chloro acid by the action of hydrochloric acid; the chloro acid in turn easily loses hydrogen chloride, forming the unsaturated compound.

3. Certain β-halogen phosphonic acids have been prepared from the unsaturated phosphonic acid.

4. These compounds easily lose hydrogen bromide and phosphoric acid when treated with sodium carbonate forming unsaturated hydrocarbons. Thus, phenyl acetylene, styrene, and α-bromostyrene were formed from the corresponding bromo-phosphonic acids.

CAMBRIDGE 38, MASSACHUSETTS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

SOME DELTA KETONIC NITRILES AND THEIR RELATION TO CYCLIC COMPOUNDS

BY E. P. KOHLER, ALICE GRAUSTEIN[1] AND D. R. MERRILL

Received May 26, 1922

By adding cyano-acetic ester, cyano-acetamide, malononitrile, benzyl cyanide and similar substances to unsaturated ketones, it is possible to obtain a great variety of closely related δ-ketonic nitriles, which pass, more or less readily, into hydropyridine derivatives. We are using these addition products to study the conditions under which the cyclic compounds are formed, the mechanism of the reactions which are involved, and, in particular, the transition from hydropyridine to pyridine derivatives.

This paper deals with the substances that were obtained by adding methyl cyano-acetate to benzal-acetophenone and benzal-*p*-chloro-acetophenone. The products from the two ketones behave alike, but the cyclic compounds and the substitution products obtained from the *p*-chloro derivatives generally melt higher and are less soluble than those derived from the chlorine-free substance. It was frequently advantageous, therefore, to determine the most favorable conditions for a reaction first with the chloro ketone.

The simplest transformation of the open-chained addition products into cyclic compounds that we have found, is represented by the equation.

$$\begin{array}{l} \mathrm{RCHCH_2COR} \\ \quad | \\ \mathrm{RO_2CCHCN} \end{array} \rightleftharpoons \begin{array}{l} \mathrm{RCH{-}CH{=}CR} \\ \quad | \quad\quad | \\ \mathrm{RO_2CCH{-}CO{-}NH} \end{array}$$

This rearrangement takes place with great ease when solutions of the addition products in indifferent media are saturated with hydrogen chloride or with hydrogen bromide. If the amount of solvent is small, the change into the cyclic compound is almost quantitative, and, when hydrogen bromide is used as agent, the reaction is completed in a few hours.

Owing to the ease with which substances like these pass into each other, it is sometimes difficult to distinguish between structural isomerism and

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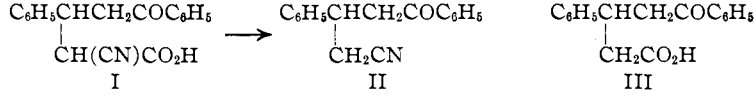
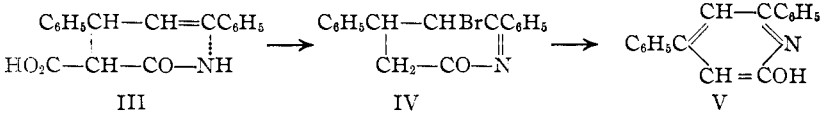
stereo-isomerism, but in the case of the cyano-acetate addition products the evidence that they are related as shown in the equation is conclusive. By a series of transformations beginning with alkaline hydrolysis the product obtained from benzal-acetophenone was converted into an open-chained compound of known structure.



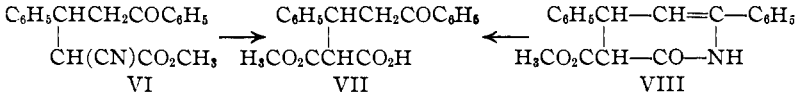
I II III

By a different series of reactions which also started with alkaline hydrolysis, the cyclic compound, likewise was transformed into a known substance:[2]



III IV V

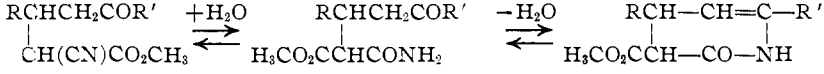
Inasmuch as the process of ring formation is reversible, the open-chained compounds and their ring isomers generally give the same products in reactions which take place in the presence of acids. Thus both dissolve in conc. sulfuric acid and when the solutions are diluted they give the same ester acid.



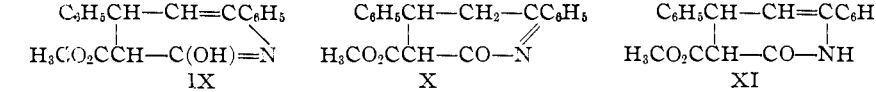
VI VII VIII

Both are also turned into the ester of this acid with equal ease.

There are various schemes based on known properties of nitriles, by which it would be possible to account for the change from open-chained to cyclic compound. Nearly all of these are excluded by the fact that while this change takes place readily in glacial acetic acid as well as in chloroform and carbon tetrachloride, it is completely inhibited by the presence of acetyl chloride or acetic anhydride. A trace of water, therefore, is essential, and the way to the cyclic compound is probably through the amide.



Neither the process by which the cyclic compound is formed nor the method used for establishing its cyclic character gives any indication of the distribution of the hydrogen atoms among the components of the ring. *A priori*, the following formulas seem equally probable.

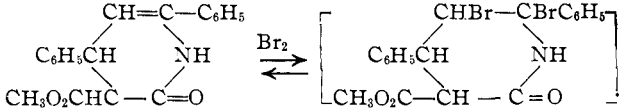


IX X XI

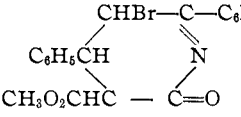
The first of these, as well as all other possible hydroxyl formulas, is excluded by the fact that the substance is quite insoluble in even the most

[2] THIS JOURNAL, **44**, 384 (1922).

concentrated alkalies. The second formula seems inconsistent with the behavior of the substance towards bromine. A compound having this structure would be expected to react like a saturated ketone, consuming bromine only as it undergoes rearrangement, while one having the structure represented by XI would be expected to behave like a diketone that is already completely enolized. A titration of the cyclic compound showed that even at 0° it instantaneously takes up almost exactly 1 mole of bromine. As this result can be reconciled with Formula X only by making the improbable assumption that the substance rearranges from Structure X to XI so rapidly that the process cannot be detected by the Kurt Meyer method, we prefer Formula XI and represent the bromination by the equation

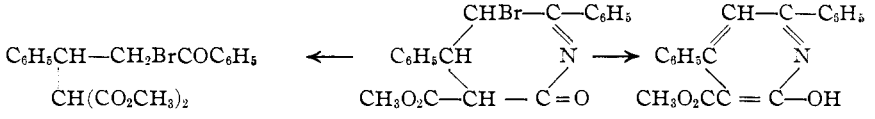


XI

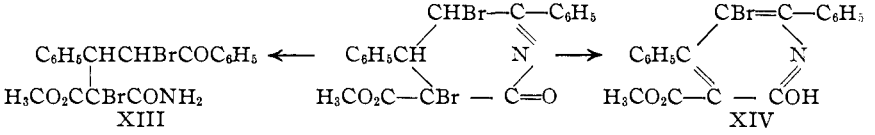


XII

The properties of the bromo compound confirm this interpretation. When its solution in methyl alcohol is saturated with hydrogen bromide it passes into an open-chained compound of known structure, and it readily parts with hydrogen bromide to form an hydroxypyridine ester.



The behavior of the monobromo compound on further bromination is also in accord with our interpretation, for while the substance lacks the extraordinary activity of the bromine-free compound, it slowly reacts with more bromine and forms a 3,5-dibromo derivative. This is unstable: in solution it slowly loses hydrogen bromide and in contact with water or alcohol it is rapidly hydrolyzed to 2 stereo-isomeric α,γ-dibromo ester amides.

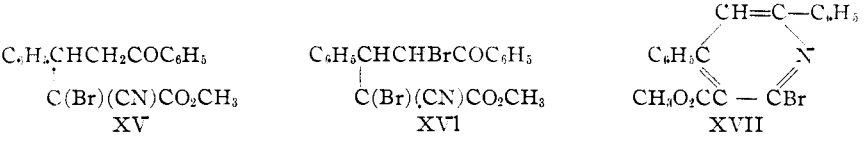


XIII XIV

In the dibromo derivative, the stability relations between the open-chained and cyclic compounds appear to be completely reversed because, in the presence of halogen acid and water, the cyclic compound passes rapidly and completely into the open-chained amides. The result is,

however, probably due not so much to the inherent instability of the cyclic compound as to the extremely slight solubility of the amide.

A second method for transforming the addition products into cyclic compounds is based on the action of bromine. Bromination of the open-chained compounds is an exceedingly involved process. Unless precautions are taken to prevent the isomerizing action of the hydrogen bromide which is formed, the process gives the entire series of bromine derivatives that we have discussed, along with others that are formed from the open-chained compounds. The bromination can be regulated in one of two ways: by providing a reagent that will combine with the hydrogen bromide as fast as it is formed, or by brominating in glacial acetic acid. It is possible to keep the concentration of the hydrogen bromide at a very low level by brominating very slowly in the presence of a large excess of fused and very finely powdered potassium acetate. Under these conditions the products are an α-bromo compound (XV), an α-γ-dibromo compound (XVI), and a pyridine derivative.



XV XVI XVII

The position of the bromine in the monobromo compound is evident from the complete inertness of the cyanogen group which cannot be either hydrolyzed or esterified. The substance must be an open-chained compound because it readily parts with hydrogen bromide and forms a cyclopropane derivative.[3] The structure of the dibromo compound is established by the ease with which it forms a cyclopropane derivative when treated with potassium iodide.[4] It is worthy of note that no γ-monobromo compounds were obtained from these cyano esters, while the corresponding malonic ester derivatives, which differ from them only in having an ester in place of a cyanogen group, gave approximately equal amounts of α- and γ-compounds.[5]

The bromopyridine ester (XVII) is the most interesting of these bromination products. The composition of the substance shows that this must be a true pyridine derivative. It can be hydrolyzed; but prolonged boiling with conc. caustic potash is necessary for complete hydrolysis, and the resulting acid can be re-esterified only by way of the silver salt. When a methyl alcoholic solution of the substance is boiled with sodium hydroxide, the bromine is slowly but completely replaced by an hydroxyl group—a property of bromopyridines in which the bromine is in the 2 position. The substance, therefore, behaves like the ester of a bromopyridine acid

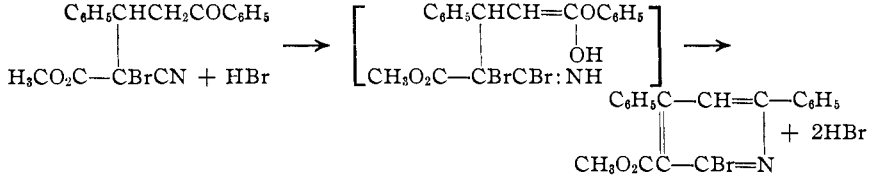
[3] THIS JOURNAL, **39**, 1404 (1917).

[4] *Ibid.*, **39**, 1413 (1917).

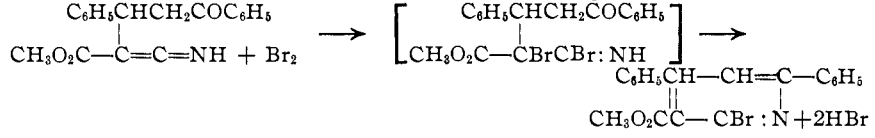
[5] *Ibid.*, **44**, 840 (1922).

in which the carboxyl group is di*ortho* substituted, and in which the bromine is in the 2 position. This excludes all possible formulas other than the one we give.

The bromopyridine ester is formed whenever the addition product is brominated; but only a trace is obtained when the operation is carried out in the presence of an adequate amount of potassium acetate, the principal product being the monobromo ester. In glacial acetic acid, on the other hand, bromination gives the pyridine derivative almost exclusively; the product contains no monobromo and only a trace of dibromo-compound. The bromopyridine ester can also be obtained, quantitatively, by saturating a chloroform solution of the monobromo compound with hydrogen bromide. Since under these conditions simple nitriles form imide bromides, the mechanism here is



The passage from the addition product to the 2-bromopyridine derivative is, doubtless, always through the unstable imide bromide, for when the ring is closed first, subsequent bromination always gives a 4-bromo derivative. When the addition product is brominated in glacial acetic acid in which all of the hydrogen bromide is retained the imide bromide may be formed either as before by addition of hydrogen bromide to an intermediate α-bromo compound or by addition of bromine to a tautomeric form of the cyano ester:



The reaction is an uncommonly clean one; it constitutes a new pyridine synthesis.

Experimental Part

Addition of Cyano-acetic ester to Unsaturated Ketones

In the presence of a small quantity of sodium methylate, methyl cyano-acetate combines as readily as methyl malonate with unsaturated ketones; but while the latter gives only one product in which the components are in the proportion of 1 to 1, the former invariably gives, in addition to a substance of this type, a "trimolecular" compound in which the components are in the proportions of 1 molecule of ester to 2 of ketone. This trimolecular compound is a secondary product, formed by the addition

of the simpler substance to a second molecule of the unsaturated ketone. In order to confine the reaction as far as possible to the first stage it is important, for reasons that are not quite clear, to operate in very dry methyl alcohol. It is important also to use the smallest quantity of sodium methylate that will serve the purpose, because these addition reactions are reversible and, in the presence of sodium methylate, the simpler substance is more or less rapidly transformed into the very sparingly soluble dimolecular product. The following illustrates the most satisfactory procedure.

A solution of 208 g. (1 mol.) of pure benzal-acetophenone and 125 g. (1.25 mol.) of methyl cyano-acetate in 300 cc. of methyl alcohol which had been distilled from magnesium methylate was warmed to 50°. A solution of sodium methylate was then added drop by drop until the liquid was perceptibly alkaline to litmus (10 to 20 drops, depending upon the amount of free acid in the ester). The temperature of the liquid rapidly rose to the boiling point. It was kept at this temperature for an hour, then cooled in ice water and inoculated with some of the solid addition product. After remaining at this temperature for about an hour, during which a large crop of white crystals separated, the mixture was cooled in a freezing mixture for another hour, when it set to a nearly solid cake. This was broken up, the resulting paste filtered, the solid washed with about 100 cc. of cold methyl alcohol and dried with suction: yield, 270 g. of crude material; m. p., 70–72°.

The solid dissolved in its own weight of boiling ether, leaving only a faint cloudiness, and hence contained only a trace of dimolecular product. The solution was cooled and inoculated. It slowly deposited 127 g. of pure product and an additional 130 g. separated when the mother liquor was diluted with its own volume of petroleum ether. The total yield of pure product was, therefore, about 83%.

The alcoholic filtrate rapidly became cloudy. On standing for 24 hours it deposited 3.5 g. of dimolecular product. The filtrate from this, concentrated to 75 cc., cooled in a freezing mixture and inoculated, yielded 22 g. of solid which melted fairly well (68–70°) but contained at least 2 g. of dimolecular product. The oils left after evaporating all filtrates and removing salts and acids gave nearly an equivalent quantity of the corresponding dibasic ester on esterification with methyl alcohol; but no more solid could be extracted from it. This may be due to the presence of a stereo-isomer, but as no isomers were obtained with *p*-chloro-benzal-acetophenone which gives higher-melting products, this seems doubtful.

Methyl γ-Benzoyl-β-phenyl-α-cyanobutyrate, $C_6H_5COCH_2CH(C_6H_5)CH(CN)CO_2CH_3$.—The monomolecular addition product crystallizes from ether in colorless, transparent prisms and melts at 76°. It is readily soluble in all common organic solvents except petroleum ether, and has a very pronounced tendency to separate from solutions as an oil. We prepared it a number of times and used it for several years before we accidentally secured solid for inoculation.

Analyses. Calc. for $C_{19}H_{17}O_3N$: C, 74.3; H, 5.5. Found: C, 74.1; H, 5.8.

THE TRIMOLECULAR PRODUCT: $C_6H_5CHCH_2COC_6H_5$ / $C(CN)CO_2CH_3$ / $C_6H_5CHCH_2COC_6H_5$.—This substance is very sparingly soluble in common organic solvents except chloroform. It was purified by crystallization from a mixture of chloroform and methyl alcohol from which it separates in small cubical crystals which melt at about 226°.

Analyses. Calc. for $C_{44}H_{29}O_4N$: C, 79.2; H, 5.6. Found: C, 79.3; H, 5.7.

Methyl γ-(*p*-Chlorobenzoyl)-β-phenyl-α-cyanobutyrate, $ClC_6H_4COCH_2CH(C_6H_5)CH(CN)CO_2CH_3$.—The product obtained by adding methyl cyano-acetate to benzal-*p*-chloro-acetophenone was purified by crystallization from methyl alcohol. It crystallizes in large lustrous needles which melt at 126°. It is readily soluble in chloroform, acetone, or benzene; moderately soluble in alcohol or ether, insoluble in petroleum ether. The yield of pure product was 87%.

Analyses. Calc. $C_{19}H_{16}O_3NCl$: C, 66.7; H, 4.7. Found: C, 66.2; H, 4.8.

THE TRIMOLECULAR PRODUCT is sparingly soluble in alcohol or ether, readily soluble in boiling chloroform, acetone, or benzene. It crystallizes from dilute solutions in large transparent prisms which melt at 230–232°.

Analyses. Calc. for $C_{34}H_{27}O_4NCl$: C, 69.9; H, 4.6. Found: C, 69.8; H, 4.9.

Methyl γ-[*p*-Chlorophenyl]-β-phenyl-α,α-methyl-cyanobutyrate, $(C_6ClC_6H_4COCH_2CHC_6H_5)C(CH_3)(CN)CO_2CH_3$.—Methyl α-cyanopropionate does not combine as readily as the acetate with unsaturated ketones, but as there is no possibility of forming a trimolecular product a larger amount of sodium methylate can be used with safety. The reaction gives 2 stereo-isomeric addition products in variable proportions. These were separated by crystallization from methyl alcohol. Both crystallize in thin plates, one melting at 108°, the other at 92°.

Analyses. Calc. $C_{20}H_{18}O_3NCl$: C, 67.5; H, 5.0. Found: (108°) C, 67.5; H, 5.2; (92°) C, 67.6; H, 5.1.

The structure of these substances was established by hydrolysis and esterification to the corresponding dibasic ester. For this purpose solutions of the compounds in dry methyl alcohol were saturated with hydrogen chloride and allowed to stand for several days. Both substances gave the same product, dimethyl-γ-[*p*-chloro-benzoyl]-β-phenyl-α-methyl malonate, $ClC_6H_4COCHCH_2(C_6H_5)C(CH_3)(CO_2CH_3)_2$, which melts at 106°. This substance was made, also, by adding dimethyl methyl-malonate to benzal-*p*-chloro-acetophenone, and the two products were found to be the same.

Analyses. Calc. for $C_{22}H_{22}O_5Cl$: C, 64.8; H, 5.4. Found: C, 64.4; H, 5.7.

Hydrolysis of the Cyano-acetic Ester Addition Products

The simple cyano ester addition products can be hydrolyzed at will to ester acids, dibasic acids, and cyano acids. The hydrolysis to ester acids must be carried out in an acid medium; it is most easily done with a solution of sulfuric acid in glacial acetic acid. For hydrolysis to the dibasic acid it is best to go from the cyano ester to the ester of the dibasic acid and hydrolyze this with bases. The hydrolysis to the cyano acids is the most difficult to carry out successfully because this must be done with bases, and unless the conditions are properly selected the addition reaction is in part reversed and the principal products are the dimolecular compound, cyano-acetic acid and various other products formed by the action of alkali on the unsaturated ketone.

γ-Benzoyl-β-phenyl-α-carboxy-methyl-butyric Acid, $C_6H_5COCH_2CH(C_6H_5)CH(CO_2CH_3)CO_2H$.—A solution of 3.5 g. of the cyano ester and 1 g. of conc. sulfuric acid in 5 cc. of glacial acetic acid was kept at room temperatures for several days, after which a drop of the liquid gave a clear solution in dil. sodium carbonate. The colorless liquid was cautiously diluted with ice water until a faint permanent milkiness appeared, and then

cooled in a freezing mixture. It deposited about 3 g. of a white solid which after one recrystallization from benzene gave 2.7 g. of pure ester acid.

Analyses. Calc. for $C_{19}H_{18}O_3$: C, 70.0; H, 5.5. Found: C, 69.7; H, 5.6.

The ester acid crystallizes from benzene in friable white needles which melt with slow decomposition at about 160° and decompose freely above 180°. The product left after heating it to 200° was identified as methyl benzoyl phenyl butyrate by comparison with a specimen on hand.

γ-Benzoyl-β-phenyl-α-cyanobutyric Acid, $C_6H_5COCHCH_2(C_6H_5)CH(CN)CO_2H$.—In a preliminary attempt at hydrolysis conc. aqueous potassium hydroxide was added to a methyl alcoholic solution of the cyano ester. The liquid turned yellow at once and soon began to deposit a crystalline solid. After a few hours the solid was filtered off and recrystallized. It proved to be largely the trimolecular addition product. The filtrate was diluted with water and the resulting oily liquid extracted with ether. The ether on evaporation deposited a crystalline solid which after recrystallization melted at 84°. An analysis and a comparison with a specimen on hand proved that this substance is benzal-diacetophenone—a product of the action of alkalies on benzal-acetophenone. The aqueous liquid left after extraction with ether, on acidifying, gave a small quantity of an oily acid. It is clear from this experiment that conc. alcoholic potash rapidly reverses the reaction by which the cyano ester was formed.

The following method of hydrolysis proved more satisfactory. Solutions of 5 g. of potassium hydroxide and 15 g. of the cyano ester, each in 100 cc. of dry methyl alcohol, were cooled in a freezing mixture and poured together. The resulting very pale yellow liquid was left in an ice-chest for 24 hours, during which it deposited a small quantity of the trimolecular compound. The filtrate from this was neutralized, then concentrated to small volume and acidified. After removing indifferent products in the usual way there remained 12 g. of a colorless oil that ultimately solidified. The solid was recrystallized from benzene from which it separated in white, friable needles that melted with slight decomposition at about 160°.

Analyses. Calc. for $C_{18}H_{15}O_3N$: C, 73.7; H, 5.2. Found: C, 73.8; H, 5.4.

γ-Benzoyl-β-phenyl-butyro-nitrile, $C_6H_5COCH_2CH(C_6H_5)CH_2CN$.—The cyano acid was decomposed at 200° and the very pale yellow melt dissolved in boiling methyl alcohol. This solution on cooling deposited colorless needles which after one recrystallization melted at 76°.

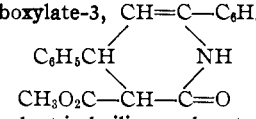
Analyses. Calc. for $C_{17}H_{15}ON$: C, 81.9; H, 6.1. Found: C, 81.8; H, 6.5.

The substance was rapidly hydrolyzed by boiling alcoholic potassium hydroxide, and the only product was γ-benzoyl-β-phenylbutyric acid. It is, therefore, the nitrile of this acid and not an isomeric dihydropyridine derivative.

The nitrile is readily soluble in methyl alcohol, moderately so in ether, and almost insoluble in petroleum ether. Concentrated solutions of the substance in chloroform and in carbon tetrachloride were saturated with hydrogen chloride and with hydrogen bromide and then kept at room temperature for a week. As none of them deposited solid products, they were then poured into ice water, freed from halogen acids, and allowed to evaporate. They left only unchanged nitrile contaminated with small quantities of uncrystallizable oils. In chloroform the nitrile reacts with bromine and forms a crystalline monobromo compound, but as this readily loses hydrogen bromide when boiled with methyl alcoholic potassium acetate it is not a bromopyridine derivative. The nitrile, therefore, does not show the tendency to form pyridine derivatives which is so marked in the case of the cyano ester.

Action of Halogen Acids on the Addition Products

Tetrahydropyridine Derivatives

Methyl 2-Keto-4,6-diphenyl-tetrahydropyridine Carboxylate-3,  .—

A solution of 60 g. of the methyl cyano-acetate addition product in boiling carbon tetrachloride was cooled and immediately saturated with dry hydrogen bromide. A colorless compound began to separate in a few minutes and the entire solution solidified in the course of a few hours. The mass was cooled in a freezing mixture, filtered, and the solid washed first with a little iced methyl alcohol and then thoroughly with water. After drying on a steam-bath the crude product weighed 57 g. It melted at 164–165°. As repeated recrystallization from methyl alcohol raised the melting point only 1°, the substance was practically pure cyclic compound.

The conversion of the open-chained compound into its cyclic isomer can be brought about just as readily with hydrogen chloride, but the process is slower, requiring 8 to 10 hours for completion. Chloroform is not as satisfactory as carbon tetrachloride because it dissolves the product freely and the recovery is not as complete. In glacial acetic acid the conversion is much slower but the product separates in the course of several days in large, transparent crystals which melt sharply at 165–166°.

Analysis. Calc. for $C_{19}H_{17}O_3N$: C, 74.2; H, 5.6. Found: C, 74.1; H, 5.6.

The tetrahydropyridine derivative is readily soluble in chloroform, moderately soluble in boiling methyl alcohol or acetone, very sparingly in ether. It separates from methyl alcohol in large transparent needles and melts at 165–166°. It does not reduce permanganate in acetone at the ordinary temperature but it rapidly decolorizes a solution of bromine in chloroform even at —20°. When its solution in methyl alcohol is warmed with a little conc. sulfuric acid or saturated with hydrogen chloride the ring is opened again and the substance passes quantitatively into the dimethyl ester of the corresponding dibasic acid.

2-Keto-4,6-diphenyl-tetrahydropyridine-carboxylic Acid-3.—When conc. alcoholic potash is added to a saturated solution of the cyclic ester in dry methyl alcohol it precipitates a bright yellow metallic derivative from which most of the ester is regenerated on addition of acids. In dil. alcoholic potash the ester dissolves freely and the yellow solution gradually becomes nearly colorless. It then contains a salt of the cyclic acid. A solution obtained in this way was concentrated under diminished pressure, the residue poured into water, and the slightly cloudy mixture extracted with ether. The colorless aqueous layer was then cooled in a freezing mixture and cautiously acidified. It deposited an exceedingly unstable acid, which was air-dried and purified by solution in cold acetone and reprecipitation with petroleum ether.

Analyses. Calc. for $C_{18}H_{15}O_3N$: C, 73.7; H, 5.2. Found: C, 73.9; H, 5.5.

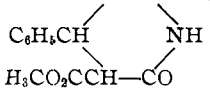
The acid crystallizes in small colorless cubes which melt and effervesce freely at about 130° when heated in a capillary tube, but give off carbon dioxide far below this temperature when heated in open vessels.

2-Keto-4,6-diphenyl-tetrahydropyridine.—The tetrahydropyridine acid was decomposed at 150° and the residue, which solidified on cooling, crystallized from methyl alcohol.

Analyses. Calc. for $C_{17}H_{15}ON$: C, 81.9; H, 6.0. Found: C, 81.9; H, 6.0.

The substance crystallizes in flat needles, melts at 130°, and is readily soluble in all organic solvents except petroleum ether. It does not reduce permanganate in the cold but readily reacts with bromine.

Methyl 2-Keto-4-phenyl-6[*p*-chlorophenyl]-tetrahydropyridine Carboxylate-3, $CH{=}C{-}C_6H_4Cl$.—Fifty g. of the product obtained by adding methyl



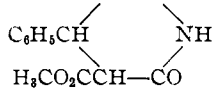
cyano-acetate to benzal-*p*-chloro-acetophenone was suspended in chloroform, and hydrogen bromide passed into the mixture until all of the solid had dissolved. The solution was allowed to stand overnight, then distilled until free from chloroform. The yellow residue, on addition of methyl alcohol, became a white solid. This was filtered with suction, washed with methyl alcohol and recrystallized from boiling methyl alcohol. The yield of crude substance was 90%. One recrystallization gave a pure product melting at 204°.

Analyses. Calc. for $C_{19}H_{16}O_3NCl$: C, 66.7; H, 4.7. Found: C, 66.3; H, 4.9.

Bromination of the Tetrahydropyridine Derivatives

All of the tetrahydropyridine derivatives react with bromine with great ease. The reaction is capable of giving a great variety of products, but if the operation is conducted with sufficient care it gives almost exclusively monobromo substitution products. When the bromination is carried out at too high a temperature the product is contaminated with the corresponding dihydropyridine derivative and when bromine is used in excess, corresponding amounts of more highly brominated compounds are formed.

Methyl 2-Keto-4,6-diphenyl-5-bromo-tetrahydropyridine Carboxylate-3, $CBr{=}C{-}C_6H_5$.—A 50% solution of bromine in chloroform was added to



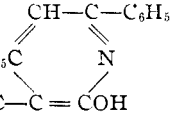
a solution of 50 g. of pure tetrahydropyridine ester in 150 cc. of dry chloroform until a permanent color developed in the solution. The first few drops of the bromine solution were added at the ordinary temperature but as soon as the reaction was well started the temperature was lowered to 0°. It required almost exactly 1 mole of bromine to produce a permanent color at this temperature. The solution was heated to the boiling point, then immediately cooled, washed with sodium bisulfite and sodium bicarbonate, and dried with calcium chloride. The chloroform was then distilled and the oily residue dissolved in the minimum quantity of dry methyl alcohol. This solution as it cooled, deposited 54.5 g. of almost pure monobromo derivative. The filtrate from this, on evaporation, yielded 4.5 g. of less pure product.

The bromine compound was purified by dissolving it in boiling chloroform and diluting this solution with an equal volume of boiling methyl alcohol. It crystallizes in large prisms which have a strong greenish-yellow fluorescence, melts at 160–161°, and is moderately soluble in cold chloroform, very sparingly soluble in methyl alcohol or ether.

Analyses. Calc. for $C_{19}H_{16}O_3NBr$: Br, 20.7. Found: 21.0, 20.7.

For the purpose of locating the bromine atom a solution of the substance in dry methyl alcohol was saturated with hydrogen bromide. After standing at room temperature for several days this solution was diluted with water and extracted with ether. The ethereal solution, after it had been washed with sodium bicarbonate, then dried and evaporated, left a colorless oil; but when this was dissolved in methyl alcohol the solution deposited γ-benzoyl-γ-bromo-β-phenyl-ethyl malonate which was identified by a mixed melting point with a specimen on hand.[5] The bromine is therefore in the 5 position.

In order to establish the character of the ring, the bromo compound was converted into a pyridine derivative of known structure. That it is not an open-chained compound is proved by the fact that it does not react with potassium acetate which would eliminate hydrogen bromide from any possible bromo compound of this type.

Methyl 2-Hydroxy-4,6-diphenyl-pyridine Carboxylate-3, 

Although the bromo compound does not react either with potassium acetate or magnesium methylate it gives up hydrogen bromide fairly readily when digested with sodium methylate or alcoholic potassium hydroxide. Sodium methylate from 1 g. of sodium was added to a boiling solution of 12 g. of the bromo compound in 200 cc. of methyl alcohol. The bright yellow solution was distilled to a small volume, diluted with water and extracted with ether. The ethereal solution contained about 2.5 g. of unchanged material. The water layer was acidified and likewise extracted with ether. A precipitate, which formed almost immediately in the ether, consisted of 3.8 g. of almost pure hydroxypyridine ester. The ether on evaporation left a small quantity of other products. Alcoholic potassium hydroxide gave the same product but there was also some hydrolysis to a bromo acid.

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

THE HYDROXYPYRIDINE ACID was obtained by hydrolyzing the ester with alcoholic potash. For this purpose 5 g. of the ester was added to a mixture of 25 cc. of methyl alcohol and 50 g. of 50% aqueous potassium hydroxide. During 3 hours' boiling a white potassium salt separated from the solution. On dilution with water this dissolved and on acidification a voluminous white precipitate was formed. This was almost pure hydroxypyridine acid. It was recrystallized from methyl alcohol in which it is sparingly soluble and from which it separates in fine yellow needles. The acid melts with decomposition, at 253°.

2-HYDROXY-4,6-DIPHENYL-PYRIDINE.—The acid was heated under diminished pressure for 15 minutes at 260°. The light yellow residue on crystallization from methyl alcohol gave very pale yellow plates which melted at 209–210°. A mixed melting point showed that this is the same hydroxy-diphenyl-pyridine whose structure was established in an earlier paper.[6] The bromo compound and the substances derived from it must, therefore, be cyclic compounds.

Methyl 2-Keto-3,5-dibromo-4,6-diphenyl-tetrahydropyridine Carboxylate-3.—The monobromo compound reacts with more bromine. The primary product is a dibromo compound, but as this is exceedingly unstable it was never obtained in a yield exceeding 50%. Thus, when 38 g. of the solid monobromo compound was added to a solution of 16 g. of bromine in 100 cc. of chloroform the color became lighter at once and a very slow evolution of hydrogen bromide commenced after a few minutes. In direct sunlight the color disappeared almost completely in the course of an hour. The solution was then washed with bisulfite and bicarbonate, dried with calcium chloride and diluted with petroleum ether. This caused the precipitation of a colorless granular solid consisting mainly of the dibromo compound. The mother liquors became acid on standing and gave other products.

The solid was purified by solution in cold chloroform and reprecipitation with petroleum ether. It was thus obtained in small colorless prisms which when rapidly heated in a capillary tube melted with decomposition at about 160°.

Analyses. Calc. for $C_{19}H_{15}O_3NBr_2$: C, 49.0; H, 3.2. Found: C, 49.1; H, 3.3.

[6] THIS JOURNAL, **44**, 384 (1922).

When a solution of the dibromo compound in dry methyl alcohol was rapidly saturated with hydrogen bromide and then cooled in a freezing mixture it deposited, besides ammonium bromide, a mixture of two organic compounds. One of these, which was fairly readily extracted with boiling methyl alcohol, melted at 132° and proved to be an α-γ-dibromo derivative of dimethyl benzoyl-phenyl-ethyl malonate. It was identified by analysis and by comparison with a specimen on hand.[7] The bromine atoms are therefore, as was to be expected, in the 3,5 positions.

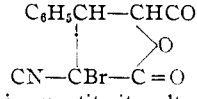
γ-Benzoyl-α,γ-dibromo-α-carboxymethyl-β-phenyl-butyramide.—The second substance that is formed when a methyl alcoholic solution of the dibromo compound is saturated with hydrogen bromide is, doubtless, this open-chained amide. It is very sparingly soluble in all solvents. From chloroform it separates in tufted needles which decompose at about 180°.

Analyses. Calc. for $C_{19}H_{17}O_4NBr_2$: C, 47.2; H, 3.5; Br, 33.1. Found: C, 47.3; H, 3.5; Br, 33.3.

An isomeric dibromo ester amide was formed when the chloroform solution in which the dibromo-dihydropyridine ester had been brominated was allowed to stand for some time in contact with air before the hydrogen bromide was washed out of it. The solution gradually deposited a large quantity of clear colorless needles which melted with decomposition at about 140°. This substance, which is much more soluble than its isomer, was recrystallized from methyl alcohol from which it separated in minute transparent needles.

Analysis. Calc. for $C_{19}H_{17}O_3NBr_2$: C, 47.2; H, 3.5. Found: C, 47.0; H, 3.7.

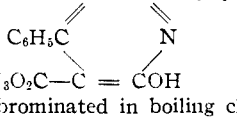
Neither of these bromo ester amides could be converted into the corresponding diester, the hindrance to the acid hydrolysis of the amide group being complete, as it frequently is in this type of compound. Both substances, however, readily undergo the transformation into furane derivations which is characteristic of γ-bromo esters.

3-Bromo-3-cyano-4-phenyl-5-benzoyl-α-furane,  .—When

the lower-melting dibromo ester amide is slowly heated in quantity it melts at about 140° and immediately decomposes rapidly, giving off water and methyl bromide. The fused mass resolidifies and does not melt again below 270°. The higher melting isomer, when heated slowly in bulk decomposes without melting. It begins to give off water and methyl bromide freely at about 170° and the residue left when the decomposition is complete looks little different from the original substance but likewise does not melt below 270°. The products obtained by heating the two substances were found to have the same composition, crystal form and solubility. Both melted at 275° and a mixture of the two likewise melted at this temperature. The two isomers, therefore, when heated give the same furane derivative.

Analyses. Calc. for $C_{18}H_{12}O_3NBr$: C, 58.4; H, 3.2. Found: C, 58.5, 58.0; H, 3.4, 3.2.

Methyl 1-Hydroxy-3,5-diphenyl-4-bromo-pyridine Carboxylate-3,



—When the monobromo-tetrahydropyridine ester is brominated in boiling chloroform, or when solutions in which this ester has been brominated are heated before the hydrogen bromide has been completely removed, the

[7] *Am. Chem. J.*, **46**, 484 (1911).

dibromo compound loses hydrogen bromide and forms the hydroxy-pyridine ester as the principal product. The substance is very sparingly soluble in all common organic solvents except boiling chloroform. It was recrystallized from mixtures of chloroform and methyl alcohol from which it separated in fine needles which melted without decomposition at 238–240°.

Analyses. $C_{19}H_{14}O_3NBr$: C, 59.4; H, 3.7. Found: C, 59.5; H, 3.8.

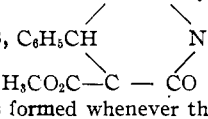
The ester does not undergo further bromination even when boiled with free bromine. It readily combines, however, with a molecule of bromine to form a perbromide. This is most easily obtained by dissolving equimolar quantities of ester and bromine in chloroform and then adding carbon tetrachloride to incipient precipitation. From conc. chloroform solution it crystallizes in large ruby-colored crystals. Both sulfur dioxide and potassium iodide rapidly remove the excess of bromine and regenerate the monobromo ester. On heating, it begins to dissociate at about 140° but at this temperature the ester is attacked by bromine vapor and forms a mixture of highly brominated substances.

The *acid* corresponding to the bromo ester was easily obtained by boiling the ester with conc. alcoholic potassium hydroxide. It crystallizes from methyl alcohol, in which it is sparingly soluble, in pale yellow prisms, which melt with decomposition at about 270°.

Analyses. Calc. for $C_{18}H_{12}O_3NBr$: C, 58.4; H, 3.2. Found: C, 58.1; H, 3.4.

1-Hydroxy-4,6-diphenyl-3-bromo-pyridine.—The bromo acid was heated to 280° under diminished pressure until the evolution of carbon dioxide ceased. The residue was ground with ether which removed a small quantity of highly colored oil, then recrystallized from alcohol. It separated in fine yellow needles which melted at 278°.

Analyses. Calc. for $C_{17}H_{12}ONBr$: C, 62.6; H, 3.7. Found: C, 62.3; H, 3.7.

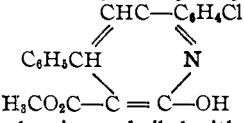
Methyl 2-Keto-4-phenyl-5-bromo-6-(*p*-chlorophenyl)-tetrahydropyridine Carboxylate-3,  .—This substance constitutes the principal product that is formed whenever the corresponding ester is brominated. It is most easily obtained in quantity by starting directly with the cyano ester addition product to benzal-*p*-chloro-acetophenone. Thus, 75 g. of this substance was dissolved in 300 cc. of chloroform, the solution saturated with hydrogen bromide and allowed to stand overnight. A solution of 38.5 g. bromine in 50 cc. chloroform was then added and the mixture warmed until the reaction was complete, which required 20 minutes. The solvent was distilled and the residue washed with methyl alcohol; yield, 98%. The crude product prepared in this way contains a small quantity of trimolecular addition product but this is easily got rid of by crystallization from benzene. The bromo compound crystallizes in needles and melts at 194°.

Analyses. Calc. for $C_{19}H_{15}O_2NClBr$: C, 54.2; H, 3.6. Found: C, 54.2; H, 3.9.

Methyl 2-Keto-3,5-dibromo-4-phenyl-6-(*p*-chlorophenyl)tetrahydropyridine Carboxylate-3.—The monobromo compound, like its chlorine-free analog reacts with more bromine. In glacial acetic acid two products were obtained in equal amounts, one melting at 250°, the other at 183°. The higher-melting product was not identified. The lower-melting compound was the 3,5-dibromo compound. It crystallized in large greenish prisms.

Analyses. Calc. for $C_{19}H_{14}O_2NClBr_2$: C, 45.6; H, 2.8. Found: C, 46.2; H, 2.9.

Methyl 2-Hydroxy - 4 - phenyl - 6 - (*p* - chlorophenyl) - pyridine Carboxylate - 3,



.—The bromo ester lost hydrogen bromide slowly when it was boiled with conc. methyl alcoholic potassium acetate but the halogen acid is much more easily removed with sodium methylate. The resulting hydroxy-pyridine ester crystallized from methyl alcohol in flat transparent needles which exhibited a fine blue fluorescence.

Analyses. Calc. for $C_{19}H_{14}O_3NCl$: C, 67.1; H, 4.1. Found: C, 67.6; H, 4.2.

The substance melts at 262°. It is moderately soluble in chloroform and very sparingly soluble in methyl alcohol. It readily dissolves in conc. alkali and is precipitated unchanged by acids.

Bromination of the Methyl Cyano-acetate Addition Products

Bromination in the Presence of Potassium Acetate

A solution of 50 g. of the pure ester obtained from benzal-acetophenone in 250 cc. of dry chloroform was introduced into a flask provided with a drying tube, an effective mechanical stirrer, and a dropping funnel containing 28 g. of bromine diluted with an equal volume of chloroform. The apparatus was placed in direct sunlight and bromination started by addition of a small quantity of bromine; 70 g. of freshly fused and very finely powdered potassium acetate was then churned into the solution and the rest of the bromine added very slowly in the course of an hour, while the mixture was stirred vigorously to keep the concentration of the hydrogen bromide at a minimum. The bromine disappeared rapidly up to the very end of the reaction. The mixture was then poured into water, the chloroform layer washed with sodium bicarbonate, dried with calcium chloride, and freed from chloroform by distillation under diminished pressure. This left a very pale yellow oil which was diluted with an equal volume of dry methyl alcohol and inoculated with the α-bromo compound. It deposited 32 g. of almost pure α-bromo compound.

The filtrate from the α-bromo compound was inoculated with α,γ-dibromo compound and cooled in a freezing mixture. It deposited 18 g. of a mixture of bromo compounds. By fractional recrystallization from methyl alcohol this was separated into α-monobromo and α,γ-dibromo compounds; it contained no pyridine derivatives. The oil left after removal of solvents yielded no more solid products; but when it was shaken with methyl alcoholic potassium acetate it gave almost an equivalent quantity of cyclopropane derivatives. In view of the results obtained with the *p*-chloro compound it is probable that it was composed mainly of an isomeric α-bromo compound.

Methyl α-Bromo-α-cyano-β-phenyl-γ-benzoyl-butyrate, $C_6H_5COCH_2CH(C_6H_5)CBr(CN)CO_2CH_3$.—The α-bromo compound crystallizes from methyl alcohol in which it is readily soluble, in large, transparent, diamond shaped plates. It melts without decomposition at 130°.

Analysis. Calc. for $C_{19}H_{16}O_3NBr$: Br, 20.7. Found: 20.7.

The substance parts with hydrogen bromide and forms a cyclopropane derivative when it is digested with methyl alcoholic potassium acetate; the bromine must, therefore, be either in the α- or the γ-position. γ-Bromo esters on heating readily lose methyl bromide and form lactones, but this substance is stable up to 200°, and when it does decompose it loses hydrogen bromide and forms a cyclopropane derivative. It does not, therefore, behave like other γ-bromo esters on heating. The great resistance that the substance offers to hydrolysis also shows that the bromine is in the α-position. When

its solution in methyl alcohol was saturated with hydrogen bromide and allowed to stand for a week it gave only unchanged substance and a small quantity of benzoyl-phenyl-ethyl malonate which was formed by reduction and subsequent hydrolysis of the bromine free compound.

Methyl α,γ-Dibromo-α-cyano-β-phenyl-γ-benzoyl-butyrate, $C_6H_5COCHBrCH(C_6H_5)C(CN)BrCO_2CH_3$.—This substance, which is one of the products obtained by brominating in the presence of potassium acetate, is easily obtained by adding the requisite amount of bromine to a solution of the α-bromo ester in boiling chloroform. As it is insensitive no precautions need to be taken to remove the hydrogen bromide formed. It is moderately soluble in boiling methyl alcohol and crystallizes from it in coarse transparent needles which melt at 177–179° and decompose at a slightly higher temperature.

Analyses. Calc. for $C_{19}H_{15}O_3NBr_2$: C, 49.0; H, 3.2. Found: C, 49.0; H, 3.3.

As the substance reacts with potassium iodide to form a cyclopropane derivative, the two bromine atoms must be in the α- and γ-positions.

Methyl α-Bromo-α-cyano-β-phenyl-γ-(*p*-chlorophenyl)butyrate, $ClC_6H_4COCH_2-CH(C_6H_5)CBr(CN)CO_2CH_3$.—The bromination was carried out essentially like that of the chlorine-free analog. The oil left after removing potassium salts and solvent was dissolved in methyl alcohol. From this solution about 85% of the calculated amount of solid bromo compounds slowly crystallized in the course of 10 days. By systematic fractional crystallization from methyl alcohol the solid was separated into 2 isomeric α-bromo compounds and a small quantity of higher-melting product.

The lower-melting isomer is readily soluble in common organic solvents and crystallizes well from methyl alcohol, ether or petroleum ether. It crystallizes in tables and melts at 91–92°.

Analyses. Calc. for $C_{19}H_{15}O_3NClBr$: C, 54.2; H, 3.6. Found: C, 54.2; H, 3.5.

The higher-melting isomer is less soluble but crystallizes from the same solvents. It separates from methyl alcohol in clusters of small white prisms, and melts at 123°.

Analyses. Calc. for $C_{19}H_{15}O_3NClBr$: C, 54.2; H, 3.6. Found: C, 54.3; H, 3.5.

The two monobromo compounds behaved alike in all reactions. Potassium acetate removed hydrogen bromide from both, and formed the same cyclopropane derivative. Both equally resisted esterification by hydrogen bromide in methyl alcohol. In chloroform, hydrogen bromide in part reduced both and in part transformed them into the same bromopyridine ester. The substances are, therefore, stereo-isomeric α-bromo compounds.

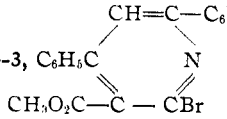
Methyl α,γ-Dibromo-α-cyano-β-phenyl-γ-(*p*-chlorobenzoyl)butyrate, $ClC_6H_5CO-CHBrCH(C_6H_5)CBr(CN)CO_2CH_3$.—This substance is generally formed whenever the cyano-acetate addition product is brominated, but it is most easily obtained by treating a solution of the addition product in methyl alcohol with an excess of bromine. A concentrated solution of hydrogen bromine was prepared by adding bromine to 20 cc. of methyl alcohol and decolorizing with sulfur dioxide. This solution was mixed with a solution of 5 g. of the addition product in methyl alcohol and 20 g. of bromine. The flask containing the mixture was protected with a calcium chloride tube and exposed sunlight. The sparingly soluble product which separated from the solution in the course of several days was practically pure dibromo compound.

Analyses. Calc. for $C_{19}H_{14}O_3NClBr_2$: C, 45.6; H, 2.8. Found: C, 45.9; H, 2.8.

The dibromo compound crystallizes from alcohol in fine white needles which melt at 193°. When digested with methyl alcoholic potassium iodide it readily parts with its 2 bromine atoms and forms a cyclopropane derivative.

Bromination in Glacial Acetic Acid

The substances obtained by brominating the addition products in glacial acetic acid are quite different from those obtained in chloroform in the presence of potassium acetate. A trifle more than 92% of the product consists of a bromopyridine ester. With this there is formed about 3% of the α,γ-dibromo compound. No monobromo compound could be isolated from the small quantity of oily products formed and no cyclopropane derivative was obtained when these oils were digested with potassium acetate.

Methyl 2-Bromo-4,6-diphenyl-pyridine Carboxylate-3,  .—To a hot solution of 30 g. of addition product in 50 cc. of glacial acetic acid 10 g. of bromine was added drop by drop. The bromine disappeared rapidly. Most of the solvent was removed under diminished pressure and the residue poured into water. The oil that precipitated solidified when the suspension was shaken with a little ether. The crude solid on recrystallization from methyl alcohol gave 36 g. of the bromopyridine derivative and 1,4 g. of the α,γ-dibromo compound. The ether on evaporation left a small quantity of oil.

The bromopyridine ester crystallizes in 6-sided prisms or coarse needles which have a marked blue fluorescence. It is readily soluble in chloroform, moderately in boiling methyl alcohol, sparingly in cold alcohols and in ether. It melts at 147°.

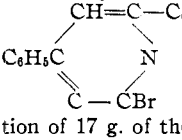
Analyses. Calc. for $C_{19}H_{14}O_2NBr$: C, 61.9; H, 3.8; N, 3.8; Br, 21.7. Found: C, 62.0; H; 4.0; N, 4.1; Br, 21.7.

Hydrogen bromide transforms the γ-bromo compound smoothly into the bromopyridine ester both in chloroform and in glacial acetic acid. A chloroform solution of the γ-bromo compound was saturated with hydrogen bromide, allowed to stand overnight, and then poured into water. After washing, drying and concentrating the chloroform layer it deposited the pyridine derivative in good yield and in almost pure condition. A solution of 1 g. of the γ-bromo ester in glacial acetic acid was treated in the same way. It gave 0.8 g. of pure pyridine derivative.

THE BROMO-PYRIDINE ACID was obtained by hydrolyzing the ester with conc. alcoholic potassium hydroxide. Eight g. of the compound was suspendeed in a mixture of 35 cc. of ethyl alcohol and 50 g. of 50% aqueous potassium hydroxide. The mixture was boiled for 2.5 hours, then diluted with water and decolorized with animal charcoal and kieselguhr. The solution, on acidification, gave a colorless acid which was crystallized from methyl alcohol.

Analysis. Calc. for $C_{18}H_{12}O_2NBr$: Br, 22.6. Found: 22.5.

The acid crystallizes in transparent needles and melts at 206–208° with decomposition. All attempts to re-esterify it with methyl alcohol and hydrogen chloride were unsuccessful, all of the acid being recovered unchanged. It was, however, easy to regenerate the bromopyridine ester by turning the acid into the silver salt and digesting this with an excess of methyl iodide.

Methyl 2-Bromo-4-phenyl-6-*p*-chlorophenyl-pyridine Carboxylate,  .—Ten g. of bromine was added drop by drop to a hot solution of 17 g. of the benzal-*p*-chloro-acetophenone addition product. The bromine reacted almost as fast as added. Most of the solvent was distilled and the only residue

dissolved in ether. The ethereal solution was freed from acid, dried and evaporated. It left an oil which was dissolved in methyl alcohol. This deposited a solid which crystallized in fluorescent, striated plates and melted at 106°.

Analyses. Calc. for $C_{19}H_{18}O_2N$ ClBr: C. 57.6; H, 3.2. Found: C, 56.2; H, 3.5.

The pyridine derivative is freely soluble in chloroform, acetone, ether or benzene, moderately soluble in methyl alcohol, and sparingly in petroleum ether. Like its chlorine-free analog it is also easily obtained by the action of hydrogen bromide on the α-bromo compound.

Bromination in Chloroform.—The addition products were brominated in chloroform before it was realized how rapidly the halogen acids transform both the substances themselves and their α-bromo substitution products into pyridine derivatives. The result was a mixture which after laborious separations gave nearly all the halogen compounds that have been described and in addition usually contained one or more cyclopropane derivatives.

Bromination in Methyl Alcohol.—It was shown in earlier papers that the methyl malonate addition products give only α-bromo compounds when brominated in methyl alcohol while in chloroform they give nearly equal quantities of α- and γ-compounds. Brominations in methyl alcohol take place slowly even in direct sunlight, consequently when bromine acts on the cyano-acetate addition products in this solvent they are in part esterified, and the resulting malonic ester derivatives also undergo bromination. With one equivalent of bromine, therefore, in methyl alcohol the cyano-acetate addition products gave mixtures that it was impossible to separate. With a large excess of bromine in concentrated solution the principal product was the α,γ-dibromo derivative. No cyclic compound of any type was formed in this reaction.

Chlorination of the Addition Products

In order to secure more evidence on the mechanism by which the true pyridine derivatives are formed the cyano-acetate addition product to benzal-*p*-chloro-acetophenone was chlorinated both in glacial acetic acid and in chloroform. No solid products were obtained in glacial acetic acid but in chloroform the reaction went so much more rapidly that excellent yields of open-chained substitution products were obtained.

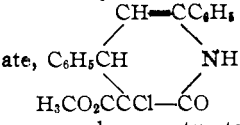
Methyl α-Chloro-α-cyano-β-phenyl-γ-(*p*-chlorophenyl)butyrate, $ClC_6H_4COCH_2$-$CH(C_6H_5)CCl(CN)CO_2CH_3$.—A carbon tetrachloride solution containing slightly more than 1 equivalent of chlorine was added to a chloroform solution of the addition product 0°. The reaction took place readily and the solvents on evaporation left only a mixture of solid products. This was separated, by crystallization from methyl alcohol, into two substances, one of which crystallized in clusters of small white prisms and melted at 106°.

Analyses. Calc. for $C_{19}H_{13}O_2NCl_2$: C, 60.6; H, 4.0. Found: C, 60.6; H, 4.2.

The other product crystallized in transparent plates and melted at 80°.

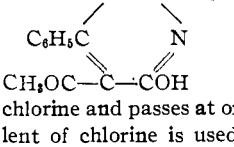
Analyses. Calc. for $C_{19}H_{13}O_2NCl_2$: C, 60.6; H, 4.0. Found: C, 60.7; H, 4.0.

The yield of these substances was almost quantitative. They are, doubtless, the two stereo-isomeric α-chloro compounds corresponding to the α-bromo compounds which they resemble closely in physical properties. They lose hydrogen chloride with equal ease to potassium acetate and form the same cyclopropane derivative. Their behavior on rearrangement with hydrogen bromide is, however, different.

Methyl 2-Keto-3-chloro-4-phenyl-6-(*p*-chlorophenyl)-tetrahydro-pyridine Carboxylate,  .—A chloroform solution of the higher-melting α-chloro compound was saturated with hydrogen bromide and boiled for several hours. On evaporation it left a solid that after several recyrstallizations from methyl alcohol was obtained in needles which melted, with decomposition, at about 197°.

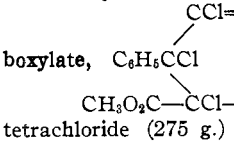
Analyses. Calc. for $C_{19}H_{15}O_3NCl_2$: C, 60.6; H, 4.0. Found: C, 61.2; H, 3.8.

The structure of this product has not been definitely established. The isomeric α-chloro compound on similar treatment gives mainly the same bromo-tetrahydropyridine derivative that is obtained by first rearranging the cyano ester addition product and then brominating the product. As this is obviously formed as a result of first reducing the α-chloro compound with hydrogen bromide it is conceivable that a similar process might give a 4-chloro compound. This, however, seems so improbable that we prefer to regard it as the 2-chloro derivative. All attempts to get a bromopyridine by a reaction analogous to that which takes place so readily with both of the corresponding α-bromo compounds were unsuccessful.

Methyl 2-Hydroxy-4-phenyl-5-chloro-6-(*p*-chlorophenyl)pyridine Carboxylate,  .—The tetrahydropyridine ester reacts readily with chlorine and passes at once into the chloropyridine ester even when less than one equivalent of chlorine is used. When 20 cc. of a saturated solution of chlorine in carbon tetrachloride was added to a chloroform solution of 5 g. of the tetrahydropyridine derivative, the solution became colorless in a few minutes. The solvents were then removed under diminished pressure and the residue shaken with ether. This extracted nearly 3 g. of unchanged substance and left a less soluble solid that was recrystallized from methyl alcohol. It separated in colorless transparent prisms and melted at 196°.

Analyses. Calc. for $C_{19}H_{13}O_3NCl_2$: C, 70.0; H, 3.5. Found: C, 69.6; H, 3.5.

The substance is readily soluble in alkalies and is reprecipitated by acids.

Methyl 2-Keto-3,4,5,trichloro-4-phenyl-6-(*p*-chlorophenyl)tetrahydropyridine Carboxylate,  .—A saturated solution of chlorine in carbon tetrachloride (275 g.) was poured into a chloroform solution containing 10 g. of the tetrahydropyridine derivative and the mixture exposed to direct sunlight. The reaction was completed in 10 minutes; its sole product was the trichloro compound. The yield of purified product was 96%.

Analyses. Calc. for $C_{19}H_{13}O_3NCl_4$: C, 51.2; H, 2.9. Found: C, 51.4; H, 3.3.

The substance forms fine white needles. It loses chlorine below the melting point which, therefore, depends on the rate of heating but in a capillary tube heated in the ordinary manner is usually found at about 260°. When boiled with zinc dust in methyl alcohol it loses 2 atoms of chlorine and passes into the chloro-hydropyridine ester that melts at 196°.

The Cyclopropane Derivatives

The cyclopropane derivatives were obtained by heating α-bromo compounds under diminished pressure, or, better, by removing hydrogen

bromide from them with potassium acetate; by removing hydrogen chloride from α-chloro compounds; and by eliminating bromine from α,γ-dibromo compounds with potassium iodide. These processes gave stereoisomeric cyclopropane derivatives. They are important because their formation furnishes the best, in some cases the only, means of distinguishing between open-chained and cyclic bromo derivatives. Their structure is based on the characteristic properties of cyclopropane derivatives of this type: lack of color and fluorescence, inability to reduce permanganate, and the ease with which they take up two atoms of hydrogen and pass into saturated compounds.

Methyl 1-Cyano-2-phenyl-3-benzoyl-cyclopropane Carboxylate, $C_6H_5CH(NC)CHCOC_6H_5$ CCO_2CH_3.—The highest melting modification of this substance was obtained both on heating the α-bromo compound (XV) and on treating it with potassium acetate in methyl alcohol. It crystallizes in small prisms that are almost cubical in habit, is very sparingly soluble in methyl alcohol and in ether, and melts at 178–180°.

Analyses. Calc. for $C_{19}H_{15}O_3N$: C, 74.7; H, 5.0. Found: C, 75.1; H, 4.9.

The substance does not reduce permanganate but is fairly easily reduced with zinc dust. Five g. of zinc dust was added to a solution of 2 g. of the substance in equal volumes of aqueous methyl alcohol and methyl acetate. The mixture was boiled for an hour, then filtered and concentrated. On cooling a small quantity of unchanged substance was formed. This was removed and the filtrate inoculated with some of the cyano-acetate addition product. It gradually deposited 1.2 g. of this substance which was identified by a mixed melting point.

An isomeric cyclopropane derivative was obtained when the oily residues, from the bromination of the addition product in chloroform, were warmed with an equal weight of potassium acetate in methyl alcohol. This gave a mixture of the cyclopropane derivative melting at 180° and an isomer melting at 106°. The two are easily separated because the lower-melting compound is readily soluble in methyl alcohol. It crystallizes in coarse needles or large transparent prisms.

Analyses. Calc. for $C_{19}H_{15}O_3N$: C, 74.7; H, 5.0. Found: C, 74.8; H, 4.8.

The substance was reduced in the same way as the isomer and gave the same result. It does not reduce permanganate in acetone.

A third isomer was obtained from the dibromo compound. A methyl alcoholic solution containing 4 g. of the dibromo compound was shaken at the ordinary temperature with the calculated quantity of potassium iodide and excess of mercury for 24 hours. The iodide of mercury was then removed and the solution cautiously diluted with water, and set aside. In the course of a week, 2.1 g. of large colorless needles separated. These, after recrystallization from methyl alcohol, melted at 110°.

Analyses. Calc. for $C_{19}H_{15}O_3N$: C, 74.7; H, 5.0. Found: C, 74.6; H, 5.2.

The substance gave the cyano-acetate addition product when reduced with zinc dust.

1-Cyano-2-phenyl-3-benzoyl-cyclopropane-carboxylic Acid.—The cyclopropane ester melting at 106° was dissolved in wet ether and this solution shaken with an excess of sodium methylate for 5 minutes. The sodium compounds were then extracted with water and acidified. The acid was precipitated as an oil that soon solidified. It separated in small transparent prisms which melted with decomposition at about 230°.

Analyses. Calc. for $C_{18}H_{13}O_3N$: C, 74.2; H, 4.5. Found: C, 73.7; H, 4.4.

Methyl 1-Cyano-2-phenyl-3-(*p*-chlorobenzoyl)-cyclopropane Carboxylate, $C_6H_5CH(CN)-CH(COC_6H_4Cl)-C(CO_2CH_3)$.—Two isomeric cyclopropane derivatives melting at 132° and 180° are formed when both the isomeric α-bromo derivatives and the α-chloro derivatives are treated with potassium acetate. The lower-melting substance is most easily obtained in quantity by starting with the cyano-acetic ester addition product. Thus 126 g. of this product and 126 g. of fused and powdered potassium acetate were suspended in 400 cc. of chloroform and treated with 65 g. bromine. As soon as bromination was complete the chloroform was distilled and 500 cc. of dry methyl alcohol added to the residue. The mixture was shaken vigorously, set aside for a few hours and then poured into water. This precipitated a yellow oil which was extracted with ether. The ethereal layer solidified almost completely and gave an 80% yield of crude product composed mainly of the lower-melting isomer.

Analyses. Calc. for $C_{19}H_{14}O_3NCl$: C, 67.1; H, 4.1. Found: C, 67.0; H, 4.3.

The substance usually separates from solutions in long fine white needles which are difficult to purify, but when a saturated solution in boiling methyl alcohol is allowed to cool very slowly it crystallizes in transparent cubes which are much more easily handled. It is readily soluble in all common organic solvents except petroleum ether.

Reduction.—Two g. of zinc dust was added to a solution of 0.6 g. of the cyclopropane derivative in 25 cc. of glacial acetic acid and the mixture boiled for 2 hours. The undissolved zinc was removed, the filtrate concentrated on a steam-bath, poured into water and extracted with ether. The ethereal solution on evaporation deposited a solid which after purification was identified as the cyano ester addition product.

The Isomeric Cyclopropane Derivative is most easily obtained from the α,γ-dibromo compound. When treated with potassium iodide in methyl alcohol it gives a 90% yield of the pure high-melting isomer. This crystallizes in long white needles, is freely soluble in acetone, moderately soluble in alcohol, very sparingly soluble in ether, and melts at 180°.

Analyses. Calc. for $C_{19}H_{14}O_3NCl$: C, 67.1; H, 4.1. Found: C, 66.8; H, 4.4.

Reduction.—A suspension of 2 g. of the substance and 5 g. of zinc dust in 25 cc. each of methyl alcohol and methyl acetate was boiled for 5 hours. The clear solution left after removing the excess of zinc was evaporated on a steam-bath and the residue extracted with ether. The ethereal solution on evaporation left 1.6 g. of the cyano ester addition product melting at 126°.

Potassium acetate converts the higher- into the lower-melting isomer. Thus, equal weights of this substance and potassium acetate were suspended in absolute methyl alcohol and the yellow mixture allowed to stand at room temperature for several days, after which the unchanged solid was removed. The filtrate slowly deposited cubical crystals which were identified as the lower-melting isomer by comparing its melting point with that of a mixture with this substance.

Summary

1. In the presence of a small quantity of sodium methylate, methyl cyano-acetate combines with α,β unsaturated ketones and forms γ-ketonic nitriles.

2. Halogen acids in indifferent media rapidly transform these γ-ketonic nitriles into equilibrium mixtures containing small quantities of the nitriles mixed with isomeric tetrahydropyridine derivatives. As the process takes place very rapidly, the open-chained compounds and

their cyclic isomers give the same products in reactions that take place in the presence of acids. In processes involving the use of bases the products obtained from the two types are different.

3. The halogens react very readily with the cyclic compounds. By alternately introducing halogen and eliminating halogen acids it is possible to go step by step from the tetrahydropyridine derivatives to true pyridines.

4. The action of halogen on the open-chained compounds results in a mixture of a great number of open-chained and cyclic bromo compounds. The action can, however, be controlled. Halogenation in the presence of potassium acetate gives only open-chained compounds while the same process in glacial acetic acid gives mainly a true pyridine derivative.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

SYMMETRICAL DI-ISOPROPYL-HYDRAZINE AND ITS DERIVATIVES. II

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Introduction

Recently, in a preliminary report [2] on the reduction of dimethyl ketazine to symmetrical di-*iso*propyl-hydrazine, the latter was prepared and characterized by a few derivatives. Since then certain results have been obtained that round out this investigation and may prove of general interest in connection with the chemistry of aliphatic hydrazines.

The value of catalytic reduction as applied to the C=N complex was pointed out in the preliminary article. The preparation of primary *iso*propyl-hydrazine, by the same method, directly from a mixture of equimolecular amounts of hydrazine and acetone, without an isolation of the acetone hydrazone formed, as described in the present paper, promises a general method of producing mono-alkyl hydrazines in any quantity desired with little labor and a minimum of expense.

It is obvious that the application of catalytic reduction to suitable hydrazones and azines may be expected to furnish a practical method of preparing hydrazino and hydrazo paraffins containing asymmetric carbon atoms. The preparation, from these compounds, of optically active hydrazines and through them, of optically active paraffins, is contemplated as one of the lines of investigation in our continuation of the work that may be expected to develop from the present research.

[1] Abstract of a thesis submitted to the Graduate Faculty of the University of Illinois, by Harry L. Lochte, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] THIS JOURNAL, **43**, 2597 (1921).