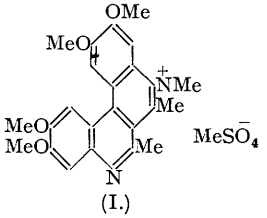
167. *Attempts to find New Antimalarials. Part XXI.*

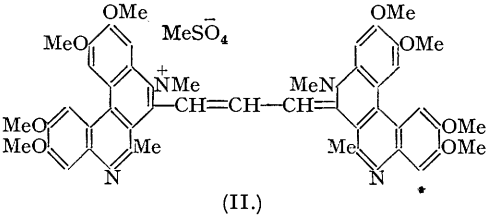
By M. J. S. Dewar.

The present investigation was undertaken with the object of testing the antimalarial properties of derivatives of heterocyclic ring systems hitherto untried in this connexion. A number of amines derived from pyrroquinolines, diveratrocopyrine, pyrazole, phenylpyrazole, and tetrazolopyrimidine have been prepared and are being tested for antimalarial and general pharmacological activity : some quaternary salts were also made with a view to possible trypanocidal action.

Derivatives of diveratrocopyrine were obtained by Lawson, Perkin, and Robinson (J., 1924, **125**, 640) by condensing β-diketones and related compounds with diaminoveratrone; the process is a double Friedländer synthesis. From the dimethyldiveratrocopyrine already described, a *methosulphate* (I) was prepared, and by the action of ethyl orthoformate in boiling pyridine this was converted into *dimethyldiveratrocopyrocyanine* (II) (M, 906). In order to introduce a basic side chain into the copyrine nucleus, *7-diethylaminoheptane-2 : 4-dione* (III) was prepared by a Claisen condensation of 5-diethylaminopentan-2-one and ethyl acetate, and this intermediate was condensed with diaminoveratrone, affording a good yield of *methyl-γ-diethylaminopropyl-diveratrocopyrine* (IV).



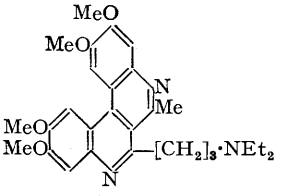
(I.)



(II.)

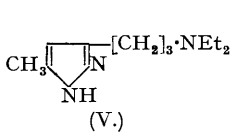
$CH_3 \cdot CO \cdot CH_2 \cdot CO \cdot [CH_2]_3 \cdot NEt_2$

(III.)



(IV.)

The same useful intermediate (III) was next employed in the preparation of several heterocyclic amines. From (III) and hydrazine, 5-*methyl*-3-(γ-*diethylaminopropyl*)*pyrazole* (V) was obtained, and phenylhydrazine gave the corresponding *phenylpyrazole*, probably as a mixture of isomerides (VI), since no crystalline derivative could be obtained. Finally *C*-aminotetrazole with (III) gave a similar mixture of methyl-γ-diethylaminopropyltetrazolopyrimidines (VII), one isomeride of unknown structure being isolated as its crystalline *picrate*.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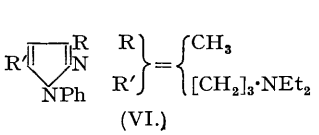
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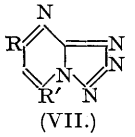
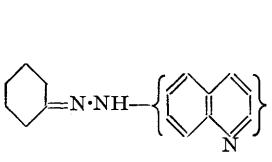

(VII.)

Attention was next turned to the pyrroquinoline series. The cyclo*hexanonehydrazones* (VIII) from 5-, 6-, and 8-quinolylhydrazines were readily cyclised by a mixture of sulphuric and acetic acids to 5 : 6- (IX), 6 : 5- (X), and 8 : 7- (XI) *tetrahydroquinolindoles*.* It was hoped that these could be nitrated and reduced, and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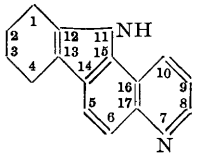
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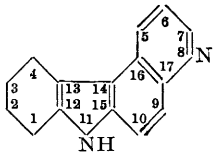
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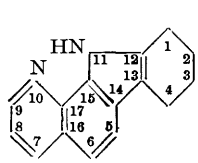
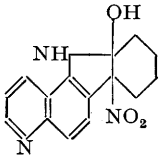
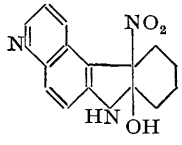

(XI.)

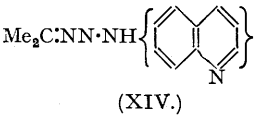
the resulting amines then condensed with suitable chloroalkylamines; but when (IX) or (X) was treated with potassium nitrate in sulphuric acid at — 15° (cf. Perkin and Plant, J., 1921, **119**, 1825), analysis showed that the unstable products were actually 13-*nitro*-12-*hydroxy*-1 : 2 : 3 : 4 : 12 : 13-*hexahydro*-5 : 6- (XII) and -6 : 5- (XIII) *quinolindoles*, formed by addition of nitric acid to the indole double bond. Such addition was observed by Perkin and Plant when tetrahydrocarbazole was treated with nitric acid in acetic acid, but that it should take place in concentrated sulphuric acid is very surprising. The occurrence of this abnormal reaction doubtless manifests the well-known deactivating influence of a pyridine ring.

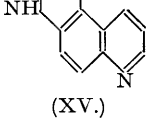
(XII.)




(XIII.)

A second line of approach was more successful. Kühn and Stein (*Ber.*, 1937, **70**, 567) synthesised gramine and two other dialkylaminomethylindoles by condensing indole with formaldehyde and secondary amines; this reaction has not been extended, but it promised a good method for introducing basic groups into the pyrroquinoline skeleton. *Acetone*-6- and -8-*quinolylhydrazones* (XIV) were prepared without difficulty, and cyclised by boiling their cymene solutions with zinc chloride (cf. D.R.-P. 238,138 : Friedländer, **10**, 333) to 6 : 5- (XV) and 8 : 7- (XVI) *pyrroquinolines*. The temperature required for cyclisation was higher than that described in the patent for normal phenylhydrazones, owing to the lesser reactivity of the quinoline ring. The products gave Ehrlich reactions; their acid solutions were coloured and, in the case of (XVI), fluorescent. In the Fischer synthesis of (XVI) a stable zinc complex was formed and prolonged boiling with alkali was necessary to liberate the free base; also (XVI) was far more volatile than (XV), indicating hydrogen bonding between the nitrogens. These results, showing the ease of chelation between the nitrogen atoms, are interesting in view of certain theories of antiplasmodial action; a similar arrangement of atoms is present in the plasmoquine molecule.


(XIV.)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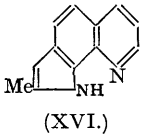
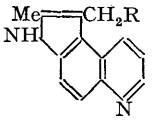

(XVI.)

The action of formaldehyde and secondary amines on (XV) and (XVI) in acetic acid furnished a series of 2-*methyl*-3-*dialkylaminomethyl*-6 : 5- (XVII) and -8 : 7-*pyrroquinolines* (XVIII). The amines used were diethylamine, dibutylamine, piperidine, morpholine, and tetrahydro*iso*quinoline. The crude yields were almost theoretical, but some loss occurred in purification which was usually effected by way of the oxalates. The 6 : 5-series gave intense colorations in hot sulphuric acid; it is interesting that the compound from

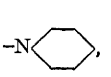
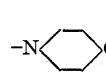
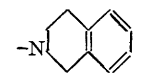
* The name quinolindole is proposed for the ring systems formed by fusion of quinoline with indole *via* its α- and β-positions; the numbers indicate the position of the attachment first of the α- and then of the β-position of indole to the quinoline system, and the final ring systems are numbered by analogy with carbazole.

piperidine gave a beautiful green colour while the others all gave shades of red. Salts of the 8 : 7-series were fluorescent in solution.

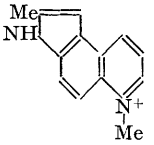


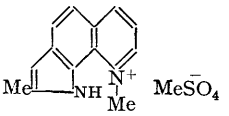
(XVII.)

(XVIII.)

R = NEt_2, NBu_2,  ,  , 

Finally an attempt was made to convert (XV) into an analogue of Fischer's base by treating it with an excess of methyl iodide in methanol under pressure. However, the product, formed in theoretical yield, was the *methiodide* (XIX) of (XV), complete inactivation of the indole ring being enforced by the positive charge at the other end of the molecule. In confirmation no colour was developed by (XIX) on heating with Ehrlich's reagent, a curious contrast to the behaviour of the *methosulphate* (XX) of (XVI), which gave a normal Ehrlich reaction.

(XIX.) 

(XX.) 

Experimental.

(All salts were dried in a high vacuum at 60° for analysis; all were hygroscopic.)

Dimethyldiveratrocopyrine Methosulphate (I).—A mixture of dimethyldiveratrocopyrine (4·33 g.) (Lawson, Perkin, and Robinson, *loc. cit.*), methyl sulphate (2·5 g.), and toluene (150 c.c.) was boiled for 6 hours under reflux, cooled, and the *methosulphate* collected; it crystallised from 90% alcohol in greenish-yellow needles (4·15 g., 72%), m. p. 250° (decomp.) (Found: C, 56·9; H, 5·5; S, 6·4. $C_{24}H_{28}O_8N_2S$ requires C, 57·1; H, 5·6; S, 6·3%). The red solution of the compound had an intense green fluorescence.

Dimethyldiveratrocopyrocyanine (II).—A mixture of the methosulphate (2 g.), ethyl orthoformate (1·18 g.), and dry pyridine (20 c.c.) was boiled for 5 hours under reflux, and when cold the *cyanine* (1·48 g., 88%) was precipitated with ethyl acetate. It crystallised from alcohol in mauve-black needles with a green lustre, m. p. 205° (Found: C, 62·9; H, 6·1; S, 3·0. $C_{48}H_{50}O_{12}N_4S,C_2H_6O$ requires C, 63·0; H, 5·9; S, 3·4%). Solutions of the compound showed an extraordinary dichroism, being crimson in bulk, blue-green in thin layers. The absorption spectrum, of normal cyanine type, showed maxima at 5600° A. (log ε = 3·45) and 6100 A. (log ε = 3·55).

7-*Diethylaminoheptan*-2 : 4-*dione*.—A suspension of sodium ethoxide (from 12·5 g. of sodium), in a mixture of toluene (125 c.c.) and dry ethyl acetate (150 c.c.), was stirred mechanically and cooled below 5° while 5-diethylaminopentan-2-one (78·5 g.) was gradually added. After 2 hours, the cooling bath was removed, and next day acetic acid (30 g.) and ether (500 c.c.) were added, the solution filtered and evaporated on a steam-bath, and the residual oil fractionated. Unchanged ketone (40 g.) distilled at 90—100°/30 mm., and then the *diketone* (34·3 g., 34%, or 70% allowing for recovery) was collected at 140—145°/30 mm.; it redistilled as a colourless oil, b. p. 139—140°/28 mm., $n_D^{20°}$ 1·6529 (Found: C, 66·4; H, 10·5; N, 6·9. $C_{11}H_{21}O_2N$ requires C, 66·3; H, 10·5; N, 7·0%). The compound was miscible with water and gave an intense cherry-red colour with aqueous or alcoholic ferric chloride.

Methyl-γ-*diethylaminopropyldiveratrocopyrine* (IV).—A solution of diaminoveratrone (5 g.) (Lawson, Perkin, and Robinson, *loc. cit.*) and diethylaminoheptanedione (5 g.) in acetic acid (25 c.c.) was boiled for 2 hours under reflux, diluted with water, basified with ammonia, filtered, and the *copyrine* then precipitated with sodium hydroxide, taken up in chloroform, dried over potassium carbonate, passed through an alumina column, recovered by evaporation, and converted into the *oxalate*, which crystallised from alcohol in orange rosettes (6·4 g.), m. p. 125° with gas evolution (Found: C, 54·1; H, 6·3; N, 5·9. $C_{28}H_{35}O_4N_3,2C_2H_2O_4,3H_2O$ requires C, 54·0; H, 6·3; N, 5·9%). The free *base* crystallised from ethyl acetate and light petroleum in cream-coloured needles, m. p. 148—149°, which were dried at 100°/0·01 mm. for analysis (Found: C, 70·0; H, 7·4; N, 9·0. $C_{28}H_{35}O_4N_3$ requires C, 70·4; H, 7·3; N, 8·8%). The *hydrochloride* crystallised from alcohol in microscopic saffron needles with no definite m. p. (Found: C, 59·2; H, 6·9; N, 7·4. $C_{28}H_{35}O_4N_3,2HCl,H_2O$ requires C, 59·1; H, 6·9; N, 7·4%).

5-*Methyl*-3-(γ-*diethylaminopropyl*)*pyrazole* (V).—A solution of hydrazine hydrate (1·25 g.) in alcohol (5 c.c.) was added to one of diethylaminoheptanedione (5 g.) in alcohol (10 c.c.), and the whole boiled for 1 hour under reflux. After distillation of the solvent, the *pyrazole* was converted in ether and acetone into its deliquescent *hydrochloride*, which crystallised on addition of absolute ether to its solution in absolute alcohol in colourless, acicular plates (6·15 g.), m. p. 210° (decomp.) (Found: C, 48·9; H, 8·5; N, 15·4. $C_{11}H_{21}N_3,2HCl$ requires C, 49·2; H, 8·6; N, 15·7%). The compound appeared to form a complex with Fehling's solution, which it did not reduce.

1-*Phenyl*-3 (or 5)-*methyl*-5 (or 3)-(γ-*diethylaminopropyl*)*pyrazole* (VI).—A solution of phenylhydrazine (3·91 g.) and diethylaminoheptanedione (7·20 g.) in alcohol (30 c.c.) was boiled under reflux for 2½ hours, the solvent distilled, and the residue fractionated. The *pyrazole* (7·52 g., 77%) was collected at 141—142°/0·15 mm. as a pale yellow oil with a faint basic smell, $n_D^{20°}$ 1·5400 (Found: C, 75·0; H, 9·4; N, 15·6. $C_{17}H_{25}N_3$ requires C, 75·2; H, 9·2; N, 15·5%). No derivative would crystallise; the *hydrochloride* was a gum (Found, in material dried in a vacuum over potassium hydroxide at room temperature: N, 10·3. $C_{17}H_{25}N_3,2HCl,1\frac{1}{2}C_2H_6O$ requires N, 10·2%).

4 (or 6)-*Methyl*-6 (or 4)-(γ-*diethylaminopropyl*)-1 : 2-(1′ : 5′-*tetrazolo*)*pyrimidine* (VII).—A mixture of aminotetrazole (3·4 g.), diethylaminoheptanedione (7·96 g.), alcohol (60 c.c.), and piperidine (4 drops) was refluxed for 60 hours, and the clear solution poured into one of picric acid (20 g.) in hot alcohol (2 l.). The *picrate* (12·5 g., 65%) after recrystallisation from alcohol had m. p. 105—120° (Found: C, 45·2; H, 4·8; N, 26·4. $C_{12}H_{20}N_6,C_6H_3O_7N_3$ requires C, 45·3; H, 4·8; N, 26·4%). By separating and crystallising from alcohol the last crop of crystals, one isomeric *picrate* was obtained pure in small canary-yellow prisms, m. p. 145—146° (Found: C, 46·0; H, 5·6. $C_{12}H_{20}N_6,C_6H_3O_7N_3,C_2H_6O$ requires C, 45·9; H, 5·5%).

cyclo*Hexanone*-6-*quinolylhydrazone*.—To a solution of 6-quinolylhydrazine dihydrochloride (19·4 g.), sodium acetate (12 g. of hydrate), and alcohol (50 c.c.) in water (150 c.c.) was added one of *cyclo*hexanone (8·2 g.) in alcohol (20 c.c.),

and the whole heated for 1 hour on a steam-bath. When cold, the *hydrazone* was collected; it crystallised from ethyl acetate in glistening, yellow, rectangular plates (9 g.), m. p. 180° (Found: C, 75·6; H, 7·3; N, 17·5. $C_{15}H_{17}N_3$ requires C, 75·3; H, 7·1; N, 17·6%).

1 : 2 : 3 : 4-*Tetrahydro*-6 : 5-*quinolindole* (X).—A solution of crude hydrazone (18·7 g.) and sulphuric acid (6 c.c.) in acetic acid (100 c.) was heated for 10 minutes on a steam-bath, then cooled, and the orange sulphate collected. The free *quinolindole* was liberated with ammonia and crystallised from acetone in large polyhedra (14·4 g., 72%), m. p. 201—202° (Found: C, 80·6; H, 6·5; N, 12·8. $C_{15}H_{14}N_2$ requires C, 81·1; H, 6·3; N, 12·6%).

cyclo*Hexanone*-5-*quinolylhydrazone*.—Prepared as before from 5-quinolylhydrazine dihydrochloride (23·7 g.), the *hydrazone* (20·6 g.; 92%) crystallised from carbon tetrachloride in bright orange needles, m. p. 131°, which were dried at 60°/0·01 mm. for analysis (Found: C, 65·0; H, 6·1; N, 15·2. $C_{15}H_{17}N_3,\frac{1}{4}CCl_4$ requires C, 65·8; H, 6·1; N, 15·1%). Drying at 100° led to decomposition.

1 : 2 : 3 : 4-*Tetrahydro*-5 : 6-*quinolindole* (IX).—Prepared as before from the hydrazone (9·1 g.) and sulphuric acid (3 c.c.) in acetic acid (50 c.c.), the *quinolindole* (7·58 g., 89%) crystallised from pyridine in microscopic rectangular plates, m. p. 286—288° (Found: C, 80·8; H, 6·1; N, 12·8%). The compound was very sparingly soluble in all solvents except acids or hot pyridine.

1 : 2 : 3 : 4-*Tetrahydro*-8 : 7-*quinolindole* (XI).—Prepared without isolation of the intermediate hydrazone, the *quinolindole* crystallised from ethyl acetate, with alumina treatment, in large trapezoidal tablets, m. p. 151° (Found: C, 80·9; H, 6·1; N, 12·8%).

13-*Nitro*-12-*hydroxy*-1 : 2 : 3 : 4 : 12 : 13-*hexahydro*-6 : 5-*quinolindole* (XIII).—To a solution of the tetrahydroquinolindole (0·74 g.) in sulphuric acid (5 c.c.) cooled below — 15° was added gradually with stirring powdered potassium nitrate (0·35 g.). After 5 minutes the solution was poured on ice, immediately basified with ammonia, and the *nitro-compound* (0·77 g., 81%) rapidly collected, washed with cold water and dried in a vacuum over sodium hydroxide. It was unstable to acids, bases, or hot solvents, but crystallised with heavy loss from methyl ethyl ketone and light petroleum in buff needles, m. p. 169° (decomp.) (Found: C, 63·4; H, 4·8; N, 14·8. $C_{15}H_{15}O_3N_3$ requires C, 63·1; H, 5·3; N, 14·7%).

13-*Nitro*-12-*hydroxy*-1 : 2 : 3 : 4 : 12 : 13-*hexahydro*-5 : 6-*quinolindole* (XII).—Prepared similarly, this *nitro-compound* was obtained as an unstable yellow powder which could not be recrystallised (Found: N, 14·6%).

Acetone-6-*quinolylhydrazone*.—The hydrazine dihydrochloride prepared from 6-aminoquinoline (14·4 g.) (Wieland and Horner, *Annalen*, 1938, **536**, 92) was dissolved in water (100 c.c.) containing acetone (10 c.c.), a solution of sodium acetate (100 g. of hydrate) in water (150 c.c.) added, and the whole warmed to 50° for 15 minutes. When cold, the *hydrazone* was collected and crystallised from dilute alcohol, forming pale yellow plates (14·5 g., 73%), m. p. 163—164° (Found: C, 71·0; H, 6·4; N, 20·9. $C_{12}H_{13}N_3,\frac{1}{4}H_2O$ requires C, 70·8; H, 6·6; N, 20·6%).

2-*Methyl*-6 : 5-(2′ : 3′-*pyrro*)*quinoline* (XV).—A mixture of the hydrazone (3·6 g.), powdered zinc chloride (4 g.), and cymene (16 c.c.) was heated under reflux in a bath at 175—180° for 3 hours. The solid product was washed with light petroleum, dried, powdered, and stirred into N-hydrochloric acid (100 c.c.), and after a few minutes the resulting suspension was poured into sodium hydroxide solution (200 c.c. of 25%). The *pyrroquinoline* was collected, and crystallised from chloroform and light petroleum in rhombs (2·83 g., 86%), m. p. 198°; it was freed from solvent for analysis by sublimation at 200°/0·5 mm. (Found: C, 78·9; H, 5·8; N, 15·9. $C_{12}H_{10}N_2$ requires C, 79·1; H, 5·5; N, 15·4%). The compound gave a scarlet colour with hot Ehrlich's reagent, fading reversibly to orange on cooling, and an amethyst solution in hot sulphuric acid.

2-*Methyl*-3-*diethylaminomethyl*-6 : 5-*pyrroquinoline* (XVII; R = NEt_2).—To a solution of the methylpyrroquinoline (0·91 g.) and diethylamine (0·37 g.) in acetic acid was added formalin (0·4 c.c. of 36·9%). Next day water was added, the solution basified, and excess diethylamine steam-distilled under reduced pressure. The methyldiethylaminomethylpyrroquinoline was then extracted with chloroform, and the chloroform solution dried over potassium carbonate, passed through an alumina column, and evaporated. The residual base was converted into its *oxalate*, which crystallised from alcohol in orange-yellow needles (2·04 g., 94%), m. p. 166° with gas-evolution (Found: C, 54·6; H, 5·7; N, 9·0. $C_{17}H_{21}N_3,2C_2H_2O_4,H_2O$ requires C, 54·2; H, 5·8; N, 9·0%). The very soluble free base had m. p. 125—130°; it was converted in ether into the *hydrochloride*, which crystallised from alcohol–ethyl acetate in microscopic lemon-yellow prisms, m. p. 202—203° (Found: C, 58·9; H, 7·6; N, 10·7. $C_{17}H_{21}N_3,2HCl,C_2H_6O$ requires C, 59·0; H, 7·5; N, 10·9%). Solutions in hot sulphuric acid were burgundy-red.

2-*Methyl*-3-*dibutylaminomethyl*-6 : 5-*pyrroquinoline* (XVII; R = NBu_2).—Prepared similarly, the *oxalate* crystallised from moist alcohol in chrome-yellow needles, m. p. 205° with gas-evolution (Found: C, 58·0; H, 6·8; N, 7·9. $C_{21}H_{29}N_3,2C_2H_2O_4,H_2O$ requires C, 57·7; H, 6·7; N, 8·1%). The *hydrochloride* crystallised from alcohol–ethyl acetate in deliquescent, chrome-yellow needles, m. p. 171° (Found: C, 61·1; H, 7·9; N, 10·5. $C_{21}H_{29}N_3,2HCl,H_2O$ requires C, 60·9; H, 8·0; N, 10·1%). The sulphuric acid colour resembled that of the diethyl analogue.

2-*Methyl*-3-*piperidinomethyl*-6 : 5-*pyrroquinoline*.—In this case the *base* crystallised from acetone in ochre rosettes, m. p. 228° (Found, in material dried at 100°/0·01 mm.: C, 77·2; H, 7·2; N, 14·9. $C_{18}H_{21}N_3$ requires C, 77·4; H, 7·5; N, 15·1%). The *hydrochloride* crystallised from 95% alcohol in long, bright yellow, radiating needles, m. p. 232° (Found: loss in weight at 60°/0·01 mm., 6·9. $C_{18}H_{21}N_3,2HCl,2H_2O$ requires $1\frac{1}{3}H_2O$, 6·2%. Found, in dried material: C, 59·2; H, 6·7; N, 11·4. $C_{18}H_{21}N_3,2HCl,\frac{2}{3}H_2O$ requires C, 59·3; H, 6·7; N, 11·5%). The solution in hot sulphuric acid was leaf-green.

2-*Methyl*-3-*morpholinomethyl*-6 : 5-*pyrroquinoline*.—The *base* crystallised from acetone in cream-coloured prisms, m. p. 228°, which were dried at 100°/0·01 mm. for analysis (Found: C, 72·4; H, 6·9; N, 14·6. $C_{17}H_{19}ON_3$ requires C, 72·6; H, 6·8; N, 14·9%). The *hydrochloride* crystallised from 90% alcohol in long, yellow needles, m. p. 230° (Found: C, 55·1; H, 6·5; N, 11·0. $C_{17}H_{19}ON_3,2HCl,H_2O$ requires C, 54·8; H, 6·2; N, 11·3%). The solution in hot sulphuric acid was cherry-red.

2-*Methyl*-3-*tetrahydro*isoquinolyl-6 : 5-*pyrroquinoline*.—The base, m. p. 199—204°, was purified by extracting its almost insoluble picrate with boiling alcohol and converted into its *hydrochloride*, which crystallised from alcohol in chrome-yellow rosettes, m. p. 196° (Found: C, 65·0; H, 6·2; N, 10·2. $C_{22}H_{21}N_3,2HCl,\frac{1}{2}C_2H_6O$ requires C, 65·2; H, 6·2; N, 9·9%). The solution in hot sulphuric acid was burgundy-red by transmitted, green by reflected light.

2-*Methyl*-6 : 5-*pyrroquinoline Methiodide* (XIX).—A mixture of the pyrroquinoline (1·4 g.), methyl iodide (5·5 g.), quinol (0·1 g.), and methanol (3 c.c.) was heated for 10 hours in a sealed tube at 130°, and the orange-red, crystalline solid (2·7 g., 100%) washed out with ether and recrystallised from aqueous alcohol, forming bright orange-red rosettes, m. p. 290° (decomp.) (Found: C, 49·0; H, 4·7; N, 8·3. $C_{13}H_{13}N_2I,\frac{1}{2}C_2H_6O$ requires C, 48·4; H, 4·6; N, 8·1%). The compound gave no colour with Ehrlich's reagent.

Acetone-8-*quinolylhydrazone*.—Prepared as for its isomer but from 8-aminoquinoline (44 g.), the *hydrazone* crystallised from dilute alcohol in large, pale yellow, rhombic plates (42·1 g., 69%), m. p. 70—71° (Found: C, 71·4; H, 6·7; N, 19·6. $C_{12}H_{13}N_3,\frac{1}{4}C_2H_6O$ requires C, 71·3; H, 6·9; N, 20·0%).

2-*Methyl*-8 : 7-*pyrroquinoline*.—A mixture of the hydrazone (6·1 g.), powdered zinc chloride (6 g.), and cymene c.c.) was heated under reflux in a bath at 175—180° for 5 hours. When cold, the solid was washed with light petro-

leum, powdered, and heated for 4 hours on a steam-bath with sodium hydroxide solution (200 c.c. of 20%), cooled, and the *pyrroquinoline* collected and crystallised from aqueous alcohol (charcoal), affording pale yellow, spear-shaped plates (3·78 g., 67%), m. p. 155—157°; it was freed from solvent for analysis by sublimation at 150°/0·01 mm. (Found: C, 78·8; H, 5·3; N, 15·1. $C_{12}H_{10}N_2$ requires C, 79·1; H, 5·5; N, 15·4%). With hot Ehrlich's reagent the compound gave a cherry-red colour, fading reversibly to orange on cooling. Compounds of this series all gave brown solutions in hot sulphuric acid, showing a green fluorescence; and solutions of their salts fluoresced markedly. The derivatives were prepared as for the 6 : 5-analogues.

2-*Methyl*-3-*diethylaminomethyl*-8 : 7-*pyrroquinoline*.—The *oxalate* crystallised from aqueous alcohol in pale yellow rosettes, m. p. 184° with gas-evolution (Found: C, 56·3; H, 5·5; N, 9·8. $C_{17}H_{21}N_3,2C_2H_2O_4$ requires C, 56·4; H, 5·6; N, 9·4%). The *hydrochloride* crystallised from 95% alcohol in golden, bladed plates, m. p. 202° with gas-evolution (Found: C, 58·5; H, 7·0; N, 12·4. $C_{17}H_{21}N_3,2HCl,\frac{1}{2}H_2O$ requires C, 58·5; H, 6·9; N, 12·0%).

2-*Methyl*-3-*dibutylaminomethyl*-6 : 5-*pyrroquinoline*.—The *oxalate* crystallised from alcohol in saffron rosettes, m. p. 167° with gas-evolution (Found: C, 59·5; H, 6·7; N, 8·6. $C_{21}H_{29}N_3,2C_2H_2O_4$ requires C, 59·6; H, 6·6; N, 8·4%). The *hydrochloride* crystallised from ethyl acetate containing a little alcohol in pale yellow rosettes, m. p. 135—136° (Found: loss in weight at 60°/0·01 mm., 5·5. $C_{21}H_{29}N_3,2HCl,2H_2O$ requires $1\frac{1}{2}H_2O$, 6·2%. Found, in dried material: C, 62·0; H, 7·6; N, 10·4. $C_{21}H_{29}N_3,2HCl,\frac{1}{2}H_2O$ requires C, 62·2; H, 7·9; N, 10·4%).

2-*Methyl*-3-*piperidinomethyl*-8 : 7-*pyrroquinoline*.—The *oxalate* crystallised from moist alcohol in canary-yellow rosettes, m. p. 135° with gas-evolution (Found: C, 57·1; H, 6·2; N, 8·6. $C_{18}H_{21}N_3,2C_2H_2O_4,C_2H_6O$ requires C, 57·0; H, 6·1; N, 8·3%). The *hydrochloride* crystallised from aqueous alcohol in saffron needles, m. p. 142° with gas-evolution (Found: loss in weight at 60°/0·01 mm., 7·4. $C_{18}H_{21}N_3,2HCl,2H_2O$ requires $1\frac{2}{3}H_2O$, 7·7%. Found, in dried material: C, 60·2; H, 6·6; N, 11·9. $C_{18}H_{21}N_3,2HCl,\frac{1}{3}H_2O$ requires C, 60·3; H, 6·6; N, 11·7%).

2-*Methyl*-3-*morpholinomethyl*-8 : 7-*pyrroquinoline*.—The *oxalate* crystallised from aqueous alcohol in fawn-yellow prisms, m. p. 155—156° with gas-evolution (Found: C, 56·4; H, 5·8; N, 8·8. $C_{17}H_{19}ON_3,2C_2H_2O_4,C_2H_6O$ requires C, 56·7; H, 6·0; N, 8·6%). The *hydrochloride* crystallised from moist alcohol in feathery, saffron needles, m. p. 228° (decomp.) (Found: loss in weight at 60°/0·01 mm., 4·2. $C_{17}H_{19}ON_3,2HCl,H_2O$ requires $\frac{3}{4}H_2O$, 3·6%. Found, in dried material: C, 56·8; H, 6·2; N, 11·5. $C_{17}H_{19}ON_3,2HCl,\frac{1}{4}H_2O$ requires C, 56·9; H, 6·0; N, 11·7%).

2-*Methyl*-3-*tetrahydroisoquinolyl*-8 : 7-*pyrroquinoline*.—The *hydrochloride* crystallised with difficulty from absolute alcohol on addition of dry ether in microscopic yellow needles, m. p. 85° (Found: loss in weight at 60°/0·01 mm., 7·9. $C_{22}H_{21}N_3,2HCl,3H_2O$ requires $2H_2O$, 7·9%. Found, in dried material: C, 63·3; H, 5·9; N, 9·7. $C_{22}H_{21}N_3,2HCl,H_2O$ requires C, 63·2; H, 6·0; N, 10·0%).

2-*Methyl*-8 : 7-*pyrroquinoline Methosulphate* (XX).—A solution of the methylpyrroquinoline (1·84 g.) and methyl sulphate (1·6 g.) in benzene (20 c.c.) was boiled for 3 hours under reflux; the *methosulphate* which separated crystallised from alcohol and ethyl acetate in long, orange-brown prisms, m. p. 157°; these were dried in a vacuum at room temperature over phosphoric oxide for analysis (Found: C, 54·7; H, 5·6; S, 10·0. $C_{14}H_{16}O_4N_4S,\frac{1}{4}C_2H_6O$ requires C, 54·5; H, 5·5; S, 10·0%). The deep red solutions of this quaternary salt had an intense green fluorescence, and with hot Ehrlich's reagent it gave a scarlet colour, fading reversibly to flame-red on cooling.

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