216. *Attempts to find New Antimalarials. Part XXVIII.* p-*Phenanthroline Derivatives substituted in the* 4-*Position.*

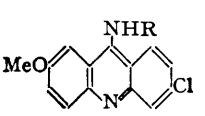
By Bryce Douglas and William O. Kermack.

The ethyl ethoxymethylenemalonate method has been employed for the synthesis of 4-chloro-, 4 : 9-dichloro-, and 4 : 5-dichloro-*p*-phenanthroline. In the first two of these, the chlorine atom has been replaced by a basic side chain, and the resulting compounds exhibit considerable activity against *P. gallinaceum* in chicks. The base obtained from 4 : 5-dichloro-*p*-phenanthroline and 3-diethylaminopropylamine is probably 4 : 5-(3′-diethylaminopropylimino)-*p*-phenanthroline (VIII). The relation of the active *p*-phenanthroline compounds to the antimalarials of the mepacrine, chloroquine, and benz- and pyridino-acridine classes is discussed.

It has been shown that when a pyridine ring is fsued on to a compound of the mepacrine type (I) so as to form a derivative of pyridino-3 : 4 : 2′ : 3′-acridine (II), the resulting base shows antimalarial activity (*J.*, 1946, 150; 1947, 678; 1948, 123). The activity of mepacrine is very

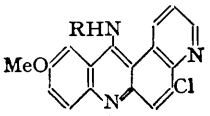
much reduced if the chlorine atom in position 2 is removed. Similarly, the pyridinoacridine derivatives are fairly highly active if they contain a chlorine atom in position 2 or 8, or in both positions, but retain only feeble activity when devoid of chlorine atoms.

It will be observed that all the more active compounds referred to above, including mepacrine itself, are derivatives of the very highly active chloroquine type (III); that is, they can be regarded as derived from 4-dialkylaminoalkylamino-7-chloroquinoline. These facts suggest that in this class of antimalarial compound, the chloroquine structure has some basic significance. Now, it is to be observed that in the active pyridoacridine compound, we may remove the benzene ring and still retain the chloroquine structure. In this way, in fact, we reach a derivative of *p*-phenanthroline of the type (IV). Such a *p*-phenanthroline derivative may be regarded as formed by the fusion of a pyridine ring to chloroquine; thus (IV) bears much the same relation to chloroquine as the active pyridinoacridines do to mepacrine.

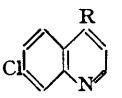


(I.)

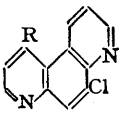
R = ·CHMe·[CH$_2$]$_3$·NEt$_2$·



(II.)



(III.)



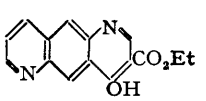
(IV.)

R = Dialkylaminoalkylamino-.

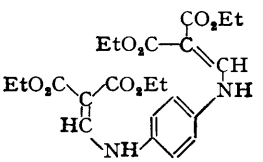
Kermack and Weatherhead (*J.*, 1940, 1164) have synthesised a number of *p*-phenanthroline derivatives carrying a basic group in the 4-position, including 4-(3′-diethylaminopropylamino)-*p*-phenanthroline and 4-(3′-diethylaminopropylamino)-2-methyl-*p*-phenanthroline; both these compounds proved inactive when tested on *P. relictum* in canaries. However, in view of the above considerations it was desirable to test similar derivatives of *p*-phenanthroline or analogous derivatives carrying a chlorine atom in position 9. The opportunity was also taken to synthesise 4-chloro-*p*-phenanthroline by a new route and to prepare 4-(4′-*diethylamino*-1′-*methylbutylamino*)-p-*phenanthroline* in the hope that even in the absence of a chlorine atom the more chemotherapeutically active *iso*amyl side chain might confer some antimalarial activity on these *p*-phenanthroline derivatives.

Ethyl ethoxymethylenemalonate condensed smoothly with 6-aminoquinoline to yield *ethyl* β-(6′-*quinolylamino*)-α-*carbethoxyacrylate*, which when heated in mineral oil afforded 4-*hydroxy*-3-*carbethoxy*-p-*phenanthroline* in good yield. The possibility that the cyclised product might be the isomeric linear diaza-anthracene derivative (V) and not the angular *p*-phenanthroline was excluded by the fact that when the ester was hydrolysed to the acid, and the latter decarboxylated, the product was 4-hydroxy-*p*-phenanthroline, already prepared by a different route (Kermack and Weatherhead, *loc. cit.*) and converted by these authors into *p*-phenanthroline by zinc dust distillation. It is useful to have this confirmation of the expected angular cyclisation of ethyl β-(6′-quinolylamino)-α-carbethoxyacrylate.

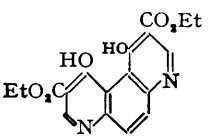
Ethyl ethoxymethylenemalonate condensed readily with 8-chloro-6-aminoquinoline to yield *ethyl* β-(8′-*chloro*-6′-*quinolylamino*)-α-*carbethoxyacrylate*. This compound cyclised in mineral oil to yield an ester, which on analogy with the results of the previous paragraph may confidently be assumed to be 9-*chloro*-4-*hydroxy*-3-*carbethoxy*-p-*phenanthroline*. The corresponding acid, on decarboxylation, affords 9-*chloro*-4-*hydroxy*-p-*phenanthroline*, which on treatment with phosphoryl chloride and phosphorus pentachloride is converted into 4 : 9-*dichloro*-p-*phenanthroline*.



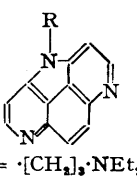
(V.)



(VI.)



(VII.)



R = ·[CH$_2$]$_3$·NEt$_2$.

(VIII.)

It was thought of interest to examine the reaction of *p*-phenylenediamine with ethyl ethoxymethylenemalonate in order to ascertain whether *p*-phenanthroline derivatives could be obtained by means of a double cyclisation of the intermediate NN′-*bis*-(2 : 2-*dicarbethoxyvinyl*)-p-*phenylenediamine* (VI). This compound was readily formed from 1 mol. of *p*-phenylenediamine and 2 mols. of ethyl ethoxymethylenemalonate, and though it did not yield the *p*-phenanthroline derivative (VII) when heated in paraffin at 250°, the double cyclisation proceeded satisfactorily in boiling diphenyl. The isolation of the intermediate compound

was unnecessary : an excellent overall yield was obtained by adding the *p*-phenylenediamine and ethyl ethoxymethylenemalonate to diphenyl and heating them under reflux for 45 minutes. Hydrolysis of the resulting ester afforded 4 : 5-*dihydroxy*-3 : 6-*dicarboxy*-p-*phenanthroline* which was decarboxylated to 4 : 5-*dihydroxy*-p-*phenanthroline*. Treatment of the latter with phosphoryl chloride and phosphorus pentachloride gave 4 : 5-*dichloro*-p-*phenanthroline*.

The *p*-phenanthrolinecarboxylic acids were difficult to purify, and it was observed that if the acids were contaminated with the sodium salts, decarboxylation, which was usually effected by heating in boiling quinoline in presence of a little copper chromite, was seriously inhibited. It was therefore necessary to ensure the purity of the acids from these contaminants. A similar observation is recorded by Lauer (*J. Amer. Chem. Soc.*, 1946, **68**, 1268) in connection with the decarboxylation of 6-chloro-4-hydroxy-3-carboxy-8-methoxyquinoline.

4-Chloro- and 4 : 9-dichloro-*p*-phenanthroline were heated with the appropriate amines to yield 4-(4′-*diethylamino*-1′-*methylbutylamino*)- and 9-*chloro*-4-(3′-*diethylaminopropylamino*)-p-*phenanthroline*. Salts of these bases with hydrochloric, hydrobromic, and various organic acids were prepared but the products, although crystalline solids, were deliquescent and became sticky on standing. For purification and analysis, the 3 : 5-dinitrobenzoates were most satisfactory, being crystalline and non-deliquescent. When 4 : 5-dichloro-*p*-phenanthroline was heated with a large excess of diethylaminopropylamine an oily base was obtained which yielded deliquescent salts with most acids but formed a crystalline *bis*-3 : 5-*dinitrobenzoate*. Analysis indicated that only one diethylaminopropylamino-group had reacted with 1 mol. of 4 : 5-dichloro-*p*-phenanthroline to yield a chlorine-free product, which probably has the structure (VIII). The failure of two separate diethylaminopropylamino-groups to attach themselves to the 4- and the 5-position of the *p*-phenanthroline nucleus may be due to steric hindrance between the two nitrogen atoms each with its attached diethylaminopropylamino-groups.

We are indebted to Dr. W. L. M. Perry of the National Institute for Medical Research for the reports on the antimalarial activity of 4-(4′-diethylamino-1′-methylbutylamino)- and 9-chloro-4-(3′-diethylaminopropylamino)-*p*-phenanthroline. These compounds have been tested against *P. gallinaceum* in chicks with the following results (bd × 4 indicates dose given twice daily for the first 4 days; D = died; K = killed) :

9-*Chloro*-4-(3′-*diethylaminopropylamino*)-p-*phenanthroline*.

	Day after infection, and % parasitæmia.														
Dosage.	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
10 Mg./20 g. ...	—	—	—	—	—	—	—	—	—	<1	1	5			
bd × 4	—	—	—	—	—	—	—	<1	2	50	K				
Nil	20	25	30	D											
	—	—	2	10	80	D									
	—	—	1	5	15	D									
	—	—	1	5	8	D									

4-(4′-*Diethylamino*-1′-*methylbutylamino*)-p-*phenanthroline*.

	Day after infection, and % parasitæmia.															
Dosage.	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
10 Mg./20 g. ...	—	—	—	—	<1	1	2	5	5	10	50	70	D			
bd × 4	—	—	—	—	—	—	—	<1	1	1	2	5	10	50	80	D
Nil	—	—	—	1	5	10	30	60	80	D						
	—	<1	1	5	10	20	10	10	50	70	D					
	—	—	—	—	1	1	2	10	50	D						
	—	—	—	—	1	2	5	30	50	70	80	D				

***Repeat test with* 4-(4′-*diethylamino*-1′-*methylbutylamino*)-p-*phenanthroline*.**

	Day after infection, and % parasitæmia.														
Dosage.	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
10 Mg./20 g. ...	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
bd × 4	—	—	—	—	—	—	—	—	—	1	5	50	D		
5 Mg./20 g.	—	—	—	—	—	—	—	<1	1	5	70	D			
bd × 4	—	—	—	<1	2	5	10	50	60	70	D				
Oral	—	—	—	—	1	10	20	70	D						
Nil	20	25	30	70	D										
	—	—	2	30	80	D									
	—	—	1	5	15	70	D								
	—	—	1	2	8	50	D								

Both compounds produced a considerable delay in the appearance of the parasites in the blood in doses of 10 mg./20 g. of body weight. The data do not allow exact comparison of the activities of these compounds with those of standard antimalarials, such as mepacrine or quinine, but they would seem to be of the same order.

The considerable activity of the second compound on *P. gallinaceum* is in accordance with the general considerations developed above. It will be seen that the compound with the *iso*amyl side chain but without the chlorine atom was also moderately active in contrast with the lack of activity of the 4-(3′-diethylaminopropylamino)-*p*-phenanthroline when tested on *P. relictum* in canaries. Further tests with this compound on *P. gallinaceum* in chicks will be required to decide if the marked contrast in activity is due to the different side chains or to a difference in susceptibility of the two species of the parasite.

Experimental.

Ethyl β-(6′-Quinolylamino)-α-carbethoxyacrylate.—6-Aminoquinoline (1 g.) and ethyl ethoxymethylenemalonate (2 c.c.) were heated under reduced pressure at 100° on the water-bath for 45 minutes to give a brown syrup which solidified on cooling; this was collected, drained, washed with light petroleum (b. p. 60—80°), and dried to give a white solid (2 g., m. p. 88—90°) which on recrystallisation from ethanol yielded large white rectangular plates, m. p. 97—98°, of *ethyl β-(6′-quinolylamino)-α-carbethoxyacrylate* (Found: C, 65·1; H, 5·7; N, 8·8. $C_{17}H_{18}O_4N_2$ requires C, 65·0; H, 5·7; N, 8·9%).

4-*Hydroxy*-3-*carbethoxy*-p-*phenanthroline.*—The foregoing ester (9 g., m. p. 88—90°) was added in small portions during 15 minutes to mineral oil (180 c.c.), preheated to 250—260°. Yellowish-brown solid was collected from the cooled oil, drained, washed with light petroleum (b. p. 60—80°), and dried to give a brown solid (7·0 g., m. p. 265—270°) which was recrystallised from ethanol (charcoal), yielding colourless rectangular prisms, m. p. 285—286°, of 4-*hydroxy*-3-*carbethoxy*-p-*phenanthroline* (Found: C, 66·9; H, 4·6; N, 10·2. $C_{15}H_{12}O_3N_2$ requires C, 67·2; H, 4·5; N, 10·45%).

4-*Hydroxy*-3-*carboxy*-p-*phenanthroline.*—The carbethoxy-compound (16 g., m. p. 265—270°) was heated under reflux with 20% methanolic potassium hydroxide (160 c.c.) for 6 hours. Water (350 c.c.) was added, and the dark brownish-red solution treated with charcoal, filtered, and made acid with glacial acetic acid. The deposited cream solid was collected, drained, washed with water, and dried (13 g., m. p. 270—280° with frothing). This product was dissolved in 2N-ammonium hydroxide, treated with charcoal, filtered, and reprecipitated with 2N-acetic acid to yield, after three treatments, cream micro-needles, m. p. 307—308° with frothing, of 4-*hydroxy*-3-*carboxy*-p-*phenanthroline* (Found: C, 60·4; H, 4·2; N, 10·4. $C_{13}H_8O_3N_2,H_2O$ requires C, 60·5; H, 3·9; N, 10·85%).

4-*Hydroxy*-p-*phenanthroline.*—(A) The preceding acid (11 g., m. p. 270—280° with frothing), copper–barium chromite catalyst (Connor, Folkers, and Adkins, *J. Amer. Chem. Soc.*, 1932, **54**, 1138) (0·1 g.), and dry redistilled quinoline (220 c.c.) were heated under reflux for 45 minutes. The mixture, cooled to 100°, was filtered, and the filtrate steam-distilled to remove the quinoline. The resulting aqueous solution was evaporated to dryness to yield a brown solid (8 g., m. p. 275—280°) which, recrystallised from boiling water (charcoal), yielded pale yellow fibrous needles, m. p. 300—301°, of 4-hydroxy-*p*-phenanthroline; the mixed m. p. with a sample prepared by the method of Kermack and Weatherhead (*loc. cit.*) was 299—300° (Found: C, 68·5; H, 4·2; N, 13·15. Calc. for $C_{12}H_8ON_2,\frac{3}{4}H_2O$: C, 68·7; H, 4·5; N, 13·4%).

(B) 4-Hydroxy-3-carboxy-*p*-phenanthroline (1 g., m. p. 270—280° with frothing) was heated at 300° in a dry test-tube until frothing ceased, to yield a solid black residue (0·7 g.) which was extracted with boiling water (3 × 50 c.c.) and the combined extracts concentrated (30 c.c.) to yield yellow needles, m. p. 298—300°, which crystallised from water in pale yellow fibrous needles, m. p. 300—301°, of 4-hydroxy-*p*-phenanthroline.

4-*Chloro*-p-*phenanthroline.*—4-Hydroxy-*p*-phenanthroline (5 g., m. p. 300—302°), phosphorus pentachloride (5 g.), and phosphoryl chloride (50 c.c.) were heated under reflux for 3 hours at 130°. The excess of phosphoryl chloride was removed at 100° under reduced pressure, and the residual syrup dissolved in ice-water, treated with charcoal, filtered, and made alkaline with 10N-sodium hydroxide. The deposited whitish-grey solid was collected, drained, washed with water, and dried (5 g., m. p. 145—146°). Recrystallisation from water yielded white felted needles, m. p. 146—147°, of 4-chloro-*p*-phenanthroline (Kermack and Weatherhead, m. p. 146—147°).

Ethyl β-(8′-Chloro-6′-quinolylamino)-α-carbethoxyacrylate.—8-Chloro-6-aminoquinoline (5 g.) and ethyl ethoxymethylenemalonate (10 c.c.) were heated under reduced pressure at 100° on the water-bath for one hour to give a brownish solid (9·2 g., m. p. 136—140°) which was collected, drained, and washed with a small quantity of light petroleum (b. p. 60—80°); this recrystallised from ethanol in yellow-orange needles, m. p. 141—142°, of *ethyl β-(8′-chloro-6′-quinolylamino)-α-carbethoxyacrylate* (Found: C, 58·2; H, 4·9; N, 8·1. $C_{17}H_{17}O_4N_2Cl$ requires C, 58·5; H, 4·9; N, 8·0%).

9-*Chloro*-4-*hydroxy*-3-*carbethoxy*-p-*phenanthroline.*—The foregoing ester (9·2 g., m. p. 136—140°) was added in small portions with efficient stirring during 10 minutes to mineral oil (150 c.c.) at 250°, and the temperature maintained for a further 5 minutes. The cooled oil was filtered and the collected yellow-brown solid was well-drained, washed with light petroleum (b. p. 60—80°) till free from oil, and dried (7·5 g., m. p. 290—295° with frothing); recrystallisation from ethanol afforded cream needles (m. p. 311—312°, decomp.) of 9-*chloro*-4-*hydroxy*-3-*carbethoxy*-p-*phenanthroline* (Found: C, 59·5; H, 3·7; N, 9·6. $C_{15}H_{11}O_3N_2Cl$ requires C, 59·5; H, 3·6; N, 9·3%).

9-*Chloro*-4-*hydroxy*-3-*carboxy*-p-*phenanthroline.*—The carbethoxy-compound (7·5 g.; m. p. 290—295°, decomp.) was heated under reflux on a water-bath with 20% methanolic potassium hydroxide (100 c.c.) for 6 hours. After 5 hours, gelatinous solid separated and was redissolved by addition of water (30 c.c.). The solution was treated with charcoal in an open flask for 5 minutes, filtered, and by the

addition of glacial acetic acid the pH was adjusted to 4. After standing for 12 hours, the solid was collected, drained, washed with water, and dried (6·5 g., m. p. 310—315° with frothing). Purification was achieved by dissolution in 2N-ammonium hydroxide and reprecipitation with 2N-acetic acid to give a light brown solid, m. p. 315—316° with frothing, or by recrystallisation from glacial acetic acid to give white fibrous needles, m. p. 319—320° with frothing, of 9-*chloro*-4-*hydroxy*-3-*carboxy*-p-*phenanthroline* (Found: C, 53·3; H, 3·2; N, 9·4. $C_{13}H_7O_3N_2Cl,H_2O$ requires C, 53·3; H, 3·1; N, 9·6%).

9-*Chloro*-4-*hydroxy*-p-*phenanthroline*.—The above acid (6·5 g., m. p. 310—315° with frothing) and copper–barium chromite catalyst (0·05 g.) were heated under reflux in dry, redistilled quinoline (130 c.c.) for 40 minutes. The solution was cooled to 100—140°, filtered, and, when cooled to room temperature, diluted with dry ether (500 c.c.) to deposit a brown solid, which was collected after 15 minutes, drained, washed liberally with fresh ether, and dried (4·5 g., m. p. 325°). This product, finely ground, was suspended in 2N-sodium carbonate for a few minutes, collected, drained, washed with cold water, and extracted 6 or 7 times with 100-c.c. portions of boiling water; the combined extracts were concentrated to 30—50 c.c., yielding yellow needles, after three purifications, m. p. 338—340°, of 9-*chloro*-4-*hydroxy*-p-*phenanthroline* (Found: C, 57·7; H, 3·5; N, 11·1. $C_{12}H_7ON_2Cl,H_2O$ requires C, 57·9; H, 3·6; N, 11·3%).

4 : 9-*Dichloro*-p-*phenanthroline*.—The foregoing chloro-compound (4 g., m. p. 325°), phosphorus pentachloride (4 g.), and phosphoryl chloride (40 c.c.) were heated under reflux for 4 hours at 140°. The excess of phosphoryl chloride was removed at 100° under reduced pressure, and the residual brownish syrup dissolved in ice-water to give a dark solution which was heated with charcoal, filtered, and made alkaline with 2N-sodium carbonate, depositing a greyish syrup which solidified after a few minutes. The solid was collected, washed with water, and dried (4 g., m. p. 225—226°). This 4 : 9-*dichloro*-p-*phenanthroline* recrystallised from ethanol in cream needles, m. p. 237—238° (Found: C, 57·6; H, 2·8; N, 11·1. $C_{12}H_6N_2Cl_2$ requires C, 57·8; H, 2·4; N, 11·25%).

NN′-*Bis*-(2 : 2-*dicarbethoxyvinyl*)-p-*phenylenediamine* (VI).—*p*-Phenylenediamine (5 g.) and ethyl ethoxymethylenemalonate (23 c.c.) were heated under reduced pressure at 100° on the water-bath for 30 minutes to yield a yellow solid, which was collected, drained, washed with light petroleum (b. p. 60—80°), and dried (17 g., m. p. 160—164°). Recrystallisation from ethanol (charcoal) yielded light yellow fibrous needles, m. p. 164—165°, of the *ester* (VI) (Found: C, 59·0; H, 6·3; N, 6·3. $C_{22}H_{28}O_8N_2$ requires C, 58·9; H, 6·25; N, 6·25%).

4 : 5-*Dihydroxy*-3 : 6-*dicarbethoxy*-p-*phenanthroline*.—(A) The preceding ester (17 g., m. p. 160—164°) was added in small amounts during 10 minutes to refluxing diphenyl (170 g.), and refluxing continued for a further 40 minutes. The mixture, cooled to 60—70°, was diluted with light petroleum (b. p. 80—100°) preheated to 70—80°, and filtered. The collected solid was extracted for 5 hours with boiling light petroleum (b. p. 80—100°) and dried (12 g., m. p. 255—260°).

(B) *p*-Phenylenediamine (5 g.) and ethyl ethoxymethylenemalonate (23 c.c.) were added to diphenyl (170 g.) and heated under reflux for 45 minutes. The product was isolated as in (A) (13·2 g., m. p. 255—260°). Recrystallisation from ethanol or aqueous pyridine yielded short white needles, m. p. 278—280° (after further drying, 283—284°), of 4 : 5-*dihydroxy*-3 : 6-*dicarbethoxy*-p-*phenanthroline* (Found: C, 57·8; H, 4·8; N, 7·95. $C_{18}H_{16}O_6N_2,H_2O$ requires C, 57·75; H, 4·8; N, 7·5%).

4 : 5-*Dihydroxy*-3 : 6-*dicarboxy*-p-*phenanthroline*.—The foregoing ester (10 g., m. p. 255—260°) was heated under reflux with 20% methanolic potassium hydroxide (100 c.c.) on a water-bath for 4 hours. Water (200 c.c.) was added, the solution treated with charcoal and filtered, and the pH adjusted to 5 with glacial acetic acid. The deposited solid was collected after 2 hours, drained, washed with water, and dried at 90° (6 g., m. p. 294—295° with frothing). This product was dissolved in 2N-ammonium hydroxide, treated with charcoal, filtered, and reprecipitated with 2N-acetic acid to yield, after three treatments, brown micro-needles, m. p. 297—298° with frothing, of 4 : 5-*dihydroxy*-3 : 6-*dicarboxy*-p-*phenanthroline* (Found: C, 50·1; H, 3·3; N, 8·4. $C_{14}H_8O_6N_2,2H_2O$ requires C, 50·0; H, 3·6; N, 8·3%).

4 : 5-*Dihydroxy*-p-*phenanthroline*.—(A) The dicarboxy-compound (10·3 g., m. p. 294—295°), copper–barium chromite catalyst (0·1 g.), and dry, redistilled quinoline (200 c.c.), preheated to 150°, were refluxed for one hour, cooled to 100°, filtered, and the filtrate concentrated (50 c.c.) under reduced pressure. The cold mixture was diluted with dry ether (500 c.c.), and the deposited solid collected, drained, washed thoroughly with ether, and dried (6·8 g., m. p. 345—350° with frothing). This compound could not be satisfactorily recrystallised from any of the common organic solvents but a relatively pure sample was obtained by extracting with a large volume of boiling water and concentrating (50 c.c.) the extract to yield yellow needles, m. p. 365—370° (decomp.), of 4 : 5-*dihydroxy*-p-*phenanthroline* (Found: C, 66·0; H, 3·9; N, 12·0. $C_{12}H_8O_2N_2,\frac{1}{4}H_2O$ requires C, 66·5; H, 3·9; N, 12·9%).

(B) 4 : 5-Dihydroxy-3 : 6-dicarboxy-*p*-phenanthroline (1 g., m. p. 294—295°) was heated at 300° in a dry test-tube till frothing ceased to yield a black residue which was treated with 2N-ammonium hydroxide, washed with water, and dried (0·6 g., m. p. 340—350°); this recrystallised from a large volume of boiling water to yield 4 : 5-dihydroxy-*p*-phenanthroline, m. p. 365—370° (decomp.).

4 : 5-*Dichloro*-p-*phenanthroline*.—4 : 5-Dihydroxy-*p*-phenanthroline (6·5 g., m. p. 350°), phosphorus pentachloride (13 g.), and phosphoryl chloride (130 c.c.) were heated under reflux for 7 hours at 140°. Excess of phosphoryl chloride was removed under reduced pressure on a water-bath, and the residual syrup was dissolved in ice-water, treated with charcoal, and rendered alkaline with 10N-sodium hydroxide. Yellow needles were deposited; these were collected, drained, washed with water, and dried (4·3 g., m. p. 235—240°). Recrystallisation from ethanol yielded yellow needles, m. p. 247—248°, of 4 : 5-*dichloro*-p-*phenanthroline* (Found: C, 57·8; H, 2·7; N, 11·3. $C_{12}H_6N_2Cl_2$ requires C, 57·8; H, 2·4; N, 11·3%).

9-*Chloro*-4-(3′-*diethylaminopropylamino*)-p-*phenanthroline*.—4 : 9-Dichloro-*p*-phenanthroline (3·1 g., m. p. 237—238°) and 3-diethylaminopropylamine (6·2 c.c.) were heated under reflux for 6 hours at 160—170°. The excess of amine was removed under reduced pressure, and the residual syrup dissolved in 2N-hydrochloric acid, the solution filtered, made alkaline with 2N-ammonium hydroxide, and

extracted with ether, the extract dried (K_2CO_3) for 6 hours, the solvent removed, and the residual brown oil dissolved in the minimum quantity of ethanol, to which a saturated ethanolic solution of 3 : 5-dinitrobenzoic acid was added till no further precipitate formed. The deposited yellow solid (9 g.) was collected and recrystallised from ethanol three times to yield yellow needles, m. p. 193—194°, of the *bis*-3 : 5-*dinitrobenzoate* of 9-chloro-4-(3′-diethylaminopropylamino)-*p*-phenanthroline (Found: C, 51·75; H, 4·0; N, 14·3. $C_{19}H_{23}N_4Cl,2C_7H_4O_6N_2$ requires C, 51·7; H, 4·1; N, 14·6%).

4-(4′-*Diethylamino*-1′-*methylbutylamino*)-p-*phenanthroline*.—4-Chloro-*p*-phenanthroline (1·4 g., m. p. 145—146°), redistilled 2-amino-5-diethylaminopentane (3 c.c.), a trace of copper powder, and a small crystal of iodine were heated under reflux for 5 hours at 180°. The product was worked up as described for the previous compound, and converted into a 3 : 5-dinitrobenzoate (5 g., m. p. 120—125°) which on recrystallisation three times from ethanol yielded yellow needles, m. p. 160—161° (loses solvent about 125°), of the *tris*-3 : 5-*dinitrobenzoate* of 4-(4′-diethylamino-1′-methylbutylamino)-*p*-phenanthroline (Found: C, 52·3; H, 4·3; N, 13·8. $C_{21}H_{28}N_4,3C_7H_4O_6N_2,C_2H_5{\cdot}OH$ requires C, 51·9; H, 4·5; N, 13·75%).

4 : 5-(3′-*Diethylaminopropylimino*)-p-*phenanthroline*.—4 : 5-Dichloro-*p*-phenanthroline (1·2 g., m. p. 247—248°) and 3-diethylaminopropylamine (6 c.c.) were heated under reflux at 160° for 18 hours. The excess of amine was removed under reduced pressure, and the residual product was dissolved in 2N-acetic acid, filtered, extracted with ether till no further yellow colour was obtained in the ether, rendered alkaline with 2N-ammonium hydroxide, and again extracted with ether; the extract was dried (K_2CO_3) and the solvent removed to yield, after two treatments, a brown oil (2 g.) which was, after unsuccessful attempts to prepare other salts which proved deliquescent, dissolved in ethanol and treated with a saturated ethanolic solution of 3 : 5-dinitrobenzoic acid. The supernatant liquid was decanted, and the syrup dissolved in methanol and allowed to crystallise; three further recrystallisations from methanol yielded soft cream needles, m. p. 194—195°, of the *bis*-3 : 5-*dinitrobenzoate* of 4 : 5-(3′-*diethylaminopropylimino*)-p-*phenanthroline* (Found: C, 53·9; H, 4·1; N, 15·4. $C_{19}H_{22}N_4,2C_7H_4O_6N_2$ requires C, 54·25; H, 4·1; N, 15·3%).

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