43. *Attempts to find New Antimalarials. Part XXIV. Derivatives of* o-*Phenanthroline* (7 : 8 : 3′ : 2′-*pyridoquinoline*).

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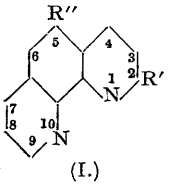
o-*Phenanthroline methiodide*, oxidised by alkaline ferricyanide, yields 1-*methyl*-2-o-*phenanthrolone*. Hence 2-*chloro*-o-*phenanthroline*, from which *o*-phenanthroline compounds carrying various basic substituents in the 2-position have been prepared. 5-Bromo-*o*-phenanthroline has been prepared from 5-bromo-8-aminoquinoline, but, on treatment with ammonia, 5-amino-*o*-phenanthroline could not be isolated.

That the nitro group in the nitro-*o*-phenanthroline, obtained by nitrating *o*-phenanthroline, is in the 5 position is proved by the synthesis of the same nitro compound from 5-nitro-8-aminoquinoline.

Various derivatives of *m*- and *p*-phenanthrolines carrying basic side-chains of the type present in mepacrine (atebrin) are described in the literature, and in a recent communication Burger, Bass, and Fredericksen (*J. Org. Chem.*, 1944, **9**, 373) have described derivatives of 4-methyl-*o*-phenanthroline carrying a basic side-chain in the 2-position. The following convenient route to *o*-phenanthroline derivatives carrying the basic side-chain in the 2-position, but with no methyl group in the 4-position, gives good results.

By the application of the Skraup reaction to *o*-phenylenediamine under the conditions described in E.P. 394,416, reasonable yields of *o*-phenanthroline were obtained with much less labour than is involved in the methods of Hieber (*Ber.*, 1928, **61**, 2150) and of Tartarini and Samaja (*Annali Chim. Appl.*, 1933, **23**, 351). The *monomethiodide* of *o*-phenanthroline when oxidised with alkaline ferricyanide yields 1-*methyl*-2-o-*phenanthrolone*. Treatment of this compound by a mixture of phosphorus oxychloride and phosphorus pentachloride slowly converts it into the desired 2-*chloro*-o-*phenanthroline* (I; R′ = Cl, R″ = H).



(I.)

As expected, the chlorine atom of 2-chloro-*o*-phenanthroline reacts readily with suitable primary and secondary amines. Thus, with aniline it yields 2-*anilino*-o-*phenanthroline* and with piperidine, 2-piperidino-*o*-phenanthroline (which was characterised as its *picrate*). With the appropriate diethylaminoalkylamines the following bases were obtained: 2-diethylaminoethylamino-*o*-phenanthroline, 2-diethylaminopropylamino-*o*-phenanthroline, and 2-(δ-diethylamino-α-methylbutylamino)-*o*-phenanthroline. None of these was obtained crystalline, or gave a satisfactory hydrochloride or hydrobromide. The picrates did not crystallise well, but the *salts* with 3 : 5-dinitrobenzoic acid were well defined and relatively easily purified.

5-Bromo-*o*-phenanthroline (I; R′ = H, R″ = Br) has been synthesised from 5-bromo-8-aminoquinoline by means of a modified Skraup reaction. This compound has recently been prepared by Richter and Smith (*J. Amer. Chem. Soc.*, 1944, **66**, 396) from 6-bromo-8-aminoquinoline. The synthesised compound, containing half a molecule of water, has m. p. 113—115°, slightly lower than that (119°) given by these authors for the anhydrous material; there is no reason to believe that the two compounds are not identical. When 5-bromo-*o*-phenanthroline is heated with ammonia, phenol, and a little copper sulphate under the conditions described by Haworth and Sykes (*J.*, 1944, 311) bromide ions are liberated, but none of the expected 5-amino-*o*-phenanthroline (I; R′ = H, R″ = NH_2) could be isolated. The only products which could be separated were *o*-phenanthroline, a compound, probably 5-*phenoxy*-o-*phenanthroline* (I; R′ = H, R″ = OPh), and some intractable tar; as the crude product gives a positive diazo reaction, the amino-derivative is probably present in small amount. It appears that, at the high temperature employed, some molecules of the 5-bromo-*o*-phenanthroline are reduced whilst others are decomposed or polymerised.

A nitro-*o*-phenanthroline, m. p. 202°, has been obtained by Hammett, Walden, and Edmonds (*J. Amer.*

Chem. Soc., **1934**, **56**, 1093) by nitrating *o*-phenanthroline. That the nitro group is in the 5-position is now proved by the synthesis of the identical nitro-*o*-phenanthroline from 5-nitro-8-aminoquinoline by the Skraup reaction. Attempts to synthesise 5-nitro-*o*-phenanthroline directly from 4-nitro-*o*-phenylenediamine by a double Skraup reaction have so far not been successful. Haworth and Sykes (*loc. cit.*) state that they could not isolate the *m*- and *p*-derivatives by this method from 4-nitro-*m*-phenylenediamine and 2-nitro-*p*-phenylenediamine.

Experimental

Preparation of o-*Phenanthroline.*—A mixture of *o*-phenylenediamine (40 g.), sulphuric acid (880 c.c., 69%), glycerol (216 g.), arsenic acid solution (200 c.c., 80%, *d* 1·9) and water (24 c.c.) was refluxed for 2—3 hours. The end of the reaction was indicated by voluminous frothing. The black liquid diluted with an equal volume of water was basified with ammonia. The tarry material was separated by filtration and the filtrate extracted with benzene. The tar was refluxed with benzene until the extracts were colourless. The benzene extracts were combined and the benzene removed. The crude material (30 g., 45%) was crystallised from benzene and the product had m. p. 108—112°.

o-*Phenanthroline Methiodide.*—Methyl iodide (5 c.c.) was added to a solution of *o*-phenanthroline (6 g.) in nitrobenzene (150 c.c.) and the mixture kept at 37° for 24 hours. The long yellow crystalline plates were separated. More methyl iodide (2·5 c.c.) was added to the filtrate and after 24 hours a further crop of crystals separated. After washing with benzene the crystals (8·5 g.) were crystallised from alcohol, m. p. 210—213° (Found: C, 48·8; H, 3·8; I, 40·2. $C_{12}H_8N_2$,MeI requires C, 48·4; H, 3·4; I, 39·4%). o-*Phenanthroline methiodide* was readily soluble in water and from the solution the metho-hydroxide was precipitated by concentrated but not by dilute sodium hydroxide or ammonia. The compound gave no colour with ferrous sulphate solution.

1-*Methyl*-2-o-*phenanthrolone.*—To a cold saturated aqueous solution of potassium ferricyanide (7·3 g.) were added alternately a little at a time saturated solutions of sodium hydroxide and *o*-phenanthroline methiodide (3 g.), excess sodium hydroxide being added until no further precipitation took place. The yellow precipitate and the pale pink residual solid, obtained by evaporating the filtrate to dryness, were refluxed with benzene to give a red extract with green fluorescence. The brown solid, obtained on removal of the benzene, crystallised from water and from benzene as rectangular plates (1·5 g.), m. p. 123—124°. The compound retained the solvent tenaciously, as shown by the analytical results obtained on samples dried at 78° under reduced pressure. (Sample, crystallised from water. Found: C, 72·6; H, 5·4. $C_{13}H_{10}ON_2$ requires C, 74·3; H, 4·8. $C_{13}H_{10}ON_2,\frac{1}{4}H_2O$ requires C, 72·7; H, 4·9%. Sample, crystallised from benzene. Found: C, 75·5; H, 5·1. $C_{13}H_{10}ON_2,\frac{1}{4}C_6H_6$ requires C, 75·8; H, 5·0%). The compound was insoluble in cold dilute sodium hydroxide, but soluble in dilute hydrochloric acid. It gave no colour with ferrous sulphate solution.

2-*Chloro*-o-*phenanthroline.*—1-Methyl-2-*o*-phenanthrolone (6 g.), phosphorus pentachloride (7·2 g.), and phosphorus oxychloride (54 c.c.) were refluxed for 8 hours. After removal of excess phosphorus oxychloride by distillation under reduced pressure, iced water was added and the solution basified with ammonia. The pale brown precipitate crystallised from hot water as colourless needles (5 g.), m. p. 129—130° (Found: Cl, 17·1. $C_{12}H_7N_2Cl$ requires Cl, 16·6%). It was soluble in dilute hydrochloric acid, insoluble in dilute sodium hydroxide, and dissolved in ferrous sulphate solution giving a deep yellow colour.

2-*Piperidino*-o-*phenanthroline.*—2-Chloro-*o*-phenanthroline (1 g.) and piperidine (0·5 g.) were heated at 100° for 2—3 hours. After excess piperidine had been removed under reduced pressure, the product was dissolved in 4N-acetic acid, basified with ammonia and extracted with ether. The ether solution was extracted with 4N-acetic acid and the acid layer separated off, basified with ammonia and again extracted with ether. The non-crystallisable orange oil, obtained on removal of the ether, was treated in alcoholic solution with picric acid and the orange *picrate* crystallised from alcohol as yellow rods, m. p. 213—217° (Found: C, 54·4; H, 4·2. $C_{17}H_{17}N_3,C_6H_3O_7N_3,H_2O$ requires C, 54·1; H, 4·3%).

2-*Anilino*-o-*phenanthroline.*—2-Chloro-*o*-phenanthroline (0·5 g.) and aniline (0·5 c.c.) were heated at 100° for 2 hours. The orange oily product was diluted with water and steam distilled. The pale brown solid left was crystallised from alcohol and then from benzene as colourless rods, m. p. 231—233° (Found: C, 79·4; H, 4·4. $C_{18}H_{12}N_2$ requires C, 79·7; H, 4·8%). It was insoluble in water and sodium hydroxide, soluble in hydrochloric acid and acetone. The compound was insoluble in cold ferrous sulphate solution, but on warming gave an orange solution.

2-*Diethylaminoethylamino*-o-*phenanthroline.*—2-Chloro-*o*-phenanthroline (3 g.) and diethylaminoethylamine (2·5 g.) were heated at 140—150° for 4 hours. Excess amine was removed under reduced pressure, and the thick residual oil was dissolved in 2N-acetic acid to form a red solution with green fluorescence. Basification with ammonia and extraction with ether gave an orange solution with faint green fluorescence. The base, a thick orange oil, was treated in alcoholic solution with 3 : 5-dinitrobenzoic acid. The *salt* quickly solidified and was recrystallised from alcohol as long yellow plates (5 g.), m. p. 190—192° (Found: C, 53·7; H, 4·4. $C_{18}H_{22}N_4,2C_7H_4O_6N_2$ requires C, 53·5; H, 4·2%).

2-Diethylaminopropylamino-*o*-phenanthroline was obtained from 2-chloro-*o*-phenanthroline (3 g.) and diethylaminopropylamine (2·5 g.) at 150—160° for 3—4 hours, the product being worked up as above. The base, a thick non-crystallisable orange oil, was converted into the *dinitrobenzoate* which crystallised from alcohol as long yellow plates (4 g.), m. p. 150—152° (Found: C, 53·8; H, 4·4. $C_{19}H_{24}N_4,2C_7H_4O_6N_2$ requires C, 54·1; H, 4·4%).

2-(δ-Diethylamino-α-methylbutylamino)-*o*-phenanthroline was obtained from 2-chloro-*o*-phenanthroline (3 g.) and δ-diethylamino-α-methylbutylamine (3·4 g.) at 160—170° for 5—6 hours. The *dinitrobenzoate* of the non-crystallisable red–brown oily base crystallised from alcohol as small yellow needles (5 g.), m. p. 157—158° (Found: C, 54·1; H, 4·9. $C_{21}H_{28}N_4,2C_7H_4O_6N_2,H_2O$ requires C, 54·0; H, 4·9%). These three dinitrobenzoates were closely similar in appearance and properties. They were slowly decomposed by dilute sodium hydroxide with liberation of the base, which could be extracted with ether.

Preparation of 5-*Bromo*-o-*phenanthroline.*—5-Bromo-8-aminoquinoline (Claus and Setzer, *J. pr. Chem.*, 1896, **53**, 405) (12 g.), sulphuric acid (56 c.c., 69%), glycerol (16 g.), arsenic acid solution (16 c.c., 80%, *d* 1·9), and water (6 c.c.) were refluxed for 2 hours, when the diazo test was negative. The acid product was diluted and basified with sodium hydroxide. The thin tar was separated and extracted by boiling in benzene. The dark red extract on removal of the benzene yielded a sticky brown solid which crystallised from ligroin as colourless needles (6 g.), m. p. 113—115° (Found, after drying at 78°, under reduced pressure: C, 54·1; H, 3·3. Calc. for $C_{12}H_7N_2Br,\frac{1}{2}H_2O$: C, 53·8; H, 3·0%). It was insoluble in dilute sodium hydroxide and soluble in dilute hydrochloric acid. The compound gave a deep red colour with ferrous sulphate solution in which it was soluble.

Attempt to prepare 5-*Amino*-o-*phenanthroline.*—5-Bromo-*o*-phenanthroline (3 g.), phenol (3 g.), concentrated aqueous ammonia (10 c.c.), and copper sulphate (0·3 g.) were heated in a sealed tube at 190° for 3 days. The thin black tar was separated and refluxed in benzene, yielding a dark brown residue and a reddish-brown extract which was shaken with dilute sodium hydroxide solution to remove phenol. On removal of the benzene the black residue was crystallised from ligroin and then from benzene. The crystalline compound (m. p. 96—112°) which separated on concentration of the benzene to small volume showed a negative diazo test, did not contain bromine and was crude *o*-phenanthroline as shown

by undepressed mixed m. p. On evaporating the benzene filtrate to dryness, an uncrystallisable orange-brown oil was obtained which gave a deep purple colour on diazotisation and coupling with β-naphthol. It was heated with acetic anhydride for an hour and the colourless solid, isolated in the usual way, crystallised from aqueous alcohol as colourless needles, m. p. 167—168°. This compound, after treatment with hot 5N-hydrochloric acid for 30 minutes, gave no diazo test, so that it did not appear to be the expected acetamido-derivative. It appeared to be *5-phenoxy-o-phenanthroline* (Found : C, 79·3; H, 4·5. $C_{18}H_{12}ON_2$ requires C, 79·4; H, 4·4%). It is probable, as shown by the positive diazo test of the crude material, that some amino-*o*-phenanthroline was actually formed, but in too small quantity for successful isolation.

Preparation of 5-Nitro-o-phenanthroline.—(i) To a solution of *o*-phenanthroline (1 g.) in concentrated sulphuric acid (10 c.c.) a mixture of fuming nitric acid (2 c.c.) and concentrated sulphuric acid (2 c.c.) was added. After the mixture had been heated at 100° for 2 hours it was diluted with water and basified with sodium hydroxide. The light brown solid crystallised from alcohol as colourless needles, m. p. 199—201° (Found : C, 63·9; H, 2·7; N, 18·5. Calc. for $C_{12}H_7O_2N_3$: C, 64·0; H, 3·1; N, 18·7%).

(ii) 5-Nitro-8-aminoquinoline (Slater, *J.*, 1931, 1938) (1·3 g.), sulphuric acid (7 c.c., 69%), glycerol (2 g.), arsenic acid solution (2 c.c., 80%), and water (0·8 c.c.) were refluxed for 1—2 hours, when the diazo test was negative. The dark red–brown liquid was added to water, basified with sodium hydroxide, and extracted with ether. The yellow extract, on removal of the ether, yielded a sticky yellow solid which crystallised from ligroin in pale yellow needles (Found : C, 63·5; H, 3·2. Calc. for $C_{12}H_7O_2N_3$: C, 64·0; H, 3·1%). It had m. p. 202° and did not depress the m. p. of the product obtained in (i). The compound was insoluble in dilute sodium hydroxide and soluble in dilute hydrochloric acid. It dissolved in ferrous sulphate solution giving a red colour.

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