## 236. *The Chemistry of the Pyrrocolines. Part I. 2-Methyl- and 2-Phenyl-pyrrocoline.*

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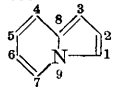
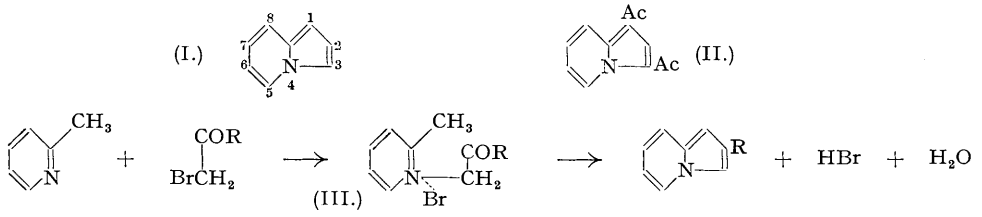
A number of derivatives of 2-methyl- and 2-phenyl-pyrrocoline has been prepared and studied.

In view of the increasing interest being shown in the chemistry of heterocyclic compounds, especially those containing nitrogen, it is perhaps surprising that little attention has been paid to the pyrrocoline ring system (I).* Scholtz [*Ber.*, 1912, **45**, 734; *Archiv Pharm.*, 1913, **251**, 666; (with Fraude), *Ber.*, 1912, **45**, 1718;

* Scholtz called this base " pyrrocoline," but later used the name " pyrindole " as suggested by Angeli (*Ber.*, 1890, **23**, 1795, 2154; *Gazzetta*, 1890, **20**, 761). Tschitschibabin and later German and Japanese workers have adopted the name " indolizine," with the following numbering : 

1913, **46**, 1069] discovered pyrrocoline during an investigation of the action of acetic anhydride on α-picoline at high temperatures, the initial compound obtained, $C_{12}H_{11}O_2N$ (II), yielding pyrrocoline after hydrolysis with hydrochloric acid. The synthesis was of limited application. Tschitschibabin [*Ber.*, 1927, **60**, 1607; (with Stepanow), 1929, **62**, 1068; 1930, **63**, 470] introduced a general method for the synthesis of 2-substituted pyrrocolines by allowing α-halogenated ketones to react with α-picoline, the resulting quaternary compounds (III) being converted into 2-substituted pyrrocolines by heating with an aqueous solution of sodium hydrogen




carbonate. Diels and his collaborators found that the pyridocoline (quinolizine) derivatives obtained by the action of acetylenedicarboxylic esters on pyridine and similar bases could readily be broken down to compounds of the pyrrocoline series (Diels and Schrum, *Annalen*, 1937, **530**, 68, and earlier papers) and Brand and Reuter (*Ber.*, 1939, **72**, 1669) isolated the parent base in small yield from the product of the reduction of 2-(γγγ-trichloro-β-hydroxypropyl)pyridine with zinc and sulphuric acid. Finally, Wilson (*J.*, 1945, 63) has recently reported pyrrocoline as one of the by-products in the catalytic conversion furan into pyrrole.

The initial product (II) of reaction between α-picoline and acetic anhydride was not thought by Scholtz to possess a pyrrocoline nucleus, but Tschitschibabin showed that it was 1 : 3-diacetylpyrrocoline, and prepared it by the stepwise acetylation of pyrrocoline itself. It is clear that Scholtz failed to assign the correct structure to (II) because ketonic reagents reacted with only one carbonyl group. Tschitschibabin pointed out that this lack of reactivity was not inconsistent with a diacetylpyrrocoline structure, since several α-acetyl-*N*-alkylpyrroles were known which behaved similarly. In support of this he found that neither the monoacetylpyrrocoline prepared by Scholtz nor the monoacetyl derivative of 2-methylpyrrocoline reacted with phenylhydrazine. Further acetylation of these two compounds gave 1 : 3-diacetyl-pyrrocoline and -2-methylpyrrocoline, respectively, both of which gave monophenylhydrazones. Scholtz did not report the failure of his compound to react with phenylhydrazine, but it is noteworthy that he found that the monoacetyl derivative of 7-methylpyrrocoline (from αγ-lutidine and acetic anhydride) readily formed a phenylhydrazone at room temperature.

Working with the readily obtainable 2-methyl- and 2-phenyl-pyrrocolines, we have found that, although their monoacetyl derivatives do not give phenylhydrazones under the usual conditions, yet 2 : 4-*dinitrophenylhydrazones* are readily formed at room temperature. The corresponding diacetyl compounds also give *monodinitrophenylhydrazones*, probably owing to the low solubility of these derivatives.

The 2-methylpyrrocoline used for this work was prepared by the method of Tschitschibabin and Stepanow but in rather lower yield. The reaction between α-picoline and chloroacetone was also carried out on the small scale in a variety of solvents, including carbon tetrachloride, acetone, alcohol, water, and acetic acid, but the yields were not improved. We have confirmed that the m. p. of 2-methylpyrrocoline is 59·5°, as found by Kondo and Osawa (*J. Pharm. Soc. Japan*, 1936, **56**, 73; *Chem. Abs.*, 1938, **32**, 5837), and not 68° as given by Tschitschibabin. The preparation of 2-phenylpyrrocoline, which Tschitschibabin carried out on the small scale, had to be effected in alcoholic solution, as the reaction was strongly exothermic and led to much decomposition when the reactants were used undiluted.

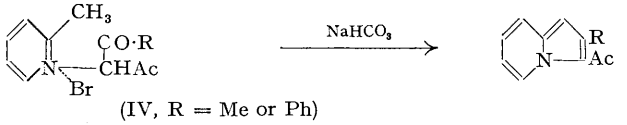
The *monoacetyl* derivative of 2-phenylpyrrocoline, not previously described, was prepared in good yield by Scholtz's method. It is a low-melting solid (m. p. 64°) rapidly hydrolysed to 2-phenylpyrrocoline by mineral acids. Solution in concentrated hydrochloric acid at room temperature, followed by dilution with water, is sufficient to remove the acetyl group, and even heating in 50% aqueous acetic acid causes slow hydrolysis. The 2-methyl analogue is rather more resistant to hydrolysis, complete deacetylation occurring after 2½ minutes' heating at 100° in dilute hydrochloric acid.

Attempts to prepare the acetyl derivative of 2-phenylpyrrocoline by heating with acetyl chloride or bromide were unsuccessful. This lack of reactivity is surprising in view of the ease with which carbonyl chloride and benzoyl chloride react with pyrrocoline itself, and especially so since 2-phenylpyrrocoline also reacts readily with benzoyl chloride to produce a *monobenzoyl* derivative. An unstable hydrochloride, believed to be 2-*phenylpyrrocoline hydrochloride*, is also formed during the reaction, but no better yields were obtained when the reaction was carried out in the presence of pyridine. This same benzoyl derivative could also be prepared by fusing the pyrrocoline with benzoic anhydride and sodium benzoate : it did not form a 2 : 4-dinitrophenylhydrazone. Ochiai (*J. Pharm. Soc. Japan*, 1940, **60**, 164; *Chem. Abs.*, 1940, **34**, 5449) has recently reported that acetyl chloride reacts with 2-methylpyrrocoline only with difficulty, even in the presence of a large excess of aluminium chloride, to give a very small yield of 1 : 3-diacetyl-2-methylpyrrocoline. He found, on the other hand, that this compound was readily formed when the monoacetyl derivative of 2-methylpyrrocoline, as prepared by Tschitschibabin, was allowed to react in tetrachloroethane solution under the same conditions. We have repeated this work on the small scale (2 g.) but could only isolate unchanged starting material from the

resulting dark gum. Since this diacetyl compound is readily prepared in fair yield by the action of acetic anhydride on the monoacetyl derivative at high temperature, the reaction with acetyl chloride was not further examined. Improvements in Tschitschibabin's method leading to a better yield (48% compared with 31%) and greater ease of isolation are described in the experimental section. 1 : 3-Diacetyl-2-methylpyrrocoline is somewhat more resistant to hydrolysis than the monoacetyl compound.

The preparation of 1 : 3-*diacetyl-2-phenylpyrrocoline* by heating the monoacetyl compound at high temperatures with acetic anhydride was less successful (13% yield) and the Friedel–Crafts reaction was therefore examined. The required product was obtained in good yield (82%) when the reaction was carried out essentially according to Ochiai's procedure for the 2-methyl analogue. This diacetyl compound is completely hydrolysed to 2-phenylpyrrocoline by heating an acid solution on the steam-bath for 2 minutes. 2-Phenylpyrrocoline itself was also found to react well with acetyl chloride in carbon disulphide solution, provided a large excess (3 mols.) of aluminium chloride were present. There was no reaction when less catalyst (1·5 mols.) was used, even on heating on the steam-bath. Besides unchanged 2-phenylpyrrocoline, and 1 : 3-diacetyl-2-phenylpyrrocoline, a monoacetyl compound, m. p. 240—241°, was also isolated from the reaction mixture. This on oxidation with perhydrol yielded α-picolinic acid *N*-oxide and *p*-acetylbenzoic acid, thus establishing with some certainty that this compound was 2-(p-*acetylphenyl*)*pyrrocoline*. The use of perhydrol to open the pyrrocoline nucleus was first carried out by Diels and Meyer (*Annalen*, **1934**, **513**, 129), and we have found it of value.

Both Scholtz and Tschitschibabin were of the opinion that the acetyl group entered the 3-position of the pyrrocoline nucleus in the monoacetyl derivatives, by analogy with the acetyl derivatives of simple pyrroles. That these groups in both the mono- and the di-acetyl derivatives of 2-methyl- and 2-phenyl-pyrrocoline are in the 5-membered ring appears very probable, since on oxidation with perhydrol α-picolinic acid *N*-oxide is formed (together with benzoic acid in the 2-phenyl derivatives). However, the importance of establishing beyond all reasonable doubt the position of the acetyl group in the monoacetyl compounds became apparent during the course of this work (see following papers) and we had hoped to effect this by the reaction of α-picoline with bromo- or chloro-acetylacetone and bromobenzoylacetone followed by ring closure of the resulting quaternary compounds with sodium hydrogen carbonate :

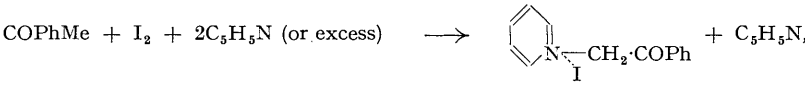



(IV, R = Me or Ph)

From the work of Kröhnke and Timmler (*Ber.*, **1936**, **69**, 614) with dibenzoylmethylpyridinium bromide it was clear that the acetyl group in these quaternary compounds would be very labile. It was expected that some of the required products would be obtained with the very mild alkali used, but with these halogenated diketones only 2-methyl- and 2-phenyl-pyrrocoline, respectively, in small yield could be isolated. The reaction of α-picoline with chloroacetylacetone was studied in some detail, and it would appear from our experiments that the required quaternary salt (as IV, R = Me) is formed in the initial reaction (albeit in very low yield) but that even on warming an aqueous solution in the presence of sodium hydrogen carbonate one acetyl group is lost. In the presence of magnesium oxide and sodium acetate there was no apparent reaction, even on prolonged heating, but in that of piperidine, 2-methylpyrrocoline was obtained even at room temperature. From the weights of the *chloroplatinates* of the quaternary compounds first formed in these reactions, it appeared that ring closure and loss of the acetyl group were practically quantitative. Attempts to prepare the ethyl esters of 2-methyl- and 2-phenyl-pyrrocoline-3-carboxylic acid from α-picoline and α-chloroacetoacetic ester and α-bromobenzoylacetic ester, respectively, in the hope that the required 3-acetyl derivatives might be synthesised in a Claisen condensation, for example, likewise led only to small yields of the parent pyrrocolines. The position of the acetyl group in these compounds was finally established by reduction, and the work carried out in this connection is reported separately (see Part IV).

The recorded preparation by Tschitschibabin of non-crystallisable benzpyrrocolines by the reaction of quinaldine with α-halogenated ketones seemed worthy of further study, and we examined the action of chloroacetone and of phenacyl bromide on this base. From the initial crystalline reaction products only quinaldine hydrochloride and bromide respectively could be isolated, however.

King (*J. Amer. Chem. Soc.*, **1944**, **66**, 894) has described a reaction between iodine and a solution of a ketone such as acetophenone in excess of pyridine to give good yields β-ketoalkylpryidinium iodides :




By using acetone and acetophenone in excess of α-picoline we adapted this reaction to the preparation of 2-methyl- and 2-phenyl-pyrrocoline, but obtained only small yields. The reaction may be useful when the required halogeno-ketone is difficult to prepare, but we have not fully investigated its potentialities.

## Experimental.

In all experiments, commercial α-picoline, dried over sodium hydroxide, b. p. 127·5—129·5°/763 mm., was employed. All m. p.'s are uncorrected.

2-*Methylpyrrocoline*.—The method described by Tschitschibabin and Stepanow (*loc. cit.*, 1929) for the preparation of this compound has been somewhat modified. A mixture of α-picoline (180 g.) and chloroacetone (b. p. 118·5—120·5°/760 mm.; Cl, 39·7% ≡ 93% of monochloroacetone) (180 g.) was heated on a steam-bath. After 10—15 mins. a vigorous reaction set in and the mixture was removed from the bath until this had subsided (external cooling was sometimes necessary). After 3 hours' heating the resulting dark brown syrup was cooled, diluted with water (2 l.), and the aqueous solution extracted several times with chloroform to remove dark gummy material. Solid sodium hydrogen carbonate was then added until effervescence had ceased, and the liberated α-picoline was extracted with ether. To the final aqueous solution, sodium hydrogen carbonate (300 g.) was added, and the mixture heated on the steam-bath for 1 hr. The 2-methylpyrrocoline was removed in a current of steam, dissolved in ether, the solution dried ($Na_2SO_4$), and the solvent removed (125 g., 49%), m. p. 57—59°.

The cream-coloured solid was sufficiently pure for most purposes, but when required completely pure it was sublimed. (We confirm Tschitschibabin's observations that sublimation is much more effective than recrystallisation or distillation in a vacuum.) In a large sublimation apparatus at 12 mm. pressure with a bath temperature rising to 80°, we have purified 50 g. at a time, in approximately 10 hours; m. p. 59·5°, b. p. 100°/12 mm.

N-*Acetonyl-α-picolinium Chloroplatinate* (as III, R = Me).—A portion of the aqueous solution, after removal of tarry by-products in the above preparation, was treated with sodium hydrogen carbonate until effervescence ceased, and the mixture warmed to about 40° to complete the liberation of α-picoline, which was then thoroughly extracted with ether. The brown aqueous layer was made slightly acid with hydrochloric acid and treated with charcoal several times at room temperature until a pale straw-coloured solution resulted. Addition of an acid solution of chloroplatinic acid precipitated the chloroplatinate as a buff-coloured powder, m. p. 205° (decomp.) after drying at 100° [Tschitschibabin, *loc. cit.*, gives m. p. 202° (decomp.)] (Found: C, 29·9; H, 3·6; N, 4·1; Pt, 26·5. Calc.: C, 29·8; H, 3·6; N, 3·9; Pt, 26·9%).

The corresponding *picrate*, similarly prepared, separated after standing in the ice-chest; recrystallised from alcohol, it formed tiny, rectangular, bright yellow platelets, m. p. 146·5—147·5° (shrinking with slight melting from 139°) (Found: C, 47·7; H, 3·7; N, 15·2. $C_{15}H_{14}O_8N_4$ requires C, 47·6; H, 3·7; N, 14·8%).

2-*Methylpyrrocoline Salts*.—*Picrate*. A concentrated solution of picric acid in dry ethyl acetate was added to an ethereal solution of freshly sublimed 2-methylpyrrocoline, and the bright yellow precipitate removed and washed well with ether [m. p. 110—111° (decomp.)]. The *picrate* separates from alcohol or ethyl acetate in greenish-yellow needles, m. p. 111—112° (decomp.) (Found: C, 50·3; H, 3·4; N, 15·4. $C_{15}H_{12}O_7N_4$ requires C, 50·0; H, 3·3; N, 15·5%). Recrystallisation from acetic acid gave greenish-yellow needles, m. p. 102—103° (decomp.), which apparently contain 0·5 mol. of acetic acid (Found: C, 49·5; H, 3·5; N, 14·5. $C_{15}H_{12}O_7N_4,0{\cdot}5C_2H_4O_2$ requires C, 49·2; H, 3·6; N, 14·4%). Attempted recrystallisation from acetone gave a greenish product which could not be completely purified, m. p. 124° (vigorous decomp.).

*Perchlorate*. 2-Methylpyrrocoline was dissolved in 60% perchloric acid and the colourless solution kept in a vacuum over phosphoric oxide for 3 days. The resulting orange syrup, on being rubbed with dry ethyl acetate, yielded a white solid, m. p. 88—92°, which separated from methyl alcohol–ethyl acetate in white needles, m. p. 92—93·5° (slight melting from 82°) (Found: C, 46·5; H, 4·4; N, 6·1; Cl, 15·6. $C_9H_{10}O_4NCl$ requires C, 46·8; H, 4·3; N, 6·1; Cl, 15·3%). This *perchlorate* darkened on keeping and the odour of 2-methylpyrrocoline became noticeable.

*Chloroplatinate*. This *salt* separated as a buff-coloured powder on adding an aqueous solution of chloroplatinic acid to a solution of the base in dilute hydrochloric acid; it gradually darkened on heating but did not melt at 360° (Found: C, 32·4; H, 3·1; N, 4·4. $C_{18}H_{20}N_2Cl_6Pt$ requires C, 32·2; H, 3·0; N, 4·2%).

2-*Phenylpyrrocoline*.—The method described by Tschitschibabin (*loc. cit.*) was modified in several respects. Phenacyl bromide (291 g.) was added to a solution of α-picoline (144 c.c.) in dry ethyl alcohol (250 c.c.), and the spontaneous reaction controlled by external cooling. Next day the hard mass was broken up, filtered off, and washed with dry alcohol (100 c.c.); 311 g., m. p. 213° (decomp.). From the filtrate and washings after concentration in a vacuum a further 15 g. of phenacyl-α-picolinium bromide (III, R = Ph) were obtained (yield, 73%). A portion recrystallised from alcohol had m. p. 214° (decomp.) [lit., m. p. 215° (decomp.), yield 60%]. Phenacyl-α-picolinium bromide (100 g.) was dissolved in water (1 l.), sodium hydrogen carbonate (100 g.) added, and the mixture brought to the boil. 2-Phenylpyrrocoline separated as a thick magma of iridescent platelets. After 0·5 hr. the mixture was cooled, the solid removed, and the filtrate again boiled to yield a further quantity of the product. The combined crops were washed well with water and dried at 80°; 64 g. (96%), m. p. 213° (decomp.). This product is sufficiently pure for most purposes but can be recrystallised from alcohol in iridescent platelets, m. p. 214° (decomp.) (lit. 215°). 2-Phenylpyrrocoline is only slightly soluble in most organic solvents, even on heating. It is, however, readily soluble in cold formic acid. It is soluble in concentrated mineral acids and is not precipitated on dilution with water.

N-*Phenacyl-α-picolinium chloroplatinate* was formed by addition of a solution of chloroplatinic acid to a solution of the bromide in dilute hydrochloric acid; it was a buff-coloured powder, m. p. 232° (decomp.) (Found: N, 3·45; Pt, 23·5. $C_{28}H_{28}O_2N_2Cl_6Pt$ requires N, 3·4; Pt, 23·4%).

2-*Phenylpyrrocoline picrate* separates when a hot saturated aqueous solution of picric acid is added to a solution of the base in dilute hydrochloric acid. Recrystallised from ethyl acetate, it forms fine greenish-yellow needles, m. p. 161° (decomp.) (Found: C, 56·8; H, 3·5; N, 12·7. $C_{20}H_{14}O_7N_4$ requires C, 56·9; H, 3·3; N, 13·3%).

*Oxidation of* 2-*Phenylpyrrocoline*.—A suspension of 2-phenylpyrrocoline (3 g.) in a mixture of acetic acid (20 c.c.) and perhydrol (20 c.c.) was warmed cautiously on the steam-bath, and the solid slowly dissolved to produce a very dark solution. When the vigorous reaction, moderated by external cooling, that commenced at this stage was over, the mixture was heated on the steam-bath for 9 hours, during which further perhydrol (20 c.c.) was added portionwise. The resulting clear yellow solution on concentration in a vacuum yielded a syrup which was triturated with water (15 c.c.). The aqueous extract and the residual undissolved products were extracted with ether (25 c.c.). From the aqueous extract, after concentration in a vacuum, a yellow syrup was obtained which deposited α-picolinic acid *N*-oxide; after recrystallisation from dry methyl alcohol, this had m. p. 161·5° (decomp.), not depressed on admixture with an authentic specimen (m. p. 162°, decomp.). From the ethereal extract benzoic acid was separated with some difficulty.

3-*Acetyl*-2-*methylpyrrocoline*.—A solution of 2-methylpyrrocoline (21 g.) in acetic anhydride (150 c.c.) containing freshly fused sodium acetate (21 g.) was heated under reflux for 7 hrs. The excess of acetic anhydride was largely removed by distillation in a vacuum, and the remainder destroyed by boiling the black residue with alcohol. Water was added to the mixture to dissolve the sodium acetate, and the dark oil extracted with chloroform. The chloroform extract was washed with 2N-sodium hydroxide, then with water, dried ($CaCl_2$), and the solvent removed; the residue was distilled in a vacuum, and the bulk of the material collected at 179—185°/16 mm.; yield 21 g. (75%). The distillate, a yellowish-green solid, was recrystallised from ligroin (charcoal), forming thick cream-coloured clumps, m. p. 83° (lit. 83°).

*Benzylidene derivative*. This was prepared by the method used by Scholtz for acetylpyrrocoline (*Ber.*, 1912, **45**, 1718). To a solution of 3-acetyl-2-methylpyrrocoline (1 g.) and benzaldehyde (1·5 c.c.) in alcohol (10 c.c.) was added 2N-sodium hydroxide (2 c.c.). After 2 days, addition of a little water to the orange solution precipitated an oil which

solidified to a mass of orange crystals on rubbing; these recrystallised from alcohol in small stout, orange needles, m. p. 102—104° (Found: C, 82·5; H, 6·4; N, 5·5. $C_{18}H_{15}ON$ requires C, 82·8; H, 5·8; N, 5·4%).

2 : 4-*Dinitrophenylhydrazone.* A concentrated solution of 2 : 4-dinitrophenylhydrazine in a mixture of concentrated sulphuric acid and alcohol was added to an alcoholic solution of 3-acetyl-2-methylpyrrocoline at room temperature. A deep red solution was produced at once, and after a few minutes an almost black crystalline powder began to separate. It recrystallised from ethyl acetate (a large volume is needed to dissolve the solid, but the resulting solution must be concentrated considerably) in tiny, almost jet-black, irregular crystals, m. p. 252° (slight decomp.). The crystals appeared blood-red by transmitted light under the microscope (Found: C, 57·9; H, 4·3; N, 19·9. $C_{17}H_{15}O_4N_5$ requires C, 57·8; H, 4·3; N, 19·8%).

3-*Acetyl-2-phenylpyrrocoline.*—2-Phenylpyrrocoline (20 g.) and fused sodium acetate (20 g.) were heated under reflux for six hours with acetic anhydride (200 c.c.). The reaction mixture was worked up essentially as for the 2-methyl analogue, except that the required product was extracted into ether. The brown oil from the dried ethereal extract was distilled rapidly at 0·05 mm., most of the material collecting between 162° and 174° as a yellow solid (22·2 g.; 91%). Distillation at higher pressures is satisfactory provided it be rapid. Recrystallisation from ligroin (b. p. 60—80°) afforded soft, white, flat prisms tinged with green, m. p. 64·5° (Found: C, 81·8; H, 5·5; N, 5·8. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%). The *product* sublimes at 120—130°/0·006 mm.

*Dinitrophenylhydrazone.* A crude derivative, m. p. 180—186°, separated slowly on addition of Brady's reagent to a solution of the monoacetyl compound in alcohol; the *compound* separated from glacial acetic acid as a dull red microcrystalline powder, m. p. 220—221° (Found: N, 16·9. $C_{22}H_{17}O_4N_5$ requires N, 16·7%).

1 : 3-*Diacetyl-2-methylpyrrocoline.*—A mixture of the monoacetyl compound (10 g.), acetic anhydride (40 c.c.), and acetic acid (30 c.c.) was heated in a sealed tube at 230—240° for 8 hrs. After cooling, the dark solution was evaporated in an open dish, alcohol being added towards the end to facilitate removal of acetic anhydride. The resulting pitch-like solid was extracted 4 times with ligroin (b. p. 100—120°, 100 c.c.) and the combined extracts cooled in the ice-chest; crude 1 : 3-diacetyl-2-methylpyrrocoline separated as a light brown powder (5·5 g.), m. p. 117—120°. Concentration of the mother-liquors in a vacuum gave a partly solid residue which was treated with a little dry acetone and then ligroin, a further 0·5 g. of the diacetyl compound being obtained (48·4% yield). The solid, purified by recrystallisation from ligroin (b. p. 100—120°) after treatment with charcoal, was obtained as stout cream-coloured needles, m. p. 122—123° (lit. m. p. 123°) (Found: C, 72·3; H, 6·0; N, 6·2. Calc.: C, 72·6; H, 6·1; N, 6·5%). Its phenylhydrazone, pale yellow platelets from alcohol, had m. p. 208—210° (decomp.) [lit., 210° (decomp.)].

The 2 : 4-*dinitrophenylhydrazone* was precipitated immediately on the addition of Brady's reagent (2 mols.) to a solution of the diacetyl compound (1 mol.) in warm alcohol, as a dark purple-brown powder. It recrystallised from pyridine in the same form, m. p. 246° (decomp.) (Found: C, 57·4; H, 4·6; N, 18·4. $C_{19}H_{17}O_5N_5$ requires C, 57·7; H, 4·3; N, 17·7%).

*Oxidation of* 1 : 3-*Diacetyl-2-methylpyrrocoline.*—A solution of the diacetyl derivative (0·5 g.) and perhydrol (5 c.c.) in acetic acid (10 c.c.) was heated under reflux for 1 hr. The solution turned almost black at first but gradually became colourless. Removal of the solvent left a syrup which on rubbing with methyl alcohol turned to a white powder. Crystallisation of this from methyl alcohol yielded α-picolinic acid *N*-oxide, m. p. 160° (decomp.) alone or mixed with an authentic specimen.

1 : 3-*Diacetyl-2-phenylpyrrocoline.*—(*a*) A solution of 3-acetyl-2-phenylpyrrocoline (6 g.) in acetic anhydride (50 c.c.) was heated in a sealed tube at 230—240° for 8 hrs. The contents of the tube, which were only slightly charred, were concentrated in a vacuum leaving a brown syrup which was heated with a little alcohol to destroy the last traces of acetic anhydride. The final residue, after removal of ethyl acetate and alcohol, was extracted with ligroin (b. p. 60—80°) and a small amount of black residue remained. The small quantity of crystalline solid which separated from the cooled ligroin extract was combined with the black residue and recrystallised from aqueous alcohol (charcoal), yielding fawn crystals, 0·95 g, m. p. 169—170°. Recrystallisation from aqueous alcohol yielded colourless platelets or needles, m. p. 172·5—173° (Found: C, 77·8; H, 5·7; N, 5·4. $C_{18}H_{15}O_2N$ requires C, 78·0; H, 5·4; N, 5·1%). From the final petrol extract most of the monoacetyl compound was recovered unchanged.

(*b*) To a solution of acetyl chloride (10 g.) in tetrachloroethane (450 c.c.), powdered aluminium chloride (48 g.) was added followed by 3-acetyl-2-phenylpyrrocoline (30 g.), and the mixture heated at 60° for 1 hr. After 24 hrs. it was poured into 2N-hydrochloric acid (500 c.c.), and the tetrachloroethane removed in a current of steam. The dark green crystalline residue, which separated on cooling, was washed with water and recrystallised from dilute alcohol (charcoal); colourless platelets, (29·2 g.; 82%), m. p. 172—173° alone or when mixed with the *compound* described in (*a*) (Found: C, 77·7; H, 5·6; N, 4·8%).

2 : 4-*Dinitrophenylhydrazone.* Addition of Brady's reagent (2 mols.) to an alcoholic solution of the diacetyl compound precipitated the 2 : 4-*dinitrophenylhydrazone* immediately in fine red crystals, which, after washing with hot acetone, had m. p. 254° (Found: C, 63·0; H, 4·4; N, 15·4. $C_{24}H_{19}O_5N_5$ requires C, 63·0; H, 4·2; N, 15·3%).

*Oxidation of* 1 : 3-*Diacetyl-2-phenylpyrrocoline.*—A solution of the diacetyl compound (1 g.) in a mixture of perhydrol (6 c.c.) and acetic acid (6 c.c.) was refluxed for 2 hrs. From the resulting clear yellow solution, benzoic acid and α-picolinic acid *N*-oxide were isolated.

*Reaction of 2-Phenylpyrrocoline with Acetyl Chloride in the Presence of Aluminium Chloride.*—To finely powdered aluminium chloride (12 g.), covered with a solution of acetyl chloride (4·5 c.c.) in dry carbon disulphide (100 c.c.), 2-phenylpyrrocoline (6 g.) was added, and the mixture heated on the steam-bath for 20 hrs. Hydrogen chloride was evolved during the first 4 or 5 hrs., and the pyrrocoline formed a homogeneous syrup with aluminium chloride. After three days, the solvent was removed in a vacuum, and the residual syrup mixed carefully with an excess of 2N-sodium hydroxide. The light brown solid that separated was filtered off, washed with water, dried (6·2 g.), and extracted several times with boiling benzene. The combined benzene extracts (320 c.c.) on cooling deposited 2-(p-*acetylphenyl*)*pyrrocoline* as a fawn crystalline solid, m. p. 225—230° (decomp.). Recrystallisation from benzene (charcoal) yielded pale green iridescent platelets, m. p. 239—241° (decomp.) (1·6 g.; 19%); and after recrystallisation from chloroform, m. p. 240—241° (decomp.) (Found: C, 81·4; H, 5·7; N, 6·1. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%). The benzene filtrate from the recrystallisation yielded, on evaporation to dryness, crude 2-phenylpyrrocoline (0·48 g.).

The original benzene extract (320 c.c.) after the removal of crude *p*-acetylphenylpyrrocoline was concentrated to 50 c.c. and cooled, 0·26 g. of solid [m.p. 212—216° (decomp.)] being obtained. This was filtered off, the filtrate evaporated to dryness in a vacuum, and the residue extracted with ligroin (b. p. 60—80°), leaving a trace of insoluble material. The ligroin extract, on cooling, deposited 2·2 g. (30%) of crude 1 : 3-diacetyl-2-phenylpyrrocoline. On concentration of the filtrate a further small quantity of this material was obtained, but no 3-acetyl-2-phenylpyrrocoline could be detected. The crude diacetyl compound after recrystallisation from ligroin had m. p. 171°, alone and on admixture with a specimen prepared by acetylation of the monoacetyl compound (Found: N, 5·3%).

2-(p-*Acetylphenyl*)*pyrrocoline* 2 : 4-*Dinitrophenylhydrazone.*—Fine red needles, which did not melt at 340°, were obtained when a hot solution of the acetyl compound in acetic acid was added to a hot solution of 2 : 4-dinitrophenylhydrazine sulphate in the same solvent. This was apparently the *sulphate* of the required derivatives (Found: N, 12·4; S, 8·4.

$C_{22}H_{17}O_4N_5,1{\cdot}5H_2SO_4$ requires N, 12·4; S, 8·5%). On treatment with warm water the solid became dark red and flocculent, m. p. approx. 290° (violet decomp.). The aqueous mother-liquors gave a white precipitate with barium chloride solution.

*Oxidation of* 2-(p-*Acetylphenyl*)*pyrrocoline*.—The acetyl derivative (1·3 g.) was heated on the steam-bath in a mixture of perhydrol (10 c.c.) and acetic acid (10 c.c.), the initial vigorous reaction being controlled by external cooling. After an hour, the mixture was refluxed for 2 hrs., more perhydrol (10 c.c.) added, and refluxing continued for a further 7 hrs. The final yellow solution was concentrated in a vacuum, and the residual yellow solid dissolved in boiling water (25 c.c.). A trace of insoluble oil was removed by filtration through kieselguhr, and the filtrate on cooling deposited a crystalline solid, m. p. 202—207°; this recrystallised from water (charcoal) in needles, m. p. 208°, alone or when mixed with *p*-acetylbenzoic acid. The semicarbazone, m. p. 268°, likewise did not depress the m. p. of *p*-acetylbenzoic acid semicarbazone. From the aqueous filtrate from the crude *p*-acetylbenzoic acid, α-picolinic acid *N*-oxide was obtained in the usual way.

3-*Benzoyl*-2-*phenylpyrrocoline*.—(*a*) 2-Phenylpyrrocoline (4 g.) was dissolved in warm benzoyl chloride (15 c.c.). After 24 hrs. the deep green solution was decanted from the green crystalline solid (1·2 g.) that had separated, and poured with stirring into ligroin (b. p. 60—80°). The crude *benzoyl* derivative which separated was removed and recrystallised twice from alcohol; pale yellow monoclinic crystals, m. p. 137—138° (2·5 g.; 40%) (Found: C, 85·1; H, 5·2; N, 4·9. $C_{21}H_{15}ON$ requires C, 84·8; H, 5·1; N, 4·7%). The green solid (1·2 g., above) was washed with acetone. It was rather deliquescent and difficult to purify, but was obtained as buff-coloured crystalline nodules, m. p. 109° (decomp.), when recrystallised cautiously from methyl cyanide. A satisfactory analysis for chlorine could not be obtained for this material, but as it was readily hydrolysed by water to give 2-phenylpyrrocoline and chlorine ions (benzoic acid was absent) it probably is 2-*phenylpyrrocoline hydrochloride* (Found: C, 83·1; H, 5·65; N, 6·9; Cl, 5·5. $C_{14}H_{11}N,0{\cdot}25HCl$ requires C, 83·1; H, 5·6; N, 6·9; Cl, 4·4%).

(*b*) A mixture of 2-phenylpyrrocoline (2 g.), benzoic anhydride (20 g.), and sodium benzoate (2 g.) was fused and kept at 140—150° for 2 hours. The cooled black melt was triturated with cold 20% sodium hydroxide solution to destroy the anhydride, and the residual brown solid was filtered off and washed with water. Recrystallisation from alcohol (charcoal) gave 3-benzoyl-2-phenylpyrrocoline (1·55 g.; 50%), m. p. 136—138°, alone or when mixed with the material prepared above (*a*).

The *picrate* separated as a red solid when an alcoholic solution of picric acid was added to a hot concentrated alcoholic solution of the benzoyl compound. Recrystallisation from alcohol yielded rust-coloured platelets, m. p. 121—122° (Found: C, 61·4; H, 3·8; N, 10·7. $C_{21}H_{15}ON,C_6H_3O_7N_3$ requires C, 61·6; H, 3·4; N, 10·6%).

3-Benzoyl-2-phenylpyrrocoline is only slightly soluble in hydrochloric acid, but dissolves slowly on heating. On keeping the resulting solution hot for a few minutes, the solid is completely hydrolysed to 2-phenylpyrrocoline. A dinitrophenylhydrazone could not be prepared.

*Reaction of* 3-*Chloroacetylacetone with* α-*Picoline*.—3-Chloroacetylacetone was prepared in 68% yield by the action of sulphuryl chloride on acetylacetone at 0°, essentially by the method used by Dey (*J.*, 1915, **107**, 1646) for the preparation of ethyl α-chloroacetoacetate (cf. Combes, *Compt. rend.*, 1890, **111**, 273). Attempts to prepare 3-bromoacetylacetone by the method of Auwers and Auffenberg (*Ber.*, 1917, **50**, 951) led only to a very unstable product.

A solution of α-picoline (9·3 g.) and chloroacetylacetone (13·5 g.) in methyl ethyl ketone (50 c.c.) was heated on the steam-bath for 30 hrs. After cooling, the dark brown solution was decanted, leaving a light brown partly solid gum which, after being washed with methyl ethyl ketone, was dissolved in water (12 c.c.), and the aqueous solution extracted with chloroform. The brown aqueous layer on clarification with charcoal at room temperature yielded a pale yellow solution. (It was established that this clarification process does not remove any quaternary compounds present.) Sodium hydrogen carbonate was added until effervescence ceased, and the liberated α-picoline extracted thoroughly with ether. To a portion (2 c.c.) of the final clarified solution (14 c.c.), acidified with hydrochloric acid, a solution of chloroplatinic acid was added. The resulting orange-buff coloured precipitate was filtered off next day, washed with water, and dried at 100° (0·15 g.), m. p. 215—216° (decomp.). Mixed with acetonyl-α-picolinium chloroplatinate (m. p. 205°, decomp.), it had m. p. 190—198°, and is therefore probably N-*diacetylmethyl*-α-*picolinium chloroplatinate* (as IV, R = Me), although the analysis indicated contamination with α-picoline chloroplatinate (Found: C, 27·9; H, 3·3; N, 4·3; Pt, 28·2. $C_{22}H_{28}O_4N_2PtCl_6$ requires C, 33·4; H, 3·5; N, 3·5; Pt, 24·6%).

To a further portion (10 c.c.) of the clarified solution excess of sodium hydrogen carbonate was added, and the solution heated under reflux for 1 hr., to yield 0·46 g. (5%) of 2-methylpyrrocoline. (The odour of α-picoline was noticed when heating was commenced.)

The remaining 2 c.c. of the original clarified solution were mixed with an alcoholic solution of picric acid, and N-*diacetylmethyl*-α-*picolinium picrate* was deposited on scratching. Recrystallised from alcohol, the picrate formed bright yellow needles, m. p. 133°, when cooled slowly, or very tiny pale yellow needles, m. p. 143—143·5°, when cooled rapidly. The analysis was carried out on the latter form (Found: C, 44·7; H, 3·5; N, 14·6. $C_{17}H_{16}O_9N_4,0{\cdot}5C_6H_3O_7N_3$ requires C, 44·9; H, 3·3; N, 14·4%). Mixed with acetonyl-α-picolinium picrate (m. p. 146·5—147·5°), it had m. p. 120—122°.

In a subsequent preparation, the reactants were heated without solvent in an oil-bath at 140—150° for 1 hr., a slightly better yield of 2-methylpyrrocoline being obtained by this procedure (7%). The reaction mixture was worked up as described above, and the final clarified aqueous solution after cautious treatment with sodium hydrogen carbonate was warmed to 40° to complete the release of α-picoline. The chloroplatinate obtained after this treatment, however, melted at 205° (decomp.). Mixed m. p. with acetonyl-α-picolinium chloroplatinate (m. p. 205°, decomp.), 202° (decomp.). Although there was a slight depression in m. p., the analysis of this chloroplatinate agrees fairly well with that for acetonyl-α-picolinium chloroplatinate (Found: C, 29·9; H, 3·5; N, 4·1; Pt, 27·7. Calc.: C, 29·8; H, 3·6; N, 3·9; Pt, 26·8%). Attempts to prepare a picrate from the remaining aqueous solution were unsuccessful, only tiny quantities of a yellow gum being obtained.

*Reaction of* 3-*Bromobenzoylacetone with* α-*Picoline*.—3-Bromobenzoylacetone (prepared by the method of Kröhnke and Timmler, *loc. cit.*, from benzoylacetone) (2 g.) was added immediately to a solution of α-picoline (1·25 c.c.) in alcohol (2·5 c.c.). After 24 hrs. the supernatant solution was decanted, the residual dark oil dissolved in water, and the α-picoline extracted with ether. The aqueous solution was clarified with charcoal, and a portion (10 c.c.) of the total (45 c.c.) was acidified with hydrochloric acid and mixed with chloroplatinic acid solution. The precipitated chloroplatinate (0·05 g.), m. p. 217° (decomp.), could not be purified. Mixed with phenacyl-α-picolinium chloroplatinate (m. p. 232°, decomp.) it had m. p. 219° (decomp.), indicating that in this case removal of the acetyl group from the quaternary compound had occurred to some extent at this stage. To another portion (25 c.c.) of the clarified aqueous solution was added sodium hydrogen carbonate (2·5 g.), and the mixture heated to boiling for a few minutes; a black oily solid was deposited from which 2-phenylpyrrocoline (0·05 g.) was isolated.

*Reaction of Ethyl* α-*Chloroacetoacetate with* α-*Picoline*.—Ethyl α-chloroacetoacetate was prepared by the action of sulphuryl chloride on ethyl acetoacetate (Dey, *loc. cit.*,) in 75% yield. A mixture of ethyl α-chloroacetoacetate (10 c.c.) and α-picoline (10 c.c.) was refluxed gently in an oil-bath for 1·5 hrs. After cooling, the dark reaction mixture was diluted with water and filtered through kieselguhr to remove the considerable quantity of tar. To the brown aqueous filtrate

sodium hydrogen carbonate (2 g.) was added, and the mixture refluxed for 1·5 hrs. A current of steam was then passed through, and 2-methylpyrrocoline (0·9 g.) obtained.

*Reaction of Ethyl α-Bromobenzoylacetate with α-Picoline.*—Ethyl benzoylacetate was prepared essentially by the method of Dorsch (*J. Amer. Chem. Soc.*, 1932, **54**, 2960), and brominated according to the procedure of McElvain and Hawk (*ibid.*, p. 287). A mixture of ethyl α-bromobenzoylacetate (2·9 g.) and α-picoline (1 g.) was kept at room temperature for 2 days, heated on the steam-bath for 3 hrs., and then kept at room temperature for a further 2 days. The resulting dark brown syrup was shaken with water and ether, the ethereal extract discarded, and the aqueous layer clarified with charcoal. To this yellow solution was added potassium hydrogen carbonate (2 g.), and the solution heated to boiling; 2-phenylpyrrocoline (0·02 g.; 1%) separated. This poor yield could not be impoved although a variety of conditions were tried.

*Reaction of Phenacyl Bromide with Quinaldine.*—A mixture of phenacyl bromide (6 g.) and quinaldine (4·2 g.) after standing at room temperature for 2 days had set to a crystalline mass. This was freed from contaminating syrup and washed with dry acetone, leaving a pale pink crystalline solid, m. p. 223°. The filtrate and acetone washings after concentration, on being heated on the steam-bath for 1 hr., yielded a further small amount of the same solid. The combined solid (3·13 g.), recyrstallised from alcohol (charcoal), yielded colourless needles, m. p. 227°, of *quinaldine hydrobromide* (Found: C, 53·4; H, 4·7; N, 6·2; Br, 35·7. $C_{10}H_{10}NBr$ requires C, 53·6; H, 4·5; N, 6·3; Br, 35·7%). The salt prepared by passing dry hydrogen bromide into an absolute alcoholic solution of the base possessed the same m. p. and mixed m. p. after recrystallisation from alcohol. Further, the picrate had m. p. 196—197°, alone or mixed with authentic quinaldine picrate (46% yield).

The final black syrup from the above preparation yielded no basic material when extracted with water.

A similar result was obtained when chloroacetone was allowed to react with quinaldine, a yield of 31% of quinaldine hydrochloride (m. p. 226°, alone and admixed) being obtained. Attempts to reduce hydrohalide formation by carrying out the reaction in solvents were equally unsuccessful.

*Reaction of Iodine with α-Picoline and Acetone: Preparation of 2-Methylpyrrocoline.*—To a mixture of acetone (5·8 g.) and α-picoline (30 c.c.), iodine (25·4 g.) was added portionwise. The resulting dark brown mixture, now warm, was heated on the steam-bath under reflux for 0·5 hr., and then in a vacuum to remove most of the unreacted α-picoline. Water was added to the resulting dark brown partly solid mass, followed by sodium hydrogen carbonate (*ca.* 10 g.), and the mixture slowly distilled in a current of steam. A small quantity of an oil, which was discarded, came over at first, followed by 2-methylpyrrocoline (2·5 g.; 19% yield) (confirmed by m. p. and mixed m. p.).

*Reaction of Iodine with α-Picoline and Acetophenone: Preparation of 2-Phenylpyrrocoline.*—To a mixture of acetophenone (8 g.) and α-picoline (12·4 g.), iodine (16·6 g.) was added portionwise. After the moderate exothermic reaction had subsided, the mixture was heated on the steam-bath for 0·75 hr. Next day the resulting thick syrup was poured into water (350 c.c.), and the heterogeneous mixture shaken with ether to remove most of the black oil. The aqueous solution was filtered through kieselguhr to remove the remainder of the oil, and then clarified with charcoal. Sodium hydrogen carbonate was added till effervescence ceased, and the liberated α-picoline extracted with ether. A portion of the final solution, after acidification, was mixed with chloroplatinic acid, to yield a buff-coloured chloroplatinate, m. p. 231° (decomp.) not depressed on admixture with an authentic specimen of phenacyl-α-picolinium chloroplatinate (m. p. 232°, decomp.). The remainder of the aqueous solution on being heated to boiling after addition of an excess of sodium hydrogen carbonate precipitated 2-phenylpyrrocoline (2·2 g.; 10% yield) (identified by m. p. and mixed m. p.).

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[*Received, April 8th,* 1946.]