[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF QUEEN'S UNIVERSITY AND BISHOP'S UNIVERSITY]

THE CONDENSATION OF BENZOIN AND BENZIL WITH ETHYL CYANO-ACETATE[1]

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Numerous interesting condensations of various types of ketones and aldehydes, capable of being expressed in enolic forms, with ethyl cyano-acetate, have been described by several authors,[2] most of whom interpreted their results on the basis that the ketone or aldehyde first reacts in its enolic form with the sodio derivative of ethyl cyano-acetate, eliminating water and giving β,γ-unsaturated cyano esters or acids. This mode of interpretation was shown by Lapworth and McRae[3] to have led to an erroneous conclusion in the condensation of cyclohexanone with ethyl cyano-acetate and Kohler and Corson[4] have demonstrated that it is clearly inapplicable in certain cases. Ingold,[2d] who has used this mechanism most recently, has now[5] abandoned it in favor of the mechanism emphasized by Lapworth and McRae, which leads to an α,β-unsaturated structure for the substances produced initially (if the aldol stage be omitted), although subsequent isomeric changes may yield a β,γ-unsaturated form. In view of the uncertainty which, therefore, is attached to the structures previously assigned to many of the substances described in the foregoing papers[2] it has seemed to us desirable to reinvestigate some of the more interesting cases in which it appears that the initial condensation has been followed by further reactions.

In the present communication we describe the results obtained on investigating the condensation of benzoin with ethyl cyano-acetate[2b] and the related condensation of benzil and ethyl cyano-acetate. We have also compared the behavior toward hydrogen cyanide of the product from the latter condensation with that of ethyl camphorylidene-cyano-acetate, derived from condensing camphorquinone (a 1,2-diketone) with ethyl cyano-acetate.[6]

Haworth obtained an acid, $C_{20}H_{14}O_4N_2$, m. p. 136°, by condensing

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[1] We gratefully acknowledge our indebtedness to the Canadian National Research Council for the award of a bursary in 1924–1925 to one of us (A. L. K.), during the tenure of which most of the work here described was carried out.

[2] (a) Harding, Haworth and Perkin, *J. Chem. Soc.*, **93**, 1943 (1908); (b) Haworth, *ibid.*, **95**, 480 (1909); (c) Gardner and Haworth, *ibid.*, **95**, 1955 (1909); Harding and Haworth, *ibid.*, **97**, 486 (1910); Simonsen and Nayak, *ibid.*, **107**, 792 (1915); (d) Ingold and Thorpe, *ibid.*, **115**, 143 (1919).

[3] Lapworth and McRae, *ibid.*, **121**, 2741 (1922).

[4] Kohler and Corson, THIS JOURNAL, **45**, 1975 (1923).

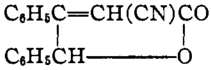
[5] Ingold, *J. Chem. Soc.*, **184** (1930).

[6] Forster and Withers, *ibid.*, **101**, 1327 (1912).

benzoin with ethyl cyano-acetate in the presence of sodium ethoxide and assigned to it the structure α,δ-dicyano-β,γ-diphenyl-Δ^{β}-butene-α,δ-dicarboxylic acid (I), based solely on the assumption that benzoin had

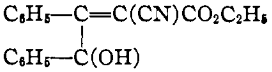
$$COOHCH(CN)C(C_6H_5){=}C(C_6H_5)(CN)COOH \quad I$$

reacted in its enolic form $C_6H_5C(OH){=}C(OH)C_6H_5$. We have carried out this condensation many times and have followed scrupulously Haworth's directions but we have failed to isolate a substance agreeing in properties or analysis with that described by Haworth. On the contrary, we have obtained consistently by acidification of the reaction mixture a substance, m. p. 141°, having the formula $C_{17}H_{11}O_2N$. The substance dissolves slowly in caustic soda and has an equivalent of 264 ($C_{17}H_{11}O_2N$ requires 261). Evidently it has been formed by the condensation of equimolecular proportions of the reactants and the only satisfactory structure we are able to assign to it is that of the *lactone of α-cyano-β,γ-diphenyl-γ-hydroxycrotonic acid* (II). This lactone has been formed apparently by the hydrolysis of the ester (III), followed by elimination of water.



$$\begin{array}{l} C_6H_5C{=}CH(CN)CO \\ \quad\ \ | \qquad\qquad\quad | \\ C_6H_5CH\text{————}O \end{array}$$

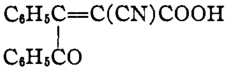
II



$$\begin{array}{l} C_6H_5{-}C{=}C(CN)CO_2C_2H_5 \\ \qquad\ \ | \\ C_6H_5{-}C(OH) \end{array}$$

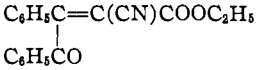
III

In agreement with the structure assigned, the substance is oxidized to benzil by chromic acid and to *α-cyano-β-benzoylcinnamic acid* (IV), by dilute nitric acid. The latter is identical with the acid produced by hydrolyzing ethyl *α-cyano-β-benzoylcinnamate* (V), which was obtained by condensing benzil with ethyl cyano-acetate.



$$\begin{array}{l} C_6H_5C{=}C(CN)COOH \\ \quad\ \ | \\ C_6H_5CO \end{array}$$

IV

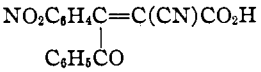


$$\begin{array}{l} C_6H_5C{=}C(CN)COOC_2H_5 \\ \quad\ \ | \\ C_6H_5CO \end{array}$$

V

An attempt was made to prepare ethyl α-cyano-β,γ-diphenyl-γ-hydroxycrotonate (III), by acting on the supposed silver salt of the corresponding acid formed from the lactone with ethyl iodide, but ethyl benzoyl α-cyanocinnamate was obtained instead, the corresponding silver salt having evidently been produced on dissolving the lactone in ammonia and treating the neutral solution with silver nitrate, oxidation taking place during the process.

The action of concentrated nitric acid on the lactone gave a markedly acidic substance, *α-cyano-β-benzoyl-β-(m-nitrophenyl)-acrylic acid* (VI).



$$\begin{array}{l} NO_2C_6H_4C{=}C(CN)CO_2H \\ \qquad\qquad\ | \\ \qquad C_6H_5CO \end{array}$$

VI

This on oxidation gave an excellent yield of *m*-nitrobenzil (m. p. 118°) which Chattaway and Coulson[7] recently described, having isolated it

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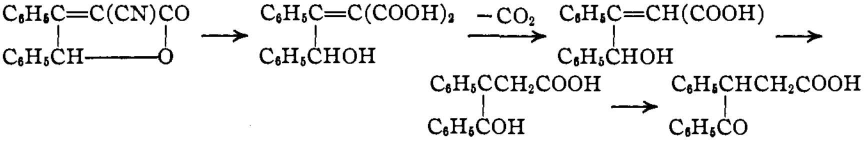
[7] Chattaway and Coulson, *J. Chem. Soc.*, 1080 (1928).

(m. p. 120°) in small quantity from the action of nitric acid on benzoin. On account of the markedly different yields in the two processes by which *m*-nitrobenzil is obtained, we assign the nitro group in (VI) to the benzene radical in closest proximity to the =C(CN)COOH group, although no other case of this group acting as a meta directing group has been observed. The identification of our substance as *m*-nitrobenzil followed from its oxidation by chromic acid into benzoic and *m*-nitrobenzoic acids, both of which were fully identified.

The foregoing lactonic structure is also in agreement with the behavior of the substance toward concentrated sulfuric acid, which converts it into β-phenyl-β-benzoylpropionic acid, whose identity was proved by direct comparison with a specimen prepared according to the description of Avery and McDole.[8] This conversion arises as follows

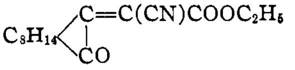


$$\begin{array}{l}C_6H_5C{=}C(CN)CO\\ \quad|\qquad\qquad\ |\\ C_6H_5CH\text{———}O\end{array} \longrightarrow \begin{array}{l}C_6H_5C{=}C(COOH)_2\\ \quad|\\ C_6H_5CHOH\end{array} \xrightarrow{-CO_2} \begin{array}{l}C_6H_5C{=}CH(COOH)\\ \quad|\\ C_6H_5CHOH\end{array} \longrightarrow$$

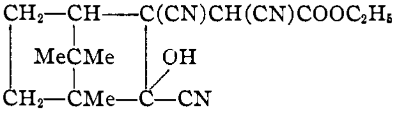
$$\begin{array}{l}C_6H_5CCH_2COOH\\ \quad\|\\ C_6H_5COH\end{array} \longrightarrow \begin{array}{l}C_6H_5CHCH_2COOH\\ \quad|\\ C_6H_5CO\end{array}$$

Forster and Withers[6] state that benzil had been condensed with ethyl cyano-acetate in Dr. Forster's laboratory but a description of the substance obtained was not published. The condensation, we have found, takes place readily with the formation of ethyl *α-cyano-β-benzoylcinnamate* (V), which curiously has the same melting point as the lactone (II) but analyses, a mixed melting point determination and hydrolysis of (V) to the acid (IV) all show that the two substances are not identical. With neither the lactone (II) nor the ester (V) were we able to effect the addition of hydrogen cyanide, a reaction which is characteristic of simple cyanoacrylic acids and esters.[9] The condensation of benzil with ethyl cyanoacetate adds another example of the occurrence of condensation between ethyl cyano-acetate and a ketone in which there is no possibility of enolization. However, we were unable to bring about condensation between ethyl cyano-acetate and the methyl ether of benzoin.

In contrast with the behavior of the ester (IV) toward hydrogen cyanide, ethyl camphorylidene-cyano-acetate (VII) reacts rapidly and adds on



VII



VIII

hydrogen cyanide both at the ethenoid linkage and the carbonyl linkage as well, giving *ethyl 1,7,7-trimethyl-2,3-dicyano-2-hydroxy-bicyclo-(1,2,2)-heptane-3-cyano-acetate* (VIII). This addition reaction agrees with the

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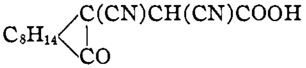
[8] Avery and McDole, This Journal, 30, 1423 (1908).

[9] *Cf.* Lapworth and McRae, Ref. 3.

structure given their substance by Forster and Withers, who rejected the alternative β,γ-unsaturated formula. This ester loses hydrogen cyanide readily on treatment with alcoholic potash, giving presumably (α′-cyanocamphoryl)-α-cyano-acetic acid (IX),  $\mathrm{C_8H_{14}}{<}\begin{array}{l}\mathrm{C(CN)CH(CN)COOH}\\ |\\ \mathrm{CO}\end{array}$ (m. p. 107–109°), although the substance has not been completely identified.

Experimental

Lactone of α-Cyano-β,γ-diphenyl-γ-hydroxycrotonic Acid. (II).—To a mixture of 21.2 g. of benzoin in 70 cc. of absolute alcohol there was added 14 g. of ethyl cyanoacetate followed by 2.3 g. of sodium dissolved in 70 cc. of absolute alcohol. There is a momentary purple color on adding sodium and heat is developed. On shaking the benzoin dissolved to form a clear reddish solution. This was heated on the water-bath under a reflux condenser for three hours, after which it was poured into 800 cc. of water. A small precipitate of unchanged benzoin was filtered off and the clear filtrate acidified. A granular semi-solid precipitate was filtered off, rubbed with a small amount of ether and the white crystals filtered from the ether; yield about 85%. Recrystallization from alcohol yielded white needles melting at 141°, soluble in chloroform, benzene and alcohol, nearly insoluble in ether.

Anal. Calcd. for $C_{17}H_{11}O_2N$: C, 78.1; H, 4.22; N, 5.36; equivalent, 261. Found: C, 77.5; H, 4.26; N, 5.48; equivalent, 264.

The lactone absorbs bromine only very slowly and failed to add hydrogen cyanide.

Hydrolysis of the Lactone α-Cyano-β,γ-diphenyl-γ-hydroxycrotonic Acid to β-Phenyl-β-benzoylpropionic Acid.—The lactone (5.2 g.) was heated with 85 cc. of concentrated sulfuric acid and 50 cc. of water at a temperature of 130–140° for five hours. The mixture after standing overnight was poured on 400 g. of cracked ice and the precipitated semi-solid brown mass was filtered off. This was warmed with a solution of dilute caustic soda and a small amount of insoluble material filtered out. The alkaline solution was acidified, when a mass of brown crystals was obtained (2.3 g.). Three recrystallizations from alcohol failed to remove a brown color. After boiling with charcoal colorless octahedra were obtained, m. p. 160.5°.

This substance was found to be identical with β-phenyl-β-benzoylpropionic acid made by oxidizing β,γ-diphenyl-γ-cyanobutyric acid according to the method of Avery and McDole[8] no depression of the melting point being observed on making a mixed melting point determination.

α-Cyano-β-(*m*-nitrophenyl)-β-benzoylacrylic Acid.—The lactone (40 g.) was heated under a reflux with concd. nitric acid (200 cc.) until the evolution of brown fumes ceased (about one hour). On cooling, pure white crystals separated which were filtered and washed thoroughly with water. It is necessary to allow the crystals to separate here, for, if the clear solution is poured into water, a sticky semi-solid mass is obtained from which pure crystals are obtained with some difficulty. After twice recrystallizing from alcohol, the substance softens at 212° and melts at 218–220° with decomposition; yield of pure crystals, 41%.

Anal. Calcd. for $C_{17}H_{10}O_5N_2$: C, 63.3; H, 3.11; N, 8.7; equivalent, 322. Found: C, 63.1; H, 3.18; N, 9.14; equivalent, 323.

The substance is soluble in hot chloroform, alcohol and benzene but insoluble in ligroin. From alcohol the crystals are obtained as colorless needles.

α-Cyano-β-(*m*-nitrophenyl)-β-benzoylacrylic acid can also be obtained by oxidizing ethyl α-Cyano-β-benzoylcinnamate with concentrated nitric acid.

Oxidation of α-Cyano-β(-*m*-nitrophenyl)-β-benzoylacrylic Acid to *m*-Nitrobenzil.—The acid (10 g.) was dissolved in 80 cc. of acetone and a saturated aqueous solution of potassium permanganate slowly added until an excess was present. The reaction mixture was kept cool during the addition of the permanganate. The mixture was allowed to stand for one hour and then the heavy precipitate of manganese dioxide was cleared by passing in sulfur dioxide and adding sulfuric acid. The yellow precipitate of nitrobenzil was filtered and recrystallized from alcohol as pale yellow crystals, m. p. 117–118°; yield, 60–70%.

This substance was shown to be *m*-nitrobenzil by oxidizing with chromic acid in boiling acetic acid solution. The mixture of *m*-nitrobenzoic acid and benzoic acid was separated by forming the methyl ester and recrystallizing from alcohol.

Anal. Calcd. for $C_{14}H_9O_4N$: N, 5.49. Found: N, 5.82.

α-Cyano-β-benzoylcinnamic Acid. Oxidation of Lactone of α-Cyano-β,γ-diphenyl-γ-hydroxycrotonic Acid to α-Cyano-β-benzoylcinnamic Acid.—Six g. of the lactone was boiled gently under a reflux condenser with 48 cc. of concentrated nitric acid to which had been added 12 cc. of water. When the evolution of brown fumes had ceased, a small amount of water was added and the solution cooled. A yellow semi-solid mass separated which was recrystallized twice from benzene and ligroin. The crystals soften at 112° and melt at 116–117°; yield, 5.4 g.

Anal. Calcd. for $C_{17}H_{11}O_3N \cdot {}^1/_2C_6H_6$: C, 75.9; H, 4.43; N, 4.43; equivalent, 316. Found: C, 75.5; H, 4.54; N, 5.03; equivalent, 317.

The crystals are soluble in alcohol, chloroform and hot benzene. The same substance can be obtained by oxidizing the lactone in hot acetic acid solution with concentrated nitric acid. These crystals were found to be identical with those prepared by the hydrolysis of ethyl α-cyano-β-benzoylcinnamate and also contained benzene of crystallization.

Attempted Esterification of the Lactone of α-Cyano-β,γ-diphenyl-γ-hydroxycrotonic Acid.—The lactone (5 g.) was dissolved in dilute ammonia and the excess ammonia boiled off. The solution was cooled and silver nitrate was added. A white precipitate was formed which immediately turned black. This silver salt was dried over sulfuric acid and boiled with 15 g. of ethyl iodide in 40 cc. of dry ether for thirteen hours. The ethereal solution was filtered and evaporated, leaving a red oil which deposited a small amount of white crystals. After two recrystallizations these melted at 141° and were shown to be identical with the ethyl α-cyano-β-benzoylcinnamate obtained by condensing benzil with cyano-acetic ester.

Anal. Calcd. for $C_{19}H_{15}O_3N$: C, 74.7; N, 4.96. Found: C, 75.2; H, 5.18.

Preparation of Ethyl α-Cyano-β-benzoylcinnamate.—Benzil (8.4 g.) was added to a solution of 1 cc. of piperidine in 60 cc. of absolute alcohol. To this was added 9.02 g. of cyano-acetic ester, when a purple color was formed which disappeared almost immediately. The mixture was heated on a water-bath under a reflux condenser for five hours and allowed to stand overnight, when crystallization took place. After acidification the crystals were filtered and washed with alcohol and usually were found now to contain no unchanged benzil and gave a constant melting point of 141° without further purification; yield, 8.2 g.

Anal. Calcd. for $C_{19}H_{15}O_3N$: C, 74.7; H, 4.96; N, 4.6. Found: C, 74.4; H, 4.97; N, 5.1.

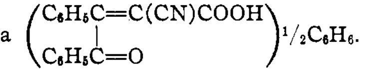
It is necessary that alcohol be not used in excess of the amount mentioned to prevent the decomposition of the benzil into benzaldehyde and ethyl benzoate. Sodium ethylate may also be used as a condensing agent.

The ester crystallizes from alcohol as colorless needles and is soluble in benzene, chloroform and hot acetic acid. It does not absorb bromine.

Benzil is readily obtained from this ester by dissolving in acetone and adding an aqueous solution of potassium permanganate.

α-Cyano-β-benzoylcinnamic Acid.—Five grams of the ester was allowed to stand with a solution of potassium hydroxide in alcohol. After fifteen minutes the crystals had all dissolved and the solution no longer became turbid on diluting with water. This was poured into 300 cc. of water and acidified and the brown oil thrown down was extracted with ether. The ether was dried and evaporated and the brown oil dissolved in benzene. When ligroin was added an oil was again obtained which solidified on standing. After another recrystallization from benzene and ligroin white crystals were obtained which softened at 112° and melted at 116–117°; yield of pure crystals, 58%.

The substance was found to contain benzene of crystallization and have the constitution represented by the formula



$$\left(\begin{array}{l}C_6H_5C{=}C(CN)COOH\\ \quad|\\ C_6H_5C{=}O\end{array}\right)^1/_2C_6H_6.$$

This substance gave an equivalent by titration of 318. Calcd. for $C_{17}H_{11}O_3N\cdot{}^1/_2C_6H_6$: equivalent, 316.

The benzene can be driven off by heating in an oven at 90° for several hours. The substance then melted at 135–136°; equivalent, 283. Calcd. for $C_{17}H_{11}O_3N$: equivalent, 277.

Colorless needle-like crystals, m. p. 135–136°, can be obtained by recrystallizing from alcohol.

Benzil can readily be obtained from α-cyano-β-benzoylcinnamic acid by oxidizing with potassium permanganate in sodium carbonate solution.

Ethyl (1,1,7)-Trimethyl-2,3-dicyano-2-hydroxy-bicyclo-(1,2,2)-heptane-3-cyano-acetate.—Ethyl camphorylidene-cyano-acetate (13.9 g.) prepared according to Forster and Withers[6] was dissolved in 85 cc. of absolute alcohol at 40–50°. Thirteen and seven-tenths g. of potassium cyanide in 40 cc. of water was added and the mixture kept at 40–50° for one hour. Six grams of glacial acetic acid in 25 cc. of water was added carefully without mixing. Overnight the product separated as long white needles. The solution had lost all of the yellow color of the camphorylidene-cyano-acetic ester, indicating that the reaction had gone to completion. The crystals were filtered and washed with 50% alcohol. The total yield obtained was almost the theoretical. After recrystallization from hot alcohol the crystals melted at 202–204°. The substance is soluble in hot alcohol, chloroform and benzene; $[\alpha]_D$ +115.1°.

Anal. Calcd. for $C_{17}H_{21}O_3N_3$: C, 64.8; H, 6.7; N, 13.3. Found: C, 64.6; H, 6.86; N, 13.3.

Summary

1. The lactone of α-cyano-β,γ-diphenyl-γ-hydroxycrotonic acid has been obtained as the principal product from the condensation of benzoin with ethyl cyano-acetate. Various reactions of this substance support the structure assigned.

2. *m*-Nitrobenzil is readily obtained by oxidizing the acid produced by nitrating the foregoing lactone.

3. Benzil has been condensed with ethyl cyano-acetate and the behavior of the product toward hydrogen cyanide has been compared with that of ethyl camphorylidene-cyano-acetate toward the same reagent.

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