[Contribution from the Chemical Laboratory of Tufts College]

SOME REACTIONS OF DELTA KETONIC NITRILES

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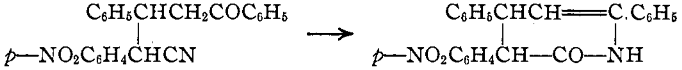
In earlier papers on δ-ketonic nitriles[1] the two most characteristic reactions were found to be those (a) with halogen acids in indifferent media and (b) with bromine. The first type was represented as follows.[1a]

$$\begin{array}{l} C_6H_5CHCH_2COC_6H_5 \\ \;\;| \\ RCHCN \end{array} \longrightarrow \begin{array}{l} C_6H_5CH-CH=C.C_6H_5 \\ \;\;|\qquad\qquad\quad\; | \\ RCH-CO-NH \end{array}$$

It was found[1c] that when R = C_6H_5 a much greater concentration of both hydrogen bromide and nitrile was necessary to bring about ring formation than when R = CN or $COOCH_3$. It seemed possible that the change might be connected in some way with the activity of the hydrogen in the position alpha to both the CN and the R, because this is known to be less active in benzyl cyanide than in cyano-acetic acid derivatives. That such a hydrogen was necessary was shown by the study of a nitrile in which it was replaced by an alkyl group;[2] neither of the above characteristic reactions took place.

In this paper, *p*-nitrobenzyl cyanide has been added to benzalacetophenone, two stereoisomeric addition products (I) being obtained; it added more easily than the cyano-acetic acid derivatives, indicating that the α-hydrogen was more active. Owing to the presence of the nitro group, these compounds have much higher melting points and are less soluble in the ordinary solvents than those prepared with the unsubstituted cyanide.



$$\begin{array}{r} C_6H_5CHCH_2COC_6H_5 \\ | \qquad\qquad\quad \\ p\text{—}NO_2C_6H_4CHCN \\ \text{I} \qquad \end{array} \longrightarrow \begin{array}{r} C_6H_5CHCH=C.C_6H_5 \\ | \qquad\quad | \; \\ p\text{—}NO_2C_6H_4CH-CO-NH \\ \text{II} \qquad\qquad \end{array}$$

When a solution of either addition product in glacial acetic acid was saturated with hydrogen bromide, the same tetrahydropyridine derivative (II) was obtained in nearly the calculated quantity. As it could not be shown that the reaction was any more rapid with these nitriles than with the unsubstituted ones,[1c] differences in rates are probably not due to the activity of the α-hydrogen, but rather to limited solubilities and hence low concentrations of the reacting substances. If the hydrogen is substituted, a tertiary nitrile, which is known to be relatively inactive, results.

The observation that the cyano-acetamide addition product III formed a hydropyridine derivative IV, the amide, instead of the cyanogen group being involved,[1b] made it appear probable that with the other nitriles, the

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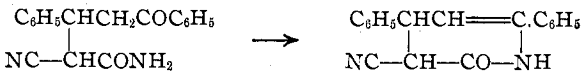
[1] Kohler and others, This Journal, (a) **44,** 2536, (b) 2903 (1922), (c) **46,** 1522 (1924).

[2] Lowry, *Dissertation,* Harvard University, **1924.**

first step consisted of the addition of water to form an amide; this seemed plausible because when a substance, such as acetyl chloride, was present to exclude traces of water, ring closure did not take place. In order to see whether or not traces of moisture were essential for ring formation, I dissolved the amide III in acetyl chloride; the product separated from the solution was the hydropyridine derivative IV.

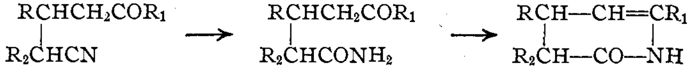


$$\begin{array}{l}C_6H_5CHCH_2COC_6H_5\\ \qquad|\\ NC{-}CHCONH_2\end{array} \longrightarrow \begin{array}{l}C_6H_5CHCH{=}C.C_6H_5\\ \qquad|\qquad\qquad|\\ NC{-}CH{-}CO{-}NH\end{array}$$

III IV

That this was not due to the presence of traces of hydrogen chloride was shown by carrying out the reaction in dimethylaniline, where no free hydrogen chloride is possible.[3] This is conclusive evidence that the presence of water is necessary to form the amide, after which ring closure takes place.

Therefore, the mechanism of the formation of tetrahydropyridine derivatives from δ-ketonic nitriles is that shown by the following scheme.



$$\begin{array}{l}RCHCH_2COR_1\\ \quad|\\ R_2CHCN\end{array} \longrightarrow \begin{array}{l}RCHCH_2COR_1\\ \quad|\\ R_2CHCONH_2\end{array} \longrightarrow \begin{array}{l}RCH{-}CH{=}CR_1\\ \quad|\qquad\qquad|\\ R_2CH{-}CO{-}NH\end{array}$$

With the nitriles considered in this paper, it was found possible to stop the reaction at the amide stage.

Experimental Part

Preparation of the Nitriles

It is very easy to add *p*-nitrobenzyl cyanide to benzalacetophenone in the presence of an alkali, only a trace of the latter being required. Ordinary methyl alcohol is a suitable solvent for the reaction, and the unsaturated ketone may be used without recrystallization, as long as it is free from alkali. The higher-melting isomer is the principal product.

α-*p*-Nitrophenyl-β-phenyl-γ-benzoyl Butyronitrile (I).—In a liter, wide-mouth flask, 80 g. of *p*-nitrobenzyl cyanide is dissolved in 500 cc. of hot methyl alcohol, and 100 g. of benzalacetophenone added. As soon as the latter has dissolved, enough alkali is added to produce a deep magenta color, and the solution allowed to stand; some of the higher-melting addition product invariably separates but is not removed. After five minutes, enough glacial acetic acid is added to discharge the red color, a dark, greenish-brown solution resulting. On stirring, the whole sets to an almost solid crystal paste. This is filtered when cold, an 85% yield of the mixed isomers being obtained.

The mixed solids are refluxed for one hour with 600 cc. of 95% ethyl alcohol containing 10 cc. of acetic acid; on filtering, most of the higher-melting addition product is left behind, and the solution, on cooling, deposits a mixture, largely the lower-melting isomer. This latter mixture is again extracted with 300 cc. of alcohol and filtered from any higher-melting nitrile. Although the separation is now fairly complete, small amounts of the latter are still present and are only removed by repeated recrystallizations.

It is worth noting that *p*-nitrobenzyl cyanide seems to add more easily than any of

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[3] Claisen, *Ber.*, **33**, 1244 (1900).

the nitriles previously used. When the solution was acidified after one minute, a yield of 81% of mixed solids was obtained.

When the lower-melting nitrile was boiled with alkali, it was largely changed to its isomer; a small amount of reddish oil was also formed, but the only solids found were the two nitriles. From the original filtrate, which smelled strongly of hydrocyanic acid, and gave a positive test for cyanide ion, brownish gums separated; these decolorized permanganate, but the only solid that could be isolated was a little more addition product.

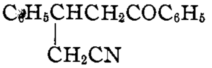
The higher-melting nitrile is easily purified by dissolving in an equal weight of hot glacial acetic acid; on cooling, it is deposited in prims; m. p., 144°; there is practically no loss; yield, 65%. It is almost insoluble in cold acetic acid, hot or cold methyl and ethyl alcohols, ether, chloroform, carbon tetrachloride and glycerol, but quite soluble in acetone and hot acetyl chloride, acetic acid and acetic anhydride.

The lower-melting isomer is best purified by repeated crystallizations from hot 95% alcohol; at room temperature the solubility is about 1 g. per 600 cc. It is slightly more soluble in chloroform and carbon tetrachloride, but very soluble in cold acetic acid, acetic anhydride and acetone. It crystallizes in tufts of needles from all solvents; m. p., 126°; yield, 19%.

Anal. Calcd. for $C_{23}H_{18}O_3N_2$: C, 74.6; H, 4.9. Found: (126°) C, 74.4; H, 5.0; (144°) C, 74.4; H, 4.9.

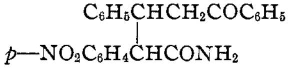
Action of Acids on the Addition Products

When a solution of either nitrile in glacial acetic acid was saturated with hydrogen bromide, the same hydropyridine derivative was formed in nearly the calculated quantity. Both addition products are very slightly soluble in hot chloroform and carbon tetrachloride; when such solutions were just saturated with hydrogen bromide, the small amounts in solution crystallized, but when an excess of the gas was passed in, a bright yellow solid separated. When the latter was immediately decomposed by dilute alcohol, the nitrile from which it was formed was regenerated, indicating that there are two yellow solids. Either, when heated in a capillary tube immediately after preparation, shrunk at 80–85°, turning white, and melted within a few degrees of the melting point of the pure nitrile; melting points of the substances mixed with portions of the corresponding addition products were not depressed. These properties agree with those shown by "amide bromides."[4] When the substances were kept in the air for a few hours, the bright color became dull, hydrogen bromide was evolved and the melting point rose to that of the hydropyridine. Lowry[2] noted the formation of a similar yellow substance, when investigating the action of hydrogen bromide on the nitrile (V) in chloroform; he did not use acetic acid as a solvent, nor obtain a tetrahydropyridine from the gum left after hydrogen bromide had been evolved.



$$\begin{array}{l} C_6H_5CHCH_2COC_6H_5 \\ \qquad | \\ \quad\ CH_2CN \end{array}$$

V



$$\begin{array}{r} C_6H_5CHCH_2COC_6H_5 \\ | \qquad\qquad\quad \\ p\text{—}NO_2C_6H_4CHCONH_2 \end{array}$$

VIII

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[4] Henry, *Bull. soc. chim.*, [2] **7**, 85 (1867). Engler, *Ann.*, **149**, 306 (1869). Biltz, *Ber.*, **25**, 2541 (1892).

When either nitrile (I) was dissolved in concd. sulfuric acid, and, after a short time, the solution poured into water or alcohol, a substance resulted, analyzing for the nitrile plus a molecule of water; this must be the amide (VIII) because it was the only product formed when *p*-nitrophenylacetamide was added to benzalacetophenone in the presence of sodium methylate. A trace of hydropyridine was also found, but when the acid solution was allowed to stand for a day before dilution, most of the product was this ring compound, with only a small amount of amide. As both nitriles formed the same amide, isomerization must take place at this stage, hence only one tetrahydropyridine derivative would be expected, and only one has been obtained with any nitrile.

The amide could not be acylated; the product was recovered unchanged when treated in the usual way by the Schotten-Baumann reaction. When it was dissolved in pyridine and benzoyl chloride was added, it lost water and formed the hydropyridine. A comparable result was obtained with the nitrile (V).

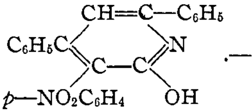
The same tetrahydropyridine derivative was also formed in the following ways; to conserve space they will not be included in the experimental part: (a) by refluxing the amide in acetyl chloride for five hours; (b) by treating an acetic acid solution of the amide with hydrogen bromide; (c) by allowing a solution of the amide bromide in acetic acid to stand for several days.

2-Keto-3-*p*-nitrophenyl-4,6-diphenyl-tetrahydropyridine (II).—Fifteen g. of the nitrile (144°) was dissolved in 50 cc. of acetic acid by gentle warming, and the solution saturated with hydrogen bromide; a little solid separated in the course of an hour. On shaking the mixture, the next day, the whole solidified. The solid was filtered off, washed, and extracted with 100 cc. of 95% alcohol; 2 g. of the nitrile was recovered. The residue was recrystallized from acetic acid; yield 12 g., or 92%.

The lower-melting isomer when treated in the same way gave the same product in the same yield.

Anal. Calcd. for $C_{23}H_{18}O_3N_2$: C, 74.6; H, 4.9. Found: C, 74.3; H, 5.2.

The tetrahydropyridine derivative crystallizes in very fine rods that melt at 236° and have a slightly greenish tinge; the latter can be removed by solution in sulfuric acid. It is moderately soluble in hot acetic acid or anhydride, but does not separate on cooling until the solution has stood for some time. It is quite soluble in hot pyridine, slightly soluble in chloroform, carbon tetrachloride and ethyl acetate, and insoluble in amyl acetate, the alcohols, acetone, benzene, xylene and nitrobenzene. It decolorizes bromine instantly. When sodium nitrite was added to a solution of the substance in acetic acid, a deep yellow color was produced, indicating possible nitrosamine formation, but the only solid isolated was an hydroxypyridine.

2-Hydroxy-3-*p*-nitrophenyl-4,6-diphenylpyridine  .—Five g. of the tetrahydropyridine was dissolved in 250 cc. of glacial acetic acid and 10 g. of sodium nitrite added in portions; a deep yellow color was produced. On the next day, the solution was poured into 800 cc. of water and the copious yellow precipitate that formed was filtered off. The latter was boiled with alcohol until the solution became clear and, in a few minutes, the hydroxypyridine separated. It was filtered and purified by repeated crystallizations from acetic acid, in which it is fairly soluble, and obtained as light yellow prisms; m. p., 311–312°, with decomposition.

Anal. Calcd. for $C_{23}H_{16}O_3N_2$: C, 75.0; H, 4.4. Found: C, 74.7; H, 4.5.

The "Amide Bromides."—Fifteen g. of the nitrile (126°) was dissolved in 240 cc. of hot carbon tetrachloride and a rapid current of hydrogen bromide passed through the solution; in a few minutes the liquid became cloudy and a bright yellow solid separated. This was filtered off, spread out on a porous plate for a few minutes and bottled; yield, 19 g., or 90% (calculated for nitrile + 2HBr). The colorless filtrate left 1 g. of nitrile on evaporation. A sample of the solid, heated in a capillary tube, turned white at 80–85°, and melted at 118–119°; a sample mixed with pure nitrile melted at 121–122°.

Anal. Calcd. for $C_{23}H_{18}O_3N_2$ + 2HBr: C, 51.9; H, 3.8; calcd. for 1HBr: C, 61.2; H, 4.2. Found: C, 52.3, 52.7; H, 2.9, 3.9.

The amide bromide constantly lost hydrogen bromide, even in a closed bottle; a portion in a weighing bottle in bright daylight generated enough pressure to blow out the stopper. The color, at first bright yellow, became dull and eventually a dirty white. A portion that had been dried in the air and then boiled with alcohol seemed to be insoluble, and a mixed melting point showed it to be the hydropyridine derivative. However, another lot, kept in a closed bottle, was readily soluble, and the cold solution deposited unchanged addition product.

The higher-melting nitrile gave a similar yellow solid showing identical properties except the melting point, the latter being close to that of the nitrile itself, and a mixed melting point showing no depression.

Both bromides dissolve very readily in ether, acetic acid, aniline and acetyl chloride, but are insoluble in chloroform and carbon tetrachloride. When they were added to alcohol, the yellow color disappeared at once, and the nitrile remained in suspension; when silver nitrate solution was added, a precipitate of silver bromide was formed. When a fresh solution in acetyl chloride was evaporated, the nitrile remained as a residue; an aniline solution poured into dil. hydrochloric acid also precipitated the nitrile.

α-*p*-Nitrophenyl-β-phenyl-γ-benzoyl Butyramide (VIII).—Five g. of the 144° nitrile was dissolved in 25 cc. of cold, concd. sulfuric acid during stirring; the clear yellow solution was allowed to stand for a half hour, and then slowly dropped into 200 cc. of vigorously-stirred methyl alcohol, cooled in a freezing mixture; the temperature rose from —0.4° to +10.5°. The clear solution soon deposited a crystalline solid, insoluble in water; this was separated off on the next day, washed free from acid and recrystallized from hot acetone, in which it was quite soluble. The original alcoholic filtrate, on dilution, yielded a little more amide; yield, 98%.

Anal. Calcd. for $C_{23}H_{20}O_4N_2$: C, 71.1; H, 5.2. Found: C, 71.1; H, 5.4.

The amide crystallizes in white needles from alcohol, or rods from acetone; m. p., 214–215°. It is very soluble in hot acetone, acetic acid, ethyl acetate and pyridine, slightly soluble in methyl and ethyl alcohols, and insoluble in chloroform and ether.

The 126° nitrile, treated similarly, formed the same amide in high yield, and 0.2 g. of the tetrahydropyridine derivative. When a similar solution of the higher-melting addition product was allowed to stand for a day and then poured into water, a 40% yield of the amide was separated from the precipitated solid, the remainder being the ring compound.

In an attempt to benzoylate the substance, 2 g. was dissolved in 15 cc. of hot pyridine and 5 cc. of benzoyl chloride added; heat was evolved. The solution was clear when cold, whereas a solution of this concentration in pyridine alone deposited the amide on cooling. After a half hour, it was run into 150 cc. of cold, dil. (1 part of acid, 2 parts of water) hydrochloric acid. The precipitated solid was filtered off, washed with water, dil. aqueous ammonia and alcohol, and recrystallized from acetic acid; 1.7 g. of the tetrahydropyridine was the only solid found.

SYNTHESIS.—Two g. of *p*-nitrophenylacetamide and 2 g. of benzalacetophenone were boiled with 50 cc. of absolute methyl alcohol containing a trace of sodium methylate for three hours; the amide slowly dissolved. The clear solution was then acidified and allowed to stand overnight, when 3.5 g. of the addition product separated; m. p., 214–215°; a mixed melting point with the amide as prepared above was likewise 214–215°.

Action of Acetyl Chloride on α-Cyano-β-phenyl-γ-benzoylbutyramide (III).—As stated in the introduction, the cyano-acetamide addition product was treated with acetyl chloride to see whether traces of water were essential for ring closure.

Five g. of the amide (III)[5] was suspended in 25 cc. of acetyl chloride and the solution allowed to stand. Although there was no apparent change, after two days the solid melted at 219–220° and decolorized a solution of bromine in chloroform instantly. A mixed melting point with a sample of the hydropyridine (IV) prepared according to the method of Kohler and Souther[1b] showed no depression. Therefore, water is not essential for formation of the tetrahydropyridine derivative from the amide.

To show that acetyl chloride functions by removal of water only, and not by the presence of hydrogen chloride, a solution of the amide in dimethylaniline and acetyl chloride was used in another experiment. As a check, a similar solution, without the halide, was carried on at the same time and under the same conditions. The amide in the solution containing the acyl chloride was transformed into the hydropyridine derivative, while that in dimethylaniline alone was recovered unchanged.

One g. of the amide was dissolved in a mixture of 10 cc. of dimethylaniline and 10 cc. of acetyl chloride, and the solution allowed to stand for five days. The acetyl chloride was then removed in a vacuum and the residual solution poured into cold, dil. sulfuric acid during vigorous stirring. The precipitate was filtered off and boiled with a little alcohol. It decolorized bromine instantly and melted at 219–220°; mixed m. p., 219–220°. The check dimethylaniline solution was treated similarly and 1 g. of the amide recovered. It did not decolorize bromine and melted at 162–163°; mixed m. p., 162–163°.

Bromination of the Addition Products

Both of the addition products reacted readily with bromine in acetic acid solution, the same types of bromine compounds being obtained as with the unsubstituted nitriles.[1c] The lower-melting isomer gave only a bromopyridine derivative (IX), while its isomer gave a mixture of two

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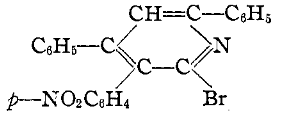
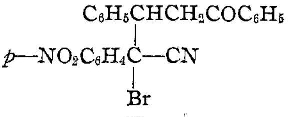
[5] The thermometer used in determining these melting points was checked in melting ice, boiling water, and at the melting points of α-cyano-β-phenyl-γ-benzoylbutyramide (162°) and 2-keto-3-cyano-4,6-diphenyl-tetrahydropyridine (220°)[1b]. Using this thermometer, a redetermination of the melting points of the following substances appearing in an earlier paper (Ref. 1c) was made, because it did not seem probable that a cyclopropane with a nitro group in a benzene ring should melt lower than the unsubstituted one. The new figures are regarded as correct.

Cyclopropane, formerly 172°, now 166°; its isomer, m. p. 178°, now 172°; bromonitrile, was 172°, now 166°; tetrahydropyridine derivative, was 173°, now 167°.

open-chain α-bromonitriles (X), and small amounts of the same bromopyridine; the latter may have been formed by the action of the hydrogen bromide on the bromonitrile first produced. On adding bromine to a solution of the lower-melting addition product in chloroform, bromination took place, with formation of the bromopyridine derivatives, until enough hydrogen bromide was liberated to form the amide bromide; the latter then separated and was not acted upon.


IX



$$\begin{array}{c} C_6H_5CHCH_2COC_6H_5 \\ | \\ p\text{—}NO_2C_6H_4C\text{—}CN \\ | \\ Br \end{array}$$

X

The bromine in the open-chain substitution products is in the position alpha to the CN group, because such products can neither be esterified nor hydrolyzed.

2-Bromo-3-*p*-nitrophenyl-4,6-diphenylpyridine (IX).—Thirteen g. of the 126° nitrile was dissolved in 50 cc. of glacial acetic acid, and 6 g. of bromine in 10 cc. of acetic acid added in portions; sunlight was usually necessary to start the reaction. After five minutes the mixture was poured into 250 cc. of water containing a little sodium bisulfite, and the precipitated gum allowed to harden. It was then separated and recrystallized from ethyl acetate or acetic acid; it formed small, glistening needles; m. p., 191°.

Anal. Calcd. for $C_{23}H_{15}O_2N_2Br$: C, 64.0; H, 3.5. Found: C, 63.4; H, 3.6.

The bromopyridine is slightly soluble in ethyl and butyl alcohols, acetone and ether, and moderately soluble in chloroform, benzene, ethyl acetate, acetic acid and pyridine.

It is also formed by saturating an acetic acid solution of either open-chain monobromonitrile (X) with hydrogen bromide, thus showing its structure.[1a]

Two g. of either bromonitrile was dissolved in 25 cc. of hot acetic acid and the solution saturated with hydrogen bromide. After several days the mixture was poured into water and the precipitated solid collected and crystallized from acetic acid; yield, 1.6 g. It melted at 188–189°; a sample mixed with pure bromopyridine melted at 189–190°.

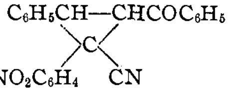
α-Bromo-α-*p*-nitrophenyl-β-phenyl-γ-benzoylbutyronitrile (X).—One hundred g. of the (144°) nitrile was dissolved in 210 cc. of hot acetic acid and a solution of 50 g. of bromine in 10 cc. of acetic acid added in portions; the reaction started very easily, and torrents of hydrogen bromide were evolved. The solution was then chilled and the crystalline solid filtered off and washed with 150 cc. of alcohol; this wash alcohol, added to the filtrate, caused 17 g. (a 14% yield) of the bromopyridine to precipitate. The solid on the funnel was transferred to a flask, refluxed for an hour with 200 cc. of ethyl acetate, and filtered from 38 g. (31.4%) of the higher-melting open-chain bromonitrile. The ethyl acetate was distilled until the solution became cloudy, and as it was cooled and stirred, 51 g. (42%) of the lower-melting isomer crystallized; it was filtered off and washed with a little alcohol. The various filtrates, on evaporation, left 14 g. of mixed solids.

Using a more dilute solute, for example, 50 g. of the nitrile in 250 cc. of acetic acid, the amount of bromopyridine was reduced, the yields being 5% of the latter, 30% of the higher-melting isomer and 55% of the lower; the rest was a mixture of the first and last.

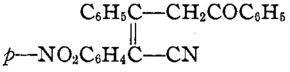
Anal. Calcd. for $C_{23}H_{17}O_3N_2Br$: C, 61.5; H, 3.8. Found: (191°) C, 61.5; H, 3.9; (151°) C, 61.3; H, 3.9.

The lower-melting bromonitrile is quite soluble in alcohol, acetone, ethyl acetate and acetic acid, from all of which it crystallizes in needles or fine rods; m. p., 151°. Its isomer is insoluble in all the above-mentioned solvents except acetic acid, in which it is moderately soluble and from which it crystallizes in fine prisms; m. p., 191°.

Both isomers dissolve readily in warm pyridine, but the process is accompanied by loss of hydrogen bromide. The products isolated are the same as those obtained when solutions in acetic acid are treated with potassium acetate. Although three formulas for the substances are possible,

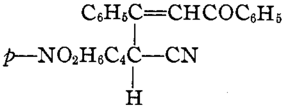


VII



$$\begin{array}{l}\mathrm{\qquad\quad C_6H_5C{-}CH_2COC_6H_5}\\ \qquad\qquad\quad \| \\ p\text{—}\mathrm{NO_2C_6H_4C{-}CN}\end{array}$$

XI



$$\begin{array}{l}\mathrm{\qquad\quad C_6H_5C{=}CHCOC_6H_5}\\ \qquad\qquad\quad | \\ p\text{—}\mathrm{NO_2H_6C_4C{-}CN}\\ \qquad\qquad\quad | \\ \qquad\qquad\quad \mathrm{H}\end{array}$$

XII

that of the cyclopropane derivatives (VII) seems most plausible, because it has been shown in the earlier papers[1] that these result when the α-bromonitriles are treated with potassium acetate.

Three isomers are formed; these are white, crystalline solids that decolorize neither permanganate nor bromine; the cyanogen group cannot be hydrolyzed. In both acid and alkaline solutions, reducing agents (which would be expected to differentiate conclusively between substances represented by these formulas) attack the nitro group and give a great variety of products. It seems best to defer further study of these compounds until other typical reactions for this type of cyanocyclopropanes are found.

Each of the bromine compounds gave a mixture of these cyclopropane derivatives which was very difficult to separate, because the solubilities in all solvents were so much alike. The higher-melting bromonitrile, when dissolved in pyridine, gave almost entirely a cyclopropane derivative; m. p., 170°;[5] whereas with potassium acetate in acetic acid, half the product is a mixture of the two lower-melting isomers. The latter are the only products resulting from a similar treatment of the lower-melting bromonitrile; when potassium acetate was used, isomer, m. p. 151°, predominated, but with pyridine about equal amounts were formed. The third cyclopropane derivative melted at 144°. When potassium acetate was used to remove hydrogen bromide a considerable amount of uncrystallizable gum resulted, but with pyridine there was only a little and the yields were larger.

1-Cyano-1-*p*-nitrophenyl-2-phenyl-3-benzoyl-cyclopropane (VII).—(a) From the 191° Bromonitrile. Five g. of the bromo compound was dissolved in 10 cc. of warm pyridine; after five hours the whole was apparently solid. Enough alcohol was added, during stirring, to make a thick mush, which was filtered, the crystals being washed with alcohol. The solid was at once extracted with 30 cc. of boiling alcohol for ten minutes and filtered off; the residue weighed 4 g. and melted at 167–168°; on recrystallization from acetic acid, 3.5 g. (86%) of pure cyclopropane (m. p., 170°) was obtained. The mother liquor deposited 0.5 g. of a mixture of the lower-melting isomers, separated as described below.

Or, 5 g. of the bromo compound and 5 g. of potassium acetate were dissolved in 50 cc. of hot acetic acid, and the solution was allowed to stand at room temperature; on the next day, the potassium bromide that had separated was removed, and on the day after, the cyclopropane was filtered off. It weighed 1.5 g. (38%) and was the isomer melting at 170°. The acetic acid solution was diluted with considerable water, and the mixture of the other isomers precipitated was filtered off; after one recrystallization, it weighed 1.5 g. (38%); the filtrate deposited a resin on evaporation.

(b) From the 151° Bromonitrile.—Twenty-five g. of bromo compound was dissolved in 50 cc. of warm acetic acid and 25 cc. of pyridine added. On the next day, 14 g. of crystals had separated; these were filtered off, extracted with a little hot alcohol, and recrystallized from ethyl acetate, when 11 g. (54%) of pure (151°) cyclopropane was obtained. From the three residual solutions, 5.5 g. (27%) of solid was recovered, largely the isomer melting at 144°, making a total yield of 81%. The process of separation was essentially as follows: the solid was refluxed for one hour with small amounts of the solvent selected—never enough to dissolve it completely—and filtered off. The crystals from the first extracts were still mixtures; the middle extracts deposited impure 144° isomer. By watching the progress of crystallization, it was sometimes possible to notice when a different kind of crystals started to form and so separate by immediate filtration. About fifty treatments were required before the pure (144°) cyclopropane was secured.

In attempts to get more of a single product, 30 g. of bromonitrile was dissolved in 30 cc. of warm pyridine; on the next day, addition of an equal volume of alcohol caused precipitation of 20 g. of essentially the same mixture, and a little more separated from the mother liquor on standing. Also, 20 g. each of bromo compound and potassium acetate were dissolved in 100 cc. of hot acetic acid; after a few minutes, potassium bromide was precipitated and filtered off. On the next day, 10 g. (61%) of almost pure cyclopropane (151°) had formed, and from the filtrate, 3 g. (18%) of a mixture separated on dilution.

Anal. Calcd. for $C_{23}H_{16}O_3N_2$: C, 75.0; H, 4.4. Found: (170°) C, 74.8; H, 4.5; (151°) C, 74.8; H, 4.4; (144°) C, 75.0; H, 4.5.

The 170° isomer is insoluble in ether, sparingly soluble in alcohol and carbon tetrachloride, moderately soluble in benzene, and readily soluble in acetic acid, ethyl acetate and acetone. The other isomers are sparingly soluble in ether and carbon tetrachloride, moderately in alcohol, but readily in the other solvents; the 151° isomer is best recrystallized from ethyl acetate. All separate from solutions as fine needles, or elongated prisms.

All three give a brilliant blue color with inorganic bases and with potassium acetate in absolute methyl alcohol; this same color is noted with the bromonitriles and bases. Attempts to eliminate hydrogen bromide by the use of potassium acetate in absolute methyl alcohol resulted only in the formation of uncrystallizable gums; similarly, when solutions of either of the bromonitriles or the cyclopropane derivatives in acetic acid were refluxed with potassium acetate, only deeply colored gums were formed.

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Summary

1. In the presence of a trace of potassium hydroxide, *p*-nitrobenzyl cyanide combines very easily with benzalacetophenone and forms two stereoisomeric δ-ketonic nitriles.

2. These have been converted into tetrahydropyridine, pyridine and cyclopropane derivatives. The closing of the hydropyridine ring from the ketonic nitrile does not seem to be connected with the activity of the hydrogen in the alpha position.

3. It has been shown that the presence of water is not essential for the formation of the tetrahydropyridine derivative from the amide.

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