47. *Potential Trypanocides of the N-Heterocyclic Series. Part I. Phenanthridinium Salts.*

By A. G. Caldwell and L. P. Walls.

The powerful trypanocidal properties of aminophenanthridinium salts suggested that further isomerides should be prepared. Those with 2- (I; R = R″ = NH_2, R′ = H) and 6- and 8- (II; R = R′ = NH_2) amino-substituents were of particular interest because of the possibilities of ionic resonance. For the synthesis of the former, 2-nitrobenzidine was converted by a number of stages into 2-acylamido-4-carbethoxyaminodiphenyls (IV; R = Me and *p*-$C_6H_4{\cdot}NO_2$), which were cyclised to the corresponding phenanthridines (V). For the 6- and 8-amino-compounds acyl derivatives of 2-*amino*-3′-*carbethoxyaminodiphenyl* (VII) were similarly cyclised, the quantitative yields illustrating the favourable influence of the urethane group on this type of ring-closure. The acetamido-compound gave a high yield of the 6-isomeride with some 8-isomeride (VIII), but the *p*-nitrobenzamido-compound gave a higher yield of 8-isomeride. An explanation is offered for this phenomenon. Quaternary salts of these new series were prepared in the usual way.

Compounds of similar structure with a 9-*p*-aminobenzyl substituent (XIII; R = R′ = NH_2) were also synthesised. Salts of this series in which R = NO_2 were readily converted into anhydro-bases (XIV).

The fact that the acetamido- is much more readily hydrolysed than is the carbethoxyamino-group was advantageously used in the preparation of intermediates, and also for the synthesis of quaternary salts containing an amino-group in the phenanthridine part of the molecule and a carbethoxyamino-group in the 9-substituent. Thus (I; R = $NH{\cdot}CO_2Et$, R′ = NH_2,

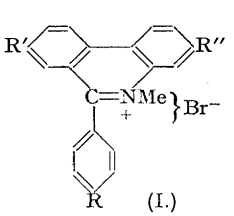
R″ = H), (I; R = NH·CO_2Et, R″ = NH_2, R′ = H), and (XIII; R = NH·CO_2Et, R′ = NH_2) were prepared.

The quaternary salts generally have a powerful *in vitro* antibacterial action not reduced in the presence of blood. Several salts show a chemotherapeutic action in streptococcal infections of mice, and some, particularly (I; R = R″ = NH_2, R′ = H) and (II; R = R′ = NH_2) are powerfully active in *T. congolense* infections in mice.

It is well known that certain important trypanocides, particularly those effective against the monomorphic trypanosomes and *T. cruzi*, are to be found among *N*-heterocyclic compounds. Previous work has shown that quaternary phenanthridine salts with free amino-groups are not only highly antibacterial *in vitro*, but exert a curative action in trypanosome infections in animals, particularly those due to the bovine parasites *T. congolense* and *T. vivax* (Browning, Browning, and Robb, *J. Path. Bact.*, 1940, **50**, 371). The trypanocidal activity is greatest in 9-phenylphenanthridinium salts containing two amino-groups, and as far as published work shows reaches a maximum in 2 : 7-diamino-9-phenyl-10-methylphenanthridinium bromide (I; R′ = R″ = NH_2, R = H; " phenanthridinium 1553 ", " dimidium bromide "). High trypanocidal activity is also present when one of the amino-groups is situated in the 9-phenyl substituent (as I; R = R′ = NH_2, R″ = H; " phenanthridinium 897 ", " phenidium chloride "). It would appear that the 7-amino-group is particularly associated with trypanocidal action, for the corresponding 3-amino-compounds are less effective, but it was clearly desirable to examine compounds of the same type with the amino-groups in other positions. The high activity of (I; R′ = R″ = NH_2, R = H) and (I; R = R′ = NH_2, R″ = H) suggested that the third member of the triad (I; R = R″ = NH_2, R′ = H) was particularly worthy of investigation. In the latter both amino-groups are capable of ionic resonance with the heterocyclic *N*-atom, whereas only one amino-group in either of the former compounds is thus suitably placed. Recently suggestions have been made that ionic resonance of the same type may be associated with parasiticidal properties (see *inter alia*, Kumler and Daniels, *J. Amer. Chem. Soc.*, 1943, **65**, 2190), and it was of interest to assess trypanocidal activity in this series from that point of view. Similar compounds containing 6- or 8-amino-groups (cf. II; R = R′ = NH_2) would likewise possess two amino-groups capable of ionic resonance. The preparation of these phenanthridinium compounds with 2-, 6-, or 8-amino-groups has been accomplished by using the method recently reported (Walls, *J.*, 1947, 67) of cyclising *o*-acylamidodiphenyls containing urethane substituents.

The 2 : 4-disubstituted diphenyls required for the synthesis of 2-aminophenanthridines are not readily available. Gull and Turner (*J.*, 1929, 496) obtained 2 : 4-dinitrodiphenyl by a " mixed " Ullmann reaction and Finzi and Bellavita (*Gazzetta*, 1938, **68**, 78) the same compound in two stages from 2-nitro-4′-aminodiphenyl, but neither method appeared to offer a good route to the phenanthridines. For this purpose a more promising starting material was 2-nitrobenzidine, from which Cain and May (*J.*, 1910, **97**, 724) obtained a substance in high yield, m. p. 186—187°, by monoacetylation. They stated that this product was 2-nitro-4-amino-4′-acetamidodiphenyl, and repetition of their work has shown that this is indeed the chief product, having m. p. 210°, but some diacetyl compound is also formed. Conversion of this monoacetyl compound into *2-nitro-4-carbethoxyamino-4′-acetamidodiphenyl* (III; R = NH·COMe) is quantitative, and by taking advantage of the marked resistance of the urethane group to acid hydrolysis, this substance may be converted into *2-nitro-4′-amino-4-carbethoxyaminodiphenyl* (III; R = NH_2). The same method of partial hydrolysis may be employed for the preparation of the useful intermediate 2-amino-4′-carbethoxyaminodiphenyl (Walls, *loc. cit.*), which is thus obtained quantitatively by hydrolysis of the readily accessible acetyl compound. The diazotisation of (III; R = NH_2) and subsequent elimination of the diazonium group to give 2-nitro-4-carbethoxyaminodiphenyl (III; R = H) presented considerable difficulty owing to the extremely sparing solubility of the salts of the amine, and of the diazonium salts. The best results were obtained when the diazonium sulphate was decomposed in aqueous alcohol by hypophosphorous acid, a complex reaction in which considerable quantities of acetaldehyde were formed. The constitution of the product was confirmed by hydrolysis of the urethane group to furnish *2-nitro-4-aminodiphenyl*, thus incidentally confirming by the difference of this substance from 2-nitro-4′-aminodiphenyl, the constitution allotted by Cain and May (*loc. cit.*) to monoacetyl-2-nitrobenzidine. Reduction of (III; R = H) furnished an amine not yet obtained crystalline, of which the appropriate *acyl* derivatives (IV) were smoothly cyclised to the *phenanthridines* (V; R = Me) and (V; R = *p*-C_6H_4·NO_2). From these products the corresponding *amines* were obtained by hydrolysis. 2-Carbethoxyamino-9-methylphenanthridine (V; R = Me) was converted into the quaternary *salt*, which was hydrolysed to the red *amino*-salt (VI). The quaternary *salt* from 2-carbethoxyamino-9-*p*-nitrophenylphen-

anthridine (V; R = *p*-C_6H_4·NO_2) was hydrolysed to the purple-black *nitro-amino*-salt (I; R = NO_2, R″ = NH_2, R′ = H), reduction of which with iron powder yielded the required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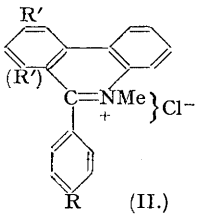
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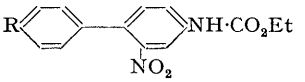
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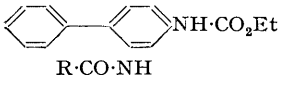
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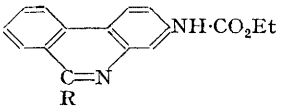
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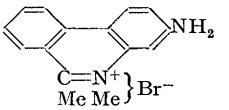
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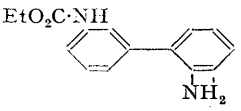
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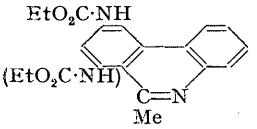
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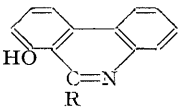
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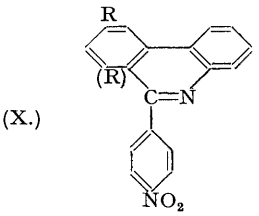
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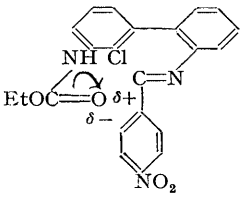
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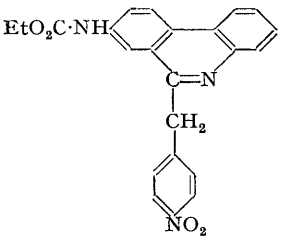
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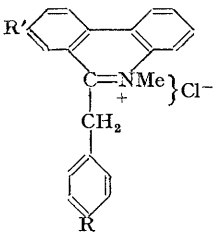
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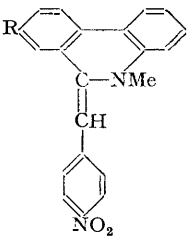
(XIV.)

diamino-salt (I; R = R″ = NH_2, R′ = H) accompanied by a sparingly soluble by-product. The properties of the salts of this series are very similar to those of the corresponding 7-series (Walls, *loc. cit.*).

For the preparation of (II; R = R′ = NH_2) 2 : 3′-dinitrodiphenyl was reduced to 2-nitro-3′-aminodiphenyl by a modification of the method due to Case (*J. Amer. Chem. Soc.*, **1939, 61, 767**). Successive carbethoxylation and reduction afforded 2-*amino*-3′-*carbethoxyamino-diphenyl* (VII). The *acetyl* derivative of (VII) was rapidly and quantitatively converted by phosphoryl chloride into a mixture of 6- and 8-*carbethoxyamino*-9-*methylphenanthridines* (VIII), this facile reaction illustrating again the favourable effect on this type of ring-closure of the urethane group, for which it may be assumed that the (+*M*) compensates for the (−*I*) effect. The isomerides were separated by crystallisation of their sulphates, and that formed in small amount was converted into the *hydroxyl* compound (IX; R = Me), which gave a strong Gibbs's indophenol reaction thus indicating the presence of a free *p*-position to the hydroxyl group. Consequently it was the 8-isomeride, and the ring-closure had yielded a preponderant amount of the 6-isomeride, as would be expected on account of both the mesomeric and the steric effects of the urethane group. A series of quaternary salts was prepared from this isomeride.

Ring-closure of the p-*nitrobenzamido*-derivative of (VII) was also almost quantitative but

presented different features from that of the acetyl compound. Again two products were isolated, one sparingly soluble substance, m. p. 250°, in 35% yield, and a much more soluble substance, m. p. 200°, in 45% yield. By hydrolysis of the latter and diazotisation of the resulting amine, an alkali-insoluble *hydroxyl* compound (IX; R = *p*-C_6H_4·NO_2) was obtained which gave a positive Gibbs's reaction; the isomeric *hydroxyl* compound was soluble in alkali and gave a negative reaction. Thus the more soluble derivative is 8-*carbethoxyamino*-9-p-*nitrophenylphenanthridine* (cf. X; R = NH·CO_2Et), and a ring-closure *o* : *p* ratio >1 obtains. A tentative explanation of the markedly different *o* : *p* ratios for the acetamido- and *p*-nitrobenzamido-compounds is that in the latter the powerful electron-attraction effect of the nitro-group greatly increases the " positivity " of the carbon atom of the iminochloride assumed to be an intermediate in ring closure [see (XI)]. Then electrostatic attraction might be possible between this carbon atom and the carbonyl oxygen of the urethane group. Such an interaction would favour formation of the 8-isomeride. Both isomerides were converted into quaternary *salts* (II; R = NO_2, R′ = NH·CO_2Et), the 8-isomeride giving a poor yield, attributable to steric hindrance by the urethane group, which is seen in models to come into close contact with the heterocyclic nitrogen atom in one phase of its rotation. These quaternary salts were hydrolysed to the *nitro-amino*-salts (II; R = NO_2, R′ = NH_2), from which the *diamino*-salts (II; R = R′ = NH_2) were obtained by reduction. The salts of the 8-series were more soluble and much more deeply coloured than those of the 6-series; thus (II; R = NO_2, R′ = NH·CO_2Et) are orange and pale yellow respectively (II; R = NO_2, R′ = NH_2) purple and light brown, and (II; R = R′ = NH_2) light red and yellow. The light-absorption properties of these compounds are being examined.

The foregoing experiments were designed to test whether ionic resonance is a necessary feature in trypanocidal compounds of this series. To this end also it was decided to modify the active type (I; R = R′ = NH_2, R″ = H) so that ionic resonance becomes impossible. For this purpose the p-*aminobenzyl* salts (XIII; R = R′ = NH_2) were chosen. 4-*Carbethoxyamino*-2′-p-*nitrophenylacetamidodiphenyl* was readily cyclised to the corresponding *phenanthridine* (XII), which was converted into a series of quaternary salts. The salts (XIII; R = NO_2, R′ = NH·CO_2Et) and (XIII; R = NO_2, R′ = NH·COMe) had the property not possessed by salts of the 9-*p*-nitrophenyl series of being converted by warm water into deep-coloured substances, the effect being reversed by dilute acid. With alkali similar substances were precipitated. They are readily soluble in ether or benzene and are undoubtedly anhydro-bases (XIV), similar to the compound obtained by Koenigs, Kohler, and Blindow (*Ber.*, 1925, **58**, 933) from 2-*p*-nitrobenzylpyridinium salts. As suggested by these authors the effect is to be ascribed to the powerful electron-attracting effect of the nitro-group, since salts of this series not possessing a nitro-substituent in the 9-benzyl group behave normally with alkali to give lightly-coloured pseudo-bases. Similar phenomena were observed with 9-p-*nitrobenzyl*-10-*methylphenanthridinium chloride* (XIII; R = NO_2, R′ = H).

In a discussion of the relationship between trypanocidal action and structure in this series, Browning, Calver, and Leckie point out (*J.*, 1947, 69) that a high degree of activity is retained when the amino-group R in (I; R = R′ = NH_2, R″ = H) is replaced by a nitro-group. In view of the effect of the urethane group on therapeutic properties (Browning, Calver, Leckie, and Walls, *Nature*, 1946, **157**, 263) it was of interest to investigate active types in which R = NH·CO_2Et. 7-*Amino*-9-p-*carbethoxyaminophenyl*-10-*methylphenanthridinium chloride* (as I; R = NH·CO_2Et, R′ = NH_2) was readily obtained by hydrolysis of the acetyl compound (Walls, *loc. cit.*) with dilute hydrochloric acid, and by a similar application of the method of partial hydrolysis (I; R = NH·CO_2Et, R″ = NH_2, R′ = H) and (XIII; R = NH·CO_2Et, R′ = NH_2) were prepared.

Compounds described in this paper have been examined by Dr. Brownlee and his colleagues at the Wellcome Physiological Research Laboratories for antibacterial properties. The quaternary salts have generally a high bacteriostatic action *in vitro* particularly against Gram-positive organisms, an effect which is not reduced by the presence of blood. Of these some afford protection against a number of lethal doses of *Streptococcus pyogenes* in mice, (VI) being the most effective in this respect. Mr. Goodwin and his colleagues at the Wellcome Laboratories of Tropical Medicine have shown that many of these salts are trypanocidal particularly against *T. congolense* in mice infections. The third member of the triad (I; R = R″ = NH_2, R′ = H) has a very powerful action as has also [II; R = R′ = NH_2 (6-isomer)], but it may be said that no convincing correlation between ionic resonance and trypanocidal action has yet been found. Full details of these and other interesting pharmacological properties will be published elsewhere.

Experimental.

2-*Nitro*-4-*amino*-4'-*acetamidodiphenyl*.—To a solution of 2-nitrobenzidine (40 g.) in boiling alcohol (360 ml.) was added hot water (360 ml. at 60°) and acetic anhydride (17 ml.). The solution was refluxed for 10 minutes, and then treated with cold water (360 ml.) and allowed to cool. The mixture (*ca.* 40 g.) of mono- and di-acetyl compounds that crystallised was dissolved in boiling acetone (500 ml.), most of the diacetyl compound (*ca.* 5 g.) remaining undissolved. Acetone was removed from the filtrate by distillation; the residue crystallised from alcohol in golden yellow plates of the monoacetyl compound (*ca.* 25 mg.), m. p. 210° (Found: C, 62·0; H, 4·85; N, 15·55. Calc. for $C_{14}H_{13}O_3N_3$: C, 61·95; H, 4·85; N, 15·5%).

2-*Nitro*-4-*carbethoxyamino*-4'-*acetamidodiphenyl* (III; R = NH·COMe).—The foregoing mono-acetyl compound (20 g.) was dissolved in boiling alcohol (250 ml.) and treated with diethylaniline (16 ml.) and then dropwise with ethyl chloroformate (8 ml.). After the vigorous reaction had subsided the solution was refluxed for 10 minutes, filtered (charcoal) from any diacetyl compound present as impurity in the starting-material, and allowed to cool. The *urethane* crystallised in yellow prisms (21 g.), which melted *ca.* 218° (efferv.) and then resolidified (Found: C, 59·85; H, 5·3; N, 12·25. $C_{17}H_{17}O_5N_3$ requires C, 59·45; H, 5·0; N, 12·25%).

2-*Nitro*-4'-*amino*-4-*carbethoxyaminodiphenyl* (III; R = NH_2).—The foregoing urethane (20 g.) was refluxed for 2½ hours in alcohol (270 ml.) and concentrated hydrochloric acid (30 ml.), yellow prismatic crystals of the hydrochloride of the *product* beginning to separate after about 2 hours. Dilution of the hot reaction mixture with water and neutralisation with alkali precipitated a yellowish-brown crystalline base (16·5 g.), which on recrystallisation from alcohol gave prisms, varying in colour from yellow to brown in different preparations (12·5 g.), m. p. 177° (Found: C, 59·85; H, 5·15; N, 13·9. $C_{15}H_{15}O_4N_3$ requires C, 59·8; H, 5·05; N, 13·95%). This amine formed extremely sparingly soluble salts with aqueous hydrochloric and sulphuric acids.

2-*Nitro*-4-*carbethoxyaminodiphenyl* (III; R = H).—The following method generally gave good results, although occasionally poor yields were inexplicably obtained. The amine (20 g.) was dissolved in boiling alcohol (600 ml.), the solution cooled to 40°, and treated with stirring with concentrated sulphuric acid (10 ml.). A sparingly soluble sulphate was precipitated by the first additions of acid, but finally redissolved. The solution was cooled rapidly to 20°, and, before an acid sulphate crystallised, sodium nitrite (7 g.) in water (120 ml.) was added with stirring; after 10 minutes hypophosphorous acid (40 ml. of *ca.* 30%) was added and stirring continued for 4 hours, a strong odour of acetaldehyde being observed. Addition of water precipitated the crude product in flocculent crystals, which were extracted with benzene, some sticky impurity remaining undissolved. The extract was washed successively with sodium hydroxide solution, water, dilute sulphuric acid, and water, and finally dried (Na_2SO_4). On evaporation of benzene the product was obtained as a brown crystalline mass. To obtain the pure substance the benzene solution was filtered through a column of alumina, impurities being strongly adsorbed. By evaporation of the yellow benzene eluate the *product* was obtained in feathery yellow needles (15 g.), m. p. 123° (Found: C, 63·5; H, 4·65; N, 9·85. $C_{15}H_{14}O_4N_2$ requires C, 62·9; H, 4·9; N, 9·8%). A solution of this nitro-compound (1 g.) in sulphuric acid (4 ml. of concentrated acid and 2 ml. of water) was heated to 125°. Rapid effervescence occurred with darkening in colour and after 15 minutes the solution was cooled and diluted with water; white crystals of a sulphate separated, from which 2-*nitro*-4-*aminodiphenyl* was liberated by alkali; it crystallised from aqueous alcohol in golden yellow plates, m. p. 109·5° (Found: C, 67·25; H, 4·8; N, 13·1. $C_{12}H_{10}O_2N_2$ requires C, 67·25; H, 4·7; N, 13·1%).

2-*Acetamido*-4-*carbethoxyaminodiphenyl* (IV; R = Me).—2-Nitro-4-carbethoxyaminodiphenyl (15 g.) was dissolved in alcohol (400 ml.), and reduced with hydrogen at 20 atmospheres' pressure in the presence of palladised charcoal (5 g.; 3%). The alcoholic solution of 2-amino-4-carbethoxyaminodiphenyl thus obtained was at first colourless, but assumed a deep purple colour on exposure. The amine was a colourless oil, which could not be induced to crystallise. On being warmed with acetic anhydride it was readily converted into the *acetyl* derivative (14 g.) which crystallised from alcohol in white needles, m. p. 169·5° (Found: C, 68·5; H, 6·1; N, 9·4. $C_{17}H_{18}O_3N_2$ requires C, 68·45; H, 6·1; N, 9·4%).

2-*Carbethoxyamino*-9-*methylphenanthridine* (V; R = Me).—When a solution of the foregoing acetyl compound (10 g.) in phosphoryl chloride (10 ml.) was heated, vigorous reaction took place and the product began to crystallise as a salt after a few minutes. After 30 minutes' refluxing, excess of phosphoryl chloride was cautiously decomposed with water, and alkali added to neutrality; the solid *product* crystallised from alcohol in white plates (7·5 g.), m. p. 197° (Found: C, 72·8; H, 5·9; N, 9·9. $C_{17}H_{16}O_2N_2$ requires C, 72·85; H, 5·75; N, 10·0%). When this substance was dissolved in hot 2N-hydrochloric acid, the *hydrochloride* crystallised in lemon-yellow needles, unmolten at 300° (Found for dried salt: N, 9·05; Cl, 11·1. $C_{17}H_{17}O_2N_2Cl$ requires N, 8·85; Cl, 11·2%).

2-*Amino*-9-*methylphenanthridine*.—The corresponding urethane (2 g.) was dissolved in sulphuric acid (2 ml.) and water (1 ml.), and the solution heated at 150° for 30 minutes. Dilution with water and neutralisation precipitated the *amine*, which crystallised from aqueous alcohol in cream-coloured plates, m. p. 174—175° (Found: C, 80·6; H, 5·6; N, 13·65. $C_{14}H_{12}N_2$ requires C, 80·7; H, 5·8; N, 13·45%).

2-*Amino*-9 : 10-*dimethylphenanthridinium Bromide* (VI).—2-Carbethoxyamino-9-methylphenanthridine (6 g.) was dissolved in nitrobenzene (60 ml.) at 160° and treated with methyl sulphate (3 ml.). The yellow crystals of the quaternary methosulphate, which separated immediately in quantitative yield, were washed with boiling benzene and dissolved in water. On addition of potassium bromide to the solution 2-*carbethoxyamino*-9 : 10-*dimethylphenanthridinium bromide* crystallised in small yellow needles, m. p. 247° (decomp.) (Found for dried salt: N, 7·65; Br, 21·7. $C_{18}H_{19}O_2N_2Br$ requires N, 7·45; Br, 21·35%). A solution of the methosulphate (5 g.) in concentrated sulphuric acid (7 ml.) and water (3·5 ml.) was heated at 150° for 15 minutes. Dilution with water and neutralisation with ammonia furnished a deep red solution from which, on addition of potassium bromide, the required *bromide* crystallised in small red needles, unmolten at 300° (Found: N, 9·1; Br, 26·2. $C_{15}H_{15}N_2Br$ requires

N, 9·25; Br, 26·4%). This salt was readily soluble in water, or in methyl alcohol, but less soluble in ethyl alcohol.

2-*Carbethoxyamino*-9-p-*nitrophenylphenanthridine* (V; R = *p*-$C_6H_4{\cdot}NO_2$).—Oily 2-amino-4-carbethoxyaminodiphenyl (12·5 g.) was dissolved in nitrobenzene at 150° and treated with *p*-nitrobenzoyl chloride (10 g.). After 30 minutes, evolution of hydrogen chloride having ceased, the solution was cooled to allow 2-p-*nitrobenzamido*-4-*carbethoxyaminodiphenyl* (IV; R = *p*-$C_6H_4{\cdot}NO_2$) to crystallise. Recrystallisation from glacial acetic acid furnished deep yellow prisms, m. p. 226·5° (Found: C, 64·7; H, 4·85; N, 10·3. $C_{22}H_{19}O_5N_3$ requires C, 65·2; H, 4·75; N, 10·35%). This substance (25 g.) was cyclised by refluxing it with phosphoryl chloride (25 ml.) for 45 minutes and then cautiously decomposing the excess of reagent with water. The solid product was dissolved in hot pyridine (100 ml.) and the solution treated with hot water (50 ml.). The *phenanthridine* (14 g.) crystallised in yellow needles, m. p. 258—259° (efferv.) (Found: C, 68·35; H, 4·65; N, 11·0. $C_{22}H_{17}O_4N_3$ requires C, 68·2; H, 4·45; N, 10·85%). This compound was hydrolysed in the manner already described. On dilution of the sulphuric acid solution a purple sulphate, insoluble in water, separated; when it was stirred with ammonia it was converted into 2-*amino*-9-p-*nitrophenylphenanthridine*, which crystallised from pyridine in small brownish-red needles, m. p. 259° (Found: C, 72·25; H, 4·25; N, 13·65. $C_{19}H_{13}O_2N_3$ requires C, 72·4; H, 4·15; N, 13·35%).

2-*Amino*-9-p-*nitrophenyl*-10-*methylphenanthridinium Chloride* (as I; R = NO_2, R″ = NH_2, R′ = H).—Methyl sulphate (8·5 ml.) was added to a solution of 2-carbethoxyamino-9-*p*-nitrophenylphenanthridine (17 g.) in nitrobenzene (100 ml.) at 175°. The quaternary methosulphate began to crystallise at once, and after 10 minutes at 175°, it was collected and washed with hot benzene. The salt was dissolved in a large volume of boiling water, filtered from a small amount of unchanged starting material, and treated with hydrochloric acid. 2-*Carbethoxyamino*-9-p-*nitrophenyl*-10-*methylphenanthridinium chloride* (as I; R = NO_2, R″ = NH·CO_2Et, R′ = H) crystallised in yellow prismatic needles (15 g.), m. p. 252—254° (decomp.) (Found: C, 63·0; H, 4·6; N, 9·7; Cl, 8·05. $C_{23}H_{20}O_4N_3Cl$ requires C, 63·1; H, 4·6; N, 9·6; Cl, 8·1%). The methosulphate (6·5 g.) was hydrolysed by sulphuric acid (7 ml. of concentrated acid and 3·5 ml. of water) by being heated at 150° for 30 minutes. On dilution with water a deep red acid salt crystallised, which on neutralisation and addition of sodium chloride was converted into 2-*amino*-9-p-*nitrophenyl*-10-*methylphenanthridinium chloride*, which crystallised from water in almost black plates, m. p. 222—224° (decomp.) (Found: C, 62·4; H, 5·2; N, 10·85; Cl, 9·4; loss at 100°, 4·85. $C_{20}H_{16}O_2N_3Cl,H_2O$ requires C, 62·55; H, 4·75; N, 10·95; Cl, 9·25; H_2O, 4·7%). When a solution of the salt (3 g.) in hot glacial acetic acid (6 ml.) was treated with acetic anhydride (1·5 ml.) the *acetyl* derivative crystallised quantitatively. On recrystallisation from a large volume of water it formed deep yellow prisms (3·1 g.), unmolten at 300° (Found: N, 10·2; Cl, 8·45; loss at 100°, 2·2. $C_{22}H_{18}O_3N_3Cl,0{\cdot}5H_2O$ requires N, 10·1; Cl, 8·5; H_2O, 2·1%).

2-*Acetamido*-9-p-*aminophenyl*-10-*methylphenanthridinium Chloride* (as I; R = NH_2, R″ = NH·COMe, R′ = H).—The foregoing acetamido-nitro-salt (2 g.) was added with stirring to a boiling suspension of "reduced" iron (4 g.) in water (100 ml.). Reduction took place rapidly, and after hot filtration the product crystallised in minute yellow needles. It was purified by warming with 0·2N-hydrochloric acid (50 ml.), thereby leaving undissolved a trace of unreduced nitro-compound. Neutralisation of the filtrate liberated the sparingly soluble *product*, and sufficient boiling water was added to bring this into solution. With cooling orange-yellow prisms of the desired salt separated (1·6 g.), m. p. 283° (decomp.) (from a bath pre-heated to 260°) (Found: N, 10·7; Cl, 9·05; loss at 100°, 5·15. $C_{22}H_{20}ON_3Cl,H_2O$ requires N, 10·6; Cl, 8·95; H_2O, 4·55%). A solution of this salt (4 g.) in hot 0·2N-hydrochloric acid (80 ml.) was stirred with ethyl chloroformate (2 ml.). 2-*Acetamido*-9-p-*carbethoxyaminophenyl*-10-*methylphenanthridinium chloride* (as I; R = NH·CO_2Et, R″ = NH·COMe, R′ = H) slowly crystallised from the mixture. It crystallised from water in orange-yellow plates, m. p. 193—195° (decomp.) (Found: N 8·85: Cl, 7·4; loss at 100°, 7·0. $C_{25}H_{24}O_3N_3Cl,2H_2O$ requires N, 8·65; Cl, 7·3; H_2O, 7·4%).

2-*Amino*-9-p-*aminophenyl*-10-*methylphenanthridinium Bromide* (I; R = R″ = NH_2, R′ = H).—(*a*) A solution of 2-acetamido-9-*p*-aminophenyl-10-methylphenanthridinium chloride (1 g.) in 4N-hydrochloric acid (8 ml.) was refluxed for 30 minutes and then neutralised with ammonia. The *diamino-chloride* was liberated as a red oil, which soon solidified. It crystallised from a small volume of water in magnificent deep red prisms, m. p. 257° (decomp.) (Found for dried salt: N, 12·75; Cl, 10·35. $C_{20}H_{18}N_3Cl$ requires N, 12·55; Cl, 10·6%). The *bromide* crystallised from methyl alcohol in deep red needles, m. p. 254° (decomp.) (Found: C, 63·0; H, 4·5; N, 11·05; Br, 21·3. $C_{20}H_{18}N_3Br$ requires C, 63·15; H, 4·75; N, 11·05; Br, 21·05%).

(*b*) Reduction of 2-amino-9-*p*-nitrophenyl-10-methylphenanthridinium chloride (4·3 g.) with "reduced" iron gave an ill-defined red solid, which was dissolved in 5N-hydrochloric acid. A brown salt crystallised, which on addition to boiling water was converted into a micro-crystalline purple-red substance (1 g.) of which the nature has not yet been elucidated. Neutralisation of the acid filtrate furnished the desired salt, which was best purified by crystallisation of the bromide (2·0 g.) from methyl alcohol.

2-*Amino*-9-p-*carbethoxyaminophenyl*-10-*methylphenanthridinium Bromide* (I; R = NH·CO_2Et, R″ = NH_2, R′ = H).—2-Acetamido-9-*p*-carbethoxyaminophenyl-10-methylphenanthridinium chloride (2 g.) was refluxed with 2N-hydrochloric acid (20 ml.). The salt slowly dissolved, and after 1 hour the solution was cooled and neutralised with ammonia. The red oil thus liberated slowly changed to a mass of orange needles, which were best purified by conversion into the *bromide*, which crystallised from water in orange-red plates, m. p. 254—256° (decomp.) (Found: C, 61·35; H, 4·85; N, 9·55; Br, 18·1. $C_{23}H_{22}O_2N_3Br$ requires C, 61·05; H, 4·9; N, 9·3; Br, 17·7%).

By the same method the corresponding 7-acetamido-salt was converted into 7-*amino*-9-p-*carbethoxyaminophenyl*-10-*methylphenanthridinium chloride*, which crystallised from water in orange-red plates, m. p. 195° (decomp.) (Found: N, 9·65; Cl, 7·95; loss at 100°, 6·6. $C_{23}H_{22}O_2N_3Cl,1{\cdot}5H_2O$ requires N, 9·65; Cl, 8·15; H_2O, 6·25%).

2-*Nitro*-3′-*aminodiphenyl*.—3-Nitrodiphenyl (25 g.) was nitrated as recommended by Case (*loc. cit.*), but the product was worked up by the method of Blakey and Scarborough (*J.*, 1927, 3000). The methyl alcohol mother-liquor from which the 3 : 4′-dinitrodiphenyl had been separated according to their method was concentrated to small bulk. The crude mixture (12 g.), consisting mainly of 2 : 3′-dinitrodiphenyl, which separated, was reduced with sodium polysulphide as previously described (Walls, *loc. cit.*) for a similar mixture of 2 : 4′- and 4 : 4′-dinitrodiphenyls. The crude semi-solid product was dissolved in 2N-hydrochloric acid, and by fractional crystallisation pure 2-nitro-3′-aminodiphenyl hydrochloride was obtained. By dissolution of this salt in water and neutralisation the base was liberated as an oil which set to a yellow crystalline solid (6 g.). Recrystallisation from methyl alcohol furnished yellow prisms, m. p. 83° (Found: C, 66·95; H, 4·9. Calc. for $C_{12}H_{10}O_2N_2$: C, 67·25; H, 4·7%).

2-*Amino*-3′-*carbethoxyaminodiphenyl* (VII).—A solution of the foregoing amine (37 g.) in boiling alcohol (200 ml.) was treated successively with diethylaniline (28 ml.) and dropwise with ethyl chloroformate (14 ml.). After 30 minutes' refluxing the solution was poured into excess of dilute hydrochloric acid, and the yellow oil thus liberated was extracted with ether. The extract was washed with dilute hydrochloric acid and then with water and dried (Na_2SO_4). Removal of ether left a quantitative yield of 2-nitro-3′-carbethoxyaminodiphenyl, which could not be induced to crystallise. It was reduced at room temperature in alcoholic solution (400 ml.) by hydrogen at 25 atmospheres, with palladised charcoal (15 g.; 3%) as catalyst. On evaporation of alcohol the *base* was obtained as a somewhat discoloured crystalline mass, which on recrystallisation from light petroleum (b. p. 60—80°) gave soft white plates, m. p. 88° (Found: C, 70·35; H, 6·7; N, 10·95. $C_{15}H_{16}O_2N_2$ requires C, 70·3; H, 6·3; N, 10·95%). On the base being warmed with acetic anhydride, the *acetyl* derivative crystallised. It crystallised from methyl alcohol in small white needles, m. p. 161° (Found: C, 68·35; H, 6·4; N, 9·45. $C_{17}H_{18}O_3N_2$ requires C, 68·45; H, 6·1; N, 9·4%).

6- *and* 8-*Carbethoxyamino*-9-*methylphenanthridines* (VIII).—When 2-acetamido-3′-carbethoxyaminodiphenyl (27 g.) and phosphoryl chloride (27 ml.) were heated together a vigorous reaction occurred with evolution of hydrogen chloride and immediate separation of white crystals. After 30 minutes' refluxing the mixture was decomposed with water and made alkaline. The white solid thus obtained was completely soluble in dilute sulphuric acid, thus indicating that ring-closure was quantitative. The isomerides were best separated by crystallisation of the sulphates. A solution of the mixture in alcohol (400 ml.) was treated with concentrated sulphuric acid (6 ml.), which precipitated 6-*carbethoxyamino*-9-*methylphenanthridine sulphate* as a mass of almost white needles (21 g.), which were recrystallised from alcohol (2·5 l.), m. p. 216° (decomp.) (Found: N, 7·35; S, 8·1. $C_{17}H_{16}O_2N_2,H_2SO_4$ requires N, 7·4; S, 8·45%). On evaporation of the mother-liquor 8-*carbethoxyamino*-9-*methylphenanthridine sulphate* crystallised in transparent yellow prisms (3 g.), m. p. 187° (decomp.) (Found: N, 7·55; S, 8·4%). 6-*Carbethoxyamino*-9-*methylphenanthridine* was liberated from its salt; it crystallised from benzene in colourless plates containing water of crystallisation evidently taken up from the damp solvent; it sintered at 110° and then had m. p. 163° (Found: C, 68·6; H, 5·8; N, 9·25; loss at 100°, 6·4. $C_{17}H_{16}O_2N_2,H_2O$ requires C, 68·45; H, 6·1; N, 9·4; H_2O, 6·05%). 8-*Carbethoxyamino*-9-*methylphenanthridine* crystallised from aqueous alcohol in colourless acicular prisms, m. p. 159·5° (Found: C, 68·9; H, 5·9; N, 9·4. $C_{17}H_{16}O_2N_2,H_2O$ requires C, 68·45; H, 6·05; N, 9·4%).

Hydrolysis of these urethanes with sulphuric acid (2 : 1) at 150° furnished: (a) 6-*Amino*-9-*methylphenanthridine*, which crystallised from aqueous alcohol in white prismatic needles, m. p. 196·5° (Found: C, 80·85; H, 5·8; N, 13·7. $C_{14}H_{12}N_2$ requires C, 80·7; H, 5·8; N, 13·45%); the *hydrochloride* crystallised from water in pale yellow needles, unmolten at 300° (Found for dried salt: N, 11·65; Cl, 14·55. $C_{14}H_{13}N_2Cl$ requires N, 11·45; Cl, 14·5%). (b) 8-*Amino*-9-*methylphenanthridine*, which crystallised from aqueous alcohol in cream-coloured prisms; it sintered at 70°, but after vacuum drying had m. p. 134·5° (Found: C, 81·05; H, 5·65; N, 13·6%); the *hydrochloride* crystallised from water in orange needles, unmolten at 300° (Found: N, 11·25; Cl, 14·6%).

8-*Hydroxy*-9-*methylphenanthridine* (IX; R = Me).—8-Amino-9-methylphenanthridine (0·5 g.) was diazotised in 2N-sulphuric acid solution (5 ml.) with sodium nitrite (0·2 g.). The solution was heated (steam-bath) until effervescence ceased, and the tarry product was extracted with sodium hydroxide solution. By neutralisation of the extract the hydroxyl compound was liberated as a yellow flocculent precipitate which was collected, dissolved in alcohol, and treated with a few drops of concentrated hydrochloric acid. The *hydrochloride* crystallised in small yellow needles, which on recrystallisation from alcohol formed large transparent greenish-yellow prisms, unmolten at 300° (Found: Cl, 14·2. $C_{14}H_{12}ONCl$ requires Cl, 14·4%).

6-*Amino*-9 : 10-*dimethylphenanthridinium Bromide*.—6-Carbethoxyamino-9-methylphenanthridine was converted quantitatively into the quaternary *methosulphate* by the method described for the 2-isomeride. The salt was readily soluble in water but was best recrystallised from alcohol, forming white needles, m. p. 238—242° (decomp.) (Found: C, 55·6; H, 5·7; N, 7·15; S, 7·95. $C_{19}H_{22}O_6N_2S$ requires C, 56·1; H, 5·45; N, 6·9; S, 7·9%). By hydrolysis with sulphuric acid the *bromide* was isolated, which crystallised from water in pale yellow prismatic needles, m. p. 297—299° (Found for dried salt: N, 9·2; Br, 26·25. $C_{15}H_{15}N_2Br$ requires N, 9·25; Br, 26·35%).

6- *and* 8-*Carbethoxyamino*-9-p-*nitrophenylphenanthridines* (X; R = $NH{\cdot}CO_2Et$).—A solution of 2-amino-3′-carbethoxyaminodiphenyl (20 g.) in boiling chlorobenzene (200 ml.) was treated with *p*-nitrobenzoyl chloride (14 g.). After 30 minutes' boiling evolution of hydrogen chloride had ceased, and, with cooling, 3-*carbethoxyamino*-2′-p-*nitrobenzamidodiphenyl* (30 g.) crystallised from the mixture; it crystallised from alcohol in cream-coloured needles (27 g.), which partially melted at 161—162°, resolidified, and melted sharply at 176° (Found: C, 65·35; H, 4·85; N, 10·4. $C_{22}H_{19}O_5N_3$ requires C, 65·2; H, 4·75; N, 10·35%). This substance (20 g.) and phosphoryl chloride (30 ml.) were heated in a bath at 130° for 1 hour, and then cautiously decomposed with water. The solid product was heated with aqueous alkali, washed, and dried; it was then refluxed with alcohol (800 ml.) and filtered hot from the 6-*isomeride* (6·2 g.). This product crystallised from a large volume of acetone in hard colourless

prisms, m. p. 248—250° (decomp.); from pyridine, in which it was fairly soluble, it gave clumps of small needles (Found: C, 68·25; H, 4·35; N, 11·05. $C_{22}H_{17}O_4N_3$ requires C, 68·2; H, 4·45; N, 10·85%). By fractional crystallisation of the alcoholic mother-liquor a further quantity of the 6-isomeride (1 g.) and the 8-*isomeride* (9·5 g.) were obtained. The latter crystallised from alcohol, in which it was much more soluble than its isomeride, in pale yellow prisms, m. p. 194° (Found: C, 68·4; H, 4·35; N, 10·9%). Hydrolysis of the 6-isomeride with sulphuric acid furnished 6-*amino*-9-p-*nitrophenylphenanthridine* (X; R = NH_2), which was very sparingly soluble in alcohol, but crystallised from pyridine in yellow needles, m. p. 260° (Found: C, 72·7; H, 4·3; N, 13·35. $C_{19}H_{13}O_2N_3$ requires C, 72·4; H, 4·15; N, 13·35%). This substance possessed weak basic properties, forming an insoluble yellow sulphate. 8-*Amino*-9-p-*nitrophenylphenanthridine*, similarly prepared, crystallised from alcohol in golden yellow needles, m. p. 180° (Found: C, 72·55; H, 4·35; N, 13·8%). It formed a bright red, slightly soluble sulphate.

Whereas the 6-amine could readily be reconverted quantitatively in acetone solution into the urethane by the general method, with the 8-amine a very poor yield was obtained, a result attributed to steric hindrance.

8-*Hydroxy*-9-p-*nitrophenylphenanthridine* (IX; R = *p*-$C_6H_4{\cdot}NO_2$).—A solution of the 8-amine (0·5 g.) in concentrated sulphuric acid (5 ml.) was cooled in ice and diazotised with a solution of sodium nitrite (0·11 g.) in concentrated sulphuric acid (2 ml.). The mixture was diluted with ice, and the yellow solution thus obtained heated (steam-bath) until effervescence ceased. The brownish-yellow precipitated *product* was insoluble in alkali. It crystallised from nitrobenzene in buff needles, m. p. 262—263° (Found: N, 9·05. $C_{19}H_{12}O_3N_2$ requires N, 8·9%).

6-*Hydroxy*-9-p-*nitrophenylphenanthridine* was similarly obtained in high yield. It was readily purified by solution in aqueous alkali and reprecipitation by acetic acid, and crystallised from cellosolve in buff prisms, m. p. 280—282° (Found: N, 9·0%).

6-*Amino*-9-p-*nitrophenyl*-10-*methylphenanthridinium Chloride* (II; R = NO_2, R′ = NH_2).—6-Carbethoxyamino-9-*p*-nitrophenylphenanthridine was converted into its quaternary salt by the method described for the 2-isomeride. The methosulphate was precipitated from the nitrobenzene reaction mixture by benzene as a semi-solid mass, which was washed with hot benzene, dried, and dissolved in water. Both the methosulphate and the *chloride* were liable to form viscid gels with water, but the latter crystallised from alcohol in cream-coloured needles, m. p. 221—223° (decomp.) (Found: C, 60·65; H, 4·95; N, 9·25; Cl, 8·1; loss at 100°, 4·05. $C_{23}H_{20}O_4N_3Cl,H_2O$ requires C, 60·65; H, 4·85; N, 9·25; Cl, 7·8; H_2O, 3·95%). Hydrolysis with sulphuric acid, followed by dilution, and neutralisation with ammonia furnished the *amino-nitro*-salt, which crystallised from water in brownish-yellow plates, m. p. 217° (decomp.) (Found for dried salt: N, 11·4; Cl, 9·45. $C_{20}H_{16}O_2N_3Cl$ requires N, 11·5; Cl, 9·7%).

6-*Amino*-9-p-*aminophenyl*-10-*methylphenanthridinium Chloride* (II; R = R′ = NH_2).—The foregoing salt (3 g.) was refluxed with alcohol (60 ml.) and concentrated hydrochloric acid (6 ml.) until a clear solution was obtained. Addition of stannous chloride (6·5 g.) precipitated a yellow salt, but as refluxing continued this went into solution as light-brown prismatic crystals began to separate. This sparingly soluble salt (3 g.) was dissolved in hot water (600 ml.), the solution neutralised, and filtered from stannic hydroxide. With cooling the *diamino*-salt crystallised in light brown prisms, unmolten at 300° (Found: C, 71·4; H, 5·1; N, 12·55; Cl, 10·7. $C_{20}H_{18}N_3Cl$ requires C, 71·5; H, 5·35; N, 12·5; Cl, 10·6%). The same compound was obtained by reduction with iron and water.

The corresponding salts of the 8-series, which were much more soluble in water, were prepared by similar methods.

8-*Carbethoxyamino*-9-p-*nitrophenyl*-10-*methylphenanthridinium chloride*, obtained in poor yield, crystallised from water in transparent orange prisms, m. p. 180—185° (decomp.), dependent on rate of heating (Found: C, 57·6; H, 4·85; N, 9·05; Cl, 7·65; loss at 100°, 7·6. $C_{23}H_{20}O_4N_3Cl,2H_2O$ requires C, 58·3; H, 5·1; N, 8·85; Cl, 7·5; H_2O, 7·6%).

8-*Amino*-9-p-*nitrophenyl*-10-*methylphenanthridinium chloride* crystallised from water in black prisms (ruby-red by transmitted light), m. p. 232—234° (decomp.) (Found: N, 10·7; Cl, 9·15; loss at 100°, 4·25. $C_{20}H_{16}O_2N_3Cl,H_2O$ requires N, 10·95; Cl, 9·25; H_2O, 4·7%).

8-*Amino*-9-p-*aminophenyl*-10-*methylphenanthridinium bromide* crystallised from water in light red prisms, m. p. 245—246° (decomp.) (Found: N, 11·0; Br, 21·2. $C_{20}H_{18}N_3Br$ requires N, 11·05; Br, 21·05%).

4-*Carbethoxyamino*-2′-p-*nitrophenylacetamidodiphenyl*.—A solution of 4-carbethoxyamino-2′-acetamidodiphenyl (20 g.; Walls, *loc. cit.*) was refluxed in alcohol (140 ml.) and concentrated sulphuric acid for 2½ hours. 2N-Ammonia was added to neutrality, and 2-amino-4′-carbethoxyaminodiphenyl crystallised in almost quantitative yield; on recrystallisation from light petroleum (b. p. 60—80°) white prismatic needles were obtained, m. p. 96°, alone or in admixture with an authentic specimen. *p*-Nitrophenylacetyl chloride (18 g.) was added portionwise to a solution of this amine (21 g.) in hot chlorobenzene (180 ml.), and the mixture was refluxed for 20 minutes, hydrogen chloride being evolved. After cooling, the crystalline *product* (33 g.) was collected, washed with light petroleum (b. p. 80—100°) followed by light petroleum (b. p. 40—60°), and dried. On crystallisation from alcohol or aqueous dioxan it formed small colourless feathery needles, m. p. 209—210° (Found: C, 66·05; H, 5·05; N, 10·2. $C_{23}H_{21}O_5N_3$ requires C, 65·9; H, 5·05; N, 10·0%).

7-*Carbethoxyamino*-9-p-*nitrobenzylphenanthridine* (XII).—The foregoing amide (20 g.) was refluxed with phosphoryl chloride (60 ml.) for 1 hour. The mixture was poured into water, and the precipitated bright yellow salt dissolved in hot aqueous pyridine, from which the *phenanthridine* derivative crystallised in almost quantitative yield. It crystallised from benzene in fine colourless needles, m. p. 186—187° (Found: C, 68·75; H, 4·85; N, 10·35. $C_{23}H_{19}O_4N_3$ requires C, 68·85; H, 4·75; N, 10·45%).

7-*Amino*-9-p-*nitrobenzylphenanthridine*.—The 7-carbethoxyamino-compound (5 g.) was heated with sulphuric acid (2 : 1) at 150° for 45 minutes, diluted with water, and the sparingly soluble sulphate collected and crystallised from aqueous pyridine. The *amine* was thus obtained in 90% yield, crystallising

from dioxan in deep yellow needles, m. p. 244—247° (decomp.) (Found: C, 72·7; H, 4·8; N, 12·5. $C_{20}H_{15}O_2N_3$ requires C, 72·95; H, 4·6; N, 12·75%). Acetylation with acetic anhydride furnished the *acetyl* derivative, which crystallised from dioxan in pale yellow needles, m. p. 252—254° (decomp.) (Found: C, 71·05; H, 5·0; N, 11·25. $C_{22}H_{17}O_3N_3$ requires C, 71·15; H, 4·6; N, 11·3%).

7-*Carbethoxyamino*-9-p-*nitrobenzyl*-10-*methylphenanthridinium Chloride* (XIII; R = NO_2, R′ = $NH{\cdot}CO_2Et$).—7-Carbethoxyamino-9-*p*-nitrobenzylphenanthridine (5 g.) in nitrobenzene (35 ml.) at 180° was treated with methyl sulphate (3 ml.). With cooling a precipitate formed, consisting of a mixture of starting material and *methosulphate*, which on crystallisation from alcohol yielded the latter (50% yield) in pale yellow needles, m. p. 234—236° (decomp.) (Found: C, 57·05; H, 5·05; N, 7·9. $C_{25}H_{25}O_8N_3S$ requires C, 56·9; H, 4·8; N, 7·95%). The *chloride* crystallised from dilute hydrochloric acid in deep yellow needles, m. p. 221° (decomp.) (Found: N, 9·65; Cl, 7·9. $C_{24}H_{22}O_4N_3Cl$ requires N, 9·3; Cl, 7·85%). When either salt was boiled with water, part dissolved and part was converted into a less soluble red substance. The salts crystallised normally from dilute acid.

7-*Amino*-9-p-*nitrobenzyl*-10-*methylphenanthridinium Chloride* (XIII; R = NO_2, R′ = NH_2).—Hydrolysis of the foregoing salt (6 g.) with sulphuric acid followed by dilution with water gave a red precipitate, which was collected and dissolved in boiling water. After addition of barium chloride (1 g.) and separation of barium sulphate, the solution deposited red platelets, m. p. 185° (decomp.), of the desired *salt*. On being dried at 110°/0·05 mm. the salt lost water of crystallisation and became almost black, regaining water and reverting to its original red colour on exposure to air (Found for dried salt: N, 10·95; Cl, 9·15. $C_{21}H_{18}O_2N_3Cl$ requires N, 11·05; Cl, 9·35%). A solution of this salt in glacial acetic acid was readily converted into 7-*acetamido*-9-p-*nitrobenzyl*-10-*methylphenanthridinium chloride* by acetic anhydride; yellow prismatic needles, m. p. 245° (decomp.), were obtained from alcohol (Found: N, 9·9; Cl, 8·35. $C_{23}H_{20}O_3N_3Cl$ requires N, 9·95; Cl, 8·4%). The same salt was also prepared from 7-acetamido-9-*p*-nitrobenzylphenanthridine and methyl sulphate. It reacted with water in a manner similar to the corresponding 7-carbethoxyamino-salt.

7-*Amino*-9-p-*aminobenzyl*-10-*methylphenanthridinium Chloride* (XIII; R = R′ = NH_2).—When the amino-nitro-salt was reduced by iron and water, the *product* separated from the hot filtrate as a gel, which could, however, be filtered off and dried; it crystallised from water in a voluminous mass of microscopic orange needles, m. p. *ca.* 205° (decomp.) (Found: C, 71·45; H, 5·8; N, 12·25; Cl, 10·3. $C_{21}H_{20}N_3Cl$ requires C, 72·05; H, 5·75; N, 12·0; Cl, 10·15%).

7-*Carbethoxyamino*-9-p-*aminobenzyl*-10-*methylphenanthridinium chloride* (XIII; R = NH_2, R′ = $NH{\cdot}CO_2Et$) was obtained by iron–water reduction of the corresponding nitro-salt. It crystallised from water in fine orange needles, m. p. 206—210° (decomp.) (bath preheated to 200°) (Found: N, 10·0; Cl, 8·25. $C_{24}H_{24}O_2N_3Cl$ requires N, 9·95; Cl, 8·4%). On hydrolysis with sulphuric acid this compound yielded the diamino-salt described above. When an aqueous solution of either salt was stirred with ethyl chloroformate, 7-*carbethoxyamino*-9-p-*carbethoxyaminobenzyl*-10-*methylphenanthridinium chloride* crystallised in bright yellow micro-needles, m. p. *ca.* 220° (decomp.) (Found: N, 8·55; Cl, 7·1. $C_{27}H_{28}O_4N_3Cl$ requires N, 8·5; Cl, 7·2%).

7-*Acetamido*-9-p-*aminobenzyl*-10-*methylphenanthridinium Chloride* (XIII; R = NH_2, R′ = $NH{\cdot}COMe$).—The acetamido-nitro-salt was reduced with iron–water; the *amino*-salt crystallised from water in deep yellow micro-needles, m. p. 262° (decomp.) (bath preheated to 250°) (Found: N, 10·7; Cl, 8·45. $C_{23}H_{22}ON_3Cl$ requires N, 10·7; Cl, 9·05%). The sparingly soluble *bromide* formed orange micro-crystals, m. p. 274° (decomp.) (Found: N, 9·6; Br, 18·35. $C_{23}H_{22}ON_3Br$ requires N, 9·65; Br, 18·35%). Treatment of an aqueous solution of the chloride with ethyl chloroformate yielded 7-*acetamido*-9-p-*carbethoxyaminobenzyl*-10-*methylphenanthridinium chloride*, which crystallised from water in pale yellow micro-needles, m. p. 242° (decomp.) (Found: N, 9·45; Cl, 7·15. $C_{26}H_{26}O_3N_3Cl$ requires N, 9·05; Cl, 7·65%). The *bromide* crystallised from water in yellow micro-needles, m. p. 255° (decomp.) (Found: N, 8·7; Br, 15·7. $C_{26}H_{26}O_3N_3Br$ requires N, 8·25; Br, 15·75%).

7-*Amino*-9-p-*carbethoxyaminobenzyl*-10-*methylphenanthridinium Chloride* (XIII; R = $NH{\cdot}CO_2Et$, R′ = NH_2).—The acetamido-carbethoxyamino-salt (6·5 g.) was refluxed for 1½ hours with 2N-hydrochloric acid (60 ml.) during which period the solid slowly dissolved. The hot solution was neutralised with 2N-ammonia to liberate a red gum, which slowly set to a red solid, m. p. 55—80°. This hydrated *salt* was heated with *n*-propyl alcohol (50 ml.), and converted into an orange powder, m. p. 244° (decomp.), which was crystallised by dissolving it in anhydrous methanol and adding dry ether (Found: N, 9·9; Cl, 8·35. $C_{24}H_{24}O_2N_3Cl$ requires N, 9·95; Cl, 8·4%).

9-p-*Nitrobenzylphenanthridine*.—Condensation of *o*-xenylamine (5·5 g.) and *p*-nitrophenylacetyl chloride (6·5 g.) in boiling chlorobenzene (35 ml.) afforded 2-p-*nitrophenylacetamidodiphenyl*, which crystallised from alcohol in long colourless needles, m. p. 188—189° (Found: C, 72·6; H, 4·9; N, 8·4. $C_{20}H_{16}O_3N_2$ requires C, 72·3; H, 4·85; N, 8·45%). This product (3 g.) was readily converted by phosphoryl chloride into the *phenanthridine* (1·9 g.), which crystallised from benzene or alcohol in clumps of colourless needles, m. p. 168—169° (Found: C, 76·4; H, 4·6; N, 9·0. $C_{20}H_{14}O_2N_2$ requires C, 76·4; H, 4·5; N, 8·9%).

9-p-*Nitrobenzyl*-10-*methylphenanthridinium methosulphate* was obtained from the foregoing compound (5 g.) and methyl sulphate (5 ml.) in nitrobenzene (30 ml.) at 180°. The crystalline product formed straw-coloured prismatic needles from methanol, m. p. 238° (decomp.) (Found: N, 6·5; S, 7·4. $C_{22}H_{20}O_6N_2S$ requires N, 6·35; S, 7·3%). This salt was only partially soluble in water, a red suspension, soluble in dilute acid, being obtained.

9-p-*Aminobenzyl*-10-*methylphenanthridinium chloride* was the product of iron–water reduction of the preceding nitro-salt. It crystallised from water in deep orange felted needles of a hydrate (2·5 H_2O), m. p. *ca.* 115—120° (efferv. at 130°), unchanged by dehydration at 80°/0·05 mm. (Found: N, 8·45; Cl, 9·45. $C_{21}H_{19}N_2Cl$ requires N, 8·35; Cl, 10·6%). The *bromide*, orange needles, m. p. 215—218°, gave satisfactory analytical results (Found: N, 7·35; Br, 21·15. $C_{21}H_{19}N_2Br$ requires N, 7·4; Br, 21·1%). The *carbethoxyl* compound crystallised as a hydrate in cream-coloured needles, m. p. 60°, efferv. 110°, resolidifying and melting finally at *ca.* 205° (decomp.). After drying at 110°/15 mm., the

compound crystallised from *n*-propyl alcohol in pale yellow micro-crystals, m. p. 220° (decomp.) (Found : N, 6·85; Cl, 8·7. $C_{24}H_{23}O_2N_2Cl$ requires N, 6·9; Cl, 8·75%).

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