The Chemistry of the Pyrrocolines. Part VII. Further Experiments with 2-Methylpyrrocoline.*

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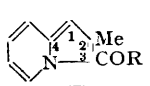
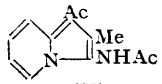
The reactions of 2-methylpyrrocoline with carbonyl chloride, benzoyl chloride, and a diazonium salt have been studied and the products orientated. Several derivatives of 2-methylpyrrocoline-3-carboxylic acid and 3-amino-2-methylpyrrocoline have been prepared. Attempted Rosenmund reduction of 2-methylpyrrocoline-3-carbonyl chloride proceeded abnormally, giving di-(2-methyl-3-pyrrocolinyl) ketone. The carbonyl group in this and other 1- or 3-acylpyrrocolines was reduced to methylene on mild treatment with lithium aluminium hydride. 3-Formyl-2-methylpyrrocoline has been prepared in high yield by the McFadyen–Stevens reaction.

The original aims of this investigation were (*a*) to see how far certain reactions of pyrrocoline (Scholtz and Fraude, *Ber.*, 1913, **46**, 1069) could be paralleled in the case of 2-methylpyrrocoline and to orientate the products and (*b*) to prepare representatives of the then unknown class of pyrrocoline aldehydes. The description of three such aldehydes by Rossiter and Saxton (*J.*, 1953, **3654**) prompted the publication of a preliminary account of some of our findings (*Chem. and Ind.*, 1954, **224**).

Scholtz and Fraude (*loc. cit.*) obtained the chloride of an unidentified carboxylic acid by treating pyrrocoline with carbonyl chloride at room temperature, and 2-methylpyrrocoline has now been found to undergo a similar reaction. Treatment of the acid chloride with methylmagnesium iodide gave only a little 2-methylpyrrocoline, presumably by the action of more Grignard reagent on the acetylpyrrocoline first formed (cf. Kondo and Osawa, *J. Pharm. Soc. Japan*, 1936, **56**, 73; *Chem. Zentr.*, 1936, **107**, ii, 2910; Borrows and Holland, *J.*, 1947, 670), but with dimethylcadmium the chloride gave a fair yield of 3-acetyl-2-methylpyrrocoline (I; R = Me) identical with an authentic specimen. The carbonyl chloride reaction product can thus be formulated as 2-methylpyrrocoline-3-carbonyl chloride (I; R = Cl): Scholtz and Fraude's product was probably similarly substituted.



(I)



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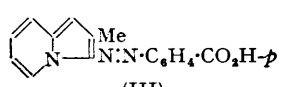

(III)

The amide (I; R = NH_2) and anilide (I; R = NHPh) were readily obtained from the chloride. In addition to the expected 2-methylpyrrocoline-3-carboxylic acid (I; R = OH) the action of cold sodium hydroxide solution on the chloride gave a larger amount of the corresponding anhydride. Perhaps because of its insolubility, the anhydride proved resistant to boiling aqueous sodium hydroxide but hot aqueous-alcoholic potassium hydroxide brought about hydrolysis to the acid. 2-Methylpyrrocoline-3-carboxylic acid is a very weak acid, being readily liberated from its sodium salt by treatment with acetic acid to pH 5—6. It is also decarboxylated with great ease: brief heating at the melting

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point afforded 2-methylpyrrocoline in excellent yield and the same product was obtained by warm hydrochloric acid.

Scholtz and Fraude (*loc. cit.*) obtained a benzoyl derivative by the action of cold benzoyl chloride on pyrrocoline, and 2-phenylpyrrocoline similarly afforded 3-benzoyl-2-phenylpyrrocoline (Borrows, Holland, and Kenyon, *J.*, 1946, 1069). Although 2-methylpyrrocoline did not react with acetyl chloride without a catalyst (*idem, ibid.*) reaction with benzoyl chloride has now given 3-benzoyl-2-methylpyrrocoline (I; R = Ph), the structure being proved by reduction to 3-benzyl-2-methylpyrrocoline (see below). The ketone (I; R = Ph) formed a 2 : 4-dinitrophenylhydrazone only with difficulty.

Scholtz and Fraude (*loc. cit.*) considered, on the basis of a colour reaction applicable to α-substituted pyrroles (Fischer and Bartholomaus, *Ber.*, 1912, **45**, 1919), that the red-brown dyes obtained from pyrrocoline and diazotised aromatic amines were 3-substituted pyrrocolines. Our product from 2-methylpyrrocoline and benzenediazonium chloride was a deep red oil, but use of diazotised *p*-aminobenzoic acid gave a crystalline dye. Reductive acetylation of the dye with zinc dust, acetic acid, and acetic anhydride gave a good yield of *p*-acetamidobenzoic acid together with a smaller amount of a colourless ketone, $C_{13}H_{14}O_2N_2$, which was characterised as the 2 : 4-dinitrophenylhydrazone. Oxidation of the ketone with hydrogen peroxide gave picolinic acid *N*-oxide, indicating that the substituents in the pyrrocoline nucleus were confined to the 5-membered ring, and since 1-acetamido-3-acetyl-2-methylpyrrocoline has m. p. 219° (Kondo and Nishizawa, *J. Pharm. Soc. Japan*, 1936, **56**, 1; *Chem. Abs.*, 1936, **30**, 3431) the present product, m. p. 190°, was considered to be 3-acetamido-1-acetyl-2-methylpyrrocoline (II). This indicates structure (III) for the dye and, by analogy, supports the suggested structures of Scholtz and Fraude's compounds.

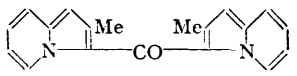
The structure of 3-acetamido-1-acetyl-2-methylpyrrocoline (II) was confirmed by an alternative synthesis. Treatment of 3-acetyl-2-methylpyrrocoline (I; R = Me) with hydrazoic acid in the presence of sulphuric acid at 0° readily gave 3-acetamido-2-methylpyrrocoline which, when heated with acetic anhydride and sodium acetate, yielded the 1-acetyl derivative (II) identical with that obtained from the dye (III). 3-Benzoyl-2-methylpyrrocoline failed to react with hydrazoic acid under the conditions which succeeded with the acetyl analogue, but prolonged treatment at room temperature gave 3-benzamido-2-methylpyrrocoline in poor yield. None of the isomeric 2-methylpyrrocoline-3-carboxyanilide, previously obtained from the acid chloride (I; R = Cl) and aniline, could be isolated. The Schmidt reaction on unsymmetrical ketones usually, but not invariably, takes place predominantly by migration of the bulkier group from carbon to nitrogen (Badger, Howard, and Simons, *J.*, 1952, 2849) and these first examples of the reaction in the pyrrocoline series follow the general tendency.

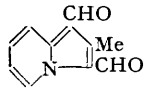
Hydrolysis of 3-acetamido-2-methylpyrrocoline by brief heating with dilute hydrochloric acid appeared to disrupt the molecule extensively since the only identifiable product was ammonium chloride. Under comparable conditions dilute phosphoric acid did not attack the amide. Hydrolysis was slowly brought about by boiling sodium hydroxide solution but the basic oil which resulted was very unstable in air and crystalline derivatives could not be prepared. The only known aminopyrrocoline, 3-acetyl-1-amino-2-methylpyrrocoline, is stated to be unstable in air (Kondo and Nishizawa, *loc. cit.*).

Attempted reduction of 2-methylpyrrocoline-3-carbonyl chloride by the Rosenmund method in boiling xylene resulted in only slow evolution of hydrogen chloride, even when unpoisoned palladised barium sulphate was used as the catalyst. Reaction in boiling anisole was faster, but in neither case was any 3-formyl-2-methylpyrrocoline (I; R = H) obtained. Instead, the product was a bright yellow solid, $C_{19}H_{16}ON_2$. It was considered that 2-methylpyrrocoline might have arisen by cleavage of the COCl group, which is known to occur in the Rosenmund reduction of certain heterocyclic acid chlorides (Mozingo and Mosettig, *Organic Reactions*, 1948, **4**, 362), and then combined with more chloride to give di-(2-methyl-3-pyrrocolinyl) ketone (IV). This was supported by production of the compound $C_{19}H_{16}ON_2$, albeit in low yield, when the acid chloride was refluxed in anisole under nitrogen. Apparently some 2-methylpyrrocoline is formed merely by thermal decomposition of the chloride, but the reducing conditions of the Rosenmund reaction are doubtless

more favourable for the production of the supposed intermediate. Formation of the presumed di-(2-methyl-3-pyrrocolinyl) ketone in high yield when 2-methylpyrrocoline was heated with the acid chloride in benzene provided still stronger support for the suggested mechanism. There is no proof of the attachment of the carbonyl group to the 3-position of both pyrrocoline nuclei, but this is the usual site of attack by acid chlorides.

In common with other acylpyrrocolines the ketone (IV) was decomposed by hot mineral acid, the yield of 2-methylpyrrocoline being virtually quantitative. The substance failed to react with the usual carbonyl reagents even on prolonged heating, but this is not surprising in view of the considerable steric hindrance and the known low reactivity of acetyl and benzoyl groups in the 3-position of the pyrrocoline nucleus.

(IV) 



(V)

With the object of substantiating the presence of the keto-group, reduction of (IV) to a secondary alcohol was attempted. The compound was not attacked by zinc dust and hot alcoholic potassium hydroxide or acetic acid or by aluminium or sodium *iso*propoxides in boiling xylene. Sodium borohydride in boiling methanol was also ineffective, but lithium aluminium hydride in ether effected rapid reduction at ordinary temperature. The product, however, was not an alcohol but di-(2-methyl-3-pyrrocolinyl)methane, which was also obtained from 2-methylpyrrocoline and formaldehyde at room temperature, thus providing further support for the symmetrical structure of the ketone (IV). Scholtz (*Ber.*, 1912, **45**, 734) reported the condensation of various aromatic aldehydes with pyrrocoline and suggested by analogy with the β-reactivity of indole, that reaction probably occurred in one of the β-(*i.e.*, 1- and 2-)positions of the pyrrocoline ring, but since the 3-position is now known to be the most reactive centre his products also were probably di-3-pyrrocolinylmethanes.

As in the case of the ketone (IV), treatment of 3-acetyl- and 3-benzoyl-2-methylpyrrocoline with lithium aluminium hydride caused elimination of oxygen and the high yields and absence of side-reactions make this method of reduction distinctly preferable to the Wolff–Kishner or modified Clemmensen procedures which have been used hitherto (Borrows, Holland, and Kenyon, *J.*, 1946, 1083). In order to determine whether a typical 1-acylpyrrocoline would be reduced in the same way, 1-acetyl-2 : 3-dimethylpyrrocoline was prepared by the action of acetic anhydride and sodium acetate on 2 : 3-dimethylpyrrocoline. The resulting ketone was characterised as the oxime, and the presence of the substituent in the only free position of the 5-membered ring was established by oxidation to picolinic acid *N*-oxide. Mild treatment of the ketone with lithium aluminium hydride gave 1-ethyl-2 : 3-dimethylpyrrocoline.

Rossiter and Saxton (*loc. cit.*) later reported the formation of 1 : 2 : 3-trimethylpyrrocoline by the action of lithium aluminium hydride on 1-formyl-2 : 3-dimethylpyrrocoline and indeed complete elimination of oxygen from a group attached to a position of high electron density is now known to be not unusual (cf. Conover and Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 3586), although only in the case of certain 3-indolyl derivatives (Leete and Marion, *Canad. J. Chem.*, 1953, **31**, 775) has it been observed under conditions as mild as those which suffice for 1- and 3-acylpyrrocolines.

When the Rosenmund reaction failed to yield 3-formyl-2-methylpyrrocoline a possible synthesis similar to that of 3-formylindole by Elks, Elliott, and Hems (*J.*, 1944, 629) was considered. 2-Methylpyrrocoline did not condense with ethyl oxalate under the conditions which succeed with indole, but treatment with ethoxalyl chloride readily gave a crystalline product which, by analogy with the behaviour of other acid chlorides, was considered to be ethyl 2-methylpyrrocoline-3-glyoxylate (I; R = CO_2Et). Alkaline hydrolysis then gave the acid (I; R = CO_2H), but attempts to convert this into the anil merely gave the aniline salt. The failure of other efforts to protect the carbonyl group in (I; R = CO_2H or CO_2Et) and of attempts to decarboxylate the unprotected keto-acid caused this approach to be abandoned.

Finally, 2-methylpyrrocoline-3-carbonyl chloride was treated with hydrazine, and the benzenesulphonyl derivative of the resulting hydrazide (I; R = $NH{\cdot}NH_2$) was heated with

sodium carbonate in ethylene glycol according to the general procedure of McFadyen and Stevens (*J.*, 1936, 584), to give a good yield of 3-formyl-2-methylpyrrocoline. Rossiter and Saxton (*loc. cit.*) obtained this aldehyde in poor yield by the action of *N*-methylformanilide and phosphorus oxychloride on 2-methylpyrrocoline, but under essentially similar conditions we isolated only a little 1 : 3-diformyl-2-methylpyrrocoline (V). As in the preparation of 3-formylindole (Tyson and Shaw, *J. Amer. Chem. Soc.*, 1952, **74**, 2273), substitution of dimethylformamide for *N*-methylformanilide increased the yield of dialdehyde. Rossiter and Saxton (*loc. cit.*) prepared the dialdehyde by the Reimer–Tiemann reaction and characterised it as the monophenylhydrazone. We have found that the action of hydroxylamine or 2 : 4-dinitrophenylhydrazine in excess similarly involves only one carbonyl group, thus recalling the behaviour of 1 : 3-diacetylpyrrocolines (Borrows, Holland, and Kenyon, *J.*, 1946, 1069).

Experimental

2-Methylpyrrocoline-3-carbonyl Chloride.—2-Methylpyrrocoline (30·7 g.) in toluene (120 ml.) was added with cooling and stirring to a 12·5% solution (180 ml.) of carbonyl chloride in toluene, at <15°. Next morning, the dark deliquescent precipitate of crude 2-methylpyrrocoline hydrochloride was removed and the filtrate was evaporated *in vacuo*. The residue was extracted with boiling light petroleum (270 ml.; b. p. 60—80°) and the extracts were cooled to give pale green needles of *2-methylpyrrocoline-3-carbonyl chloride* (25·0 g.), m. p. 68—69°. This was sufficiently pure for most purposes but recrystallised (with considerable loss) from light petroleum forming lemon-yellow needles, m. p. 73° (Found: C, 61·9; H, 4·2; N, 7·4; Cl, 18·5. $C_{10}H_8ONCl$ requires C, 62·0; H, 4·2; N, 7·2; Cl, 18·3%). The product was stable for 2—3 weeks at 0°. The yield was not increased by the inclusion of pyridine.

Reaction of 2-Methylpyrrocoline-3-carbonyl Chloride with Dimethylcadmium.—A stirred solution of dimethylcadmium in ether (from 10 g. of anhydrous cadmium chloride) was treated with 20 ml. of a solution prepared from the pure acid chloride (10 g.) and dry ether (120 ml.). After warming to initiate the reaction the source of heat was removed and the remainder of the acid chloride solution was added during 30 min. so as to maintain gentle reflux. After being kept overnight the mixture was treated with crushed ice, followed by 5N-sulphuric acid (40 ml.), and filtered. The solid was discarded after being washed with water and ether. The aqueous phase of the filtrate was neutralised with sodium carbonate and extracted with ether, and the combined ether solutions were washed with dilute sodium hydroxide solution, then with water, and dried. Removal of the ether left crude 3-acetyl-2-methylpyrrocoline as a yellow-green solid (4·33 g., 48%), which crystallised from light petroleum (charcoal) in stout cream-coloured needles, m. p. 83° not depressed by admixture with an authentic specimen (Borrows, Holland, and Kenyon, *J.*, 1946, 1069) (Found: C, 76·7; H, 6·8; N, 8·4. Calc. for $C_{11}H_{11}ON$: C, 76·3; H, 6·4; N, 8·1%). The 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 253° (slight decomp.).

2-Methylpyrrocoline-3-carboxyamide.—A suspension of 2-methylpyrrocoline-3-carbonyl chloride (6 g.) in aqueous ammonia (*d* 0·88; 60 ml.) was shaken for 2 hr., set aside overnight, and filtered. The light green solid (4·51 g.) crystallised from ethyl acetate (charcoal) as colourless needles of the *amide*, m. p. 185—187° (Found: C, 69·3; H, 6·1; N, 16·6. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·8; N, 16·1%).

2-Methylpyrrocoline-3-carboxyanilide.—A solution of the acid chloride (3 g.) and aniline (4 ml.) in benzene (25 ml.) was heated on the steam-bath for 45 min., then poured into water. The light green solid was collected and concentration of the benzene layer furnished a further quantity (combined yield 3·04 g.). The *anilide* crystallised from alcohol (charcoal) in colourless needles, m. p. 142—143° (Found: C, 77·1; H, 5·8; N, 11·6. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%).

Hydrolysis of 2-Methylpyrrocoline-3-carbonyl Chloride.—A suspension of the acid chloride (16 g.) in 10% sodium hydroxide solution (180 ml.) was shaken for 90 min. and filtered. Crystallisation of the solid (7·56 g., 55%) from chloroform–ether and finally from ethyl acetate (charcoal) gave the pale lemon-yellow *anhydride*, m. p. 203—204° (Found: C, 72·7; H, 5·0; N, 8·2. $C_{20}H_{16}O_3N_2$ requires C, 72·3; H, 4·8; N, 8·4%).

The aqueous filtrate was treated with acetic acid (27 ml.) and *2-methylpyrrocoline-3-carboxylic acid* was collected, washed with water, and dried as rapidly as possible between filter papers and finally in a vacuum-desiccator to give 4·09 g. (28%) of an olive-coloured powder. (The finely divided acid was difficult to filter and the crude moist product tended to undergo spontaneous

decarboxylation during drying. Alternatively the acid could be extracted into ether and dried over anhydrous sodium sulphate.) Crystallisation from ether–light petroleum gave colourless crystals, m. p. 115° (vigorous decomp.) (Found : C, 68·5; H, 5·3; N, 8·2. $C_{10}H_9O_2N$ requires C, 68·5; H, 5·2; N, 8·0%).

Hydrolysis of 2-Methylpyrrocoline-3-carboxylic Anhydride.—A mixture of the anhydride (3 g.), ethanol (40 ml.), and 50% aqueous potassium hydroxide (20 ml.) was refluxed for 1 hr., then concentrated to remove alcohol and diluted with water. Addition of acetic acid precipitated crude 2-methylpyrrocoline-3-carboxylic acid (2·68 g., 85%) which, after purification as described above, had m. p. and mixed m. p. 115° (vigorous decomp.).

Decarboxylation of 2-Methylpyrrocoline-3-carboxylic Acid.—(*a*) The pure acid (0·35 g.) decomposed rapidly at 130°/14 mm. After 20 min. colourless crystalline 2-methylpyrrocoline (0·21 g., 80%) which had sublimed was removed; it had m. p. and mixed m. p. 59°. (*b*) A solution of the acid (0·4 g.) in concentrated hydrochloric acid (5 ml.) was kept at 60° for 30 min., then poured into cold sodium hydroxide solution. The precipitated base (0·25 g., 85%) had m. p. 56—57°, raised to 59° (mixed m. p.) by sublimation.

3-Benzoyl-2-methylpyrrocoline.—A mixture of 2-methylpyrrocoline (20 g.) and benzoyl chloride (25 ml.) in benzene (50 ml.) was set aside overnight, then poured into sodium hydroxide solution. A little 2-methylpyrrocoline was removed by steam-distillation and the residue extracted with chloroform. Evaporation of the extracts left a dark oil which was rubbed with light petroleum containing a little ether to give a yellow-green powder (33·1 g.). *3-Benzoyl-2-methylpyrrocoline* crystallised from light petroleum in flat yellow needles, m. p. 63° (Found : C, 81·7; H, 5·9; N, 5·6. $C_{16}H_{13}ON$ requires C, 81·6; H, 5·6; N, 6·0%).

The ketone (0·5 g.) and 2 : 4-dinitrophenylhydrazine (0·5 g.) in ethanol (50 ml.) containing concentrated hydrochloric acid (0·5 ml.) were refluxed for 90 min. The *hydrazone* (0·17 g.) which separated on cooling was dissolved in hot pyridine and the blood-red solution was concentrated to about 6 ml. and diluted with hot alcohol (6 ml.) to give black crystals, m. p. 288—290° (decomp.) (Found : C, 63·7; H, 4·0; N, 16·6. $C_{22}H_{17}O_4N_5$ requires C, 63·6; H, 4·1; N, 16·9%).

3-p-Carboxyphenylazo-2-methylpyrrocoline (III).—Diazotised *p*-aminobenzoic acid (5·48 g.), brought to pH 8 by sodium hydroxide solution, was added to a solution of 2-methylpyrrocoline (5·24 g.) in ethanol (120 ml.). After dilution with 10% aqueous acetic acid (220 ml.) the crimson solid was collected and thoroughly washed with water and ether. The *dye* (10·6 g., 95%) had m. p. 249° (decomp.), unchanged on crystallisation from 2-ethoxyethanol (Found : C, 68·7; H, 5·0; N, 14·8. $C_{16}H_{13}O_2N_3$ requires C, 68·8; H, 4·7; N, 15·0%).

Reductive Acetylation of the Dye (III).—A solution of the dye (5 g.) in acetic acid (100 ml.) and acetic anhydride (100 ml.) was boiled for 20 min. whilst zinc dust (10 g.) was added portionwise, and then for 10 min. more. The brown mixture was cooled and filtered, and the solid was washed with acetic acid. The filtrate and washings were evaporated *in vacuo*, the residual tar was treated with sodium hydroxide solution, and the mixture was extracted with chloroform. Acidification of the aqueous layer gave crude *p*-acetamidobenzoic acid (2·60 g., 81%), m. p. and mixed m. p. 252°. The dark chloroform solution was dried, concentrated to about 20 ml., diluted with benzene (60 ml.), and chromatographed on alumina. The chromatogram was developed with benzene–acetone and the eluate from the leading cream-coloured band was evaporated to an oil, which crystallised on trituration with ether. The solid (0·24 g.) crystallised from ethyl acetate to give colourless silky needles of *3-acetamido-1-acetyl-2-methylpyrrocoline*, m. p. 190° (Found : C, 67·5; H, 6·2; N, 12·2. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·1; N, 12·2%). Treatment of a methanolic solution of the ketone with Brady's reagent gave the purple-black 2 : 4-*dinitrophenylhydrazone*, which separated from 2-ethoxyethanol in needles, m. p. 265° (Found : C, 55·5; H, 4·5. $C_{19}H_{18}O_5N_6$ requires C, 55·6; H, 4·4%).

Oxidation of 3-Acetamido-1-acetyl-2-methylpyrrocoline.—A mixture of the pyrrocoline (0·25 g.), acetic acid (6 ml.), and 30% hydrogen peroxide (3 ml.) was refluxed for 1 hr. and evaporated *in vacuo*. The residual colourless syrup was dried in a vacuum-desiccator, then triturated with a little dry methanol to give picolinic acid *N*-oxide (0·04 g.), m. p. and mixed m. p. 161°.

3-Acetamido-2-methylpyrrocoline.—A solution of 3-acetyl-2-methylpyrrocoline (12·8 g.) in chloroform (50 ml.) was treated with hydrazoic acid in chloroform (100 ml. of 3·44% w/v) and added dropwise during 30 min. to vigorously stirred concentrated sulphuric acid (40 ml.) and chloroform (80 ml.) at −5° to 0°. After being stirred for a further 30 min. at the same temperature the mixture was poured on ice and made alkaline with 40% aqueous sodium hydroxide. The layers were separated, the aqueous phase was extracted with chloroform, and the combined chloroform solutions were dried and evaporated. Trituration of the sticky residue with ether gave crude *3-acetamido-2-methylpyrrocoline* (9·56 g., 69%), which crystallised from benzene in

colourless hair-like needles, m. p. 148° (Found : C, 70·3; H, 6·8; N, 14·3. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%).

Acetylation of 3-Acetamido-2-methylpyrrocoline.—The pyrrocoline (1·88 g.), acetic anhydride (15 ml.), and anhydrous sodium acetate (3 g.) were refluxed for 3 hr., and evaporated *in vacuo*. The residue was treated with sodium hydroxide solution and extracted with chloroform. Evaporation of the dried extracts and trituration of the residue with ether gave a very crude solid, which on crystallisation from ethyl acetate (charcoal) gave 0·30 g. of fairly pure 3-acetamido-1-acetyl-2-methylpyrrocoline, m. p. 187—188°. Further crystallisation raised the m. p. to 190°, not depressed by admixture with the product from the reductive acetylation of the dye (III).

3-Benzamido-2-methylpyrrocoline.—A solution of 3-benzoyl-2-methylpyrrocoline (3·2 g.) in chloroform (20 ml.) was treated with hydrazoic acid in the same solvent (24 ml. of 3·07% w/v) and the mixture was added dropwise with stirring during 30 min. to concentrated sulphuric acid (10 ml.) and chloroform (20 ml.) at 0—10°. After 27 hours' stirring at room temperature the mixture was poured on ice, the aqueous layer was extracted with chloroform, and the combined chloroform solutions were dried and evaporated. Rubbing the residual gum with a little cold acetone gave a yellow-brown solid (2·18 g., m. p. about 160°) which, however, could not be purified by recrystallisation. A solution of the solid (2 g.) in chloroform (50 ml.) was diluted with benzene (100 ml.) and chromatographed on alumina. The leading yellow band was eluted with chloroform–benzene (1 : 2) and the solvent was removed to leave crude *3-benzamido-2-methylpyrrocoline* (0·35 g.), pale yellow crystals (from benzene), m. p. 196° (Found: C, 76·8; H, 5·7; N, 11·5. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%). Elution of the remaining bands from the alumina column gave only tars.

Attempted Rosenmund Reduction of 2-Methylpyrrocoline-3-carbonyl Chloride.—Dry hydrogen was passed into a vigorously stirred solution of the acid chloride (7·5 g.) in boiling xylene (130 ml.) in the presence of 5% palladised barium sulphate until, after 16½ hr., evolution of hydrogen chloride ceased at 89% of the theoretical quantity. After cooling in a stream of hydrogen, the mixture was filtered and the solvent was removed *in vacuo*. Trituration of the residual deep red gum with light petroleum containing a little ether gave crude *di-(2-methyl-3-pyrrocolinyl) ketone* (3·74 g.) which crystallised from alcohol or light petroleum in elongated yellow plates, m. p. 114—115° (Found : C, 79·1; H, 6·2; N, 10·0. $C_{19}H_{16}ON_2$ requires C, 79·1; H, 5·6; N, 9·7%). Neither distillation of the mother-liquor *in vacuo* nor treatment with Brady's reagent gave any evidence of the presence of 3-formyl-2-methylpyrrocoline.

Di-(2-methyl-3-pyrrocolinyl) Ketone.—A solution of 2-methylpyrrocoline-3-carbonyl chloride (4·54 g.) and 2-methylpyrrocoline (6·15 g.) in benzene (80 ml.) was refluxed under nitrogen for 14 hr. and evaporated *in vacuo* to a dark oil. Sodium hydroxide solution was added, 2-methylpyrrocoline was removed by steam-distillation, and the residual mixture was extracted with ether. The washed and dried extracts were treated with charcoal and evaporated to a gum, which gave the ketone (4·73 g., 70%) when rubbed with light petroleum containing a little ether. Recrystallisation from ethanol gave a product, m. p. 114—115°, identical with that from the attempted Rosenmund reaction.

Hydrolysis of Di-(2-methyl-3-pyrrocolinyl) Ketone.—The ketone (1 g.) in concentrated hydrochloric acid (10 ml.) was heated on the steam-bath for 1 hr., cooled, and poured into an excess of sodium carbonate solution. Steam-distillation gave 0·9 g. of crude 2-methylpyrrocoline, m. p. 54—55°, raised to 59° (mixed m. p.) by sublimation.

Di-(2-methyl-3-pyrrocolinyl)methane.—(*a*) The ketone (IV) (2 g.) in ether (50 ml.) was added during 30 min. to a stirred suspension of lithium aluminium hydride (0·4 g.) in ether (50 ml.) at room temperature, the brilliant yellow colour of the ketone disappearing at once at each addition. Water (5 ml.) and 40% sodium hydroxide solution (20 ml.) were added and the layers were separated (decomposition of the complex with mineral acid was best avoided since it gave an intense indigo colour). The aqueous phase was extracted with chloroform and the combined solvent layers were dried and evaporated. Crystallisation of the green residue from ethyl acetate (charcoal) gave small colourless prisms of *di-(2-methyl-3-pyrrocolinyl)methane* (1·42 g., 75%), m. p. 159—161° (Found : C, 83·1; H, 6·5; N, 10·3. $C_{19}H_{18}N_2$ requires C, 83·2; H, 6·6; N, 10·2%).

(*b*) Aqueous formaldehyde (40%; 0·5 ml.) was added to 2-methylpyrrocoline (1 g.) in ethanol (10 ml.) and next morning di-(2-methyl-3-pyrrocolinyl)methane (0·99 g., 95%) was collected and crystallised from ethyl acetate (charcoal); it had m. p. and mixed m. p. 159—160°.

3-Ethyl-2-methylpyrrocoline.—3-Acetyl-2-methylpyrrocoline (8·3 g.) was reduced with lithium aluminium hydride (3 g.) as described for the reduction of the ketone (IV) except that the ether solution was refluxed for 100 min. 3-Ethyl-2-methylpyrrocoline (5·81 g., 76%) was isolated by

ether-extraction and distilled; it had b. p. 116—118°/9 mm., n_D^{18} 1·5973 [chloroplatinate, m. p. 174° (decomp.) (Found : C, 36·7; H, 4·2; Cl, 29·2. Calc. for $C_{22}H_{28}N_2Cl_6Pt$: C, 36·3; H, 3·9; Cl, 29·2%)]. Borrows, Holland, and Kenyon (*J.*, 1946, 1083) give b. p. 124°/15 mm., n_D^{20} 1·5968 [chloroplatinate, m. p. 174° (decomp.)].

3-Benzyl-2-methylpyrrocoline.—3-Benzoyl-2-methylpyrrocoline (7·05 g.) was reduced with lithium aluminium hydride (2·5 g.) as described above, to give 3-benzyl-2-methylpyrrocoline (4·02 g., 61%), m. p. 86—88° raised to 93—94° by sublimation at 0·1 mm. and not depressed by admixture with an authentic specimen (Holland and Nayler, *J.*, 1955, in the press). The chloroplatinate had m. p. and mixed m. p. 178—179° (decomp.).

1-Acetyl-2 : 3-dimethylpyrrocoline.—2 : 3-Dimethylpyrrocoline (29 g.), acetic anhydride (180 ml.), and anhydrous sodium acetate (30 g.) were refluxed for 7 hr. and evaporated *in vacuo*. After addition of water the dark mixture was extracted with chloroform and the washed and dried extracts were distilled, to give *1-acetyl-2 : 3-dimethylpyrrocoline* (18·6 g., 50%) as a green oil, b. p. 130—140°/0·1 mm., which solidified. The ketone crystallised from light petroleum in colourless needles, m. p. 81—82° (Found : C, 77·4; H, 7·4; N, 7·9. $C_{13}H_{13}ON$ requires C, 77·0; H, 7·0; N, 7·5%). Heating the ketone with hydroxylamine hydrochloride and sodium acetate in aqueous alcohol gave the *oxime*, pale yellow prisms (from ethyl acetate), m. p. 216° (decomp.) (Found : C, 71·7; H, 6·9; N, 13·5. $C_{12}H_{14}ON_2$ requires C, 71·3; H, 7·0; N, 13·9%). Oxidation of the ketone (0·25 g.) with 100-vol. hydrogen peroxide, as described for 3-acetamido-1-acetyl-2-methylpyrrocoline, gave picolinic acid *N*-oxide (0·04 g.).

1-Ethyl-2 : 3-dimethylpyrrocoline.—1-Acetyl-2 : 3-dimethylpyrrocoline (10 g.) was reduced with lithium aluminium hydride (3 g.) as before, to give *1-ethyl-2 : 3-dimethylpyrrocoline* (6·2 g., 67%) as a yellow oil, b. p. 91—92°/0·2 mm. (Found : C, 82·6; H, 8·6; N, 8·1. $C_{12}H_{15}N$ requires C, 83·2; H, 8·7; N, 8·1%). The insoluble *chloroplatinate* formed golden needles, m. p. 177—178° (decomp.) (Found : C, 38·4; H, 4·2; Pt, 25·6. $C_{24}H_{32}N_2Cl_6Pt$ requires C, 38·1; H, 4·3; Pt, 25·8%).

Ethyl 2-Methylpyrrocoline-3-glyoxylate.—A mixture of ethoxalyl chloride (Adickes, Brunnert, and Lücker, *J. prakt. Chem.*, 1931, **130**, 169) (12·5 g.) and 2-methylpyrrocoline (12 g.) in benzene (120 ml.) was kept at ordinary temperature overnight (or, alternatively, refluxed for 30 mins.) and poured into ice-water. The aqueous phase was extracted with chloroform and the combined organic solutions were washed and dried. Removal of the solvents and crystallisation of the dark residue from alcohol (charcoal) gave the yellow-green *ester* (14·1 g., 67%). Further crystallisation gave pale yellow elongated plates, m. p. 105—106° (Found : C, 67·7; H, 6·3; N, 6·1. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·7; N, 6·1%).

2-Methylpyrrocoline-3-glyoxylic Acid.—A suspension of the ester (15 g.) in 2N-sodium hydroxide (150 ml.) was shaken overnight, then heated at 70° for 30 min. The dark solution was decolorised with charcoal and made strongly acid with hydrochloric acid, to give a precipitate (12·3 g., 93%), m. p. 148—150° (decomp.). The *acid* crystallised from chloroform–light petroleum in greenish-yellow prisms, m. p. 151° (decomp.) (Found : C, 64·9; H, 4·7; N, 6·9. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·5; N, 6·9%).

A suspension of the acid (6 g.) and aniline (3 g.) in water (60 ml.) was heated on the steam-bath for 30 min. and cooled, whereupon the *aniline salt* crystallised (5·73 g.). Recrystallisation from alcohol gave bold yellow-green needles, m. p. 149—150° (decomp.) (Found : C, 69·0; H, 5·5; N, 9·5. $C_{17}H_{16}O_3N_2$ requires C, 68·9; H, 5·4; N, 9·5%). The product was not the anil since on dissolution in sodium hydrogen carbonate solution aniline was liberated (extracted with ether and identified as acetanilide), whilst acidification of the aqueous layer precipitated the glyoxylic acid.

3-Methylpyrrocoline-3-carboxyhydrazide.—A solution of 2-methylpyrrocoline-3-carbonyl chloride (25 g.) in ether (500 ml.) was added during 1 hr. to a stirred mixture of 90% hydrazine hydrate (80 ml.) and ethanol (500 ml.) kept at 0—10°. After storage at 0° overnight the colourless crystals were collected and thoroughly washed with water and ether (15·6 g., m. p. 171—173°). Evaporation of the filtrate *in vacuo* gave a further 5·7 g., m. p. 167—169° (total yield 87%). The *hydrazide* crystallised from ethyl acetate as colourless glistening rectangular plates, m. p. 171—172° (Found : C, 63·8; H, 6·0; N, 22·5. $C_{10}H_{11}ON_3$ requires C, 63·5; H, 5·9; N, 22·2%).

3-Formyl-2-methylpyrrocoline.—Benzenesulphonyl chloride (19·2 ml.) was added during 30 min. to a stirred suspension of the hydrazide (23·1 g.) in pyridine (150 ml.) at −5° to 0°, and the mixture was then stirred at room temperature for 90 min. The turbid orange solution was poured on crushed ice, the crude yellow *benzenesulphonyl derivative* was collected and washed first with dilute hydrochloric acid, then with water, and dried in a vacuum-desiccator [36·5 g.

(91%); m. p. 177—178° (decomp.)]. It crystallised from acetonitrile in cream-coloured needles, m. p. 183—184° (decomp.) (Found: C, 58·3; H, 4·7; N, 13·1. $C_{16}H_{15}O_3N_3S$ requires C, 58·3; H, 4·6; N, 12·8%).

The crude intermediate (36·5 g.) in ethylene glycol (250 ml.) was heated in an oil-bath and when the internal temperature reached 140° anhydrous sodium carbonate (20 g.) was added in several portions during 1 min. Evolution of nitrogen was vigorous, but subsided rapidly. After a further 2 min. at 140—145° the solution was diluted with hot water (250 ml.), cooled, and poured into a further 500 ml. of water. The mixture was extracted with ether (3 × 150 ml.), and the extracts were dried (Na_2SO_4) and distilled. 3-Formyl-2-methylpyrrocoline, b. p. 102—107°/0·3 mm., crystallised in the receiver (yield 13·6 g., 77%) and sublimation *in vacuo* gave pale yellow crystals, m. p. 56° (Found: C, 75·0; H, 5·9; N, 9·2. Calc. for $C_{10}H_9ON$: C, 75·4; H, 5·7; N, 8·8%).

Addition of Brady's reagent to the aldehyde in methanol gave the sparingly soluble 2 : 4-*dinitrophenylhydrazone*. The intense blood-red solution of this derivative in hot pyridine deposited almost black needles, m. p. 267° (decomp.), when cooled (Found: C, 59·0; H, 4·4; N, 20·4. $C_{16}H_{13}O_4N_5,0{\cdot}5C_5H_5N$ requires C, 58·7; H, 4·1; N, 20·3%). Rossiter and Saxton (*loc. cit.*) were unable to purify this derivative from ethyl acetate.

1 : 3-*Diformyl-2-methylpyrrocoline*.—Phosphorus oxychoride (20 ml.) was gradually added with stirring to dimethylformamide (80 ml.) below 10°, after which 2-methylpyrrocoline (12 g.) was added portionwise during 10 min. while the temperature rose to 30°. After the mixture had been stirred for 30 min. at 25—30° calcium carbonate (40 g.) was added during 5 min. and the mixture was warmed cautiously. When a vigorous reaction set in the mixture was cooled strongly to keep it at 55—60° until after 5 min. the reaction subsided. After a further 10 min. at 50° the mixture, which now contained much solid, was cooled to 10°, treated with stirring with sodium acetate trihydrate (85 g.) in water (200 ml.), and set aside overnight. The dark green suspension was then poured into 6% sodium hydroxide solution (800 ml.), boiled for 2 hr. to expel dimethylamine, and filtered hot. The solid was thoroughly extracted with boiling chloroform and the filtrate was extracted with the cold solvent. The combined extracts (600 ml.) were dried and evaporated, and the sticky residue was washed with ether to give crude 1 : 3-diformyl-2-methylpyrrocoline (4·84 g., 28%), m. p. 209—212°. Crystallisation from alcohol (charcoal) gave colourless needles, m. p. 214—215° not depressed by admixture with the product of the Reimer–Tiemann reaction (Rossiter and Saxton, *loc. cit.*) (Found: C, 70·7; H, 5·2; N, 7·2. Calc. for $C_{11}H_9O_2N$: C, 70·6; H, 4·9; N, 7·5%). Rossiter and Saxton describe the dialdehyde as pale yellow needles, m. p. 210°.

Hydrogen peroxide oxidised the dialdehyde (0·5 g.) to picolinic acid *N*-oxide (0·21 g.).

Solutions of the dialdehyde (0·3 g.) in hot ethanol (25 ml.) and of hydroxylamine hydrochloride (0·3 g.) and sodium acetate trihydrate (0·5 g.) in water (15 ml.) were mixed and set aside overnight to give the *mono-oxime* (0·18 g.), which crystallised from 33% aqueous alcohol in pale yellow needles, m. p. 196—197° (Found: C, 65·3; H, 5·2; N, 14·2. $C_{11}H_{10}O_2N_2$ requires C, 65·3; H, 5·0; N, 13·9%). Addition of Brady's reagent (1 mol. or excess) to the dialdehyde in methanol gave the insoluble red-brown *mono*-2 : 4-*dinitrophenylhydrazone*, decomp. >315° (Found: C, 55·0; H, 3·7; N, 19·2. $C_{17}H_{13}O_5N_5$ requires C, 55·5; H, 3·6; N, 19·1%).

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