[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Syntheses of 7,8-Benzopyrrocoline Derivatives. A Novel Reaction of Reissert Compounds

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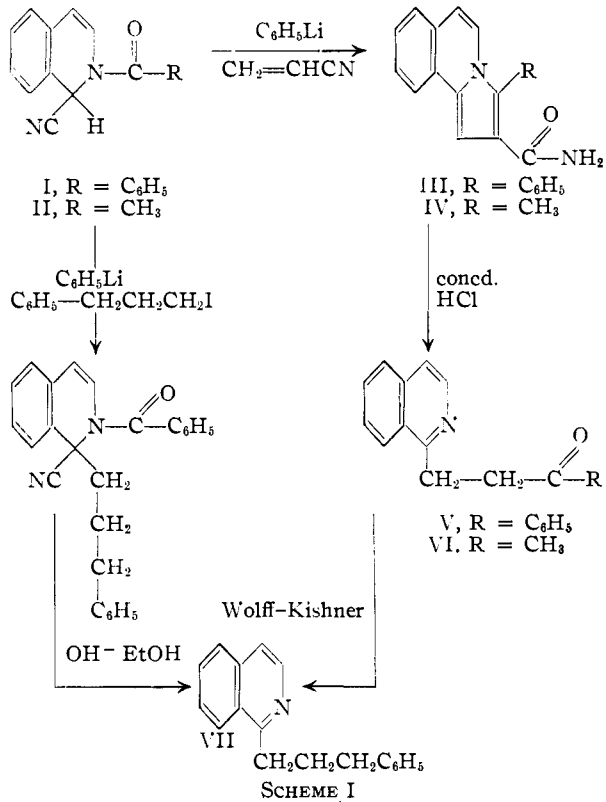
It is shown that the Michael condensation of 1-cyano-2-acyl-1,2-dihydroisoquinoline derivatives (Reissert compounds) and α,β-unsaturated compounds leads to involvement of the N-acyl group. In the case of acrylonitrile, the products are the corresponding 3-substituted-2-formamido-7,8-benzopyrrocolines, whose structures were established in each instance by removing the formamido group and synthesizing independently the resulting benzopyrrocoline. When 2-vinylpyridine and ethyl acrylate are employed as the acceptors, the products are not benzopyrrocoline derivatives but instead are α-substituted-β-(1-isoquinolyl)-ethyl phenyl ketones. These ketones, though, on treatment with strong acid undergo cyclization and give the corresponding benzopyrrocolines. This is a new, and possibly general, method for preparing substituted pyrrocolines.

In previous publications, we have reported on the alkylation and some rearrangements of Reissert compounds.[2-4] These reactions have proved to be particularly convenient for the synthesis of 1-substituted isoquinolines. In the hope of extending this method to the synthesis of certain alkaloids, we have now investigated the use of Reissert compounds in condensations of the Michael type. Somewhat unexpectedly we found that, in all of the cases so far studied, condensation involves participation by the N-acyl group and results in rearrangement. In the present paper, evidence is presented establishing the structures of the products of these rearrangements and a possible mechanism is proposed for the reaction.

The first condensation attempted was that between acrylonitrile and 1-cyano-2-benzoyl-1,2-dihydroisoquinoline. This gave a brilliant orange-red compound, whose composition agreed with the empirical formula $C_{19}H_{14}NO$. Although this material was soluble in neither dilute acid nor base, it differed from the usual alkylated Reissert derivatives in that it was unaffected by heating with alkali.[2] It did dissolve in concentrated hydrochloric acid, and, on being heated with this reagent, it was converted to a basic amine, m.p. 112–113°.[5] In addition to the usual amine derivatives, this base gave carbonyl derivatives and exhibited an absorption peak at 5.96 μ in the infrared, indicating that it contained a phenyl carbonyl grouping.[6,7] The carbonyl group was removed by subjecting the base to a Wolff–Kishner reduction and the resulting product was shown to be 1-(γ-phenyl)-propylisoquinoline (VII). To establish the identity of the 1-(γ-phenyl)-propylisoquinoline this compound was synthesized in an independent manner by alkylating 1-cyano-2-benzoyl-1,2-dihydroisoquinoline with hydrocinnamyl iodide and hydrolyzing the resulting product with alkali, as shown in Scheme I.[2,4]



SCHEME I

The formation of 1-(γ-phenyl)-propylisoquinoline during the Wolff–Kishner reduction made it evident that the amino ketone, m.p. 112–113°, had structure V. However, the structure of the brilliant orange-red alkylation product was still open to question. The observations leading to our assignment of structure III to this alkylation product were made as follows. A test with Ehrlich's reagent was strongly positive indicating the presence of a pyrrole ring. The ultraviolet absorption spectrum (see Fig. 1) of the alkylation product showed strong absorption at much longer wave lengths than could be explained by any simple alkylated Reissert compound or isoquinoline derivative. Finally, the infrared spectrum of this product showed a strong absorption peak at 6.15 μ, indicating a primary amide group,[8] and the presence of this group was further confirmed by the fact that the compound was reduced by lithium aluminum hydride to the corresponding basic aminomethyl derivative.

(1) National Science Foundation Predoctoral Fellow, 1952–1953.

(2) V. Boekelheide and C. Ainsworth, THIS JOURNAL, **72**, 2134 (1950).

(3) V. Boekelheide and C. T. Liu, *ibid.*, **74**, 4920 (1952).

(4) V. Boekelheide and J. Weinstock, *ibid.*, **74**, 660 (1952).

(5) The spectrophotometric method devised by Cunningham, Dawson and Spring (*J. Chem. Soc.*, 2304 (1951)) for determining the molecular weights of picrates of amines has proved to be very useful for following the molecular weights of intermediates in this study.

(6) H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949, p. 166.

(7) A comparable ketone, γ-(2-quinolyl)-propyl phenyl ketone, has a carbonyl peak at 5.97 μ, see Boekelheide and Marinetti, THIS JOURNAL, **73**, 4015 (1951).

(8) See ref. 5, p. 126.

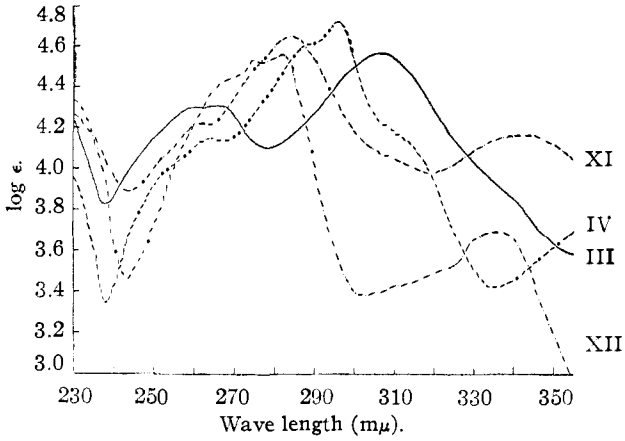
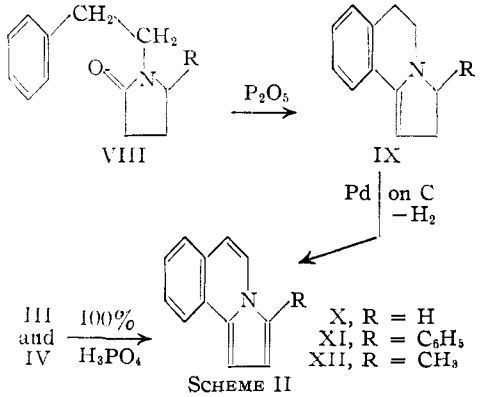


Fig. 1.—Ultraviolet absorption spectra of 2-formamido-3-phenyl-7,8-benzopyrrocoline (III, —); 2-formamido-3-methyl-7,8-benzopyrrocoline (IV, – – –); 3-methyl-7,8-benzopyrrocoline (XII, ·-·-·); and 3-phenyl-7,8-benzopyrrocoline (XI, —·—·—) in ethanol.

To accommodate these facts, it seemed necessary to postulate a benzopyrrocoline structure, such as III, for the orange-red alkylation product. In attempting to find conditions for hydrolyzing the amide group without cleaving the pyrrocoline ring, we investigated the procedure of Berger and Olivier using 100% phosphoric acid.[9] Under these conditions the formamido group was completely removed, presumably by hydrolysis followed by decarboxylation, but the benzopyrrocoline ring system remained intact. Since the resulting product, 3-phenyl-7,8-benzopyrrocoline (XI), seemed susceptible to synthesis, we then began investigating possible methods for preparing 7,8-benzopyrrocoline derivatives. The procedure, which proved most successful, is illustrated in Scheme II.



SCHEME II

The method employed for preparing the vinyl amines illustrated by IX was in general similar to that previously utilized by Pailer and Brandstetter in their studies on emetine.[10] In the first model studies on the preparation of the unsubstituted 7,8-benzopyrrocoline (X), β-phenethylamine was condensed with γ-butyrolactone to give VIII (R = H). This readily underwent cyclization over phosphorus pentoxide and the resulting vinyl amine (IX, R = H), was dehydrogenated over palladium-on-charcoal to give 7,8-benzopyrrocoline (X).

When β-phenethylamine was reductively alkylated using methyl β-benzoylpropionate, it gave directly the corresponding N-phenethyl-5-phenyl-2-pyrrolidone (VIII, R = C_6H_5). This was cyclized by treatment with phosphorus pentoxide and the resulting vinyl amine (IX, R = C_6H_5) was subjected to dehydrogenation over a 10% palladium-on-charcoal catalyst in the same manner as before. The product in this case, though, had the composition required for a dihydro derivative of the expected benzopyrrocoline. Since this compound gives a positive Ehrlich test, we have assumed that it is 3-phenyl-5,6-dihydro-7,8-benzopyrrocoline. When a mixture of this dihydro derivative and the 10% palladium-on-charcoal catalyst was heated at 200°, the desired 3-phenyl-7,8-benzopyrrocoline sublimed out of the reaction mixture. This sample of 3-phenyl-7,8-benzopyrrocoline was identical with the material obtained by the phosphoric acid hydrolysis of III, as was shown by a comparison of their ultraviolet and infrared absorption spectra and by a mixed melting point determination. Thus, the presence of the 3-phenyl-7,8-benzopyrrocoline nucleus is established and structure III can be assigned to the Michael condensation product of acrylonitrile and 1-cyano-2-benzoyl-1,2-dihydroisoquinoline. Although the position of the formamido group has not been rigorously proven, the only logical location for it is the 2-position.

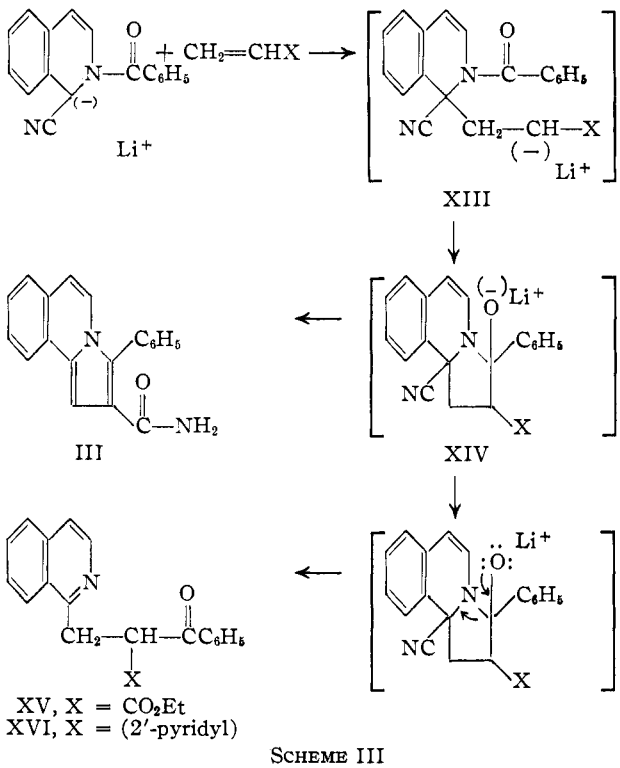
The only previous investigation of 7,8-benzopyrrocolines appears to be that of Sprague,[11] who prepared some 2-substituted-7,8-benzopyrrocolines by the Chichibabin reaction using 1-methylisoquinoline. Since the condensation of acrylonitrile with Reissert's compound proceeds in excellent yield, this reaction appears to offer a simple and convenient way of preparing other examples of this interesting class of heterocycles. By comparison the synthetic approach shown in Scheme II is fairly lengthy and proceeds in rather poor yield. To test the generality of the Michael reaction we have repeated the acrylonitrile condensation using 1-cyano-2-acetyl-1,2-dihydroisoquinoline and found, as expected, that the product was 3-methyl-2-formamido-7,8-benzopyrrocoline. This derivative was comparable in all respects to the phenyl derivative, previously studied. On hydrolysis in concentrated hydrochloric acid it gave methyl β-(1-isoquinolyl)-ethyl ketone (VI) in good yield. Also, treatment of the methyl derivative with 100% phosphoric acid resulted in removal of the formamido group and gave 3-methyl-7,8-benzopyrrocoline (XII). As before, the structure of the 3-methyl-7,8-benzopyrrocoline was established by an independent synthesis following the method outlined in Scheme II. The starting material in this case was ethyl levulinate and it was carried through to give a sample of 3-methyl-7,8-benzopyrrocoline which was identical in all respects with the same material obtained through the acrylonitrile condensation. Thus, the reaction appears to be general with respect to Reissert compounds having different N-acyl groups and, in view of the ready availability of these derivatives, the method can probably be eas-

(9) G. Berger and S. C. J. Olivier, *Rec. trav. chim.*, **46**, 600 (1927).
(10) M. Pailer and W. Brandstetter, *Monatsh.*, **85**, 523 (1952).
(11) R. H. Sprague, U. S. Patent 2,622,082 (Dec. 16, 1952).

ily extended to give other substituted 7,8-benzopyrrocolines.

A single attempt was made to see whether Reissert compounds derived from quinoline would also give pyrrocolines. However, when 2-cyano-1-benzoyl-1,2-dihydroquinoline was treated with acrylonitrile, the only product isolated was that corresponding to normal cyanoethylation. Whether condensation occurred at the 2- or 4-position of the quinoline ring was not established.

To explain the participation of the N-acyl group during the Michael condensation we feel that the reaction pathway shown in Scheme III most nearly fits the present evidence. In the general case, addition of an α,β-unsaturated compound, $CH_2{=}CHX$, to Reissert's compound would yield an ionic intermediate, for which formula XIII represents one of the possible structures contributing to the resonance hybrid. This intermediate is favorably arranged to undergo ring closure and give XIV. The final steps would be aromatization by loss of the elements of hydrogen cyanide and lithium hydroxide followed by hydration of the nitrile to give the formamido group. How the nitrile group becomes hydrated under the conditions of the reaction is not clear.

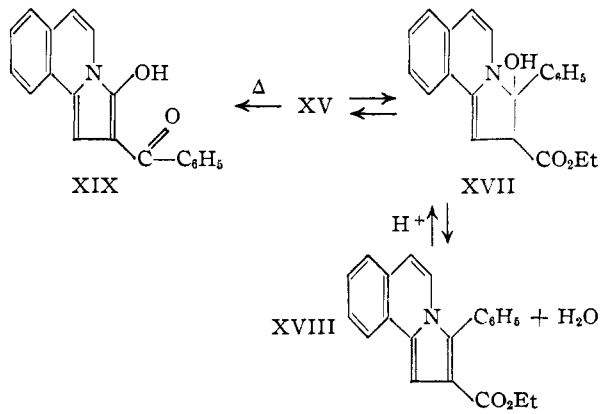


SCHEME III

In the hope of gaining further insight into the mechanism of the rearrangement, we investigated the Michael condensations of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline with both ethyl acrylate and 2-vinylpyridine. With these α,β-unsaturated derivatives, the reaction took a somewhat different course, yielding the open chain ketones, XV and XVI, instead of the expected 7,8-benzopyrrocoline derivatives. As shown in Scheme III, the formation of XV and XVI can be explained by the proposed mechanism, if it is assumed that the intermediate, XIV, undergoes aromatization in different manner. It is not evident, though, why the group X should be so influential in deciding the path of decomposition of XIV.

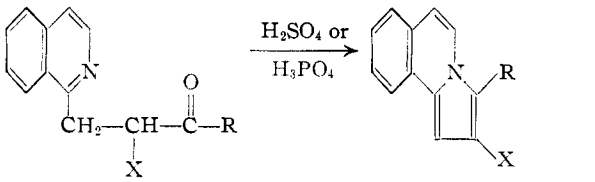
The assignment of formula XV to the ethyl acrylate addition product is based both on the composition of the material as well as its properties. The ultraviolet absorption spectrum of this adduct is almost identical with that of β-(1-isoquinolyl)-ethyl phenyl ketone (V) and quite different from that of the benzopyrrocoline derivatives. Also, its infrared spectrum has absorption peaks at 5.79 and 5.97 μ, which correspond to the peaks usually observed for ester and phenyl carbonyl groups, respectively.[6,7] Also, compound XV showed the normal basicity of an isoquinoline derivative and, on mild acid hydrolysis, it was converted to β-(1-isoquinolyl)-ethyl phenyl ketone (V). Thus, the evidence is fairly conclusive that the ethyl acrylate addition product is correctly represented by the open chain ketone, XV.

The possibility that XV exists in equilibrium with the hydroxybenzopyrrocoline form, XVII, was given some consideration. If such an equilibrium could be demonstrated, it would explain nicely the acid hydrolysis whereby III and IV are converted to the open chain ketones, V and VI, respectively. Also, an equilibrium of this type would explain why the original Michael condensation sometimes leads to benzopyrrocoline derivatives and in other cases the products are isoquinolyl ketones. However, if such an equilibrium prevails, the amount of XVIII which is present under ordinary conditions must be very small. The infrared absorption spectrum of XV is completely lacking in absorption in the hydroxyl region. Furthermore, when XV was subjected to sublimation in an attempt to force the equilibrium in the direction of the benzopyrrocoline derivative, the product was not XVIII but was, instead, the hydroxypyrrocoline (XIX), resulting from cyclization with the ester group with loss of ethanol. That the sublimation product had structure XIX was evident from its composition, from its infrared absorption spectrum which had peaks corresponding to an associated hydroxyl (3.43 μ) and a phenyl carbonyl (5.96 μ), and from its red color. Compound XIX, also, was quite unstable, which is characteristic of α-hydroxypyrroles.



The Michael condensation product of 2-vinylpy-

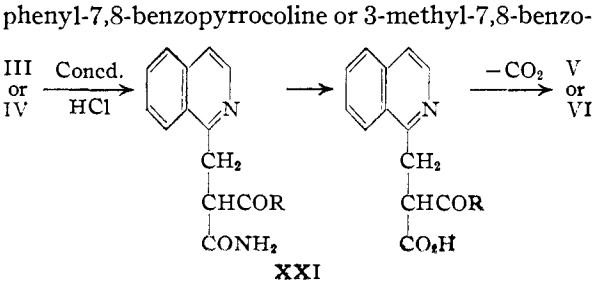
ridine and 1-cyano-2-benzoyl-1,2-dihydroisoquinoline has been given structure XVI in accord with its composition and by analogy with the ethyl acrylate addition product. The infrared and ultraviolet absorption spectra of this adduct are also in full agreement with this structure. In view of our previous experience with XV, we likewise subjected XVI to similar experiments in an attempt to effect dehydration and obtain the desired benzopyrrocoline in this case. When concentrated sulfuric acid was employed as a dehydrating agent, it was found that XVI was converted to the corresponding benzopyrrocoline (XX) in good yield. Thus, whether or not the hypothetical equilibrium between XV and XVII actually occurs as postulated, it is possible under the proper conditions to convert β-(1-isoquinolyl)-ethyl ketones to 7,8-benzopyrrocolines as illustrated below.



XX, R = C_6H_5, X = (2-pyridyl)

Upon further experimentation it was found that 100% phosphoric acid was preferable to sulfuric acid for effecting the cyclization of the β-(1-isoquinonyl)-ethyl ketones to the corresponding benzopyrrocolines. With this reagent it was possible to convert β-(1-isoquinolyl)-ethyl phenyl ketone (V) to 3-phenyl-7,8-benzopyrrocoline (XI) in 89% yield. As an additional example, the methyl ketone (VI) was converted to 3-methyl-7,8-benzopyrrocoline (XII) in 53% yield using the sulfuric acid procedure. The apparently general nature of this method of cyclization broadens the possible application of this new rearrangement of Reissert compounds for preparing 7,8-benzopyrrocoline derivatives. It is quite possible that this acid cyclization procedure would find useful application in the preparation of simple pyrrocolines as well, since there are few good methods of synthesis for these compounds at present.

The hydrolysis of III and IV in concentrated hydrochloric acid to give the corresponding isoquinolyl ketones, V and VI, apparently represents a reversal of the ring closure reaction. As shown below, the hydrolysis would be expected to give the corresponding β-keto amide (XXI) in the first stage, which on further hydrolysis and decarboxylation would give the ketones isolated. Attempts to show that this type of reverse hydrolysis is a general reaction have been unsuccessful. When either 3-phenyl-7,8-benzopyrrocoline or 3-methyl-7,8-benzopyrrocoline were heated for long periods of time with concentrated hydrochloric acid, they were unaffected and could be recovered unchanged.



XXI

Experimental[12]

2-Formamido-3-phenyl-7,8-benzopyrrocoline (III).—To a solution of 15.0 g. of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline[13] in 200 ml. of purified dioxane maintained under a nitrogen atmosphere and cooled to 0°, there was added dropwise with stirring 65 ml. of a 0.9 *M* ethereal solution of phenyllithium. The solution immediately developed the deep red color which is characteristic of the lithium salt of Reissert compounds. A solution of 9.2 g. of freshly distilled acrylonitrile in 38 ml. of dioxane was then added dropwise with continued stirring and cooling. The deep red color of the solution largely disappeared during the addition of the acrylonitrile. After the solution had warmed to room temperature, it was allowed to stand with stirring for 18 hours. At the end of this time 100 g. of solid carbon dioxide and 125 ml. of water were added with rapid stirring. The two layers which formed were separated and the aqueous layer was extracted five times with 125-ml. portions of ether, and the combined dioxane and ethereal extracts were concentrated under reduced pressure. The resulting red solid was recrystallized from 300 ml. of absolute ethanol to give 11.6 g. of brilliant orange-red crystals, m.p. 168–169°, softening at 165°. Concentration of the mother liquor gave an additional 0.95 g. (total yield 76%) of crystals. In several of the earlier runs, the product was obtained as copper-colored crystals, m.p. 168–169°, softening at 165°. The reason for this is not clear, since the copper-colored crystals did not depress the melting point of the orange-red crystals and, on recrystallization from ether, the copper-colored crystals likewise became identical in color and form with the orange-red crystals. Treatment of the orange-red crystals with Ehrlich reagent gave a strong cherry red color.

Anal. Calcd. for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.79. Found: C, 79.54; H, 5.01; N, 9.56.

2-Aminomethyl-3-phenyl-7,8-benzopyrrocoline.—A sample of 1.00 g. of 2-formamido-3-phenyl-7,8-benzopyrrocoline (III) was placed in a Soxhlet apparatus and extracted continuously with 90 ml. of a 1 *M* ethereal solution of lithium aluminum hydride for 4 hours. Then the reaction mixture was decomposed by the addition of 60 ml. of a 10% aqueous solution of sodium hydroxide. When the ether layer was separated and treated with 25 ml. of 3 *N* hydrochloric acid, there separated 850 mg. (77%) of the crystalline amine hydrochloride, m.p. 173–178° dec. The free base was obtained by treating 200 mg. of the hydrochloride salt with aqueous base and extracting with ether. Concentration of the ether extracts gave a solid residue, which was taken up in absolute ether and chromatographed over *Florisil*. Concentration of the ether eluate gave beautiful, light yellow crystals, m.p. 127–128°.

Anal. Calcd. for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92. Found: C, 84.08; H, 5.96.

3-Phenyl-7,8-benzopyrrocoline (XI).—A mixture of 200 mg. of 2-formamido-3-phenyl-7,8-benzopyrrocoline in 4 ml. of 100% phosphoric acid was heated at 140–160° for one-half hour. The solid dissolved when the temperature reached 100° and gas evolution began immediately. After the mixture had cooled to room temperature, it was poured onto 4 g. of cracked ice. This caused the separation of an oil which soon crystallized. Recrystallization of this solid from absolute ethanol gave 135 mg. (79%) of colorless crystals, m.p. 98.5–99°.

Anal. Calcd. for $C_{18}H_{13}N$: C, 88.85; H, 5.38. Found: C, 88.72; H, 5.38.

Phenyl β-(1-Isoquinolyl)-ethyl Ketone (V).—A solution of 6.99 g. of 2-formamido-3-phenyl-7,8-benzopyrrocoline in 700 ml. of 10 *N* hydrochloric acid was boiled under reflux until carbon dioxide was no longer evolved (2 hours). The solution was then cooled and made basic with dilute sodium hydroxide (evolution of ammonia). The solid, which separated, was extracted with ether and the ether extract was concentrated. Recrystallization of the residual solid

(12) Analyses by Miss Claire King and Miss Viola Williams.

(13) J. J. Padbury and H. J. Lindwall, THIS JOURNAL, **67**, 1268 (1945).

from an ethanol–water mixture gave 6.05 g. (95%) of white crystals, m.p. 112–112.5°.

Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.81; H, 5.53; N, 5.46.

The **picrate** of phenyl β-(1-isoquinolyl)-ethyl ketone formed readily in ethanol and was obtained, after recrystallization from the same solvent, as yellow crystals, m.p. 199–199.5° dec. A molecular weight determination of this picrate by the method of Cunningham, Dawson and Spring[5] gave a value of 490 ± 2 (theor. 490).

Anal. Calcd. for $C_{24}H_{18}N_4O_8$: C, 58.78; H, 3.71. Found: C, 59.10; H, 4.02.

The **oxime** of phenyl β-(1-isoquinolyl)-ethyl ketone was prepared using the pyridine procedure and, after crystallization from an ethanol–water mixture, it was obtained as white crystals, m.p. 150–150.5°.

Anal. Calcd. for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84. Found: C, 78.14; H, 6.08.

The **methiodide** of phenyl β-(1-isoquinolyl)-ethyl ketone formed readily and was obtained, after crystallization from a chloroform–benzene mixture, as white crystals, m.p. 183–184° dec.

Anal. Calcd. for $C_{19}H_{18}NOI$: C, 56.60; H, 4.49. Found: C, 57.18; H, 4.52.

1-(γ-Phenyl)-propylisoquinoline (VII). (a) By the Wolff-Kishner Reduction of V.—A solution containing 1.00 g. of phenyl β-(1-isoquinolyl)-ethyl ketone, 1 ml. of 100% hydrazine hydrate and 1.2 g. of potassium hydroxide in 17 ml. of trimethylene glycol was heated under reflux at 120–130° for one hour. The condenser was then removed and the temperature of the bath was raised to 165°. Finally, the mixture was heated under reflux at 190° for an additional 3 hours. After the mixture had cooled, it was diluted with 25 ml. of water and extracted with ether. The ethereal solution was extracted in turn with 2 *N* hydrochloric acid, after which the aqueous layer was separated and concentrated. When the aqueous concentrate was made basic and extracted with ether, an oil was obtained which was treated directly with an ethanolic solution of picric acid. This gave 1.58 g. (87%) of yellow crystals which, after recrystallization from ethanol, melted at 156.5–157°.

Anal. Calcd. for $C_{24}H_{20}N_4O_7$: C, 60.50; H, 4.23. Found: C, 60.76; H, 4.33.

(b) **By the Alkylation of Reissert's Compound with Hydrocinnamyl Iodide.**—To a solution containing 14.0 g. of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline,[13] 20 ml. of ether and 75 ml. of purified dioxane and maintained under a nitrogen atmosphere at −10°, there was added dropwise with stirring 60 ml. of a 1 *N* ethereal solution of phenyllithium. A solution of hydrocinnamyl iodide (prepared from 35 g. of hydrocinnamyl bromide[14] by the sodium iodide exchange reaction) in 50 ml. of ether was then added dropwise with stirring to the deep-red mixture. After the resulting solution had been stirred for two hours at −10°, it was allowed to warm to room temperature and stand overnight. The mixture was then washed with water and dilute hydrochloric acid, and the organic layer was concentrated. This gave a viscous amber oil which was taken up in a solution containing 11 g. of potassium hydroxide, 50 ml. of water and 25 ml. of ethanol and boiled under reflux for one-half hour. The mixture was cooled, extracted with ether, and the ethereal solution was extracted in turn with 3 *N* hydrochloric acid. Neutralization of the acid extract gave an oil which was converted directly to its picrate derivative by treatment with ethanolic picric acid. The resulting solid, after recrystallization from ethanol, gave 12.0 g. (44%) of yellow crystals, m.p. 156.5–157.5°. The picrate of 1-(γ-phenyl)-propylisoquinoline obtained in this way showed no depression of melting point when mixed with a sample of the picrate from (a). Also, the infrared spectra of the two samples of picrates were identical.

Anal. Calcd. for $C_{24}H_{20}N_4O_7$: C, 60.50; H, 4.23. Found: C, 60.58; H, 4.45.

1-(γ-Phenyl)-propylisoquinoline was obtained as the free base by treating a sample of the picrate with a 5% lithium hydroxide solution and extracting with ether. After removal of the ether, the residue was distilled to give a hygroscopic colorless oil; b.p. 160–161° at 0.5 mm., $n^{25}D$ 1.6148. This crystallized on standing to give white crystals, m.p. 42.5–43.5°.

Anal. Calcd. for $C_{18}H_{17}N$: C, 87.42; H, 6.91. Found: C, 87.56; H, 7.06.

2-Formamido-3-methyl-7,8-benzopyrrocoline (IV).—This was prepared following the procedure described for the preparation of 2-formamido-3-phenyl-7,8-benzopyrrocoline (III). From 8.9 g. of 1-cyano-2-acetyl-1,2-dihydroisoquinoline[4] and 7.0 g. of acrylonitrile there was obtained 6.0 g. (60%) of bright yellow crystals, m.p. 189–190°, after recrystallization from benzene. This material gave an orange color with Ehrlich reagent.

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.96; H, 5.39. Found: C, 75.02; H, 5.75.

3-Methyl-7,8-benzopyrrocoline (XII).—When 100 mg. of 2-formamido-3-methyl-7,8-benzopyrrocoline (IV) was treated with 100% phosphoric acid in the same manner described previously for the preparation of 3-phenyl-7,8-benzopyrrocoline, it gave 50 mg. (60%) of white crystals, m.p. 129–130°, after recrystallization from an ethanol–water mixture. This gave a deep purple solution in the Ehrlich test.

Anal. Calcd. for $C_{13}H_{11}N$: C, 86.15; H, 6.12. Found: C, 86.25; H, 6.33.

1-(1′-Isoquinolyl)-3-butanone (VI).—When 5.40 g. of 2-formamido-3-methyl-7,8-benzopyrrocoline was hydrolyzed with hydrochloric acid using the procedure described previously for the preparation of phenyl β-(1-isoquinolyl)-ethyl ketone (V), there was obtained 3.0 g. (63%) of a light yellow oil, b.p. 126–134° at 0.5 mm. This solidified on standing and, after recrystallization from a methanol–water mixture, gave white crystals, m.p. 50–51°.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.52. Found: C, 78.19; H, 6.70.

The **picrate** of the 1-(1′-isoquinolyl)-3-butanone formed readily in absolute ethanol and, after recrystallization from this solvent, was obtained as yellow crystals, m.p. 137–138°.

Anal. Calcd. for $C_{19}H_{16}N_4O_8$: C, 53.27; H, 3.77. Found: C, 53.22; H, 4.02.

N-(β-Phenethyl)-2-pyrrolidone (VIII, R = H).[15]—This was prepared by the condensation of β-phenethylamine and γ-butyrolactone using a sealed tube following the general technique described by Späth and Lintner for N-benzyl-2-pyrrolidone.[16] The N-(β-phenethyl)-2-pyrrolidone was obtained in essentially quantitative yield as a very hygroscopic, colorless oil; b.p. 129–132° at 1.0 mm., $n^{27}D$ 1.5391.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.14; H, 7.99. Found: C, 76.27; H, 8.22.

2,3,5,6-Tetrahydro-7,8-benzopyrrocoline (IX, R = H).—The cyclization of N-(β-phenethyl)-2-pyrrolidone to 2,3,5,6-tetrahydro-7,8-benzopyrrocoline required somewhat more drastic conditions than those indicated by Pailer and Brandstetter,[10] because of the absence of activating groups in the aromatic ring. The following represents a typical run. To a suspension of 15 g. of phosphorus pentoxide in 80 ml. of boiling tetralin there was added 6.0 g. of N-(β-phenethyl)-2-pyrrolidone. After the mixture had boiled under reflux for one-half hour, an additional 25 g. of phosphorus pentoxide in 50 ml. of tetralin was added and heating was continued for 45 minutes longer. After the mixture had cooled, the tetralin was removed by decantation, and the phosphorus pentoxide residue and tetralin layer were separately decomposed by the addition of large amounts of ice. The combined aqueous layers were then extracted with ether and neutralized with dilute potassium hydroxide. The oil which separated was taken up in ether. The ethereal solution was dried and concentrated, and the residue was distilled to give 4.4 g. (80%) of a light orange oil, b.p. 125–129° at 3 mm. This oil was quite unstable and the final operations in its isolation were carried out under a nitrogen atmosphere.

Anal. Calcd. for $C_{12}H_{13}N$: C, 84.17; H, 7.65. Found: C, 83.66; H, 7.96.

(14) H. Rupe and J. Bürgin, *Ber.*, **43**, 178 (1910).

(15) We are indebted to Mr. A. E. Anderson, Jr., who carried out the first preparations of N-(β-phenethyl)-2-pyrrolidone and 2,3,5,6-tetrahydro-7,8-benzopyrrocoline in connection with another study.

(16) E. Späth and J. Lintner, *Ber.*, **69**, 2727 (1936).

7,8-Benzopyrrocoline (X).—A mixture of 2.1 g. of 2,3,5,6-tetrahydro-7,8-benzopyrrocoline, 2.5 g. of naphthalene and 150 mg. of a 10% palladium-on-charcoal catalyst[17] was boiled under reflux in a carbon dioxide atmosphere until hydrogen was no longer evolved. After the reaction mixture had cooled, it was taken up in ether and the catalyst was removed. The ethereal solution was washed with dilute acid to remove any basic material, and then 75 ml. of concentrated hydrochloric acid was added to dissolve the 7,8-benzopyrrocoline and separate it from the naphthalene. 7,8-Benzopyrrocoline and 3-methyl-7,8-benzopyrrocoline are soluble in concentrated hydrochloric acid but not in dilute. The concentrated hydrochloric acid extract was then neutralized with base and extracted with ether. Concentration of the ether extract gave a solid which, after crystallization from an ethanol–water mixture, yielded 430 mg. (30%) of white crystals, m.p. 83.5–84°.

Anal. Calcd. for $C_{12}H_9N$: C, 86.19; H, 5.43. Found: C, 86.00; H, 5.73.

N-(β-Phenethyl)-5-phenyl-2-pyrrolidone (VIII, R = C_6H_5).—This was prepared according to the general procedure of Pailer and Brandstetter.[10] A solution containing 15.0 g. of methyl β-benzoylpropionate, 9.45 g. of β-phenethylamine and 300 mg. of a palladium-on-charcoal catalyst[17] in 65 ml. of absolute ethanol was subjected to hydrogenation at 60° under 1 atm. pressure of hydrogen. Hydrogen absorption ceased at the end of 46 hours. After removal of the catalyst and solvent, a green oil remained which, on dilution with ether, deposited white crystals, m.p. 85.5–86.5°. The composition of this solid (found: C, 76.05; H, 8.34; N, 4.86) does not allow a clear decision regarding its structure and the material was not investigated further. The ether solution, from which the crystals separated, was concentrated and the residual oil was distilled, giving 6.0 g. of a viscous yellow oil; b.p. 175° (pot temp.) at 0.1 mm., $n^{30}D$ 1.5772. This became solid on standing and, after sublimation, was obtained as light yellow crystals, m.p. 43–44.5°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.49; H, 7.22. Found: C, 81.23; H, 7.43.

3-Phenyl-5,6-dihydro-7,8-benzopyrrocoline.—A 2.0 g. sample of N-(β-phenethyl)-5-phenyl-2-pyrrolidone was converted to the corresponding 3-phenyl-2,3,5,6-tetrahydro-7,8-benzopyrrocoline (IX, R = C_6H_5) using the same procedure described for the preparation of 2,3,5,6-tetrahydro-7,8-benzopyrrocoline (IX, R = H) itself. Because of the instability of the vinyl amine (IX, R = C_6H_5), no attempt was made to isolate it in a pure state but, instead, it was distilled (b.p. 150–160° at 0.5 mm.) directly into the flask for dehydrogenation. To this light orange oil there was then added 2.5 g. of naphthalene and 150 mg. of a 10% palladium-on-charcoal catalyst.[17] After this mixture had boiled under reflux until hydrogen was no longer evolved (2 hr.), the mixture was cooled, dissolved in ether, and the catalyst was removed. The solution was then concentrated and the naphthalene was removed by heating the residue at 100° in a stream of nitrogen at atmospheric pressure. When naphthalene ceased to sublime, the remaining oil was taken up in 15 ml. of ether, filtered, and then the ether solution was extracted four times with 8-ml. portions of 1 *N* hydrochloric acid to remove any basic material (see below). Concentration of the ethereal solution gave a solid residue which, after several recrystallizations from an ethanol–water mixture, yielded 480 mg. (26% over-all yield) of white crystals, m.p. 107.5–108.5°. The composition of this compound indicates that it is a dihydrobenzopyrrocoline and, since the presence of the pyrrole nucleus was evidenced by a positive Ehrlich test (purple), we have assumed the compound to be 3-phenyl-5,6-dihydro-7,8-benzopyrrocoline. As would be expected, the ultraviolet absorption spectrum of this compound is rather different from that of the fully aromatic pyrrocolines.

Anal. Calcd. for $C_{18}H_{15}N$: C, 88.13; H, 6.16. Found: C, 88.29; H, 6.16.

When the aqueous solution from the acid extractions (see above) was neutralized, a small amount of base separated. This was shown to be 1-(γ-phenyl)-propylisoquinoline by its conversion to the corresponding picrate, m.p. 155–157°, alone or mixed with a authentic sample of the picrate of 1-(γ-phenyl)-propylisoquinoline.

(17) R. Mozingo, *Org. Syntheses*, **26**, 77 (1946).

3-Phenyl-7,8-benzopyrrocoline (XI).—A mixture of 110 mg. of 10% palladium-on-charcoal catalyst and 97 mg. of 3-phenyl-5,6-dihydro-7,8-benzopyrrocoline was heated at 200° at 70 mm. pressure. Slow sublimation occurred giving 62 mg. of slightly yellow needles, m.p. 89–93°. After this material was recrystallized twice from absolute ethanol and sublimed once more, it was obtained as white crystals, m.p. 98–99°. When a sample of these crystals was mixed with a sample of 3-phenyl-7,8-benzopyrrocoline obtained from the Michael condensation of acrylonitrile and Reissert compound, there was no depression of melting point. Also, the ultraviolet and infrared spectra of the two compounds were identical.

Anal. Calcd. for $C_{18}H_{13}N$: C, 88.85; H, 5.38. Found: C, 88.72; H, 5.51.

N-(β-Phenethyl)-5-methyl-2-pyrrolidone (VIII, R = CH_3).—A mixture containing 20.0 g. of ethyl levulinate, 16.8 g. of β-phenethylamine, 370 mg. of a 10% palladium-on-charcoal catalyst and 75 ml. of ethanol was subjected to hydrogenation at 60° under an atmospheric pressure of hydrogen until hydrogen absorption ceased (six days). After removal of the catalyst and solvent, the residual oil was distilled giving 18.8 g. (63%) of a light yellow oil; b.p. 103° at 0.6 mm., $n^{26}D$ 1.5261.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 76.44; H, 8.44.

3-Methyl-7,8-benzopyrrocoline.—When 8.0 g. of N-(β-phenethyl)-5-methyl-2-pyrrolidone was subjected to the same procedure used in the cyclization of N-phenethyl-2-pyrrolidone, there resulted 4.0 g. (55%) of the intermediate vinyl amine, 3-methyl-2,3,5,6-tetrahydro-7,8-benzopyrrocoline (IX, R = CH_3); b.p. 85° at 0.6 mm., $n^{25}D$ 1.5942. Because of its instability, it was dehydrogenated immediately by heating it with a mixture of 5 g. of naphthalene and 500 mg. of a 10% palladium-on-charcoal catalyst. The mixture was boiled under reflux in an atmosphere of carbon dioxide until hydrogen was no longer evolved. After the mixture had cooled, it was dissolved in ether, the catalyst was removed, and the ethereal solution was extracted with concentrated hydrochloric acid. When the acid extracts were neutralized, an oil separated which was extracted with ether. Concentration of the ether extract gave 1.95 g. (50%) of a solid which, after several recrystallizations from ethanol, gave white crystals, m.p. 128.5–129.5°. The melting point of a sample of these crystals was not depressed by admixture of a sample of 3-methyl-7,8-benzopyrrocoline obtained *via* the Michael condensation. Also, the two samples of 3-methyl-7,8-benzopyrrocoline possessed identical ultraviolet and infrared spectra.

Anal. Calcd. for $C_{13}H_{11}N$: C, 86.15; H, 6.12. Found: C, 85.84; H, 6.35.

α-Carbethoxy-β-(1-isoquinolyl)-propiophenone (XV).—To a solution obtained by adding 40 ml. of a 1 *N* ethereal solution of phenyllithium to 10.0 g. of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline[13] in 200 ml. of dioxane and maintained at 0°, there was added dropwise with stirring 11.5 g. of ethyl acrylate in 40 ml. of dioxane. Although the deep red color of the mixture disappeared when the addition was complete, the mixture was allowed to warm to room temperature and stand with stirring for 20 hours. The reaction mixture was then decomposed by adding 100 g. of solid carbon dioxide and 250 ml. of water. After removal of the organic layer, the aqueous solution was extracted 3 times with 150-ml. portions of ether. Concentration of the combined extracts gave 8.9 g. of a solid residue. This was dissolved in ether and extracted five times with 35-ml. portions of 6 *N* hydrochloric acid. When the aqueous extract was neutralized, a solid separated which after recrystallization from ethanol gave 6.6 g. (58%) of white crystals, m.p. 126–128°. On further recrystallization from ethanol crystals were obtained that melted at 129–130°.

Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74. Found: C, 75.66; H, 5.49.

When a 500-mg. sample of α-carbethoxy-β-(1-isoquinolyl)-propiophenone (XV) was boiled under reflux with concentrated hydrochloric acid for 2 hours, it gave, on neutralization, 340 mg. (87%) of white crystals, m.p. 112–113°. That this material was phenyl β-(1-isoquinolyl)-ethyl ketone was shown by preparing the corresponding picrate (m.p. 198–199°) and oxime (m.p. 149–150°) and comparing these derivatives, as well as the free base, by mixed melting-

point determination with an authentic sample of this ketone and its derivatives.

2-Benzoyl-3-hydroxy-7,8-benzopyrrocoline (XIX).—When a 500-mg. sample of α-carbethoxy-β-(1-isoquinolyl)-propiophenone was sublimed by heating at 170° at 0.05 mm., it gave a deep-red solid. This, on recrystallization from an ethanol–water mixture, gave 390 mg. (90%) of red needles, m.p. 117–118°. The compound appeared to be rather unstable in solution and the sample for analysis (m.p. 117–118°) was obtained by re-sublimation.

Anal. Calcd. for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56. Found: C, 79.58; H, 4.64.

α-(2′-Pyridyl)-β-(1-isoquinolyl)-propiophenone (XVI).—To a solution obtained by adding 60 ml. of a 1 *N* ethereal solution of phenyllithium to 15.0 g. of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline in 250 ml. of dioxane and maintained at 0°, there was added dropwise with stirring 18.2 g. of freshly-distilled 2-vinylpyridine. After the mixture had warmed to room temperature, it was allowed to stand with stirring for 17 hours. Then, the mixture was decomposed by addition of 100 g. of solid carbon dioxide and 250 ml. of water, the organic layer was separated, and the aqueous layer was extracted three times with 150-ml. portions of ether. Concentration of the combined organic extracts gave a yellow gum, which was triturated with hot hexane to remove polymeric material. The residual solid was then dissolved in benzene and chromatographed over *Florisil*. On elution with benzene, only 1-cyano-2-benzoyl-1,2-dihydroisoquinoline was found in the eluate. However, elution with benzene containing 3% methanol gave, on concentration of the eluate, 5.98 g. of white crystals, m.p. 116–117°. On recrystallization from hexane, the crystals showed no change in melting point.

Anal. Calcd. for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28. Found: C, 81.88; H, 5.40; N, 8.25.

The **dipicrate** of α-(2′-pyridyl)-β-(1-isoquinolyl)-propiophenone (XVI) was prepared in ethanol and was obtained, after crystallization from the same solvent, as yellow crystals, m.p. 193–194° (dec.). A molecular weight determination of this picrate, according to the procedure of Cunningham, Dawson and Spring,[5] gave a value of 801 ± 4 (theor. 797).

Anal. Calcd. for $C_{35}H_{24}N_8O_{15}$: C, 52.77; H, 3.04. Found: C, 52.81; H, 3.02.

2-(2′-Pyridyl)-3-phenyl-7,8-benzopyrrocoline (XX).—A solution of 500 mg. of α-(2′-pyridyl)-β-(1-isoquinolyl)-propiophenone (XVI) in 5 ml. of concentrated sulfuric acid was heated on a steam-bath for 30 minutes, cooled and poured onto 30 g. of ice. The brown gum, which separated, redissolved on addition of dilute hydrochloric acid. Thorough extraction of the solution with chloroform, followed by concentration of the chloroform extracts, gave a yellow gum which crystallized when it was triturated with hydrochloric acid. This solid, which appeared to be an insoluble amine hydrochloride, was warmed with 20 ml. of ethanol containing 1.2 g. of potassium hydroxide. When the solution was cooled and diluted with water, a white solid separated. This, on recrystallization from an ethanol–water mixture, gave 240 mg. (50%) of white needles, m.p. 156–157°. An attempt to apply the phosphoric acid method for this cyclization failed to give any cyclized material.

Anal. Calcd. for $C_{23}H_{16}N_2$: C, 86.22; H, 5.04; N, 8.74. Found: C, 86.20; H, 4.89; N, 8.87.

When 70 mg. of 2-(2′-pyridyl)-3-phenyl-7,8-benzopyrrocoline (XX) in 5 ml. of concd. hydrochloric acid was boiled under reflux for 2 hours, the starting material was recovered quantitatively after the solution was cooled and neutralized with base.

The **picrate** of 2-(2′-pyridyl)-3-phenyl-7,8-benzopyrrocoline (XX) was prepared in ethanol and obtained, after recrystallization from this solvent, as yellow crystals, m.p. 251–252° (dec.).

Anal. Calcd. for $C_{29}H_{19}N_5O_7$: C, 63.39; H, 3.49. Found: C, 63.68; H, 3.48.

Cyclization of 1-(1′-Isoquinolyl)-3-butanone (VI) to 3-Methyl-7,8-benzopyrrocoline (XII).—A solution of 360 mg. of 1-(1′-isoquinolyl)-3-butanone in 5 ml. of concd. sulfuric acid was heated on a steam-bath for 30 minutes and then poured onto 30 g. of cracked ice. After the solution was diluted with 75 ml. of water, it was extracted twice with 50-ml. portions of ether. The solid, resulting on concentration of the ether extracts, was recrystallized from an ethanol–water mixture to give 140 mg. of white crystals, m.p. 127–128°. The melting point of these crystals was not depressed by admixture of an authentic sample of 3-methyl-7,8-benzopyrrocoline.

Cyclization of Phenyl β-(1-Isoquinolyl)-ethyl Ketone (V) to 3-Phenyl-7,8-benzopyrrocoline (XI).—A solution of 300 mg. of phenyl β-(1-isoquinolyl)-ethyl ketone in 3 ml. of 100% phosphoric acid was heated at 185° for 30 minutes. When the mixture was cooled and poured onto 40 g. of ice, a solid separated which was extracted with ether. Concentration of the ether gave 250 mg. (89%) of white crystals which, after recrystallization from absolute ethanol, melted at 97–99°, alone or mixed with an authentic sample of 3-phenyl-7,8-benzopyrrocoline.

Attempts to reverse this cyclization by boiling 3-phenyl-7,8-benzopyrrocoline with concd. hydrochloric acid led to the quantitative recovery of 3-phenyl-7,8-benzopyrrocoline. A similar result was also obtained with 3-methyl-7,8-benzopyrrocoline.

Condensation of Acrylonitrile with 1-Benzoyl-2-cyano-1,2-dihydroquinoline.—This was carried out following exactly the same procedure described for the preparation of 2-formamido-3-phenyl-7,8-benzopyrrocoline (III). When 15.0 g. of 1-benzoyl-2-cyano-1,2-dihydroquinoline was allowed to react with 9.2 g. of acrylonitrile, the neutral fraction obtained from the reaction mixture was a red gum. This was hydrolyzed directly by heating it under reflux for three hours with a solution of 24.0 g. of potassium hydroxide in 75 ml. of water. The mixture was then diluted with 100 ml. of water and extracted continuously with chloroform until no more colored material was removed. This removed the tarry material and the quinoline resulting from hydrolysis of starting material. The aqueous solution was then brought to a *p*H of 1.0 and extracted with chloroform to remove benzoic acid (0.70 g.). When the solution was brought to a *p*H of 6.0 and extracted with chloroform, it gave a gum which was taken up in an ethanol–ether mixture and treated with dry hydrogen chloride. This caused the separation of 900 mg. of white crystals, m.p. 193–196° (dec.), which had the properties of the expected amino acid hydrochloride. When this hydrochloride was recrystallized from absolute ethanol containing a little ether, it was converted to white crystals, m.p. 147.5–149°, which now had the properties of an amino ester hydrochloride. As shown below the composition of this amino ester hydrochloride agrees with that required for ethyl β-quinolylpropionate hydrochloride. The structure of this material was not further investigated since there are no readily available reference compounds for comparison. By analogy with previous alkylations of 1-benzoyl-2-cyano-1,2-dihydroquinoline,[4] this product is probably either ethyl β-(2-quinolyl)-propionate hydrochloride or the corresponding 4-quinolyl derivative.

Anal. Calcd. for $C_{14}H_{16}NO_2Cl$: C, 63.27; H, 6.07. Found: C, 63.55; H, 6.23.

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