331. *Attempts to find New Antimalarials. Part XXVI. Further Derivatives of* p-*Phenanthroline.*

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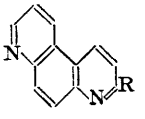
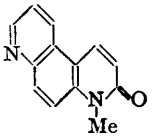
2-Chloro-*p*-phenanthroline has been prepared by the action of phosphorus oxychloride and pentachloride on (*a*) 1-methyl-*p*-phenanthrol-2-one (II) and (*b*) 2-hydroxy-*p*-phenanthroline (I; R = OH). The former was prepared either by the oxidation of *p*-phenanthroline methiodide with alkaline ferricyanide or from 6-amino-1-methylcarbostyril by Skraup reaction; (I; R = OH) was similarly prepared from 6-aminocarbostyril. Phosphorus oxychloride reacts with *p*-phenanthroline *N*-oxide to yield 2-chloro-*p*-phenanthroline (I; R = Cl), and with *p*-phenanthroline di-*N*-oxide to yield 2 : 7-dichloro-*p*-phenanthroline, which was independently synthesised by the action of phosphorus oxychloride and pentachloride on 2 : 7-diketo-1 : 8-dimethyl-1 : 2 : 7 : 8-tetrahydro-*p*-phenanthroline (III) obtained by oxidising the methiodide of 1-methyl-*p*-phenanthrol-2-one. Derivatives of *p*-phenanthroline with basic side chains have been prepared by condensation of 2-chloro-*p*-phenanthroline with appropriate amines.

Certain derivatives of *p*-phenanthroline, including a number carrying basic side chains in positions 2 and 4, have been described by Kermack and Weatherhead (*J.*, 1940, 1164). 2-*Chloro*-p-*phenanthroline* (I; R = Cl) has now been prepared by oxidising the methiodide of *p*-phenanthroline with alkaline ferricyanide to 1-*methyl*-p-*phenanthrol*-2-*one* (II) followed by treatment of this with phosphorus oxychloride containing phosphorus pentachloride. That the chlorine atom in this compound is in fact in the 2-position was proved by preparing it from 6-aminocarbostyril, which by means of a Skraup reaction was converted into 2-*hydroxy*-p-*phenanthroline* (I; R = OH), and the latter with phosphorus oxychloride and pentachloride readily yielded the same chloro-*p*-phenanthroline as that obtained by the other route. Further confirmation was obtained by an independent synthesis of 1-methyl-*p*-phenanthrol-2-one by means of a Skraup reaction on 6-amino-1-methylcarbostyril.



(I.)



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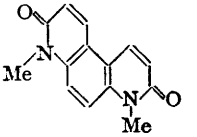

(III.)

An entirely different route for the synthesis of 2-chloro-*p*-phenanthroline has also been explored, similar to that used by Kermack and Tebrich (*J.*, 1945, 375) for the synthesis of 2-chloro-*m*-phenanthroline. When *p*-phenanthroline was treated with approximately 1 mol. of

perbenzoic acid the mono-*N*-oxide, m. p. 232—233°, along with some impure di-*N*-oxide was obtained. The di-*N*-oxide, m. p. 324—325°, was isolated from an experiment in which a larger proportion of perbenzoic acid was used. Evans and Linsker (*J. Amer. Chem. Soc.*, **1946**, **68**, 403) claim to have formed the di-*N*-oxide by the action of hydrogen peroxide on the base in acetic acid, but their m. p. (308°) is lower than ours. The action of phosphorus oxychloride on the mono-*N*-oxide gave 2-chloro-*p*-phenanthroline as main product; by treating the di-*N*-oxide in a similar way a compound, m. p. 315—316°, was isolated which was shown to be 2 : 7-*dichloro*-p-*phenanthroline* in the following way. The *methiodide* of 1-methyl-*p*-phenanthrol-2-one was oxidised with alkaline ferricyanide to 2 : 7-*diketo*-1 : 8-*dimethyl*-1 : 2 : 7 : 8-*tetrahydro*-p-*phenanthroline* which, when heated in a sealed tube at 150° for 24 hours with phosphorus oxychloride and pentachloride, yielded 2 : 7-*dichloro*-p-*phenanthroline* identical with a compound isolated from the product of the action of phosphorus oxychloride on the di-*N*-oxide of *p*-phenanthroline. An attempt was made to form the dimethiodide of *p*-phenanthroline by treating the base with methyl iodide under a variety of conditions including heating with a large excess of methyl iodide in nitrobenzene in a sealed tube, but the product consisted practically entirely of the monomethiodide.

As expected, 2-chloro-*p*-phenanthroline reacted readily with primary amines to form compounds such as 2-(2-diethyaminoethylamino)-, 2-(3-diethylaminopropylamino)-, and 2-(4-diethylamino-1-methylbutylamino)-*p*-phenanthroline, characterised respectively as *trihydrobromide*, *trihydrobromide*, and *tris*-3 : 5-*dinitrobenzoate*.

Experimental

p-*Phenanthroline Methiodide.*— *p*-Phenanthroline (25 g.) was heated under reflux with methyl iodide (100 c.c.) in nitrobenzene (250 c.c.) for 2 hours on a water-bath. Yellow needles of the *methiodide* separated during the reaction, and on cooling a further amount was deposited; the combined products were dried in a vacuum and recrystallised from water; yield 38 g., m. p. 270—271° (Found: I, 38·7. $C_{13}H_{11}N_2I$ requires I, 39·4%.)

1-*Methyl*-p-*phenanthrol*-2-*one.*—(a) A mixture of 6-amino-1-methylcarbostyril (3·9 g.), 69% sulphuric acid (42 g.), 80% arsenic acid (12 g.), and 90% glycerol (7·2 g.) was refluxed in an oil-bath for 2½ hours at 150°. The mixture, after dilution with an equal bulk of water followed by filtration, was made strongly alkaline with 10N-sodium hydroxide solution, and the precipitate collected. This brown solid was purified by prolonged extraction with ether (Soxhlet), the ether yielding 2·5 g., long yellow needles of 1-*methyl*-p-*phenanthrol*-2-*one*, m. p. 242° (Found: C, 74·2; H, 5·0. $C_{13}H_{10}ON_2$ requires C, 74·3; H, 4·8%).

(b) To a solution of potassium ferricyanide (21·9 g. in 200 c.c. of water) were added alternately small portions of solutions of *p*-phenanthroline methiodide (9 g. in 500 c.c. of water) and sodium hydroxide (4·2 g. in 100 c.c. of water). When the addition of both solutions had been completed, the mixture was set aside for ½ hour and then made strongly alkaline with 10N-sodium hydroxide (250 c.c.). The yellow precipitate was collected, dried on a porous plate, and extracted for 3—4 hours with benzene (250 c.c.) under reflux. After filtration, the process was repeated twice. On cooling, the benzene deposited 4·5 g. of a light yellow material, m. p. 245—246°, and on concentration a further 0·6 g. was obtained, m. p. 245—246°, mixed m. p. with 1-methyl-2-*p*-phenanthrolone, prepared as above, 243—244°.

2-*Hydroxy*-p-*phenanthroline.*—A mixture of 6-aminocarbostyril (2·6 g.), arsenic acid (3·2 g.), concentrated sulphuric acid (4·4 g.), and glycerol (4·8 g.) was refluxed gently for 5 hours, then diluted with water to about 50 c.c. An inorganic brown solid (0·5 g.) was filtered off, and the filtrate, on neutralization with 10N-sodium hydroxide solution, deposited a brown solid which redissolved in excess of sodium hydroxide. The alkaline solution was neutralised with acetic acid and the precipitate which formed was filtered off, yielding 2·7 g. of a brown solid, m. p. 305—310°. Recrystallised several times from ethanol, 2-*hydroxy*-p-*phenanthroline* formed yellow needles, m. p. 302—303° (Found: C, 66·75; H, 5·0. $C_{12}H_8ON_2,H_2O$ requires C, 67·3; H, 4·7%.)

2-*Chloro*-p-*phenanthroline.*—(1) *From* 2-*hydroxy*-p-*phenanthroline.* A mixture of 2-hydroxy-*p*-phenanthroline (1 g.), phosphorus pentachloride (1 g.), and phosphorus oxychloride (10 c.c.) was refluxed for 32 hours in an oil-bath, almost complete solution then having taken place. The excess of oxychloride was removed by distillation in a vacuum, and the resulting mass treated with about 100 c.c. of water. Traces of a reddish oil separated and were removed by filtration. After the filtrate had been made slightly alkaline with 10N-sodium hydroxide solution, the white flocculent precipitate was filtered off and dried on the water-bath; yield 1·2 g. Recrystallised from aqueous ethanol, this yielded 0·7 g. of long white needles of 2-*chloro*-p-*phenanthroline*, m. p. 189—190° (Found: C, 66·6; H, 3·7. $C_{12}H_7N_2Cl$ requires C, 67·1; H, 3·3%).

(2) *From* 1-*methyl*-p-*phenanthrol*-2-*one.* A mixture of 1-methyl-*p*-phenanthrol-2-one (8 g.), phosphorus pentachloride (8 g.), and phosphorus oxychloride (48 c.c.) was divided into two parts and heated in two sealed tubes for 5 hours at 150°. After removal of excess of oxychloride by distillation in a vacuum, the reddish product was treated with ice, the solution made alkaline with ammonia, and the precipitate collected, washed with water, and dried on the water-bath, yielding 3·6 g. of a greyish-brown powder, m. p. 188°; recrystallised from ligroin, it formed white needles, m. p. 191° (Found: C, 67·1; H, 3·6%), showing no depression on admixture with a sample prepared as in (1).

p-*Phenanthroline* N-*Oxide.*—*p*-Phenanthroline (10 g., m. p. 172°), dissolved in dry chloroform (60 c.c.), was mixed with a solution of perbenzoic acid (8 g.) in chloroform (420 c.c.) (prepared as in *Org. Synth.*, Coll. Vol. I, 1st edn., p. 422). The mixture was kept below 0° for 24 hours, the chloroform removed, the

residue extracted four times with 10-c.c. portions of 2N-hydrochloric acid, and the extract rendered alkaline and extracted with chloroform (10-c.c. portions). The first six extracts on removal of the chloroform yielded material, m. p. 200—210° (4·5 g.), which after two recrystallisations from ethanol yielded white needles of p-*phenanthroline* N-*oxide*, m. p. 233—234° (3·5 g.) (Found : C, 73·8; H, 4·2. $C_{12}H_8N_2O$ requires C, 73·5; H, 4·1%). Further chloroform extracts yielded some impure di-*N*-oxide (2 g.).

p-*Phenanthroline Di*-N-*oxide*.—*p*-Phenanthroline (10 g., m. p. 172°), dissolved in dry chloroform (60 c.c.), was mixed with a solution of perbenzoic acid (12 g.) in chloroform (1030 c.c.) and kept below 0° for 2 days. Pale yellow needles, which separated, were collected, drained, washed with chloroform, and dried (11 g., m. p. 320—321°). The filtrate was evaporated to dryness, the residue extracted three times with 10-c.c. portions of 2N-hydrochloric acid, and the extract made alkaline with 10N-sodium hydroxide solution and extracted with chloroform. On removal of the chloroform, 0·2 g. of m. p. 309—310° was obtained. The total crude product was recrystallised from hot water, yielding white needles (8·8 g., m. p. 324—325°) (Found : C, 68·3; H, 4·1; N, 13·7. Calc. for $C_{12}H_8O_2N_2$: C, 67·9; H, 3·8; N, 13·2%).

2-*Chloro*-p-*phenanthroline from* p-*Phenanthroline* N-*Oxide*.—Phosphorus oxychloride (3 c.c.) was added to the dry oxide (1 g., m. p. 232—233°), heat being evolved. The mixture was refluxed for 2 hours at 120—125°, the excess of oxychloride removed in a vacuum, and the greyish syrup treated with cold water (25 c.c.). The solution was rendered alkaline with 10N-sodium hydroxide solution, the deposited solid collected after 24 hours, drained, washed with water, dried, and recrystallised from ethanol; yield 0·3 g., m. p. 190—191° undepressed on admixture with a specimen prepared as above.

2-*Keto*-1-*methyl*-1 : 2-*dihydro*-p-*phenanthroline Methiodide*.—1-Methyl-*p*-phenanthrol-2-one (0·6 g.) was heated under reflux with methyl iodide (4 c.c.) in nitrobenzene (10 c.c.) for 8 hours on a water-bath. The mixture was cooled, and the crystals collected, washed with fresh nitrobenzene, and dried, m. p. 289—290°. Recrystallisation from methanol gave yellow needles of 2-*keto*-1-*methyl*-1 : 2-*dihydro*-p-*phenanthroline methiodide*, m. p. 290—291° (Found : C, 47·9; H, 3·9. $C_{14}H_{13}N_2I$ requires C, 47·7; H, 3·7%).

2 : 7-*Diketo*-1 : 8-*dimethyl*-1 : 2 : 7 : 8-*tetrahydro*-p-*phenanthroline*.—A solution of sodium hydroxide (0·3 g.) in water (7·2 c.c.) and a solution of potassium ferricyanide (1·6 g.) in water (15 c.c.) were added alternately to a solution of 1-methyl-*p*-phenanthrol-2-one methiodide (0·7 g.) in water (36 c.c.), and the solution kept for ½ hour at room temperature. The deposited crystals were collected and 10N-sodium hydroxide solution (18 c.c.) was added to the filtrate, whereupon more crystals separated; recrystallisation of the crude material from water gave yellow needles of 2 : 7-*diketo*-1 : 8-*dimethyl*-1 : 2 : 7 : 8-*tetrahydro*-p-*phenanthroline* (0·4 g., m. p. 363—364°) (Found : C, 67·0; H, 5·1; N, 11·3. $C_{14}H_{12}O_2N_2,\frac{1}{2}H_2O$ requires C, 67·5; H, 5·2; N, 11·2%).

2 : 7-*Dichloro*-p-*phenanthroline*.—(1) A mixture of the foregoing compound (0·2 g.), phosphorus pentachloride (1 g.), and phosphorus oxychloride (3 c.c.) was heated in a sealed tube for 24 hours at 150°. The excess of oxychloride was decomposed with iced water, and the solution made strongly alkaline with 10N-sodium hydroxide solution. The deposited greyish material was collected, washed with water, dried in a vacuum, extracted with hot ethanol, and the concentrated extract allowed to crystallise, yielding white needles, m. p. 310—311°; further crystallisation from ethanol yielded 2 : 7-*dichloro*-p-*phenanthroline*, m. p. 315—316° (Found : C, 53·6; H, 2·7; N, 10·1. $C_{12}H_6N_2Cl_2,H_2O$ requires C, 53·9; H, 3·0; N, 10·5%).

(2) Phosphorus oxychloride (24 c.c.) was added to dry *p*-phenanthroline di-*N*-oxide (2 g.), heat being evolved. The mixture was heated at 125° for 5 hours, the excess of oxychloride removed in a vacuum, and the residue dissolved in 11N-hydrochloric acid (40—50 c.c.) to give a muddy brown solution which was rendered alkaline with 10N-sodium hydroxide solution to precipitate whitish material which was collected and dried, m. p. 240—250°. Prolonged extraction (1 day) with hot ethanol yielded 1 g. of material, m. p. 300—310°, which on recrystallisation from ethanol yielded 0·2 g. of 2 : 7-dichloro-*p*-phenanthroline, m. p. 315—316°; mixed m. p. with a sample prepared as above showed no depression.

2-(2-*Diethylaminoethylamino*)-p-*phenanthroline*.—2-Chloro-*p*-phenanthroline (0·4 g.) was refluxed with 2-diethylaminoethylamine (1 c.c.) at 140° for 3 hours. The excess of the latter was removed in a vacuum on a boiling water-bath to yield a solid yellow residue; this was dissolved in ethanol, and to it were added a few drops of ethanolic hydrobromic acid followed by a few drops of acetone, affording cream platelets of the *hydrobromide* (0·3 g.), m. p. 284—285° (Found : C, 40·0; H, 5·0. $C_{18}H_{22}N_4,3HBr$ requires C, 40·2; H, 4·65%).

2-(3-*Diethylaminopropylamino*)-p-*phenanthroline*.—2-Chloro-*p*-phenanthroline (0·5 g.) was refluxed with 3-diethylaminopropylamine (1 c.c.) for 2 hours at 160°. When the product was worked up as above, but without addition of acetone, it afforded a *hydrobromide* which, recrystallised three times from ethanol, yielded pale yellow platelets (0·3 g.), m. p. 268—270° (Found : C, 39·9; H, 4·9; N, 9·8. $C_{19}H_{24}N_4,3HBr,H_2O$ requires C, 40·1; H, 5·1; N, 9·8%).

2-(4-*Diethylamino*-1-*methylbutylamino*)-p-*phenanthroline*.—2-Chloro-*p*-phenanthroline (0·2 g.) was refluxed with 4-diethylamino-1-methylbutylamine (0·4 c.c.) for 5 hours at 180°. The excess of reagent was removed in a vacuum, the syrupy residue dissolved in ethanol, and a few drops of a saturated ethanolic solution of 3 : 5-dinitrobenzoic acid added. An oil was deposited which solidified on standing for 2 weeks. The collected *tris*-3 : 5-*dinitrobenzoate*, recrystallised five times from ethanol, had m. p. 93—94° (Found : C, 51·8, 52·4; H, 4·8, 4·7; N, 14·1. $C_{21}H_{28}N_4,3C_7H_4O_6N_2,C_2H_5OH$ requires C, 52·0; H, 4·5; N, 13·7%).

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