692. *Potential Trypanocides of the* N-*Heterocyclic Series. Part V. Structural Conditions for Activity against* Trypanosoma cruzi *in the Phenanthridine Series.*

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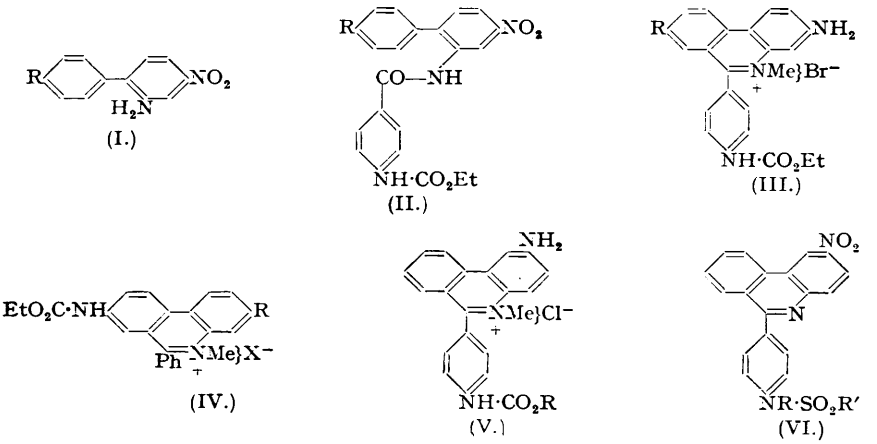
Hitherto the most effective phenanthridinium salt for the treatment of *Trypanosoma cruzi* infection in mice had been 2-amino-9-*p*-carbethoxyamino-10-methylphenanthridinium bromide. An attempt to obtain this compound from 2 : 4′-diamino-4-nitrodiphenyl (I; R = NH_2) failed, but the 7-methoxy-derivative was obtained. By an analogous process the monourethane (I; R = $NH{\cdot}CO_2Et$) was converted into 2-amino-7-carbethoxyamino-10-methyl-9-phenylphenanthridinium chloride. 2-Amino-5-nitrodiphenyl was converted by successive stages into 2-*p*-carbethoxyaminobenzamido-5-nitrodiphenyl and 9-*p*-carbethoxyaminophenyl-3-nitrophenanthridine, the quaternary salt of which was reduced to 3-amino-9-*p*-carbethoxyaminophenyl-10-methylphenanthridinium chloride (V; R = Et). This salt is highly active in mouse *T. cruzi* infections, but homologous urethanes (V; R = Me, Pr, Pr^i, Bu) proved to be much less active. The formal *S*-analogues of (V) were also synthesised from 9-*p*-aminophenyl-3-nitrophenanthridine, but are inactive.

In this series of papers attention has been directed chiefly to the high activity of phenanthridinium salts against *Trypanosoma congolense,* the causative parasite of bovine trypanosomiasis. A further characteristic of some urethanes of this class is activity against *T. cruzi* (Browning, Calver, Leckie, and Walls, *Nature*, 1946, **157**, 263), the trypanosome of Chagas' disease, a human infection prevalent in Central and South America. Organic arsenicals and other drugs successfully used in the treatment of the various African trypanosomiases are ineffective; certain rather toxic bismuth compounds and the antimalarial, pentaquine, show some activity in experimental infections, but the only substance of clinical value is the quinoline derivative, Bayer 7602 (Jensch, *Angew. Chem.*, 1937, **50**, *B*, 91). Mr. L. G. Goodwin and his colleagues at the Wellcome Laboratories of Tropical Medicine showed that on administration to mice during the incubation period of *T. cruzi* infection several phenanthridinium salts delayed or prevented the appearance of the parasites in the peripheral blood. It was deduced that activity was highest for 2 : 7-diamino-9-aryl salts, which are also the most effective against *T. congolense,* and for urethano-salts, thus confirming the earlier observation. The known refractory nature of *T. cruzi* infections to drug treatment revealed itself when the more promising compounds were tested against the established infection in mice. Only two compounds were markedly active, namely 3-carbethoxyamino- and 2-amino-9-*p*-carbethoxyaminophenyl-10-methylphenanthridinium bromide (III; R = H) (Caldwell and Walls, *J.*, 1948, 188). The synthesis of the 2-amino-compound is long and tedious, and attention was turned to possible more favourable routes, and to the preparation of analogous substances.

As expected, monoacetylation of 2 : 4′-diamino-4-nitrodiphenyl (I; R = NH_2) (Finzi and Mangini, *Gazzetta*, 1932, **62**, 664) gave a quantitative yield of (I; R = NHAc), which was condensed with *p*-carbethoxyaminobenzoyl chloride to form (II; R = NHAc). Differential hydrolysis of this substance readily afforded (II; R = NH_2) but it was not possible to convert this amine smoothly into (II; R = H), and so this prospective route to (III; R = H) was not investigated further. Replacement of the amino-group of (II; R = NH_2) by hydroxyl was readily effected by the diazo-reaction, and the product (II; R = OH) was converted by the methyl iodide–potassium carbonate method into (II; R = OMe). The methoxy-compound was cyclised under mild conditions to 9-*p*-carbethoxyaminophenyl-7-methoxy-2-nitrophenanthridine, reduction of the quaternary salt of which furnished (III; R = OMe; Cl for Br), which is only slightly active.

It was possible also to convert (I; R = NH_2) smoothly into the monourethane (I; R = $NH{\cdot}CO_2Et$), from which was obtained by successive stages of condensation with benzoyl chloride, ring-closure, formation of the quaternary salt (IV; R = NO_2), and reduction, 2-amino-7-carbethoxyamino-10-methyl-9-phenylphenanthridinium chloride (IV; R = NH_2). This salt and 7-amino-2-nitro-10-methyl-9-phenylphenanthridinium chloride which was obtained from (IV; R = NO_2) by hydrolysis are active in the incubation period of *T. cruzi* infection in mice, but fail in the established disease.

2-Amino-5-nitrodiphenyl was converted by successive stages of condensation with *p*-carbethoxyaminobenzoyl chloride and ring-closure of the product under mild conditions into 9-*p*-carbethoxyaminophenyl-3-nitrophenanthridine. Reduction of the quaternary salt of this substance furnished (V; R = Et), which is at least as active as its isomeride (III; R = H). Variation of the urethane group of (V) (R = Me, Pr, Pr^i, Bu) was then effected by reaction between the appropriate alkyl chloroformate and (*a*) 9-*p*-aminophenyl-10-methyl-3-nitrophenanthridinium chloride, obtained from the corresponding urethano-salt by hydrolysis, or



(*b*) 9-*p*-aminophenyl-3-nitrophenanthridine in acetone–diethylaniline, followed by formation of quaternary salt and reduction. Alternatively, condensation of 2-amino-5-nitrodiphenyl and *p*-carbopropoxyaminobenzoyl chloride followed by the operations already outlined gave (V; R = Pr). None of the salts obtained by these routes equalled (V; R = Et) in their action on *T. cruzi* infections, the best being (V; R = Bu).

The results of a pharmacological and chemotherapeutic investigation of some of these compounds have recently been published (Goodwin, Goss, Lock, and Walls, *Brit. J. Pharmacol.*, 1950, **5**, 277; Goodwin, Goss, and Lock, *ibid.*, p. 287).

The urea (V; $CO{\cdot}NH_2$ for CO_2R) was also prepared (*J.*, 1946, 1033), but is inactive.

Condensation of 9-*p*-aminophenyl-3-nitrophenanthridine in pyridine solution with methane- and ethane-sulphonyl chloride furnished (VI; R = H, R′ = Me) and (VI; R = H, R′ = Et), of which the former was methylated by the methyl iodide–potassium carbonate method to yield (VI; R = R′ = Me). These three sulphonamides were smoothly converted by the nitrobenzene–methyl sulphate method into quaternary salts, which were reduced to the formal *S*-analogues of (V), but all are inactive

Experimental.

(Analyses refer to samples dried at 100°.)

4′-Acetamido-2-amino-4-nitrodiphenyl (I; R = NH·COMe).—This compound has been described by Finzi (*Gazzetta*, 1931, **61**, 33), but the following method of preparation is more convenient. Hot water (54 ml.) was added to a solution of 2 : 4′-diamino-4-nitrodiphenyl (6 g.) in boiling alcohol (54 ml.). Some diamine was precipitated, but on addition of acetic anhydride (2·6 ml.) a clear solution was obtained, followed in a few minutes by separation of light-brown needles of the acetyl compound (5·4 g.), m. p. 225—229°, raised on recrystallisation from alcohol to 231—232° (Finzi gave 225°) (Found: C, 62·05; H, 4·85; N, 15·45. Calc. for $C_{14}H_{13}O_3N_3$: C, 61·95; H, 4·85; N, 15·5%).

4′-Acetamido-2-p-carbethoxyaminobenzamido-4-nitrodiphenyl (II; R = NH·COMe) was obtained by condensation of the foregoing acetyl compound (27 g.) with *p*-carbethoxyaminobenzoyl chloride (27 g.) in nitrobenzene (240 ml.) at 140°. After 45 minutes the solution was cooled, and the product that crystallised was collected, washed with cold alcohol, and recrystallised from aqueous pyridine in buff-

coloured leaves (44 g.), m. p. 244—245° (effervescence) (Found : C, 62·25; H, 4·65; N, 12·4. $C_{24}H_{22}O_6N_4$ requires C, 62·3; H, 4·8; N, 12·1%).

4′-*Amino*-2-p-*carbethoxyaminobenzamido*-4-*nitrodiphenyl* (II; R = NH_2).—The foregoing amide (5 g.) was refluxed with alcohol (65 ml.) and concentrated sulphuric acid (3·5 ml.) for 5 hours, complete dissolution being effected in about 4 hours. This solution was diluted with 2N-ammonia, and the orange *amine* thus precipitated was crystallised from 90% aqueous pyridine in orange plates (3·7 g.), m. p. 240—241° (decomp.) (Found : C, 62·7; H, 4·8; N, 13·3. $C_{22}H_{20}O_5N_4$ requires C, 62·85; H, 4·8; N, 13·3%).

2-p-*Carbethoxyaminobenzamido*-4′-*hydroxy*-4-*nitrodiphenyl* (II; R = OH).—A solution of the amine (10 g.) in concentrated sulphuric acid (80 ml.) and acetic acid (40 ml.) was diazotised with powdered sodium nitrite (2·0 g.); ice was then added cautiously, and finally water, to give 500 ml. The suspension of a yellow solid was then heated (steam-bath) until effervescence ceased. The solid, now brown in colour, was then collected and lixiviated with hot acetic acid. The residual *phenol* was crystallised twice from aqueous puridine, forming buff-coloured acicular prisms (6 g.), m. p. 251° (decomp.), which contained pyridine of crystallisation (Found : C, 64·4; H, 4·65; N, 10·85; loss, 14·5. $C_{22}H_{19}O_6N_3,C_5H_5N$ requires C, 64·75; H, 4·8; N, 11·2; C_5H_5N, 15·8%. Found, for the compound dried at 100° in a vacuum : C, 62·6; H, 4·45; N, 9·75. $C_{22}H_{19}O_6N_3$ requires C, 62·65; H, 4·65; N, 9·95%).

2-p-*Carbethoxyaminobenzamido*-4′-*methoxy*-4-*nitrodiphenyl* (II; R = OMe).—A solution of the hydroxy-compound (8·5 g.) in acetone (300 ml.) was refluxed with anhydrous potassium carbonate (8·5 g.) and methyl iodide (8·5 ml.). The original dark-brown acetone solution lightened in colour, and after 2 hours was separated, distilled to small bulk, and diluted with an equal volume of water. The crystalline *urethane* thus obtained recrystallised from acetic acid in light-brown leaves (6·5 g.), m. p. 203—205° (Found : C, 63·1; H, 4·9; N, 9·45. $C_{23}H_{21}O_6N_3$ requires C, 63·4; H, 4·85; N, 9·65%).

9-p-*Carbethoxyaminophenyl*-7-*methoxy*-2-*nitrophenanthridine*.—2-*p*-Carbethoxyaminobenzamido-4′-methoxy-4-nitrodiphenyl (5 g.) and phosphoryl chloride (7·5 ml.) were heated for 2 hours (steam-bath) and the solution was then decomposed with ice. The yellow solid *phenanthridine* was collected, heated with N-sodium carbonate, washed with water, and crystallised from acetone. It separated in greenish-yellow microscopic needles (2·6 g.), m. p. 221—223° (Found : C, 66·2; H, 4·7; N, 10·05. $C_{23}H_{19}O_5N_3$ requires C, 66·2; H, 4·6; N, 10·05%). This substance was heated with nitrobenzene–methyl sulphate at 175°, and since the methosulphate did not crystallise the nitrobenzene was distilled in steam. On addition of sodium chloride to the aqueous residue the quaternary *chloride* crystallised in small buff prisms, m. p. 235—236° (effervescence) (Found : C, 60·9; H, 4·45; N, 8·85; Cl, 7·7. $C_{24}H_{22}O_5N_3Cl$ requires C, 61·55; H, 4·75; N, 9·0; Cl, 7·6%).

2-*Amino*-9-p-*carbethoxyaminophenyl*-7-*methoxy*-10-*methylphenanthridinium chloride* (III; R = OMe) was obtained by reduction of the foregoing nitro-salt in aqueous solution with ferrous hydroxide. Addition of sodium chloride to the filtrate caused the *amino*-salt to separate in red needles which, recrystallised from methanol–ethanol, were unmolten at 300° (Found : C, 65·65; H, 5·45; N, 10·1; Cl, 8·3. $C_{24}H_{24}O_3N_3Cl$ requires C, 65·8; H, 5·55; N, 9·6; Cl, 8·1%).

2-*Amino*-4′-*carbethoxyamino*-4-*nitrodiphenyl* (I; R = $NH{\cdot}CO_2Et$).—2 : 4′-Diamino-4-nitrodiphenyl (5 g.) was dissolved in boiling alcohol (50 ml.) and treated with diethylaniline (3·5 ml., 1 equiv.) and ethyl chloroformate (2 ml., 1 equiv.). After 10 minutes at the boil the solution was stirred into 0·5N-hydrochloric acid (200 ml.). The brown *urethane* precipitated was collected and crystallised from alcohol in brownish-red transparent prisms, m. p. 153° (Found : C, 59·7; H, 4·65; N, 14·3. $C_{15}H_{15}O_4N_3$ requires C, 59·8; H, 5·0; N, 13·95%).

2-*Benzamido*-4′-*carbethoxyamino*-4-*nitrodiphenyl*.—Benzoyl chloride (9 ml.) was added to a solution of the foregoing amine (22·5 g.) in nitrobenzene (90 ml.) at 135°. Hydrogen chloride was evolved, and after 30 minutes the solution was cooled. The *product* that crystallised was collected, and recrystallised from benzene in almost white, elongated plates (24·5 g.), m. p. 197° (Found : C, 65·1; H, 4·6; N, 10·7. $C_{22}H_{19}O_5N_3$ requires C, 65·15; H, 4·75; N, 10·35%). With slow heating this substance may first melt at 188°, then resolidify and remelt at 197°.

7-*Carbethoxyamino*-2-*nitro*-9-*phenylphenanthridine*.—The benzoyl compound (10 g.) and phosphoryl chloride (10 ml.) were heated in a bath at 120° for 1 hour and then cautiously treated with ice-water. The solid thus liberated was lixiviated with hot aqueous sodium carbonate, washed with water, dried, and extracted with chloroform. A very sparingly soluble by-product (2·7 g.; a urea?) was thus left undissolved. Evaporation of the chloroform extract left a yellow crystalline solid (7 g.) of rather indefinite m. p. It was purified by dissolving it in boiling acetone (250 ml.) and adding concentrated hydrochloric acid (10 ml.); a deep yellow crystalline hydrochloride separated, which was converted into the *base* (4 g.) by being heated with dilute aqueous ammonia; this crystallised from acetone in yellow prisms, m. p. 247—249° (Found : C, 68·3; H, 4·4; N, 10·8. $C_{22}H_{17}O_4N_3$ requires C, 68·2; H, 4·45; N, 10·85%).

This product (3 g.) was converted into the quaternary salt by adding methyl sulphate (2 ml.) to its solution in nitrobenzene (30 ml.) at 180°. With cooling 7-*carbethoxyamino*-10-*methyl*-2-*nitro*-9-*phenylphenanthridinium methosulphate* (IV; R = NO_2) crystallised; it was purified by recrystallisation from water, forming yellow needles or plates, decomp. 158—160° (Found : N, 8·25; S, 6·0. $C_{24}H_{23}O_8N_3S$ requires N, 8·2; S, 6·25%).

This salt was hydrolysed by sulphuric acid (*d* 1·66) at 150°. Dilution with water followed by neutralisation with ammonia and addition of sodium chloride to the hot solution caused 7-*amino*-10-*methyl*-2-*nitro*-9-*phenylphenanthridinium chloride* to crystallise in brownish-purple elongated plates, m. p. 231° (decomp.) (Found : C, 65·3; H, 4·15; N, 11·3; Cl, 9·55. $C_{20}H_{16}O_2N_3Cl$ requires C, 65·65; H, 4·4; N, 11·5; Cl, 9·7%).

7-*Amino*-2-*nitro*-9-*phenylphenanthridine*.—7-Carbethoxyamino-2-nitro-9-phenylphenanthridine (1 g.) was heated with sulphuric acid (3 ml.; *d* 1·66) for 30 minutes at 140°. On dilution with 2 volumes of

water a greenish-yellow hydrogen sulphate crystallised, converted by further dilution into a carmine lower sulphate, which was collected, washed with water, and heated with aqueous sodium carbonate. The *base* crystallised from alcohol in orange needles, m. p. 227·5° (Found: C, 72·3; H, 4·15; N, 13·45. $C_{19}H_{13}O_2N_3$ requires C, 72·35; H, 4·15; N, 13·35%).

2-Amino-7-carbethoxyamino-10-methyl-9-phenylphenanthridinium Chloride (IV; R = NH_2).—7-Carbethoxyamino-10-methyl-2-nitro-9-phenylphenanthridinium methosulphate (2 g.) was dissolved in boiling water (200 ml.) and treated with a suspension of ferrous hydroxide prepared from ferrous sulphate (12 g.) and barium hydroxide (12·5 g.). Rapid reduction occurred, and after 30 minutes the crimson filtrate was concentrated under reduced pressure to 100 ml. Addition of sodium chloride precipitated the *amino*-salt, which on recrystallisation from water formed crimson plates unmolten at 300° (Found: N, 10·7; Cl, 8·85. $C_{23}H_{22}O_2N_3Cl$ requires N, 10·3; Cl, 8·7%)

7-Acetamido-2-amino-10-methyl-9-phenylphenanthridinium Ethanesulphonate.—Acetic anhydride (14 ml.) was added to a solution of 7-amino-10-methyl-2-nitro-9-phenylphenanthridinium chloride (3 g.) in hot acetic acid, and the solution brought to the boil and then diluted with water. On addition of sodium chloride a mass of yellow needles of *7-acetamido-10-methyl-2-nitro-9-phenylphenanthridinium chloride* formed, unmolten at 300° (Found: N, 10·75; Cl, 8·65. $C_{22}H_{18}O_3N_3Cl$ requires N, 10·3; Cl, 8·7%). By ferrous hydroxide reduction this salt was converted into the sparingly soluble amino-chloride, from which the *ethanesulphonate* was obtained by metathesis with silver ethanesulphonate; it formed scarlet needles, unmolten at 300° (Found: N, 9·05; S, 6·9. $C_{24}H_{25}O_4N_3S$ requires N, 9·3; S, 7·1%).

2-p-Carbethoxyaminobenzamido-5-nitrodiphenyl.—*p*-Carbethoxyaminobenzoyl chloride (14·5 g.) was added to a solution of 2-amino-5-nitrodiphenyl (14·5 g.) in boiling chlorobenzene (70 ml.). After 1 hour's boiling the solution was cooled, and an almost quantitative yield of the *amide* crystallised in white plates, m. p. 209°, after recrystallisation from acetic acid (Found: C, 64·9; H, 4·6; N, 10·5. $C_{22}H_{19}O_5N_3$ requires C, 65·15; H, 4·75; N, 10·35%).

9-p-Carbethoxyaminophenyl-3-nitrophenanthridine.—The foregoing amide (50 g.) and phosphoryl chloride (100 ml.) were heated (steam-bath) for 2 hours. Excess of phosphoryl chloride was distilled off under reduced pressure, and the residual gum taken up in boiling chloroform (250 ml.), and concentrated hydrochloric acid (50 ml.) added. The orange hydrochloride thus precipitated was collected, and heated with N-sodium carbonate until converted into the pale yellow *base* (22 g.), crystallisation of which from acetone or pyridine furnished yellow prisms, m. p. 245—250°, followed by resolidification (Found: C, 67·75; H, 4·45; N, 10·65. $C_{22}H_{17}O_4N_3$ requires C, 68·2; H, 4·45; N, 10·85%). The chloroform filtrate contained mostly unchanged amide.

Hydrolysis of this compound with sulphuric acid (*d* 1·66) at 140°, followed by dilution with water, caused a sulphate to crystallise. This salt was collected and heated with dilute aqueous ammonia, the *9-p-aminophenyl-3-nitrophenanthridine* thus obtained being crystallised from nitrobenzene or pyridine in light-brown needles, m. p. 297° (decomp.) (Found: C, 72·1; H, 4·15; N, 13·35. $C_{19}H_{13}O_2N_3$ requires C, 72·35; H, 4·15; N, 13·35%).

By the nitrobenzene–methyl sulphate method a high yield of *9-p-carbethoxyaminophenyl-10-methyl-3-nitrophenanthridinium methosulphate* was obtained, which crystallised from water or methanol in light-brown plates, decomp. 248° (Found: N, 7·7; S, 6·35. $C_{24}H_{23}O_8N_3S$ requires N, 8·2; S, 6·25%). Hydrolysis in the usual way converted it into *9-p-aminophenyl-10-methyl-3-nitrophenanthridinium chloride*, which crystallised from water in brownish-purple plates, decomp. 280° (Found: N, 11·4; Cl, 9·7. $C_{20}H_{16}O_2N_3Cl$ requires N, 11·5; Cl, 9·7%).

3-Amino-9-p-carbethoxyaminophenyl-10-methylphenanthridinium Ethanesulphonate.—*9-p*-Carbethoxyaminophenyl-10-methyl-3-nitrophenanthridinium chloride was reduced with ferrous hydroxide. The *chloride* (V; R = Et) crystallised from water in yellow prisms, unmolten at 300° (Found: N, 10·7; Cl, 8·9. $C_{23}H_{22}O_2N_3Cl$ requires N, 10·3; Cl, 8·7%). The *ethanesulphonate* crystallised from water in deep yellow prisms, m. p. 288—290° (decomp.) (Found: N, 8·75; S, 6·45. $C_{25}H_{27}O_5N_3S$ requires N, 8·75; S, 6·65%). The *sulphate* obtained by metathesis of the chloride in methanol with silver sulphate crystallised from methanol in deep yellow plates, m. p. *ca.* 250° (decomp.). This salt is extremely soluble in water (Found: C, 65·95; H, 5·1; N, 9·8. $C_{23}H_{22}O_2N_3,\frac{1}{2}SO_4$ requires C, 65·7; H, 5·3; N, 10·0%).

9-p-Carbomethoxyaminophenyl-3-nitrophenanthridine.—A suspension of *9-p*-aminophenyl-3-nitrophenanthridine (4 g.) in acetone (200 ml.), diethylaniline (4 ml.), and methyl chloroformate (2 ml.) was heated under reflux until a clear solution was obtained (about 1 hour). With cooling, the *product* crystallised in pale yellow needles (4 g.). Recrystallisation from pyridine afforded talc-like crystals, decomp. 269° (Found: C, 67·7; H, 3·8; N, 11·25. $C_{21}H_{15}O_4N_3$ requires C, 67·55; H, 4·05; N, 11·25%).

The following compounds were prepared substantially by the methods already described (solvent for crystallisation in parentheses):

9-p-Carbomethoxyaminophenyl-10-methyl-3-nitrophenanthridinium methosulphate, light-brown needles (water), decomp. 233° (Found: N, 8·4; S, 6·3. $C_{23}H_{21}O_8N_3S$ requires N, 8·4; S, 6·4%).

3-Amino-9-p-carbomethoxyaminophenyl-10-methylphenanthridinium chloride, yellow prisms (water), decomp. 290° (Found: N, 11·0; Cl, 9·15. $C_{22}H_{20}O_2N_3Cl$ requires N, 10·65; Cl, 9·0%).

p-Carbopropoxyaminobenzoic acid (cf. Copp and Walls, *J.*, 1950, 315), white needles (aqueous alcohol), m. p. 195° (Found: C, 59·5; H, 6·0; N, 6·2. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·85; N, 6·2%).

2-p-Carbopropoxyaminobenzamido-5-nitrodiphenyl, white prisms (acetic acid), m. p. 195° (Found: C, 65·7; H, 5·0; N, 9·6. $C_{23}H_{21}O_5N_3$ requires C, 65·85; H, 5·05; N, 10·0%).

9-p-*Carbopropoxyaminophenyl*-3-*nitrophenanthridine*, yellow plates (pyridine), m. p. 265° (decomp.) (Found : C, 69·0; H, 4·75; N, 10·55. $C_{23}H_{19}O_4N_3$ requires C, 68·8; H, 4·75; N, 10·5%).

9-p-*Carbopropoxyaminophenyl*-10-*methyl*-3-*nitrophenanthridinium methosulphate*, light-brown plates (water), m. p. 242 (decomp.) (Found : N, 8·05; S, 5·95. $C_{25}H_{25}O_8N_3S$ requires N, 7·95; S, 6·05%). The *chloride* was obtained by metathesis with sodium chloride, or by the interaction of an aqueous solution of the amino-nitro-chloride and propyl chloroformate, as light-brown plates, decomp. 262° (Found : N, 9·3; Cl, 8·0. $C_{24}H_{22}O_4N_3Cl$ requires N, 9·3; Cl, 7·85%).

3-*Amino*-9-p-*carbopropoxyaminophenyl*-10-*methylphenanthridinium chloride*, yellow needles (water), unmolten at 300° (Found : N, 10·25; Cl, 8·6. $C_{24}H_{24}O_2N_3Cl$ requires N, 9·95; Cl, 8·4%), and *ethanesulphonate*, yellow plates, effervesces at 120° (Found : N, 8·55; S, 6·4. $C_{26}H_{29}O_5N_3S$ requires N, 8·5; S, 6·45%).

9-p-*Carboisopropoxyaminophenyl*-3-*nitrophenanthridine*, pale yellow leaves (acetone), m. p. 272° (decomp.) (Found : C, 69·05; H, 4·7; N, 10·55%). The quaternary *methosulphate* formed brown plates (water), decomp. 246° (Found : N, 7·85; S, 6·25%).

3-*Amino*-9-p-*carboisopropoxyaminophenyl*-10-*methylphenanthridinium chloride*, yellow plates (water), unmolten at 300° (Found : N, 10·0; Cl, 8·55%), and *ethanesulphonate*, deep yellow prisms, effervesces at *ca.* 175° (Found : N, 8·8; S, 5·0%).

9-p-*Carbobutoxyaminophenyl*-3-*nitrophenanthridine*, pale buff needles (aqueous pyridine), m. p. 251° (effervescence) (Found : C, 69·4; H, 5·05; N, 10·2. $C_{24}H_{21}O_4N_3$ requires C, 69·4; H, 5·1; N, 10·1%), and the quaternary *methosulphate*, thin yellow plates (alcohol), m. p. 245° (decomp.) (Found : N, 7·75; S, 5·9. $C_{26}H_{27}O_8N_3S$ requires N, 7·75; S, 5·9%).

3-*Amino*-9-p-*carbobutoxyaminophenyl*-10-*methylphenanthridinium methosulphate*, elongated yellow plates (water), m. p. 197° (effervescence) (Found : N, 8·05; S, 6·1. $C_{26}H_{29}O_6N_3S$ requires N, 8·2; S, 6·25%).

2-m-*Carbethoxyaminobenzamido*-5-*nitrodiphenyl*, white microscopic needles (alcohol), m. p. 166° (Found : C, 65·55; H, 4·5; N, 10·35. $C_{22}H_{19}O_5N_3$ requires C, 65·15; H, 4·75; N, 10·35%).

9-m-*Carbethoxyaminophenyl*-3-*nitrophenanthridine*, thin pale yellow plates (aqueous pyridine), partial melting at 185°, resolidification, re-melting 232° (Found : C, 68·7; H, 4·0; N, 8·7. $C_{22}H_{17}O_4N_3$ requires C, 68·2; H, 4·45; N, 10·85%), and its *methochloride*, yellow prisms (water), m. p. 247° effervescence) (Found : N, 9·65; Cl, 8·1. $C_{23}H_{20}O_4N_3Cl$ requires N, 9·6; Cl, 8·1%).

3-*Amino*-9-m-*carbethoxyaminophenyl*-10-*methylphenanthridinium chloride* : deep yellow needles (water), decomp. *ca.* 290° (Found : N, 10·25; Cl, 8·6. $C_{23}H_{22}O_2N_3Cl$ requires N, 10·3; Cl, 8·7%).

9-p-*Carbamidophenyl*-10-*methyl*-3-*nitrophenanthridinium chloride* was prepared from 9-*p*-aminophenyl-10-methyl-3-nitrophenanthridinium chloride by the method already described (Walls, *J.*, 1946, 103). It crystallised from water in copper-coloured prisms, unmolten at 300° (Found : N, 13·6; Cl, 8·9. $C_{21}H_{17}O_3N_4Cl$ requires N, 13·7; Cl, 8·7%).

3-*Amino*-9-p-*carbamidophenyl*-10-*methylphenanthridinium chloride* was prepared from the nitro-salt by the ferrous hydroxide method; it crystallised from water in deep yellow needles, decomp. *ca.* 270° (Found : N, 14·4; Cl, 9·5. $C_{21}H_{19}ON_4Cl$ requires N, 14·8; Cl, 9·35%).

9-p-*Methanesulphonamidophenyl*-3-*nitrophenanthridine* (VI; R = H, R′ = Me).—9-*p*-Aminophenyl-3-nitrophenanthridine (3 g.) in hot pyridine (36 ml.) was treated with methanesulphonyl chloride (1 ml.), and the solution refluxed for 30 minutes. It was then diluted with water (36 ml.), so that the product crystallised in light-brown plates, recrystallisation of which from aqueous pyridine afforded yellow plates, m. p. 259—262° (decomp.) (Found : C, 61·15; H, 3·75; N, 10·6; S, 7·55. $C_{20}H_{15}O_4N_3S$ requires C, 61·05; H, 3·85; N, 10·7; S, 8·15%). The quaternary *methosulphate* was obtained by the nitrobenzene–methyl sulphate method. It crystallised from water in yellow prismatic needles, decomp. 280° (Found : N, 8·0; S, 12·0. $C_{22}H_{21}O_8N_3S_2$ requires N, 8·1; S, 12·3%).

3-*Amino*-9-p-*methanesulphonamidophenyl*-10-*methylphenanthridinium chloride* was obtained by reduction of the foregoing salt with ferrous hydroxide, and addition of sodium chloride to the filtrate. It crystallised from water in orange-yellow prisms, decomp. 278° (Found : N, 10·2; Cl, 8·95; S, 7·6. $C_{21}H_{20}O_2N_3ClS$ requires N, 10·15; Cl, 8·6; S, 7·75%).

The following were similarly prepared :

9-p-*Ethanesulphonamidophenyl*-3-*nitrophenanthridine* (VI; R = H, R′ = Et). The pyridine solution must not be heated above 50°. The product crystallised from acetic acid in small brown prisms, m. p. 223—224° (Found : C, 62·0; H, 4·1; N, 10·5; S, 7·55. $C_{21}H_{17}O_4N_3S$ requires C, 61·9; H, 4·2; N, 10·3; S, 7·85%). The *methochloride* crystallised from water in buff needles, decomp. 224° (Found : N, 9·2; Cl, 7·85; S, 6·65. $C_{22}H_{20}O_4N_3Cl$ requires N, 9·15; Cl, 7·75; S, 7·0%).

3-*Amino*-9-p-*ethanesulphonamidophenyl*-10-*methylphenanthridinium chloride* crystallised from methanol in brick-red prisms, m. p. 269—270° (decomp.) (Found : N, 10·2; Cl, 8·25; S, 6·85. $C_{22}H_{22}O_2N_3ClS$ requires N, 9·8; Cl, 8·3; S, 7·5%).

9-p-*Methanesulphon*-N-*methylamidophenyl*-3-*nitrophenanthridine* (VI; R = R′ = Me).—9-*p*-Methanesulphonamidophenyl-3-nitrophenanthridine (5·5 g.) and anhydrous potassium carbonate (11 g.) were suspended in acetone (110 ml.) with methyl iodide (16·5 ml.). After 3 hours' refluxing the filtrate was separated, evaporated to small bulk, and diluted with water. The solid thus precipitated was collected, and washed first with *N*-sodium hydroxide and then with water. The residue (5·1 g.) crystallised from pyridine in yellow leaflets, m. p. 274—275° (Found : C, 61·8; H, 4·05; N, 10·3. $C_{21}H_{17}O_4N_3S$ requires C, 61·9; H, 4·2; N, 10·3%). The *methochloride* crystallised from water in light-brown needles, m. p. 275—276° (decomp.) (Found : N, 9·25; Cl, 7·9; S, 6·75. $C_{22}H_{20}O_4N_3Cl$ requires N, 9·15; Cl, 7·75; S, 7·0%).

3-*Amino*-9-p-*methanesulphon*-N-*methylamidophenyl*-10-*methylphenanthridinium chloride* crystallised from methanol in large, reddish-brown plates, decomp. 245—248° (Found: N, 9·85; Cl, 8·2; S, 7·1. $C_{22}H_{22}O_2N_3ClS$ requires N, 9·8; Cl, 8·3; S, 7·5%).

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