[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

DELTA KETONIC NITRILES AND THEIR RELATION TO CYCLIC COMPOUNDS. III

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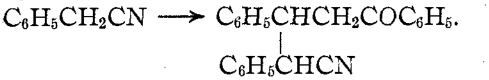
In earlier papers[1] it was shown that many δ-ketonic nitriles can be transformed into cyclic compounds with great ease. The conditions under which these transformations take place were adequately defined and some of the steps in the process were clearly established; but much of the mechanism was left in doubt. In continuation of this work we have studied a somewhat different type of δ-ketonic nitrile which was obtained by adding benzyl cyanide to benzalacetophenone: $C_6H_5CH:CHCOC_6H_5$ +



$$C_6H_5CH_2CN \longrightarrow \begin{array}{l} C_6H_5CHCH_2COC_6H_5. \\ \quad\;\;| \\ C_6H_5CHCN \end{array}$$

This reaction was expected to yield stereo-isomeric nitriles and, therefore, to furnish material for studying the influence of configuration upon the ease of ring formation. It seemed probable, moreover, that these nitriles would be less sensitive than those obtained by adding derivatives of cyano-acetic acid, and consequently better adapted for clearing up obscure points of mechanism. It was hoped, also, that they would lead to a particularly interesting type of cyclopropane derivatives.

Most of these expectations were realized. The reaction gives two stereo-isomeric compounds which are less sensitive than the addition products obtained with derivatives of cyano-acetic acid but which can, nevertheless, be transformed into the different types of cyclic compounds described in the earlier papers. With these isomers it was possible to relate ease of ring formation to configuration, to secure definite evidence on the mechanism by which pyridine derivatives are formed, and to make cyclopropane derivatives that in some respects behave differently from those obtained from the addition products described heretofore.

That the two benzyl cyanide addition products are stereo-isomeric open-chained nitriles was established by esterification and hydrolysis. Methyl alcoholic hydrogen chloride converts the higher-melting product into an ester that melts at 150°; the lower product into an isomeric ester melting at 139°. When these esters are hydrolyzed they give the same acid, and this on re-esterification gives the ester that melts at 139°. The only substance other than the open-chained nitrile (I) which could give these products is the isomeric tetrahydro-pyridine derivative (II). This was made and found to be different.

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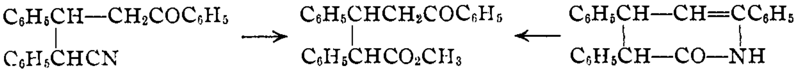
[1] THIS JOURNAL (a) **44**, 2536 (1922); (b) **44**, 2903 (1922).



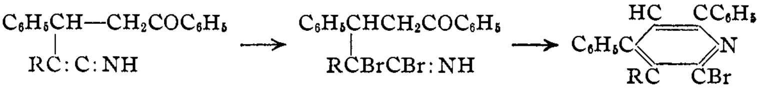
$$\underset{\displaystyle C_6H_5CHCN}{C_6H_5CH{-}CH_2COC_6H_5} \longrightarrow \underset{\displaystyle C_6H_5CHCO_2CH_3}{C_6H_5CHCH_2COC_6H_5} \longleftarrow \underset{\displaystyle C_6H_5CH{-}CO{-}NH}{C_6H_5CH{-}CH{=}CC_6H_5}$$

I III II

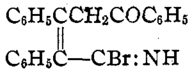
The isomeric addition products are readily transformed into each other as well as into the hydropyridine derivative. When a dilute solution of either of the isomers in glacial acetic acid is saturated with hydrogen bromide, the nitrile rapidly changes to the tetrahydro-pyridine derivative. Both nitriles give the same cyclic compound which is obtained in nearly the calculated quantity. When a concentrated solution of the lower-melting compound, which is much more soluble than its isomer, is treated in the same way, the higher-melting isomer is deposited and the solution contains only the tetrahydro-pyridine derivative. Owing to the rapidity with which the lower-melting nitrile is changed to its isomer and the probability that the change in the reverse direction takes place with equal ease, it was impossible to establish with certainty from which isomer the cyclic compound is formed; but since the lower-melting nitrile and the hydropyridine derivative give the same product when esterified with methyl alcoholic hydrogen chloride, these substances must be similar in configuration.

The relation between configuration and the ease of ring formation is shown more clearly by a comparison of the products which are obtained when two isomeric nitriles are treated with bromine; the lower-melting nitrile gives only cyclic compounds while the higher-melting isomer, when treated in the same way, gives almost exclusively open-chained bromine compounds. The ease of ring formation, therefore, depends on space relations, and differences that are noted in comparing substances of which only one modification is available may be due entirely to differences in configuration.

In earlier papers the formation of bromopyridines from δ-ketonic nitriles was accounted for by assuming that bromine first adds to the imide form of the nitrile, and that the resulting addition product loses both hydrogen bromide and water.

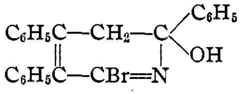


We have now for the first time secured an intermediate product in this reaction. When the lower-melting isomer was brominated in chloroform we generally obtained variable quantities of a substance which is evidently closely related to the bromopyridine into which it passes when treated with potassium acetate or with dehydrating agents. The composition of this substance differs from that of the bromopyridine by one molecule of water. It contains an atom of hydrogen that can be replaced with a benzoyl group by means of the Schotten-Baumann reaction. As it can be recrystallized from alcohols and does not lose hydrogen bromide when digested with alkalies it cannot be an imide bromide such as is represented by IV. It must, therefore, be the cyclic hydroxyl compound (V) which represents the next to the last step in the formation of the bromopyridine (VI).

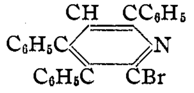


$$\begin{array}{l} C_6H_5CCH_2COC_6H_5 \\ \quad\| \\ C_6H_5C—CBr{:}NH \end{array}$$

IV

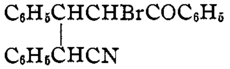


V



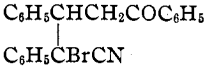
VI

The bromopyridine (VI) is generally the only product formed in brominating the lower-melting nitrile. It is also occasionally formed in small quantities from the higher-melting nitrile, but usually the mixture obtained from this substance is composed entirely of two monobromo substitution products. These must be open-chained compounds because potassium acetate converts them into cyclopropane derivatives. They cannot be the γ-bromo compounds represented by VII, because neither of them can be either hydrolyzed to an acid or esterified with methyl alcoholic hydrogen chloride. They behave, therefore, like open-chained tertiary nitriles and hence must be the two stereo-isomeric α-bromo compounds represented by Formula VIII.



$$\begin{array}{l} C_6H_5CHCHBrCOC_6H_5 \\ \quad| \\ C_6H_5CHCN \end{array}$$

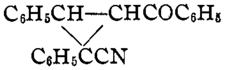
VII



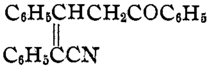
$$\begin{array}{l} C_6H_5CHCH_2COC_6H_5 \\ \quad| \\ C_6H_5CBrCN \end{array}$$

VIII

From these open-chained bromine compounds alkaline reagents remove hydrogen bromide and form three isomeric substances. Any one of these might be either a cyclopropane derivative (IX) or an ethylenic nitrile (X) or (XI); none can be a pyridine derivative, because all give one or the other of the saturated open-chained nitriles when reduced.

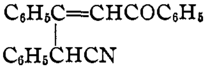


IX



$$\begin{array}{l} C_6H_5CHCH_2COC_6H_5 \\ \quad\| \\ C_6H_5CCN \end{array}$$

X



$$\begin{array}{l} C_6H_5C{=}CHCOC_6H_5 \\ \quad| \\ C_6H_5CHCN \end{array}$$

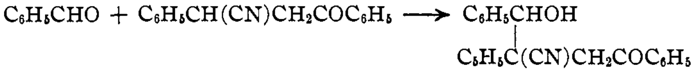
XI

The ethylenic ketone (XI) has been made synthetically by adding benzyl cyanide to phenylbenzoyl acetylene;[2] it is different from all of the substances obtained from the bromine compounds. Moreover, it is not changed when it is boiled with potassium acetate, a treatment which converts two of the products from the bromine compounds into the third. It seemed unlikely, therefore, that any of these was one of the ethylenic ketones. Definite proof that all three of them are cyclopropane derivatives was finally obtained by studying their behavior towards bases. They are not very sensitive to weak bases, but alcoholic potassium hydroxide converts all three into an hydroxyl compound which is formed by addition of water. Of the many possible formulas for a product obtained

[2] Kohler and Barrett, This Journal, **46,** 747 (1924).

in this way all but two were eliminated by synthesizing the same substance from benzaldehyde and α-phenyl-β-benzoyl-propionitrile.

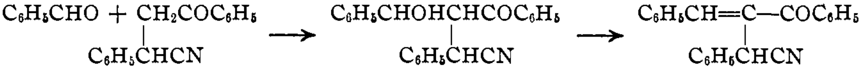
Lapworth[3] found that when phenylbenzoyl-propionitrile combined with an α,β-unsaturated ketone in the presence of the bases the hydrogen from the carbon atom holding the cyanogen group was involved in the reaction. A similar reaction with benzaldehyde would proceed in accordance with the scheme,



$$C_6H_5CHO + C_6H_5CH(CN)CH_2COC_6H_5 \longrightarrow \begin{array}{l} C_6H_5CHOH \\ \quad | \\ C_6H_5C(CN)CH_2COC_6H_5 \end{array}$$

XII

The only other possibility worth while to consider was that the hydrogen alpha to carbonyl was affected, leading to the reaction represented by the equation,

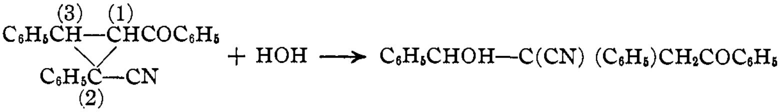


$$\begin{array}{c} C_6H_5CHO + CH_2COC_6H_5 \\ | \\ C_6H_5CHCN \end{array} \longrightarrow \begin{array}{c} C_6H_5CHOHCHCOC_6H_5 \\ | \\ C_6H_5CHCN \end{array} \longrightarrow \begin{array}{c} C_6H_5CH{=}C{-}COC_6H_5 \\ | \\ C_6H_6CHCN \end{array}$$

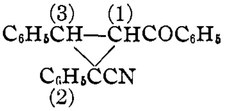
XIII XIV

An hydroxyl compound of the type represented by XIII, in which active hydrogen and hydroxyl are in combination with adjoining carbon atoms, would lose water with great ease, while one of the type represented by XII would be incapable of forming an unsaturated compound. The substance obtained in this reaction is the same as that which is formed by the action of potassium hydroxide on our product. It can be dissolved in concd. sulfuric acid and reprecipitated by adding water to the solution. When it is boiled with acetic anhydride it does not lose water but forms an acetate. It is, therefore, the hydroxyl compound represented by XII, and the substances from which it was formed by the action of alkali must be three of the four possible cyclopropane derivatives represented by IX.

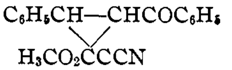
The facts, which have been cited, show that potassium hydroxide in this case opens the ring between the carbon atoms numbered 1 and 3.



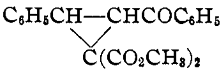
As these are cyclopropane derivatives of a somewhat unusual type we have compared their behavior towards bases with that of two isomeric cyclopropane derivatives described in an earlier paper.[1a]



IX



XV



XVI

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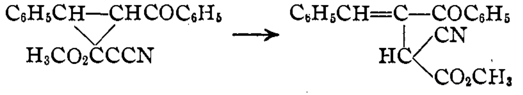
[3] Hann and Lapworth, *J. Chem. Soc.*, **85**, 1356 (1904).

We found that the cyano ester derivatives (XV), like the malonic ester derivatives (XVI), are extremely sensitive to bases, being rapidly attacked by magnesium methylate which has no effect on the benzyl cyanide derivatives. The reaction is involved and it has not been possible as yet to establish the nature of all the compounds that are formed, but the principal products are unsaturated compounds which form metallic derivatives, give benzaldehyde when oxidized with permanganate, and are isomeric with the cyclopropane derivatives from which they originate. They are, therefore, analogous to the products from the malonic ester derivatives, and they result from opening the ring between the carbon atoms numbered 2 and 3.



XVII

Preparation of the Nitriles

It is fairly easy to add benzyl cyanide to benzalacetophenone in the presence of sodium methylate. When only sufficient condensing agent is used to produce definite alkalinity, the principal product is a sparingly soluble substance composed of two molecules of the ketone and one of the cyanide. This same trimolecular product is also formed in large quantities in the presence of one equivalent of the methylate when the addition takes place in concentrated solutions. Its formation can be prevented almost completely by using one equivalent of condensing agent, operating in solutions of moderate concentrations and employing vigorous stirring to prevent the mixture from becoming inhomogeneous.

The following procedure for making the primary addition products was found to be satisfactory.

In a 2-liter flask, fitted with reflux condenser, mechanical stirrer and dropping funnel, a solution of 208 g. of benzalacetophenone and about one equivalent of sodium methylate in 750 cc. of dry methyl alcohol was heated to the boiling point. The heating was then stopped, the stirrer started and 120 g. of benzyl cyanide added at a rate sufficient to cause rapid boiling of the mixture, about five minutes being required for adding the entire amount. The mixture was boiled for 15 minutes, acidified with 65 cc. of glacial acetic acid without interrupting the stirring, transferred to a beaker and cooled first in ice water and finally in a freezing mixture, the stirring being continued for an hour to insure the separation of small crystals. The solid was then separated by filtration under suction, washed with a little ether, and boiled with 800 cc. of alcohol. This dissolved all of the primary addition product and left nearly all of the trimolecular compound. When the alcoholic solution was cooled it deposited a mixture of the two nitriles which was practically free from other substances. The average yield was 85%.

The mixture of nitriles was separated by fractional crystallization first from ethyl and finally from methyl alcohol. By means of ethyl alcohol it was easy to isolate 45–50% of the higher-melting isomer, the rest of the material being deposited as a mixture that melted fairly constantly at 92–93°. From this the lower-melting compound was obtained in yields of 20–25% by recrystallization from methyl alcohol. Both addition products crystallize in prisms. The higher-melting compound is most easily purified by dissolving it in the minimum quantity of methyl alcohol, diluting this solution with water, and then cooling it. It melts at 118°. The solubility of the lower-melting isomer is nearly the same in cold and hot methyl alcohol. It melts at 109°.

Analyses. Calc. for $C_{23}H_{19}ON$: C, 84.9; H, 5.9. Found: (118°) C, 84.3; H, 6.1: (109°) C, 84.9; H, 5.9.

The Methyl Esters.—The methyl esters of the acids corresponding to these nitriles were made by saturating solutions of the nitriles in methyl alcohol with hydrogen chloride, allowing the mixture to stand at the ordinary temperature for three days, and then pouring them into water and recrystallizing the precipitates from methyl alcohol. Both esters crystallize in needles; the one from the higher-melting nitrile melts at 150° while that from the lower-melting isomer melts at 139°.

Analyses. Calc. for $C_{24}H_{22}O_3$: C, 80.4; H, 6.1. Found: (150°) C, 80.5; H, 6.1: (139°) C, 80.2; H, 6.1.

α,β-Diphenyl-γ-benzoyl Butyric Acid.—Neither of the nitriles could be hydrolyzed to the corresponding acid by boiling it with bases. Ammonia was given off slowly when either of them was boiled with alcoholic potassium hydroxide; but the only substances that could be isolated from the resulting mixture were the "trimolecular addition product," phenylacetic acid and unchanged nitrile. The first effect of the base, therefore, is to reverse in part the addition reaction. The resulting benzalacetophenone combines with unchanged nitrile to form the more complex addition product while the benzyl cyanide is hydrolyzed to phenylacetic acid.

The acid was, however, easily obtained by hydrolyzing the esters with alkalies. Both esters gave the same acid. This was purified by crystallization from methyl alcohol from which it separated in needles melting at 239°. When re-esterified with methyl alcoholic hydrogen chloride, the acid gave only the ester melting at 150°.

Analyses. Calc. for $C_{23}H_{20}O_3$: C, 80.2; H, 5.8. Found: C. 80.2; H, 6.0.

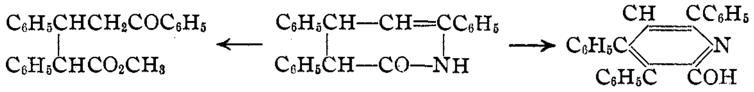
The Trimolecular Product.—This was formed in variable quantities during the addition reaction as well as by the action of alcoholic potassium hydroxide on the nitriles. It is very slightly soluble in alcohol but can be purified by recrystallization from chloroform. It separates in microscopic needles and melts at 257°.

Analyses. Calc. for $C_{38}H_{31}O_2N$: C, 85.8; H, 5.8; N, 2.7. Found: C, 85.6; H, 5.8; N, 2.6.

Isomerization of the Nitriles

Both addition products are readily soluble in chloroform and in carbon tetrachloride; but when a concentrated solution of the higher-melting compound in either solvent was saturated with hydrogen bromide, nearly all of the substance was reprecipitated. When a similar solution of the lower-melting nitrile was treated in the same way the higher-melting isomer was precipitated. In solutions sufficiently dilute to avoid these precipitations hydrogen bromide produced very little change, probably because all concentrations were low. Chloroform is, therefore, an excellent solvent in which to turn the lower- into the higher-melting isomer, but is not suitable for rearranging either nitrile into a cyclic compound.

In glacial acetic acid, which is an excellent solvent both for the nitriles and for hydrogen bromide, the substances are rapidly rearranged into the same cyclic compound. Proof that this is a tetrahydro-pyridine derivative was secured by treating it with methyl alcoholic hydrogen chloride which formed an open-chained ester, and by subjecting it to the action of nitrous acid which converted it into an hydroxypyridine.



III II XVIII

2-Keto-3,4,6-triphenyl-tetrahydro-pyridine (II).—A solution containing 20 g. of the nitrile (118°) in 300 cc. of glacial acetic acid was saturated with dry hydrogen bromide while immersed in an ice-bath, and then kept at the ordinary temperature for two days. It became cloudy when it was shaken and deposited a crystalline solid. This was separated by filtration and recrystallized from methyl alcohol. The filtrate was poured into water which precipitated a resin from which 2 g. more of the same material was isolated, making the total yield of pure product 18 g., or 90%.

The lower-melting isomer, treated in the same way, gave the same product; but more resinous material was formed, it was more difficult to get a pure cyclic compound and the yield was less.

Analyses. Calc. for $C_{23}H_{19}ON$: C, 84.9; H, 5.8. Found: C, 85.0; H, 5.9.

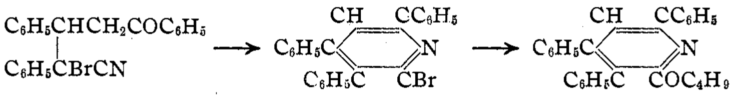
The tetrahydro-pyridine derivative crystallizes in needles and melts at 173°. It is insoluble in potassium hydroxide, instantaneously decolorizes bromine and is readily changed into an ester of the open-chained acid. Thus the methyl ester melting at 139° (III) was obtained in the calculated quantity when a methyl alcoholic solution containing 1 g. of the substance was saturated with hydrogen chloride, allowed to stand overnight at the ordinary temperature and then poured into water.

2-Hydroxy-3,4,6-triphenyl-pyridine (XVIII).—In order to prove the cyclic character of the tetrahydro-pyridine derivative a concentrated aqueous solution of 1.5 g. of sodium nitrite was added slowly to a solution of 2 g. of the substance in 40 cc. of glacial acetic acid. The solution gradually turned brown and in the course of a week deposited a few fluorescent prisms. It was diluted with water which precipitated a gum from which 0.7 g. of the hydroxypyridine was isolated by treatment with methyl alcohol. The substance crystallizes in fluorescent prisms and melts at 263°.

Analyses. Calc. for $C_{23}H_{17}ON$: C, 85.4; H, 5.2. Found: C, 85.4; H, 5.3.

Bromination of the Lower-melting Nitrile

The result of brominating the lower-melting nitrile depends to some extent upon the solvent, but in no case could any open-chained substances be detected in the product. In glacial acetic acid only one compound was formed, the bromopyridine derivative (VI). In chloroform this was the principal product, but along with it the bromohydroxy-tetrahydropyridine was usually formed in variable amounts. The structure of the bromopyridine derivative was established by making it from an open-chained compound of known structure, as well as by proving that the bromine can be replaced by alkoxyl groups—a characteristic reaction of 2-bromopyridines.



XIX VI XX

2-Bromo-3,4,6-triphenyl-pyridine (VI).—A solution of 5 g. of the nitrile (109°) in hot glacial acetic acid was treated with a little bromine and exposed to sunlight which was usually necessary to start the bromination. An acetic acid solution containing 2.5 g. of bromine in 5 cc. was then added slowly to the boiling solution. After all had been added the mixture was boiled for 20 minutes, cooled and poured into a dilute solution of sodium bisulfite. The gummy precipitate, when recrystallized from alcohol, gave 5.3 g. of pure bromine compound.

Analyses. Calc. for $C_{23}H_{16}NBr$: C, 71.5; H, 4.2. Found: 71.6; H, 4.3.

The bromopyridine is very soluble in ether, chloroform and boiling ethyl alcohol, moderately soluble in glacial acetic acid and sparingly soluble in cold alcohol. It crystallizes in characteristic needles which appear to be slightly fluorescent, and it melts at 110°. It is less active than any of the 2-bromopyridines described in the earlier papers, being but little affected by prolonged boiling with sodium methylate and ethylate. Sodium butylate, however, replaces the bromine with butoxyl.

2-Butoxy-3,4,6-triphenyl-pyridine (XX).—When a solution containing 4 g. of the bromopyridine and 2 g. of sodium in 65 cc. of *n*-butyl alcohol was boiled it soon became cloudy with sodium bromide. After boiling for two hours the salt was filtered from the hot solution. This on cooling deposited clusters of small needles which were recrystallized from methyl alcohol. The pure product melted at 94°.

Analysis. Calc. for $C_{27}H_{25}ON$: C, 85.5; H, 6.6. Found: C, 85.3; H, 6.4.

2-Bromo-3,4,6-triphenyl-6-hydroxy-dihydropyridine (V).—When the lower-melting nitrile was brominated in chloroform it frequently gave, along with the bromopyridine, some of this hydroxyl compound. In one experiment the hydroxyl compound constituted 40% of the product, but in most cases the amount was much smaller. It was isolated by recrystallizing the residues, from which most of the bromopyridine had been removed, from methyl alcohol and thus obtained in colorless needles melting at 100°.

Analyses. Calc. for $C_{23}H_{18}ONBr$: C, 68.3; H, 4.5. Found: C, 68.6; H, 4.5.

THE BENZOATE.—In order to establish the presence of an hydroxyl group, a solution containing 2 g. of the substance and 4 g. of benzoyl chloride in 15 cc. of ether was shaken with 25 cc. of dil. sodium hydroxide solution until the benzoyl chloride had disappeared. The ethereal layer was removed and evaporated. It left a mixture which when separated by crystallization from methyl alcohol gave 1 g. of the 2-bromopyridine and 0.6 g. of a new substance which crystallized in pointed rods and melted at 137°.

Analyses. Calc. for $C_{30}H_{22}O_2NBr$: C, 70.8; H, 4.3. Found: C, 70.8; H, 4.2.

The formation of the 2-bromopyridine during benzoylation illustrates the ease with which the hydroxyl compound loses water. In an experiment designed to test the activity of the bromine in the substance, a methyl alcoholic solution containing 1.8 g. of it and 4 g. of potassium acetate was boiled for several hours. The result was 1.5 g. of the bromopyridine, only water having been eliminated. The bromopyridine also was obtained in calculated quantities when solutions of the substances in methyl alcohol or glacial acetic acid were saturated with hydrogen bromide. None of it, therefore, would be expected to remain in brominations carried out in these solvents. In accordance with this it was found only when the nitrile was brominated in chloroform where its insolubility protected it from dehydration.

Bromination of the Higher-melting Nitrile

Bromination of the higher-melting nitrile invariably led to the formation of two open-chained monobromo compounds. The relative amounts of these varied with the solvents and other conditions. In chloroform small quantities of 2-bromopyridine and the hydroxy-dihydropyridine were frequently observed, but these may have been due to contamination of the nitrile with its lower-melting isomer. The lower-melting bromo compound is in part converted into its isomer when subjected to the action of hydrogen bromide; as the higher-melting compound is more easily handled the solutions containing the hydrogen bromide and the mixed bromo derivatives were usually boiled for 20 minutes after the bromination had been completed.

α-Bromo-α,β-diphenyl-γ-benzoyl-butyronitrile (VIII).—A solution of 30 g. of the nitrile (118°) in 100 cc. of chloroform was heated with a little bromine in direct sunlight until bromination started. The rest of the calculated amount of bromine was then added and the boiling continued for 20 minutes longer. The cooled solution was shaken in succession with sodium bisulfite, dilute alkali and water, and freed from chloroform by distillation. The residue solidified; it was boiled for an hour with methyl alcohol which extracted the lower-melting bromo compound and left the isomer in practically pure condition. The lower-melting compound was recrystallized from methyl alcohol. The yields were 55% of the substance melting at 172° and 35% of the one which melts at 131°. When the mixture was not boiled after all the bromine had been added the yields were 30% of the higher-melting compound, and 60% of its isomer.

Analyses. Calc. for $C_{23}H_{18}ONBr$: Br, 19.8. Found: (172°) 19.4; (131°) 19.8.

Both bromine compounds crystallized in plates. Neither of them could be hydrolyzed to the corresponding acid, or changed to the corresponding ester. Alkaline reagents removed hydrogen bromide and formed a cyclopropane derivative. In methyl alcohol neither hydrogen chloride nor hydrogen bromide had any effect on either substance. In glacial acetic acid hydrogen bromide first turned the lower-melting compound into its isomer and then slowly in the course of weeks converted this into the 2-bromopyridine. These are characteristic properties of α-bromo nitriles containing a tertiary cyanogen group.

The Cyclopropane Derivatives

Three of the four possible stereo-isomeric cyclopropane derivatives were obtained by boiling methyl alcoholic solutions of the α-bromo compounds with potassium acetate. Each of the bromine compounds gave all three of these cyclopropane derivatives, the result depending more on the duration of the heating than on the bromine compound that was used. If the operation is interrupted before the reaction is complete the principal product is the isomer melting at 143°; it is difficult to separate a mixture composed of this substance and unchanged bromine compound. After more prolonged heating the result is a mixture composed almost entirely of the isomers melting at 143° and 172°; these are easily separated from each other. On still longer heating a third isomer melting at 178° is formed in large quantities. As this prolonged heating leads to the formation of a larger quantity of resinous by-products and the mixture of the derivatives melting at 172° and 178° tends to separate in mixed crystals which melt at 145° it is better to secure the highest-melting isomer by rearrangement of one of the lower-melting forms. This is readily accomplished by boiling either one with methyl alcoholic potassium acetate. The procedure for making the cyclopropane derivatives was as follows.

A suspension of 10 g. of the bromo compound and 20 g. of fused potassium acetate in 50 cc. of dry methyl alcohol was boiled on a steam-bath for five hours during which the bromine compound disappeared and the liquid turned yellow. It was first shaken with water, then ether was added and the whole shaken again. The cyclopropane derivative melting at 172° usually separated as a crystalline deposit between the water and ether layers. The water layer was drawn off, the ether layer filtered, the solid washed with ether and recrystallized from benzene or glacial acetic acid, from which it separated in six-sided prisms.

The ethereal filtrate was evaporated; it left the isomeric cyclopropane derivative melting at 143° embedded in a yellow gum. This substance was purified by repeated recrystallization from methyl alcohol which deposited it in prisms.

The third isomer which was obtained after prolonged heating, or better by boiling a methyl alcoholic solution of either of the other two for several hours with potassium acetate, was purified by crystallization from acetic acid. It crystallizes in fine needles and melts at 178°.

Analyses. Calc. for $C_{23}H_{17}ON$: C, 85.4; H, 5.3. Found: (143°) C, 85.4; H, 5.2: (172°) C, 85.6; H, 5.5: (178°) C, 85.4; H, 5.2.

The isomer melting at 178°, as would be expected, is the most stable of the three; it is, indeed, surprisingly stable, distilling almost without decomposition at 275° under a pressure of 29 mm. None of the three substances reduces permanganate, and none could be esterified, the tertiary cyanogen group being, as usual, completely inactive.

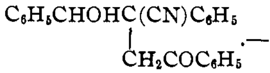
REDUCTION.—The three cyclopropane derivatives are easily reduced to the saturated open-chained nitriles. The reduction was carried out as follows. Three g. of zinc dust and 6 cc. of water were added to a solution of 2 g. of the substance in 25 cc. of glacial acetic acid. The mixture was boiled for an hour, then poured into water which precipitated a gum that solidified when it was brought in contact with alcohol. The form melting at 172° gave the nitrile melting at 109°; both of the others were reduced to the isomeric nitrile melting at 118°.

ACTION OF ALKALIES.—Preliminary tests showed that all three cyclopropane derivatives are attacked by alkalies and that the principal products are the same with sodium methylate, sodium ethylate and methyl alcoholic potassium hydroxide. Since the last gave the smallest amount of oily by-product, it was used. A solution containing 1 g. of potassium hydroxide in 4 cc. of water was added to 5 g. of the cyclopropane derivative suspended in 60 cc. of methyl alcohol. The mixture was boiled for five hours during which the cyclopropane dissolved and the solution turned brown. The brown solution was diluted with water which precipitated a thick oil that gradually solidified. After purification by recrystallization from methyl alcohol, the weight of pure product was 4 g., representing 80% of the cyclopropane derivative used.

By this treatment the cyclopropane melting at 172° was converted into a substance melting at 156°, while the others gave a product melting at 218°.

Analyses. Calc. for $C_{23}H_{19}O_2N$: C, 80.9; H, 5.5. Found: (172°) C, 80.9; H, 5.6: (218°) C, 80.9; H, 5.6.

β-Cyano-β,γ-diphenyl-γ-hydroxy-butyrophenone,



$$\begin{array}{l}C_6H_5CHOHC(CN)C_6H_5\\ |\\ CH_2COC_6H_5\end{array}$$

.—The lower-melting compound was recrystallized from methyl alcohol, the higher-melting from glacial acetic acid. Both crystallize in stout needles. They are, doubtless, stereo-isomers because they behave in the same way and are readily converted into each other. Thus a saturated solution of the lower-melting compound in glacial acetic acid gradually deposited the less soluble isomer, but when a methyl alcoholic solution of the higher-melting compound was saturated with hydrogen chloride, allowed to stand for three days, and then diluted with water, it yielded only the lower-melting isomer. The intensely crimson solutions that are obtained by dissolving the substances in cold concd. sulfuric acid, when diluted with water, also yield only the lower-melting compound.

As the higher-melting hydroxyl compound is more easily obtained in a pure condition, this was used in most of the following experiments. It is very sparingly soluble in ether, moderately soluble in acetone and ethyl acetate and readily soluble in glacial acetic acid, from which it separates very slowly on cooling. When heated above its melting point it dissociates smoothly into benzaldehyde and α-phenyl-β-benzoylpropionitrile.

THE ACETATE.—A solution of 5 g. of the hydroxyl compound (218°) in 25 cc. of acetic anhydride containing a few drops of sulfuric acid was boiled for two hours, and then poured slowly into iced sodium carbonate solution. The resulting brown solid was purified by crystallization from a mixture of methyl alcohol and water. It was thus obtained in stout needles that melted at 121°.

Analyses. Calc. for $C_{25}H_{21}O_3N.H_2O$: C, 74.6; H, 5.6. Found: C, 74.7; H, 5.5.

The composition of the product corresponds to that of an acetate of the hydroxyl compound plus a molecule of water. No water could be removed from the substance by heating it, other decomposition products being formed at a relatively low temperature, but the anhydrous form was obtained by boiling it with acetyl chloride and recrystallizing from the same solvent.

Analyses. Calc. for $C_{25}H_{23}O_3N$: C, 78.3; H, 5.5. Found: C, 78.3; H, 5.7.

The anhydrous acetate crystallized in microcrystalline plates and melted at 142°. When it was recrystallized from aqueous methyl alcohol it reverted to the hydrated form. The two hydroxyl compounds gave the same acetate because acetic anhydride rapidly converts the lower- into the higher-melting compound. When the acetate was hydrolyzed by shaking an ethereal solution with aqueous ammonia it gave the lower-melting hydroxyl compound.

OXIDATION.—A solution containing 5 g. of the aldol and 1 g. of chromic acid in 25 cc. of glacial acetic acid rapidly turned green when heated. It was boiled for two hours, and then poured into 175 cc. of water. The pasty precipitate solidified when it was allowed to stand in contact with the mother liquor overnight.

α-Phenyl-α-cyano-α,β-dibenzoyl Ethane,

$$\begin{array}{l}C_6H_5C(CN)COC_6H_5\\ |\\ CH_2COC_6H_5\end{array}$$

.—The oxidation product of the hydroxyl compound was purified by recrystallization from methyl alcohol. It separated in prisms and melted at 206°. The yield of pure product was 3 g.

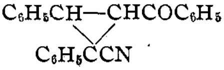
Analyses. Calc. for $C_{23}H_{17}O_2N$: C, 81.4; H, 5.2. Found: C, 81.4; H, 4.9.

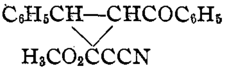
SYNTHESIS.—The properties of the hydroxyl compound supplied very strong evidence as to its structure, but by opening the cyclopropane ring in another manner it was possible to write formulas of other substances that might show similar properties.

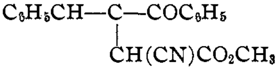
To exclude these it was necessary to resort to synthesis. To this end sodium methylate which had been made by dissolving 3.5 g. of sodium in 50 cc. of ordinary methyl alcohol was added to a solution of 35 g. of the nitrile and 17 g. of benzaldehyde in 300 cc. of the same solvent which was contained in a flask fitted with reflux condenser and dropping funnel. The mixture turned yellow, became hot, and finally boiled vigorously. As soon as the temperature began to fall, the mixture was filtered into a beaker, acidified, and chilled in ice water. It deposited a bright yellow, crystalline solid which became colorless after repeated recrystallization from acetic acid. The melting point of this substance was 218°, and the melting point of a mixture of this substance with the higher-melting hydroxyl compound obtained by opening the cyclopropane ring with alkali likewise was 218°.

Action of Bases on Related Cyclopropane Derivatives

An earlier paper[1a] contained a description of two isomeric compounds which are closely related to the cyclopropane derivatives that we have studied.


IX


XV


$$C_6H_5CH{-}\underset{\displaystyle CH(CN)CO_2CH_3}{\underset{|}{C}}{-}COC_6H_5$$
XVI

The structure of the cyano esters (XV) was established by the method of preparation, their indifference to permanganate and by the ease with which they are reduced to saturated open-chained compounds.

We have studied the behavior of these substances towards bases. Both react readily with magnesium methylate at the ordinary temperature, the lower-melting compound more rapidly than its isomer, possibly because of its greater solubility. No conditions could be found under which either substance gave a single product when treated with a base, and in no case could all the products of the reaction with a base be isolated, but it was possible to prove that the principal reaction results in the formation of the unsaturated open-chained compound. This was isolated by the following procedure.

A suspension of magnesium methylate was made by allowing 6 g. of magnesium to act on 100 cc. of dry methyl alcohol in the presence of a trace of mercuric chloride. Fifteen g. of the cyclopropane derivative was added to this suspension and the mixture shaken at the ordinary temperature. It first turned yellow, then a deep orange as the amount of magnesium derivative increased. After it had been shaken for 20 minutes it was poured into a freezing mixture of ice and hydrochloric acid which was vigorously stirred during the operation. This produced a light colored precipitate that collected as a sticky gum as the temperature rose. A small quantity of methyl alcohol dissolved nearly the whole of this gum, leaving only 0.7 g. of solid which proved to be the isomeric cyclopropane derivative melting at 180°.

The methyl alcoholic solution was mixed with ether, the mixture freed from alcohol by washing with calcium chloride solution and from strong acids by extraction with bicarbonate, and then shaken with a 50% solution of potassium carbonate. This led to the separation of three layers, an ethereal layer containing non-acidic products, a layer composed mostly of the strong carbonate solution in which the potassium derivative is sparingly soluble and, between the two, a deep red layer containing most of the metallic derivative. The two aqueous layers were drawn off, acidified and extracted with ether. The residue, after removing the ether, weighed about 7.5 g., or half the weight of the cyclopropane derivative used in the experiment. When it was dissolved in twice its volume of methyl alcohol and set aside, it deposited nearly 4 g. of a solid product; the remainder could not be obtained in a solid form.

The ethereal solution from which the acidic compounds had been extracted with potassium carbonate also deposited an oil when evaporated. The effect of treating the cyclopropane ester with magnesium methylate was, therefore, to convert half of it into a non-acidic product, and the rest into products soluble in potassium carbonate, of which one was obtained as a solid. The isomeric cyclopropane derivative gave exactly the same result.

Methyl α-Cyano-β-benzoyl-β-benzal-propionate (XVII).—The solid substance obtained by the action of magnesium methylate on the cyclopropane derivative crystallizes in prisms and melts at 104°.

Analyses. Calc. for $C_{19}H_{15}O_3N$: C, 74.7; H, 4.9. Found: C, 74.5; H, 5.0.

The substance does not combine with bromine, but its solution in acetone rapidly reduces permanganate, giving first benzaldehyde and then benzoic acid. Like the products obtained from the corresponding dicarboxylic ester[4] it forms a complex product when oxidized with permanganate in dry acetone, but in the presence of sufficient water to prevent the formation of a metallic derivative it yields one molecule of benzoic acid. Attempts to transform it into the dicarboxylic ester by esterifying the cyanogen group were unsuccessful but the behavior on oxidation and the similarity in other properties leave no doubt as to its structure.

The oil that was obtained along with the solid from the potassium carbonate solution is doubtless a mixture of the solid and its isomers; it behaves like the solid towards bases and towards permanganate in dry acetone, and gives an equivalent amount of benzoic acid when oxidized in the presence of water. There is as yet no clue as to the nature of the oil that is insoluble in potassium carbonate.

Summary

1. In the presence of sodium methylate, benzyl cyanide combines with benzalacetophenone and forms two stereo-isomeric δ-ketonic nitriles.
2. These have been converted into tetrahydro-pyridine, dihydropyridine, pyridine and cyclopropane derivatives.
3. It has been shown that in isomeric saturated compounds the ease of ring formation may vary greatly with the configuration.
4. The difference in the behavior of two closely related cyclopropane derivatives has been illustrated and discussed.

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[4] Kohler and Conant, THIS JOURNAL, **39**, 1415 (1917).