THE CHEMISTRY OF THE PYRROCOLINES AND THE OCTAHYDROPYRROCOLINES

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I. INTRODUCTION

Whereas the chemistry of the pyrrocolines so far has had a solely academic interest, that of the octahydropyrrocolines has received attention, mainly because of the suggested presence of the ring in several alkaloids. The difference has offered a natural subdivision for this review, and the pyrrocolines and octahydropyrrocolines will hence be dealt with separately.

II. THE CHEMISTRY OF THE PYRROCOLINES

The increasing interest shown in recent years in the chemistry of heterocyclic compounds has left the unusual pyrrocoline ring system comparatively unexplored. Hence, although it first received major attention at the hands of Scholtz in 1912 and onwards, possibly with the hope of devising a new source of dyes, it has failed so far to find a place in such a field. However, light-screening agents for photographic emulsions have been prepared in the form of polymethine dyes of 2-phenyl-, 2,3-dimethyl-, and 2-methyl-pyrrocolines by reaction with 2-β-

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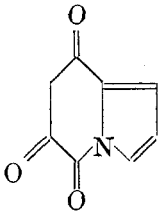
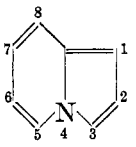
acetanilidovinylbenzoxazole ethiodide to yield (3-ethyl-2-benzoxazole) (pyrrocoline) dimethine cyanine iodides (16a).

In 1890 Angeli (2, 3, 4) reported the preparation of the imine-anhydride of pyrroylpyruvic acid (I) and suggested that the completely unsaturated parent



I

base should be named pyrindole. However, other names—including pyrrodine, pyrrocoline, and indolizine—have been suggested since, and three systems of numbering (II, III, and IV) have been employed.



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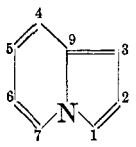

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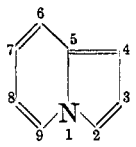
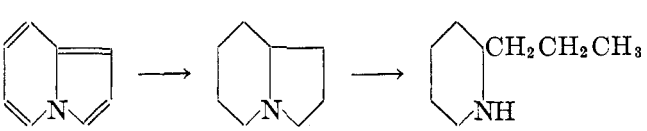


IV

Throughout this review the name pyrrocoline and the system of numbering (II) adopted by the American Chemical Society (75) will be used.

The parent base, pyrrocoline, was first synthesised by Scholtz (81), who obtained it by acid hydrolysis of a compound, $C_{12}H_{11}O_2N$, prepared by the treatment of α-picoline with acetic anhydride. The new compound, a colorless crystalline solid, m.p. 74°C. and b.p. 205°C., volatile in steam, had but feeble basic properties from which it was considered not to be a true derivative of pyridine. Furthermore, the compound gave, with isatin and with a pine splint, reactions typical of pyrroles; on fusion with oxalic acid it yielded a dark melt which produced a violet-red coloration in aqueous solution, a reaction typical of indoles. On this evidence, and in view of the fact that the compound possessed the same empirical formula (C_8H_7N) as indole and isoindole, Scholtz proposed the now accepted ring structure for his new compound.

Direct support for this formulation was produced by Diels and Alder (34), who demonstrated the presence of four double bonds by catalytic reduction of pyrrocoline to a derivative shown to be identical in all respects with δ-conicëine (octahydropyrrocoline) previously prepared by Löffler *et al.* (63, 64). This, on degradation with cyanogen bromide, yielded *dl*-coniine (α-*n*-propylpiperidine).



dl-Coniine

Further evidence substantiating the pyrrolopyridine formulation for pyrrocoline arises from a consideration of the numerous syntheses described below.

III. SYNTHESES OF PYRROCOLINE AND ITS DERIVATIVES

A. Reaction of α-picoline and its derivatives with acid anhydrides

The reaction of acetic and of propionic anhydride with α-picoline and its derivatives may be described as a general method of preparing pyrrocolines by way of their acyl derivatives.

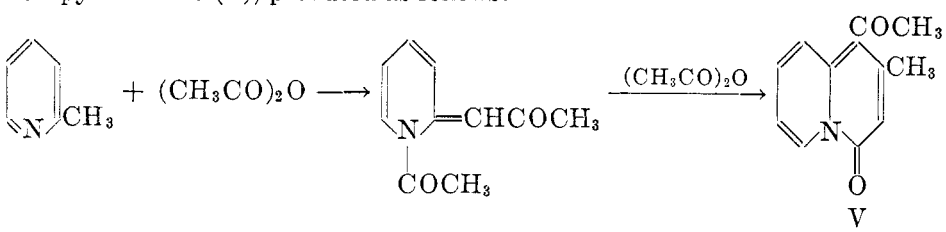
Scholtz (81) found that acetic anhydride and α-picoline at 200–220°C. yielded a crystalline compound, $C_{12}H_{11}O_2N$, which he called "picolide." The formation of this product corresponded to the following equation:

$$C_6H_7N + 2(CH_3CO)_2O \rightarrow C_{12}H_{11}O_2N + CH_3COOH + 2H_2O$$

The presence of one carbonyl group in "picolide" was readily demonstrated by the preparation of an oxime, a phenylhydrazone, and a semicarbazone, but it did not give reactions characteristic of aldehydes. It readily condensed with two molecules of aromatic aldehydes and underwent hydrolysis with 25 per cent hydrochloric acid to yield pyrrocoline, with the loss of two acetyl groups.

$$C_{12}H_{11}O_2N \rightarrow C_8H_7N + 2CH_3COOH$$

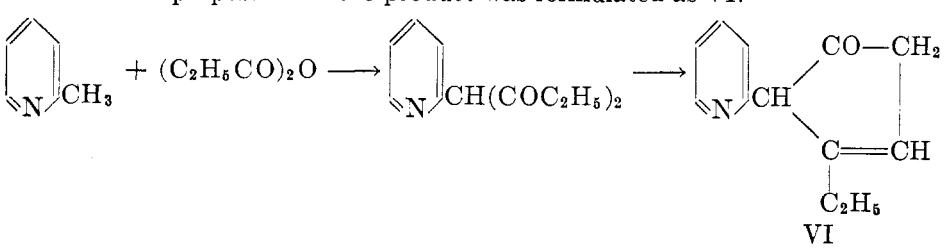
As "picolide" possessed no basic properties and failed to react in other precipitation reactions characteristic of organic bases, Scholtz and Fraude (84) assumed the nitrogen to be acylated and, having taken into account all its known properties, considered the most suitable structure to be 1-acetyl-2-methyl-4-ketopyridocoline (V), produced as follows:



V

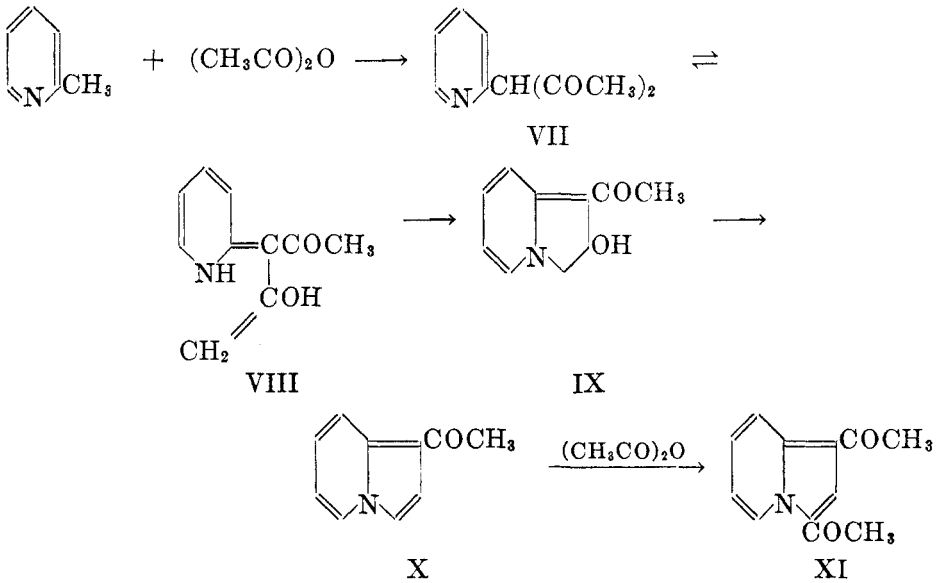
With this structure for "picolide" it was necessary to propose a complicated initial cleavage, followed by ring closure to a five-membered pyrrole ring, in order satisfactorily to explain its formation upon the hydrolysis of pyrrocoline.

This mechanism became untenable for the reaction of propionic anhydride with α-picoline, as here only one mole of anhydride was involved (84), yet the product still contained one reactive carbonyl group. A different mechanism was therefore proposed and the product was formulated as VI.



VI

These reaction mechanisms were unacceptable to Chichibabin and Stepanow (19), who claimed that the pyrrocoline nucleus was present in both products and that with acetic anhydride the reaction proceeded as follows:



According to this mechanism the first product is the ω-diacetylpicoline (VII), which reacts in a tautomeric form (VIII) to undergo ring closure to 2-hydroxy-1-acetyl-2,3-dihydropyrrocoline (IX). Dehydration of the latter yields 1-acetylpyrrocoline (X), which is then further acetylated to produce "picolide" or 1,3-diacetylpyrrocoline (XI).

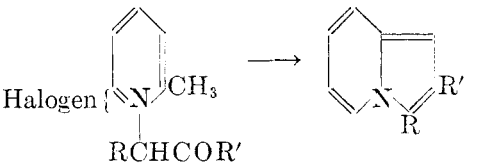
Similarly, the reaction of propionic anhydride with α-picoline was considered to produce 1-propionyl-3-methylpyrrocoline, which failed to undergo further acylation under the conditions employed. The apparent non-reactivity of the second acetyl group in "picolide" (XI) was not thought to detract from the validity of the new formulation, for derivatives of *N*-methylpyrrole containing an acyl group in the α-position do not readily undergo ketonic reactions (87). The presence of the pyrrocoline ring in picolide was finally substantiated by the monoacetylation of pyrrocoline, as described by Scholtz (82), to yield an acetylpyrrocoline, followed by further acetylation at 200°C. to yield picolide. Furthermore, monoacetylation of 2-methylpyrrocoline yielded an acetyl compound possessing no reactivity towards ketonic reagents under normal conditions. The presence of the pyrrocoline nucleus in the presumed 1-propionyl-3-methylpyrrocoline was demonstrated by deacylation to 3-methylpyrrocoline, the structure of which was finally established by Ochiai and Tsuda (73).

This mode of preparation has been extended to the use of α,γ-lutidine and α-phenyl-α-methylpyridine with acetic anhydride (83) to produce 7-methyl- and 5-phenyl-1,3-diacetylpyrrocoline, respectively, which on hydrolysis give 7-methyl- and 5-phenyl-pyrrocolines. Attempts to extend the reaction to other

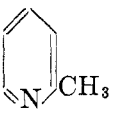
acid anhydrides (84) and to quinaldine with acetic anhydride (10) have met with failure.

B. Reaction of α-halogenoketones with pyridine bases

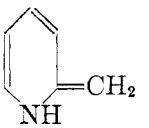
A more widely applicable method, which appears to be of considerable practical value for the preparation of pyrrocolines, is the ring closure of quaternary compounds formed from α-picoline and its derivatives and α-halogenoketones.



The existence of tautomerism in α- and γ-amino- and α- and γ-hydroxypyridines led Chichibabin (18) to suggest that a similar tautomerism could occur in α- and γ-alkylated pyridines. In particular, α-picoline on this theory would be expected to react either as the true α-methylpyridine (XII) or as α-pyridonemethide (XIII),

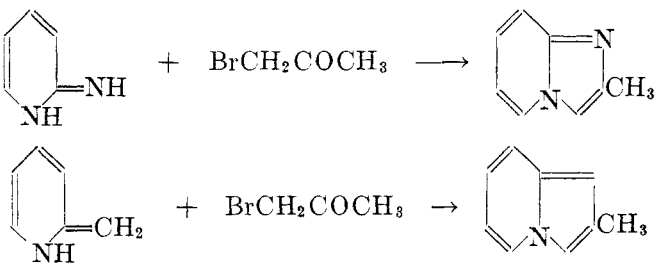


XII



XIII

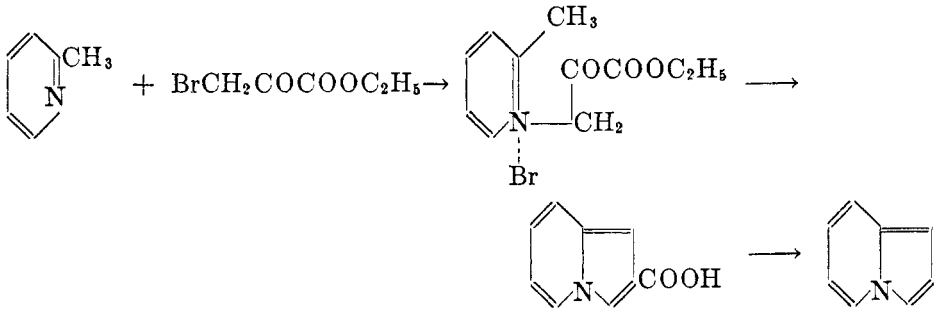
indicating the possibility of obtaining with form XIII ring closures similar to those already known for α-pyridoneimide, as represented by the following formulae:



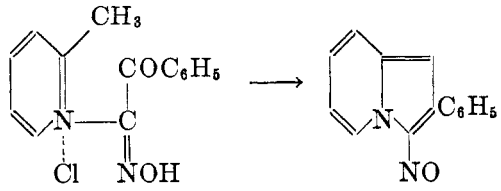
Theory was confirmed by the synthesis of 2-substituted pyrrocolines from bromo- and chloro-acetones and ω-bromoacetophenone, the quaternary picolinium compounds first formed undergoing ring closure to 2-methyl- and 2-phenylpyrrocolines on treatment with aqueous alkalis, preferably bicarbonate (11). Unfortunately, when the synthesis was attempted with an α-halogenated aldehyde, employing α-bromodimethylacetal, α-bromoacetaldehyde, and dibromoparaldehyde, the quaternary compounds from α-picoline were produced less readily and only with the second did pyrrocoline result on ring closure and then in very small yield.

The method has been applied satisfactorily to the preparation of 2,3-dimethyl-, 2,5-dimethyl-, 2-methyl-3-ethyl-, 1-phenyl-2-methyl-, and 2-phenyl-3-ethyl-pyrrocolines (14, 18, 73), and in some instances the preparation of the intermediate quaternary compounds by the procedure of King (49), from α-picoline, iodine, and the ketone, followed by ring closure, has been examined (11, 50). It is of interest that the substitution of quinaldine for α-picoline in the reaction with chloroacetone and ω-bromoacetophenone merely produced quinaldine hydrohalides (11) and none of the desired quaternary compound, a result which is in direct contradiction to a report (18) of Chichibabin. As to the influence of the nature of the α-halogenoketone on yields, there is evidence that bromo compounds are superior to chloro compounds (14) and that the yields drop progressively on substitution of the α-hydrogen by larger hydrocarbon residues (10, 11, 14).

Borrows, Holland, and Kenyon (9, 11) have attempted to extend the scope of the reaction to the preparation of acyl and carbalkoxy derivatives by the use of α-halogeno-β-diketones, α-halogeno-β-keto esters and a β-halogeno-α-keto ester, namely, α-chloroacetylacetone, α-bromobenzoylacetone, ethyl α-chloroacetoacetate, ethyl α-bromobenzoylacetate, and bromopyruvic acid or ester. With all but the last, difficulties arose at the quaternizing stage and on ring closure only 2-methyl- or 2-phenyl-pyrrocoline, respectively, could be isolated. However, ethyl bromopyruvate, and in poorer yield the acid, readily gave pyrrocoline-2-carboxylic acid. As this acid can be decarboxylated to pyrrocoline (32, 34), the method presents a new and possibly superior route to it.



Extension of this synthesis is exemplified by the preparation of ω-isonitrosophenacyl-α-picolinium chloride, from which 3-nitroso-2-phenylpyrrocoline arose in excellent yield (12).

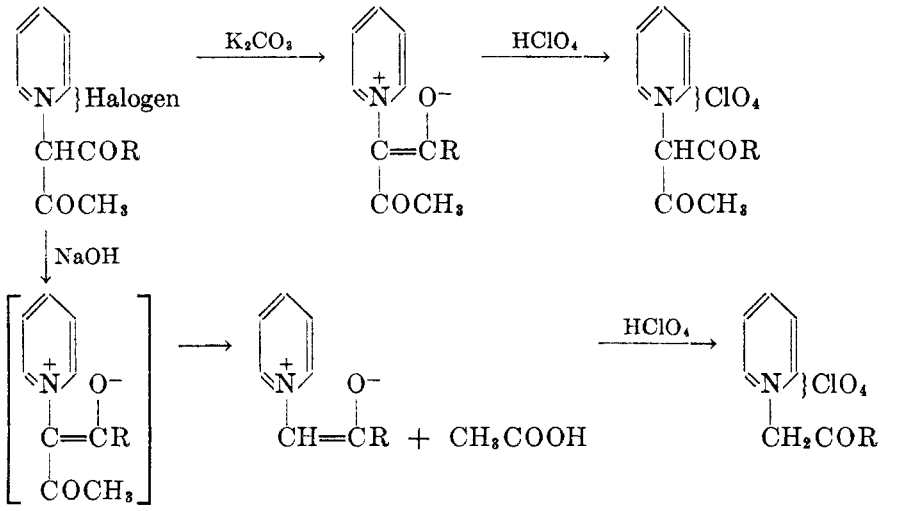


In contrast, the preparation of the corresponding quaternary nitro body from ω-nitrobromoacetophenone could not be effected (13).

A further variant of this method was attempted with the replacement of α-picoline by α-pyridyl-2-propanol and α-pyridylacetone, using ω-bromoacetophenone as the halogenoketone (8). In the first example no difficulty occurred in the preparation of the quaternary compound, but on attempted ring closure loss of the hydroxyethyl group resulted, with formation of 2-phenylpyrrocoline. Pyridylacetone, on the other hand, produced none of the desired quaternary product and to some extent acetone was cleaved from the base (10).

At this point an exposition of the possible mechanism of the Chichibabin synthesis seems appropriate. The behavior towards various alkaline reagents of quaternary compounds, formed from bases of the pyridine type with α-halogenoketones and β-diketones, has received considerable attention from Kröhnke *et al.* (56, 57, 58, 59, 60). These authors established that such quaternaries on treatment with alkalis of suitable strength yield "enol-betaines," which could undergo a so-called "acid cleavage" with loss of an acyl group, the smaller of the two present being lost by the quaternaries prepared from diketones. The over-all reaction can be effected directly by a more vicious alkaline treatment, weak bases such as potassium acetate or benzoate being ineffective.

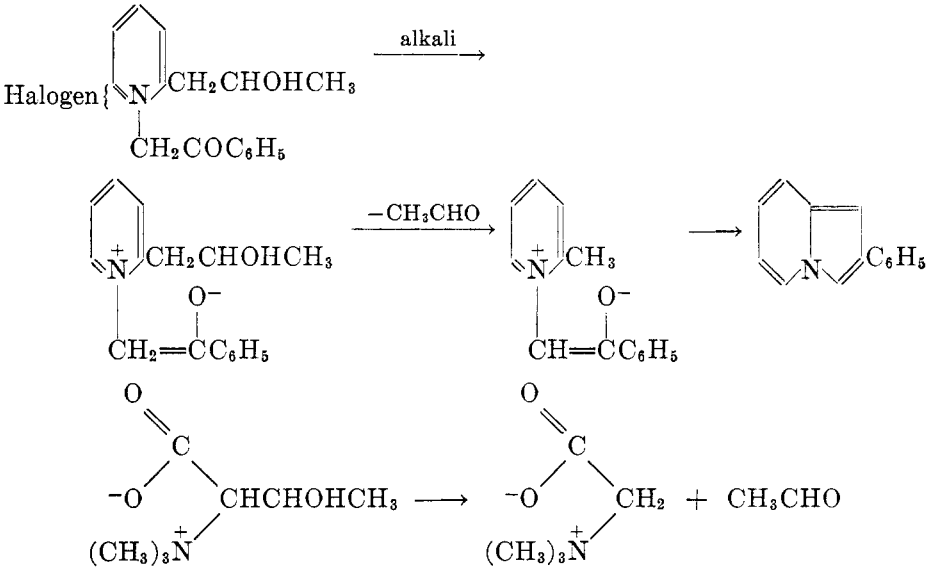
The reactions with quaternaries from α-halogenodiketones are exemplified as follows:



This work therefore explains the advantage of using weak bases for the ring closure in the pyrrocoline synthesis and suggests "enol-betaine" formation as an intermediate step, during which acyl or carboalkoxy groups may be cleaved. This cleavage of the "enol-betaine" may occur also during the preparation of the quaternary compound, owing to the influence of the tertiary base. Thus, α-bromobenzoylacetone was reported (60) to yield α-phenacylpyridinium bromide on reaction with pyridine, and the failure of the similar reaction (11) with α-picoline to give on ring closure an acylpyrrocoline can probably be explained in this way. That the pyridine bases are capable at times of eliminating halogen

acid from the related quaternaries with the possible formation of "enol-betaines" is shown by the formation (*a*) of benzoic acid from the reaction of ω-nitrobromoacetophenone with α-picoline, (*b*) of α-picoline hydrohalides as by-products in most of the preparations of the quaternaries, and (*c*) of quinaldine hydrohalides arising from the use of quinaldine with α-halogenoketones.

The loss of a hydroxyethyl group during attempted ring closure of phenacyl-α-pyridinium-2-propanol bromide probably results at the betaine stage by a retrograde aldol condensation in a manner analogous to the similar reaction reported to occur (17) on treatment of the betaines of threonine and allothreonine with alkali:



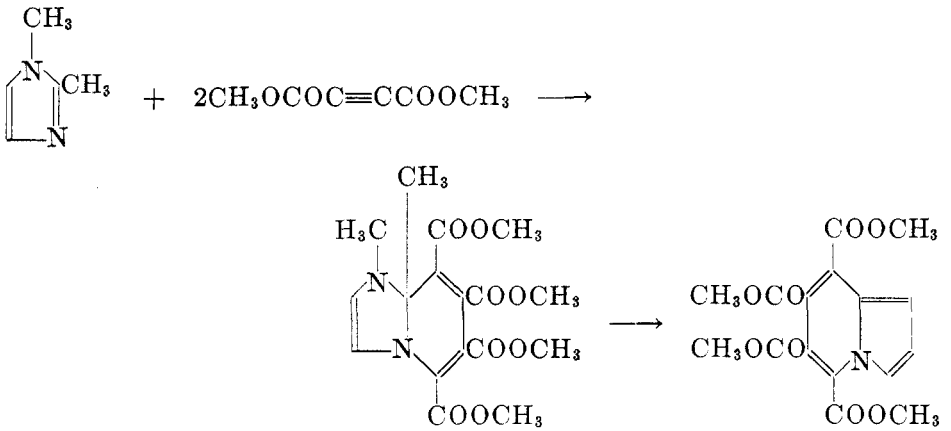
The stimulating review by Bergstrom (7) of the chemistry of pyridine, quinoline, and isoquinoline, based on the relationships of such heterocyclic systems to an ammonia system, suggests that α-pyridylacetone may be regarded as a "mixed" aquoketone-ammonoketone and hence related to α,β-diketones of the water system. On these grounds the loss of acetone (10) and the difficulty of preparing the desired quaternary upon treatment of α-pyridylacetone with ω-bromoacetophenone become understandable.

C. Reaction of pyridine bases with acetylenedicarboxylic esters

Diels and his collaborators have published a series of papers on the reaction of acetylenedicarboxylic esters with bases such as pyrrole, glyoxaline, pyridine, quinoline, isoquinoline, α-picoline, stilbazole, and quinaldine (32–34, 36–42, 69). From many of these investigations carboxylic ester derivatives of pyridocolines and, at times, of pyrrocolines were derived. As the former may be degraded conveniently to pyrrocolines, this work affords another general method for pre-

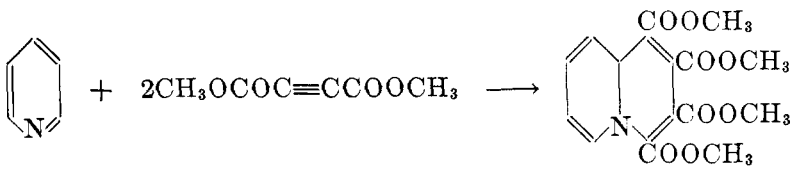
paring pyrrocoline and its derivatives, especially carboxy and carbalkoxy compounds.

Dimethyl acetylenedicarboxylate on reaction with 1,2-dimethylglyoxaline yields tetramethyl 1,8-dimethyl-1,8-dihydropyrimidazole-4,5,6,7-tetracarboxylate, which on treatment with acetic acid loses methylamine to produce tetramethyl pyrrocoline-5,6,7,8-tetracarboxylate (XIV) (36).



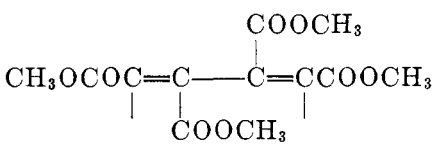
XIV

Pyridine (32, 33, 34) reacts similarly with dimethyl acetylenedicarboxylate in ether to yield tetramethyl pyridocoline-1,2,3,4-tetracarboxylate, a yellow "stable adduct" (XV).



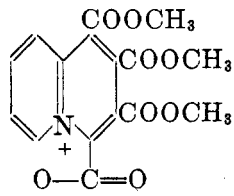
XV

This product was considered to have arisen by the condensation of the pyridine N=C bond with the unsaturated chain,

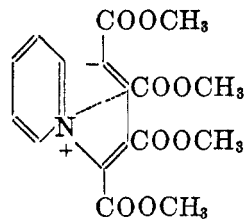


formed by the interaction of two molecules of the ester. That the initial condensation did not proceed by condensation of one molecule of ester to yield α-pyridylmaleate was evidenced by the observation that quinaldine, which possesses no α-hydrogen atom, condensed likewise with the ester (33, 38). Furthermore, in addition to the yellow "stable adduct" two other products were isolated;

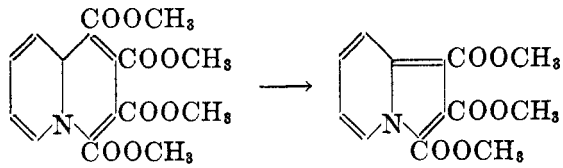
one, called the Kashimoto compound, was given the following formula:



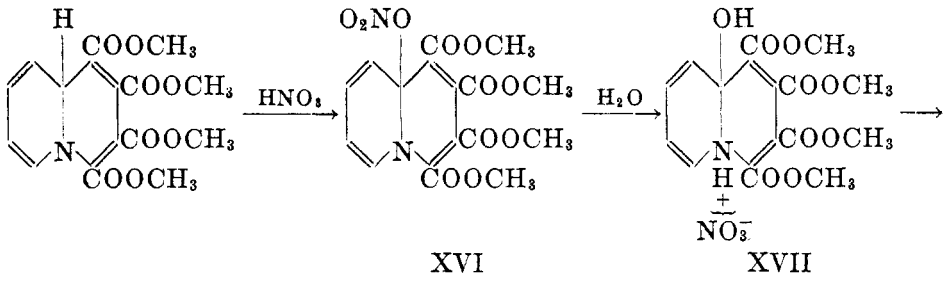
The second product, a red "labile adduct," could be converted readily into the yellow "stable adduct" by recrystallization from 50 per cent acetic acid or by heating. The "labile adduct" was an intermediate therefore in the formation of the "stable adduct," and it was shown by a considerable amount of unequivocal evidence to possess the following structure:



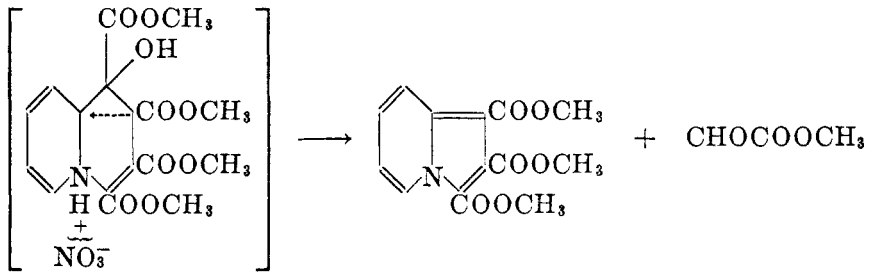
Oxidation of tetramethyl pyridocolinetetracarboxylate with nitric or chromic acid yields trimethyl pyrrocoline-1,2,3-tricarboxylate, and both compounds were shown to possess a pyridine moiety by oxidation with perhydrol in acetic acid to α-picolinic acid *N*-oxide.



The mechanism of the chromic acid oxidation according to Diels and Alder is very obscure, but when nitric acid is employed, oxalic acid and intermediate products of the degradation can be isolated (32). Thus, treatment of the tetramethyl pyridocolinetetracarboxylate with concentrated nitric acid followed by evaporation produces a compound, $C_{17}H_{17}O_{14}N_3$, assigned the formula XVI, and this when treated with a limited quantity of water gives rise to a so-called "oxynitrate," $C_{17}H_{18}O_{12}N_2$ (XVII), which proves stable to hot water but on warming with dilute nitric or sulfuric acid yields trimethyl pyrrocoline-1,2,3-tricarboxylate (XIX). The last transformation was presumed to occur *via* a hydroxyl shift, yielding a hypothetical intermediate (XVIII), from which the pyrrocoline arose by cleavage of methyl glyoxalate.

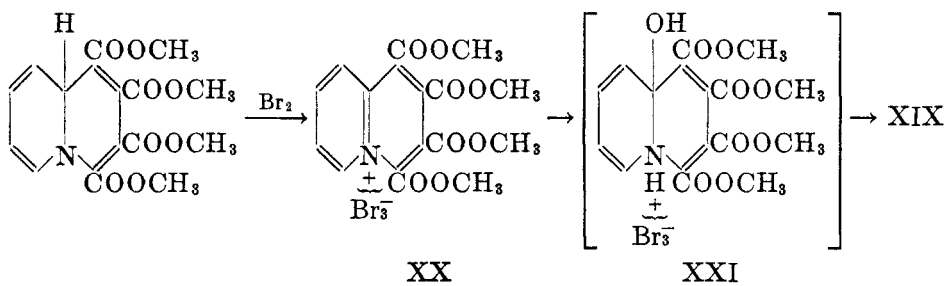


XVI XVII



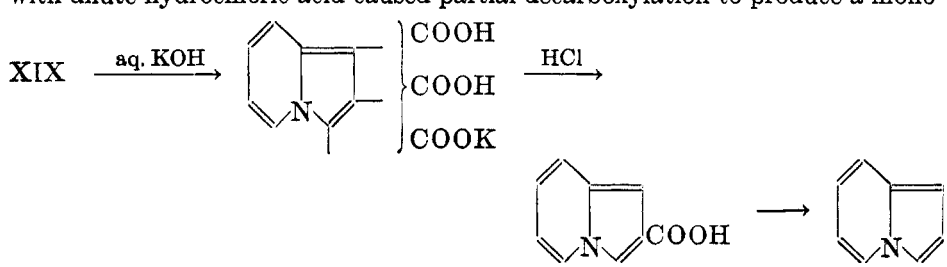
XVIII XIX

The pyridocoline adduct can also be converted to the pyrrocolinetricarboxylate by the action of bromine, to yield a perbromide (XX) from which the pyrrocoline (XIX) arises on hydrolysis with loss of methyl glyoxalate. The reaction mechanism, involving a hypothetical "oxybromide" (XXI), is expressed as follows:



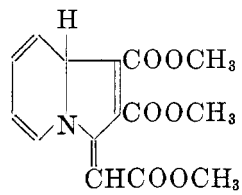
XX XXI

Hydrolysis of the trimethyl pyrrocoline-1,2,3-tricarboxylate with aqueous caustic potash yielded a monopotassium salt of the free acid, which on heating with dilute hydrochloric acid caused partial decarboxylation to produce a mono-

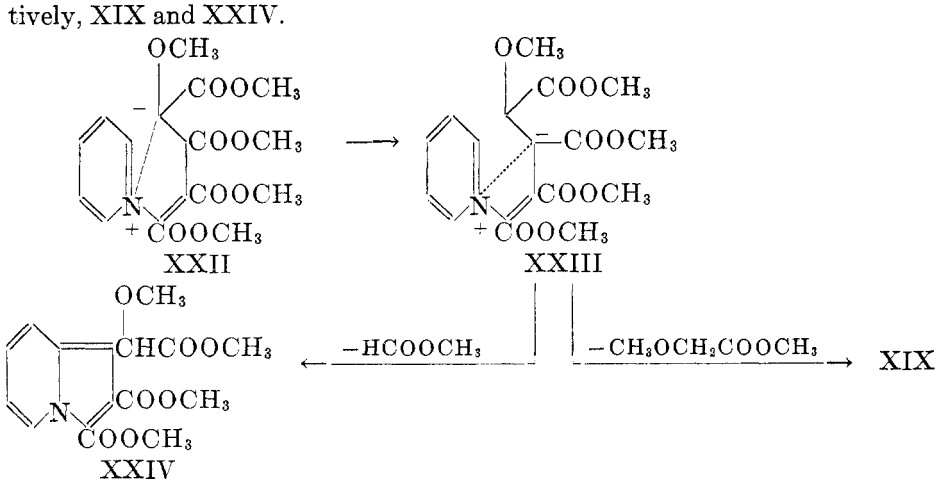


carboxylic acid; this on distillation with calcium oxide gave rise to pyrrocoline (32). The latter monocarboxylic acid has since been identified as pyrrocoline-2-carboxylic acid (9).

During the course of the above investigations much evidence accrued to show that the pyridocoline ring system could be degraded to pyrrocoline under much milder conditions than by the processes already mentioned. Thus, boiling tetramethyl pyridocolinetetracarboxylate with phenol or formic acid was shown to yield a pyrrocolinetricarboxylic ester (39) and not the pyridocoline derivative, as had earlier been thought. Furthermore, attempted preparation of pyridocoline itself by saponification and decarboxylation of the above tetracarboxylate gave rise to a crude product which after hydrogenation was shown by Diels and Schrum (42) to be a mixture of 3-methyloctahydropyrrocoline and octahydropyrrocoline. The transformation to a pyrrocoline ring system was thought by these authors to occur during the initial hydrolysis and decarboxylation, the structure of the resulting compound being as follows:

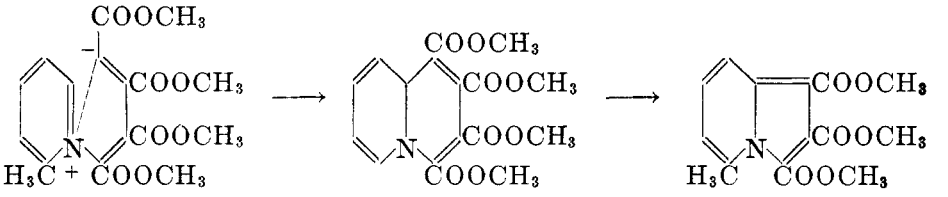


Unlike its action in ethereal solution, according to Diels and Meyer (39) the reaction of dimethyl acetylenedicarboxylate in methyl alcoholic solution with pyridine yielded derivatives of pyrrocoline directly. When the reaction was allowed to proceed unchecked, trimethyl pyrrocoline-1,2,3-tricarboxylate (XIX) resulted, whereas at 0°C. a "white adduct" arose and was shown to be dimethyl 1-methoxycarbomethoxymethylpyrrocoline-2,3-dicarboxylate (XXIV). Both of these products were considered to be formed from a common adduct (XXII) reacting *via* a hypothetical intermediate (XXIII), which was thought to lose either a molecule of methyl methoxyacetate or methyl formate to yield, respectively, XIX and XXIV.



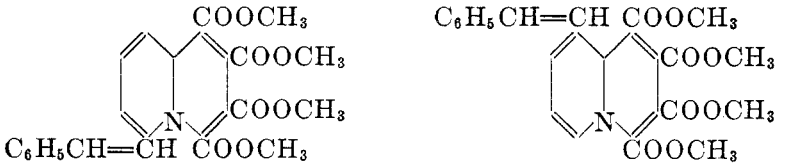
It was also reported that the "white adduct" (XXIV) could be successfully converted to XIX by treatment with bromine in methanol or acetic acid. There is a report (13), however, that an attempt to repeat the direct preparation of XIX resulted only in the formation of XXIV.

From the reaction of α-picoline with dimethyl acetylenedicarboxylate Diels and Pistor (41) isolated a yellow "labile adduct" (XXV), which was converted *via* the "stable adduct" (XXVI) to trimethyl 5-methylpyrrocoline-1,2,3-tricarboxylate (XXVII) by the usual methods.

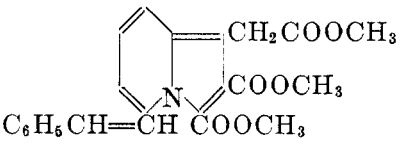


XXV XXVI XXVII

Similarly, stilbazole (40) yielded a "labile adduct" which could be converted to either of the two stable adducts XXVIII and XXIX.



XXVIII XXIX



XXX

Trimethyl 5-styrylpyrrocoline-1,2,3-tricarboxylate was obtained from the "labile adduct" or from XXVIII on oxidation with chromic acid, but heating these with phenol or boiling alone was considered to yield XXX.

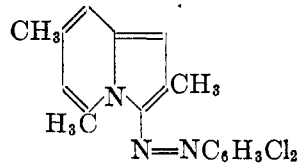
D. Other methods

A synthesis of pyrrocoline which appears to be of little practical importance was reported by Brand and Reuter (15). Thus the reduction of 2-(γ,γ,γ-trichloro-β-hydroxypropyl)pyridine hydrochloride in aqueous sulfuric acid with zinc dust gave rise in small yield to 2-(γ-chloro-β-hydroxypropyl)pyridine, which on treatment with strong caustic soda yielded pyrrocoline.

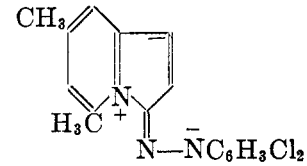
Wilson (89) has reported the formation of pyrrocoline in small yield during the aluminum oxide catalyzed conversion of furan to pyrrole in the presence of ammonia.

Prolonged heating of collidine with the betaine-like compound arising from the action of pyridine with the imino-chloride of *N*-2,4-dichlorophenylpyruvic

hydrazide gave rise to a red-brown product which was given either of the two alternative formulae XXXI and XXXII (68).



XXXI



XXXII

Only one attempt to dehydrogenate the octahydropyrrocoline ring system has been recorded in the literature. Prelog and Balenović (76), employing palladized charcoal and selenium catalysts, failed to isolate any definite product from the dehydrogenation of octahydropyrrocoline.

IV. PROPERTIES

Pyrrocoline and all the known alkylpyrrocolines are either low-melting solids or high-boiling liquids, volatile in steam, unstable in air and light. On the other hand, with the attachment of an aromatic benzene ring at the 2- or 5-position stable solids non-volatile in steam result. All give colors in the pine splint test, characteristic of pyrrole, and colored melts on fusion with oxalic acid, a test characteristic of indole. A third diagnostic test is the treatment of the pyrrocolines in dilute sulfuric acid with a crystal of potassium iodate, when pyrrocoline and its 7-methyl and 5-phenyl derivatives produce deep indigo-blue colors (83). Many pyrrocolines in solution or as vapors or solids exhibit in sunlight or under ultraviolet light characteristic fluorescence. The ultraviolet absorption spectra of 2-phenylpyrrocoline and its 3-acetyl and 3-ethyl derivatives have been recorded (10, 14) (see Section XII).

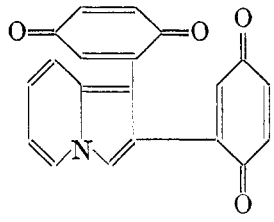
Alkyl- and aryl-pyrrocolines can be characterized quite satisfactorily by the preparation of the usual types of salts such as picrates, chloroplatinates, etc.

On present evidence it is difficult to assess the stability of the pyrrocoline nucleus to oxidizing agents. Thus there are reports (81, 83) that the parent base and its 7-methyl and 5-phenyl derivatives are sensitive to potassium permanganate and chromic oxide in sulfuric acid, but in comparison it is necessary to draw attention to the apparent stability of trimethyl pyrrocoline-1,2,3-tricarboxylate which arises from the oxidation of tetramethyl pyridocoline-1,2,3,4-tetracarboxylate (8, 32, 33, 34). Here, however, the reactive pyrrole ring is protected by the carboxylic ester groups. The successful oxidation of nitroso to nitro groups in the pyrrocoline nucleus has been effected under critical conditions with perhydrol (12, 13). This agent, however, rapidly attacks the nucleus and is thus useful for degradative purposes (Section XIII).

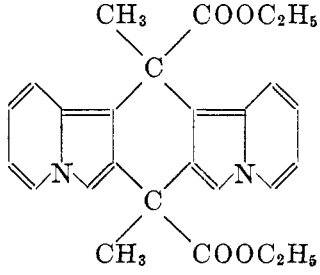
Whereas pyrrole reacts with isatin to yield the blue dye pyrrole indophenine (22) and a colorless crystalline compound (65), pyrrocoline in acetic acid with excess isatin produces a violet coloration and, with equal quantities, a colorless crystalline product of unknown constitution formed as follows (82):

$$2C_8H_7N + 2C_8H_5O_2N \rightarrow C_{32}H_{22}O_3N_4 + H_2O$$

Analogously to indole, pyrrocoline condenses with quinone to yield a diquinonylpyrrocoline formulated (82) as follows:



Also similarly to pyrrole and indole, pyrrocoline and its 7-methyl and 5-phenyl derivatives condense with aldehydes in alcoholic solution to yield dipyrrocolinylmethanes (81, 83), the exact structures of which are as yet undetermined. Whereas these products tend to become blue in air, those prepared from pyrrocoline itself with simple ketones in acetic acid appear to be quite stable. Ethyl acetoacetate also condenses (84) with pyrrocoline in alcoholic hydrochloric acid to produce a compound believed to possess the following structure:



V. ALKYL DERIVATIVES

Many of the procedures of synthesis outlined in Section III are adaptable to the preparation of alkyl derivatives. In addition, Scholtz (82, 83) claimed by analogy with pyrroles that two methyl groups were introduced directly into the pyrrole moiety of the parent base and the 7-methyl derivative by treatment in alcohol with methyl iodide at 120°C. The Clemmensen and Kishner–Wolff methods with suitable modifications (14) are suitable for reducing acyl to alkyl and aralkyl pyrrocolines.

VI. HALOGENO DERIVATIVES

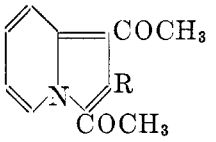
The reaction of halogens with pyrrocolines has received little attention. However, unstable and uncharacterizable crystalline compounds are reported to arise on treatment of pyrrocoline with bromine, and a diiodo compound of a similar nature is also recorded (84). Two unstable products were also obtained on addition of bromine to a chloroform solution of 1,3-diacetylpyrrocoline (81), corresponding to dibromo and tetrabromo compounds. In contrast, 3-acetyl-2-phenylpyrrocoline may be iodinated readily in alcohol to yield 1,3-diiodo-2-phenylpyrrocoline hydriodide and, in the presence of sodium acetate, 1-iodo-3-acetyl-2-phenylpyrrocoline (8).

VII. ACYL DERIVATIVES

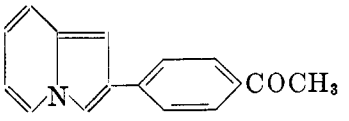
The direct synthesis of acylpyrrocolines would appear to be restricted to the action of acid anhydrides on α-picoline and its derivatives (81, 83, 84), as attempts to employ the method of Chichibabin, using halogenodiketones and α-picoline (11) or α-pyridylacetone and ω-bromoacetophenone (8), have been unsuccessful.

However, the pyrrocoline nucleus can readily be acylated by heating with acid anhydrides in the presence of the sodium salt of the corresponding acid. The monoacetyl derivatives of pyrrocoline (82), 7-methylpyrrocoline (83), 2-methylpyrrocoline (11, 19), and 2-phenylpyrrocoline (11), and the monobenzoyl derivative of 2-phenylpyrrocoline (11) have been prepared in this way. By further treatment with acetic anhydride at higher temperatures the monoacetyl derivatives of pyrrocoline (19), 2-methylpyrrocoline (11, 19), and 2-phenylpyrrocoline (11) have been converted to the corresponding 1,3-diacetyl compounds (XXXIII).

The application of the Friedel–Crafts reaction to the pyrrocoline nucleus has been successful in some instances. Ochiai (70) reported that 1,3-diacetyl-2-methylpyrrocoline (XXXIII, R = CH_3) could be prepared by the action of acetyl chloride on 3-acetyl-2-methylpyrrocoline in tetrachloroethane solution in the presence of a large excess of aluminum chloride, but only a very small yield of this compound could be obtained from 2-methylpyrrocoline itself and then only in carbon disulfide solution. With 2-phenylpyrrocoline, on the other hand, Borrows, Holland, and Kenyon (11) have found that reaction proceeds readily in carbon disulfide to yield a mixture of 1,3-diacetyl-2-phenylpyrrocoline (XXXIII, R = C_6H_5) and 2-*p*-acetylphenylpyrrocoline (XXXIV).



XXXIII



XXXIV

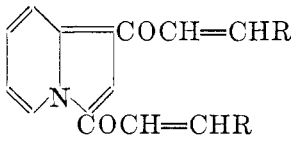
3-Acetyl-2-phenylpyrrocoline reacts well in tetrachloroethane solution to give the 1,3-diacetyl derivative. In the absence of the catalyst both acetyl chloride and acetyl bromide fail to react with 2-phenylpyrrocoline, an observation which is in marked contrast to the ready reaction of benzoyl chloride, which yields the same monobenzoyl derivative as that obtained by the action of benzoic anhydride. The facile reactivity of pyrrocoline itself with benzoyl chloride to yield a monobenzoyl derivative was also noted by Scholtz (84), who similarly obtained an unstable acid chloride by the action of phosgene on the parent base.

Acylpyrrocolines are reasonably stable, well crystalline solids, although Scholtz (82) recorded that 3-acetylpyrrocoline becomes green and finally blue on exposure to air and the 2-methyl derivative behaves similarly if impure (19). They give positive reactions in the pine splint test and colored melts on fusion with oxalic acid (14, 19) and, although Scholtz stated that 1,3-diacetylpyrroco-

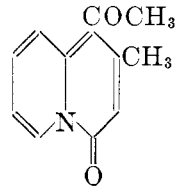
line ("picolide") possessed none of the properties of pyrrole (81), Chichibabin and Stepanow found that the homologous 1,3-diacetyl-2-methylpyrrocoline gave a slowly developing red color in the pine splint test (19).

The acyl groups are readily removed from these compounds by hydrolysis with mineral acids (11, 19, 20, 81, 83) and even boiling aqueous acetic acid is effective with 3-acetyl-2-phenylpyrrocoline (11). Diacyl derivatives appear to be somewhat more resistant than monoacyl derivatives (11) and those compounds containing a nitro (13, 82) or nitroso (12) group in the nucleus cannot be hydrolyzed in this way. 3-Acetylpyrrocoline has been reported to be stable to boiling alcoholic potash (82) but heating 3-acetyl-2-phenylpyrrocoline in alcoholic solution in the presence of sodium ethoxide at high temperature and pressure removed the acetyl group (14).

The condensation of aromatic aldehydes with 1,3-diacetylpyrrocoline in alkaline solution to give compounds of the type of XXXV has been carried out by Scholtz (81), who also obtained some monoarylidene derivatives; phenylacetaldehyde and *m*-hydroxybenzaldehyde failed to react (84). Similar derivatives have also been obtained from 1,3-diacetyl-7-methyl- and 1,3-diacetyl-5-phenylpyrrocolines (83) and 3-acetyl-2-methylpyrrocoline (11).



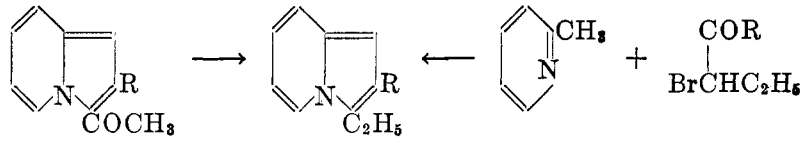
XXXV



XXXVI

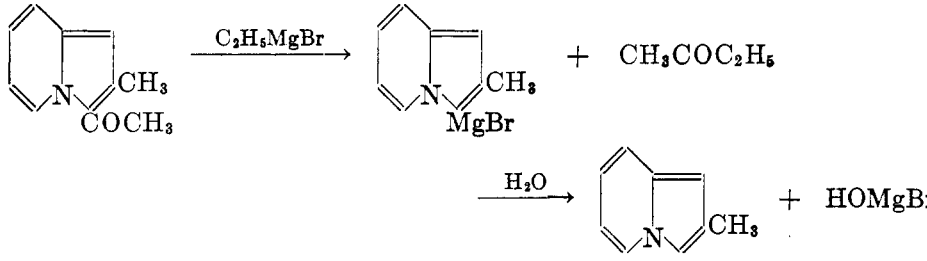
1,3-Diacetylpyrrocolines yield only mono derivatives with ketonic reagents (11, 19, 81, 83), a fact which led Scholtz to believe that "picolide" (1,3-diacetylpyrrocoline) did not contain a pyrrocoline nucleus and to ascribe to it the structure XXXVI (84). Chichibabin, however, prepared "picolide" by the stepwise acetylation of pyrrocoline (19), showing without a doubt that the pyrrocoline nucleus is indeed present in this compound.

Although 3-acetyl-2-methyl- and 3-acetyl-2-phenyl-pyrrocolines readily yield dinitrophenylhydrazones (11), none of the monoacetyl derivatives give rise to a phenylhydrazone or oxime under normal conditions except for the acetyl derivative of 7-methylpyrrocoline (83). From the lack of ketonic properties in these compounds Chichibabin assumed that the acetyl groups occupied the 3-position by analogy with the similar behavior of α-acetyl-*N*-alkylpyrroles. That this is so has been proved for the monoacetyl derivatives of 2-methyl- and 2-phenylpyrrocolines by reduction to their 3-ethyl derivatives and comparison with the compounds prepared by direct synthesis. Proof that the benzoylation of 2-phenylpyrrocoline also occurs in the 3-position has been established in a similar fashion (14). The reduction of the acyl groups in these compounds was effected by a modification of the Clemmensen method for 3-acetyl-2-methylpyrrocoline,

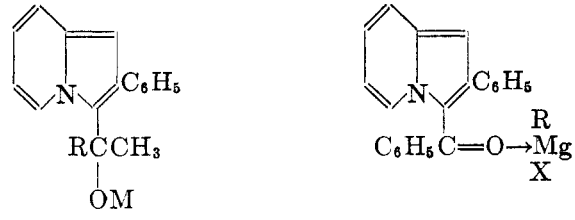


a mixture of the required 3-ethyl derivative and 2-methyl-3-α-hydroxyethylpyrrocoline being formed, and by Kon's modification (51) of the Kishner–Wolff method for 3-acetyl- and 3-benzoyl-2-phenylpyrrocolines (14).

Chichibabin and Stepanow (19) recorded that the action of ethylmagnesium bromide on 3-acetyl-2-methylpyrrocoline gave rise to 2-methyl-3-ethylpyrrocoline, the same compound apparently being formed by the action of amalgamated aluminum in moist ether. However, the compound obtained was later shown by Kondo and Osowa (55) to be 2-methylpyrrocoline itself, and since methyl ethyl ketone was detected the reaction was considered to have taken the following course:



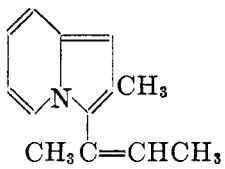
The present authors (8), working with 3-acetyl-2-phenylpyrrocoline, have recently shown that with a variety of organometallic compounds (RM) the reaction does not follow this course. The normal tertiary alcohol complex (XXXVIIa) is formed first, since it gives a negative result in the Gilman and Schultz test for carbon–metal linkages (47), and this breaks down to 2-phenylpyrrocoline and the methyl ketone ($RCOCH_3$) on hydrolysis. With 3-benzoyl-2-phenylpyrrocoline and methylmagnesium iodide it appears that a coördination compound of the type of XXXVIIb (46) is formed, since 3-benzoyl-2-phenylpyrrocoline was recovered on hydrolysis, but intramolecular rearrangement to the tertiary alcohol derivative occurred to some extent, for it was possible to isolate a small quantity of 2-phenylpyrrocoline and the ketone.



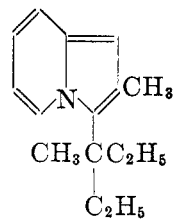
XXXVIIa XXXVIIb

By using an excess of ethylmagnesium bromide on 3-acetyl-2-methylpyrrocoline Kondo and Kokeguchi (53) obtained, besides 2-methylpyrrocoline, 2-methyl-

3-(2-but-2-enyl)pyrrocoline (XXXVIII) and 2-methyl-3-(α-methyl-α-ethylpropyl)pyrrocoline (XXXIX). The former compound was considered to arise by loss of magnesium hydroxybromide from the normal tertiary alcohol complex and the latter by the addition of a further molecule of the reagent to the double bond of XXXVIII.



XXXVIII

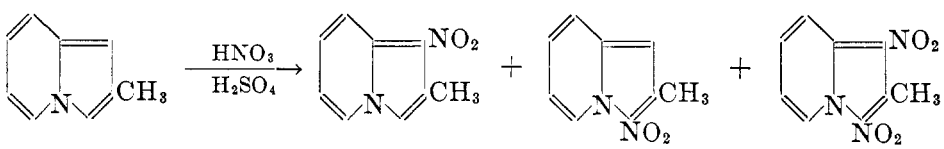


XXXIX

The action of Grignard reagents on diacylpyrrocolines was studied briefly by Scholtz and Fraude (84), who obtained monotertiary alcohols by the action of methyl- and phenyl-magnesium iodides on picolide.

VIII. NITRO DERIVATIVES

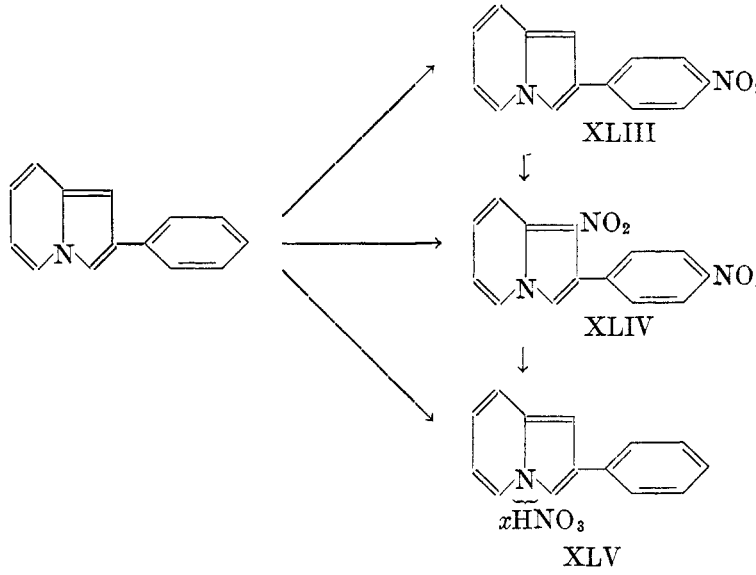
Although Scholtz (82) prepared a nitroacetyl- and a dinitro-pyrrocoline by the action of nitric acid on 1,3-diacetylpyrrocoline, he stated that pyrrocoline itself could not be nitrated because of its sensitivity to oxidizing agents. However, work with 2-methyl- and 2-phenyl-pyrrocolines has recently shown (13) that it is possible to effect the direct nitration of this ring system for, while the action of nitric acid on these compounds at moderate temperatures caused mainly oxidation, rapid reaction at higher temperatures gave the 1,3-dinitro bodies in small yield in both instances. Furthermore, in concentrated sulfuric acid at low temperatures nitration was found to proceed readily with but little decomposition. Under these conditions 2-methylpyrrocoline yields 1-nitro-2-methylpyrrocoline (XL) as the main product, together with very small quantities of the 3-nitro isomeride (XLI) and 1,3-dinitro-2-methylpyrrocoline (XLII).



XL XLI XLII

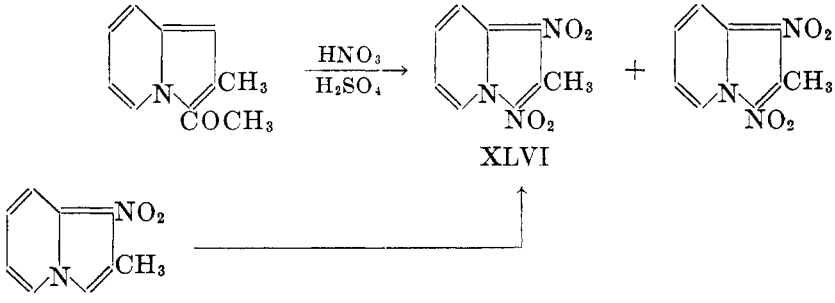
With 2-phenylpyrrocoline the benzene ring is attacked first to give 2-*p*-nitrophenylpyrrocoline (XLIII), a result which parallels the nitration of *N*-phenylpyrrole under similar conditions to yield *N*-*p*-nitrophenylpyrrole (31). The same compound is produced by nitration in phosphoric acid or by the action of sodium nitrate on a solution of the pyrrocoline in sulfuric acid. Further nitration of 2-*p*-nitrophenylpyrrocoline in sulfuric acid or dinitration of 2-phenylpyrrocoline in the same medium yields a dinitro body believed by analogy with the 2-methyl compound to be 1-nitro-2-*p*-nitrophenylpyrrocoline (XLIV), also

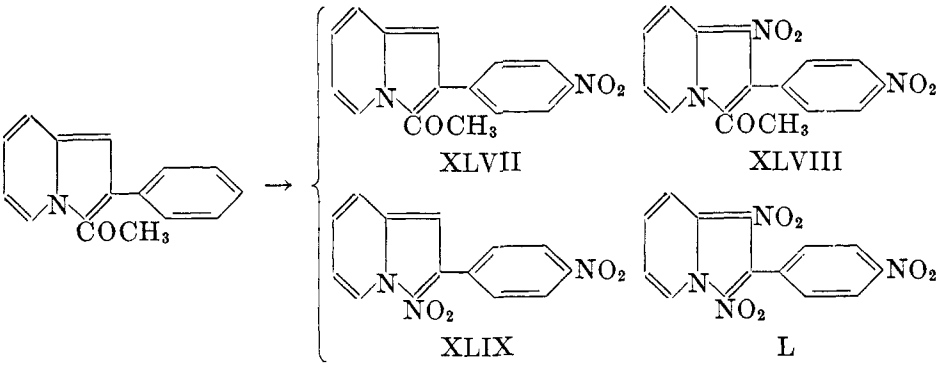
formed by the dehydration of 2-phenylpyrrocoline nitrate (XLV) with sulfuric acid.



Further nitration of 1-nitro-2-methylpyrrocoline in sulfuric acid is accompanied by extensive decomposition and in hot acetic acid leads only to a small yield of 1,3-dinitro derivative. 3-Nitro-2-methylpyrrocoline is readily converted to the dinitro compound under the latter conditions.

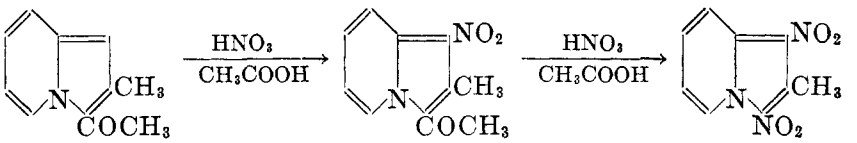
The nitration of the 3-acetyl derivatives of 2-methyl- and 2-phenyl-pyrrocolines in concentrated sulfuric acid at low temperatures also proceeds readily. 3-Acetyl-2-methylpyrrocoline gives rise to 1-nitro-3-acetyl-2-methylpyrrocoline (XLVI), accompanied by a small quantity of the 1,3-dinitro compound, while 3-acetyl-2-phenylpyrrocoline yields a mixture of 3-acetyl-2-*p*-nitrophenylpyrrocoline (XLVII), 1-nitro-3-acetyl-2-*p*-nitrophenylpyrrocoline (XLVIII), 3-nitro-2-*p*-nitrophenylpyrrocoline (XLIX), and 1,3-dinitro-2-*p*-nitrophenylpyrrocoline (L). Three of these compounds (XLVIII, XLIX, L) are light sensitive, the yellow crystalline solids rapidly turning green on exposure to air and light.





1-Nitro-2-methylpyrrocoline can be acetylated to the 3-acetyl derivative (XLVI); hence the position of the nitro group in this compound is established, but 1-nitro-2-*p*-nitrophenylpyrrocoline (XLIV) could not be acetylated to the 3-acetyl derivative (XLVIII) nor could this compound be deacetylated by acid hydrolysis. The structures of the former compound and of the suspected 3-nitro isomeride (XLIX) have thus not been completely established.

The preparation of a nitroacetyl- and a dinitro-pyrrocoline was carried out by Scholtz (82) by the action of 25 per cent nitric acid and concentrated nitric acid, respectively, on an acetic acid solution of 1,3-diacetylpyrrocoline. As the 1,3-diacetyl derivatives of 2-methyl- and 2-phenyl-pyrrocolines behave similarly to yield the 1-nitro-3-acetylpyrrocolines with 25 per cent acid and 1,3-dinitro compounds with concentrated acid (13), the compounds prepared by Scholtz would seem to be similarly substituted. The action of excess concentrated nitric acid either alone or in acetic acid solution on the monoacetyl derivatives of 2-methyl- and 2-phenyl-pyrrocolines also gives the 1,3-dinitro compounds, but attempts to effect mononitration under the conditions used by Scholtz for 1,3-diacetylpyrrocoline were unsuccessful. However, with 3-acetyl-2-methylpyrrocoline it is possible to prepare 1-nitro-3-acetyl-2-methylpyrrocoline, thus showing that in acetic acid solution the 1-position is substituted before the acetyl group is replaced:



The nitroacetyl derivatives of 2-methyl- and 2-phenyl-pyrrocolines have also been obtained from the corresponding 1-nitroso-3-acetylpyrrocolines by careful oxidation with perhydrol (13), and 3-nitro-2-methylpyrrocoline has been prepared in small yield from the 3-nitroso compound in the same way (12). By the action of concentrated nitric acid on these nitroso derivatives the 1,3-dinitropyrrocolines are obtained.

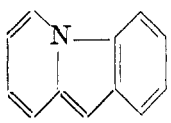
IX. NITROSO DERIVATIVES

The direct nitrosation of the pyrrocoline nucleus has been applied to 2-methyl- and 2-phenyl-pyrrocolines and their 3-acetyl derivatives and to 2-methyl-3-ethylpyrrocoline (12, 54) to yield the mononitroso compounds.

The 3-acetylpyrrocolines yield 1-nitroso derivatives, since on careful oxidation with perhydrol the corresponding 1-nitro-3-acetyl compounds are formed. Similarly, the derivative from 2-methylpyrrocoline has been shown to be the 3-nitroso body by its oxidation to 3-nitro-2-methylpyrrocoline. 3-Nitroso-2-phenylpyrrocoline cannot be converted to the nitro derivative in this way, but its structure has been ascertained by direct synthesis from ω-isonitrosophenacyl-α-picolinium chloride (12). The oxidation of the nitroso derivative from 2-methyl-3-ethylpyrrocoline to α-picolinic acid N-oxide confirms its structure as 1-nitroso-2-methyl-3-ethylpyrrocoline.

The acetyl groups could not be removed by acid hydrolysis from the above-mentioned compounds, nor could the 3-nitroso derivatives be acetylated.

The above nitrosopyrrocolines are green in color, but give yellow or red solutions in dilute acid, indicating that as cations they lose the true nitroso group (86). Further, both 3-nitroso-2-methyl- and 1-nitroso-2-methyl-3-ethyl-pyrrocolines are soluble in water to yield red solutions indicating that under these conditions also, they lose the true nitroso group. von Braun, Nelles, and May (16) record a similar phenomenon with the mononitroso derivative of benzo[*b*]-pyrrocoline (LI) and presumably, therefore, the nitroso group occupies the only free position in the five-membered ring of this compound. These compounds are not more soluble in alkali than they are in water.



LI

X. AMINO AND AZO DERIVATIVES

By the action of diazonium chlorides on pyrrocoline Scholtz and Fraude (84) obtained monoazo derivatives in which it was believed that the 3-position had been attacked. More recently Kondo and Nishizawa (54) have prepared 3-acetyl-2-methylpyrrocoline-1-azobenzene in a similar way and obtained 1-amino-3-acetyl-2-methylpyrrocoline by the catalytic reduction of the corresponding sodium azobenzenesulfonate. This same aminopyrrocoline was obtained by these workers by the catalytic reduction of 1-nitroso-3-acetyl-2-methylpyrrocoline and is the only known aminopyrrocoline. It is reported to be unstable in air.

Attempts to introduce an amino group into the pyrrocoline nucleus by reaction with sodium amide have been unsuccessful (10).

XI. CARBOXYLIC ACID DERIVATIVES

The preparation of carboxylic acid derivatives of pyrrocoline by the action of acetylenedicarboxylic esters on pyridine and other bases and the synthesis of

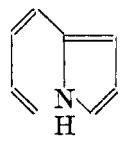
pyrrocoline-2-carboxylic acid by ring closure of the quaternary compound formed by the action of ethyl bromopyruvate on α-picoline have already been discussed in detail (Sections III, B and III, C).

The direct introduction of a carboxyl group into pyrrocoline itself was effected by Scholtz and Fraude (84) by reaction with phosgene and treatment of the first formed unstable acid chloride with alkali. Reaction with ammonium carbonate or sodium bicarbonate under pressure, a method effective with many simple pyrroles (21), was unsuccessful however, and attempts to convert 2-methylpyrrocoline into pyrrocoline-2-carboxylic acid by fusion with potassium hydroxide (9), effective with skatole and 2-methylindole (23), were also unavailing.

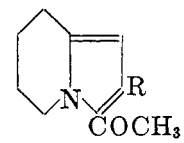
Condensation of 2-methylpyrrocoline with maleic anhydride yields a compound believed to be 2-methylpyrrocoline-1,3-disuccinic anhydride (52), as in the condensation with pyrrole to produce 2-methylpyrrole-5-succinic acid (35).

XII. REDUCTION

The reduction of the pyrrocoline nucleus was first attempted by Scholtz (81), who obtained a dihydro derivative on treatment of the parent base with sodium and alcohol. This compound, which gave a red color in the pine splint test but a colorless melt on fusion with oxalic acid, appeared to be a true pyrrole derivative, and Scholtz made the unlikely suggestion that it was α-butadienylpyrrole (LII), even though very energetic treatment with sodium and alcohol caused no further reduction. It seems more likely that the compound is a dihydropyrrocoline, the six-membered ring having been partially reduced, for tetrahydropyrrocolines have recently been obtained and behave similarly in the two color tests to the compound prepared by Scholtz. It seems reasonable to assume that the five-membered ring in them has not been reduced, since the positive pine splint test is indicative of the presence of a pyrrole ring (14).



LII

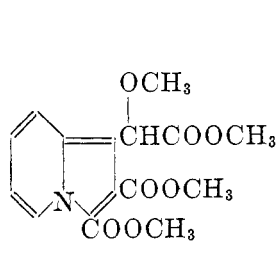


LIII

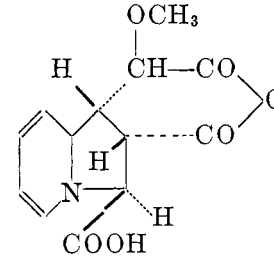
Thus, the hydrogenation of 3-acetyl-2-methylpyrrocoline at room temperature and pressure in the presence of platinum oxide as catalyst yields 3-acetyl-2-methyl-5,6,7,8-tetrahydropyrrocoline (LIII, R = CH_3) as the main product and similar treatment of the corresponding 2-phenyl derivative using Raney nickel gives the analogous compound (LIII, R = C_6H_5). The acetyl group in the last compound was readily removed by acid hydrolysis to yield 2-phenyl-5,6,7,8-tetrahydropyrrocoline as an unstable solid which could easily be reacetylated to the original compound (LIII, R = C_6H_5); the facility of the hydrolysis and reacetylation is further evidence for the ascribed structures. The reduction of 2-phenyl-3-ethylpyrrocoline in the presence of Raney nickel similarly yielded a tetrahydro derivative which gave a positive result in the pine splint test and was therefore considered to be 2-phenyl-3-ethyl-5,6,7,8-tetrahydropyrrocoline. This compound was also obtained, together with 2-phenyl-3-ethyloctahydropyrroco-

line, by the reduction, under more vigorous conditions, of 3-acetyl-2-phenylpyrrocoline using copper chromite as catalyst.

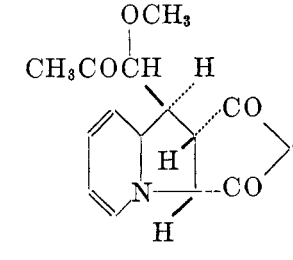
Although the above work indicates the preferential reduction of the six-membered ring of the pyrrocoline nucleus, Diels and Meyer (39) obtained evidence that in the reduction of methyl 1-methoxycarbomethoxymethylpyrrocoline-2,3-dicarboxylate (LIV), using platinum oxide as catalyst, the five-membered ring was reduced. Thus, on hydrogenation a tetrahydro compound was isolated which, after hydrolysis to the corresponding tricarboxylic acid and treatment with acetic anhydride, yielded an anhydride which differed from that obtained when the ester was hydrolyzed first and then hydrogenated. The composition of the latter compound indicated that it was a ketodicarboxylic acid anhydride, and it was conjectured therefore that the five-membered ring had been reduced in both instances, the formation of different anhydrides being due to *cis*- and *trans*-isomerism. The respective structures LV and LVI were suggested for these compounds.



LIV



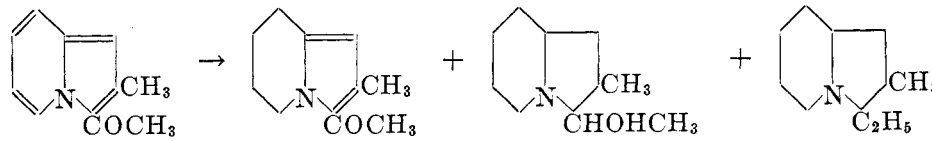
LV



LVI

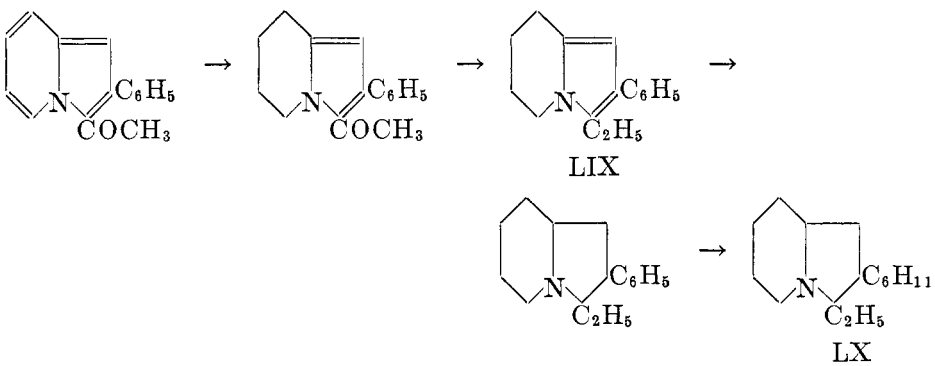
The reduction of methyl 1-nitropyrrocoline-2,3-dicarboxylate to an aminotetrahydropyrrocolinedicarboxylic ester was likewise considered by the above workers to involve the five-membered ring.

The complete reduction of the pyrrocoline nucleus has been reported by several workers. Pyrrocoline and 2-methyl-, 3-methyl-, 2,3-dimethyl-, and 2-methyl-3-ethyl-pyrrocolines have all successfully been converted to the octahydro compounds by catalytic reduction, using platinum oxide (14, 32, 34, 42, 73), and Ochiai and Kobayashi (72) obtained a mixture of 2-methyl-3-ethyl- (LVII) and 2-methyl-3-α-hydroxyethyl-octahydropyrrocolines (LVIII) by the hydrogenation of 3-acetyl-2-methylpyrrocoline under the same conditions. Borrows, Holland, and Kenyon (14), however, obtained only small quantities of these two compounds in this reduction, the main product being the tetrahydroacetyl derivative (LIII, R = CH_3) referred to above; complete reduction was best effected by using Raney nickel at high temperature and pressure.



LVIII LVII

3-Acetyl-2-phenylpyrrocoline similarly was readily converted to 2-phenyl-3-ethyloctahydropyrrocoline in this way, only small quantities of 2-phenyl-3-ethyl-5,6,7,8-tetrahydropyrrocoline (LIX) being produced. The formation of larger proportions of this last compound when using copper chromite as catalyst under comparable conditions is in agreement with the known tendency of this catalyst to effect the reduction of a carbonyl group rather than a C=C bond. Under more drastic conditions it was found possible to reduce 3-acetyl-2-phenylpyrrocoline to 2-cyclohexyl-3-ethyloctahydropyrrocoline (LX), using Raney nickel as catalyst, and it would appear that the stages in this reduction are as follows:



These results show some analogy with the catalytic reduction of substituted pyrroles, for, while it is well known that pyrrole is less susceptible to catalytic hydrogenation than is benzene or pyridine (1), Signaigo and Adkins (85) showed that its *N*-carbethoxy and *N*-phenyl derivatives could be reduced at much lower temperatures using Raney nickel as catalyst, *N*-phenylpyrrolidine being the major product in the latter instance. Rainey and Adkins (79), however, found later that *N*-methyl- and *N*-ethyl-pyrroles were nearly as resistant as pyrrole itself. It is not surprising that the six-membered ring, which has a pyridone structure, should be reduced before the pyrrole nucleus. The resulting tetrahydro compounds, which are, in effect, *N*-alkylated pyrroles, are presumably less resistant than is the benzene ring; hence in the phenyl derivatives the five-membered ring is preferentially reduced.

In connection with the elucidation of the structure of 2-phenyl-3-ethyloctahydropyrrocoline the ultraviolet absorption spectra of a few pyrrocoline derivatives have been examined. Whereas 2-phenyl- and 2-phenyl-3-ethyl-pyrrocolines exhibited in alcohol characteristic powerful absorptions, $\lambda_{max.}$ = 2570 Å., ϵ = 45,700 and $\lambda_{max.}$ = 2550 Å., ϵ = 38,000, respectively, 3-acetyl-2-phenylpyrrocoline has a spectrum consisting of three chromophores, $\lambda_{max.}$ = 2330 Å., ϵ = 29,000; $\lambda_{max.}$ = 2640 Å., ϵ = 24,000; $\lambda_{max.}$ = 3650 Å., ϵ = 15,000; $\lambda_{min.}$ = 2510 Å., ϵ = 20,800; $\lambda_{min.}$ = 3120 Å., ϵ = 4000 (10). The 5,6,7,8-tetrahydro derivative of the latter, however, possessed one maximum, $\lambda_{max.}$ = 3030 Å., ϵ = 16,700; $\lambda_{min.}$ = 2530 Å.; ϵ = 5900, and the corresponding 2-phenyl-3-ethyl-5,6,7,8-tetrahydropyrrocoline $\lambda_{max.}$ = 2780 Å., ϵ = 7700; $\lambda_{min.}$ = 2660 Å., ϵ = 6960 and inflection = 2300 Å., ϵ = 11,000 (10).

Scholtz has recorded that the pyrrocoline ring is resistant to the reducing action of zinc and hydrochloric acid (81) and that hydrogenation using palladized charcoal as catalyst proceeds slowly (10).

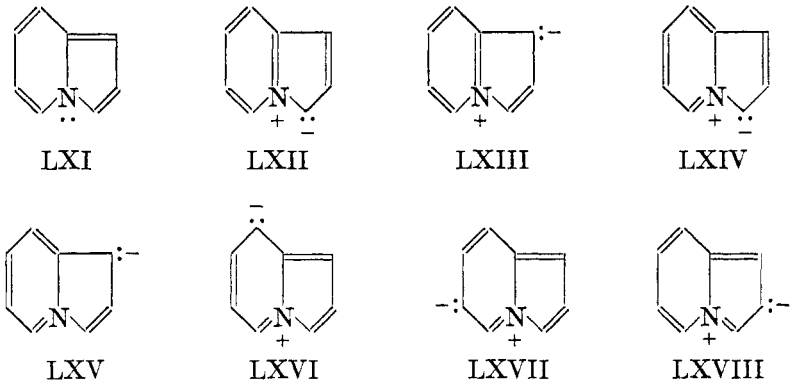
XIII. OXIDATION AND DEGRADATION

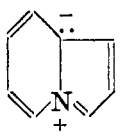
Although Scholtz (81) was unable to isolate α-picolinic acid by permanganate oxidation of 1,3-diacetylpyrrocoline, Diels and Alder (34) found that trimethyl pyrrocoline-1,2,3-tricarboxylate could be oxidized with a mixture of perhydrol and acetic acid to α-picolinic acid *N*-oxide. This reaction was used later by Diels and Meyer (39) to show the absence of a nitro group in the six-membered ring of dimethyl 1-nitropyrrocoline-2,3-dicarboxylate and has been successfully used subsequently by Borrows, Holland, and Kenyon (11–14) in orientation studies on derivatives of 2-methyl- and 2-phenyl-pyrrocolines. Diels and Meyer also showed that oxidation with nitric acid yields α-picolinic acid by its action on 1-methoxycarboxymethylpyrrocoline-2,3-carboxylic acid.

The complete reduction of a pyrrocoline to its octahydro derivative followed by degradation with cyanogen bromide has also proved useful in establishing structures in this field, and was employed by Diels and Alder (34), Ochiai and Tsuda (73), and Diels and Schrum (42) on pyrrocoline and its alkyl derivatives. It would appear that degradation with cyanogen bromide results in the selective cleavage of the five-membered ring of the octahydropyrrocolines to yield alkylpiperidines and not alkylpyrrolidines, but Diels and Schrum obtained evidence that with 2-methyloctahydropyrrocoline cleavage of the six-membered ring took place to some extent.

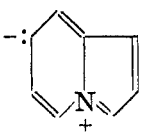
IV. CONCLUSIONS ON THE CHEMISTRY OF THE PYRROCOLINES

The application of the theory of resonance to explain the stability of pyrrole and similar heterocyclic compounds (66) has been extended to the pyrrocoline ring system by Wilson (89) (*cf.* also Ochiai (74)), and there can be little doubt that its aromatic character can be attributed to the unshared electrons on the nitrogen atom resonating among all the atoms of the ring, the true structure being a resonance hybrid of the following forms:

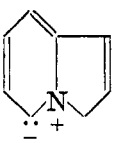




LXIX

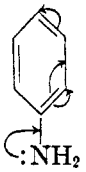


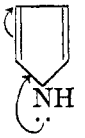
LXX

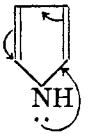


LXXI

Pyrrocoline, like pyrrole and indole, is much more reactive towards the usual cationoid reagents than is benzene, which again can be attributed to the presence of unshared electrons on the nitrogen atom. In pyrrole Robinson (80) has pointed out that the β-positions are analogous to the ortho positions of aniline or phenol, while the α-positions are analogous to the para positions.







In the pyrrocoline nucleus similar activation of all the positions in the two rings by the lone pair of electrons apparently does not occur, since the bulk of the evidence indicates that only the five-membered ring is attacked by electrophilic reagents. This can be explained by the reasoning used to account for the chemical reactivity of naphthalene (45), for examination of the above electronic structures for pyrrocoline shows that four forms (LXII, LXIII, LXIV, LXV) allow of an unshared pair of electrons on the 1- and 3-positions, while for each of the other positions of these electrons only one form can contribute. Thus the five-membered ring, and in particular the 1- and 3-positions, will be polarized by the attacking group and substitution will occur there. An alternative explanation is that in the forms LXII, LXIII, LXIV, and LXV resonance of the Kekulé type can take place in the six-membered ring without decreasing the number of double bonds in the five-membered ring, and hence these forms make the greatest contribution to the resonance hybrid structure. This view is in contrast to that put forward by Wilson, who stated that the Kekulé type of resonance could not occur in the pyrrocoline nucleus. It is noteworthy that similar considerations for the indole nucleus show the β-position to be the most reactive, a result which is in agreement with the general reactions of this ring system.

That the 1- and 3-positions are indeed reactive has frequently been established and the ready loss by acid hydrolysis of the carboxyl groups in the 1- and 3-positions but not in the 2-position of pyrrocoline-1,2,3-tricarboxylic acid affords further evidence of an increased electron density at the 1- and 3-positions by analogy with the similar ready decarboxylation of *o*- and *p*-hydroxybenzoic acids which Fieser and Fieser (44) have explained by the tendency of the hydroxyl group to increase the electron density at the carboxylated positions.

On calculation of the π-electron densities and bond orders in pyrrocoline Longuet-Higgins and Coulson (64a) found that position 3 had a much higher

electron density than position 1, the latter being higher than for the 2-position in pyrrole. They anticipated therefore that the molecule would be readily attacked by cationoid (electrophilic) reagents first at position 3 and then at position 1, and if both were blocked, at positions 2 and 5. Their predictions are therefore verified by the chemistry reviewed herein.

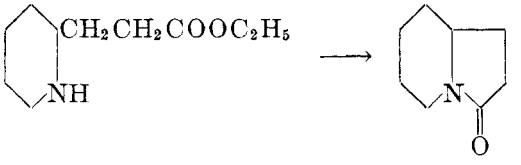
It would appear then that, while the chemical reactivity of pyrrocoline is, in general, similar to that of pyrrole and of indole, the position of ingoing substituents cannot be arbitrarily determined by analogy with these compounds. Thus the supposition made by Scholtz that aldehydes and ketones and similar compounds react with pyrrocoline at the 1- and 2-positions (the two β-positions) because pyrrole and indole react in this way is probably untrue, reaction occurring at the 1- and 3-positions. The formation of a dimethylpyrrocoline rather than a trimethylpyrrocoline by reaction with methyl iodide can be explained in this way, as can the formation of a diacetyl- rather than a triacetyl-pyrrocoline in Scholtz's "picolide" synthesis. On the other hand, it would seem that comparison of the 3-position of the pyrrocoline nucleus with the α-position of pyrrole is generally sound and has, in fact, been established in some instances.

Other differences between pyrrocoline and pyrrole and indole also become apparent from the above review. For example, the ready nitration of the pyrrocoline nucleus and the formation of true nitroso derivatives by the direct action of nitrous acid are rarely successful in the other ring systems.

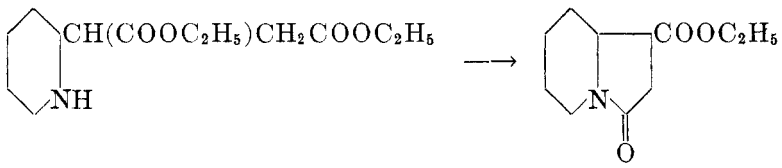
XV. OCTAHYDROPYRROCOLINES AND OTHER REDUCED FORMS OF PYRROCOLINES

A. Octahydropyrrocolines

One of the six conicëines obtained in various ways from the hemlock alkaloids is *l*-δ-coniciëne, an optically active (levorotatory) tertiary base arising from the action of concentrated sulfuric acid at 130°C. on *d*-*N*-bromoconiine (61). The compound was characterized in 1890 by Lellmann, who ascribed to it an octahydropyrrocoline structure. This formulation was confirmed by Loffler *et al.* (63, 64), who showed the inactive base, δ-conicëine, prepared from *dl*-coniine, to be identical in all respects with octahydropyrrocoline, which they synthesized by the following methods: In addition to the preparation of octahydropyrrocoline (δ-conicëine, piperolidine) from *N*-bromo-*dl*-coniine, they prepared the compound by the action of phosphorus pentoxide or a mixture of sulfuric and acetic acids on 2-γ-hydroxypropylpiperidine, by the action of hydriodic acid and phosphorus to yield iodoconiine (2-γ-iodopropylpiperidine), which underwent ring closure on treatment with alkali, and by reduction with sodium and alcohol of 3-ketoöctahydropyrrocoline (piperolidone) (II). The latter was obtained by distillation of β-piperidylpropionic acid, a ring closure which Clemo and Ramage (36) preferred to effect on the corresponding ethyl ester (I).



I II

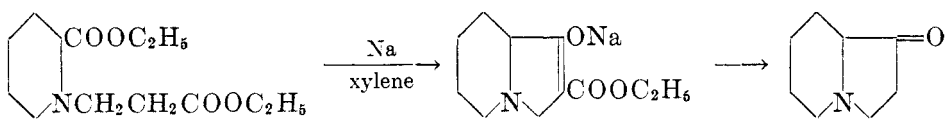


III IV

The method has been extended (27) to the preparation of the 1-carbethoxy-3-keto derivative (IV) by distillation of III.

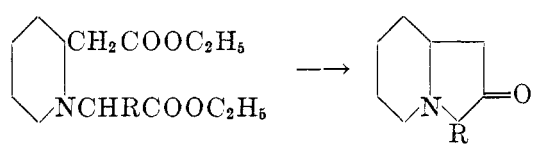
Beets has reported that reduction of β-(2-pyridyl)propionaldehyde diethylacetal in dilute acetic acid solution with platinum as catalyst yielded octahydropyrrocoline rather than the piperidylaldehyde produced in concentrated solution (6); the pyrrocoline picrate was obtained also by reduction in hydrochloric acid solution containing picric acid (5). On the other hand, reduction of ethyl β-(2-piperidyl)acrylate with Raney nickel as catalyst yields 3-ketoöctahydropyrrocoline (88).

In connection with the structure of lupinane and other alkaloids Clemo and his colleagues have synthesized several keto derivatives of octahydropyrrocoline. Thus, the 1-keto compound (VI) was obtained (24, 29) by the Dieckmann condensation of the requisite piperidyl ester (V) followed by hydrolysis and decarboxylation.

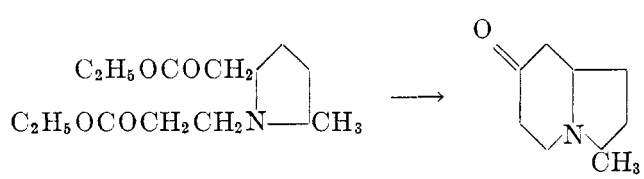


V VI

Similarly (24, 26) from VII (R = H or CH_3) arose the 2-keto derivatives VIII (R = H or CH_3).



VII VIII



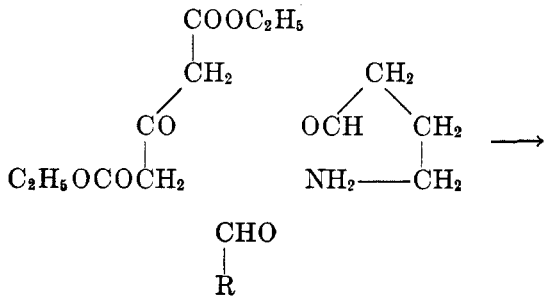
IX X

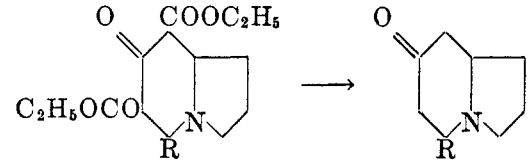
The condensation was successfully extended (25) to the pyrrolidine ester (IX) to give 3-methyl-7-ketoöctahydropyrrocoline (X).

Prelog and Metzler synthesized 6-ethyloctahydropyrrocoline by one of the methods employed by Loffler *et al.* (*vide supra*) for preparing the parent com-

pound, involving alkaline ring closure of 2-(γ-bromopropyl)-5-ethylpiperidine (77).

An elegant synthesis devised by Lions and Willison (62) produces 5-alkyl- and 5-aryl-7-ketoöctahydropyrrocolines in excellent yield. The method involves the simultaneous condensation of an aldehyde, acetonedicarboxylic ester, and γ-aminobutyraldehyde to give unstable dicarboxylic esters (XI) from which the stable keto derivatives (XII) may be readily obtained. The yield of XI for aliphatic aldehydes is of the order of 90–95 per cent.





R = H, CH_3, *sec*-C_4H_9, C_6H_5 XI XII

It will be noted that most of the syntheses yield keto derivatives. Of these, Clemo and Metcalfe (24) have employed the 1- and 2-ketoöctahydropyrrocolines for the preparation of alkyl derivatives, by reacting with methyl- or ethyl-magnesium bromide to yield the secondary carbinols which on dehydration by phosphorus pentachloride or potassium hydrogen sulfate gave hexahydro derivatives. The latter can then be reduced to give 1- or 2-alkyloctahydropyrrocolines. Whereas Clemmensen reduction of 1-ketoöctahydropyrrocoline (VI) (29) and the 7-keto derivatives (XIV) (62) proceeds normally, those of 2-keto and 1-methyl-2-keto derivatives yield secondary carbinols; complete reduction is however effected by the Kishner–Wolff method (24, 26). The reduction of the 3-keto derivative has been effected catalytically using copper chromite as catalyst (88).

Clemo and Ramage (29) report the isolation of two forms of octahydropyrrocoline, as picrates, on Clemmensen reduction of VI. Contrary to the balance of published opinion that the three nitrogen valencies in ring systems are coplanar, Clemo *et al.* (30) considered the two forms of the closely related octahydropyridocoline to be *cis-trans* isomers of the decalin type, owing to the non-planarity of the tervalent nitrogen, but Prelog and Seiwerth (78) have recently shown one of the two forms to be identical with bicyclo[0.3.5]aza-1-decane. The derivation of the two forms of octahydropyrrocoline therefore is thus still obscure.

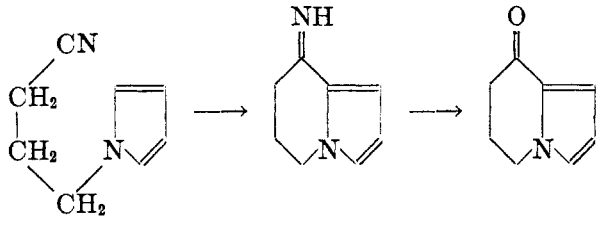
Numerous pyrrocolines have been reduced catalytically to the corresponding octahydro forms, as summarized in Section XII of this review.

Ochiai and coworkers (71) have shown that treatment of 2-methyloctahydropyrrocoline can be converted to the *N*-oxide by treatment with perhydrol.

Hirosawa has reported on the minimal lethal doses for 2-methyl- and 2,3-dimethyl-octahydropyrrocolines, and 1-acetyl-2-methyl-3-aminopyrrocoline which were said to cause convulsions and motor and respiratory paralysis (48).

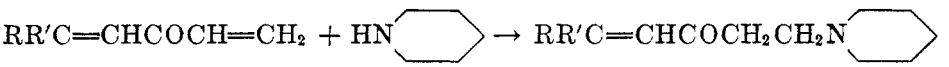
B. Partially reduced pyrrocolines

Selective catalytic hydrogenation of pyrrocolines would appear to be the most suitable method for preparing 5,6,7,8-tetrahydro derivatives (14). 8-Keto-5,6,7,8-tetrahydropyrrocoline is available by ring closure of γ-1-pyrrylbutyronitrile (XIII) to yield an imine hydrochloride (XIV) from which the keto compound (XV) was isolated via the semicarbazone (28).

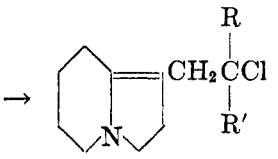


XIII XIV XV

Nazarov and Zaretskaya (67) have reported the preparation of chloro derivatives (XVII) of hexahydropyrrocolines by addition of piperidine to divinyl ketones (XVI), followed by ring closure by treatment with hydrogen chloride gas.



XVI



XVII

R = R' = C_2H_5 and R = CH_3, R' = C_3H_7

Other hexahydro derivatives are available by the method of Clemo and Metcalfe (24) involving dehydration of secondary carbinols resulting from the action of Grignard reagents on 1- and 2-ketoöctahydropyrrocolines.

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