289. *Trypanocides of the Phenanthridine Series. Part II.* Pyrimidinyl-phenanthridines.*

By T. I. WATKINS.

Phenanthridinium compounds, some of which exhibit a highly curative action in bovine trypanosomiasis, and 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide gave pyrimidinyl-phenanthridines, some of which are potent trypanophylactics.

MANY phenanthridinium compounds prepared by Morgan and Walls [1] and Watkins [2] are effective against *Trypanosoma congolense* infections of mice and *T. congolense* and *T. vivax* infections of cattle. However, the period of protection from infection conferred [3–5] by these compounds is short compared with that claimed for " Antrycide Pro-salt " (I; X = Cl and $MeSO_4$).[6,7]

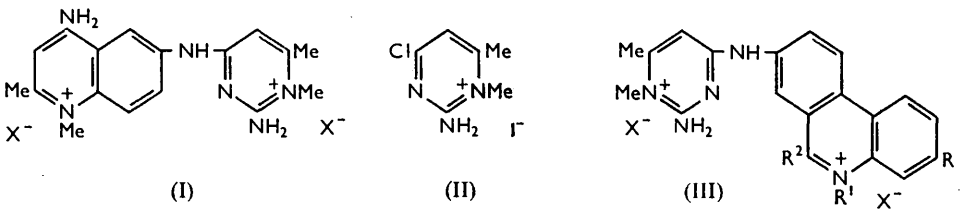
The high prophylactic activity shown by " Antrycide " may be due, in part, to the presence of the pyrimidinium moiety. Compounds were therefore prepared in which this moiety had been introduced into the more active phenanthridinium salts. Some of these, prepared from a phenanthridinium salt and 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (II), were highly prophylactic in *T. congolense* infections of mice [8] and in *T. congolense* and *T. vivax* infections of cattle.[9] It was surprising that these compounds are also highly efficient curative agents in *T. congolense* infections of mice since the efficiency of the phenanthridinium compounds in this respect is markedly reduced by substitution of the free amino-groups.[10–13]

Compounds, of four main types, (III), (IV), (V), and (VI), were synthesised, all from the pyrimidinium iodide (II): compounds (III) from the 7-amino-grouping of a phenanthridinium compound, structures (IV) from 2 : 7-diaminophenanthridinium salts, structures (V) from a 3-aminophenanthridinium compound (VIII), and compound (VI) from the appropriate 9-*p*-aminophenylphenanthridinium salt. In structure (V) the

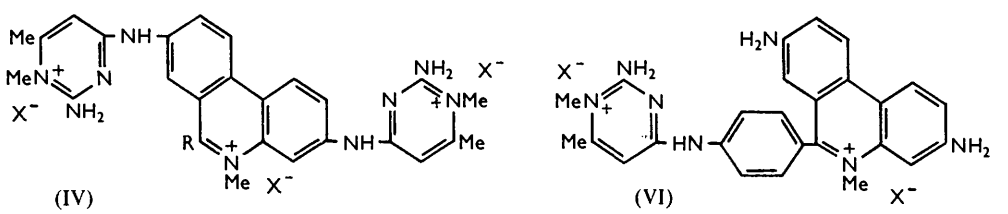
* Part I, *J.*, 1952, 3059.

[1] Morgan and Walls, *J.*, 1938, 389, and subsequent papers.
[2] Watkins, *J.*, 1952, 3059.
[3] Goodwin and Chandler, *Brit. J. Pharmacol.*, 1952, **7**, 591.
[4] Karib and Meal, *ibid.*, 1954, **9**, 37.
[5] Leach, Karib, Ford, and Wilmshurst, *J. comp. Path.*, 1955, **65**, [2], 130.
[6] Curd and Davey, *Brit. J. Pharmacol.*, 1950, **5**, 25.
[7] Davey, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1950, **43**, 583 *et seq.*
[8] Woolfe, in the press.
[9] Watkins and Woolfe, *Nature*, 1956, **178**, 368.
[10] Walls *et al.*, *J.*, 1945, 294.
[11] *Idem*, *ibid.*, 1946, 1031.
[12] *Idem*, *ibid.*, 1947, 67.
[13] Woolfe, *Brit. J. Pharmacol.*, 1956, **11**, 334.

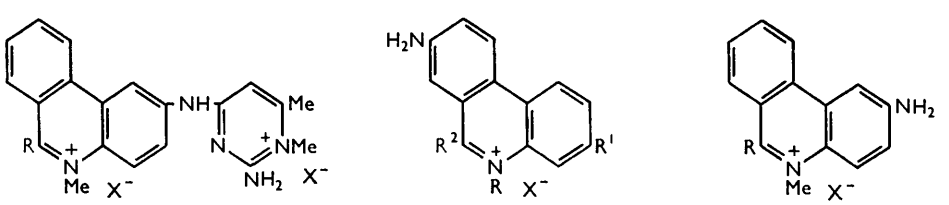
skeleton of the " Antrycide " molecule has been retained, and compound (VI) was of interest in that all the features essential for maximal activity in a phenanthridinium compound [10,12] were present. Compounds (III) and (V) were prepared in hot aqueous solution, in the presence of one equivalent of hydrochloric acid, which facilitated dissolution of the phenanthridinium compound and in one preparation had catalytic effect (cf. preparation of " Antrycide " and its derivatives [14]). When both 2- and 7-amino-groupings of the



(I) (II) (III)



(IV) (VI)



(V) (VII) (VIII)

phenanthridinium compound were available for reaction [*e.g.* preparation of compounds (III; R = NH_2)] preferential substitution occurred at the 7-amino-position (see also the monoacetylation [15] of 2 : 7-diaminophenanthridinium compounds). Walls suggests [10] that the dark-red colour of the 2 : 7-diaminophenanthridinium compounds is due to a benzenoid–quinonoid resonance in which the positive charge of the quaternary nitrogen atom is shared by the 2-amino-group, thus reducing the electronegative character of the latter. Proof that the major product from the condensation of the iodide (II), with 2 : 7-diamino-10-methyl-9-phenylphenanthridinium bromide (VII; R = Me, R′ = NH_2, R^2 = Ph, X = Br) was a 2-amino-7-(2-amino-6-methyl-4-pyrimidinylamino)-9-phenylphenanthridine 10 : 1′-dimetho-salt (III; R = NH_2, R^1 = Me, R^2 = Ph) was obtained by its unequivocal synthesis from 7-amino-10-methyl-2-nitro-9-phenylphenanthridinium chloride (VII; R = Me, R^1 = NO_2, R^2 = Ph, X = Cl) [16] and the pyrimidinium iodide (II), followed by reduction.

Compounds (IV) could not be prepared pure in aqueous solution or in aqueous solution in the presence of one or two equivalents of hydrochloric acid. The condensation proceeded smoothly, however, in phenol.

Experimental

Unless otherwise stated, compounds were dried for 2 hr. at 100°/2 mm. before analysis, since when compounds had been crystallised from an alcohol the solvent could not always be

[14] Barrett, Curd, and Hepworth, *J.*, 1953, 50.
[15] B.P. 746,027.
[16] Walls, *J.*, 1950, 3511.

completely removed at 100° under normal pressure. Pyrimidinylphenanthridinium chlorides quickly absorbed atmospheric moisture.

All analyses for water were carried out in a Karl Fischer apparatus modified to semimicro-scale.

*Preparation of Phenanthridinium Compounds.**

2 : 7-*Dinitrophenanthridines*.—*p*-Toluoyl chloride (14·2 ml.) and 2-amino-4 : 4′-dinitrodiphenyl [18] (25·9 g.) were heated in refluxing chlorobenzene (125 ml.) for 1 hr. to give 4 : 4′-*dinitro*-2-p-*toluamidodiphenyl* (35 g.), prisms, (from acetic acid), m. p. 203° (Found: N, 11·2. $C_{20}H_{15}O_5N_3$ requires N, 11·1%). The amide (30 g.), phosphorus oxychloride (10 ml.), and nitrobenzene (170 ml.) were heated under reflux for 2½ hr. Unchanged phosphorus oxychloride and some nitrobenzene were removed by distillation and ethanol (100 ml.) was then added at 80—100°. The *phenanthridine* (25 g.) which separated formed cream-coloured elongated plates (from acetic acid), m. p. 271—272° (Found: N, 11·9. $C_{20}H_{13}O_4N_3$ requires N, 11·7%).

2-p-iso*Propylbenzamido*- (94%), prisms (from acetic acid), m. p. 196—197° (Found: N, 10·3. $C_{22}H_{19}O_5N_3$ requires N, 10·35%), 2-p-*chlorobenzamido*- (94%), plates (from acetic acid), m. p. 211—212° (Found: N, 10·8. $C_{19}H_{12}O_5N_3Cl$ requires N, 10·55%), and 2-*anisoylamino*-4 : 4′-*dinitrodiphenyl* (91%), needles (from acetic acid), m. p. 211—212° (Found: N, 10·5. $C_{20}H_{15}O_6N_3$ requires N, 10·7%), were similarly prepared and cyclised to the following 2 : 7-*dinitrophenanthridines*: 9-p-iso*propylphenyl*- (86%), plates (from 2-ethoxyethanol), m. p. 275—276° (Found: N, 10·7. $C_{22}H_{17}O_4N_3$ requires N, 10·85%); 9-p-*chlorophenyl*- (89%), yellow plates (from 2-ethoxyethanol), m. p. 317—319° (Found: C, 60·3; H, 2·65; N, 11·4. $C_{19}H_{10}O_4N_3Cl$ requires C, 60·0; H, 2·6; N, 11·05%); and 9-p-*methoxyphenyl*- (83%), yellow needles (from 2-ethoxyethanol), m. p. 263—264° (Found: N, 11·0. $C_{20}H_{13}O_5N_3$ requires N, 11·2%).

2 : 7-*Diamino*-10-*methylphenanthridinium Bromides* (as VII; R = Me, $R^1 = NH_2$, X = Br).—2 : 7-Dinitro-9-*p*-tolylphenanthridine (7·5 g.) and methyl sulphate (4 ml.) were heated in nitrobenzene (50 ml.) for 1 hr. at 180°. After removal of nitrobenzene addition of hydrobromic acid solution (48%; 5 ml.) gave the quaternary bromide which was reduced by iron powder (9 g.) for 4 hr. in boiling ethanol (150 ml.), water (300 ml.), and 5N-hydrobromic acid (0·5 ml.). The mixture was filtered and the pH of the filtrate raised to 8·5 with ammonia solution. This mixture was set aside overnight and then filtered through kieselguhr. The filtrate was concentrated to about 50 ml., and the deposit crystallised from ethanol yielding dark-red plates of 2 : 7-*diamino*-10-*methyl*-9-p-*tolylphenanthridinium bromide* (3·8 g.), m. p. 270—271° (decomp.) (Found: N, 10·4; Br, 20·6. $C_{21}H_{20}N_3Br$ requires N, 10·65; Br, 20·3%).

The following 2 : 7-*diamino*-10-*methylphenanthridinium bromides* were similarly prepared from the dinitrophenanthridines described above: 9-p-iso*propylphenyl*- (41·5%), purple plates (from methanol), m. p. 272—274° (decomp.) (Found: C, 65·35; H, 5·6; N, 9·8. $C_{23}H_{24}N_3Br$ requires C, 65·4; H, 5·7; N, 9·95%); and 9-p-*methoxyphenyl*- (53%), dark-red plates (from methanol–propan-2-ol), m. p. 230—231° (decomp.) (Found: N, 10·05; Br, 19·65. $C_{21}H_{20}ON_3Br$ requires N, 10·2; Br, 19·5%).

2 : 7-*Diamino*-10-*ethyl*-9-p-*tolylphenanthridinium Bromide* (VII; R = Et, $R^1 = NH_2$, R^2 = *p*-Me·C_6H_4, X = Br).—2 : 7-Dinitro-9-*p*-tolylphenanthridine (12 g.) and ethyl toluene-*p*-sulphonate were heated for 4½ hr. at 185°. The melt was cooled and poured into toluene (250 ml.), and the precipitate extracted with a hot mixture of ethanol (110 ml.), water (80 ml.), and 5N-sulphuric acid (1 ml.). The filtered extract was added to a hot stirred suspension of iron powder (9 g.) in water (300 ml.). This mixture was stirred under reflux for 4 hr. and then cooled, and sodium hydroxide solution (40% w/w; 100 ml.) and toluene (200 ml.) were added with stirring. The toluene layer, containing the pseudo-base ethyl ether, was extracted with dilute hydrochloric acid solution. The pH of the acid extract was raised to 8·5 by ammonia solution, and ammonium bromide added to salt out the *diamino-bromide*. It crystallised (much methanol) in dark-red plates, m. p. 270—271° (Found: N, 10·2; Br, 19·0. $C_{22}H_{22}N_3Br$ requires N, 10·3; Br, 19·6%).

2 : 7-*Diamino*-9-p-iso*propylphenylphenanthridine*.—2 : 7-Dinitro-9-*p*-*iso*propylphenylphenanthridine (8·3 g.) was heated for 1 hr. at 100° with stannous chloride (60 g.) in water (20 ml.), ethanol (80 ml.), and concentrated hydrochloric acid (60 ml.). The resulting solution was

* See Woolfe (refs. 13, 17), for biological testing of these compounds.

[17] Woolfe, *Brit. J. Pharmacol.*, 1956, **11**, 330.

[18] Finzi and Bellavita, *Gazzetta*, 1938, **68**, 77.

poured on ice and excess of sodium hydroxide solution. The yellow precipitate was extracted with hot ethanol (350 ml.); concentration (to 60 ml.) gave the *diamino*-compound as yellow needles (6 g.), m. p. 222—223° (Found: N, 12·8. $C_{22}H_{21}N_3$ requires N, 12·8%).

10-*Allyl*-2 : 7-*diamino*-9-p-iso*propylphenylphenanthridinium Chloride* (VII; R = Allyl, R^1 = NH_2, R^2 = *p*-$Pr^i \cdot C_6H_4$, X = Cl).—2 : 7-Diamino-9-*p*-*iso*propylphenylphenanthridine (5·5 g.) was heated with ethyl chloroformate (3·8 ml.) and diethylaniline (8 ml.) in ethanol (200 ml.), and the mixture then diluted with water. 2 : 7-*Bisethoxycarbonylamino*-9-p-iso*propylphenylphenanthridine* (6·3 g.) formed buff-coloured elongated plates (from ethanol), m. p. 216—217° (decomp.) (Found: N, 8·9. $C_{28}H_{29}O_4N_3$ requires N, 8·9%). This compound (6 g.) was heated with allyl iodide (4 ml.) in nitrobenzene (30 ml.) for 3½ hr. at 100°. Addition of ether (30 ml.) to the cooled solution precipitated the *quaternary iodide* (5·3 g.), which was crystallised by dissolution in warm nitrobenzene followed by addition of ether, forming yellow needles, m. p. 212—215° (decomp.) (Found: I, 19·5. $C_{31}H_{34}O_4N_3I$ requires N, 19·9%). The iodide was converted into the corresponding methanesulphonate by metathesis with silver methanesulphonate in aqueous methanol acidified with methanesulphonic acid. It separated as yellow needles, m. p. 210—214° (decomp.). Hydrolysis [15] with 75—80% w/w sulphuric acid at 125—130° gave the required diamine (2·4 g.) which was isolated as the *chloride*, purple plates (from ethanol), m. p. 264° (decomp.) (Found: N, 10·4; Cl, 7·8. $C_{25}H_{26}N_3Cl$ requires N, 10·4; Cl, 8·0%).

Other 10-*allyl*-2 : 7-*bisethoxycarbonylaminophenanthridinium iodides* prepared by similar quaternisation were 9-p-*chlorophenyl*- (for 30 hr.) (71%), yellow needles (from methanol), m. p. 220° (decomp.) (Found: I, 19·8. $C_{28}H_{27}O_4N_3ClI$ requires I, 20·1%); and 9-p-*nitrophenyl*- (for 24 hr.) (44%), yellow needles (from nitrobenzene–ether), decomp. *ca.* 225° (Found: N, 8·5; I, 21·3. $C_{28}H_{27}O_6N_4I$ requires N, 8·7; I, 19·8%). They were converted, as already described, into the 10-*allyl*-2 : 7-*diaminophenanthridinium chlorides*: 9-p-*chlorophenyl*- (44%), purple plates (from ethanol), m. p. 230—232° (decomp.) (Found: N, 10·4; Cl, 9·2. $C_{22}H_{19}N_3Cl_2$ requires N, 10·6; Cl, 9·0%); and 9-p-*nitrophenyl*- (51%), purplish-black plates (from water containing a little ammonium chloride), m. p. 265—267° (decomp.) (Found: N, 13·7; Cl, 8·3. $C_{22}H_{19}O_2N_4Cl$ requires N, 13·75; Cl, 8·7%).

9-p-*Chlorophenyl*-2 : 7-*bisethoxycarbonylaminophenanthridine*.—(a) *p*-Chlorobenzoyl chloride (9·5 g.) was heated with 2-amino-4 : 4′-bisethoxycarbonylaminodiphenyl (17 g.)[12] in chlorobenzene (125 ml.) for 1 hr. to give 2-p-*chlorobenzamido*-4 : 4′-*bisethoxycarbonylaminodiphenyl* (20·1 g.), which formed flat needles, m. p. 121—122°, from a small volume of ethanol (Found: N, 8·7. $C_{25}H_{24}O_5N_3Cl$ requires N, 8·7%). This compound (18 g.) was heated with phosphorus oxychloride (40 ml.) for 1 hr. and the product treated with aqueous ammonia and then twice crystallised from ethanol. The *phenanthridine* (7·8 g.) formed pale-yellow needles, m. p. 222° (Found: N, 8·9. $C_{25}H_{22}O_4N_3Cl$ requires N, 9·05%).

(b) A suspension of 9-*p*-chloro-2 : 7-dinitrophenanthridine (30 g.) was reduced with stannous chloride (220 g.) in concentrated hydrochloric acid (220 ml.) containing 5N-sulphuric acid (20 ml.). The red precipitate was decomposed with sodium hydroxide solution. The *diamine* (10·1 g.) formed yellow needles, m. p. 236—237° (from ethanol) (Found: N, 13·1. $C_9H_{14}N_3Cl$ requires N, 13·1%). This diamine (10 g.) with ethyl chloroformate (7 ml.) in ethanol (300 ml.) and diethylaniline (14 ml.) gave 9-*p*-chlorophenyl-2 : 7-bisethoxycarbonylaminophenanthridine (11·5 g.), as pale yellow needles (from methanol), m. p. 222°, undepressed on admixture with the product obtained by method (a) (Found: N, 9·3%).

2 : 7-*Diamino*-9-p-*chlorophenyl*-10-*methylphenanthridinium Chloride* (VII; R = Me, R^1 = NH_2, R^2 = *p*-$Cl \cdot C_6H_4$, X = Cl).—The foregoing phenanthridine (4·5 g.) and methyl sulphate (2 ml.), heated in nitrobenzene (15 ml.), gave 9-p-*chlorophenyl*-2 : 7-*bisethoxycarbonylamino*-10-*methylphenanthridinium methyl sulphate* (5 g.), yellow needles (from ethanol), m. p. >250° (Found: N, 6·9. $C_{27}H_{28}O_8N_3SCl$ requires N, 7·1%). Hydrolysis with 75—80% (w/w) sulphuric acid at 125—130°, as previously described, gave the diamine (1·7 g.) isolated as *chloride*, which crystallised from methanol–ethanol as small purple plates, m. p. 253—255° (decomp.; slow heating) (Found: C, 64·5; H, 4·6; N, 11·1. $C_{20}H_{17}N_3Cl_2$ requires C, 64·9; H, 4·6; N, 11·35%).

2 : 7-*Diamino*-10-*ethyl*-9-*nitrophenylphenanthridinium Chlorides* (VII; R = Et, R^1 = NH_2, R^2 = *p*-$NO_2 \cdot C_6H_4$, X = Cl) *and* (VII; R = Et, R^1 = NH_2, R^2 = *m*-$NO_2 \cdot C_6H_4$, X = Cl).—By use of ethyl sulphate and a series of reactions similar to those of the preceding experiment 2 : 7-bisethoxycarbonylamino-9-*p*-nitrophenylphenanthridine [19] was converted into 2 : 7-*diamino*-10-*ethyl*-9-p-*nitrophenylphenanthridinium chloride* (37%). This formed black plates

[19] Walls and Whittaker, *J.*, 1950, 41.

with bronze lustre (from water containing ammonium chloride), m. p. 268—270° (decomp.) (Found, in material heated for 10 hr. at 100°: C, 61·6; H, 5·35; N, 13·3; Cl, 8·8; H_2O, 6·0. $C_{21}H_{19}O_2N_4Cl,H_2O$ requires C, 61·1; H, 5·1; N, 13·6; Cl, 8·6; H_2O, 4·4%. Found, in material dried for 2 hr. at 100°/2 mm.: N, 14·05. $C_{21}H_{19}O_2N_4Cl$ requires N, 14·2%).

The 10-ethyl-*m*-nitrophenyl compound was obtained in the same way (by Dr. J. S. NICHOLSON). It separated from hydrochloric acid as a *chloride monohydrochloride*, m. p. 240—245° (decomp.) (Found, in material dried at 100°: N, 12·4; H_2O, 6·2. $C_{21}H_{19}O_2N_4Cl,HCl,1\frac{1}{2}H_2O$ requires N, 12·2; H_2O, 5·9%).

2 : 7-*Diamino*-9-p-*nitrophenyl*-10-*propylphenanthridinium Chloride* (VII; R = Pr, R^1 = NH_2, R^2 = *p*-NO_2·C_6H_4, X = Cl).—This was obtained from 2 : 7-bisethoxycarbonylamino-9-*p*-nitrophenylphenanthridine (24 g.) and propyl toluene-*p*-sulphonate (22 g.) in nitrobenzene (16 ml.) by the reactions described above. The *chloride* (4 g.) crystallised from water in black plates with bronze lustre, m. p. 278—279° (Found : N, 14·1; Cl, 8·9. $C_{22}H_{21}O_2N_4Cl$ requires N, 13·7; Cl, 8·7%).

2 : 7-*Diamino*-9-p-*aminophenyl*-10-*alkylphenanthridinium Chlorides* (VII; R = Et, Pr, or allyl, R^1 = NH_2, R^2 = *p*-NH_2·C_6H_4, X = Cl).—These salts were obtained by reduction of the corresponding 9-*p*-nitrophenyl salts with ferrous hydroxide by Walls and Whittaker's method.[19] Thus were obtained (from ethanol–propan-2-ol) the 10-*ethyl* compound, dark-red plates, m. p. 290° (decomp.) (Found: N, 15·2; Cl, 9·9. $C_{21}H_{21}N_4Cl$ requires N, 15·3; Cl, 9·7%); the 10-propyl compound, dark-red plates, m. p. 294° (decomp.); and the 10-*allyl* compound, purple prisms, m. p. 245° (decomp.) (Found: N, 14·6; Cl, 9·5. $C_{22}H_{21}N_4Cl$ requires N, 14·8; Cl, 9·4%).

2 : 7-*Diamino*-10-*ethyl*-9-*methylphenanthridinium Bromide* (VII; R = Et, R^1 = NH_2, R^2 = Me, X = Br).—2 : 7-Bisethoxycarbonylamino-9-methylphenanthridine [12] (10 g.) with (*a*) ethyl toluene-*p*-sulphonate (50 g.) for 1 hr. at 150° gave 2 : 7-*bisethoxycarbonylamino*-10-*ethyl*-9-*methylphenanthridinium toluene*-p-*sulphonate*, yellow plates (from methanol) (13·1 g.), m. p. >300° (Found: N, 7·6. $C_{29}H_{33}O_7N_3S$ requires N, 7·4%), or (*b*) ethyl sulphate (10 ml.) in nitrobenzene (15 ml.) at 145° for ¾ hr. gave 2 : 7-*bisethoxycarbonylamino*-10-*ethyl*-9-*methylphenanthridinium ethyl sulphate*, yellow plates (from methanol) (11·8 g.), m. p. >300° (Found: N, 8·2. $C_{24}H_{31}O_8N_3S$ requires N, 8·1%). Either salt on hydrolysis with 75—80% (w/w) sulphuric acid, followed by metathesis to the bromide, gave 2 : 7-*diamino*-10-*ethyl*-9-*methylphenanthridinium bromide*, red prisms (from methanol), m. p. 263—265° (decomp.) (Found: N, 12·4; Br, 23·6. $C_{16}H_{18}N_3Br$ requires N, 12·65; Br, 24·1%).

3-*Amino*-10-*methyl*-9-*phenylphenanthridinium Bromide* (VIII; R = Ph, X = Br).—3-Nitro-9-phenylphenanthridine [21] heated with methyl sulphate in nitrobenzene gave a quantitative yield of 10-*methyl*-3-*nitro*-9-*phenylphenanthridinium methyl sulphate*, yellow plates (from ethanol), m. p. 295—297° (decomp.) (Found: N, 6·35. $C_{21}H_{18}O_6N_2S$ requires N, 6·55%). Reduction with iron in acidified aqueous alcohol solution yielded the corresponding amino-compound. This was isolated as the *bromide*, orange-coloured plates (from water containing a little ammonium bromide) (68%), m. p. 193° (decomp.) (Found: N, 7·7; Br, 22·2. $C_{20}H_{17}N_2Br$ requires N, 7·65; Br, 21·9%).

3-*Ethoxycarbonylamino*-9-p-*nitrophenylphenanthridine*.—2-Acetamido-5-ethoxycarbonylaminodiphenyl [21] (16 g.) was hydrolysed with 2·5N-hydrochloric acid in aqueous ethanol solution. The crude 2-amino-5-ethoxycarbonylaminodiphenyl isolated was stirred with *p*-nitrobenzoyl chloride (13 g.) in pyridine (20 ml.) at 20—25° for 1½ hr. and then at 100° for 1 hr. The product was precipitated by dilute acid and crystallised from ethanol. 5-*Ethoxycarbonylamino*-2-p-*nitrobenzamidodiphenyl* (16·4 g.) formed plates, m. p. 183—184° (Found: N, 10·3. $C_{22}H_{19}O_5N_3$ requires N, 10·35%). The compound (16 g.) was heated with phosphorus oxychloride (13 ml.) in nitrobenzene (20 ml.) to give 3-*ethoxycarbonylamino*-9-p-*nitrophenylphenanthridine* (8·4 g.), yellow plates (from aqueous pyridine), m. p. >320° (Found: N, 10·9. $C_{22}H_{17}O_4N_3$ requires N, 10·85%).

3-*Amino*-10-*methyl*-9-p-*nitrophenylphenanthridinium Bromide* (VIII; R = *p*-NO_2·C_6H_4, X = Br).—The foregoing compound (4 g.) was heated with methyl sulphate (3·3 ml.) in nitrobenzene (17 ml.) to give the 10-*methyl-phenanthridinium methyl sulphate* (4 g.), yellow plates (from nitrobenzene), m. p. 246—248° (decomp.) (Found: N, 8·2. $C_{24}H_{23}O_8N_3S$ requires N, 8·2%). This compound was hydrolysed with 75—80% (w/w) sulphuric acid as in previous examples, and the

[20] B.P. 679,148.
[21] Mamalis and Petrow, *J.*, 1950, 703.

TABLE 1. *Pyrimidinylphenanthridines* (III) *prepared from the salts* (VII).

Substituent in (III)			X in (VII)		Yield		Found, %			Required, %			
R	R^1	R^2	X		(%)	Formula	N	I	H_2O	N	I	H_2O	Description
NH_2	Me	Ph	I [a]	Br	73	$C_{26}H_{26}N_6I_2,2H_2O$ [b]	12·1	34·8	4·7	11·8	35·65	5·05	Small red plates [c]
NH_2	Me	Ph	I [a,d]	—	67	$C_{26}H_{26}N_6I_2,2H_2O$ [b]	—	—	—	—	—	—	,, ,, [c]
NH_2	Me	Ph	CH_3SO_3 [e]	Br	—	$C_{28}H_{32}O_6N_6S_2,2H_2O$ [b]	13·15	—	6·3	12·95	—	5·55	Elongated red plates [f]
NH_2	Me	Ph	Br [g]	Br	65	$C_{26}H_{26}N_6Br_2$ [h]	14·2	—	—	14·4	—	—	,, ,,
NH_2	Et	Ph	I	Br	72	$C_{27}H_{28}N_6I_2$	12·0	38·0	—	12·2	37·4	—	Red plates [c]
NH_2	Et	Ph	CH_3SO_3 [j]	Br	61	$C_{29}H_{34}O_6N_6S_2,H_2O$ [b]	13·1	—	3·1	13·0	—	2·8	,, [c]
NH_2	Et	Ph	Cl	Br	63	$C_{27}H_{28}N_6Cl_2,H_2O$ [b,k]	16·2	—	2·9	16·0	—	3·4	,, [c]
H	Me	p-$NO_2{\cdot}C_6H_4$	I	Br(Cl)	83	$C_{26}H_{24}O_2N_6I_2,2H_2O$ [b]	11·1	33·6	4·7	11·3	34·2	4·9	Small brown plates [l]
H	Me	p-$NH_2{\cdot}C_6H_4$	I [m]	—	64	$C_{26}H_{26}N_6I_2$	12·5	36·9	—	12·4	37·6	—	Brick-red microcrystals [l]
NH_2	Me	p-$NO_2{\cdot}C_6H_4$	I	Br	54	$C_{26}H_{25}O_2N_7I_2$	13·8	34·4	—	13·6	35·2	—	Small red plates [n]
NH_2	Me	p-$NC_2{\cdot}C_6H_4$	Cl	Br	45	$C_{26}H_{25}O_2N_7Cl_2,2H_2O$ [b,o,p]	17·3	—	2·4	17·1	—	3·1	,, ,, [c]
NH_2	Me	p-$NO_2{\cdot}C_6H_4$	CH_3SO_3	Br	—	$C_{28}H_{31}O_8N_7S_2,2H_2O$ [b]	13·9	—	5·6	14·1	—	5·2	,, ,, [c]
NH_2	Me	p-$NH_2{\cdot}C_6H_4$	Br [m,q]	—	43	$C_{26}H_{27}N_7Br_2$ [r,s]	16·6	—	—	16·4	—	—	Red microcrystals [c]
NH_2	Et	p-$NO_2{\cdot}C_6H_4$	I	Br	55	$C_{27}H_{27}O_2N_7I_2,2H_2O$ [b]	12·8	—	4·2	12·7	—	4·7	Minute red plates [c]
NH_2	Et	p-$NH_2{\cdot}C_6H_4$	Br [m]	—	38	$C_{27}H_{29}N_7Br_2,2H_2O$ [t]	15·2	—	5·0	15·15	—	5·55	Small red plates [c]
NH_2	Me	m-$NH_2{\cdot}C_6H_4$	Br [u]	Br	20	$C_{26}H_{27}N_7Br_2$	16·1	—	—	16·4	—	—	Red solid [v]
NH_2	Et	m-$NH_2{\cdot}C_6H_4$	Br [u]	Br [w]	22	$C_{27}H_{29}N_7Br_2,H_2O$ [t,x]	16·0	—	2·6	15·6	—	2·6	Red microcrystals [c]
NH_2	Me	p-Me·C_6H_4	I	Br	70	$C_{27}H_{28}N_6I_2$	12·0	—	36·3	12·2	36·8	—	Small red plates [c]
NH_2	Me	p-Me·C_6H_4	Cl	Br	64	$C_{27}H_{28}N_6Cl_2,6H_2O$ [t]	13·6	—	17·1	13·6	—	17·55	,, ,, [c]
NH_2	Me	p-$Pr^i{\cdot}C_6H_4$	I	Br	78	$C_{29}H_{32}N_6I_2$	11·9	36·0	—	11·7	35·4	—	Red microcrystals [v]
NH_2	Me	p-$Pr^i{\cdot}C_6H_4$	Cl	Br	65	$C_{29}H_{32}N_6Cl_2,6H_2O$ [t]	13·3	—	16·3	13·1	—	16·8	,, ,, [c]
NH_2	Allyl	p-$Pr^i{\cdot}C_6H_4$	I	Cl	65	$C_{31}H_{34}N_6I_2$	11·25	33·5	—	11·3	34·1	—	,, ,, [v]
NH_2	Me	p-Cl·C_6H_4	I	Cl	64	$C_{26}H_{25}N_6ClI_2$	11·9	37·4	—	11·8	37·75	—	,, ,, [v]
NH_2	Me	p-Cl·C_6H_4	Cl	Cl	51	$C_{26}H_{25}N_6Cl_3,6H_2O$ [t]	13·2	—	16·7	13·2	—	17·0	,, ,, [c]
NH_2	Me	p-MeO·C_6H_4	I	Br	69	$C_{27}H_{28}ON_6I_2$	12·3	35·8	—	11·9	36·0	—	Small red plates [c]
NH_2	Me	p-MeO·C_6H_4	Cl	Br	62	$C_{27}H_{28}ON_6Cl_2,6H_2O$ [t]	13·1	—	16·5	13·3	—	17·1	,, ,, [c]
NH_2	Me	p-Dimethylamino-styryl	I	Br	70	$C_{30}H_{33}N_7I_2$	12·9	33·4	—	13·15	34·1	—	Small purple-black plates [n]
NH_2	Me	p-Dimethylamino-styryl	Cl	Br	59	$C_{30}H_{33}N_7Cl_2,4H_2O$ [t]	15·6	—	11·1	15·5	—	11·35	,, ,, [n]
NH_2	Et	p-Dimethylamino-styryl	I	Cl	74	$C_{31}H_{30}N_7I_2$	12·7	33·7	—	12·9	33·5	—	,, ,, [n]
NH_2	Me	Me	I	Br	79	$C_{21}H_{24}N_6I_2$	13·5	42·0	—	13·7	41·4	—	Red plates [v]
NH_2	Me	Me	CH_3SO_3	Br	65	$C_{23}H_{30}N_6O_6S_2$	14·4	—	5·8	14·3	—	6·1	Red needles [c]
H	Me	Ph	I [y]	Br	82	$C_{26}H_{25}N_5I_2$	10·5	37·5	—	10·6	38·4	—	Yellow needles [i]
H	Me	Ph	CH_3SO_3 [z]	Br	62	$C_{28}H_{31}O_6N_5S_2,H_2O$ [aa]	11·0	—	6·2	11·0	—	5·7	Yellow plates [ab]

[a] M. p. >300° but shrinking occurred at 281°. [b] Compound dried at 100°. [c] From methanol. [d] Prepared from 7-amino-10-methyl-2-nitro-9-phenylphenanthridinium chloride. The intermediate condensation product was reduced with ferrous hydroxide. M. p. undepressed by admixture with previous compound. Also, the two compounds had identical infrared spectra and paper chromatograms (developed in butanol–water). [e] M. p. 238—240° (decomp.). [f] From methanol–ethylene dichloride. [g] M. p. 299° (decomp.). [h] Found: Br, 27·2. $C_{26}H_{26}N_6Br_2$ requires Br, 27·5%. [i] From water. [j] M. p. 245° (decomp.). [k] The compound formed a tetrahydrate on exposure to air (Found: N, 14·7; H_2O, 12·6. $C_{27}H_{28}N_6Cl_2,4H_2O$ requires N, 14·5; H_2O, 12·4%). [l] From water containing a little potassium iodide. [m] Prepared by ferrous hydroxide reduction of the foregoing nitropyrimidinylphenanthridine after metathesis with silver methanesulphonate. [n] From aqueous methanol. [o] Found: C, 53·9; H, 5·2. $C_{26}H_{25}O_2N_7Cl_2,2H_2O$ requires C, 54·0; H, 5·1%. [p] The compound formed a tetrahydrate on exposure to air (Found: H_2O, 12·2. $C_{26}H_{25}O_2N_7Cl_2,4H_2O$ requires H_2O, 11·8%). [q] The compound was also prepared from the mixture obtained from the nitropyrimidinylphenanthridine preparation. Metathesis with silver methanesulphonate was first carried out and the

filtrate, obtained on separation of the silver salts, was then reduced with ferrous hydroxide. The product was twice crystallised from methanol (Found, in compound dried at 100° and then exposed to air: N, 15·3; H_2O, 6·0. $C_{26}H_{27}N_7Br_2,2H_2O$ requires N, 15·5; H_2O, 5·7%). [r] Found: Br, 26·1. $C_{26}H_{27}N_7Br_2$ requires Br, 26·8%. [s] This compound formed a *dihydrate* on exposure to air for 2 days. Found: C, 49·4; H, 5·0; N, 15·6; H_2O, 6·3. $C_{26}H_{27}N_7Br_2,2H_2O$ requires C, 49·3; H, 4·9; N, 15·5; H_2O, 5·7%. [t] Compound dried at 100° and then exposed to air. [u] Prepared by Dr. J. S. Nicholson, from 2 : 7-diamino-10-methyl-9-*m*-nitrophenylphenanthridinium chloride. The intermediate nitropyrimidinylphenanthridine, isolated as a dichloride, was reduced with ferrous hydroxide. [v] From aqueous ethanol. [w] M. p. 263—265° (decomp.). [x] Found: Br, 25·7. $C_{27}H_{29}N_7Br_2,H_2O$ requires Br, 25·4%. [y] M. p. 301° (decomp.). [z] M. p. 303° (decomp.). [aa] Found: C, 52·6; H, 5·8. $C_{28}H_{31}O_6N_5S_2,H_2O$ requires C, 53·0; H, 5·5%. [ab] From ethanol.

TABLE 2. *Pyrimidinylphenanthridines* (V) *prepared from the bromides* (VIII; X = Br).

Substituent R	X	M. p. (decomp.)	Yield (%)	Formula	Found, % N	I	H_2O	Required, % N	I	H_2O	Description
Me	I	285°	85	$C_{21}H_{23}N_5I_2$	11·8	43·0	—	11·7	42·4	—	Small yellow plates [a]
Me	CH_3SO_3	306—308°	73	$C_{23}H_{29}O_6N_5S_2,H_2O$ [b]	12·5	—	2·9	12·6	—	3·25	Yellow plates [c]
Ph	I	293—294°	79	$C_{26}H_{25}N_5I_2$	10·8	38·5	—	10·6	—	38·4	Yellow needles [d]
Ph	CH_3SO_3	232°	66	$C_{28}H_{31}O_6N_5S_2$	11·6	—	—	11·7	—	—	Yellow needles [c]
p-NH_2·C_6H_4 [e]	I	295°	68	$C_{26}H_{26}N_6I_2$	12·5	38·2	—	12·3	37·5	—	Orange prisms [d]

[a] From water containing a little potassium iodide. [b] Compound dried at 100° and then exposed to air. [c] From methanol. [d] From water. [e] Prepared from the *p*-nitrophenyl compound; the intermediate 3-(2-amino-6-methyl-4-pyrimidinylamino)-9-*p*-nitrophenylphenanthridine 10 : 1′-dimethochloride was reduced in aqueous solution with ferrous hydroxide.

TABLE 3. *Dipyrimidinylphenanthridines* (IV).

Substituent R	X	Starting material	Yield (%)	Formula	Found, % N	I	H_2O	Required, % N	I	H_2O	Description
Ph	I	VII; R = Me, R^1 = NH_2, R^2 = Ph, X = Br	78	$C_{32}H_{34}N_9I_3$	13·8	41·3	—	13·6	41·7	—	Yellow plates [a]
Ph	Br	,, ,, ,,	—	$C_{32}H_{34}N_9Br_3$ [b]	15·9	—	—	16·1	—	—	Yellow needles [c]
p-NO_2·C_6H_4	I	VII; R = Me, R^1 = NH_2, R^2 = *p*-NO_2·C_6H_4, X = Br	82	$C_{32}H_{33}O_2N_{10}I_3,H_2O$ [d]	14·0	37·1	3·8	13·9	37·8	3·6	Orange microcrystals [e]
p-NH_2·C_6H_4	I [f]	—	79	$C_{32}H_{35}N_{10}I_3$	15·2	40·2	—	14·9	40·5	—	Small red plates [c]
p-Me·C_6H_4	I	III; R = NH_2, R^1 = Me, R^2 = *p*-Me·C_6H_4, X = Cl	78	$C_{33}H_{36}N_9I_3$	13·8	40·1	—	13·4	40·6	—	Orange microcrystals [a]
p-Me·C_6H_4	Cl	,, ,, ,,	—	$C_{33}H_{36}N_9Cl_3,6H_2O$ [g]	16·5	—	13·9	16·3	—	14·0	,, ,, [a]
p-Pr^i·C_6H_4	I	III; R = NH_2, R^1 = Me, R^2 = *p*-Pr^i·C_6H_4, X = Cl	81	$C_{35}H_{40}N_9I_3$	13·3	39·0	—	13·0	39·4	—	,, ,,
p-Pr^i·C_6H_4	Cl	,, ,, ,,	—	$C_{35}H_{40}N_9Cl_3,4H_2O$ [g]	16·2	—	9·5	16·45	—	9·45	,, ,,
p-Cl·C_6H_4	Cl	III; R = NH_2, R^1 = Me, R^2 = *p*-Cl·C_6H_4, X = Cl	75	$C_{32}H_{33}N_9Cl_4,6H_2O$ [g]	15·8	—	13·1	15·9	—	13·6	,, ,,
p-MeO·C_6H_4	I	III; R = NH_2, R^1 = Me, R^2 = *p*-MeO·C_6H_4, X = Cl	80	$C_{33}H_{36}ON_9I_3$	13·2	39·2	—	13·2	39·9	—	,, ,,
p-MeO·C_6H_4	Cl	,, ,, ,,	—	$C_{33}H_{36}ON_9Cl_3,2H_2O$ [h]	17·6	—	5·5	17·6	—	5·0	,, ,,
Me	I	VII; R = Me, R^1 = NH_2, R^2 = Me, X = Br	83	$C_{27}H_{32}N_9I_3$	14·3	44·3	—	14·6	44·1	—	Small red plates [a]
Me	Cl	,, ,, ,,	71	$C_{27}H_{32}N_9Cl_3,2H_2O$ [g,i]	20·1	—	6·2	20·2	—	5·8	,, ,, [a]

[a] From water containing a little potassium iodide. [b] Found: Br, 30·1. $C_{32}H_{34}N_9Br_3$ requires Br, 30·6%. [c] From methanol. [d] Compound dried at 100°. [e] From water. [f] Prepared by reduction with ferrous hydroxide of the previous nitro-compound. [g] Dried at 100° and then exposed to air. [i] Found: Cl, 16·5. $C_{27}H_{32}N_9Cl_3,2H_2O$ requires Cl, 17·05%.

product isolated as 3-*amino*-10-*methyl*-9-p-*nitrophenylphenanthridinium bromide* (from water containing a little ammonium bromide), yellow plates, m. p. 230° (decomp.) (Found: N, 10·4; Br, 19·2. $C_{20}H_{16}O_2N_3Br$ requires N, 10·2; Br, 19·5%).

Preparation of Pyrimidinylphenanthridines (III) *and* (V).

The phenanthridinium salt and 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (II) [23] (1 mol.) were heated in water containing hydrochloric acid (1 equiv.) for 45—60 min. The progress of the reaction was followed by potentiometric titration of the acid formed with sodium hydroxide solution. In one case (preparation of III; R = H, R^1 = Me, R^2 = Ph) the rate of formation of this acid was greater when 1 equiv. of acid was already present. In most preparations the product separated during this heating period, otherwise the solution was cooled. The solid, of mixed anion content, was collected and washed with water. It was then characterised, after metathesis, as follows: (*a*) the solid was dissolved in hot water and excess of potassium iodide added; the precipitated di-iodide was characterised as such, or converted by heating with a silver salt in aqueous or aqueous alcoholic solution or suspension into a more water-soluble salt or (*b*) the solid was refluxed in aqueous suspension with silver chloride, and a salt, which could be characterised, was then precipitated from the filtered solution. The compounds were purified by crystallisation from water, methanol, or ethanol, or mixtures of these. The *compounds* listed in Tables 1 and 2 were thus prepared. All m. p.s were >275° unless otherwise stated.

Preparation of Pyrimidinylphenanthridines (IV).

Attempted preparations of compounds of type (IV) by reaction of the phenanthridinium compound with 2 mols. of the pyrimidinium iodide (II) in water or in water containing 1 or 2 equivs. of hydrochloric acid gave products of indefinite melting point and analysis. The latter indicated, however, a higher nitrogen content than that expected for a monocondensation product.

The reaction proceeded smoothly in phenol. The phenanthridinium compound and the pyrimidine (II) (2 mols.) were heated in phenol (30—50 mols.) for 1 hr. at 140°. The cooled solution was poured into an excess of ether; the product quickly solidified, and was then well boiled out with ether to remove traces of phenol. Potassium iodide was added to an aqueous solution to precipitate the tri-iodide, which was crystallised from water. The bis-compound could also be prepared from 1 mol. of a monocondensation product (III; R = NH_2) and 1 mol. of the pyrimidine (II) in phenol for 1 hr. at 140°. The *products* are detailed in Table 3 (all m. p.s were >300°).

Preparation of the Pyrimidinylphenanthridine (VI).

2 : 7-*Diacetamido*-9-p-(2-*amino*-6-*methyl*-4-*pyrimidinylamino*)*phenylphenanthridine* 10 : 1′-*Dimethiodide*.—Prepared by heating 2 : 7-diacetamido-9-*p*-aminophenyl-10-methylphenanthridinium chloride (4 g.) [22] and the pyrimidine (II) in phenol for 1 hr. at 140°, the *iodide* formed brownish-red prisms (from water containing a little potassium iodide), m. p. >300° (Found: N, 13·0; I, 32·3. $C_{30}H_{31}O_2N_7I_2$ requires N, 12·65; I, 32·65%).

2 : 7-*Diamino*-9-p-(2-*amino*-6-*methyl*-4-*pyrimidinylamino*)*phenylphenanthridine* 10 : 1′-*Dimethiodide* (VI).—The foregoing compound was heated with boiling 2N-hydrochloric acid (45 min.). Adjustment of pH to 7 and addition of potassium iodide gave the required diamine as the *iodide* (3·4 g.), small dark-red prisms (from water containing a little potassium iodide), m. p. >300° (Found: N, 14·1; I, 36·2. $C_{26}H_{27}N_7I_2$ requires N, 14·2; I, 36·75%). The *methanesulphonate*, prepared from the iodide by metathesis, formed small purple prisms (from ethanol), m. p. 290° (decomp., slow heating) (Found, in compound dried at 100° and then exposed to air: N, 14·5; H_2O, 5·9. $C_{28}H_{33}O_6N_7S_2,2H_2O$ requires N, 14·8; H_2O, 5·4%).

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RESEARCH LABORATORIES,
BOOTS PURE DRUG CO. LIMITED, NOTTINGHAM.

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