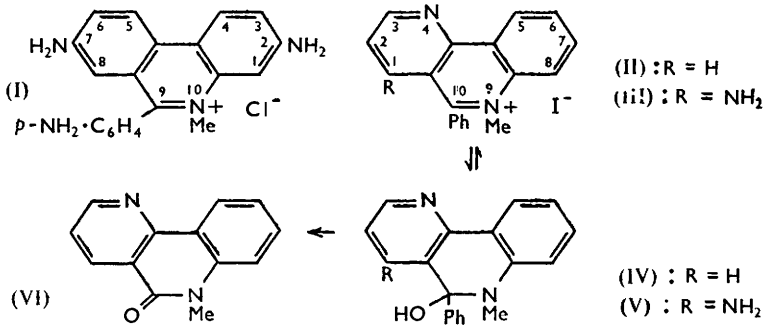
161. *A Search for New Trypanocides. Part V.* Some Derivatives of 10-Phenyl-4 : 9-diazaphenanthrene.*

By M. Davis.

Several quaternary salts derived from 10-phenyl-4 : 9-diazaphenanthrene, an aza-analogue of 9-phenylphenanthridine, have been prepared as potential trypanocides. Only three compounds showed weak activity against *Trypanosoma congolense* in mice. None was active against *T. rhodesiense*.

4 : 9-Diazaphenanthrene has features in common with both phenanthridine and 4-aminoquinoline and it was considered possible that suitably constituted derivatives might possess the trypanocidal activity shown by many compounds derived from these systems.[1]

Only a few 4 : 9-diazaphenanthrenes are recorded in the literature. Marckwald [2] applied the Skraup and Döbner–Miller reactions to 4-aminoquinaldine and obtained small amounts of 10-methyl- and 3 : 10-dimethyl-4 : 9-diazaphenanthrene. Lions and Ritchie [3] showed that 4-aminoquinaldine failed to undergo the Conrad–Limpach reaction, but reacted at 160° with acetoacetic ester, the resulting amide being cyclised by concentrated sulphuric acid to 3-hydroxy-1 : 10-dimethyl-4 : 9-diazaphenanthrene. Hauser and Reynolds [4] subjected 4-aminoquinoline to the Conrad–Limpach, Knorr, and ethoxymethylenemalonic ester syntheses, obtaining 1-hydroxy-3-methyl- and 3-hydroxy-1-methyl-4 : 9-diazaphenanthrene and ethyl 1-hydroxy-4 : 9-diazaphenanthrene-2-carboxylate, respectively.



In the phenanthridine series trypanocidal activity, which is perceptible even in 10-methyl-9-phenylphenanthridinium chloride, increases steadily as one, two, or three amino-groups are introduced (in appropriate positions) into the molecule, one of the most active compounds being Trimidium chloride [5] (I). It was decided, therefore, to prepare the analogous 9-methyl-10-phenyl-4 : 9-diazaphenanthrene 9-methiodide (II) and to

* Part IV, Ashley and Davis, *J.*, 1957, 812.

[1] *E.g.*, Walls, *J.*, 1950, 3511 and earlier papers; Jensch, *Annalen*, 1950, **568**, 73 and earlier papers; Pratt and Archer, *J. Amer. Chem. Soc.*, 1948, **70**, 4065.

[2] Marckwald, *Annalen*, 1894, **279**, 1.

[3] Lions and Ritchie, *J. Proc. Roy. Soc., New South Wales*, 1940, **74**, 443.

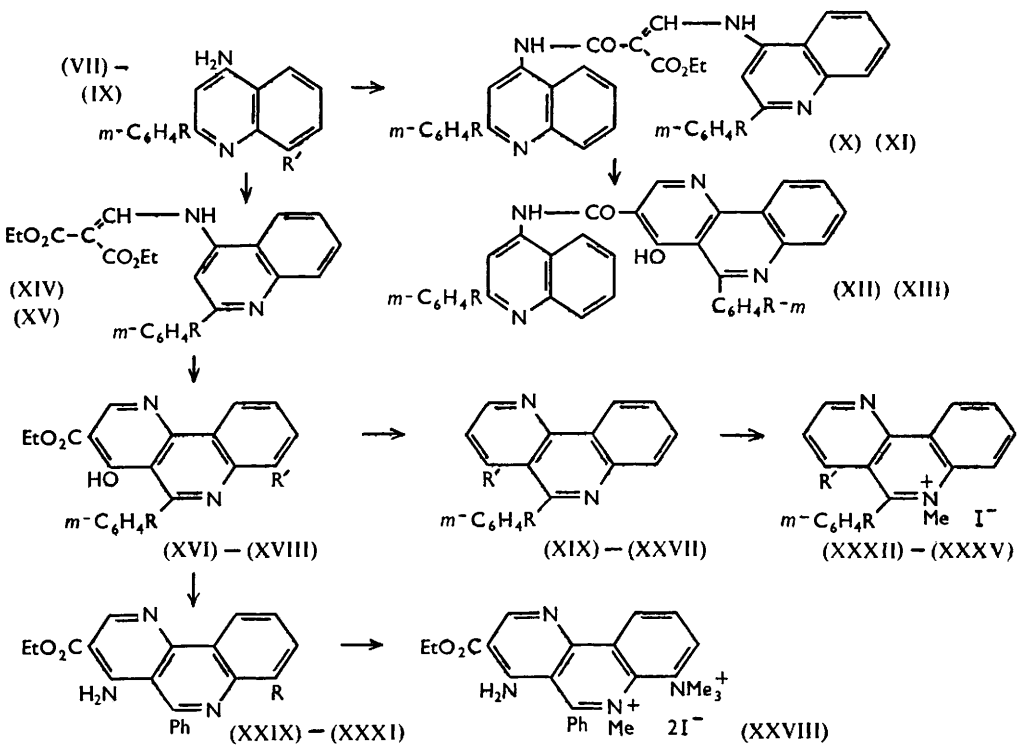
[4] Hauser and Reynolds, *J. Org. Chem.*, 1950, **15**, 1224.

[5] Walls and Whittaker, *J.*, 1950, 43.

investigate the effect of introducing amino- and ethoxycarbonylamino-groups into the molecule.

10-Phenyl-4 : 9-diazaphenanthrene was obtained in moderate yield from 4-amino-2-phenylquinoline (VII) by the Skraup reaction and was converted by excess of methyl iodide into a monomethiodide, considered to be (II). It is not the 4-methiodide because its aqueous solution with dilute ammonia afforded the water-insoluble pseudo-base (IV) which was unaffected by boiling alkaline ferricyanide but regenerated the original methiodide on treatment in dilute hydrochloric acid with potassium iodide.[6]

Introduction of an amino-group into the newly formed pyridine ring of the 4 : 9-diazaphenanthrene was next attempted, the 1-position being selected as being, not only the most accessible, but also capable of exhibiting the tautomerism characteristic of 4-aminoquinoline derivatives, some of which are active trypanocides.



	R	R′
VII	H	H
VIII	NO_2	H
IX	H	NO_2
X	H	
XI	NO_2	
XII	H	
XIII	NO_2	
XIV	H	
XV	NO_2	
XVI	H	H

	R	R′
XVII	NO_2	H
XVIII	H	NO_2
XIX	H	OH
XX	H	Cl
XXI	H	NH_2
XXII	H	OPh
XXIII	NO_2	Cl
XXIV	NO_2	OPh
XXV	NH_2, HCl	H

	R	R′
XXVI	NH_2	NH_2
XXVII	NH·CO_2Et	NH·CO_2Et
XXIX	NH_2	
XXX	NHAc	
XXXI	NH·CO_2Et	
XXXII	NHAc	NHAc
XXXIII	NMe_3}I	NH_2
XXXIV	NH_2	NH_2
XXXV	NH·CO_2Et	NH·CO_2Et

4-Amino-2-phenylquinoline failed to condense with acetoacetic ester in boiling ethanol (containing a catalytic amount of hydrochloric acid), but treatment with excess of the ester above 180° afforded 4-acetoacetamido-2-phenylquinoline in low yield. However, it reacted readily with ethoxymethylenemalonic ester in boiling xylene (although not in

[6] Cf. Petrow and Wragg, *J.*, 1947, 1410; 1950, 3516.

chloroform).[7] The expected diethyl (2-phenyl-4-quinolylaminomethylene)malonate (XIV) was accompanied by the monoamide (X), formed by interaction of the diester with a further molecule of the base; this was readily cyclised in boiling Dowtherm to the diazaphenanthrene amide (XII) which was also formed in appreciable amounts when 4-amino-2-phenylquinoline and ethoxymethylenemalonic ester were condensed together directly in boiling Dowtherm. Similar amides have been encountered during the preparation of 4-aminoquinoline from aniline.[8] Diethyl (2-phenyl-4-quinolylaminomethylene)malonate was cyclised in boiling Dowtherm to the diazaphenanthrene (XVI) which was hydrolysed and decarboxylated to 1-hydroxy-10-phenyl-4 : 9-diazaphenanthrene (XIX).

The corresponding 1-chloro-compound (XX), prepared from this phenol by phosphorus oxychloride, reacted with ammonia in boiling phenol,[9] giving the required 1-amino-10-phenyl-4 : 9-diazaphenanthrene (XXI). At a slightly lower temperature amination was incomplete and the 1-phenoxy-derivative (XXII) was also isolated. The amino-compound formed only a monomethiodide (III), the structure of which follows from its conversion by ammonia into the pseudo-base (V), which was oxidised by alkaline ferricyanide to the amide (VI), the phenyl group being eliminated.[6,10] 4-Aminoquinaldine was similarly converted into ethyl 1-hydroxy-10-methyl-4 : 9-diazaphenanthrene-2-carboxylate, although when the condensation was carried out directly in Dowtherm the only product isolated was the diazaphenanthrene amide analogous to (XII).

The trypanocides Phenidium chloride and Metidium chloride carry an amino-group in the *para*- and the *meta*-position, respectively, of the 9-phenyl substituents, in addition to the 7-amino-group in the phenanthridine nucleus. Preparation of a 10-*p*- or 10-*m*-aminophenyl-4 : 9-diazaphenanthrene was therefore undertaken. As large amounts of cinchophen (2-phenylquinoline-4-carboxylic acid) were available, its conversion into 4-amino-2-*m*- and 4-amino-2-*p*-nitrophenylquinoline was investigated.

Direct nitration of cinchophen was claimed[11] to give 2-*p*-nitrophenylquinoline-4-carboxylic acid, but no experimental details were recorded. Adding cinchophen to fuming nitric acid at room temperature gave a mixture of *m*- and *p*-nitro-derivatives, converted by the Curtius reaction into azides yielding pure 4-ethoxycarbonylamino-2-*m*- and -2-*p*-nitrophenylquinoline. Authentic specimens were prepared for comparison from pure samples of the *m*- and *p*-nitro-acid, which were obtained (in low yield) by the Döbner synthesis from the corresponding aldehydes.[11] Hydrolysis of the more readily available *m*-nitro-urethane furnished 4-amino-2-*m*-nitrophenylquinoline (VIII) which, in contrast to 4-amino-2-phenylquinoline, reacted only slowly and incompletely in boiling xylene with ethoxymethylenemalonic ester, giving a mixture of the ester (XV), amide (XI), and unchanged base. The condensation was therefore carried out directly in Dowtherm, a large excess of ethoxymethylenemalonic ester being employed to minimise the formation of the amide (XIII) which, however, was always present in considerable quantity. The principal product (XVII) was successively hydrolysed, decarboxylated, and chlorinated in the usual manner. Amination of 1-chloro-10-*m*-nitrophenyl-4 : 9-diazaphenanthrene (XXIII) in phenol at 190—200° gave only the 1-phenoxy-compound (XXIV) and longer heating at higher temperatures led to extensive decomposition. Preliminary catalytic reduction of the nitro-group was hence carried out, Raney nickel in ethanol being used since concomitant dehalogenation to 10-*m*-aminophenyl-4 : 9-diazaphenanthrene hydrochloride (XXV) was much less than when platinum oxide or palladium oxide was employed. 10-*m*-Aminophenyl-1-chloro-4 : 9-diazaphenanthrene, thus prepared, reacted normally with ammonia in phenol, giving the 1-amino-compound (XXVI) in almost quantitative yield. The diacetyl derivative of this base gave a monomethiodide,

[7] Cf. Steck, Hallock, and Suter, *J. Amer. Chem. Soc.*, 1948, **70**, 4063.
[8] Kermack and Storey, *J.*, 1950, 607.
[9] Backeberg and Marais, *J.*, 1942, 381; Albert, Brown, and Duewell, *J.*, 1948, 1284.
[10] Schofield and Theobald, *J.*, 1951, 2992.
[11] D.R.-P. 279,195.

considered to be (XXXII), which was hydrolysed to the required 1-amino-10-*m*-aminophenyl-4 : 9-diazaphenanthrene 9-methiodide (XXXIV).

The diamine (XXVI) with methyl iodide and sodium carbonate in methanol afforded a bismethiodide which is probably (XXXIII). The diamine gave the expected bisurethane (XXVII), which was likewise converted into its 9-methiodide (XXXV).

The highly active trypanocide Dimidium bromide contains amino-groups in the 2 : 7-positions of the phenanthridine system, the 9-phenyl group remaining unsubstituted. The preparation of a nuclear diamino-10-phenyldiazaphenanthrene was therefore investigated, although initially no attempt was made to obtain an exact positional analogue. 8-Nitro-2-phenylquinoline-4-carboxylic acid,[12] which is readily available, was converted by the Curtius reaction into 4-amino-8-nitro-2-phenylquinoline (IX). This with a large excess of ethoxymethylenemalonic ester in Dowtherm gave the diazaphenanthrene (XVIII) in good yield, no appreciable quantity of amide by-product being produced. The corresponding acid could not be satisfactorily decarboxylated in Dowtherm, either as the free acid or as the silver salt. Difficulties in the decarboxylation of 3-carboxy-4-hydroxyquinolines containing nitro-groups in the benzene ring have been previously encountered.[13] The remaining stages of the synthesis were therefore carried out on the ester (XVIII). This was successively chlorinated, aminated in phenol, and reduced catalytically to ethyl 1 : 8-diamino-10-phenyl-4 : 9-diazaphenanthrene-2-carboxylate (XXIX). The latter diamine formed a monoacetyl derivative and a monourethane, probably the 8-derivatives (XXX) and (XXXI) respectively. Neither derivative could be quaternised, probably for steric reasons.[14]

The original diamine (XXIX) gave a bismethiodide, probably (XXVIII).

In view of the low trypanocidal activity found with these compounds the original intention of preparing derivatives more closely related to the active phenanthridines was not further pursued.

The author thanks Mrs. R. Stone, B.Sc., for the following biological results: the methiodides (XXXIV), (XXXV), and (XXXVIII) were effective, but not curative against *T. congolense* in mice; they were inactive against *T. rhodesiense*. Compounds (II), (III), and (XXXIII), the hydrochlorides of (XIX), (XXI), (XXVI), (XXIX), and (XXXI), and the metho(methyl sulphate) of (XX) were inactive against both organisms.

Experimental

4-Acetoacetamido-2-phenylquinoline.—4-Amino-2-phenylquinoline [15] (0·5 g.) in excess of acetoacetic ester was boiled for 1 min., and the solution was cooled and evaporated *in vacuo*. Crystallisation of the residue from ethanol gave *4-acetoacetamido-2-phenylquinoline* (0·2 g.) in needles, m. p. 158—160° (Found: C, 74·5; H, 5·2; N, 9·0. $C_{19}H_{16}O_2N_2$ requires C, 75·0; H, 5·3; N, 9·2%). When 4-amino-2-phenylquinoline was boiled with excess of acetoacetic ester for 30—60 min. the sole product isolated was a compound which crystallised from aqueous acetone or pyridine in plates, m. p. 256—258° (Found: C, 79·9; H, 5·45; N, 7·6%), and was unaffected by concentrated sulphuric acid at 100°.

10-Phenyl-4 : 9-diazaphenanthrene.—A mixture of 4-amino-2-phenylquinoline (10 g.), arsenic pentoxide (10 g.), glycerol (20 g.), and concentrated sulphuric acid (20 g.) was heated at 145—155° for 5 hr. The resinous product was extracted successively with boiling water (250 ml.) and hot 2N-sulphuric acid (3 × 200 ml.). The combined extracts were basified and the precipitate was filtered off, washed, dried, and extracted with hot benzene (charcoal). The extracts were evaporated, giving *10-phenyl-4 : 9-diazaphenanthrene* (3·2 g.; m. p. 140—145°), which separated from methanol in prisms, or from light petroleum (b. p. 80—100°) in needles, m. p. 144—145° (Found: C, 84·7; H, 4·8; N, 10·5. $C_{18}H_{12}N_2$ requires C, 84·3; H, 4·7; N,

[12] Buchman, McCloskey, and Seneker, *J. Amer. Chem. Soc.*, 1947, **69**, 380.
[13] Baker, Lappin, Albisetti, and Riegel, *ibid.*, 1946, **68**, 1267.
[14] Cf. Caldwell and Walls, *J.*, 1948, 188.
[15] John, *Ber.*, 1926, **59**, 1447.

10·9%). The 9-*methiodide* (II) separated from chloroform in bright yellow plates (becoming orange on drying), m. p. 193° (decomp.) (Found: N, 6·6; I, 31·9. $C_{19}H_{15}N_2I$ requires N, 7·0; I, 31·9%). Treatment of the methiodide with aqueous ammonia and crystallisation of the product from benzene gave 9 : 10-*dihydro*-10-*hydroxy*-9-*methyl*-10-*phenyl*-4 : 9-*diazaphenanthrene* (IV), decomp. >148° (Found: C, 78·7; H, 5·7. $C_{19}H_{16}ON_2$ requires C, 79·1; H, 5·6%), also obtained by boiling the methiodide (0·1 g.) with potassium ferricyanide (0·3 g.) and 2N-sodium hydroxide (2 ml.) in water (10 ml.) for 20 min. Solutions of the pseudo-base exhibited blue fluorescence.

2-m-*Nitrophenylquinoline*-4-*carboxylic Acid*.—90% Pyruvic acid (6·6 g.) in ethanol (20 ml.) was added during 10 min. to a refluxing solution of aniline (6 g.) and *m*-nitrobenzaldehyde (10 g.) in ethanol (30 ml.). After a further 1·5 hr. the solution was cooled and filtered. Recrystallisation of the precipitate from acetic acid gave the acid (2·45 g.; 13%), m. p. 264—265° (Found: N, 9·4. Calc. for $C_{16}H_{10}O_4N_2$: N, 9·5%) (lit.,[11] m. p. 260°). A similar preparation using *p*-nitrobenzaldehyde yielded 2-*p*-nitrophenylquinoline-4-carboxylic acid (6%) m. p. 260—262° (decomp.) (Found: C, 65·2; H, 3·15; N, 9·6. Calc. for $C_{16}H_{10}O_4N_2$: C, 65·3; H, 3·4; N, 9·5%) (lit.,[11] m. p. 255—256°).

Nitration of 2-*Phenylquinoline*-4-*carboxylic Acid*.—The acid (200 g.) was slowly added to nitric acid (*d* 1·5; 500 ml.), stirred and cooled so that the temperature remained <30°. After 30 min., the solution was poured into water (4 l.) and the pH was adjusted to 5 with aqueous ammonia. The solid was filtered off, washed with water, and crystallised from acetic acid (4—6 l.), giving a mixture (122—154 g., 51—65%), m. p. 225—227°, of principally the 2-*m*- and the 2-*p*-nitrophenyl compound. No separation was achieved by recrystallisation from acetic acid, butanol, acetone, or dimethylformamide.

4-*Ethoxycarbonylamino*-2-m-*nitrophenylquinoline*.—(*a*) 2-*m*-Nitrophenylquinoline-4-carboxylic acid (0·8 g.; prepared from *m*-nitrobenzaldehyde) was refluxed with excess of thionyl chloride for 3 hr. and the solution was evaporated. The residue was triturated with ether and filtered, and the solid was suspended in acetone and treated with excess of aqueous sodium azide. After 5 min., sodium hydrogen carbonate solution was added and the azide was filtered off, washed with water, and dissolved in chloroform. The washed and dried chloroform solution was then slowly added to boiling absolute ethanol, the chloroform being continuously removed through a short column. The ethanol solution was boiled for 30 min., then concentrated, cooled, and filtered. Crystallisation of the product from chloroform gave the *urethane* in needles, m. p. 202—204° (Found: C, 63·3; H, 4·5; N, 12·8. $C_{18}H_{15}O_4N_3$ requires C, 64·1; H, 4·5; N, 12·5%).

8-Nitro-2-phenylquinoline-4-carboxylic acid [12] similarly gave 4-*ethoxycarbonylamino*-8-*nitro*-2-*phenylquinoline* (41%), needles, m. p. 200° (Found: C, 64·0; H, 4·3; N, 12·5. $C_{18}H_{15}O_4N_3$ requires C, 64·1; H, 4·5; N, 12·5%), from ethanol or chloroform.

(*b*) The mixture (80 g.) of acids obtained by nitration of 2-phenylquinoline-4-carboxylic acid was similarly converted into the urethane. Crystallisation of the product from chloroform gave the *m*-nitro-urethane (22·65 g., 27%), m. p. 196—198°, raised by recrystallisation to 203—204° (not depressed on admixture with an authentic specimen). Evaporation of the mother-liquors and repeated crystallisation of the residue from acetone gave a small amount of 4-*ethoxycarbonylamino*-2-p-*nitrophenylquinoline* in needles, m. p. 197—198° (Found: C, 64·3; H, 4·55; N, 12·6. $C_{18}H_{15}O_4N_3$ requires C, 64·1; H, 4·5; N, 12·5%), depressed to <180° by the *m*-isomer but not depressed by a specimen, m. p. 195—197°, prepared from the authentic *p*-nitro-acid.

(*c*) The mixed nitro-acids (25 g.) were converted into the ethyl ester (24·6 g.), m. p. 95—98° (Found: C, 67·0; H, 4·4; N, 8·55. Calc. for $C_{18}H_{14}O_4N_2$: C, 67·0; H, 4·4; N, 8·7%), from acetone–50% ethanol. The mixed esters (30 g.) and hydrazine hydrate (7·1 g.) in pentan-1-ol (120 ml.) were refluxed for 20 hr. The hydrazide (19·5 g.), after crystallisation from ethanol, had m. p. 242—245° (Found: C, 62·2; H, 4·25; N, 17·8. Calc. for $C_{16}H_{12}O_3N_4$: C, 62·3; H, 3·9; N, 18·2%). A solution of this hydrazide (20 g.) in 0·68N-hydrochloric acid (95 ml.) and acetic acid (210 ml.) was stirred and cooled to 10°. 0·5N-Sodium nitrite (130 ml.) was added dropwise and the mixture was stirred for a further 0·75 hr. and diluted with water. The precipitated azide was converted into the urethane as previously described, giving 6·35 g. of *m*-nitrophenyl isomer, m. p. 200° (softens 194°) (Found: C, 63·8; H, 4·7; N, 12·7%).

Ethyl 8-nitro-2-phenylquinoline-4-carboxylate [12] similarly yielded successively the *hydrazide* (87%), m. p. 226—228° (Found: C, 62·4; H, 4·1; N, 17·5. $C_{16}H_{12}O_3N_4$ requires C, 62·3; H, 3·9; N, 18·2%), and the urethane (32%), m. p. 202—204°.

2-m-*Aminophenyl*-4-*ethoxycarbonylaminoquinoline*.—The nitro-compound was reduced over Raney nickel in ethanol. The *amine* separated from chloroform–light petroleum (b. p. 40—60°) in needles, m. p. 180—181° (Found: C, 69·9; H, 5·8; N, 13·7. $C_{18}H_{17}O_2N_3$ requires C, 70·3; H, 5·6; N, 13·7%). The *acetyl* derivative formed needles, m. p. 191—192° (Found: N, 11·8. $C_{20}H_{19}O_3N_3$ requires N, 12·0%), from chloroform.

4-*Amino*-2-m-*nitrophenylquinoline* (VIII).—A mixture of 4-ethoxycarbonylamino-2-*m*-nitrophenylquinoline (16 g.) and concentrated hydrochloric acid (400 ml.) was refluxed overnight, then cooled, and the hydrochloride was filtered off. A suspension of the hydrochloride in dilute aqueous sodium hydroxide was stirred for 15 min. at 100°, cooled, and filtered. Crystallisation of the product from aqueous acetone gave the *amine* (11·25 g., 89%; m. p. 296°) which formed needles or plates, m. p. either 206—208° or 304—306° (melts and resolidifies <200°) (Found: C, 68·1; H, 4·4; N, 15·85. $C_{15}H_{11}O_2N_3$ requires C, 67·9; H, 4·2; N, 15·85%), from ethanol or chloroform.

Similar hydrolysis of 4-ethoxycarbonylamino-8-nitro-2-phenylquinoline gave 4-*amino*-8-*nitro*-2-*phenylquinoline* (IX) (78%), yellow prisms (from chloroform) or plates (from aqueous acetone), m. p. 144—146° (Found: C, 67·8; H, 4·2; N, 15·5. $C_{15}H_{11}O_2N_3$ requires C, 67·9; H, 4·2; N, 15·85%). The *hydrochloride*, yellow prisms from ethanol, decomposed at 290—300° (Found: C, 59·5; H, 4·1; N, 13·4; Cl, 11·7. $C_{15}H_{11}O_2N_3$,HCl requires C, 59·7; H, 4·0; N, 13·9; Cl, 11·8%).

Condensation of 4-*Aminoquinolines with Ethoxymethylenemalonic ester*.—(*a*) A solution of 4-amino-2-phenylquinoline (15 g.) and ethoxymethylenemalonic ester (17 g.) in xylene (200 ml.) was boiled for 3·5 hr. The residue obtained on evaporation under reduced pressure was crystallised from ethanol, giving *diethyl* (2-*phenyl*-4-*quinolylaminomethylene*)*malonate* (XIV) (19·2 g.; m. p. 118—122°) in rectangular plates, m. p. 123—124° (Found: C, 70·6; H, 5·7; N, 7·1. $C_{23}H_{22}O_4N_2$ requires C, 70·8; H, 5·7; N, 7·2%). In a similar experiment (but using only 15 g. of ester and boiling for 6 hr.) there was obtained in addition to the above ester (12·6 g.; m. p. 120—123°) an ethanol-insoluble compound (5 g., m. p. 237—240°), probably *ethyl* β-(2-*phenyl*-4-*quinolylamino*)-α-(2-*phenyl*-4-*quinolylcarbamoyl*)*acrylate* (X), which separated from chloroform in long prisms, m. p. 238—239° (Found : C, 75·3; H, 4·9; N, 9·6. $C_{36}H_{28}O_3N_4$,0·5H_2O requires C, 75·4; H, 5·1; N, 9·8%). Cyclisation of this compound is described below.

(*b*) A similar condensation, using 4-amino-2-*m*-nitrophenylquinoline, yielded *ethyl* β-(2-m-*nitrophenyl*-4-*quinolylamino*)-α-(2-m-*nitrophenyl*-4-*quinolylcarbamoyl*)*acrylate* (XI), prisms, m. p. 276° (decomp.) (Found: N, 12·9. $C_{36}H_{26}O_7N_6$ requires N, 12·8%), from ethanol, and *diethyl* (2-m-*nitrophenyl*-4-*quinolylaminomethylene*)*malonate* (XV), prisms, m. p. 180—182° (softens 176°) (Found: N, 9·7. $C_{23}H_{21}O_6N_3$ requires N, 9·65%), from ethanol.

(*c*) 4-Aminoquinaldine likwise gave *diethyl* 2-*methyl*-4-*quinolylaminomethylenemalonate*, m. p. 103—105° (Found: C, 66·1; H, 6·1; N, 8·75. $C_{18}H_{20}O_4N_2$ requires C, 65·8; H, 6·2; N, 8·5%), from ethanol.

Cyclisation of the Aminomethylenemalonic Esters to 4 : 9-*Diazaphenanthrenes*.—(*a*) Diethyl (2-phenyl-4-quinolylaminomethylene)malonate (XIV) (12·6 g.) was boiled with Dowtherm for 15 min. The cooled solution was diluted with light petroleum (b. p. 40—60°), and the precipitate was collected and recrystallised from benzene–light petroleum (b. p. 40—60°), yielding *ethyl* 1-*hydroxy*-10-*phenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate* (XVI) (10·6 g.; m. p. 235—240°), which formed blades, m. p. 252—254° (Found: C, 72·8; H, 4·8; N, 8·1. $C_{21}H_{16}O_3N_2$ requires C, 73·3; H, 4·7; N, 8·1%), from ethanol.

(*b*) Diethyl 2-methyl-4-quinolylaminomethylenemalonate similarly gave *ethyl* 1-*hydroxy*-10-*methyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate*, m. p. 208—210° (Found: C, 66·2; H, 5·4; N, 10·0. $C_{16}H_{14}O_3N_2$,0·5H_2O requires C, 66·0; H, 5·2; N, 9·6%).

Direct Formation of 4 : 9-*Diazaphenanthrenes from* 4-*Aminoquinolines and Ethoxymethylenemalonic Ester*.—(*a*) A solution of 4-amino-2-phenylquinoline (11 g.) and ethoxymethylenemalonic ester (10·8 g.) in Dowtherm (150 ml.) was heated at 130° for 1 hr., then boiled for 30 min., cooled, and diluted with light petroleum (b. p. 40—60°). Next morning the precipitate was collected and repeatedly crystallised from ethanol and from benzene–light petroleum (b. p. 40—60°), giving the diazaphenanthrene (XVI) (6·7 g.; m. p. 240—248°) together with a sparingly soluble compound (2·3 g.), probably 1-*hydroxy*-10-*phenyl*-2-(2-*phenyl*-4-*quinolylcarbamoyl*)-4 : 9-*diazaphenanthrene* (XII), which separated from pyridine in needles, m. p. 345—348° (decomp.) (Found: C, 77·5; H, 4·8; N, 10·4. $C_{34}H_{22}O_2N_4$,0·5H_2O requires C, 77·3; H, 4·4; N, 10·6%). The same compound was formed by cyclisation in Dowtherm of the

corresponding acrylate, m. p. 238—239°, described above. It was unaffected when boiled for several hours with concentrated hydrochloric acid or sodium hydroxide, but yielded an amorphous *chloro-derivative* (Found: Cl, 5·8. $C_{34}H_{21}ON_4Cl$ requires Cl, 6·6%) with phosphorus oxychloride.

(*b*) After a similar experiment with 4-amino-2-*m*-nitrophenylquinoline (but boiling for 10 min.), the precipitate was collected, dissolved in chloroform, and filtered from 1-*hydroxy*-10-m-*nitrophenyl*-2-(2-m-*nitrophenyl*-4-*quinolylcarbamoyl*)-4 : 9-*diazaphenanthrene* (XIII), prisms, decomp. 345° (Found: C, 66·75; H, 3·4; N, 13·4. $C_{34}H_{20}O_6N_6$ requires C, 67·1; H, 3·3; N, 13·8%), which could not be satisfactorily recrystallised. The chloroform solution was filtered through a short column of alumina, which was washed with more solvent. The combined filtrates were concentrated and diluted with light petroleum (b. p. 40—60°), yielding *ethyl* 1-*hydroxy*-10-m-*nitrophenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate* (XVII) (56%), which formed prisms, m. p. 284—286° (decomp.) (Found: C, 63·8; H, 3·8; N, 10·3. $C_{21}H_{15}O_5N_3,0·5H_2O$ requires C, 63·7; H, 4·1; N, 10·6%), from ethanol. In other experiments the yield varied from 50 to 89%.

(*c*) 4-Amino-8-nitro-2-phenylquinoline likewise yielded *ethyl* 1-*hydroxy*-8-*nitro*-10-*phenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate* (XVIII) (72%), which after chromatography in benzene and recrystallisation from chloroform–benzene formed plates, m. p. 290—292° (decomp.) (Found: C, 65·1; H, 3·7; N, 10·9. $C_{21}H_{15}O_5N_3$ requires C, 64·7; H, 3·9; N, 10·8%). The pure nitro-compound is sparingly soluble in benzene. Reduction of the nitro-compound over platinum oxide in ethyl acetate, or Raney nickel in ethanol, and crystallisation of the product from chloroform–ether, gave *ethyl* 8-*amino*-1-*hydroxy*-10-*phenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate*, m. p. 274—276° (decomp.) (Found: N, 12·0. $C_{21}H_{17}O_3N_3$ requires N, 11·7%).

(*d*) In a similar experiment with 4-aminoquinaldine, the only product isolated was 1-*hydroxy*-10-*methyl*-2-(2-*methyl*-4-*quinolylcarbamoyl*)-4 : 9-*diazaphenanthrene* which formed yellow needles, m. p. >320° (Found: C, 68·7; H, 4·9; N, 13·7. $C_{24}H_{18}O_2N_4,1·5H_2O$ requires C, 68·4; H, 5·0; N, 13·3%), from pyridine.

Hydrolysis of 4 : 9-*Diazaphenanthrene*-2-*carboxylic Esters and Thermal Decarboxylation of the Derived Acids.*—(*a*) Ethyl 1-hydroxy-10-phenyl-4 : 9-diazaphenanthrene-2-carboxylate (5·65 g.) was boiled with 2N-sodium hydroxide (100 ml.) for 2 hr. The hot solution was filtered (charcoal) and the filtrate was acidified with acetic acid. The precipitated 2-*carboxylic acid* (4·7 g., 91%) was washed with boiling water and dried. An analytical specimen, recrystallised from nitrobenzene, had m. p. >360° (Found: C, 71·9; H, 3·9; N, 9·0. $C_{19}H_{12}O_3N_2$ requires C, 72·2; H, 3·8; N, 8·9%). The foregoing acid (11·1 g.) was slowly added to boiling Dowtherm (400 ml.), boiling being continued until a clear solution was obtained (0·75—1 hr.). 1-*Hydroxy*-10-*phenyl*-4 : 9-*diazaphenanthrene* (XIX) (9·2 g., 96%), which crystallised from the cooled solution, was filtered off, washed with benzene and ether, and dried. It was pure enough for chlorination. A specimen recrystallised from ethanol formed prisms, m. p. >340° (Found: C, 79·3; H, 4·5; N, 10·1. $C_{18}H_{12}ON_2$ requires C, 79·5; H, 4·5; N, 10·3%). The *hydrochloride* separated from a mixture of acetic and 2N-hydrochloric acid in prisms, m. p. 345—346° (decomp.) (Found: N, 9·3; Cl, 11·7. $C_{18}H_{12}ON_2,HCl$ requires N, 9·1; Cl, 11·5%).

(*b*) 1-Hydroxy-10-*m*-nitrophenyl-4 : 9-diazaphenanthrene-2-carboxylic acid (60—80%; used without purification) and 1-*hydroxy*-10-m-*nitrophenyl*-4 : 9-*diazaphenanthrene* (73—88%), m. p. 334—336° (decomp.) (Found: C, 68·0; H, 3·8; N, 13·1. $C_{18}H_{11}O_3N_3$ requires C, 68·1; H, 3·5; N, 13·25%), were similarly obtained.

Formation of 1-*Amino*-4 : 9-*diazaphenanthrenes from* 1-*Hydroxy*-4 : 9-*diazaphenanthrenes* via *the* 1-*Chloro-derivatives.*—(*a*) 1-Hydroxy-10-phenyl-4 : 9-diazaphenanthrene (2·05 g.) was boiled with phosphorus oxychloride (15 ml.) for 15 min. The residue obtained after removal of excess of reagent *in vacuo* was treated with dilute aqueous sodium hydroxide, and the precipitate (1·9 g., 87%; m. p. >170°) was collected, washed, and dried. Recrystallisation from ethanol gave 1-*chloro*-10-*phenyl*-4 : 9-*diazaphenanthrene* (XX) in needles, m. p. 176—178° (Found: N, 9·3; Cl, 12·2. $C_{18}H_{11}N_2Cl$ requires N, 9·6; Cl, 12·2%). The *metho*(*methyl sulphate*), prepared in boiling toluene and purified from methanol–ether, had m. p. 170—180° (decomp.) (Found: N, 6·7. $C_{20}H_{17}O_4N_2ClS$ requires N, 6·7%). A solution of the chloro-compound (5 g.) in phenol (50 g.) was heated at 180—200° while a rapid stream of ammonia was passed in for 7·5 hr. After the removal of phenol by steam-distillation the solution was basified and the precipitate was filtered off, washed, and dried. Crystallisation of the product from benzene gave 1-*amino*-10-*phenyl*-4 : 9-*diazaphenanthrene* (XXI) (4·1 g., 88%; m. p. 218—220°) which separated from

ethanol in plates, m. p. 224° (Found: C, 79·7; H, 5·4; N, 15·3. $C_{18}H_{13}N_3$ requires C, 79·7; H, 4·8; N, 15·5%). The *hydrochloride* had m. p. 294—295° (Found: N, 13·1; Cl, 11·9. $C_{18}H_{13}N_3$,HCl requires N, 13·6; Cl, 11·6%). The *methiodide* (89%) formed yellow prisms, m. p. 236—238° (decomp.) (Found: N, 10·2; I, 30·7. $C_{19}H_{16}N_3I$ requires N, 10·2; I, 30·7%). Treatment of the methiodide with aqueous ammonia and purification of the precipitate from benzene–light petroleum (b. p. 40—60°) gave 1-*amino*-9 : 10-*dihydro*-10-*hydroxy*-9-*methyl*-10-*phenyl*-4 : 9-*diazaphenanthrene* (V), an amorphous solid, decomp. >90° (Found: N, 14·0. $C_{19}H_{17}ON_3$ requires N, 13·9%), which showed strong green fluorescence in solution. When the methiodide (0·5 g.) in water (50 ml.) was boiled for 15 min. with potassium ferricyanide (1·5 g.) and 2N-sodium hydroxide (10 ml.), and the insoluble product was purified from benzene–light petroleum and sublimed at 180°/0·05 mm., 1-*amino*-9 : 10-*dihydro*-9-*methyl*-10-*oxo*-4 : 9-*diazaphenanthrene* (VI) was obtained as prisms, m. p. 178—179° (Found: C, 68·7; H, 4·85; N, 18·6. $C_{13}H_{11}ON_3$ requires C, 69·3; H, 4·9; N, 18·7%).

(*b*) 1-*Chloro*-10-m-*nitrophenyl*-4 : 9-*diazaphenanthrene* (XXIII), similarly prepared (67%), formed prisms, m. p. 216—219° (Found: N, 12·5; Cl, 10·6. $C_{18}H_{10}O_2N_3Cl$ requires N, 12·5; Cl, 10·6%), from chloroform–light petroleum (b. p. 40—60°). A suspension of 1-chloro-10-*m*-nitrophenyl-4 : 9-diazaphenanthrene (3·2 g.) and Raney nickel in warm ethanol (200 ml.) was shaken with hydrogen. When the theoretical uptake had occurred (3·25 hr.) the suspension was filtered and the catalyst was washed with chloroform. The combined filtrates were evaporated and a solution of the residue in chloroform was filtered through alumina (to remove by-product; see below), concentrated, and diluted with ether, giving 10-m-*aminophenyl*-1-*chloro*-4 : 9-*diazaphenanthrene* (2·25 g., 77%) in prisms, m. p. 202—204° (Found: N, 13·75; Cl, 11·7. $C_{18}H_{12}N_3Cl$ requires N, 13·7; Cl, 11·7%). When the reduction was carried out over platinum oxide, a considerable amount of 10-m-*aminophenyl*-4 : 9-*diazaphenanthrene hydrochloride* (XXV), prisms (from ethanol), m. p. >360° (Found: N, 12·5; Cl, 11·15. $C_{18}H_{13}N_3$,HCl,H_2O requires N, 12·9; Cl, 10·9%), was formed as by-product.

10-*m*-Aminophenyl-1-chloro-4 : 9-diazaphenanthrene was aminated in the usual way. Crystallisation of the product from chloroform gave 1-*amino*-10-m-*aminophenyl*-4 : 9-*diazaphenanthrene* (XXVI) (97%, m. p. 233—234°) which formed prisms, m. p. 221° and 236—238° (Found: C, 75·1; H, 4·85; N, 19·7. $C_{18}H_{14}N_4$ requires C, 75·5; H, 4·9; N, 19·6%), from benzene. The base formed a *trihydrochloride* (Found: N, 14·0; Cl, 27·6. $C_{18}H_{14}N_4$,3HCl requires N, 14·2; Cl, 27·0%) and a *diacetyl* derivative, which separated from ethanol in rhombs, m. p. 288—290° (Found: C, 71·0; H, 5·45; N, 14·8. $C_{22}H_{18}O_2N_4$ requires C, 71·3; H, 4·9; N, 15·1%). The diacetyl derivative with excess of methyl iodide gave the 9-*methiodide* (84%), which formed yellow prisms, m. p. 284—286° (Found: N, 10·9; I, 23·6. $C_{23}H_{21}O_2N_4I$ requires N, 10·9; I, 24·8%), from methanol–ether.

(*c*) *Ethyl* 1-*chloro*-8-*nitro*-10-*phenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate* (93%) formed needles, m. p. 182° (Found: N, 9·9; Cl, 8·35. $C_{21}H_{14}O_4N_3Cl$ requires N, 10·3; Cl, 8·7%), from chloroform–ether. It was converted into *ethyl* 1-*amino*-8-*nitro*-10-*phenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate* (75%) which was crystallised from chloroform–light petroleum, giving needles, m. p. 217—219° (Found: C, 65·25; H, 4·35; N, 14·5. $C_{21}H_{16}O_4N_4$ requires C, 64·95; H, 4·2; N, 14·4%).

1-*Phenoxy*-10-*phenyl*-4 : 9-*diazaphenanthrene* (XXII).—Ammonia was passed for 3·5 hr. into a solution of 1-chloro-10-phenyl-4 : 9-diazaphenanthrene (1·75 g.) in phenol (10 g.) maintained at 180°. The product, isolated in the usual way, was crystallised twice from ethanol, giving the *phenoxy-compound* (0·6 g.) in long prisms, m. p. 182° (Found: C, 81·1; H, 4·6; N, 8·1. $C_{24}H_{16}ON_2$,0·5H_2O requires C, 80·7; H, 4·8; N, 7·8%). From the mother-liquors was obtained some of the amino-compound, m. p. 224°.

10-m-*Nitrophenyl*-1-*phenoxy*-4 : 9-*diazaphenanthrene* (XXIV).—The 1-chloro-compound (0·6 g.) in phenol (10 g.) at 190—200° was treated with ammonia for 5·5 hr. and the product was isolated in the usual way. The 1-*phenoxy-compound* (0·25 g.; m. p. 168—170°) formed prisms, m. p. 177—179° (Found: N, 10·6. $C_{24}H_{15}O_3N_3$ requires N, 10·7%), on recrystallisation from aqueous ethanol and from benzene.

1-*Amino*-10-m-*aminophenyl*-4 : 9-*diazaphenanthrene* 9-*Methiodide* (XXXIV).—1-Acetamido-10-*m*-acetamidophenyl-4 : 9-diazaphenanthrene methiodide (1·1 g.) was refluxed with concentrated hydrochloric acid (20 ml.) for 4 hr. and the solution was evaporated *in vacuo*. A solution of the residue in hot water was filtered (charcoal), adjusted to pH 7 with sodium hydrogen carbonate, treated with sodium iodide, and cooled. The *methiodide* (0·8 g.)

was filtered off, washed with a little cold water, and crystallised from methanol–ether (Found: N, 12·45; I, 27·8. $C_{19}H_{17}N_4I,H_2O$ requires N, 12·55; I, 28·4%).

1-*Amino*-10-m-*dimethylaminophenyl*-4 : 9-*diazaphenanthrene* 3′ : 9-*Dimethiodide* (XXXIII).—A mixture of 1-amino-10-*m*-aminophenyl-4 : 9-diazaphenanthrene (1·19 g.), anhydrous sodium carbonate (0·44 g.), and methyl iodide (30 ml.) in methanol (30 ml.) was refluxed for 20 hr., concentrated, cooled, and filtered. The *dimethiodide* (1·2 g., 48%) separated from methanol in irregular prisms (Found: N, 9·6; I, 42·0. $C_{22}H_{24}N_4I_2$ requires N, 9·4; I, 42·4%).

1-*Ethoxycarbonylamino*-10-m-*ethoxycarbonylaminophenyl*-4 : 9-*diazaphenanthrene* 9-*Methiodide*.—A mixture of 1-amino-10-*m*-aminophenyl-4 : 9-diazaphenanthrene (1 g.), ethyl chloroformate (1 g.) and diethylaniline (1·2 g.) in dry ethanol (50 ml.) was refluxed for 2 hr. and evaporated, and the residue was diluted with water, basified with ammonia, and extracted with chloroform. The dried extract was filtered through alumina, the filtrate was evaporated, and the residue was triturated with light petroleum (b. p. 40—60°). The amorphous product (1 g.) was heated with methyl iodide at 110°, yielding the *methiodide* (XXXV) (0·6 g.), decomp. 190—200° (Found: I, 21·8. $C_{25}H_{25}O_4N_4I$ requires I, 22·2%).

1 : 8-*Diamino*-2-*ethoxycarbonyl*-10-*phenyl*-4 : 9-*diazaphenanthrene* (XXIX).—The 8-nitro-compound was reduced catalytically (Raney nickel) in ethanol, giving the *diamine* (84%) as yellow rhombs, m. p. 213° (Found: N, 15·4. $C_{21}H_{18}O_2N_4$ requires N, 15·6%), from ethanol. The *hydrochloride* formed orange rhombs (Found: N, 12·8; Cl, 12·7. $C_{21}H_{18}O_2N_4,1·5HCl,H_2O$ requires N, 13·0; Cl, 12·4%). The 8-*acetyl derivative* (XXX), prepared by treatment with acetic anhydride–pyridine at 90°, formed needles, m. p. 207—208° or 233—235° (Found: C, 69·0; H, 5·2; N, 14·0. $C_{23}H_{20}O_3N_4$ requires C, 69·0; H, 5·0; N, 14·0%), from chloroform–light petroleum (b. p. 40—60°). The 8-*ethoxycarbonyl derivative* (XXXI) (1·1 g., 92%), prepared by refluxing a mixture of the diamine (1 g.), ethyl chloroformate (0·5 g.), and diethylaniline (0·6 g.) in dry ethanol (50 ml.) for 1 hr., separated from chloroform–ethanol in needles, m. p. 200° (Found: C, 66·5; H, 4·95; N, 12·9; OEt, 20·8. $C_{24}H_{22}O_4N_4$ requires C, 66·9; H, 5·2; N, 13·0; OEt, 20·9%). Its *hydrochloride* crystallised from ethanol in plates, m. p. 248—250° (decomp.) (Found: N, 11·95; Cl, 7·45. $C_{24}H_{22}O_4N_4,HCl$ requires N, 12·0; Cl, 7·6%).

1 : 8-*Diamino*-10-*phenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylic acid*, obtained by hydrolysis of the corresponding ethyl ester, formed yellow needles, m. p. 286° (decomp.) (Found: C, 68·6; H, 4·5; N, 16·4. $C_{19}H_{14}O_2N_4,0·25H_2O$ requires C, 68·1; H, 4·2; N, 16·7%), from aqueous ethanol.

Ethyl 1-*Amino*-8-*dimethylamino*-10-*phenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate* 8 : 9-*Dimethiodide* (XXVIII).—Ethyl 1 : 8-diamino-10-phenyl-4 : 9-diazaphenanthrene-2-carboxylate (0·716 g.), sodium carbonate (0·212 g.), excess of methyl iodide, and methanol were refluxed for 18 hr., then evaporated. The residue was triturated with acetone and filtered, and the solid crystallised from methanol, giving the *dimethiodide* (1·25 g., 93%) in yellow prisms, m. p. 150—152° (decomp.) (Found: N, 8·35; I, 38·5. $C_{25}H_{28}O_2N_4I_2$ requires N, 8·35; I, 37·9%).

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