ing at 120°, which agrees with the melting point given by Hirsch.[6]

Reaction of 4,7-Dichloroquinoline with Dimethylamine.—Despite the fact that 4,7-dichloroquinoline reacts smoothly with ammonia in the presence of phenol, a similar reaction with dimethylamine was unsuccessful, resulting in the recovery of unchanged dichloroquinoline. The only conditions under which a reaction leading to the isolation of an identifiable product other than dichloroquinoline took place are the following.

A mixture of 74 g. of 4,7-dichloroquinoline, 337.5 g. of phenol and 300 ml. of anhydrous dimethylamine was heated and shaken in an American Instrument Co. bomb at 200° for twenty-four hours. The dark brown mixture was poured into a solution of 200 g. of sodium hydroxide in 1500 ml. of water. The tan solid (50.2 g.) was filtered and washed thoroughly with water. Recrystallization from isopropanol gave a substance melting at 265–266°. The analytical figures agreed best with those for bis-(4,7-dimethylamino)-quinoline.

Anal. Calcd. for $C_{11}H_{11}ClN_2$: C, 63.9; H, 5.4. For $C_9H_5Cl_2N$: C, 54.9; H, 2.5. For $C_{13}H_{17}N_3$: C, 72.5; H, 7.9. Found: C, 72.0; H, 7.8.

4-(β-Hydroxyethylamino)-7-chloroquinoline.— A mixture of 39.6 g. of 4,7-dichloroquinoline and 36.6 g. of redistilled ethanolamine was heated in an oil-bath. When the dichloroquinoline was melted, vigorous stirring was begun and the temperature raised to 150° during fifteen minutes, at which temperature the opaque solution suddenly cleared. The temperature was raised to 185° and held for thirty minutes. The cooled crystalline cake was broken up and ground with 200 ml. of 10% sodium hydroxide solution. The insoluble material was boiled with 100 ml. of methanol and cooled without filtering. The crystalline insoluble product as thus obtained is pure and melts at 214°, which agrees with the reported melting point. The yield was 40 g. (91%).

4-(β-Chloroethylamino)-7-chloroquinoline.—A mixture of 30 g. of 4-(β-hydroxyethylamino)-7-chloroquinoline and 90 ml. of phosphorus oxychloride was refluxed two hours, and the volatile material was removed at the water pump. Careful addition of 50 ml. of water to the residue yielded a greenish-brown oil which gradually solidified on careful addition of 150–200 ml. of ammonium hydroxide (d. 0.9). Extraction of the solid with boiling benzene (1 liter) for removal of benzene insoluble salts yielded 18.5 g. (60%) of material melting at 155°. The substance is reported melting at 154°.[4]

4-(β-Bromoethylamino)-7-chloroquinoline.—A solution of 60 g. of 4-(β-hydroxyethylamino)-7-chloroquinoline in 90 ml. of redistilled, colorless constant boiling hydrobromic acid (sp. gr. 1.48) and 30 ml. of sulfuric acid (sp. gr. 1.84) was heated at gentle reflux (bath temperature 160–170°) for three and a half hours. The cooled solution was dropped into ice-water on which a heavy brown oil separated. The mixture was made basic with ammonium hydroxide. After three hours with stirring and rubbing, the insoluble mass crystallized and was filtered off and air-dried. It was then extracted with 400 ml. of boiling toluene. The pale yellow toluene solution was decanted while still hot from a dark brown solid residue, boiled with charcoal, filtered and refrigerated. The yield of colorless needles melting at 139–140° was 56 g. (73%).

Anal. Calcd. for $C_{11}H_{10}BrClN_2$: C, 46.3; H, 3.5. Found: C, 46.3; H, 3.6.

When the hydroxy compound was refluxed with hydrobromic acid alone, no reaction ensued. With phosphorus tribromide, no bromide could be isolated. With thionyl bromide, a dark product of proper melting point could be isolated in very poor yield.

Summary

1. A new synthesis for 4-amino-7-chloro- and 4-amino-6-methoxyquinoline has been described.

2. The preparation of 4-(β-hydroxyethylamino)-7-chloroquinoline and of the bromide and chloride derived from it has been described.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

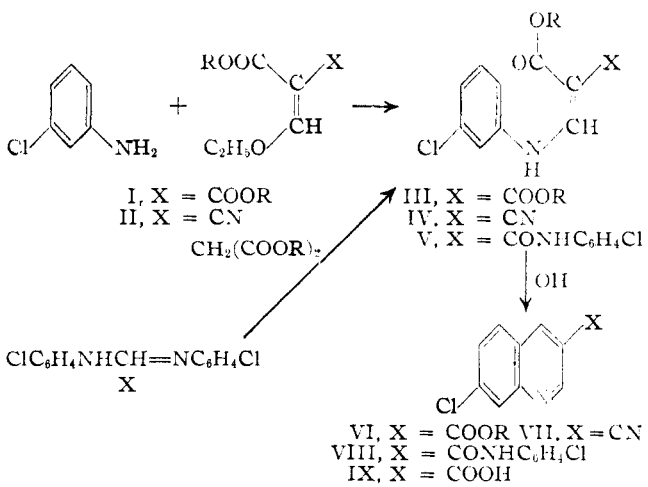
Synthesis of 4-Hydroxyquinolines. II. Preparation Through 3-Cyano and 3-Carbanilido Derivatives[1]

BY CHARLES C. PRICE,[2] NELSON J. LEONARD AND HARRY F. HERBRANDSON

Since one of the principal disadvantages of the synthesis of 4-hydroxyquinolines through ethoxymethylenemalonic ester (I)[3] is the mediocre yield in the preparation of I itself, an investigation of alternate routes was considered desirable.

It has been found that ethoxymethylenecyanoacetic ester (II) reacts with *m*-chloroaniline to give ethyl β-*m*-chloroanilino-α-cyanoacrylate (IV).

The preparation of II, however, appears to offer no particular advantage over the preparation of I and the acrylate IV was found to require much higher dilution for the cyclization to VII than did III to form VI.



(1) The work reported in this paper 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 Illinois.

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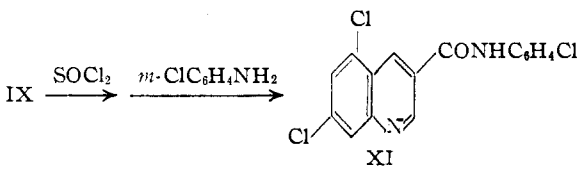
(3) Price and Roberts, THIS JOURNAL, **68**, 1204 (1946).

The observations of Dains[4] that arylformamidines may be condensed with active methylene compounds to form β-anilinoacrylates has been applied to the condensation of *bis*-(*m*-chlorophenyl)-formamidine (X) with malonic ester. The product, V, was cyclized to VIII but the reaction required as high a dilution as did the cyclization of IV.

The hydrolysis of the cyano (VII) and anilido (VIII) quinolines was readily accomplished in 50 and 70% sulfuric acid, respectively, to yield the corresponding acid (IX). An experiment designed to convert IX to VIII by conversion to the acid chloride with thionyl chloride, followed by treatment with *m*-chloroaniline, gave a product (XI) corresponding to VIII but with the 4-hydroxyl group replaced by chlorine.



XI

Experimental[5]

Ethyl Ethoxymethylenecyanoacetate.—This compound was prepared essentially according to the procedure of de Bollemont.[6] The ethyl acetate was removed by continuous distillation at 140–150°, after which the acetic acid and excess acetic anhydride were removed under diminished pressure. The residue was recrystallized from aqueous alcohol to give an average yield of 52% for two runs.

Ethyl β-*m*-Chloroanilino-α-cyanoacrylate.—A mixture of 50.7 g. (0.3 mole) of ethoxymethylenecyanoacetic ester and 38.1 g. (0.3 mole) of *m*-chloroaniline was heated at 120–130° for one hour. Ethyl alcohol distilled from the reaction during the first half hour. The crude acrylate was usually cyclized without purification, but an analytical sample was crystallized from ethanol as white needles; m. p. 126.5–127.5°.

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.49; H, 4.42; N, 11.18. Found: C, 57.43; H, 4.47; N, 11.35.

7-Chloro-3-cyano-4-hydroxyquinoline.—Seven hundred milliliters of diphenyl ether was added to 26.2 g. (0.104 mole) of ethyl β-*m*-chloroanilino-α-cyanoacrylate and, with nitrogen bubbling through the solution, it was heated to boiling. After two hours, a crystalline precipitate began to form, and heating was continued for one half hour longer, when the evolution of alcohol appeared to cease. The product, as light brown flakes, was removed by filtration, washed well with petroleum ether (b. p. 90–110°), and dried, 8.4 g. (39%). Although very unsatisfactory, pyridine was the best solvent found for recrystallization The analytical sample was sublimed *in vacuo* as a light yellow powder; m. p. about 370° (dec.).

Anal. Calcd. for $C_{10}H_5ClN_2O$: C, 58.69; H, 2.46. Found: C, 59.05; H, 2.70.

***bis*-(*m*-Chlorophenyl)-formamidine.**—A solution of 29.6 g. (0.2 mole) of distilled ethyl orthoformate and 50.8 g. (0.4 mole) of *m*-chloroaniline was heated under reflux with a water-cooled condenser for about two and one-half hours. Then for one-half hour the water was turned off and alcohol was permitted to distil from the reaction mixture. The solution solidified to a white mass when it was cooled. The amidine recrystallized from petroleum ether (b. p. 90–110°) as a white powder, m. p. 116.5–117°. The yield, after recrystallization, was 49.1 g. (93%).

Anal. Calcd. for $C_{13}H_{10}Cl_2N_2$: C, 58.89; H, 3.80. Found: C, 59.02; H, 3.84.

Ethyl α-*m*-Chlorocarbanilido-β-(*m*-chloroanilino)-acrylate.—Eight grams (0.05 mole) of malonic ester and 13.3 g. (0.05 mole) of *bis*-(*m*-chlorophenyl)-formamidine were heated together at 150–165° for two hours. A yield of 13.3 g. (70%) of fine, white needles was obtained after one recrystallization of the product from aqueous alcohol; m. p. 113–114°. The unrecrystallized product was generally cyclized directly.

Anal.[7] Calcd. for $C_{18}H_{16}Cl_2N_2O_3$: C, 57.00; H, 4.25. Found: C, 56.71; H, 4.50.

7-Chloro-3-*m*-chlorocarbanilido-4-hydroxyquinoline.—Seven hundred milliliters of diphenyl ether was added to the acrylanilide prepared from 17.5 g. (0.066 mole) of N,N'-di-(*m*-chlorophenyl)-formamidine and 10.6 g. (0.066 mole) of malonic ester. After refluxing for three hours, the solution was cooled, and the crystals which separated were removed by filtration. The product was obtained as light brown plates; 12.8 g. (58%), m. p. 300–305°. The analytical sample, recrystallized from glacial acetic acid and aqueous ethanol, melted at 321–322° (dec.).

Anal. Calcd. for $C_{16}H_{10}ClN_2O_2$: C, 57.68; H, 3.03. Found: C, 57.83; H, 2.86.

7-Chloro-3-carboxy-4-hydroxyquinoline. A. From 7-Chloro-3-cyano-4-hydroxyquinoline.—A solution of 13. 6 g. (0.067 mole) of 7-chloro-3-cyano-4-hydroxyquinoline in 67 ml. of concentrated sulfuric acid and 80 ml. of water was refluxed for one hour and the solution cooled and filtered through a sintered glass funnel. The solid was dissolved in dilute sodium hydroxide, the hot solution treated with Darco and filtered. Acidification of the filtrate yielded 12.7 g. (86%) of acid; m. p. 270–272° (dec.). Mixed with an authentic sample[1] of the acid, the decomposition point was undepressed.

From the sulfuric acid solution, poured onto ice and neutralized, was obtained an additional 1.7 g. of solid melting below 240° (dec.) which was not further investigated.

B. From 7-Chloro-3-*m*-chlorocarbanilido-4-hydroxyquinoline.—Two grams of the anilide was refluxed with 20 g. of 70% sulfuric acid for ten minutes. This was poured into water and the precipitate was separated by filtration, washed well with water, and dried; m. p. 265–267° (dec.). The decomposition point of the acid was not depressed when it was mixed with an authentic sample[1] of 7-chloro-4-hydroxy-3-quinolinecarboxylic acid.

4,7-Dichloro-3-*m*-chlorocarbanilidoquinoline.—Two-tenths of a gram of 7-chloro-3-carboxy-4-hydroxyquinoline and 2 ml. of thionyl chloride were refluxed together for fifteen minutes. Ten milliliters of benzene and then 2 ml. of *m*-chloroaniline in 20 ml. of benzene were added. The emulsion was washed with water, dilute hydrochloric acid and dilute sodium hydroxide. The solid was then removed by filtration, washed with alcohol and recrystallized as fine, white needles from aqueous alcohol; m. p. 224.5–226°.

Anal. Calcd. for $C_{16}H_9Cl_3N_2O$: C, 54.65; H, 2.58; Cl, 30.25. Found: C, 54.55; H, 2.41; Cl, 30.06.

Summary

The preparation of 3-cyano- and 3-*m*-carbanilido-7-chloro-4-hydroxyquinoline have been reported.

URBANA, ILLINOIS RECEIVED APRIL 5, 1946

(4) Dains, *Ber.*, **35**, 2507 (1902); *Univ. of Kansas Sci. Bull.*, **19**, 215 (1930).

(5) Except where noted, all melting points and boiling points are uncorrected. The microanalyses were carried out by Miss Theta Spoor, Miss Lillian Hruda, and Mr. Howard Clark.

(6) de Bollemont, *Bull. soc. chim.*, (3) **25**, 20 (1901).

(7) The analytical sample was purified by Dr. R. E. Jones.