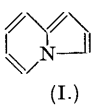
239. *The Chemistry of the Pyrrocolines. Part IV. Reduction of Acyl Derivatives.*

By E. T. Borrows, D. O. Holland, and J. Kenyon.

The position of the acetyl group in 3-acetyl-2-methyl- and -2-phenyl-pyrrocoline has been determined by the reduction of these derivatives to 2-*methyl*- and 2-*phenyl*-3-*ethylpyrrocoline* respectively, and comparison with the same compounds prepared by direct synthesis. The catalytic reduction of these compounds has also been studied. The position of the benzoyl group in 3-benzoyl-2-phenylpyrrocoline has been established in a similar manner.

Unsuccessful attempts to confirm the position of the acetyl group in 3-acetyl-2-methyl- and -2-phenyl-pyrrocoline (I, R = Me or Ph; R′ = Ac), either by direct synthesis or *via* the corresponding 3-carboxylic esters, have already been recorded (Part I). The desirability of establishing this position became apparent in the work on the nitrosation and nitration of the pyrrocoline ring system (Parts II and III), since the orientation of the nuclear substituents in the compounds was largely dependent on the position of the acetyl group. The possibility of solving this problem by means of the corresponding 3-ethylpyrrocolines (I; R = Me or Ph, R′ = Et) was therefore examined and the direct synthesis of these compounds in good yield from α-picoline and 3-*bromo*-2-*pentanone* and α-bromobutyrophenone respectively is now described, using the method of Tschitschibabin (*Ber.*, 1927, **60**, 1607). Ochiai and Tsuda (*Ber.*, 1934, **67**, 1011) have prepared 2 : 3-dimethylpyrrocoline in a similar fashion, using 3-bromobutanone, and it would appear therefore that Tschitschibabin's method is generally applicable for the synthesis of 2 : 3-dialkyl- or -aryl-substituted pyrrocolines. Only a very small yield (*ca.* 1%) of 2-*methyl*-3-*ethylpyrrocoline* was



(I.)

obtained when the 3-chloro-ketone was used, compared with 75% in the case of the bromo-ketone, indicating the advisability of using bromo-ketones in this type of reaction.

In common with all other known alkyl- and aryl-pyrrocolines, 2-methyl-3-ethyl- and *2-phenyl-3-ethylpyrrocoline* exhibit in solution a bluish-violet fluorescence and give positive reactions in the pine-splinter test (red) and a coloured melt on fusion with oxalic acid (2-methyl, green; 2-phenyl, blue). The 2-methyl-3-ethyl derivative is even more unstable to air and light than is 2-methylpyrrocoline, while the 2-phenyl derivative, a comparatively low-melting solid (m. p. 94°), is quite stable, as are other known arylpyrrocolines.

Attention was then directed to the possibility of reducing the acetylpyrrocolines to the corresponding ethyl derivatives. Tschitschibabin and Stepanow (*Ber.*, 1929, **62**, 1068) record that the action of ethylmagnesium bromide on 3-acetyl-2-methylpyrrocoline gives rise to the 2-methyl-3-ethyl compound, reduction with aluminium amalgam in moist ether apparently giving the same compound. The product they obtained, however, was later shown to be 2-methylpyrrocoline by Kondo and Osawa (*J. Pharm. Soc. Japan*, 1936, **56**, 73; *Chem. Zentr.*, 1936, **107**, ii, 2910). Since the acetyl groups in these pyrrocolines are so readily removed by hydrolysis with mineral acid (Part I), it was clear that a normal Clemmensen reduction would be useless, but the possibility of using dry alcohol saturated with dry hydrogen chloride with the amalgamated zinc was examined (cf. Adams, Cain, and Baker, *J. Amer. Chem. Soc.*, 1940, **62**, 2201; Schneider and Spielman, *J. Biol. Chem.*, 1942, **142**, 345). This reagent, however, converted 3-acetyl-2-methylpyrrocoline almost exclusively into 2-methylpyrrocoline. A control experiment, without zinc, showed that alcoholysis was responsible for this result, a 92% conversion into 2-methylpyrrocoline being obtained after refluxing for 15 hrs.

Scholtz (*Ber.*, 1912, **45**, 734) has already shown the pyrrocoline nucleus to be unaffected by zinc and acetic acid, and we therefore employed glacial acetic acid as the medium for the Clemmensen reduction, passing a slow stream of dry hydrogen chloride through the reaction mixture. The product obtained, a yellow, unstable, fluorescent oil, distilled over a wide range, even on careful fractionation, and was an obvious mixture. It was finally separated into two main products by fractional crystallisation of the crude picrate and the identity of one of these as 2-methyl-3-ethylpyrrocoline was established through its *chloroplatinate* and suspected picrate: the other product was probably 2-methyl-3-α-hydroxyethylpyrrocoline (II) since it yielded a *phenylurethane*.

Although these 3-acetyl-pyrrocolines are unreactive towards phenylhydrazine, the preparation of 2 : 4-dinitrophenylhydrazones (Part I) indicated that Kon's modification (*J.*, 1940, 1325) of the Kishner–Wolff method might be effective. This proved to be the case, and 2-phenyl-3-ethylpyrrocoline was obtained by this method, although a larger proportion of 2-phenylpyrrocoline was also formed during the reaction. The introduction of ethyl groups into the pyrrole nucleus by heating with alcoholic sodium ethoxide is well known (Fischer and Bartholomäus, *Z. physiol. Chem.*, 1912, **80**, 7, 15), and Knorr and Hess (*Ber.*, 1912, **45**, 2634) have replaced the acetyl group in 3-acetyl-2 : 4 : 5-trimethylpyrrole by an ethyl group in the same way. It was necessary, therefore, in view of the isolation of 2-phenylpyrrocoline, to establish that the reaction had not proceeded by deacetylation of the acetyl derivative, followed by the introduction of an ethyl group. 2-Phenylpyrrocoline was recovered unchanged after being heated in a sealed tube with alcoholic sodium ethoxide, and the 3-acetyl derivative, under the same conditions, was converted mainly into 2-phenylpyrrocoline, together with a comparatively small quantity of an unidentified unstable yellow oil.

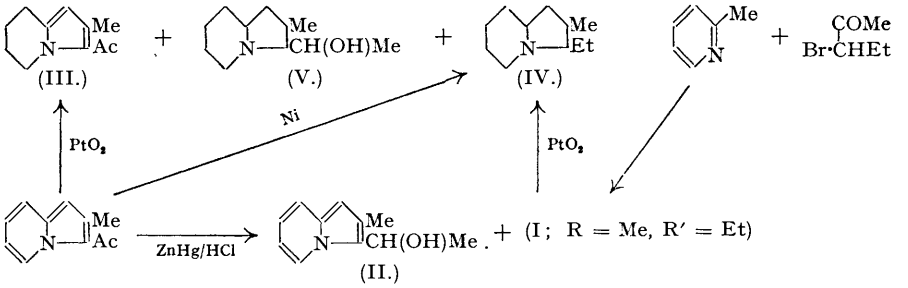
The isolation of 2-phenyl-3-ethylpyrrocoline from the original reaction mixture may, therefore, be safely assumed to be due to direct reduction of the acetyl group, *via* the hydrazone, thus establishing the position of this in the initial material.

Attempts to prepare a thioacetal derivative of the acetyl compounds, with a view to employing the recent method of Wolfrom and Karabinos (*J. Amer. Chem. Soc.*, 1944, **66**, 909) for converting carbonyl into methylene groups, were unsuccessful.

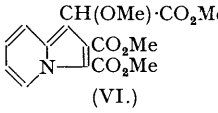
The Kishner–Wolff method was also successfully used for the reduction of 3-benzoyl-2-phenylpyrrocoline (Part I), *2-phenyl-3-benzylpyrrocoline* being isolated in 26% yield, together with a 49% yield of 2-phenylpyrrocoline. The same compound was obtained (25% yield) by direct synthesis from α-picoline and α-bromo-α-benzylacetophenone, thus establishing the position of the benzoyl group in the original compound. The hydrochloride of this pyrrocoline was an oil, and the *picrate*, m. p. 112·5—113·5°, also tended to form an oil unless carefully crystallised.

The possibility of employing catalytic reduction for the conversion of the acetyl into an ethyl group was also investigated, but it soon became clear that selective reduction of this group without affecting the nucleus was impossible. Signaigo and Adkins (*J. Amer. Chem. Soc.*, 1936, **58**, 709) found that acylpyrroles such as 3-acetylpyrrole could be reduced to the corresponding ethylpyrrole when Raney nickel or copper chromite was used as catalyst. We find that 3-acetyl-2-phenylpyrrocoline is reduced to a tetrahydro-compound, probably *3-acetyl-2-phenyl-5 : 6 : 7 : 8-tetrahydropyrrocoline* (X) in the presence of Raney nickel, even at room temperature and pressure. A similar *compound* (III) is obtained as the main product when 3-acetyl-2-methylpyrrocoline is reduced at room temperature and pressure using Adams's catalyst, although Ochiai and Kobayashi (*J. Pharm. Soc. Japan*, 1936, **56**, 376; *Chem. Abs.*, 1936, **30**, 6364; *Chem. Zentr.*, 1936, **107**, ii, 1938) record that 2-methyl-3-ethyl- (IV) and 2-methyl-3-α-hydroxyethyl-octahydropyrrocoline (V) were produced under similar conditions. We obtained only small quantities of two products believed to be identical with these two compounds, however, and it seems probable that the Japanese workers added the catalyst portionwise to their reaction mixture.

The products obtained from 3-acetyl-2-methylpyrrocoline in this reduction, the Clemmensen reduction above, and those to be mentioned later are given in the following scheme :



Both tetrahydro-compounds are low-melting solids, and give slowly-developing colours in the pine-splinter test (2-methyl, red; 2-phenyl, purple), but fusion with oxalic acid gives colourless melts. Failure to form urethanes, and the preparation of dinitrophenylhydrazones, indicated that the acetyl group had not been reduced. Since the original 3-acetylpyrrocolines gave coloured (green) melts with oxalic acid, it appeared probable that the 6-membered ring had been reduced in these compounds, a conclusion supported by the fact that on heating with mineral acid the 2-phenyl analogue (X) readily lost the acetyl group to give *2-phenyl-5 : 6 : 7 : 8-tetrahydropyrrocoline*, m. p. 76·5—77° (XI); this compound regenerates the acetyl derivative on heating with acetic anhydride and fused sodium acetate. The apparent reduction of the 6-membered ring of the pyrrocoline nucleus, by the action of sodium on an alcoholic solution of the parent base, was noted by Scholtz (*loc. cit.*). Two atoms of hydrogen were introduced in this way to produce an unstable oil which gave a positive result in the pine-splinter test but a colourless melt with oxalic acid. Scholtz considered that the compound was α-butadienylpyrrole, but it seems more likely that it was a dihydropyrrocoline. It may be noted in this connection, however, that Diels and Meyer (*Annalen*, 1934, **513**, 129) considered that when the tricarboxylic ester (VI) was hydrogenated with platinum oxide as catalyst, the 5-membered ring was reduced, since the acids obtained on hydrolysis before and after hydrogenation gave different anhydrides on treatment with acetic anhydride, a difference which was explained by *cis-* and *trans*-isomerism, assuming the 5-membered ring to have been reduced.

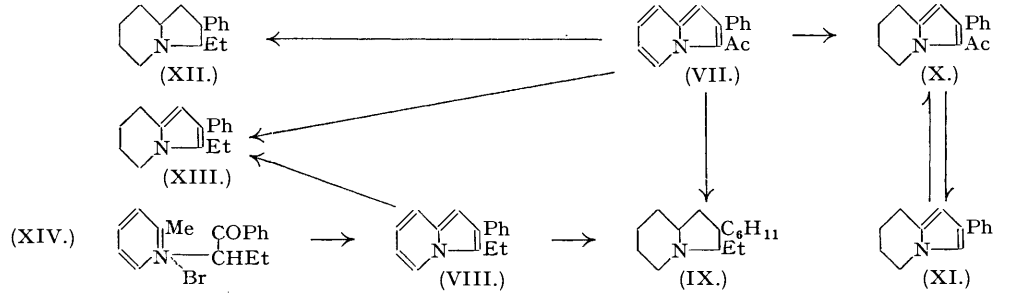


(VI.)

Using copper chromite as catalyst, the main product when 3-acetyl-2-phenylpyrrocoline was hydrogenated at 170—175° for 1·5 hrs. under 150 atm. was a white solid, m. p. 100—101°, believed to be *2-phenyl-3-ethyl-5 : 6 : 7 : 8-tetrahydropyrrocoline* (XIII). This same compound, obtained in good yield when 2-phenyl-3-ethylpyrrocoline was hydrogenated at room temperature and pressure in the presence of Raney nickel, gave a purple-red colour in the pine-splinter test and a colourless oxalic acid melt, whilst its solutions in organic solvents exhibited a violet fluorescence. Under more vigorous conditions increasing amounts of *2-phenyl-3-ethyloctahydropyrrocoline* (XII) were obtained with both Raney nickel and copper chromite. This compound, a high boiling oil, was at first considered to be 2-*cyclo*hexyl-3-ethyl-5 : 6 : 7 : 8-tetrahydropyrrocoline, both from the analytical data and from its red-purple coloration in the pine-splinter test. Its absorption spectrum, however, which was very low ($\lambda_{max.}$ 2980 A., ε 55, with general absorption below 2710 A.), was not in harmony with this structure and showed little resemblance to, *e.g.*, that of 2-phenyl-3-ethyl-5 : 6 : 7 : 8-tetrahydropyrrocoline.

That the product was, in fact, contaminated with a " pyrrole " impurity was shown by treatment of the crude base in ligroin with dry hydrogen chloride to yield as the major product *2-phenyl-3-ethyloctahydropyrrocoline hydrochloride*, which was isolated in two isomeric forms, m. p. 199—200° and m. p. 231—232°. The free base from both of these salts gave a negative pine-splinter test and by oxidation with potassium permanganate yielded benzoic acid.

With Raney nickel as catalyst it was possible, finally, to obtain the fully-reduced 2-cyclo*hexyl*-3-*ethyloctahydropyrrocoline* (IX) from both (*a*) 3-acetyl-2-phenylpyrrocoline and also (*b*) 2-phenyl-3-ethylpyrrocoline, the reduction being considerably slower in the latter case. The various products are shown in the scheme :



The *hydrochlorides* and the hydrobromides prepared from both specimens (*a*) and (*b*) of the fully-reduced base possessed the same m. p.'s, which were not depressed on admixture. The *methiodides*, however, were quite different : that from the base (*a*) had m. p. 201—202°, and that from (*b*) m. p. 188—189°. The m. p. of mixtures of these two solids was in all cases 201—202°, unless only a very small proportion of the higher-melting derivative was present, whereupon the mixtures melted at 197°. All attempts at interconversion of these two forms were unsuccessful, and when the higher-melting derivative was fused (1—2 mins.) a third form was produced, m. p. 208—209°, after crystallisation from acetone–ligroin. Careful fractional crystallisation of the crude methiodides from each of the bases showed that each was uncontaminated with the other (synthetic mixtures were readily separated from acetone–ligroin), but a small quantity of a fourth form, m. p. 177—178°, was isolated in this way from the crude methiodide of (*b*).

A similar phenomenon was observed with the methiodide of 2-methyl-3-ethyloctahydropyrrocoline. Ochiai and Kobayashi (*loc. cit.*), who prepared this derivative, give the m. p. as 197°. By reducing the 3-acetyl-2-methyl compound, following their method (see above), and converting the appropriate fraction into its methiodide, a rather deliquescent solid was obtained from which it was only possible to isolate very small quantities of two solids, m. p. 218—220°, and m. p. 196—198°, which could not be completely purified. It is interesting to note that the fraction corresponding to 2-methyl-3-α-hydroxyethyloctahydropyrrocoline gave a phenylurethane, m. p. 137° (Ochiai and Kobayashi, m. p. 137°) which was readily purified. 2-Methyl-3-ethyl-octahydropyrrocoline (*c*) prepared from the 3-acetyl compound by hydrogenation at high temperature and pressure using Raney nickel as catalyst, gave a methiodide which was not deliquescent in the crude state and was more readily purified, m. p. 197—198°. The methiodide of the fully-reduced base (*d*) obtained by the reduction of 2-methyl-3-ethylpyrrocoline using Adams's catalyst (following Ochiai and Tsuda, *loc. cit.*), however, had m. p. 229—229·5°. The m. p.s of mixtures of these two forms behaved similarly to those described above for the corresponding 2-phenyl analogue. The perchlorates, hydriodides, and hydrobromides prepared from both specimens (*c*) and (*d*) possessed the same m. p.s, which were not depressed on admixture. Clemo and Ramage (*J.*, 1932, 2969) have recorded the isolation of two picrates of octahydropyrrocoline which behaved similarly to the methiodides described above.

Experimental.

All m. p.'s are uncorrected.

3-Chloro-2-pentanone.—Freshly distilled sulphuryl chloride (43 c.c.) was added dropwise during 90 mins. to stirred 2-pentanone (43 g.) at 0—5°, and the mixture slowly heated on a steam-bath for 30 mins. The cooled liquid was diluted with ether, washed with water until neutral (Congo-red), dried, and distilled, the fraction, b. p. 124—140°, being collected (22·2 g.; 36·7%). On redistillation, the principal fraction had b. p. 36—38°/12 mm.

3-Bromo-2-pentanone.—No reference to this *compound* being found in the literature, we have prepared it essentially by the method used for bromoacetone (*Org. Synth.*, Coll. Vol. II, 88). Bromine (14·9 c.c.) was added dropwise to a stirred solution of 2-pentanone (25 g.) in a mixture of acetic acid (100 c.c.) and water (60 c.c.) at 65—70°, at such a rate that decolorisation was almost immediate (40 mins.). Absorption was rapid, and the reaction mixture maintained itself at 65° without external heating. The cooled mixture was poured into water (500 c.c.), neutralised with sodium carbonate (Congo-red), the liberated heavy lachrymatory oil separated, and the aqueous layer extracted twice with chloroform. The combined oil and extracts were washed with sodium carbonate solution, then with water and dried. The bromo-ketone was fractionally distilled through a Vigreux column, and the main bulk collected at 57—59°/18 mm. as a colourless, mobile, lachrymatory liquid (25·2 g.; 52·5%). A portion was analysed after refractionation (b. p. 53°/14 mm.) (Found : Br, 48·8. C_5H_9OBr requires Br, 48·5%); $n_D^{20°}$ 1·4629.

2-Methyl-3-ethylpyrrocoline.—A mixture of 3-bromo-2-pentanone (37·1 g.) and α-picoline (22·5 c.c.) was heated on a steam-bath for 15 hrs., and the resulting dark-brown gum shaken with water, the residual oily material being removed with chloroform. The aqueous layer was extracted with chloroform and mixed with sodium bicarbonate until effervescence ceased, and the liberated α-picoline extracted with ether. Additional bicarbonate (30 g.) was then added, the mixture heated on the steam-bath for 3 hrs., and the liberated *2-methyl-3-ethylpyrrocoline* removed in a current of steam as a heavy pale yellow oil. Distilled in a vacuum, it had b. p. 124°/15 mm. (27·1 g.; 75%) (Found : C, 83·0; H, 8·2; N, 9·0. $C_{11}H_{13}N$ requires C, 83·0; H, 8·2; N, 8·8%); $n_D^{20°}$ 1·5968. Its *chloroplatinate*, a buff-coloured powder, had m. p. 174° (decomp.) (Found : C, 36·5; H, 3·7; N, 4·3; Pt, 27·6. $C_{22}H_{28}N_2PtCl_6$ requires C, 36·3; H, 3·9; N, 3·9; Pt, 26·8%).

3-Pentan-2-onyl-α-picolinium chloroplatinate was obtained as a yellowish-buff powder, m. p. 225° (decomp.), from a portion of the aqueous solution after removal of α-picoline (as above), acidification with hydrochloric acid, and clarification with charcoal (Found : N, 4·0; Pt, 25·3. $C_{22}H_{32}O_2N_2Cl_6Pt$ requires N, 3·7; Pt, 25·6%).

Reaction of 3-Chloro-2-pentanone with α-Picoline.—A mixture of the ketone (7·9 g.) and α-picoline (6·6 c.c.) was heated on a steam-bath for 20 hrs., and the resulting dark syrup worked up as described above. The heavy yellow oil (0·13 g.) obtained possessed an odour similar to that of 2-methylpyrrocoline, and gave a red colour in the pine-splinter test and a green melt with oxalic acid. It was not further identified as 2-methyl-3-ethylpyrrocoline, but the chloroplatinate of the quaternary compound before ring closure was prepared and found to be identical with that described above, m. p. 220° (decomp.) (Found : N, 3·3; Pt, 25·9%).

2-Phenyl-3-ethylpyrrocoline.—A mixture of α-bromobutyrophenone (12·2 g.) and α-picoline (5 g.) was heated on a steam-bath for 3 hrs., the resulting brown syrup extracted with hot water (50 c.c.), and the insoluble oil removed with ether. The clarified aqueous solution was mixed with sodium hydrogen carbonate (30 g.), the liberated α-picoline extracted with ether, and the aqueous solution refluxed for 90 mins. The dark, fluorescent oil that separated solidified on cooling and was crystallised twice from alcohol (charcoal) as thin rhombic platelets, m. p. 94° (6·6 g.; 58% overall yield from α-picoline) (Found : C, 86·8; H, 7·1; N, 6·6. $C_{16}H_{15}N$ requires C, 86·9; H, 6·8; N, 6·3%). Its *picrate*, prepared in alcoholic solution and recrystallised from the same solvent, formed greenish-yellow needles, m. p. 157—158° (decomp.) (Found, N, 12·1. $C_{22}H_{18}O_7N_4$ requires N, 12·5%).

α-Butyrophenonyl-α'-picolinium chloroplatinate was obtained, from a portion of the clarified aqueous solution described above, as a buff-coloured precipitate, m. p. 178° (decomp.) (Found : N, 3·2; Pt, 21·5. $C_{32}H_{36}O_2N_2PtCl_6$ requires N, 3·2; Pt, 22·0%).

Reduction of 3-Acetyl-2-methylpyrrocoline (Clemmensen Method).—Amalgamated zinc wool (100 g.), washed several times with alcohol and finally with acetic acid, was mixed with a solution of the acetyl compound (20 g.) in anhydrous

acetic acid (250 c.c.), and the whole heated under reflux for 7 hrs., whilst a slow stream of hydrogen chloride was passed in. The colourless solution, separated from the zinc, was rendered strongly alkaline with sodium hydroxide, and the liberated oil removed in a current of steam (12·3 g.). This distilled at 104—128°/12 mm., giving two main fractions: (i) b. p. 104—107° (2·32 g.), (ii) b. p. 120—125° (2·66 g.). By combination with picric acid and fractional crystallisation of the resulting salts from acetone–ether (i) yielded as the main product, 2-*methyl*-3-(α-*hydroxyethyl*)*pyrrocoline picrate*, pale yellow platelets from methyl alcohol, m. p. 141·5—142° (Found: C, 50·4; H, 4·4; N, 14·2. $C_{17}H_{16}O_8N_4$ requires C, 50·5; H, 4·0; N, 13·9%). By reaction with phenyl *iso*cyanate, the corresponding *urethane* was obtained, needles from alcohol, m. p. 142—142·5° (Found: N, 9·2. $C_{18}H_{18}O_2N_2$ requires N, 9·5%). Fraction (ii) yielded, as the main product, a picrate as greenish-yellow needles from alcohol, m. p. 124° (decomp.), which was not depressed on admixture with the picrate, m. p. 124° (decomp.), prepared in a similar way from 2-methyl-3-ethylpyrrocoline. Good analyses could not be obtained with either specimen of this derivative (N values varied from 12·5 to 13·6%), but it was possible to convert it into a chloroplatinate, m. p. 174° (decomp.), not depressed on admixture with 2-methyl-3-ethylpyrrocoline chloroplatinate.

Examination in the same way of the other fractions from the distillation showed that they were mixtures of the two products described above.

Reduction of 3-*Acetyl*-2-*phenylpyrrocoline* (*Kishner–Wolff Method*).—The pyrrocoline (7 g.), hydrazine hydrate (30 c.c. of 85%), and a solution of sodium (14 g.) in absolute alcohol (280 c.c.) were heated together in a steel autoclave at 180° for 22 hrs. From the cooled contents of the autoclave, 2-phenylpyrrocoline (2·6 g.; identified by m. p. and conversion into picrate) was removed by filtration. The filtrate, freed from alcohol, diluted with water, and extracted with ether yielded 2-phenyl-3-ethylpyrrocoline, rhombic platelets (2·3 g., 35% yield) from ligroin; m. p. 94° alone and mixed with an authentic specimen (Found: C, 87·0; H, 6·7; N, 6·0%). Its picrate had m. p. 157—158° (decomp.) alone and mixed.

2-*Phenyl*-3-*benzylpyrrocoline*.—Benzylideneacetophenone (20·8 g.) was reduced (*Org. Synth.*, Coll. Vol. I, 95) to benzylacetophenone (19·1 g.). Bromination of the latter (Kohler and Kimball, *J. Amer. Chem. Soc.*, 1934, **56**, 730) gave the required α-bromo-α-benzylacetophenone in good yield. A mixture of this bromo-ketone (10·2 g.) and α-picoline (3·8 g.) was heated on the steam-bath for 30 mins.; after 3 days the resulting thick brown oil was extracted several times with hot water, and the aqueous solution clarified by extraction with ether and shaking with charcoal. To the major portion (120 c.c.) sodium hydrogen carbonate (12 g.) was added, the mixture heated under reflux for 1 hr., and the liberated oil extracted with ether. The extract, after two recrystsllisations from alcohol, gave 2-*phenyl*-3-*benzylpyrrocoline* (2·54 g.), colourless needles, m. p. 100—101° (Found: C, 88·9; H, 6·2; N, 5·0. $C_{21}H_{17}N$ requires C, 89·0; H, 6·0; N, 5·0%). Its *picrate*, prepared in alcoholic solution and recrystallised from *iso*propyl alcohol, forms yellow irregular rhombs, m. p. 112·5—113·5° (decomp.) (Found: C, 63·7; H, 4·4; N, 10·6. $C_{27}H_{20}O_7N_4$ requires C, 63·3; H, 3·9; N, 10·9%).

N-(α-*Benzylphenacyl*)-α′-*picolinium chloroplatinate* separated, from a portion of the clarified aqueous solution described above, as a buff-coloured powder, m. p. 142—143° (decomp.) (Found: N, 2·7; Pt, 19·4. $C_{42}H_{40}O_2N_2Cl_6Pt$ requires N, 2·9; Pt, 19·3%).

Reduction of 3-*Benzoyl*-2-*phenylpyrrocoline* (*Kishner–Wolff Method*).—A mixture of the pyrrocoline (7 g.), hydrazine hydrate (30 c.c. of 95%), and a solution of sodium (4 g.) in absolute alcohol (150 c.c.) was heated for 20 hrs. at 170° in a steel autoclave. Filtration of the cooled product removed a crystalline solid (4·18 g.) which, after purification by extraction with hot alcohol (30 c.c.), was identified as 2-phenylpyrrocoline (2·2 g.). From the alcoholic extract, needles were obtained on cooling, separated from contaminating 2-phenylpyrrocoline by solution in dry benzene (5 c.c.). The original filtrate, after concentration in a vacuum, dilution with water and extraction of the insoluble oil into ether, yielded a crude solid which was mixed with the benzene extract described above. From this mixture 2-phenyl-3-benzylpyrrocoline was obtained, (1·75 g.), needles from alcohol, m. p. 100—101° alone or when mixed with the material prepared by the method described above (Found: C, 88·8; H, 6·2; N, 4·8%). The picrate, m. p. 112·5—113·5° (decomp.), likewise proved to be identical with that of 2-phenyl-3-benzylpyrrocoline described above (Found: N, 11·2%).

Reduction of 3-*Acetyl*-2-*methylpyrrocoline* (*by Use of Platinum Oxide*).—A solution of the acetyl compound (9 g.) in A.R. glacial acetic acid (15 c.c.) was hydrogenated in the presence of Adams's catalyst (0·5 g.) at room temperature and pressure. Reaction ceased after 15 hrs., when 5·1 l. of hydrogen had been absorbed (7·7 l. required for complete reduction). The solution on dilution with water deposited white, greasy platelets of crude 3-*acetyl*-2-*methyl*-5 : 6 : 7 : 8-*tetrahydropyrrocoline*, m. p. 71—73°. The solid was removed, and the filtrate neutralised with sodium hydroxide, another 0·34 g. of the same compound separating (4·2 g. total). It recrystallised from dilute alcohol (charcoal) as colourless needles, m. p. 74—74·5° (Found: C, 74·2; H, 8·2; N, 8·3. $C_{11}H_{15}ON$ requires C, 74·6; H, 8·5; N, 7·9%).

The neutral filtrate was rendered strongly alkaline and shaken with ether to extract a brown oil (4·2 g.). This was fractionally distilled to give two clear-cut fractions: (i) b. p. 80—85°/11 mm. (1·43 g.), (ii) b. p. 106—110°/11 mm. (1·93 g.), leaving a brown residue. Reaction of fraction (i) with methyl iodide yielded a brown oil, obtained as a pale yellow rather deliquescent solid on rubbing with dry ethyl acetate. Fractional crystallisation of this from alcohol–ethyl acetate gave a very small quantity of an amorphous powder, m. p. 218—220°, and tiny rhombic platelets, m. p. 196—198°, which liquefied rapidly in air. Fraction (ii) combined with phenyl *iso*cyanate to yield the phenylurethane of 2-methyl-3-(α-hydroxyethyl)octahydropyrrocoline, a microcrystalline powder, m. p. 136—137° (Found: C, 71·3; H, 8·8; N, 9·0. Calc. for $C_{18}H_{26}O_2N_2$: C, 71·5; H, 8·6; N, 9·3%).

The *benzylidene* derivative of 3-acetyl-2-methyl-5 : 6 : 7 : 8-tetrahydropyrrocoline, prepared from a solution of the acetyl derivative (2·0 g.), benzaldehyde (3·0 c.c.), and sodium hydroxide (4 c.c. of 2N) in alcohol (20 c.c.), was deposited after 3 days on scratching as yellow prisms; recrystallised from alcohol, m. p. 126—127° (Found: C, 80·9; H, 7·2; N, 5·5. $C_{18}H_{19}ON$ requires C, 81·5; H, 7·2; N, 5·3%); and the 2 : 4-*dinitrophenylhydrazone*, purified by dissolving it in a large volume of hot ethyl acetate and concentration until solid began to separate, formed tiny, black, monoclinic prisms, appearing ruby-red under the microscope, m. p. 209—210° (Found: C, 57·4; H, 5·3; N, 19·7. $C_{17}H_{19}O_4N_5$ requires C, 57·1; H, 5·3; N, 19·6%). Attempts to prepare a phenylhydrazone of 3-acetyl-2-methyl-5 : 6 : 7 : 8-tetrahydropyrrocoline were unsuccessful.

3-*Acetyl*-2-*phenyl*-5 : 6 : 7 : 8-*tetrahydropyrrocoline*: *Reduction of* 3-*Acetyl*-2-*phenylpyrrocoline at Room Temperature* (*using Raney Nickel*). *Expt.* I (*see Table*).—The hydrogen absorption, which ceased after 25 hrs., could not be induced to continue by addition of fresh catalyst. After removal of the catalyst, the solution was concentrated in a vacuum to give an almost colourless oil which by solution in hot ligroin (b. p. 40—60°) yielded 3-*acetyl*-2-*phenyl*-5 : 6 : 7 : 8-*tetrahydropyrrocoline*; needles, m. p. 81—82° (9·3 g.; 91%) (Found: C, 80·3; H, 7·0; N, 5·9. $C_{11}H_{17}ON$ requires C, 80·3; H, 7·1; N, 5·9%). Its 2 : 4-*dinitrophenylhydrazone*, prepared in alcoholic solution and recrystallised from acetic acid, formed red needles, m. p. 228—229° (Found: N, 16·3. $C_{22}H_{21}O_4N_5$ requires N, 16·7%).

Hydrolysis of 3-*Acetyl*-2-*phenyltetrahydropyrrocoline*: *Preparation of* 2-*Phenyl*-5 : 6 : 7 : 8-*tetrahydropyrrocoline*.—Hydrolysis of this pyrrocoline (2 g.) proceeded readily at room temperature by solution in concentrated hydrochloric acid (5 c.c.) for 10 minutes. The solution was made alkaline, and the precipitated *tetrahydropyrrocoline* was filtered off, washed, with water, and dried in a vacuum (P_2O_5), being obtained as a pale pink solid, m. p. 74—77°. Purification proved difficult: it sublimed slowly at 70°/0·006 mm. to an almost white sublimate which rapidly became buff and then more slowly, on exposure to air, brown. Recrystallisation was not very satisfactory, and absolute ethyl alcohol alone proved useful, the compound being obtained from this solvent as yellow crystalline rods tinted with brown, m. p. 76·5—

Summary of result of hydrogenation of 3-*acetyl*-2-*phenylpyrrocoline with Raney nickel and copper chromite as catalyst.*

Expt.	Wt. of acetyl cpd. (g.).	Vol. of dioxan (c.c.).	Catalyst and wt.	H_2 press. at room temp. (atm.)	Temp.	Time (hrs.).	Products.*
I	10	60	Ni, 4 g.	1	15°	25	A (9·3 g.)
II	5	160	Ni, 5 g.	70	130	1	A (3 g.); C (1·5 g.)
III	10	250	Ni, 7·5 g.	85	125—135	1	A (4·6 g.); C (2·6 g.); B (0·54 g.)
IV	15	250	,,	120	170—175	1·1	C (11·4 g.); 1·4 g. of oil, b. p. 160—180°/12 mm., not investigated
V	30	250	Ni, 10 g.	117	180	2·5	C (24·3 g.); two uninvestigated oils, b. p. 168°/12 mm. and 120—140°/0·25 mm.
VI	25	300	Ni, 10 g.	125	190	10·2	D (23·0 g.)
VII	10	200	$CuCrO_3$, 2 g.	150	170—175	1·5	C (4·28 g.); B (3·7 g.)
VIII	12	200	$CuCrO_3$, 2 g.	120	180—200	4	C (5·4 g.); B (2·5 g.)

* A = 3-Acetyl-2-phenyl-5 : 6 : 7 : 8-tetrahydropyrrocoline; B = 2-phenyl-3-ethyl-5 : 6 : 7 : 8-tetrahydropyrrocoline; C = 2-phenyl-3-ethyloctahydropyrrocoline; D = 2-*cyclo*hexyl-3-ethyloctahydropyrrocoline.

77·5° (Found : N, 7·2. $C_{14}H_{15}N$ requires N, 7·1%). An immediate deep purple colour was obtained in the pine-splint test. Its *picrate* separated from alcoholic solution as a red solid, unstable to prolonged heating in organic solvents, picric acid being set free. It was recrystallised from a warm mixture of alcohol and ligroin (b. p. 80—100°), forming fine red needles, m. p. 111·5—112·5° (Found : C, 56·1; H, 4·3; N, 13·4. $C_{20}H_{18}O_7N_4$ requires C, 56·3; H, 4·2; N, 13·1%).

Acetylation of 2-*Phenyl*-5 : 6 : 7 : 8-*tetrahydropyrrocoline*.—The tetrahydropyrrocoline (0·65 g.) was heated under reflux in acetic anhydide (8 c.c.) in the presence of fused sodium acetate (0·1 g.) for 2·25 hrs. The resulting almost black solution was concentrated under reduced pressure, and the residual oil shaken with water and ether. The ethereal solution, after being dried and concentrated left a residue which after being crystallised twice from ligroin gave 3-acetyl-2-phenyl-5 : 6 : 7 : 8-tetrahydropyrrocoline (0·4 g.), m. p. 81—82° alone and when mixed with an authentic specimen. It yielded a dinitrophenylhydrazone, m. p. 228—229°, similarly not depressed by an authentic specimen.

2-*Phenyl*-3-*ethyl*-5 : 6 : 7 : 8-*tetrahydropyrrocoline*.—(a) *By reduction of* 3-*acetyl*-2-*phenylpyrrocoline* (*with copper chromite*). *Expt.* VIII (*see Table*). Distillation of the resulting fluorescent oil gave two fractions, (i) b. p. 158—161°/12 mm. (5·4 g.), (ii) b. p. 198—204°/12 mm. Fraction (ii) yielded, on dissolving in hot *iso*propyl alcohol, 2-*phenyl*-3-*ethyl*-5 : 6 : 7 : 8-*tetrahydropyrrocoline* (2·5 g.) which after recrystallisation had m. p. 100—101° (Found : C, 85·4; H, 8·3; N, 6·1. $C_{16}H_{19}N$ requires C, 85·3; H, 8·4; N, 6·2%). A picrate could not be prepared, and the chloroplatinate, m. p. 115—120° (decomp.), could not be purified. It was best characterised by its U.V. absorption spectrum : $\lambda_{max.}$ 2780 A., ϵ 7700; λ min. 2660 A., ϵ 6960; inflexion 2400 A., ϵ 1100. Fraction (i) yielded a mixture of two hydrochlorides, m. p. 199—200° and 231—232°, identical with the hydrochlorides of 2-phenyl-3-ethyloctahydropyrrocoline described below. The hydrochloride obtained in larger amount, m. p. 231—232°, only was analysed (Found : C, 72·3; H, 9·1; N, 5·3%), and converted into the free *base* which had b. p. 156—157°/11 mm., $n_D^{20°}$ 1·5350 (Found : C, 83·6; H, 10·1; N, 6·2. $C_{16}H_{23}N$ requires C, 83·9; H, 10·0; N, 6·1%).

(b) *By reduction of* 2-*phenyl*-3-*ethylpyrrocoline* (*with Raney nickel*). A solution of the pyrrocoline (2·5 g.) in dioxan (25 c.c.) was hydrogenated at room temperature and pressure with Raney nickel (*ca.* 2 g.) as catalyst. Absorption of hydrogen ceased after 4·5 hrs. when 580 c.c. had been consumed (545 c.c. required for 2 mols. of hydrogen). The filtered solution was concentrated in a vacuum, and the residue crystallised from alcohol to yield 2-phenyl-3-ethyl-5 : 6 : 7 : 8-tetrahydropyrrocoline, needles, m. p. 100—101° (2·32 g.; 92%), identical in all respects, including ultra-violet absorption spectrum, with the compound prepared in Expt. VIII. On oxidation with boiling permanganate it yielded benzoic acid.

2-*Phenyl*-3-*ethyloctahydropyrrocoline*.—*Expt.* III (*see Table*). The oily product obtained on concentration in a vacuum of the filtered dioxan solution from the hydrogenation gave 3-acetyl-2-phenyl-5 : 6 : 7 : 8-tetrahydropyrrocoline (4·6 g.), m. p. 81—82°, on crystallisation from ligroin. This product was identified in the usual manner. The ligroin filtrate yielded an oil (5·4 g.) which on distillation gave two fractions : (i) b. p. 158—162°/12 mm. (2·6 g.), (ii) b. p. 180—211°/12 mm. (2·2 g.). Fraction (ii), a yellow oil, deposited 2-phenyl-3-ethyl-5 : 6 : 7 : 8-tetrahydropyrrocoline (0·54 g.) from ligroin, needles, m. p. 100—101° alone and admixed with that from Expt. VIII (Found : C, 85·3; H, 8·4; N, 6·1%). Fraction (i) gave a positive reaction (reddish-purple) in the pine-splinter test and was freed from the " pyrrole " constituent by conversion into a mixture of hydrochlorides, m. p. 199—200° and 231—232°, which did not depress the m. p. of the 2-phenyl-3-ethyloctahydropyrrocoline hydrochlorides arising from Expt. V.

Expt. V (*see Table*). The product on fractional distillation gave a major fraction (24·3 g.), b. p. 156—158°/12 mm., $n_D^{20°}$ 1·5327 (Found : C, 82·7; H, 10·8; N, 5·8%). This oil, which gave a reddish-purple colour in the pine-splinter test, could not be purified by redistillation or chromatography and was finally freed from the " pyrrole " constituent by conversion into a mixture of two hydrochlorides which were separable by crystallisation. The acetone-insoluble *hydrochloride*, m. p. 231—232°, crystallised from methyl cyanide as colourless needles (Found, after drying in a vacuum at room temp. : C, 71·5; H, 8·7. $C_{16}H_{23}N,HCl,0·2H_2O$ requires C, 71·3; H, 9·1%. Found, after drying in a vacuum at 160° : C, 72·6; H, 9·2; N, 5·2; Cl, 13·5. $C_{16}H_{23}N,HCl$ requires C, 72·3; H, 9·0; N, 5·3; Cl, 13·4%). The acetone-soluble fraction on crystallisation from acetone–ligroin (b. p. 60—80°) yielded a *hydrochloride*, m. p. 199—200°, as a microcrystalline powder. (Found, after drying in a vacuum at room temp. : C, 71·5; H, 9·1%. Found, after drying in a vacuum at 110° : C, 72·0; H, 8·9; N, 5·4; Cl, 13·3%). Regeneration of 2-phenyl-3-ethyloctahydropyrrocoline from the first hydrochloride gave an oil, b. p. 156—157°/11 mm., $n_D^{20°}$ 1·5345 (Found : C, 84·3; H, 10·2; N, 5·7%). Oxidation of the oil with boiling permanganate in the presence of sodium hydrogen carbonate yielded benzoic acid.

Similarly the base derived from the hydrochloride, m. p. 199—200°, analysed satisfactorily (Found : C, 83·8; H, 10·0; N, 5·9%); $n_D^{20°}$ 1·5348.

Mixtures of the two hydrochlorides melted between 200° and 230° according to the proportions used; both gave a large depression of m. p. on admixture with 2-*cyclo*hexyl-3-ethyloctahydropyrrocoline hydrochloride (m. p. 219—220°) (below) and none of this was detected in the above reaction product.

2-cyclo*Hexyl*-3-*ethyloctahydropyrrocoline*.—(a) *By reduction of* 3-*acetyl*-2-*phenylpyrrocoline* (*with Raney nickel*). *Expt.* VI (*see Table*). The product on distillation gave 2-cyclo*hexyl*-3-*ethyloctahydropyrrocoline* as the sole fraction, b. p. 156—158°/12 mm., $n_D^{20°}$ 1·4988 (23·03 g.; 92%), a colourless oil which gave negative results in the pine-splinter and oxalic acid melt tests (Found : C, 81·7; H, 12·4; N, 6·2. $C_{16}H_{29}N$ requires C, 81·7; H, 12·3; N, 6·0%). The *hydrochloride*,

which was initially somewhat deliquescent, recrystallised from acetone as white needles, m. p. 219—220° (Found : C, 70·8; H, 11·0; N, 5·3; Cl, 13·0. $C_{16}H_{29}N$,HCl requires C, 70·7, H, 11·1; N, 5·2; Cl, 13·1%). The hydrobromide was prepared by evaporation of a solution of the base in hydrobromic acid (30%) under reduced pressure. The resulting oil crystallised from acetone–ether as a microcrystalline powder, m. p. 211—212°.

On admixture of the 2-*cyclo*hexyl-3-ethyloctahydropyrrocoline with an equal volume of methyl iodide a homogeneous solution resulted from which a yellow oil slowly separated to form a discrete upper layer, which gradually increased until the whole was once more homogeneous. This on trituration with ethyl acetate yielded the *methiodide* as a crystalline solid which recrystallised from acetone–ligroin (b. p. 60—80°) as white platelets, m. p. 201—202° (Found : C, 53·8; H, 8·4; N, 3·7; I, 33·5. $C_{17}H_{32}NI$ requires C, 54·1; H, 8·5; N, 3·7; I, 33·7%).

(b) *From 2-phenyl-3-ethylpyrrocoline.* A solution of this pyrrocoline (18 g.) in dioxan was hydrogenated in the presence of Raney nickel (10 g.) for 18 hrs. at 180°, with an initial hydrogen pressure of 123 atm. The oily product on distillation gave 2-*cyclo*hexyl-3-ethyloctahydropyrrocoline as a major fraction, b. p. 156—158°/12 mm., $n_D^{20°}$ 1·4989 (15·4 g.; 80%) (Found : C, 81·4; H, 12·2; N, 6·0%). The hydrochloride melted at 219—220° alone and on admixture with that from Expt. VI (Found : C, 70·8; H, 11·0; N, 4·9; Cl, 12·8%). Similarly the hydrobromide, m. p. 211—212°, was not depressed in m. p. on admixture with the specimen from Expt. VI.

When the methiodide was prepared essentially as in Expt. VI, it separated as a discrete lower layer from the initially homogeneous mixture. The white powder obtained on trituration of the yellow oil with ethyl acetate crystallised from acetone–ligroin (b. p. 60—80°) as white platelets, m. p. 188—189° (Found : C, 53·9; H, 8·5; N, 3·7; I, 34·1%).

2-*Methyl-3-ethyloctahydropyrrocoline.*—(a) *By reduction of 3-acetyl-2-methylpyrrocoline (using Raney nickel).* A solution of the acetyl compound (20 g.) in dioxan (200 c.c.) was hydrogenated at 180° for 5 hrs. at an initial pressure of 150 atm., Raney nickel (*ca.* 6 g.) being used as catalyst. The mobile ammoniacal liquid (14·3 g.) obtained after filtering and concentrating the solution was distilled, b. p. 79—86°/11 mm. It gradually discoloured on standing and deposited a heavy brown oil (Found : C, 79·2; H, 12·9; N, 8·0. $C_{11}H_{21}N$ requires C, 79·0; H, 12·6; N, 8·4%), $n_D^{20°}$ 1·4686. The pine-splint and oxalic acid melt tests were negative. Addition of methyl iodide to an ethereal solution of the base caused precipitation of the methiodide as a white powder; it recrystallised from alcohol–ethyl acetate as tiny needles, m. p. 197—198° (Found : C, 46·8; H, 7·4; N, 4·8; I, 40·9. Calc. for $C_{12}H_{24}NI$: C, 46·6; H, 7·8; N, 4·5; I, 41·1%). The perchlorate, precipitated as a pinkish powder on addition of 60% perchloric acid to a hydrochloric acid solution of the base, recrystallised from alcohol–ether as tiny colourless needles, m. p. 221·5—223° (lit. 220—221°) (Found : C, 49·3; H, 7·9. Calc. : C, 49·4; H, 8·2%). The hydrobromide was obtained by concentration in a vacuum of a solution of the base in hydrobromic acid at room temperature; it recrystallised from alcohol–ethyl acetate as colourless needles, m. p. 236·5—237°. The hydriodide, prepared similarly, had m. p. 248·5—251° (decomp.) (lit. 248°).

(b) *By reduction of 2-methyl-3-ethylpyrrocoline (using platinum oxide).* A solution of the pyrrocoline (5 g.) in acetic acid (20 c.c.) was hydrogenated in the presence of Adams's catalyst (0·4 g.) at room temperature and pressure. The theoretical quantity of hydrogen was absorbed after 5 hrs. After dilution with water, the solution was rendered alkaline, the ammoniacal liquid released extracted into ether, and the product distilled; b. p. 83—85°/12 mm. The colourless mobile liquid obtained possessed a faint violet fluorescence, and gave a positive result in the pine-splinter test, but a colourless melt with oxalic acid. The fluorescence persisted on redistillation (Found : C, 79·1; H, 12·8%). The methiodide, prepared as above, was obtained initially as a jelly-like mass, but recrystallised from alcohol–ethyl acetate as tiny, colourless needles, m. p. 229—229·5° (Found : C, 46·7; H, 7·7; N, 4·5; I, 41·5%). The perchlorate, m. p. 221·5—222° was not depressed in m. p. on admixture with that described above (Found : C, 49·0; H, 8·1; Cl, 13·1. Calc. : C, 49·4; H, 8·2; Cl, 13·3%). Similarly, the hydrobromide, m. p. 234—235·5°, and the hydriodide, m. p. 249—251° (decomp.), did not depress the m. p. of the corresponding derivatives described above on admixture.

Thanks are expressed to Glaxo Laboratories Ltd., Greenford, for generously providing laboratory facilities for two of us (E. T. B. and D. O. H.) and for the supply of materials used in this and the preceding three communications.

Battersea Polytechnic, S.W. 11.
Glaxo Laboratories Ltd., Greenford.

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