[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Synthesis of Some Chloromethoxyquinolines[1]

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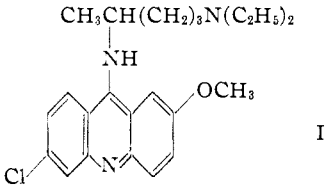
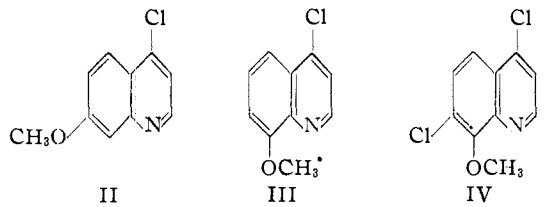
Atebrin, the common antimalarial, possesses structure I.



I

Substituted 4-aminoquinolines, which contain chlorine and/or methoxyl groups in the quinoline nucleus, therefore represent compounds of interest in a study of potential antimalarial drugs. Accordingly, three intermediates, 4-chloro-7-methoxyquinoline (II), 4-chloro-8-methoxyquinoline (III) and 4,7-dichloro-8-methoxyquinoline (IV) were prepared, preparatory to the attachment of side chains in the 4-position.[2]



II III IV

The three intermediates were prepared by making use of the procedure of Price and his co-workers. The starting materials used were *m*-anisidine, *o*-anisidine and 2-chloro-6-aminoanisole, respectively.

Experimental[3]

3-Carbethoxy-4-hydroxy-7-methoxyquinoline.—*m*-Anisidine (122 g., 1 mole) and ethoxymethylenemalonic ester (192 g., 1 mole) were heated in an oil-bath for one hour at 110–120°. At the end of this heating period, the anil was added to hot diphenyl ether through which a rapid stream of nitrogen was passed. The temperature was rapidly increased to 240° (a deep red color developed during the 200–240° interval) and maintained at 240–250° for about twenty minutes. After cooling to room temperature, the reaction mixture was filtered, washed with carbon tetrachloride and dried. Approximately 102 g. of crude ester was obtained. This ester can be sublimed *in vacuo* or recrystallized from cyclohexanone or isophorone, m. p. 275° (dec.).

Anal. Calcd. for $C_{13}H_{13}O_4N$: C, 63.16; H, 5.28. Found: C, 63.5; H, 5.5.

4-Hydroxy-7-methoxyquinoline.—An alkaline hydrolysis of the ester was carried out after the ester was subjected to steam distillation to remove any diphenyl ether. Four times the calculated amount of aqueous sodium hydroxide (10%) was used. Acidification with hydrochloric acid, followed by digestion on the steam-bath, yielded the free acid (m. p. 257–260°; 89.1 g. from 102 g. of the ester).

Decarboxylation of 3-carboxy-4-hydroxy-7-methoxyquinoline to produce 4-hydroxy-7-methoxyquinoline was accomplished as follows: Small batches of the free acid were heated in a wide test-tube immersed in a metal-bath maintained at a temperature of 290°. After several minutes of heating, gas evolution ceased and the black product was crystallized from water. The average yield in this step was 74% and the recrystallized product melted at 215°.

Anal. Calcd. for $C_{10}H_9O_2N$: C, 68.6; H, 5.1. Found: C, 68.1; H, 5.3.

4-Chloro-7-methoxyquinoline.—4-Hydroxy-7-methoxyquinoline (25.5 g.) was added slowly to a mixture of phosphorus pentachloride (31.2 g.) and phosphorus oxychloride (30 ml.), which was maintained at a temperature of 80°. The bath temperature was then increased to 120–130° and the reaction mixture maintained under reflux for one-half hour. At the end of this period the major portion of the phosphorus oxychloride was removed by distillation (bath temp. at end of distillation 150–160°). The contents of the distilling flask were then added slowly to an ice-water mixture. The yellow precipitate was crystallized from alcohol; (yield 25.0 g., m. p. 75–77°). Sublimation under low pressure gave a pure product (m. p. 82–83°).[4]

Anal. Calcd. for C_9H_6ONCl: C, 60.18; H, 3.37. Found: C, 60.00; H, 3.54.

***o*-Methoxyphenylaminomethylenemalonic Ester.**—*o*-Anisidine (123 g.) and ethoxymethylenemalonic ester (216 g.) were heated together at 100° for two hours during which time dry nitrogen was passed through the mixture to remove the ethanol which was formed. On cooling the entire product solidified; yield practically quantitative, m. p. 47.5–48.5°, after crystallization from petroleum ether (b. p. 65–110°).

Anal. Calcd. for $C_{15}H_{19}O_5N$: C, 61.4; H, 6.5. Found: C, 61.7; H, 6.9.

3-Carbethoxy-4-hydroxy-8-methoxyquinoline.—The above anil was melted and added dropwise (45 min.) to boiling diphenyl ether (500 ml.) through which dry nitrogen was bubbled. Heating was continued for an additional period of forty-five minutes. On cooling, the crude ester (196 g.; m. p. (from cyclohexanone) 234–236°) separated.

Anal. Calcd. for $C_{13}H_{13}O_4N$: C, 63.16; H, 5.28. Found: C, 63.28; H, 5.58.

3-Carboxy-4-hydroxy-8-methoxyquinoline.—The crude ester (196 g.) was refluxed for three hours with a solution of sodium hydroxide (130 g.) in water (1700 ml.). At the start of the saponification, water (200 ml.) was separated by distillation in order to remove any remaining diphenyl ether. The hot solution of the sodium salt was treated with norite, filtered, cooled and acidified with hydrochloric acid. The yield of free acid was practically quantitative; m. p. (from cyclohexanone) 280° (dec.).

Anal. Calcd. for $C_{11}H_9O_4N$: C, 60.27; H, 4.14. Found: C, 60.21; H, 4.25.

4-Hydroxy-8-methoxyquinoline.—The hydroxy acid (20 g.) was pulverized and decarboxylated by heating at reflux temperature in diphenyl ether (150 ml.) for one hour. Cooling caused the separation of the product (12 g.).

(1) This work was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Minnesota.

(2) Attachment of the side chains was carried out in the laboratories of the University of Maryland, under the direction of Dr. Nathan L. Drake.

(3) All melting points are uncorrected.

(4) *Chem. Zentr.*, **110**, II, 2446 (1939), records an I. G. Patent (Ind. P. 25,810) in which the m. p. is given as 91°. No details of preparation are given. The same patent gave a correspondingly higher m. p. of 4,7-dichloroquinoline (93–94°); *cf.* Surrey and Hammer, THIS JOURNAL, **68**, 115 (1946), give 83.5–84.5°.

Recrystallization from water yielded a hydrate (m. p. 134–135°). Heating above 135° gave anhydrous material (m. p. 168–169°).

4-Chloro-8-methoxyquinoline.—4-Hydroxy-8-methoxyquinoline (47.8 g.) was added slowly to a mixture of phosphorus pentachloride (60 g.) and phosphorus oxychloride (60 g.) at 70–80°. After the addition was completed, the temperature of the reaction mixture was raised to 130–140° for thirty minutes and finally to 150–160° under 20 mm. pressure. Removal of phosphorus oxychloride in this manner gave a residue which was broken up and added slowly to ice (300 g.) and water (100 g.). After filtration, the acidic solution was made basic with aqueous sodium hydroxide (10%). The solid product was air dried at 35–40° (yield, 39–40 g., m. p. 79–80 (after crystallization from aqueous ethanol or sublimation *in vacuo*)).

Anal. Calcd. for $C_{10}H_8ONCl$: C, 62.04; H, 4.16. Found: C, 61.85; H, 4.23.

2-Chloro-6-nitroanisole (m. p. 55–57°) was prepared by methylating 2-chloro-6-nitrophenol with dimethyl sulfate and anhydrous potassium carbonate in xylene solution.

2-Chloro-6-aminoanisole.—The reduction of 2-chloro-6-nitroanisole was carried out with iron powder. In a three-necked flask, equipped with a reflux condenser and a dropping funnel, were placed 2-chloro-6-nitroanisole (120 g.), ethanol (100 ml.), and water (100 ml.). Iron (112 g., filings smaller than 40-mesh), was added with mechanical stirring. Finally a solution of concd. hydrochloric acid (10.5 ml.) in water (40 ml.) was added dropwise and the mixture was heated under reflux with stirring for seven hours.

The product was separated from the reaction mixture by steam distilling the alkaline solution. The steam distillate was extracted with benzene (850 ml.). The amine was then extracted from the benzene with six portions (100 ml. each) of 2 *N* hydrochloric acid. The acid extract was next made alkaline with sodium hydroxide, and then taken up in benzene. The benzene extract upon distillation yielded water-white 2-chloro-6-aminoanisole (85.1 g., b. p. 112–116° at 10 mm.).

A sample of this amine was acetylated. The 2-acetamino-6-chloroanisole (m. p. 84–85°) was analyzed.

Anal. Calcd. for $C_9H_{10}O_3NCl$: C, 54.33; H, 5.03. Found: C, 54.48; H, 5.31.

Catalytic reduction of 2-chloro-6-nitroanisole in our hands was unsuccessful. It is conceivable that the high-melting product of Chien and Adams[5] was the hydrochloride of *o*-anisidine.

3-Carbethoxy-4-hydroxy-7-chloro-8-methoxyquinoline.—2-Chloro-6-aminoanisole (126 g.) and ethoxymethylenemalonic ester (180 ml.) heated in diphenyl ether according to the procedure of Price and Roberts gave an excellent yield (202 g., m. p. 225–240°) of the desired substituted quinoline.

3-Carboxy-4-hydroxy-7-chloro-8-methoxyquinoline.—The crude ethyl ester was hydrolyzed with an excess of aqueous sodium hydroxide. Any insoluble material was removed by filtration. The filtrate was acidified by pouring the alkaline solution into a slight excess of 6 *N* hydrochloric acid. The precipitate was digested on a steam-bath, filtered, washed and dried at 105°. This method of acidification was employed to prevent the presence of any sodium salt, since it was found that even traces of the sodium salt would completely alter the behavior of the acid on decarboxylation.

(5) Chien and Adams, THIS JOURNAL, **56**, 1790 (1934).

4-Hydroxy-7-chloro-8-methoxyquinoline.—Decarboxylation was accomplished by adding 3-carboxy-4-hydroxy-7-chloro-8-methoxyquinoline (31.0 g.) in small portions to boiling diphenyl ether (200 ml.). Each portion was brought into solution before the next addition was made. The time of addition was approximately fifteen minutes, but heating was continued for forty-five minutes longer. Upon cooling a brown precipitate formed. The diphenyl ether which adhered to the precipitate was removed by washing with carbon tetrachloride, and then subjecting the product to steam distillation. The aqueous suspension of the residue was concentrated and the ethanol was then added. The alcohol–water solution yielded 4-hydroxy-7-chloro-8-methoxyquinoline (17.8 g., m. p. 222–223° after recrystallization from water).

Anal. Calcd. for $C_{10}H_8O_2NCl$: C, 57.28; H, 3.82. Found: C, 57.61; H, 4.22.

4,7-Dichloro-8-methoxyquinoline.—Phosphorus pentachloride (45.2 g.) and phosphorus oxychloride (45 ml.) were heated together (70–80°) and then 4-hydroxy-7-chloro-8-methoxyquinoline (42.0 g.) was added portionwise over a period of about fifteen minutes. The reaction mixture was then heated to 130–140° for fifteen minutes at the end of which the phosphorus oxychloride was removed by distillation under reduced pressure. The dark sirupy residue was then poured into ice water. (The dichloroquinoline is a very weak base and it was frequently necessary to add more acid to dissolve all of the desired product.) The filtrate was made alkaline and the curdy precipitate (44 g.) was washed with water and dried at room temperature because of its tendency to sublime at higher temperatures.

A pure product (32 g., m. p. 91.0–91.5°) was obtained by sublimation at reduced pressure.

Anal. Calcd. for $C_{10}H_7ONCl_2$: C, 52.63; H, 3.06; N, 6.14. Found: C, 52.45; H, 3.26; N, 6.32.

In one of the early attempts to prepare 4,7-dichloro-8-methoxyquinoline by the above procedure, **4,7-dichloro-8-hydroxyquinoline** (m. p. 156–156.5°) was obtained. Instead of adding the reaction mixture to ice water, water was added to the reaction mixture which still contained considerable phosphorus oxychloride. During this operation there was vigorous evolution of hydrochloric acid. Further addition of concentrated hydrochloric acid was necessary to prevent the deposition of solid material. After filtration, the filtrate was made strongly alkaline with aqueous sodium hydroxide (20%). The green-yellow curdy precipitate (40 g. from 42 g. of 4-hydroxy-7-chloro-8-methoxyquinoline) apparently a sodium salt, was then dissolved in hot water, filtered and made slightly acid with dilute hydrochloric acid. A colorless product (m. p. 156–156.5° after crystallization from 50% ethanol) was obtained.

Anal. Calcd. for $C_9H_5ONCl_2$: C, 50.47; H, 2.34; Cl, 33.18. Found: C, 50.46; H, 2.70; Cl, 33.1.

Methylation with diazomethane gave 4,7-dichloro-8-methoxyquinoline (m. p. and mixed m. p. 91–92°).

Summary

The preparation of 4-chloro-7-methoxyquinoline, 4-chloro-8-methoxyquinoline and 4,7-dichloro-8-methoxyquinoline using the method for ring closure developed by Price and Roberts, is described.

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