91. *Synthesis of 4-Hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline (4-Hydroxy-*m*-phenanthroline).*

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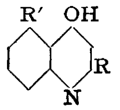
Treatment of *m*-phenanthroline oxide with phosphoryl chloride yielded 2-chloro-*m*-phenanthroline and no 4-chloro-derivative. With sulphuryl chloride, a dichloro-*m*-phenanthroline was formed. *Ethyl 5-amino-4-hydroxyquinoline-2-carboxylate* has been synthesised from *m*-aminoacetanilide hydrochloride and ethyl sodio-oxaloacetate, and decarboxylation of the free acid yields 5-*amino*-4-*hydroxyquinoline*. 4-*Hydroxy*-m-*phenanthroline* has been obtained from the latter by the Skraup reaction. Evidence is adduced in favour of the constitution assigned to the amino-4-hydroxyquinoline and to the hydroxyphenanthroline.

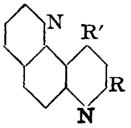
An attempt has been made to synthesise 4-chloro-*m*-phenanthroline (II; R = H, R′ = Cl) from *m*-phenanthroline by a method which works successfully in the quinoline series. Meisenheimer (*Ber.*, 1926, **59**, 1852) found that, when quinoline oxide is treated with sulphuryl chloride, 4-chloroquinoline is formed, whilst if sulphuryl chloride is replaced by phosphoryl chloride a mixture of 2- and 4-chloroquinoline is obtained. Magidson and Rubzov (*J. Gen. Chem.*, 1937, 1900) applied this reaction to 6-methoxyquinoline oxide, and though they failed to obtain the expected product with sulphuryl chloride they isolated both 2- and 4-chloro-6-methoxyquinoline from the reaction product with phosphoryl chloride.

We have found that a mono-oxide of *m*-phenanthroline (II; R = R′ = H) is readily obtained by the action of perbenzoic acid in chloroform, and when this compound was treated with phosphoryl chloride a monochloro-*m*-phenanthroline was formed, but this proved to be 2-chloro-*m*-phenanthroline (II; R = Cl, R′ = H) as shown by a mixed melting point with an authentic specimen (Kermack and Webster, J., 1942, 213). Though no 4-chloro-*m*-phenanthroline could be detected, the oxygen atom in the oxide evidently attaches itself as expected in the 1-position in accordance with the fact already proved by Kermack and Webster (*loc. cit.*) that in the monomethosulphate the methyl group is also attached in this position and not on the other nitrogen atom. Treatment of the oxide with sulphuryl chloride under moderate conditions left the oxide unchanged, but heating the mixture in a sealed tube on the water-bath for 3 hours yielded a dichloro-derivative in which one of the two chlorine atoms was presumably in the benzene ring.

In view of this failure to introduce a chlorine atom in the 4-position by this method, recourse was had to a synthesis from *m*-aminoacetanilide and ethyl oxaloacetate by the Conrad and Limpach reaction. It was found a great advantage to use *m*-aminoacetanilide hydrochloride and the commercially available ethyl sodio-oxaloacetate directly instead of isolating the free ester and base. The salts react in alcoholic solution to yield impure ethyl *m*-acetamidoanilinofumarate, which, when suspended in a large volume of hot paraffin and quickly heated to 240°, undergoes cyclisation. The yield of crystalline *ethyl* 5-*acetamido*-4-*hydroxyquinoline*-2-*carboxylate* (I; R = CO_2Et, R′ = NHAc) is poor and somewhat variable but no other crystalline compound has so far been isolated from the cyclisation product. Hydrolysis of this ester with hydrochloric acid yielded the somewhat insoluble hydrochloride of 5-*amino*-4-*hydroxyquinoline*-2-*carboxylic acid* (I; R = CO_2H, R′ = NH_2), from which the free amino-acid was readily obtained by treatment with dilute sodium acetate solution. Decarboxylation of this compound presented difficulties, as tarring readily occurred, but when it was boiled with quinoline for 30 minutes in presence of a very small amount of copper chromite decarboxylation took place and 5-*amino*-4-*hydroxyquinoline* (I; R = H, R′ = NH_2) was obtained. A Skraup reaction carried out on this base under the modified conditions of E.P. 394,416 yielded 4-*hydroxy*-5 : 6 : 2′ : 3′-*pyridoquinoline* (II; R = H, R′ = OH).

(I.)





(II.)

The above synthesis is not unambiguous, as the cyclisation to the quinoline derivative might form either a 5- or a 7-acetamido-derivative. That this compound is the 5-acetamido-derivative is probable on account of the 5-acetamido-4-hydroxy-2-methylquinoline being formed in the analogous reaction between *m*-amidoacetanilide and ethyl acetoacetate (cf. Kermack and Webster, *loc. cit.*) Also the m. p. of the resulting 4-hydroxypyridoquinoline is curiously low, just as is that of the methyl homologue (4-hydroxy-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline, m. p. 142°; 4-hydroxy-2-methyl-7 : 8 : 2′ : 3′-pyridoquinoline, m. p. 395°; new compound, m. p. 108°). These unusually low melting points may be due to the formation of a chelate ring between the hydroxyl group and the adjacent ring nitrogen atom in these compounds.

Confirmatory evidence of the position of the amino-group was obtained by treating the small amount available of the amino-4-hydroxyquinoline in acid solution with nitrous acid. The resulting diazo-compound coupled readily in alkaline solution with β-naphthol, but lost nitrogen in hot acid solution only slowly and with difficulty. The product was tarry and unpromising, but partial purification was effected by high-vacuum distillation. The compound to be expected on the assumption that the starting material was 5-amino-4-hydroxyquinoline would be 4 : 5-dihydroxyquinoline, recently obtained by Musajo and Minchilli (*Gazzetta*, 1941, 762). According to these authors 4 : 5-dihydroxyquinoline sublimes at 175—195°/0·005 mm., and after recrystallisation melts at 231—232°. Our product sublimed at about the same temperature and melted at 210—215°. The product was evidently slightly impure, but insufficient was available for further purification. It gave very characteristic colour tests with ferric chloride which agree exactly with those reported by Musajo and Minchilli.

The unexpected stability of the diazonium compound may be due to the formation of an anhydride with the hydroxyl group in the 4-position, so as to yield an oxy-diazine ring. Conrad and Limpach have described the formation of an analogous oxydiazole ring on the diazotisation of 3-amino-4-hydroxyquinoline (*Ber.*, 1888, **21**, 1981). It is realised that the above evidence in favour of the location of the amino-group at position 5 of the quinoline nucleus is not conclusive, but taken as a whole it appears to lend high probability to the position assigned.

EXPERIMENTAL.

m-*Phenanthroline* N-*Oxide*.—Redistilled, dry *m*-phenanthroline (9 g.), m. p. 75°, dissolved in dry chloroform (40 c.c.), was mixed with a cold solution of perbenzoic acid (10 g.) in chloroform (450 c.c.) prepared from benzoyl peroxide according to " Organic Syntheses," Coll. Vol. I (1st Ed.), 422. The mixture was kept below 0° and frequently shaken, the reaction, checked by iodometric titration, being complete after 2 hours. The yellow solution, after being kept in the refrigerator over-night, was filtered, concentrated in a vacuum at 30° to 250 c.c., and extracted five times with 4N-hydrochloric acid (40 c.c.). A small amount of benzoic acid which separated was filtered from the acid extract, and the latter neutralised with 5N-sodium hydroxide, a heavy precipitate of fine white needles, (7·3 g.), m. p. 185—187°, being obtained. Recrystallised from boiling water, the product had m. p. 188°. For analysis it was dried in a vacuum at 78° (Found : C, 73·5; H, 4·1; N, 14·6. $C_{12}H_8ON_2$ requires C, 73·5; H, 4·1; N, 14·3%). m-*Phenanthroline* N-*oxide* is soluble in dilute hydrochloric acid, alcohol and benzene, moderately soluble in water and acetone, and insoluble in ether and alkali. On addition of concentrated hydrochloric acid to an alcoholic solution the dihydrochloride separated in yellow needles, m. p. 229°. One mol. required 2 mols. of silver nitrate on Volhard titration.

Action of Phosphoryl Chloride on m-*Phenanthroline* N-*Oxide*.—The oxide (1 g., dried in a vacuum) was mixed with freshly distilled phosphoryl chloride (5 g.), the temperature rising to 55°. The yellow mixture was warmed on a boiling water-bath for 15 minutes and poured on ice. The resulting grey precipitate (0·5 g., m. p. 275—280°) was sparingly soluble in hot water but dissolved on addition of a very little concentrated hydrochloric acid. Neutralisation with sodium hydroxide solution gave a colourless flocculent precipitate, m. p. 150°, not depressed by 2-chloro-*m*-phenanthroline prepared from *m*-phenanthroline methylsulphate according to German Patent 654,444 (cf. Kermack and Webster, *loc. cit.*).

Action of Sulphuryl Chloride on m-*Phenanthroline* N-*Oxide Dihydrochloride under Pressure*.—The dihydrochloride (2·5 g.) was heated in a sealed tube with sulphuryl chloride (25 c.c.) on the water-bath for 3 hours. The excess of sulphuryl chloride was then filtered off, and the remaining crystalline material (0·7 g.) washed with cold water. It separated from hot alcohol in fine colourless needles, m. p. 174—178°. Recrystallised from benzene, the product melted at 187° (Found : C, 57·9; H, 2·7. $C_{12}H_7N_2Cl$ requires C, 64·7; H, 3·1%. $C_{12}H_6N_2Cl_2$ requires C, 57·9; H, 2·4%). It was very sparingly soluble in hot water, contained no halogen ions, but gave a positive chlorine test, and therefore was probably a *dichlorophenanthroline*.

Ethyl 5-Acetamido-4-hydroxyquinoline-2-carboxylate.—*m*-Aminoacetanilide hydrochloride (18 g.), ethyl sodio-oxaloacetate (21 g.), and absolute alcohol (1700 c.c. containing 0·1 c.c. of concentrated hydrochloric acid) were refluxed on the water-bath for 2 hours, the dark brown solution decanted from sodium chloride, and the alcohol distilled off, first at atmospheric and finally under reduced pressure. As the isolation of the condensation product, ethyl *m*-acetamidoanilinofumarate, in a crystalline form was not achieved, the brown gum obtained after removal of the alcohol was directly cyclised. It was divided into six equal portions, each of which was vigorously stirred with 200 c.c. quantities of liquid paraffin, pre-heated to 150°, and the supernatant emulsion poured off and rapidly heated to 240°. On cooling, the cyclisation product separated in yellow crystals, which were filtered off, washed with light petroleum and dried on the water-bath; yield 12·0 g., m. p. 180—200°. After recrystallisation from alcohol the yield was 4·0 g., m. p. 235°; on repeated crystallisation from alcohol the m. p. rose to 240° (Found : C, 60·9; H, 5·2. $C_{14}H_{14}O_4N_2$ requires C, 61·3; H, 5·1%). The *compound* was insoluble in water, benzene, ether and chloroform, and moderately soluble in alcohol, methyl alcohol and acetone.

5-Amino-4-hydroxyquinoline-2-carboxylic Acid.—Ethyl 5-acetamido-4-hydroxyquinoline-2-carboxylate (4 g.) was refluxed with 3·5N-hydrochloric acid (100 c.c.) for 2 hours. A solution was formed after 30 minutes, from which, on further heating, the hydrochloride of the desired acid separated in yellow leaflets, which were collected after cooling. When treated with water, the hydrochloride underwent hydrolysis, completed by addition of some sodium acetate, to the free amino-acid (2·7 g.), m. p. 303° (decomp.). The product, which was insoluble in most organic solvents, but readily soluble in sodium carbonate and sodium hydroxide solution, gave a positive diazo-test. For analysis it was purified by solution in hot N-hydrochloric acid, precipitation of the hydrochloride by addition of concentrated hydrochloric acid, and hydrolysis to the free base (Found : N, 14·1. $C_{10}H_8O_3N_2$ requires N, 13·7%). The yellow hydrochloride, like the free amino-acid, melted at 303°, and it seems likely that on heating it loses hydrogen chloride before melting.

The sulphate, m. p. 270—275°, was obtained by hydrolysing the acetamido-ester with 3·5N-sulphuric acid.

5-Amino-4-hydroxyquinoline.—A solution of the amino-carboxylic acid (3·2 g.) in dry quinoline (40 c.c.) containing copper chromite catalyst (40 mg.), prepared according to Connor, Folkers, and Adkins (*J. Amer. Chem. Soc.*, 1932, **54**, 1138), was refluxed for 30 minutes. The liquid was filtered, and the quinoline removed by steam-distillation. The clear brown solution was evaporated in a vacuum; *5-amino-4-hydroxyquinoline* then remained as brown crystals (1·6 g.), m. p. 176—178°. Recrystallised from hot water (charcoal), the base separated from the filtrate, to which a drop of aqueous ammonia had been added, in almost colourless needles, m. p. 189° (Found : C, 67·0; H, 4·6. $C_9H_8ON_2$ requires C, 67·5; H, 5·0%), insoluble in ether and benzene, moderately soluble in water and alcohol, soluble in dilute acids and alkali, and easily soluble in acetone. Its alcoholic solution gave a green colour with ferric chloride.

The hydrochloride crystallised in rectangular prisms, m. p. 251—255°, insoluble in acetone, moderately soluble in alcohol, and easily soluble in water.

4-Hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline.—5-Amino-4-hydroxyquinoline (0·9 g.), 69% sulphuric acid (10·8 g.), 90% glycerol (1·9 g.), and 80% aqueous arsenic acid (3·1 g.) were mixed in the above order and heated in an oil-bath. At 160° solution was complete. The temperature was raised to 170—180°, and boiling continued for 1 hour, the diazo-test then being negative. The mixture was diluted with an equal volume of water, filtered, and basified with ammonia, and the light brown precipitate filtered off and dried over sulphuric acid in a desiccator. Yield 0·6 g., m. p. 97—100°. The product separated from water in fawn-coloured needles, m. p. 107—108°, containing 1 mol. of water of crystallisation, which was not removed at 78° in a vacuum (Found : C, 67·4; H, 4·6; N, 13·0. $C_{12}H_8ON_2,H_2O$ requires C, 67·4; H, 4·7; N, 13·1%). The *compound* was very soluble in alcohol, soluble in ether, moderately soluble in cold and very soluble in hot benzene, insoluble in cold, soluble in hot water. From hot ligroin the base separated in fine needles. The acidified aqueous solution showed a blue fluorescence under the arc.

4 : 5-Dihydroxyquinoline.—5-Amino-4-hydroxyquinoline (0·2 g.), dissolved in a mixture of concentrated sulphuric acid (0·25 c.c.) and water (2 c.c.), was diazotised below 5° (sodium nitrite, 0·11 g.; water, 1 c.c.), and the diazonium solution added to boiling sulphuric acid (2 c.c.) of the same concentration in presence of a trace of copper bronze. Copious nitrogen evolution took place, accompanied by considerable darkening and tarring. The reaction mixture was exactly neutralised with barium hydroxide, and the filtrate evaporated in a vacuum on the water-bath. From the residue, a very small quantity of pale yellow material sublimed at 180—200°/0·005—0·0025 mm., m. p. 210—215°. Its alcoholic solution gave a violet colour with ferric chloride, changing to green on acidification, and then to pink on addition of sodium bicarbonate.

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