4 ml. of ether. The titration was conducted with potassium thiocyanate to a red-pink end-point that persisted on shaking. It was shown that the chloroquinoline did not hydrolyze under these conditions. As a general rule, a small amount of color in the reaction mixture did not interfere with observation of the end-point.

A. **Reaction of 4,7-Dichloroquinoline with 1-Diethylamino-4-aminopentane.**—A mixture of 1 g. (0.005 mole) of 4,7-dichloroquinoline and 2.30 g. (0.014 mole) of 1-diethylamino-4-aminopentane was heated at 170–175° under an atmosphere of dry nitrogen. When a sample was to be taken, the reaction flask was allowed to cool for several minutes. Then the sample was removed and the flask immediately lowered into the bath. Titrations were performed as above.

TABLE III

Time, min.	$AgNO_3$, ml.	Reaction, %
0	0	0
25	0.38	5
60	1.09	15
120	2.00	28
180	4.93	68
225	6.57	91
300	6.72	93

The reaction product was isolated by removal of excess 1-diethylamino-4-aminopentane by distillation under reduced pressure. The crude picrate melted at 197–200°. (The pure material melts at 205°.)[14]

B. **Reaction of 4,7-Dichloro-5-methoxyquinoline with 1-Diethylamino-4-aminopentane.**—In each of the following experiments, 1 g. (0.004 mole) of chloroquinoline and 3.0 g. (0.019 mole) of 1-diethylamino-4-aminopentane were treated as in A. The temperature of the mixture of the first experiment was 175–180°; of the second, 160–165°.

TABLE IV

Time, min.	$AgNO_3$, ml.	Reaction, %
	(1)	
30	3.99	78
80	5.07	100
140	5.08	100
	(2)	
0	0	0
40	2.80	50
60	3.68	66
95	4.81	87
115	5.49	99
145	5.54	100

The product from the second experiment was the more readily purified.

Summary

A number of halogen-containing 4-aminoquinoline derivatives were prepared by a series of reactions involving the initial condensation of various anilines with ethoxymethylenemalonic ester. The intermediates are described.

An analytical procedure was devised for following the course of reaction of 4-chloroquinolines with amines.

URBANA, ILLINOIS RECEIVED SEPTEMBER 23, 1946

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[14] C. C. Price, private communication.

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

Synthesis of 4-Hydroxyquinolines. IX. 4-Chloro-7-cyanoquinoline and 4-Chloro-5-cyanoquinoline[1]

BY CHARLES C. PRICE,[2] H. R. SNYDER, ORVILLE H. BULLITT, JR.,[3] AND PETER KOVACIC[3a]

In continuation of the studies on antimalarial agents, 4-chloro-7-cyanoquinoline and 4-chloro-5-cyanoquinoline were synthesized as intermediates for the preparation of 4-dialkylaminoalkylaminoquinolines.

A modification of the method of Price and Roberts[4] was utilized for the preparation of 4-chloro-7-cyanoquinoline. 3-Carbethoxy-4-hydroxy-7-nitroquinoline was obtained in the usual manner from *m*-nitroaniline and ethoxymethylenemalonic ester. Subsequent reduction of the nitro group and hydrolysis of the carbethoxyl group gave 7-amino-3-carboxy-4-hydroxyquinoline in good yield. A satisfactory procedure was devised for decarboxylation of the acid. The structure of 7-amino-4-hydroxyquinoline was proved by conversion to 7-chloro-4-hydroxyquinoline which was identical with the authentic material. The preparation of the 7-cyano compound by the Sandmeyer reaction of 7-amino-4-hydroxyquinoline could be effected only in low yield; the occurrence of tautomerization[5] in the 4-hydroxyquinoline could account for the difficulties involved in diazotization.

In the early work involving the cyclization of ethyl α-carbethoxy-β-(*meta*-substituted)-anilinoacrylates, there was no indication of the presence of isomers when the syntheses were carried out on a laboratory scale. Only one isomer was isolated from a Price–Roberts synthesis with *m*-chloroaniline,[4] *m*-nitroaniline, *m*-trifluoromethylaniline,[6] 3-chloro-5-methoxyaniline[6] and 3-chloro-4-methoxyaniline.[6] After the discovery that the cyclization of ethyl α-carbethoxy-β-(*m*-fluoro-

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[4] Price and Roberts, THIS JOURNAL, **68**, 1204 (1946).

[5] Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, New York, N. Y., 1942, p. 552.

[6] Snyder, Freier, Kovacic and Van Heyningen, THIS JOURNAL, **69**, 371 (1947).

anilino)-acrylate yielded a mixture of isomers,[6] it was found in large-scale operations that about 15% of 3-carbethoxy-5-chloro-4-hydroxyquinoline is formed in the cyclization of ethyl α-carbethoxy-β-(*m*-chloroanilino)-acrylate.[7]

Furthermore, during the present investigation, it was found that only 4-chloro-5-cyanoquinoline could be isolated from a Price–Roberts synthesis with *m*-cyanoaniline. The mixture melting point with authentic 4-chloro-7-cyanoquinoline showed a marked depression. Reduction in the presence of palladium-charcoal catalyst yielded a compound whose melting point agrees with that reported[8] for 5-cyanoquinoline.

Experimental[9]

Ethyl α-Carbethoxy-β-(*m*-nitroanilino)-acrylate (I).—A mixture of 69 g. (0.5 mole) of *m*-nitroaniline (technical) and 108 g. (0.5 mole) of ethoxymethylenemalonic ester was heated with stirring at 110° for forty minutes. Crystallization of the product from a mixture of benzene and chloroform gave 138 g. (90%) of yellow crystalline solid, m. p. 79–81°.

3-Carbethoxy-4-hydroxy-7-nitroquinoline (II).—To 550 ml. of refluxing diphenyl ether was added 53.9 g. (0.175 mole) of the acrylate (I). Vigorous refluxing was maintained for forty-five minutes. The mixture was then cooled to room temperature, diluted with 200 ml. of petroleum ether (b. p. 90–110°) and filtered. There was obtained 38.9 g. (85%) of material which melted above 300°.

7-Amino-3-carboxy-4-hydroxyquinoline (III).—A mixture of 78.6 g. (0.3 mole) of the ester (II), 500 ml. of glacial acetic acid and 200 ml. of water was heated to 110°. Then 54 g. (0.97 mole) of 100-mesh iron powder was added over a period of one and three-quarters hours with stirring. After the mixture was heated under reflux for three-quarters of an hour longer, the solvents were removed by distillation until a viscous mass remained. A solution of 70 g. of sodium hydroxide in 350 ml. of water was added and hydrolysis was effected by heating under reflux with stirring for three-quarters of an hour. The contents were filtered while hot and the residue was digested with a solution of 15 g. of sodium hydroxide in 200 ml. of water. The filtrates were combined, filtered and acidified with glacial acetic acid. The solid was removed by filtration, and the residual slurry was digested with 200 ml. of water and filtered. After being dried, the yellow powder weighed 59 g. (96.5% yield based on the ester (II), m. p. 214–216° (dec.).

7-Amino-4-hydroxyquinoline (IV).—To 100 ml. of diphenyl ether at 225° was added 22.3 g. (0.139 mole) of the acid (III) in portions. Heating was maintained at 225° for ten to fifteen minutes with occasional stirring, and then the mixture was heated rapidly to 245° at which temperature heating was discontinued. The contents were allowed to cool to room temperature, diluted with 150 ml. of petroleum ether (b. p. 90–110°) and filtered. After being washed with petroleum ether and then dried, the crude product weighed 18.2 g.

The crude material was extracted with 800 ml. of alcohol in a Soxhlet apparatus. The alcoholic solution was decolorized with Darco and then concentrated to a volume of 150 ml. After the addition of 700 ml. of petroleum ether (b. p. 90–110°), the mixture was cooled and filtered. The yield of tan solid was 13.2 g. (75%).

A sample for analysis was prepared by sublimation under reduced pressure; m. p. 290° (dec.).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.48; H, 5.03. Found: C, 67.68; H, 5.02.

Proof of Structure of 7-Amino-4-hydroxyquinoline.—A solution of 6.4 g. (0.04 mole) of crude 7-amino-4-hydroxyquinoline, m. p. 263°, in 20 ml. of glacial acetic acid was added dropwise to a stirred solution[10] of 2.9 g. (0.041 mole) of sodium nitrite in 30 ml. of concentrated sulfuric acid. The addition was carried out over a period of one hour while the temperature of the reaction mixture was kept below 15°. The mixture was allowed to warm to room temperature and then was added dropwise over a period of one hour to a stirred solution of 4.95 g. (0.05 mole) of cuprous chloride in 40 ml. of concentrated hydrochloric acid while the temperature was kept below 15°. After the addition of 20 ml. of concentrated hydrochloric acid and 25 ml. of water, the mixture was allowed to stand at room temperature for two hours. The contents were then heated to 75° on a steam-cone, cooled in an ice-bath and filtered. The filtrate and residue were treated separately as follows.

The filtrate was made basic with concentrated ammonium hydroxide and filtered. The light brown residue was washed successively with ammonium hydroxide solution and water; m. p. 263°. After recrystallization from water, the white solid melted at 270–274°. The mixture melting point with an authentic sample of 7-chloro-4-hydroxyquinoline (m. p. 271–276°) was 271–272.5° (a mixture of 7-amino- and 7-chloro-4-hydroxyquinolines melted at 218–230°).

The original residue was washed with 100 ml. of water, whereupon about one-half dissolved. The remaining solid was added to concentrated ammonium hydroxide and a pink solid, m. p. 250–263°, was separated by filtration.

Upon the addition of concentrated ammonium hydroxide to the aqueous extract of the original residue, a tan solid separated. After recrystallization from water, the material melted at 272–273°; the mixture melting point with authentic 7-chloro-4-hydroxyquinoline was 271–271.5°. The picrate melted at 245–248° (dec.) and a mixture melting point of 247–250° (dec.) was obtained with an authentic sample of the picrate (m. p. 245–250° (dec.)) of 7-chloro-4-hydroxyquinoline.

Price, Leonard and Reitsema report[11] that 5-chloro-4-hydroxyquinoline melts at 266–268° (cor.), its picrate at 264° (dec.) (cor.) and that the mixture melting point of the 5- and 7-chloro compounds shows a marked depression (40 to 50°), as is also the case with the picrates.

The total weight of crude 4-hydroxy-7-chloroquinoline was 2.6 g. (36%).

7-Cyano-4-hydroxyquinoline.—To 8 g. (0.05 mole) of 7-amino-4-hydroxyquinoline were added a solution of 10 g. of sodium hydroxide in 60 ml. of water and 3.5 g. (0.05 mole) of sodium nitrite. This mixture was added dropwise with stirring to a solution of 75 ml. of concentrated hydrochloric acid in 50 ml. of water. The addition was carried out over a period of one hour while the temperature was kept below 5°. After being stirred for fifteen minutes longer, the diazonium solution was added dropwise over a period of one and one-half hours to 60 ml. of 1 *N* cuprous cyanide solution while the temperature was kept below 5°. The mixture was allowed to stand at room temperature for one hour, then heated to 50° and finally cooled in an ice-bath. The brown precipitate was collected by filtration, washed with water and dried; wt. 4.6 g. (54%).

Attempts to purify the material by recrystallization were unsuccessful.

4-Chloro-7-cyanoquinoline.—To a mixture of 10 ml. of phosphorus oxychloride and 2.3 g. (0.011 mole) of phosphorus pentachloride was added 2 g. (0.011 mole) of crude 7-cyano-4-hydroxyquinoline. The mixture was gently refluxed for one and one-third hours and then allowed to cool to room temperature. The reaction mixture was added to cracked ice and neutralized in the cold with dilute

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[7] G. W. Stacy, private communication.

[8] Fieser and Hershberg, THIS JOURNAL, **62**, 1640 (1940).

[9] The microanalyses were carried out by Miss Theta Spoor and Mr. Howard Clark. All melting points are uncorrected unless otherwise indicated.

[10] Hodgson and Walker, *J. Chem. Soc.*, 1620 (1933).

[11] Price, Leonard and Reitsema, THIS JOURNAL, **68**, 1256 (1946).

sodium hydroxide solution. The brown slurry was filtered and the residue washed with water. The material was steam-distilled; there was obtained 0.6 g. (27%) of a fluffy, white solid, m. p. 165–167°.

Anal. Calcd. for $C_{10}H_5N_2Cl$: C, 63.67; H, 2.67; N, 14.86. Found: C, 63.52; H, 2.84; N, 14.72.

3-Carboxy-5-cyano-4-hydroxyquinoline (V).—The acid (V) was obtained from *m*-cyanoaniline by a series of reactions similar to those described by Price and Roberts[4] for the preparation of 3-carboxy-7-chloro-4-hydroxyquinoline. The yield was 90% (based upon *m*-cyanoaniline).

5-Cyano-4-hydroxyquinoline (VI).—A mixture of 20 g. of the acid (V) and 200 ml. of diphenyl ether was refluxed vigorously for one hour. A large amount of dark material was present in addition to some white, crystalline solid. The reaction mixture was allowed to cool to room temperature and was used directly to form the chloroquinoline (VII).

4-Chloro-5-cyanoquinoline (VII).—After 13 ml. of phosphorus oxychloride was added to the above reaction mixture, the contents were heated with stirring at 100–110° for forty-five minutes and then filtered while hot. Ice, water and 200 ml. of petroleum ether (b. p. 90–110°) were added to the filtrate and the whole was filtered to remove a small amount of dark material. The aqueous layer was separated and made basic with 30% sodium hydroxide solution while the temperature was kept below 20°. The tan precipitate was collected by filtration and washed with water; wt. 7.8 g., m. p. 250–255°.

The solid was extracted with ethyl ether in a Soxhlet apparatus. After the ether solution was evaporated to dryness, there remained 4.3 g. (24% based upon the acid (V)) of solid, m. p. 147–152°. A sample was recrystallized from petroleum ether (b. p. 90–110°) to give white flocks, m. p. 155–156°.

Anal. Calcd. for $C_{10}H_5N_2Cl$: C, 63.67; H, 2.67. Found: C, 63.86; H, 2.76.

The mixture melting point with authentic 4-chloro-7-cyanoquinoline, m. p. 165–167°, was 125–140°.

Proof of Structure of 4-Chloro-5-cyanoquinoline.—A mixture of 2 g. (0.01 mole) of 4-chloro-5-cyanoquinoline, 0.9 g. of palladium–charcoal (10%), 1.2 g. of potassium hydroxide and 150 ml. of absolute ethanol was shaken under a pressure of 2–3 atmospheres of hydrogen at room temperature. After the absorption of hydrogen was complete, the solution was filtered. The slightly yellow filtrate was evaporated to dryness in an air stream. The residual solid was triturated with 20 ml. of water, collected on a filter and washed with 15 ml. of water. After being dried, the material weighed 1.37 g. (85%), m. p. 84–87°.

After recrystallization from petroleum ether (b. p. 90–110°), the white solid melted at 87–88° (Fieser and Hershberg report[8] that 5-cyanoquinoline melts at 87–88° (cor.)).

Summary

4-Chloro-7-cyanoquinoline has been synthesized by the intermediate formation of 7-amino-4-hydroxyquinoline.

4-Chloro-5-cyanoquinoline has been synthesized from *m*-cyanoaniline.

URBANA, ILLINOIS RECEIVED SEPTEMBER 23, 1946

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF ALBERTA AND QUEEN'S UNIVERSITY]

Studies on the Structures of Some Dibenznaphthacenes

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The work reported in this communication was carried out because of a publication by Bergmann[2] in which he suggested the desirability of synthesizing 1,2,7,8-dibenznaphthacene and testing it for carcinogenic action. The synthesis of a dibenznaphthacene (IV) m. p. 341–343°, by the pyrolysis of 2-methyl-1-naphthyl-3′-phenanthryl ketone (I) has been reported by Cook,[3] who assigned to *hydrocarbon IV* the structure of 1,2,9,10-dibenznaphthacene. A small amount of an orange hydrocarbon (II) m. p. 245–248°, was obtained from the xylene liquors of IV and according to Cook, II was probably isomeric with IV. The present results show that there is fairly good synthetic evidence that *hydrocarbon II*, m. p. 245–248°, is 1,2,9,10-dibenznaphthacene. Clar[4] has furnished additional evidence, mainly spectroscopic, in support of this structure. If this structure is correct, then it is probable that *hydrocarbon IV*, m. p. 341–343°, is 1,2,7,8-dibenznaphthacene. Since Cook, Hieger, Kennaway and Mayneord[5] have found this hydrocarbon to be non-carcinogenic, it seems likely that Bergmann's wish has been granted.

Due to war conditions, some of our work was carried out before we were able to obtain Clar's original paper. In one series of experiments we reinvestigated the pyrolysis of 2-methyl-1-naphthyl-3′-phenanthryl ketone (I) and obtained hydrocarbons II and IV[6] as Cook has already reported. We also investigated the pyrolysis of 2-methyl-1-naphthyl-2′-phenanthryl ketone (III) and 2-methyl-1-naphthyl-2′-(9,10-dihydrophenanthryl) ketone (V) and obtained in both cases, hydrocarbon IV and a pale yellow (sometimes almost white) hydrocarbon (VI), m. p. 383–385°. Clar applied the Elbs reaction to a mixture of ketones I and III and reported the formation of hydrocarbons IV and VI but not the expected II. A by-product which we found common to all of

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(2) Bergmann, *Cancer Research*, **2**, 660 (1942).

(3) Cook, *J. Chem. Soc.*, 499 (1931).

(4) (a) Clar, *Ber.*, **76B**, 149 (1943); (b) Clar, "Aromatische Kohlenwasserstoffe," Springer, Berlin, 1941 (copyright vested in the Alien Property Custodian, lithoprinted by Edwards Brothers, Inc., Ann Arbor, Michigan, 1944), p. 179.

(5) Cook, Hieger, Kennaway and Mayneord, *Proc. Roy. Soc.* (London), **B111**, 455 (1932).

(6) To account for IV, Clar assumes a rearrangement of ketone I to ketone III.