The position of the nucleus chlorines was established by preparing 2,4-dichloro-aniline from the above substance. A small portion was heated for 2 hours with 10% sodium hydroxide solution, and the oil repeatedly washed with water. After solidification, it was recrystallized from 50% aqueous alcohol and gave finally long needle-like crystals of 2,4-dichloro-aniline, melting at 61–62° (uncorr.).[5]

Summary

1. A study of the preparation of phenylimido-phosgene from phenyl mustard oil and from formanilide has been made.

2. Phenyl mustard oil is best prepared from thiocarbanilide by using 3 parts by weight of dil. sulfuric acid and refluxing the mixture before distillation with steam.

3. Phenylimido-phosgene was prepared in 95% yields by chlorination of phenyl mustard oil, using carbon disulfide or carbon tetrachloride as a solvent, and omitting the addition of water as recommended by Nef.

4. Formanilide, chlorinated in the presence of sulfur chlorides, gives 2,4-chloro-formanilide.

5. Formanilide, chlorinated in the presence of thionyl chloride gives a series of products identified, respectively, as 2,4-dichloro-formanilide, phenylimido-phosgene, *p*-chloro-phenylimido-phosgene and 2,4-dichloro-phenylimido-phosgene.

EVANSTON, ILLINOIS

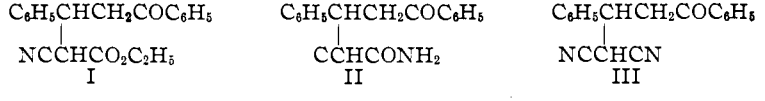
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

DELTA KETONIC NITRILES AND THEIR RELATION TO CYCLIC COMPOUNDS. II

BY E. P. KOHLER AND B. L. SOUTHER

Received July 10, 1922

In continuation of the study of δ ketonic nitriles we have added cyano-acetamide and cyano-acetonitrile to benzalacetophenone, and have thus secured 2 related nitriles to compare with the methyl cyano-acetate addition product described in the earlier paper.[1]

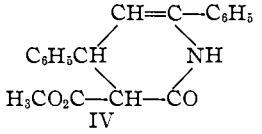


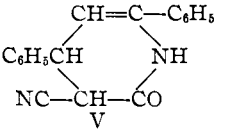
I II III

The behavior of these 3 closely related substances towards most reagents is surprisingly different: indeed, the only reaction in which all behave exactly alike is esterification. Thus while all 3 form cyclic compounds when subjected to the action of halogen acids in indifferent media, only the first forms a tetrahydropyridine (IV) derivative by molecular rearrangement. The second also forms a tetrahydropyridine derivative (V); but in accordance with the mechanism proposed in the first paper,

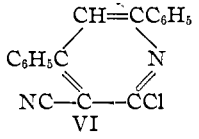
[1] THIS JOURNAL, **44**, 2536 (1922).

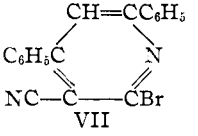
ring formation involves the amide in place of the cyanogen group and the process is accompanied by loss of water.


IV


V

Under exactly the same conditions, the dinitrile III, which is equally sensitive to halogen acids, forms only a trace of a tetrahydropyridine derivative. Instead of this, it forms a mixture composed almost entirely of pyridine and hexahydropyridine derivatives.


VI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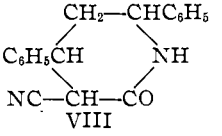
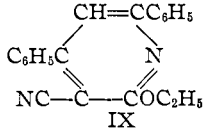

VIII

A similar mixture of pyridine and piperidine derivatives is formed by the action of alcoholic potassium hydroxide on the dinitrile.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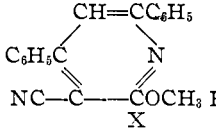
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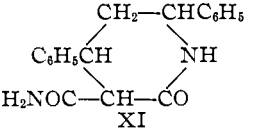
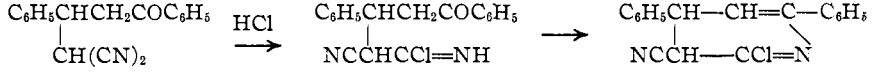
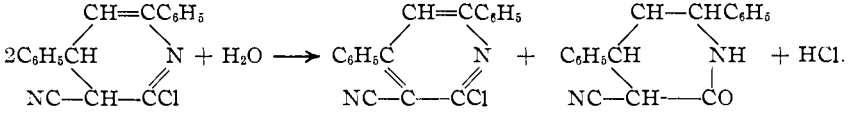

XI

These mixtures are, doubtless, due to a series of reactions which start with the addition of halogen acid or alcoholate to one of the cyanogen groups and end with the spontaneous oxidation and reduction of an intermediate dihydropyridine derivative. In the case of halogen acids, for example, the probable steps to the dihydropyridine are,



The cyclic compound then undergoes oxidation and reduction, a part of the halogen being replaced in the process.

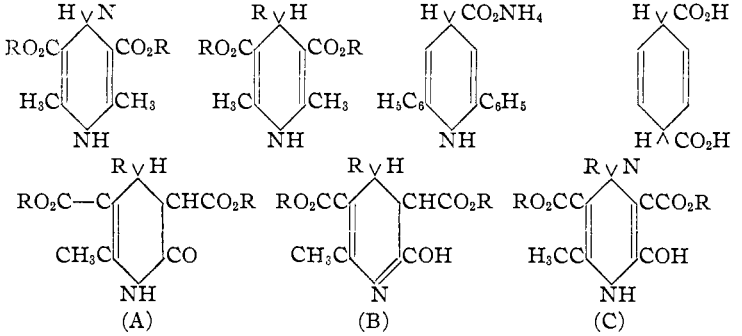


Reciprocal oxidation and reduction of hydropyridine derivatives has been known for a long time. As early as 1882 Hantzsch[2] found that when he saturated an ethereal solution of diethyl dihydrocollidine dicarboxylate with hydrogen chloride and poured the mixture into water, he obtained, along with undefined decomposition products, the hydrochloride of the ester of collidine dicarboxylic acid. A little later, Paul and Strasser[3] treated diphenacyl-acetic acid with alcoholic ammonia, both at the ordinary

[2] Hantzsch, *Ann.*, **215**, 37 (1882).

[3] Paul and Strasser, *Ber.*, **20**, 2756 (1887).

temperature and in sealed tubes at 125°. At the ordinary temperature they obtained dihydro-diphenyl-pyridine carboxylic acid, while at the higher temperature they obtained only diphenyl-pyridine carboxylic acid and the hexahydro reduction product, showing that in the presence of alcoholic ammonia the dihydro compound undergoes oxidation and reduction. After Griess and Harrow[4] had shown that the esters of dihydrolutidine dicarboxylic acid behave in the same way, Knoevenagel began an extended investigation of the phenomenon.[5] Knoevenagel and his coworkers[6] found that the oxidation-reduction reaction can be induced or catalyzed by palladium black as well as by acids and bases. After a comparison of the behavior of a number of cyclic and open-chained compounds when heated with palladium black, they decided that, in cyclic compounds, only dihydro derivatives of a particular type either undergo oxidation-reduction or lose hydrogen when heated with palladium black. Thus, the substances represented by the first 4 of the following formulas behave alike, while those represented by the fifth do not change to a mixture of pyridine and hexahydro-pyridine derivatives, are not oxidized to pyridine derivatives by nitrous or nitric acids, and do not surrender hydrogen when heated with palladium black.



(A) (B) (C)

They concluded that substances of the relatively inactive type represented by A may react in the desmotropic modification B but not in that of C, and that only substances that can assume this structure undergo reciprocal oxidation and reduction.

Our results in the main confirm the plausible view that such oxidation-reduction reactions are associated with the extraordinary activity of hydrogen which is in combination with atoms that are flanked on both sides by unsaturated groups; but they do not support the conclusion that hydropyridine derivatives are incapable of reacting in all possible desmotropic modifications.

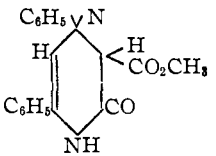
Thus while both the ester IV and the nitrile V, which are perfectly anal-

[4] Griess and Harrow, *Ber.*, **21**, 2743 (1888).

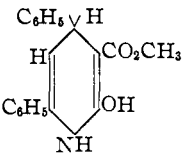
[5] Knoevenagel, *ibid.*, **35**, 1790 (1902).

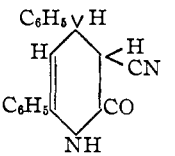
[6] Knoevenagel, *et al.*, *ibid.*, **36**, 2813 (1903).

ogous to A, are quite stable in the presence of acids, they both undergo oxidation in alkaline solutions. In acid solutions the ketonic form would be expected to predominate; in bases, the enolic.

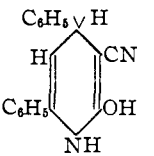


IV

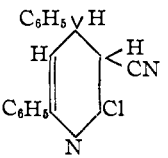


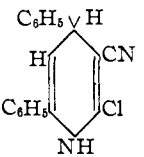


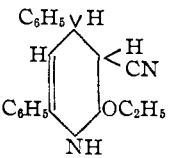
V

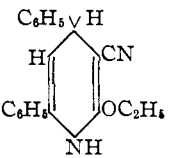


The intermediate hydropyridine derivatives that it seems necessary to assume in order to account for the formation of pyridine derivatives from the dinitrile are:









It is not surprising that the chloro compound should assume a *para* quinoid form in the presence of acids; but it is not so evident why the ether should tend to assume the same form in the presence of bases. It seems best, therefore, to defer an extended discussion of this phenomenon until a more varied experimental material is available.

Experimental Part

The Addition Reaction

The most favorable conditions for adding cyano-acetamide and cyano-acetonitrile to benzalacetophenone are the same as those which had previously been used to add cyano-acetic ester. The materials as well as the alcohol used as medium should be as dry as possible and the amount of methylate barely sufficient to produce definite alkalinity. Better yields were obtained with methyl than with ethyl alcohol as medium.

α-Cyano-β-phenyl-γ-benzoyl-butyramide (Formula I).—A small quantity of a saturated solution of sodium methylate was added to a boiling solution of 22 g. of benzalacetophenone and 8.4 g. of recrystallized and air-dried cyano-acetamide in 25 cc. of dry methyl alcohol. The reaction proceeded without further heating and the contents of the flask soon solidified. After standing over-night at room temperature, the mixture was filtered and the solid was washed, first with a small quantity of methyl alcohol, and then repeatedly with water. It was purified by recrystallization from methyl alcohol; yield, 22.4 g., or 72.5%.

Several experiments were tried with cyano-acetamide which had not been recrystallized from alcohol but had been thoroughly dried in a steam oven. In each case it was necessary to add a few drops of conc. aqueous ammonia to start the reaction, and the yield was much less than with the pure amide.

Analyses. Calc. for $C_{18}H_{16}O_2N$: C, 73.9; H, 5.5. Found: C, 74.1; H, 5.4.

The amide is sparingly soluble in ether, in chloroform and in carbon tetrachloride

moderately soluble in methyl alcohol and in acetone. It crystallizes in needles or small prisms which melt at 161–163°. It may be obtained by the action of ammonia on the cyano-acetic ester addition product to benzalacetophenone. This method of formation serves to establish its structure as an open-chained compound, but it is of little use as a method of preparation because the yield is small and the separation of the mixture of products troublesome.

α-Cyano-β-phenyl-γ-benzoyl-butyronitrile (Formula II).—In the presence of a small quantity of sodium methylate, cyano-acetonitrile combined very readily with benzalacetophenone. The product was purified by crystallization from ethyl alcohol or carbon tetrachloride.

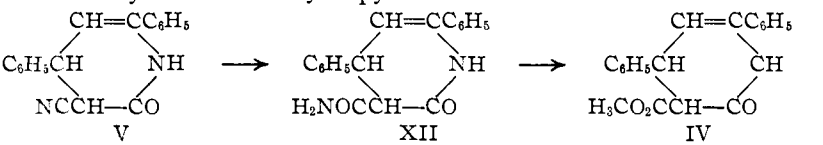
Analyses. Calc. for $C_{18}H_{14}ON_2$: C, 78.8; H, 5.2. Found: C, 78.5; H, 5.3.

The nitrile crystallizes in needles or small prisms and melts at 125–126°. It is sparingly soluble in ether and methyl alcohol, moderately in boiling ethyl alcohol, acetone and carbon tetrachloride, very readily in cold chloroform.

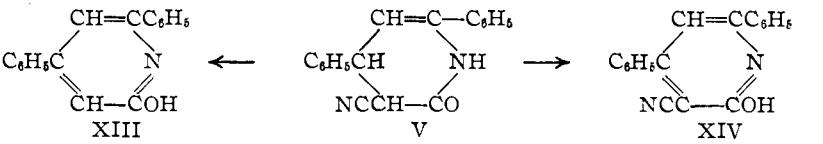
Action of Halogen Acids on the Cyano-acetamide Addition Product

In methyl alcohol the halogen acids esterify the cyano-acetamide addition product and form the ester which had previously been obtained by adding dimethyl malonate to benzalacetophenone. In chloroform or carbon tetrachloride the halogen acids rapidly eliminate water and transform the amide, almost quantitatively, into a cyclic compound.

The structure of the cyclic compound is established by the following reactions. The substance is readily soluble in conc. sulfuric acid; when this solution is poured into water, it yields an amide which is isomeric with the original addition product, and when it is poured into methyl alcohol it yields a tetrahydropyridine derivative of known structure.



Boiling alcoholic potash eliminates hydrogen cyanide and forms an hydroxypyridine of known structure, while nitrous acid readily removes 2 atoms of hydrogen—a well known reaction of dihydro-pyridine derivatives.



2-Keto-3-cyano-4,6-diphenyl-tetrahydropyridine (Formula V).—When dry hydrogen chloride or bromide is passed into dry, alcohol-free chloroform in which the amide is suspended, the mixture soon becomes pasty owing to separation of water. The melting point of the solid gradually rises until it attains a maximum of about 215°. The chloroform is then removed, the solid washed with water until free from acid, and boiled with a small quantity of alcohol. This leaves a product which is analytically pure but generally has a greenish-yellow tint. A colorless product can be obtained by recrystallization of it from a mixture of benzene and alcohol, in which it is sparingly soluble.

Analyses. Calc. for $C_{18}H_{14}O_2N$: C, 78.8; H, 5.2; N, 10.2. Found: C, 79.2; H, 5.1; N, 9.8.

The cyclic nitrile crystallizes in fine, white needles and melts at 220°. It is very sparingly soluble in nearly all common organic solvents. It dissolves in about 10 times its weight of boiling glacial acetic acid, but the crystals which separate as the solution cools, while they melt at the same temperature as the pure substance, have a greenish-yellow color which is extremely difficult to remove.

Hydrolysis and Esterification of the Cyclic Nitrile. 2-Keto-3-carbamyl-4,6-diphenyl-tetrahydropyridine (Formula XII).—The cyclic nitrile dissolves in sulfuric acid quite readily, giving an amber-colored solution. If this is at once poured onto ice, the nitrile is reprecipitated, but if it is kept for 8 or 10 hours, it becomes undistinguishable from solutions obtained by dissolving either the cyano-acetamide or cyano-acetonitrile addition products in the same acid. All of these when poured onto cracked ice give, mainly, the cyclic amide. This was washed with water and recrystallized from acetone containing a few drops of ammonia.

Analyses. Calc. for $C_{18}H_{16}O_2N_2$: C, 73.9; H, 5.5. Found: C, 73.4; H, 5.5.

The amide crystallizes in small, transparent prisms and melts at 181–182°. It is sparingly soluble in alcohol and in chloroform, and moderately soluble in acetone. Like the cyclic nitrile, it dissolves readily in conc. sulfuric acid, and when this solution is poured into cooled methyl alcohol the solid product consists mainly of the corresponding cyclic ester (Formula IV), which melts at 166°.[7]

Transformation of Hydropyridine into Pyridine Derivatives. 1-Hydroxy-3-cyano-4,6-diphenylpyridine (Formula XIV).—The cyclic nitrile has 2 hydrogen atoms that are easily removed both by bromine and by nitrous acid. A conc. aqueous solution containing 2.7 g. of sodium nitrite was added very slowly to a solution of 5 g. of the hydropyridine derivative in 100 cc. of glacial acetic acid. The solution gradually turned brown and, in the course of several days, deposited 2.7 g. of a granular brown powder. This was recrystallized from glacial acetic acid from which it separated in greenish-yellow plates which melted at 313–315°. The substance is very sparingly soluble in all common organic solvents.

Analyses. Calc. for $C_{18}H_{12}ON_2$: C, 79.4; H, 4.4; N, 10.3. Found: C, 79.0; H, 4.6; N, 10.3.

2-Hydroxy-4,6-diphenylpyridine (Formula XIII).—A suspension of 10 g. of the hydropyridine derivative in a solution of 2 g. of potassium hydroxide in 40 cc. of methyl alcohol was boiled on a steam-bath. The odor of ammonia became perceptible and cyanide ion was detected in the solution after 10 minutes. After boiling for 5 hours, the mixture on cooling slowly deposited a pale yellow potassium compound. This compound was washed with alcohol and ether, dissolved in water and the solution acidified. After recrystallization from alcohol the solid thus obtained was identified by comparison with a specimen of the hydroxypyridine on hand.

The filtrate from the potassium compound contained other substances which separated as an oil when it was acidified. The process is evidently involved but the appearance of cyanide ion in the solution shows that a part of the product at any rate is formed by direct elimination of hydrogen cyanide. The reaction with sulfuric acid is equally confused. A solution of the hydropyridine derivative in conc. sulfuric acid was gradually diluted with water until precipitation started, then cleared with a few drops of conc. sulfuric acid, boiled for 10 minutes and allowed to cool. It deposited about half the possible quantity of almost pure hydroxypyridine. The filtrate on dilution gave only uncrystallizable oils.

[7] Ref. 1, p. 2544.

Oxidation and Reduction. 2-Keto-3-cyano-4,6-diphenyl-piperidine, (Formula VIII).—Preliminary experiments showed that the dihydropyridine derivative undergoes a very slow spontaneous oxidation when left in contact with alcoholic ammonia at the ordinary temperature and that while the same process takes place more rapidly at the temperature of a steam-oven, it is far less clean at the higher temperature. A suspension of 10 g. of the finely divided substance was, therefore, shaken with 30 cc. of conc. alcoholic ammonia for 2 weeks. The liquid immediately turned yellow, and gradually acquired an intense blue fluorescence. The solid gradually changed from a light powder to a crystalline sediment. The mixture was filtered and the solid washed with alcohol. It proved to be almost pure hydroxypyridine and was identified by a mixed melting point. The yield was 4.1 g.

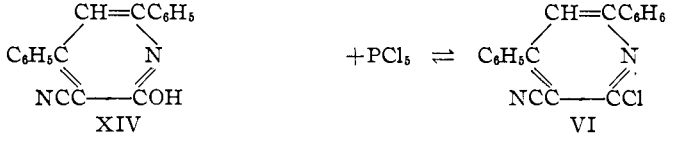
The solution was evaporated to dryness under diminished pressure. It left an oil which was readily soluble in ether. The ethereal solution was washed with water until free from ammonia, dried and allowed to evaporate, yielding a solid imbedded in oil. The solid, 3.2 g., was purified by recrystallization from a mixture of acetone and petroleum ether.

Analyses. Calc. for $C_{18}H_{15}ON_2$: C, 78.3; H, 5.8; N, 10.2. Found: C, 78.1; H, 6.0; N, 10.2.

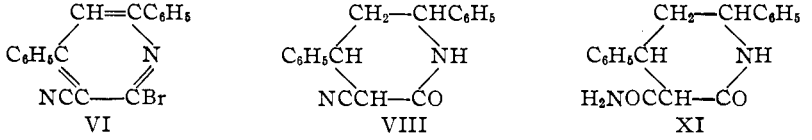
The piperidine derivative crystallizes in fine white needles which have an intense blue fluorescence. It is readily soluble in organic solvents other than petroleum ether and melts at 188–189°.

Action of Halogen Acids on the Malononitrile Addition Product

The halogen acids act as readily on the dinitrile as on the cyano-acetamide addition product, but it is far more difficult to isolate the substances formed because the piperidine derivatives, when impure, show little tendency to crystallize. The principal product that was isolated when hydrogen chloride was used, was a chloropyridine derivative whose structure was easily established by relating it to an hydroxypyridine of known structure.



The experiments with hydrogen bromide were more satisfactory because nearly all of the material could be accounted for. The product was composed almost entirely of nearly equivalent quantities of a bromopyridylnitrile and one or two piperidine derivatives.



2-Chloro-3-cyano-4,6-diphenylpyridine (Formula VI).—A solution of 3 g. of the dinitrile in 25 cc. of dry chloroform was saturated with dry hydrogen chloride. It immediately turned yellow and soon became cloudy. Colorless crystals began to separate after a few hours. When these no longer increased in amount, they were filtered off

and washed with alcohol. After recrystallization from acetic acid they weighed 0.5 g. and were identified as 2-keto-3-cyano-4,6-diphenyl-tetrahydropyridine (VIII).

The filtrate, on evaporation, left a pasty solid which was washed with ether and recrystallized from methyl alcohol.

Analyses. Calc. C, 74.2; H, 3.8; Cl, 12.1. Found: C, 74.5; H, 3.7; Cl, 12.4.

The substance crystallizes in long, silky filaments and melts at 154.5°. It is very readily soluble in chloroform, sparingly soluble in methyl alcohol and in ether. The yield was 1 g.

The same substance was obtained in a yield exceeding 85% by dissolving the corresponding hydroxypyridine derivative (XIV) in phosphorus oxychloride, adding a slight excess of phosphorus pentachloride to this solution and warming the mixture on a steam-bath for a few minutes. The chloro compound separated as a solid when the chlorides of phosphorus were decomposed with ice water, and one recrystallization from methyl alcohol gave a pure product.

2-Bromo-3-cyano-4,6-diphenylpyridine (Formula VII).—A solution of 15 g. of dinitrile in 125 cc. of dry chloroform was saturated with dry hydrogen bromide. The solution became cloudy at once and a red oil soon began to accumulate at the bottom of the liquid. After remaining at the ordinary temperature for 36 hours, the mixture was poured into a solution of sodium bicarbonate, whereupon the oil solidified.

The filtrate from the solid was washed with water, dried, concentrated to small volume by distillation and diluted with hot methyl alcohol. This precipitated 6.3 g. of bromo compound which was purified by recrystallization from a mixture of chloroform and methyl alcohol.

Analyses. Calc. for $C_{18}H_{11}N_2Br$: C, 64.5; H, 3.3. Found: C, 64.4; H, 3.6.

The substance is readily soluble in chloroform, sparingly in ether and in methyl alcohol. It crystallizes in silky needles and melts at 169–170°.

2-Keto-3-carbamyl-4,6-diphenyl-piperidine (Formula XII).—The solid that separated when the oily product came in contact with bicarbonate, was recrystallized from glacial acetic acid. It gave 5.5 g. of the amide.

Analyses. Calc. for $C_{18}H_{18}O_2N_2$: C, 73.4; H, 6.1. Found: C, 72.8; H, 6.1.

The amide is sparingly soluble in all common organic solvents except glacial acetic acid. It crystallizes in minute needles and melts at about 170° when a capillary tube containing it is dipped into a bath which has this temperature; at 230–232° when its temperature is raised in the ordinary way.

The amide is obtained in calculated quantity when the corresponding nitrile (VIII) is hydrolyzed with acids. It was, doubtless, formed in this manner in the experiment which has been described, for when a smaller quantity of the dinitrile was treated in the same way but allowed to stand for only 3 instead of 36 hours the nitrile was obtained in place of the amide.

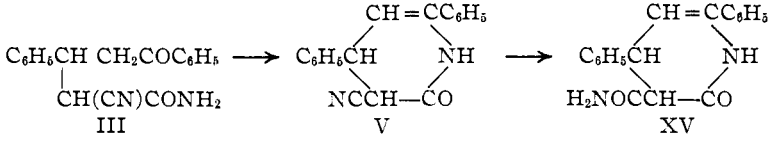
Methyl-2-keto-4,6-diphenyl-piperidine Carboxylate.—The amide was suspended in methyl alcohol and the mixture saturated with hydrogen chloride. The amide gradually dissolved and after several days the clear solution was poured onto cracked ice. This precipitated an oil which solidified when shaken with ether. The solid was recrystallized from a mixture of acetone and petroleum ether. It separated in colorless needles that sintered at 173° and melted to a clear liquid at 177°. The ester is readily soluble in acetone and chloroform, sparingly soluble in ether and methyl alcohol.

Analyses. Calc. for $C_{19}H_{19}O_3N$: C, 73.7; H, 6.2. Found: C, 74.3; H, 5.9.

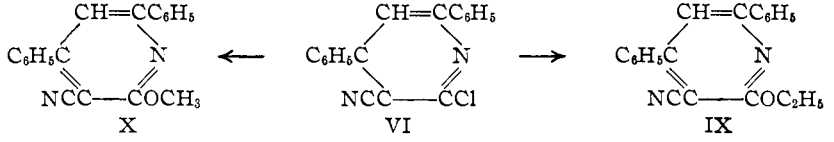
Action of Alkalies on the Addition Products

The two addition products react with alkalies with equal ease, but the

mode of reaction is quite different. The cyano-amide is, for the most part, transformed into an isomeric cyclic compound, the only other product being a "trimolecular" compound. As the cyclic amide is also readily obtained by hydrolyzing the corresponding cyclic nitrile with bases, its formation from the open-chained compound may, doubtless, be represented as follows,



From the products of the action of alcoholic potassium hydroxide on the dinitrile only pyridyl ethers could be isolated. The structure of these was established without difficulty, because they are readily made by the action of alcoholates on the corresponding chloropyridine derivative.



The yield of ethers was always under 50%. As they are manifestly formed by a process of oxidation we assume that the uncrystallizable oils that accumulated in the mother liquors were piperidine derivatives.

2-Methoxy-3-cyano-4,6-diphenylpyridine (Formula X).—A solution of 3 g. of the dinitrile in a mixture of 20 cc. of 10% potassium hydroxide and 5 cc. of water was kept at the ordinary temperature for 24 hours, then poured into water and extracted with ether. The water solution contained no organic material. The ethereal solution, on evaporation, left an oil that partially solidified on addition of methyl alcohol. The oil left after removing the solid yielded a minute quantity of a solid melting at 70–72°, but the bulk of it failed to crystallize and no substance of definite composition could be isolated when a larger quantity was distilled under diminished pressure.

The solid product of the reaction was recrystallized from methyl alcohol. The yield was 1 g.

Analyses. Calc. for $C_{19}H_{14}ON_2$: C, 79,7; H, 4.9. Found: C, 79.4; H, 5.0.

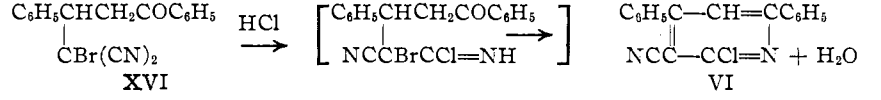
The ether is readily soluble in ether, alcohol and in acetone; it crystallizes from methyl alcohol in silky needles which melt at 110°. Its preparation from the bromopyridine derivative was carried out as follows. A solution of 5.9 g. of the bromine compound was boiled with a slight excess of sodium methylate solution for about 6 hours. The alcohol was then evaporated, the residue poured into water, and the organic material extracted with chloroform. On concentrating the chloroform solution and adding methyl alcohol, 4.2 g. of pyridyl ether was deposited.

2-Ethoxy-3-cyano-4,6-diphenylpyridine (Formula IX).—The ethyl ether was obtained both by the action of alcoholic potassium hydroxide on the dinitrile and by that of sodium ethylate solution on the corresponding chloropyridine. The procedure in both cases was the same as that used for the methyl ether. The ether crystallizes in small needles and melts at 112°.

Analyses. Calc. for $C_{20}H_{16}O_2$: C, 80.0; H, 5.4. Found: C, 79.5; H, 5.1.

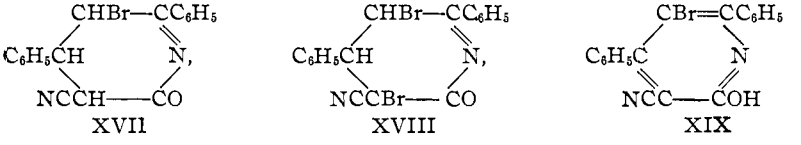
Bromination

The rearrangement of the cyano-acetamide addition product to cyclic compounds takes place so easily that only cyclic bromine compounds were obtained from it even when the bromination was carried out in the presence of potassium acetate.[8] From the dinitrile it was possible to obtain one open-chained bromo compound by brominating in the presence of potassium acetate. The behavior of this substance towards halogen acids confirms the view expressed in the first paper regarding the mechanism by which bromopyridine derivatives are formed when bromine acts on open-chained ketonic nitriles,[9] for when dry hydrogen chloride is passed into chloroform solution of the bromo compound, the product is a *chloro* pyridine derivative.



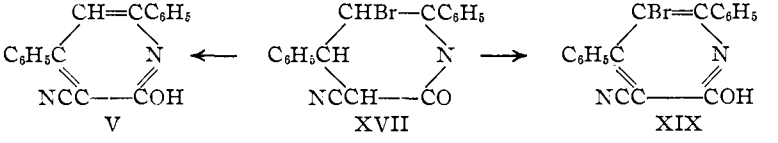
XVI VI

At least 3 cyclic bromine compounds are formed by the action of bromine on the cyano-acetamide addition product. These are also obtained by brominating the hydropyridine derivative into which the open-chained compound changes under the influence of hydrogen bromide. Their structure is represented by the formulas,



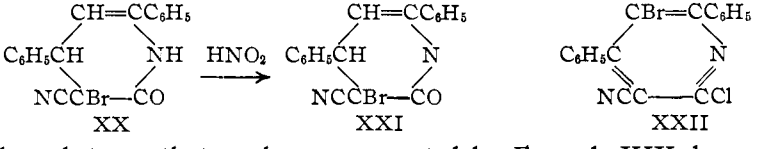
XVII XVIII XIX

The substance represented by the first formula (XVII) loses hydrogen bromide when boiled with potassium acetate and gives an hydroxypyridine of known structure (V); it also loses hydrogen when treated with nitrous acid and gives a bromo-hydroxypyridine (XIX);



V XVII XIX

The only other possible way of representing these relations would be to ascribe to the first and last products, Formulas XX and XXI.



XX XXI XXII

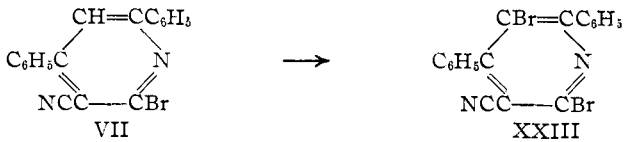
The substance that we have represented by Formula XIX, however, be-

[8] Ref. 1, p. 2539.

[9] Ref. 1, p. 2540.

haves like an hydroxypyridine; it reacts readily with phosphorus pentachloride and forms a chloro-bromopyridine which must be represented by XXII. Formulas XX and XXI are, therefore, excluded. The structure of the dibromo compound follows from the fact that it passes into the bromo-hydroxypyridine, XIX, when treated with alkalies.

Only one cyclic bromo compound was obtained from the dinitrile. The structure of this is established by the fact that it is also formed by brominating a 2-bromopyridine derivative.



VII XXIII

α-Bromo-α,α-dicyano-β-phenyl-γ-benzoyl-butyronitrile (Formula XVI).—A mixture of 5 g. each of the dinitrile and finely powdered potassium acetate was suspended in chloroform and treated with 1 cc. of bromine. This was decolorized as fast as it was added. The mixture was poured into water, the chloroform layer washed, dried, concentrated and diluted with methyl alcohol. This precipitated 5 g. of almost pure bromo compound. The melting point after one recrystallization from methyl alcohol was 126–127°.

Analyses. Calc. for $C_{18}H_{13}ON_2Br$: C, 61.2; H, 3.7. Found: C, 61.2; H, 3.5.

The bromo compound crystallizes in small needles. It is readily soluble in chloroform, acetone or boiling methyl alcohol, and sparingly so in cold methyl alcohol. Potassium acetate in methyl alcohol rapidly eliminates hydrogen bromide at the ordinary temperature.

2-Keto-3-cyano-4,6-diphenyl-5-bromo-tetrahydropyridine (Formula XVII).—This is the principal product formed whenever the cyano-amide addition product is allowed to react with one equivalent of bromine. It was obtained in chloroform, in the presence of a large excess of fused potassium acetate, and in glacial acetic acid.

Analyses. Calc. for $C_{18}H_{13}ON_2Br$: C, 61.2; H, 3.7. Found: C, 61.4; H, 3.8.

The substance is readily soluble in chloroform, acetone or boiling alcohol. It crystallizes in fine needles. Its melting point as determined by the "dip" method is at about 165°, but when the temperature is raised in the ordinary way it loses hydrogen bromide below the melting point and consequently does not melt below 312°—the melting point of 2-hydroxy-3-cyano-4,6-diphenylpyridine (XIV). It loses hydrogen bromide very slowly when its alcoholic solution is boiled with potassium acetate, but sodium methylate rapidly converts it into the same hydroxypyridine that is obtained by heating it.

The *corresponding chloro compound* is the first product of the action of phosphorus pentachloride on the cyclic nitrile. It crystallizes in long needles, is readily soluble in acetone, alcohol, and chloroform, and melts at 178–181°.

Analyses. Calc. for $C_{18}H_{13}ON_2Cl$: C, 70.0; H, 4.2. Found: C, 69.7; H, 4.4.

2-Keto-3-cyano-3,5-dibromo-4,6-diphenyl-tetrahydropyridine (Formula XVIII).—The dibromo compound was obtained from the cyano-acetamide addition product, from the cyclic nitrile (?), and from the bromonitrile (XVII) by brominating with excess of bromine in hot carbon tetrachloride. It loses hydrogen bromide so readily that a perfectly pure product is difficult to obtain. It crystallizes in small yellow plates and decomposes with effervescence at about 195°.

Analyses. Calc. for $C_{18}H_{12}ONBr_2$: C, 50.0; H, 2.8. Found: C, 49.8; H, 2.9.

2-Hydroxy-3-cyano-5-bromo-4,6-diphenylpyridine (Formula XIX).—The 5-bromopyridine is one of the by-products formed in brominating the amide in glacial acetic acid. It is easily made by the action of nitrous acid on the cyclic bromo compound, XVII. To a solution of 1 g. of this bromo compound in 25 cc. of glacial acetic acid 1 g. of sodium nitrite was added in small portions. The mixture was poured into water and the solid thus precipitated recrystallized from glacial acetic acid and from methyl alcohol. It melts, with charring, at 303–306°.

Analyses. Calc. for $C_{18}H_{11}ON_2Br$: C, 61.6; H, 3.2. Found: C, 61.6; H, 3.2.

2-Chloro-3-cyano-5-bromo-4,6-diphenylpyridine (Formula XXII).—A mixture of 2.5 g. of the bromo-hydroxypyridine (XIX 1), 2 cc. of phosphorus oxychloride and 1.7 g. phosphorus pentachloride was heated in a tube until the brisk evolution of hydrogen chloride ceased. The tube was then sealed and the heating continued in a steam-oven for about an hour. The mixture was then poured onto ice and the oil dissolved in chloroform. The washed and dried chloroform solution on evaporation left an oil that solidified. The solid was recrystallized from a mixture of acetone and petroleum ether from which it separated in pale yellow plates that melted at 181–182°. It is readily soluble in chloroform, moderately soluble in acetone, almost insoluble in alcohol.

Analyses. Calc. for $C_{18}H_{10}ONClBr$: C, 58.5; H, 2.7; Cl-Br, 31.2. Found: C, 58.4; H, 2.6; Cl-Br, 31.2.

2,5-Dibromo-3-cyano-4,6-diphenylpyridine.—The dibromo compound was one of the products formed when the dinitrile was brominated with excess of bromine in the presence of potassium acetate. It was also obtained by brominating the 1-bromopyridine in the sunlight. It crystallizes from a mixture of acetone and petroleum ether in clusters of pale yellow prisms which melt at 189–190°.

Analyses. Calc. for $C_{18}H_{10}N_2Br_2$: C, 52.2; H, 2.4. Found: C, 52.7; H, 2.6.

Summary

1. The δ ketonic nitriles obtained by combining cyano-acetamide and cyano-acetonitrile with benzalacetophenone give cyclic compounds when treated with acids or bases.

2. The addition product obtained with cyano-acetamide forms a tetrahydropyridine derivative by internal condensation involving the carbamide group.

3. The addition product with cyano-acetonitrile combines with a molecule of acid or base, and the resulting compound then undergoes condensation to a dihydropyridine derivative. These dihydropyridine derivatives spontaneously undergo oxidation and reduction into a mixture of pyridine and piperidine derivatives.

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