238. *The Chemistry of the Pyrrocolines. Part III. Nitration.*

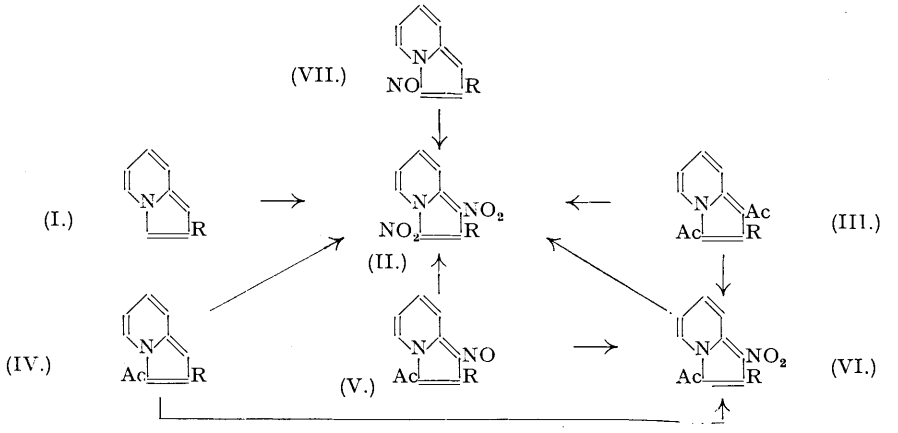
By E. T. Borrows, D. O. Holland, and J. Kenyon.

2-Methyl- and 2-phenyl-pyrrocolines and their 3-acetyl and 1 : 3-diacetyl derivatives have been nitrated to yield a variety of nitro-compounds in which the positions of the substituents have been determined.

According to Scholtz (*Ber.*, 1912, **45**, 1718) pyrrocoline cannot be nitrated directly because of its sensitivity to oxidising agents, but the 1 : 3-diacetyl derivative (cf. Part I) can be nitrated progressively in acetic acid with 25% and with concentrated nitric acid to yield respectively a nitro-acetyl- and a dinitro-pyrrocoline. In a similar manner Diels and Meyer (*Annalen*, 1934, **513**, 129) prepared methyl 1-nitropyrrocoline-2 : 3-dicarboxylate from methyl 1-methoxycarbomethoxymethylpyrrocoline-2 : 3-dicarboxylate. Pyrrocoline would appear to behave in this respect similarly to pyrrole.

When 2-methyl- and 2-phenyl-pyrrocoline were allowed to react with nitric acid under a variety of conditions considerable oxidation took place with the formation, in the main, of water-soluble products. This appeared to be particularly the case when the reaction was carried out at moderate temperatures, oxidation proceeding slowly with little evidence of nitration. Nevertheless, it has proved possible to convert these pyrrocolines (I) by the action of hot nitric acid into 1 : 3-*dinitro*-derivatives (II) : in the case of the 2-methyl compound nitration resulted even with hot dilute nitric acid, but it was effected best by concentrated nitric acid in acetic acid containing a few drops of concentrated sulphuric acid. These dinitro-compounds were better

prepared from the respective 3-acetyl and 1 : 3-diacetyl derivatives (IV and III) by essentially the same method of dinitration as that described by Scholtz (*loc. cit.*) or, in the case of the monoacetyl compounds, by direct action of cold nitric acid; the 3-nitroso-derivatives of 2-methyl- and 2-phenyl-pyrrocoline (VII) were converted also by the former method into the dinitro-compounds (II). The structures were assigned on evidence afforded by oxidation of both compounds (II) with perhydrol to yield α-picolinic acid *N*-oxide and, in the case of the 2-phenyl derivative, benzoic acid.



(R = Me or Ph.)

The conditions described by Scholtz (*loc. cit.*) for the mononitration of 1 : 3-diacetylpyrrocoline were applied to the 2-methyl and the 2-phenyl compound (IV), 1-*nitro*-3-*acetyl* derivatives (VI) being obtained. The reaction proceeded readily in the case of (IV, R = Ph), but with (IV, R = Me) considerable decomposition took place and only a very poor yield of the desired product was obtained accompanied by a little 1 : 3-dinitro-2-methylpyrrocoline (II, R = Me). On attempting the reaction under a variety of conditions on 3-acetyl-2-phenylpyrrocoline no tractable product other than 2-phenylpyrrocoline or its 1 : 3-dinitro-derivative could be isolated; this was probably due to the extreme mobility of the acetyl group in this compound. The 2-methyl analogue (IV, R = Me) likewise failed to yield the 1-nitro-compound on application of this method, but treatment under carefully regulated conditions in hot acetic acid with concentrated nitric acid gave rise to (VI, R = Me) in 36% yield and some dinitro-compound. It seems likely from this experiment that in the reaction of nitric acid in acetic acid on the monoacetyl compounds (IV) to form (II) the nitro-acetyl compounds (VI) are intermediates; indeed, it was shown that the latter could be converted into (II) by further treatment with this reagent. This conversion established that the nitro-group in (VI) is attached to the pyrrole ring, and its position was determined finally by the preparation of (VI) from the 1-nitroso-3-acetyl derivatives (V) of 2-methyl- and 2-phenyl-pyrrocoline (Part II) by oxidation with perhydrol. By analogy, the nitroacetylpyrrocoline prepared by Scholtz (*loc. cit.*) would seem to be the 1-nitro-3-acetyl derivative. The nitroacetyl pyrrocolines (VI), like the nitroso-derivatives (V) (Part II), are resistant to acid hydrolysis, and no satisfactory method for their deacetylation has been devised.

1-Nitroso-3-acetyl-2-phenylpyrrocoline (V, R = Ph) was also converted into (II, R = Ph) as independent evidence that the nitroso-group is attached to the pyrrole ring.

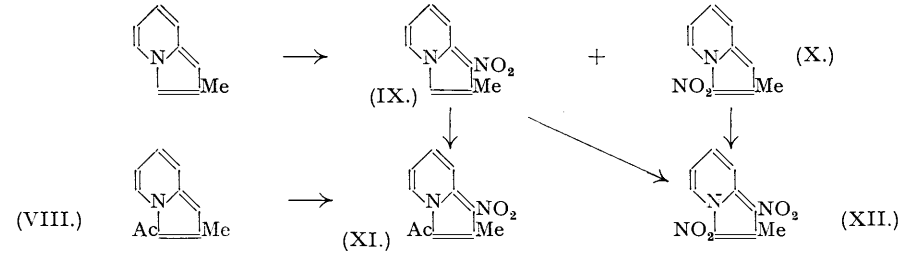
The study on nitration was continued by attempting the reaction in concentrated sulphuric acid. In this way 2-methylpyrrocoline gives two mononitro-compounds and a little dinitro-compound (XII). Of the former, only that produced in major proportion (m. p. 154·5—155·5°; 82% yield) could be acetylated by acetic anhydride, and then with some difficulty (5 days' refluxing), to yield 1-nitro-3-acetyl-2-methylpyrrocoline (XI). The other mono-nitro-compound, m. p. 103—104° (1·5% yield), could not be acetylated and was recovered unchanged even after treatment at 200° with acetic anhydride, to which it showed a marked stability. The acetylation of the nitro-compound, m. p. 154·5—155·5°, and its oxidation to α-picolinic acid *N*-oxide afford unequivocal proof that it is 1-*nitro*-2-*methylpyrrocoline* (IX), and the isomeric product, m. p. 103—104°, is therefore the 3-*nitro*-derivative (X). These compounds behaved quite differently on attempted further nitration. The 3-nitro-compound (X), similarly to 3-nitroso-2-methylpyrrocoline (VII, R = Me), is readily converted by the action of a hot mixture of concentrated nitric acid and acetic acid into (XII), which confirms the suggested structure. On the other hand, the 1-nitro-isomer (IX) could not be nitrated by this procedure or by a mixture of nitric and sulphuric acids, and the reaction was eventually effected by the method employed for the dinitration of 2-methylpyrrocoline.

This preferential nitration of the pyrrocoline structure in position 1 is in marked contrast to the facile 3-nitrosation reported previously (Part II).

Dhont and Wibaut (*Rec. Trav. chim.*, 1943, **62**, 177) record that nitration of *N*-phenylpyrrole by nitric acid and acetic anhydride yields the 2- and the 3-nitro-derivative, but application of this procedure to 2-methylpyrrocoline has yielded an intractable tar as the main product.

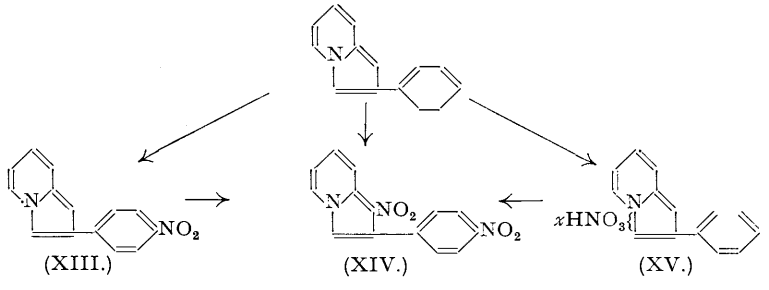
On addition of an ethereal solution of nitric acid to 3-acetyl-2-methylpyrrocoline in the same solvent a

dinitrate separated which could be dehydrated by boiling acetic acid to give 1-nitro-3-acetyl-2-methylpyrrocoline (XI) in poor yield. The latter compound was formed in good yield (59%) along with some (XII) when the acetyl derivative in cold sulphuric acid solution was treated with nitric acid.



In several experiments the accompanying 1 : 3-dinitro-2-methylpyrrocoline (XII) could only be separated from the principal nitro-products by chromatography of the yellow solution of the mixture in dry benzene on a column of alumina. Under such conditions (XII) exhibited a very striking phenomenon, for it produced a red chromatogram, quite distinct from the yellow ones produced by the other nitro-compounds. The depth of the red colour appeared to be dependent on the character of the particular batch of alumina, and indeed one batch produced a yellow chromatogram in place of the usual red one.

Addition of 1 mol. of nitric acid to 2-phenylpyrrocoline in concentrated sulphuric acid solution at 0° yielded a product from which a mononitro-compound was isolated in 41% yield, accompanied by a much smaller quantity of a dinitro-compound (m. p. 235·5—236°). The former was shown by oxidation to be 2-p-*nitrophenylpyrrocoline* (XIII), for it yielded as major products α-picolinic acid *N*-oxide and *p*-nitrobenzoic acid. An identical mononitro-compound (XIII) was also prepared by nitration in phosphoric acid solution or by the action of sodium nitrate and sulphuric acid; these methods did not appear to offer any advantage over that just described. The dinitro-compound, m. p. 235·5—236°, was identified later by comparison with a specimen of 1-*nitro*-2-p-*nitrophenylpyrrocoline* (XIV) and it is prepared more conveniently by the further nitration of 2-*p*-nitrophenylpyrrocoline or by the dinitration of 2-phenylpyrrocoline with nitric acid.

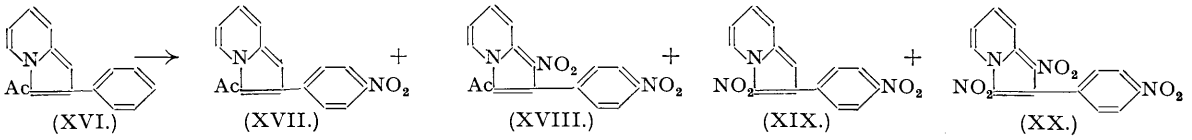


Little tractable material resulted from any of the numerous experiments essayed to nitrate 2-phenylpyrrocoline in acetic acid solution by addition of nitric acid of various concentrations : owing to the low solubility of the pyrrocoline most of these experiments were carried out on the steam-bath. Subsequently it was discovered that the pyrrocoline would slowly dissolve in acetic acid at room temperature in the presence of 1 mol. of concentrated nitric acid to give a yellow solution from which it separated unchanged on dilution with water : considerable oxidation of the pyrrocoline appears to take place on keeping the solution for 24 hrs. at room temperature. Addition of a second mol. of concentrated nitric acid, however, to the original yellow solution immediately precipitated a *nitrate* of 2-phenylpyrrocoline in monoclinic needles which appear to contain *ca.* 1·8 mols. of nitric acid. Dehydration of the nitrate was effected satisfactorily only by sulphuric acid, 1-nitro-2-*p*-nitrophenylpyrrocoline (XIV) being obtained in 40% yield. The latter compound yielded on oxidation α-picolinic acid *N*-oxide and *p*-nitrobenzoic acid; but numerous attempts, described later, failed to determine unambiguously the position of the second nitro-group. However, it has been shown already that nitration of 2-methylpyrrocoline under conditions identical with those used for the preparation of (XIV) yielded 1-nitro-2-methylpyrrocoline and hence it is highly probable that the structure assigned to (XIV) is correct.

Although nitration of 2-phenylpyrrocoline in sulphuric acid preferentially occurred at the para-position in the benzene ring in contrast to the facile nitrosation at position 3 (Part II), it is not entirely unexpected, for similar treatment of *N*-phenylpyrrole yields *N*-*p*-nitrophenylpyrrole (Dhont and Wibaut, *loc. cit.*).

Results of the nitration of 2-phenylpyrrocoline in sulphuric acid solution suggested a method of preparing, from (XVI), 1-nitro-3-acetyl-2-*p*-nitrophenylpyrrocoline (XVIII), of possible value in the orientation of (XIV), assuming that the labile acetyl group in (XVI) would not be removed too readily under the experimental conditions. For this investigation 1 or 2 mols. of nitric acid were employed and in both cases a mixture of at least four nitro-compounds was obtained, the separation of which proved laborious; a difficulty enhanced by

the inherent light-sensitivity of three of the compounds (XVII, XIX, and XX). All three are yellow crystalline solids which rapidly turn green when exposed to air and sunlight.



(XVI.) (XVII.) (XVIII.) (XIX.) (XX.)

The respective yields of the nitro-compounds are dependent on the amount of nitric acid employed, but with 2 mols. a larger total quantity of crude products resulted in addition to the anticipated increase in polynitration. Three of the products, 1-*nitro*-3-*acetyl*- (XVIII), 3-*nitro*- (XIX), and 1 : 3-*dinitro*-2-p-*nitrophenylpyrrocoline* (XX), on oxidation gave rise with varying ease to α-picolinic acid *N*-oxide and *p*-nitrobenzoic acid. The fourth, 3-*acetyl*-2-p-*nitrophenylpyrrocoline* (XVII), proved to be identical with the product of the acetylation of 2-*p*-nitrophenylpyrrocoline (XIII), whence its formulation follows; the acetyl group in (XVII) appears to be slightly less labile to hydrolysis than that in (XVI). The preparation of (XVII) from (XIII) by a short period of refluxing with sodium acetate–acetic anhydride indicates that the difficult acetylation of nitro-pyrrocolines is restricted to those with the nitro-group attached to the pyrrole ring.

Attention was directed to the acetylation of the 1-nitro- (XIV) and the 3-nitro-derivative (XIX) of 2-*p*-nitrophenylpyrrocoline, following the failure to effect deacetylation of (XVIII) under a variety of conditions. Whereas the 1-nitro-compound (XIV) can be recovered, accompanied by charred material, after 48 hrs.' heating at 200° with acetic anhydride or after being heated under reflux with acetic anhydride and sodium acetate for 2—6 days, the 3-nitro-isomeride (XIX) under similar conditions yields a yellow intractable oil along with unchanged material. However, on one occasion a small quantity (*ca.* 10 mg. from 0·5 g.) of crystalline yellow powder, m. p. 234—235°, was separated from (XIX) after 5 days' refluxing. This product could not be purified in sufficient quantity for analysis and several attempts to prepare more were unsuccessful, but it depressed the m. p. on admixture with (XIV), m. p. 235·5—236°, and (XX), m. p. 234—235° (decomp.).

In view of this inconclusive result an attempt was made to synthesise 3-nitro-2-phenylpyrrocoline from ω-nitrobromoacetophenone and α-picoline, by a method similar to that employed successfully for the 3-nitroso-derivative (Part II). ω-Nitrobromoacetophenone was prepared by the bromination (Thiele, *Annalen*, 1902, **325**, 13) of ω-nitroacetophenone which was prepared by the method of Jaberkowitsch (*J. pr. Chem.*, 1935, **142**, 37; cf. Fujise *et al.*, *Ber.*, 1935, **68**, 1272). The latter method for nitroacetophenone proved more expeditious than that described by Thiele (*loc. cit.*) and gave good yields. The bromo-ketone reacted slowly at room temperature with α-picoline to form a syrup which appeared to contain little quaternary compound but a large portion of a salt of α-picoline (probably hydrobromide) and a little benzoic acid; attempted ring closure under a variety of conditions on the aqueous extract of the syrup, after removal of α-picoline and benzoic acid, yielded a negligible quantity of red product. The formation of benzoic acid recalls the recorded loss of acyl groups from quaternary compounds prepared from pyridine or α-picoline and α-halogeno-β-diketones (cf. Part I; also Krohnke and Timmler, *Ber.*, 1936, **69**, 614).

The direct nitration of the pyrrocoline ring, herein described, would appear to show once more that this interesting ring system is not so closely allied in its properties to pyrrole and indole as might be anticipated from its structure.

Experimental.

All m. p.'s are uncorrected. Savory and Moore standardised Brockmann alumina was employed for all chromatographic purifications. The ligroin used had b. p. 60—80°, and the nitric acid *d* 1·4 unless otherwise stated.

1 : 3-*Dinitro*-2-*methylpyrrocoline*.—(a) *From* 2-*methylpyrrocoline*. To a solution of the latter (0·5 g.) in acetic acid (5 c.c.) was added concentrated sulphuric acid (0·25 c.c.) followed by nitric acid (1 c.c.). The mixture was heated carefully over a flame until a vigorous reaction set in which was allowed to continue for *ca.* 2 mins.,; the mixture was then poured into water, and the yellow precipitate (0·19 g.; 22%), m. p. 214—215° (decomp.), filtered off, washed, dried, and recrystallised from acetone to yield 1 : 3-*dinitro*-2-*methylpyrrocoline* as a yellow microcrystalline powder, m. p. 218—219° (decomp.) (Found : N, 19·0. $C_9H_7O_4N_3$ requires N, 18·8%). The omission of sulphuric acid in this preparation gave a much cruder product and a low yield of the dinitro-compound.

(b) *From* 3-*acetyl*-2-*methylpyrrolocine*. When the acetyl compound (5 g.) in acetic acid (50 c.c.) was mixed with nitric acid (38 c.c.) a spontaneous reaction set in with evolution of nitrous fumes and deposition of a bright yellow solid. The reaction mixture was heated for 5 mins. on the steam-bath, diluted with water, filtered, and the solid product washed and dried (3·65 g.; 58%), m. p. 218—219° (decomp.); it separated from acetone as a yellow microcrystalline powder with unaltered m. p. (Found : C, 48·9; H, 3·3; N, 19·2. $C_9H_7O_4N_3$ requires C, 48·9; H, 3·2; N, 18·8%). An identical product was obtained when the acetyl compound was dissolved in nitric acid; it separated from the solution after 1 min.

(c) *From* 1 : 3-*diacetyl*-2-*methylpyrrocoline*. A solution of the latter (0·2 g.) in acetic acid (2 c.c.) and nitric acid (1·5 c.c.) was heated for 10 mins. on the steam-bath. The dinitro-compound separated almost immediately and was filtered off after dilution of the reaction mixture with water and crystallised from acetone, m. p. 218—219° (decomp.) alone and admixed with the compound prepared by procedure (*a*); yield 0·12 g.; 59%.

(d) *From* 1-*nitro*-3-*acetyl*-2-*methylpyrrocoline*. This compound (0·5 g.) yielded the dinitro-compound (0·5 g.), m. p. 218—219° (decomp.), almost quantitatively when treated as in (c).

(e) *From* 3-*nitroso*-2-*methylpyrrocoline*. This compound (0·25 g.), on treatment as in (c), also yielded the dinitro-compound (0·12 g.). m. p. 218—219° (decomp.) (Found : N, 18·4%).

A solution of 1 : 3-dinitro-2-methylpyrrocoline (0·3 g.) in acetic acid (5 c.c.) and perhydrol (5 c.c.), heated for 2 hrs., gave α-picolinic acid *N*-oxide, m. p. and mixed m. p. 162° (decomp.).

1 : 3-*Dinitro*-2-*phenylpyrrocoline*.—(a) *From* 2-*phenylpyrrocoline*. A solution of the pyrrocoline (2 g.) in nitric acid (10 c.c.) was warmed cautiously over a free flame until a vigorous reaction set in which was controlled by immediate

cooling. Heating was then resumed until the active evolution of nitrous fumes recommenced, and the mixture was then cooled and poured on ice. The washed and dried reddish-orange precipitate (0·8 g.) was extracted with hot ethyl acetate (100 c.c.) to remove insoluble material, which was neglected. The ethyl acetate solution was heated with charcoal and cooled, greenish-orange crystals (0·38 g.; m. p. 233—238°) separating; concentration of the filtrate yielded a second crop (0·2 g.). The combined crops were recrystallised from acetic acid to give 1 : 3-*dinitro*-2-*phenylpyrrocoline* (0·4 g.; 14%) as fine yellow needles, m. p. 246—247°, having a green tint. The green colour was removed by sublimation at 180—190°/0·02 mm. (Found : N, 14·9. $C_{14}H_9O_4N_3$ requires N, 14·8%).

(b) *From* 3-*acetyl*-2-*phenylpyrrocoline*. This reaction was effected essentially as described above for the 2-methyl analogue, the acetyl compound (0·2 g.) giving the dinitro-compound (0·15 g.; 51%) as yellow needles, m. p. 246—247° alone and admixed with the compound obtained in (a) (Found : C, 59·5; H, 3·4; N, 14·5. $C_{14}H_9O_4N_3$ requires C, 59·4; H, 3·2; N, 14·8%). It can also be prepared in 48% yield by solution of the acetyl compound in nitric acid at room temperature.

From (c) 1 : 3-*diacetyl*-, (d) 1-*nitro*-3-*acetyl*-, *and* (e) 1-*nitroso*-3-*acetyl*-2-*phenylpyrrocoline*. These reactions were carried out essentially by the procedures already described. The dinitro-compound was obtained in yields of 78%, 66%, and 67%, respectively, from these compounds.

(f) *From* 3-*nitroso*-2-*phenylpyrrocoline*. A solution of this compound (0·2 g.) in acetic acid (2 c.c.) with nitric acid (1 c.c.) was heated for 10 mins. on the steam-bath, cooled, and diluted with water. The small amount (0·1 g.) of precipitated material was collected, purified, and characterised in the usual manner.

Oxidation of 1 : 3-dinitro-2-phenylpyrrocoline (1 g.) in acetic acid (20 c.c.) with perhydrol (15 c.c.) for 2 hrs. on the steam-bath yielded α-picolinic acid *N*-oxide (0·2 g.), m. p. 162° (decomp.), and benzoic acid (0·25 g.).

Preparation of 1-*Nitro*-3-*acetyl*-2-*methylpyrrocoline*.—To a solution of 3-acetyl-2-methylpyrrocoline (3 g.) in acetic acid (30 c.c.) at 90° nitric acid (2·25 c.c.) was added dropwise at a rapid rate; a vigorous reaction set in with evolution of nitrous fumes. After the reaction had proceeded for 30 seconds the mixture was poured into water. The orange-yellow precipitate (2·3 g.) was washed, dried, and dissolved in boiling ethyl acetate (50 c.c.), leaving a little black insoluble material. The deeply coloured solution was heated with charcoal, filtered, and concentrated; the residue, dissolved in acetone (50 c.c.), was passed through a column of alumina to yield a narrow brown, a deep red, and a wide bright yellow chromatogram. The last was eluted with acetone to yield a yellow solid (1·75 g.), m. p. 134—136°, which was a mixture of 1-nitro-3-acetyl- and 1 : 3-dinitro-2-methylpyrrocoline inseparable by fractional crystallisation.

The mixture was dissolved in dry benzene and passed through a column of alumina, an orange-red chromatogram being formed at the lower end of a yellow band; these were separated by extrusion of the column and cutting at the appropriate point. The orange-red portion was eluted with acetone–alcohol, and the extracted material crystallised from acetone, 1 : 3-dinitro-2-methylpyrrocoline being obtained as yellow needles (4% yield), m. p. 218—219° (decomp.). From the eluate of the yellow chromatogram 1-*nitro*-3-*acetyl*-2-*methylpyrrocoline* (1·6 g.; 36%) was isolated; it crystallised from alcohol in yellow needles, m. p. 140·5—141° (Found : C, 60·1; H, 4·5; N, 12·8. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6; N, 12·8%).

When the reaction of 1 : 3-diacetyl-2-methylpyrrocoline (0·5 g.) in acetic acid (5 c.c.) with 25% nitric acid (2·5 c.c.) was allowed to proceed for 24 hrs. at room temperature both nitro-compounds were produced but in very low yields.

The 2 : 4-*dinitrophenylhydrazone* of 1-nitro-3-acetyl-2-methylpyrrocoline, prepared by mixing alcoholic solutions of the reagents, separated as a scarlet, crystalline powder, m. p. 276—277° (decomp.) (Found : N, 20·8. $C_{17}H_{14}O_6N_6$ requires N, 21·1%).

Oxidation of the nitroacetyl compound (0·4 g.) in refluxing acetic acid (5 c.c.) with perhydrol (5 c.c.) for 1 hr. yielded α-picolinic acid *N*-oxide, m. p. 162° (decomp.).

Oxidation of 1-*Nitroso*-3-*acetyl*-2-*methylpyrrocoline*.—When a solution of the pyrrocoline (1 g.) in acetic acid (20 c.c.) and perhydrol (5 c.c.) was heated to boiling, a reaction set in which was allowed to proceed unaided for 20 seconds. The mixture was then cooled, poured into water, and the yellow precipitate collected, washed and dried. Crystallisation from ethyl acetate (charcoal) yielded the nitro-compound, yellow needles, m. p. 140·5—141° alone and admixed with that prepared as above (Found : C, 60·35; H, 4·5; N, 13·1%). The 2 : 4-dinitrophenylhydrazone also was identical with that described above, m. p. 276—277° (decomp.) alone and admixed.

Preparation of 1-*Nitro*-3-*acetyl*-2-*phenylpyrrocoline*.—A solution of 1 : 3-diacetyl-2-phenylpyrrocoline (4·5 g.) in a mixture of 25% nitric acid (22·5 c.c.) and acetic acid (45 c.c.) during 2 days at room temperature deposited 1-*nitro*-3-*acetyl*-2-*phenylpyrrocoline* as yellow needles. The reaction mixture was diluted with water, and the solid product crystallised from alcohol; bright yellow needles (2·3 g.; 50%), m. p. 169° (Found : C, 68·6; H, 4·3; N, 10·3. $C_{16}H_{12}O_3N_2$ requires C, 68·5; H, 4·3; N, 10·0%). The 2 : 4-*dinitrophenylhydrazone* slowly separated as red crystalline platelets when an alcoholic solution of the nitroacetyl compound and Brady's reagent was heated; it recrystallised from methyl cyanide as red needles, m. p. 253° (decomp.) (Found : N, 18·05. $C_{22}H_{16}O_6N_6$ requires N, 18·25%).

Oxidation of 1-*Nitroso*-3-*acetyl*-2-*phenylpyrrocoline*.—When a solution of the nitroso-derivative (0·5 g.) in a mixture of acetic acid (7 c.c.) and perhydrol (8 c.c.) was brought to the boil it continued boiling of its own accord for 4 mins.; the solution was then cooled and the nitro-compound (0·25 g.; 47%), m. p. 168—169°, separated; it recrystallised from acetic acid as yellow needles, m. p. 169° alone and admixed with the specimen prepared as described above (Found : C, 68·2; H, 4·0; N, 10·5%). Its identity was confirmed by the preparation of the 2 : 4-dinitrophenylhydrazone, m. p. 253° (decomp.) alone and admixed (Found : N, 18·0%).

Nitration of 2-*Methylpyrrocoline in Sulphuric Acid*.—Nitric acid (12 c.c.) was added slowly to a stirred solution of 2-methylpyrrocoline (12 g.) in concentrated sulphuric acid (35 c.c.) at 0°. After 5 mins. the resultant dark red solution was poured on crushed ice, and the orange-red precipitate immediately filtered off, washed thoroughly, and dried in a vacuum; yield 11·3 g., m. p. 149—153°. The product deteriorated rapidly when it was not thoroughly washed with water before drying.

The solid was dissolved in acetone (400 c.c.) and the filtered brown solution passed through a column of alumina. A wide yellow chromatogram rapidly developed and spread down the column, leaving a dark brown zone at the top. The former was eluted with acetone, and the eluate concentrated to yield a bright yellow solid, m. p. 154—155° (10·0 g.; 62%). Recrystallisation of this from acetic acid gave 1-*nitro*-2-*methylpyrrocoline*, yellow needles, m. p. 154·5—155·5° (Found : C, 61·6; H, 4·5, N, 16·2. $C_9H_8O_2N_2$ requires C, 61·3; H, 4·6; N, 15·9%).

The original acid filtrate was made alkaline by careful addition of 40% sodium hydroxide, and the resulting dark precipitate was filtered off, washed with water, and dried in a vacuum (3·0 g.). This was subjected to steam-distillation to remove 2-methylpyrrocoline (1·6 g.) and the distillation was discontinued when a yellow solid commenced to distil. The residual bright yellow aqueous solution was decanted from a considerable quantity of black tar which was extracted with several portions of boiling water until the aqueous extracts were colourless. The combined aqueous solutions were extracted with ether to yield a yellow solid (0·25 g.; 1·5%) which, after recrystallisation from aqueous alcohol gave 3-*nitro*-2-*methylpyrrocoline* as yellow needles, m. p. 103—104° (Found : C, 61·0; H, 4·5; N, 16·5%).

Oxidation of 1-nitro-2-methylpyrrocoline (0·5 g.) with a mixture of perhydrol (5 c.c.) and acetic acid (10 c.c.) for 45

mins. under reflux yielded α-picolinic acid *N*-oxide (0·15 g.), m. p. 159·5° (decomp.) alone and on admixture with an authentic specimen.

On one occasion a small quantity of 1 : 3-dinitro-2-methylpyrrocoline was isolated. This was effected by chromatography of a portion of the crude product dissolved in dry benzene on a column of alumina; a distinct red chromatogram was obtained quite separate from the larger yellow one containing the above two mononitro-compounds. The dinitropyrrocoline was removed and identified in the usual manner.

Preparation of 1 : 3-*Dinitro*-2-*methylpyrrocoline*.—(a) *From* 1-*nitro*-2-*methylpyrrocoline*. A solution of the 1-nitro-compound (0·5 g.) in acetic acid (10 c.c.) was mixed with concentrated sulphuric acid (0·5 c.c.) and nitric acid (0·8 c.c.), and heated carefully over a small flame until a reaction set in which was allowed to continue for 1 min. away from the heat source; the mixture was then poured into water. The precipitated brown solid (0·15 g.), after recrystallising from acetone (charcoal), yielded 1 : 3-dinitro-2-methylpyrrocoline, m. p. 218—219° (decomp.) alone and on admixture with an authentic specimen.

(b) *From* 3-*nitro*-2-*methylpyrrocoline*. A solution of the 3-nitro-compound (0·05 g.) in nitric acid (0·5 c.c.) and acetic acid (1 c.c.) was warmed on the steam-bath for 1 min., diluted with water, and the precipitate, m. p. 217—218°, (decomp.), recrystallised from acetone, a yellow microcrystalline powder, m. p. 218—219° (decomp.) alone and when mixed with an authentic specimen of 1 : 3-dinitro-2-methylpyrrocoline, being obtained.

Acetylation of 1-*Nitro*-2-*methylpyrrocoline*.—A solution of the nitro-compound (1 g.) and fused sodium acetate (2 g.) in acetic anhydride (25 c.c.) was refluxed for 5 days, mixed with alcohol, and evaporated to dryness on a steam-bath. Trituration of the dark residue with water yielded an oil which solidified; this was washed with water, dried, and dissolved in benzene. The benzene solution, filtered from black insoluble material (0·4 g.), was poured down a column of alumina, and a bright yellow chromatogram that spread rapidly down the column was obtained. The extruded column of alumina was cut to remove two narrow brown chromatograms at the top, and the remaining yellow one was eluted with alcohol. The alcoholic eluate was concentrated to leave a sticky yellow solid (0·8 g.), m. p. 85—115°, which by fractional crystallisation from alcohol was separated into more soluble unchanged 1-nitro-2-methylpyrrocoline (0·4 g.) and 1-nitro-3-acetyl-2-methylpyrrocoline (0·2 g.), m. p. 140·5—141° alone and on admixture with the product prepared by direct nitration (Found: N, 12·3%). The 2 : 4-dinitrophenylhydrazone, prepared in the usual manner, had m. p. 276—277° (decomp.) alone and on admixture with specimens prepared by other routes.

3-*Acetyl*-2-*methylpyrrocoline Nitrate*.—On addition of a solution of fuming nitric acid (0·3 c.c.) in ether (10 c.c.) to 3-acetyl-2-methylpyrrocoline (0·5 g.) in ether (10 c.c.), a purple colour developed and a pale green solid (0·18 g.) separated. The solid, which was washed with ether, decomposed at 115—116° with explosive violence but was quite stable at 100° (30 mins.) (Found: N, 14·2. $C_{11}H_{11}ON,2HNO_3$ requires N, 14·1%). Dehydration of this *salt* in boiling toluene was unsatisfactory, but in acetic acid it yielded, after 1 min.'s boiling, a dark brown solid, from which a small quantity of 1-nitro-3-acetyl-2-methylpyrrocoline was isolated, m. p. 140·5—141° alone and on admixture with an authentic specimen.

Nitration of 3-*Acetyl*-2-*methylpyrrocoline in Sulphuric Acid*.—A solution of the acetyl compound (10 g.) in concentrated sulphuric acid (100 c.c.) was stirred and kept at 0° during the dropwise addition of a mixture of nitric acid (4·5 c.c.) and sulphuric acid (20 c.c.). After 15 mins. the mixture was poured on crushed ice, and the precipitated yellow solid filtered off, washed, and dried in a vacuum; yield 9·6 g., m. p. 132—136°. The yellow solid was dissolved in cold acetone (350 c.c.), and the red brown solution filtered down a column of alumina (27 × 3 cm.). The bright yellow chromatogram that rapidly swept down the column was completely eluted, and the dark brown band remaining at the top of the column was discarded. The acetone eluate on concentration yielded an orange-yellow solid (9·0 g.), m. p. 135—136°, which was dissolved in dry benzene and chromatographed on a column of alumina in a similar manner to that employed in the preparation of 1-nitro-3-acetyl-2-methylpyrrocoline by the action of nitric acid in acetic acid. By this procedure 1-nitro-3-acetyl- (7·5 g.; 59%) and 1 : 3-dinitro-2-methylpyrrocoline (0·79 g.; 6%) were isolated and identified in the usual manner.

Nitration of 2-*Phenylpyrrocoline in Concentrated Sulphuric Acid*.—2-Phenylpyrrocoline (10 g.) was added with stirring to concentrated sulphuric acid (60 c.c.) cooled in ice-salt, and the temperature was kept at 0° during the dropwise addition (30 mins.) of nitric acid (3·5 c.c.). The orange-yellow product [8·7 g.; m. p. 218—230° (decomp.)] precipitated by pouring the thick reaction mixture on crushed ice was filtered off immediately and washed repeatedly before being dried in a vacuum. The dried material, crystallised from ethyl acetate (charcoal), yielded 2-p-*nitrophenylpyrrocoline* (5·8 g.), m. p. 245·5—246° (decomp.), which separated from methyl cyanide in yellow platelets (5 g.; 41%), m. p. 250—251° (decomp.) (Found: C, 70·8; H, 4·35; N, 12·2. $C_{14}H_{10}O_2N_2$ requires C, 70·6; H, 4·2; N, 11·8%). The original ethyl acetate mother-liquor was concentrated to a small volume, filtered through a column of alumina, and the eluate and washings were concentrated. The residue yielded, by fractional crystallisation from acetone, 30 mg. of 1-nitro-2-*p*-nitrophenylpyrrocoline as yellow needles, m. p. 235·5—236° alone and on admixture with an authentic specimen.

2-*p*-Nitrophenylpyrrocoline, refluxed for 3 hrs. in glacial acetic acid (20 c.c.) with perhydrol, yielded α-picolinic acid *N*-oxide and *p*-nitrobenzoic acid.

2-*p*-Nitrophenylpyrrocoline was obtained in 37% yield when a mixture of 2-phenylpyrrocoline (1·2 g.) in phosphoric acid (25 c.c.) and nitric acid (0·41 c.c.) was left for 16 hrs. at room temperature. Trituration of 2-phenylpyrrocoline (0·5 g.) in concentrated sulphuric acid (2 c.c.) with sodium nitrate (0·24 g.) in the cold and finally on the steam-bath gave rise to 2-*p*-nitrophenylpyrrocoline (0·2 g.; 31%), m. p. 250—251° (decomp.) alone and admixed with an authentic specimen.

Acetylation of 2-p-*Nitrophenylpyrrocoline*.—A solution of the nitro-compound (2 g.) and fused sodium acetate (2 g.) was refluxed for 24 hrs. in acetic anhydride (80 c.c.), and the solvent removed in a vacuum. From the residue there was obtained, by chromatography on alumina, 3-*acetyl*-2-p-*nitrophenylpyrrocoline*, yellow needles, m. p. 190·5—191°, after crystallisation from methyl cyanide. The nitro-compound can be sublimed at 150°/0·001 mm. without change in m. p. (Found: C, 68·7; H, 4·5; N, 10·2. $C_{16}H_{12}O_3N_2$ requires C, 68·6; H, 4·3; N, 10·0%).

1-*Nitro*-2-p-*nitrophenylpyrrocoline*.—(*a*) Nitric acid (0·35 c.c.) was added dropwise to an ice-cold, stirred solution of 2-phenylpyrrocoline (0·5 g.) in concentrated sulphuric acid (1·5 c.c.), and the reaction mixture poured on ice. The precipitated material, after recrystallisation from methyl cyanide and then acetone (charcoal), yielded 1-nitro-2-nitrophenylpyrrocoline (0·33 g.; 45%), yellow needles, m. p. 235—236° alone and on admixture with an authentic specimen described below (Found: N, 14·4%).

(*b*) In a similar manner nitration of 2-*p*-nitrophenylpyrrocoline (0·2 g.) in sulphuric acid (2 c.c.) at 0° with nitric acid (0·07 c.c.) yielded an identical product (0·08 g.), m. p. 235—236°.

2-*Phenylpyrrocoline Nitrate*.—On addition of nitric acid (0·08 c.c.) to a solution of 2-phenylpyrrocoline in acetic acid (6 c.c.) containing nitric acid (0·08 c.c.) monoclinic needles separated; these melted at 134° with vigorous decomposition (Found, after drying at room temp. in a vacuum: C, 54·5; H, 4·8; N, 13·0. $C_{14}H_{11}N,1·8HNO_3$ requires C, 54·8; H, 4·2; N, 12·8%). Recrystallisation from ethyl acetate results in a gradual fall in the content of nitric acid, the free base being obtained eventually. The nitrate was prepared in larger quantity as follows. 2-Phenylpyrrocoline (10 g.) was triturated with a mixture of concentrated nitric acid (10 c.c.) and glacial acetic acid (100 c.c.), and the flocculent mass removed,

washed with successive small portions of acetic acid, and well pressed. The product, m. p. 134° (decomp.), was identical with that described above.

The nitrate was added portionwise to stirred concentrated sulphuric acid (30 c.c.) kept below 10°, the clear yellow syrup poured on ice, and the solid product immediately filtered off, washed thoroughly with water, and dried. The dark orange solid (11·5 g.), crystallised thrice from hot methyl cyanide, yielded 1-*nitro*-2-p-*nitrophenylpyrrocoline*, yellow needles, m. p. 235·5—236°. A portion was sublimed at 180°/0·005 mm. for analysis (Found : C, 59·6; H, 3·3; N, 14·7. $C_{14}H_9O_4N_3$ requires C, 59·4; H, 3·2; N, 14·8%). Examination of the original methyl cyanide mother-liquor yielded no tractable product other than an additional quantity (1·1 g.) of the dinitro-compound, bringing the total yield to 47·5%.

Oxidation of 1-nitro-2-*p*-nitrophenylpyrrocoline (1·4 g.) with perhydrol (15 c.c.) and acetic acid (10 c.c.) yielded α-picolinic acid *N*-oxide (0·2 g.) and *p*-nitrobenzoic acid (0·4 g.).

Nitration of 3-*Acetyl*-2-*phenylpyrrocoline*.—(a) *With* 1 *mol. of nitric acid.* A solution of the acetyl compound (30 g.) in concentrated sulphuric acid (140 c.c.) was stirred and kept at −10° to −5° during the dropwise addition of nitric acid (8·3 c.c.) and then added slowly to vigorously stirred ice-water (1000 c.c.). The precipitated greenish-yellow solid rapidly darkened during this operation and the subsequent filtration and washing with water (1000 c.c.). The crude solid (21·5 g.), dissolved in the minimum volume of cold acetone, was filtered down a column (2 × 10 cm.) of alumina, which was washed with fresh acetone until the eluate became pale. The contents of the multi-coloured chromatograms proved intractable. The residue (13 g.) after evaporation of the acetone eluates was dissolved in the minimum quantity of benzene and filtered down a fresh column (3 × 30 cm.) of alumina. The chromatogram was developed with fresh benzene, giving a yellow and a green chromatogram with a brown zone at the top. From the green chromatogram benzene extracted a fraction (3·2 g.) which, after crystallisation from methyl cyanide (charcoal) and then chloroform–ligroin, yielded 1 : 3-*dinitro*-2-p-*nitrophenylpyrrocoline* (2·3 g.), a yellow micro-crystalline powder, m. p. 232—233° (decomp.) (Found : C, 51·5; H, 2·2; N, 17·1. $C_{14}H_8O_6N_4$ requires C, 51·2; H, 2·4; N, 17·0%).

The yellow chromatogram yielded, after systematic fractional crystallisation : (i) 1 : 3-dinitro-2-*p*-nitrophenylpyrrocoline (1·2 g.); (ii) 3-*nitro*-2-p-*nitrophenylpyrrocoline* (2·8 g.), yellow monoclinic needles from chloroform–ligroin, m. p. 211° (largely depressed when mixed with the 1-nitro-isomeride, m. p. 235·5—236°) (Found : N, 14·6%); (iii) 3-acetyl-2-*p*-nitrophenylpyrrocoline (1·6 g.), yellow needles from methyl cyanide, m. p. 190·5—191° alone and when mixed with the compound obtained by acetylation of 2-*p*-nitrophenylpyrrocoline (Found : N, 10·4%); (iv) 1-nitro-3-acetyl-2-*p*-nitrophenylpyrrocoline, yellow nodules (0·6 g.) from chloroform–ligroin, m. p. 173—175° alone or mixed with an authentic specimen.

(b) *With* 2 *mols. of nitric acid.* Nitration of 3-acetyl-2-phenylpyrrocoline (30 g.) with 2 mols. of nitric acid (16·5 c.c.) was carried out essentially as in (a). The dried product (30 g.) in acetone was filtered down a column of alumina and the eluate concentrated to yield a mixture of nitro-compounds (26 g.), from which by crystallisation from methyl cyanide (700 c.c.) a crop of crystals (9·1 g.) was obtained. This by crystallisation from chloroform was separated into 1 : 3-dinitro-2-*p*-nitrophenylpyrrocoline (3·9 g.), m. p. 232—233° (decomp.) alone or when admixed with the compound isolated from preparation (a) (Found : C, 51·4; H, 2·7; N, 16·8%), and 3-nitro-2-*p*-nitrophenylpyrrocoline, yellow needles (3·3 g.) m. p. 211°, from chloroform–ligroin (Found : C, 59·5; H, 3·5; N, 14·6%). The methyl cyanide mother-liquor (700 c.c.) was concentrated in a vacuum, and the residue fractionally crystallised from chloroform–ligroin to remove a trace of the less soluble 1 : 3-dinitro-2-*p*-nitrophenylpyrrocoline and to yield 1-*nitro*-3-*acetyl*-2-p-*nitrophenylpyrrocoline* (8·35 g.), which separated in yellow needles, m. p. 173—175° (Found : C, 59·0; H, 3·6; N, 12·9. $C_{16}H_{11}O_5N_3$ requires C, 59·1; H, 3·4; N, 12·9%). From the various filtrates, there was isolated, by chromatography on alumina, 3-acetyl-2-*p*-nitrophenylpyrrocoline (50 mg.), yellow needles, m. p. 190·5—191° alone and admixed with an authentic specimen.

Oxidation of 1-nitro-3-acetyl-, 3-nitro- and 1 : 3-dinitro-2-*p*-nitrophenylpyrrocoline in acetic acid with perhydrol gave, in each case, α-picolinic acid *N*-oxide and *p*-nitrobenzoic acid.

BATTERSEA POLYTECHNIC, S.W. 11.
GLAXO LABORATORIES LTD., GREENFORD.

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