3-Phenyl-4,7-dichloroquinoline, VIII.—This was prepared by the same method as was IV. From 175 g. of crude VII, 190.5 g. of crude VIII was obtained. One recrystallization from alcohol (3 l.) gave 150 g. of a mixture of the assumed 5-chloro isomer and the desired 7-chloro isomer melting at 103–110°. Pure VIII was obtained as colorless needles melting at 121–122° by three additional recrystallizations from methanol–ethanol (1:2). Pure VIII was also obtained directly starting from pure VII. However, because of the great insolubility of VII it is more convenient to purify the final product at the stage of VIII.

Anal. Calcd. for $C_{15}H_9Cl_2N$: C, 65.7; H, 3.3. Found: C, 66.0; H, 3.5.

Oxidation of 3-Phenyl-4-hydroxy-7-chloroquinoline.[6]—Six grams of VII was refluxed five hours with a solution of 25 g. of potassium permanganate and 2.5 g. of potassium hydroxide in 1500 ml. of water. After acidification of the filtrate from the manganese dioxide, the excess permanganate was destroyed with sulfurous acid. The precipitate (3 g.) melted at 222–223° after one recrystallization from acetic acid. Hann[10] gives 223.5° as the melting point for 4-chloro-N-benzoylanthranilic acid. The identity of the latter acid was confirmed by hydrolysis of the benzoyl group on heating the benzoyl acid with hydrochloric acid (sp. gr. 1.19) in a sealed tube at 130–150° for two hours. From the reaction mixture benzoic acid and 4-chloroanthranilic acid melting at 234–235° (dec.) after recrystallization from dilute alcohol, were obtained. 4-Chloroanthranilic acid is reported as melting at 235–236° and 6-chloroanthranilic acid (which would arise from 3-phenyl-4,5-dichloroquinoline) at 146–147°.[11]

Summary

3-Phenyl-4-chloroquinoline and 3-phenyl-4,7-dichloroquinoline have been prepared. The structure of the latter has been demonstrated.

(10) Hann, THIS JOURNAL, **45**, 1024 (1923).

(11) Cohn, *Monatsh.*, **22**, 485 (1901).

NEW YORK 27, N. Y. RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Synthesis of 4,6- and 4,8-Dichloroquinoline[1]

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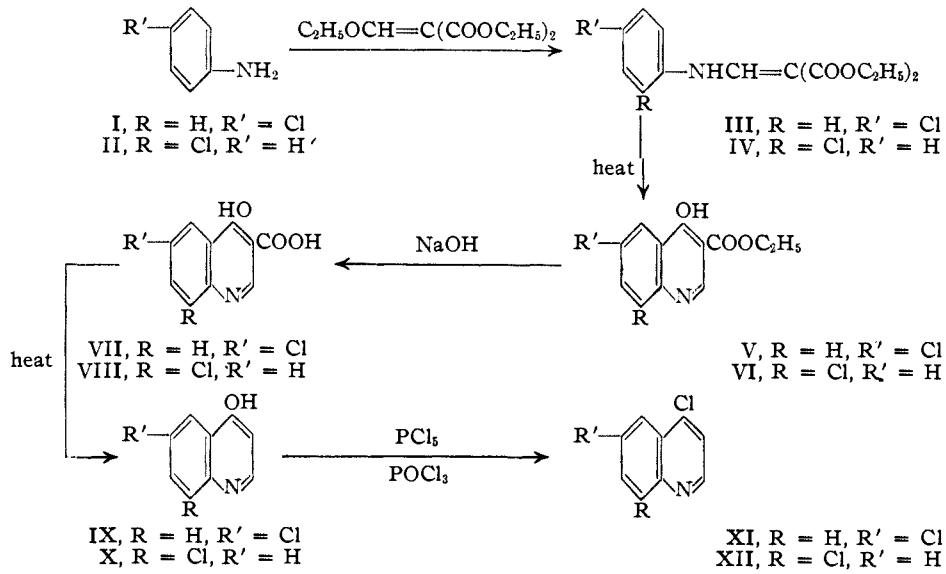
4,6- and 4,8-dichloroquinoline have been prepared from *p*-chloroaniline and *o*-chloroaniline respectively by the Price–Roberts synthesis.[2] The reactions involved are



The ring closure of the anilino compound IV to the 3-carbethoxy-4-hydroxy-8-chloroquinoline VI proceeded much more slowly than in the case of the *p*-chloro compound III, or the corresponding *m*-chloro derivative of Price and Roberts. The products VI, VIII and X were more difficult to purify than V, and some by-product seemed to be formed; this situation was unchanged by rigorous purification of the starting *o*-chloroaniline through its crystalline acetyl derivative. The whole series of reactions with the *p*-chloro isomer was far more satisfactory. Bachmann and Cooper[3] have previously prepared 4,6-dichloroquinoline (XI) by the Meisenheimer[4] procedure from the N-oxide, and have hydrolyzed it to the hydroxy compound IX.

Experimental[5]

Ethyl α-Carbethoxy-β-(2-chloroanilino)-acrylate (IV).—*o*-Chloroaniline (148 g.) was heated at 120–130° for one

(1) The work described in this report was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Rochester.

(2) Price and Roberts, THIS JOURNAL, **68**, 1204 (1946).

(3) Bachmann and Cooper, *J. Org. Chem.*, **9**, 302 (1944).

(4) Meisenheimer, *Ber.*, **59**, 1848 (1926).

(5) All melting points corrected; analyses by Lois E. May, Columbia University, and by the Micro-Tech Laboratories.

hour with 250 g. of ethoxymethylenemalonic ester; alcohol was evolved, and the product, except for 3.8 g., was cyclized to give VI.

The 3.8 g., recrystallized from 20 cc. of ethanol, yielded 3.2 g., m. p. 92–93°; the melting point was unchanged by further recrystallization.

Anal. Calcd. for $C_{14}H_{16}ClNO_4$: C, 56.47; H, 5.42. Found: C, 56.91; H, 5.74.

Ethyl α-Carbethoxy-β-(4-chloroanilino)-acrylate (III).—This compound, prepared in the same way as the isomer, was recrystallized three times from ethanol (5 cc. per g.), and melted at 81–82°.

Anal. Calcd. for $C_{14}H_{16}ClNO_4$: C, 56.47; H, 5.42. Found: C, 56.94; H, 5.66.

3-Carbethoxy-4-hydroxy-8-chloroquinoline (VI).—Diphenyl ether (600 cc.) in a 2-liter round-bottom flask, fitted with a ground glass joint to an air condenser, was heated to boiling, and the anilino compound IV described above was added in two portions. The mixture was refluxed six hours, and, after standing overnight, the crystalline product obtained by filtration was washed with petroleum ether (wt., 182 g., 63% over-all yield from *o*-chloroaniline). The melting point crude was 235–247°, and, after two recrystallizations from glacial acetic acid (6 cc. per g.), 150 g. of product, m. p. 249–252° was obtained. A small sample recrystallized twice from ethanol (about 60 cc. per g.) had the m. p. 253–254°.

Anal. Calcd. for $C_{12}H_{10}ClNO_3$: C, 57.27; H, 4.01. Found: C, 57.32; H, 3.76.

When the cyclization was run in the manner used by Price and Roberts for the *m*-chloro isomer (using about four times the above volume of diphenyl ether and refluxing for only forty minutes), the starting material was recovered largely unchanged; the smaller volume of solvent increases the rate by raising the reflux temperature and allows more complete crystallization of the cyclization product at the end of the reaction.

3-Carbethoxy-4-hydroxy-6-chloroquinoline (V).—The recrystallized compound III (15 g.) was added to 50 cc. refluxing diphenyl ether; a crystalline precipitate formed in about five minutes, and refluxing was continued for twenty-five minutes longer. The crude product (12.7 g., a quantitative yield) decomposed at about 300°, and could be crystallized satisfactorily from boiling nitrobenzene, m. p. 303–305° with dec. It was only slightly soluble in boiling glacial acetic acid or pyridine.

Anal. Calcd. for $C_{12}H_{10}ClNO_3$: C, 57.27; H, 4.01. Found: C, 57.28; H, 4.14.

4-Hydroxy-8-chloroquinoline-3-carboxylic Acid (VIII).—The ester VI (108 g.) was refluxed with 750 cc. of 10% potassium hydroxide solution for a total of one and three-quarters hours; after cooling, the alkaline solution was neutralized with 6 *N* hydrochloric acid, the acid being added slowly with stirring, and twice adding more water to make the suspension of acid stir better. The product after filtration was transferred to a beaker and washed with about 500 cc. of water, filtered again, using a rubber dam to remove as much water as possible, and dried in an oven at 130° overnight; wt. 89 g. (93%), m. p.24 8–250° with dec., the m. p. varying with rate of heating. In some runs, if the product was not carefully washed, some inorganic salt appeared after the next step.

Anal. Calcd. for $C_{10}H_6ClNO_3$: C, 53.71; H, 2.70. Found: C, 53.71; H, 2.59.

4-Hydroxy-6-chloroquinoline-3-carboxylic Acid (VII).—The ester V was hydrolyzed by essentially the above procedure, except that the sodium salt of the acid precipitated from the hydrolysis solution and was dissolved by addition of more water. The acidification was carried out by adding the alkaline solution slowly with stirring to the hydrochloric acid. The product, obtained in nearly quantitative yield, melted with decomposition at around 250°, and was only slightly soluble in hot acetic or propionic acid, somewhat more so in nitrobenzene.

Anal. Calcd. for $C_{10}H_6ClNO_3$: C, 53.71; H, 2.70. Found: C, 53.00; H, 2.70.

4-Hydroxy-8-chloroquinoline (X).—The acid VIII (89 g.) was decarboxylated in two portions by heating in an Erlenmeyer flask in a Wood's metal-bath at 260–280°, until the evolution of carbon dioxide had stopped, stirring constantly by hand to prevent foaming. There was much sublimation of material on the sides of the flask, and, after gas evolution had stopped, the sides of the flask were heated with a free flame to melt down the sublimed product, which melted with decomposition and hence probably contained some starting material. The solid cake of product was dissolved by refluxing for an hour with three successive 200-cc. portions of ethanol, the combined extracts were filtered and, by successive concentrations, four crops of material were obtained, totaling 61.0 g. of crude (85%), m. p. around 198–208°. Probably a better way of working up the reaction mixture would be to the digest product with hot acetic acid and recrystallize it from that solvent.

Purification of the crude product by recrystallization from ethanol was unsatisfactory; long extraction with ethyl acetate in a Soxhlet was more effective, the product crystallizing from the extract melting at 210–212°. The best method of purification was recrystallization from glacial acetic acid (6 cc. per g.); material which had first been purified by extraction with ethyl acetate yielded, after three crystallizations from acetic acid, long white needles, m. p. 212–213°. The compound when pure melts without decomposition.

Anal. Calcd. for C_9H_6ClNO: C, 60.18; H, 3.37. Found: C, 60.20, H, 3.07.

4-Hydroxy-6-chloroquinoline (IX).—The acid VII (148 g.) was decarboxylated in two lots by heating at 250–290° for fifteen minutes; the reaction went more smoothly than with the 8-chloro isomer and there was less sublimation. The reaction cake was dissolved in hot acetic acid with no insoluble residue, showing that decarboxylation was complete; on cooling, the product was obtained by filtration, wt., 110 g. (92%), m. p. 261–263°.[6]

4,8-Dichloroquinoline (XII).—Phosphorus pentachloride (36.4 g.) was dissolved in 50 cc. of phosphorus oxychloride, contained in a glass-jointed flask with reflux condenser, by warming to 80° in an oil-bath. 4-Hydroxy-8-chloroquinoline (X, 30 g., m. p. 204–209°) was added, and the mixture heated to 130–140° for thirty minutes. The reflux condenser was replaced by an all-glass still-head and condenser, the phosphorus oxychloride removed by distillation with the oil-bath heated up to 180°, and the last trace removed under diminished pressure. About 500 cc. of water was added to the viscous residue in the flask, the contents transferred to a beaker and heated on the steam bath. The resulting white solid was collected, wt., 31.5 g., m.p. 152–155°. The acidic filtrate from this product yielded 3.6 g. of additional product, m. p. in part 152–156°, but apparently containing much inorganic material. The first fraction (31.5 g.) was recrystallized from about 300 cc. of ethanol, with charcoal, and 19 g. of 4,8-dichloroquinoline obtained, m. p. 155–156° (57%). No pure product could be obtained from the mother liquors.

The analytical sample was recrystallized from ethanol (10 cc. per g.) and melted at 155–156°.

Anal. Calcd. for $C_9H_5Cl_2N$: C, 54.76; H, 2.53. Found: C, 54.79; H, 2.82.

4,6-Dichloroquinoline (XI).—4-Hydroxy-6-chloroquinoline (35 g.), 48 g. of phosphorus pentachloride and 150 cc. of phosphorus oxychloride yielded, by the same procedure, 28.5 g. of 4,6-dichloroquinoline (74%), m. p. 104–105° after recrystallization of the crude reaction product from 300 cc. of methanol. The reported[3] melting point is 104°.

Summary

The synthesis of 4,6- and 4,8-dichloroquinoline by the Price-Roberts method is reported, and a number of new intermediates in each synthesis are described.

ROCHESTER, NEW YORK RECEIVED APRIL 5, 1946

(6) Bachmann and Cooper[3] report the melting point as 269°.