esters, with concentrated hydrochloric acid solution under pressure. Three hours' heating at 150° gave satisfactory results. When the temperature of the melting point apparatus is increased at the rate of about 1° per minute, the reading is 225–228° (corr.); melting point of ethyl ester, 93.3° (corr.); methyl ester, 143.0° (corr.). The methyl ester made by the method of Borsche melted at the same temperature as the methyl ester made from the pure acid by the action of methyl alcohol and hydrochloric acid, and not 7° lower as found by Meerwein and Dott,[10] and cited by them as an evidence of the presence of an admixture of a stereoisomer. It appears, therefore, that only the "fumaroid" form, to follow Kishner's designation, is found in the synthesis of α,β-diphenylglutaric acid by the method of Avery and McDole or by the method of Borsche.

2-Keto-4,5,6-triphenyl-5-cyanohexahydrobenzoic Ethyl Ester.—The following is a modification of Erlenmeyer's method: 3 g. of sodium as sodium ethylate, nearly free from ethyl alcohol, was mixed with 7.5 g. of benzyl cyanide and 22.5 g. of ethyl cinnamate was added. To the mixture 75 cc. of toluene was added and the whole boiled with a return flow condenser for three hours. After cooling, glacial acetic acid was added in a quantity sufficient to neutralize the sodium, then ligroin in excess and the solids were filtered under pressure. The cake formed was digested with 95% alcohol, cooled and filtered, washed with alcohol and finally with water; yield, 15.5 g., which on recrystallizing from 95% alcohol gave 13 g. of nearly pure white crystals.

Almost equally good results can be obtained by heating the mixture of cyanide, sodium ethylate and ester over a hot-plate to 101°, stirring constantly. On cooling, a resinous product is formed which on acidifying with acetic acid and digesting with 95% alcohol gives a light yellow, crystalline residue. This is filtered off and washed first with alcohol, then with water and recrystallized from alcohol.

The ester is purified as follows. After dissolving in a small quantity of chloroform, butyl or amyl alcohol is added. The solution is then concentrated to crystallization on the steam-bath; melting point, 208–209° (corr.).

This substance can also be prepared by heating at 100° equal moles of β,γ-diphenyl-β-cyanobutyric ethyl ester, ethyl cinnamate and sodium ethylate. A yield of approximately 50% of the theoretical has been obtained. Finally, the same substance is obtained when β,γ,δ-triphenyl-γ-cyanopimelic ester is treated with sodium ethylate. These reactions leave no doubt in regard to the structure of the compound.

2-Keto-4,5,6-triphenyl-5-cyanohexahydrobenzoic Methyl Ester.—This substance was prepared by Bessie F. Whitney using the methods described under the ethyl ester. It crystallizes in beautiful beveled plates; melting point, 242–244° (corr.); more difficultly soluble in alcohol, benzene, chloroform, etc., than the ethyl ester.

Anal. Calcd. for $C_{27}H_{23}O_3N$: C, 79; H, 5.7; N, 3.4. Found: C, 79; H, 5.8; N, 3.3.

The ester was also prepared as follows: 0.39 g. of potassium in 5 cc. of absolute methyl alcohol was mixed with 2.79 g. of β,γ-diphenyl-γ-cyanobutyric methyl ester and 1.62 g. of methyl cinnamate. The mixture was stirred with a thermometer and then heated in an oil-bath until the thermometer read above 100°. One cc. of acetic acid and 25 cc. of chloroform were added and the resinous mass was brought into solution by heating and stirring. The nearly clear, straw-colored solution was concentrated to 15 cc., 15 cc. of butyl alcohol was added and the solution again concentrated to about 15 cc., when crystals began to form. After cooling these were washed first with butyl alcohol and then with water. The white, glistening crystals weighed 2.5 g., 59% of the theoretical yield. Recrystallized once, the substance melted at 242–244° (corr.).

Finally, the ester under consideration was prepared as follows: 0.88 g. of β,γ,δ-triphenyl-γ-cyanopimelic methyl ester was dissolved in ether and a drop of absolute methyl alcohol added; 0.08 g. of potassium was added and when nearly dissolved 2 cc. of absolute methyl alcohol also, and the solution was warmed and acidified with acetic acid. Water was added and the mixture warmed to drive off the ether, crystals gradually forming. It was then cooled, filtered and washed. The crystalline mass

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[10] Meerwein and Dott, *J. prakt. Chem.*, 97, 269 (1918).

was recrystallized and found to melt at 242–244° (corr.). The crystalline form was identical with that of the substance prepared by other methods.

β,γ,δ-Triphenyl-γ-cyanopimelic Acid.—This compound is to be expected as the result of saponifying an ester of 2-keto-4,5,6-triphenyl-5-cyanohexahydrobenzoic acid. Ten g. of the ethyl ester was placed in a flask, 50 cc. of 95% alcohol added and 5 cc. of a 50% solution of potassium hydroxide. The mixture was heated on the steam-bath for about ten minutes, then transferred to an evaporator, 25 cc. of water added and evaporated nearly to dryness. The residue was again treated with strong, alcoholic potassium hydroxide, again evaporated nearly to dryness, diluted and filtered. The filtrate was acidified strongly with hydrochloric acid, yielding a wax-like solid and a milky liquid, the former gradually passing into a crystalline mass and the latter into loose crystals. The snowy white, well washed and dried substance weighed 9.8 g. It is most easily purified by dissolving in ether, evaporating to a small volume, adding benzene and condensing to crystallization. It crystallizes from dilute alcohol as prisms, apparently containing alcohol of crystallization, which it loses on the steam-bath, becoming amorphous; melting point, 218–219° (corr.).

Anal. Calcd. for $C_{26}H_{23}O_4N$: C, 75.5; H, 5.6; N, 3.4. Found: C, 75.6; H, 5.6; N, 3.4.

It was found by the combustion analysis, by titration and in respect to the melting point and solubilities, to be identical with the substance isolated by Avery and McDole.

β,γ,δ-Triphenyl-γ-cyanopimelic Methyl Ester.—Ten g. of the corresponding acid was placed in a flask with 50 cc. of absolute methyl alcohol and hydrogen chloride was passed in to saturation. The acid dissolved and a granular precipitate gradually formed. On refluxing and cooling, an almost solid mass of white crystals formed. The mother liquor was filtered off, the crystals were washed with cold methyl alcohol, and then recrystallized from hot methyl alcohol; yield, about 90% of the theoretical; melting point, 108.2° (corr.). It crystallized from methyl alcohol in needles or spikes depending on the rate of cooling.

Anal. Calcd. for $C_{28}H_{27}O_4N$: C, 76.2; H, 6.2. Found: C, 76.2; H, 6.3.

On saponifying the ester, the corresponding pimelic acid is formed. On treating the ester with methyl alcohol the corresponding hexahydrobenzoic methyl ester is formed.

β,γ,δ-Triphenyl-γ-cyanopimelic Ethyl Ester.—This substance was made exactly as the methyl ester except that ethyl alcohol was used; melting point, 102.5° (corr.). Solubilities and crystalline form were similar to those of the methyl ester. On saponification, the corresponding pimelic acid is regenerated.

Anal. Calcd. for $C_{30}H_{31}O_4N$: C, 76.9; H, 6.7; N, 3. Found: C, 77.0; H, 6.9; N, 3.

Composition of the Compound Tentatively Designated as an "Anhydride" of a Dibasic Acid by Avery and McDole[11]

This substance was first prepared by the action of sodium methylate on a mixture of ethyl cinnamate and benzyl cyanide. (At that time the migration of ester radicals had been studied only slightly.) A body was obtained melting not very sharply at 231–232° (236–237°, corr.). The analytical data corresponded fairly well to the theoretical composition of such a body, namely, $C_{26}H_{21}O_3N$. It corresponds equally well to $C_{27}H_{23}O_3N$, which it really is.

[11] Avery and McDole, This Journal, **30**, 599 (1908).

When the work of Avery and McDole was repeated recently, using, however, methyl instead of ethyl cinnamate, the same results were obtained except that the product melted at 242–244° (corr.). When, however, ethyl ester and alcohol were used, the product melted at 208–209° (corr.). The "supposed anhydride" is therefore 2-keto-4,5,6-triphenyl-5-cyanohexahydrobenzoic methyl ester, synthesized from the ethyl ester through the migration of methyl group from the sodium methylate used in the reaction and probably containing small amounts of the ethyl ester, as shown by the lower melting point.

Summary

The compounds resulting from the union of one molecule of sodium benzyl cyanide with one of the cinnamic ester, and also the compounds resulting from the union of one molecule of sodium benzyl cyanide with two molecules of cinnamic ester, have been prepared and studied.

The reaction of benzyl cyanide with cinnamic ester in the cold with moisture carefully excluded has been found to be exactly analogous to Michael's reaction in the classic example of sodium malonic ester. Complete hydrolysis leads to compounds of the glutaric series.

At higher temperatures the first condensation product of benzyl cyanide with cinnamic ester unites with a second molecule of cinnamic ester and forms derivatives leading by hydrolysis to the pimelic series. The reactions in passing from the ketohexahydrobenzoic ester to the pimelic esters are reversible.

In so far as appears to be possible, all compounds of both series have been hydrolyzed in successive stages. Methyl and ethyl esters have been made not only by direct synthesis but also by esterifying the free acids.

Through the preparation of a number of new compounds both series are now fairly complete. These explain more fully than heretofore the nature of the reactions involved. Errors in the literature of the subject have been corrected.

LINCOLN, NEBRASKA