inoacrylamides with phosphorus oxychloride or phosphorus pentoxide a number of substituted 4-amino-7-chloroquinolines have been prepared.

The substituted β-*m*-chloroanilinoacrylamides were prepared by treating the amide of an acid having an adjacent active methylene group with an aryl amine and ethyl orthoformate.

URBANA, ILLINOIS RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Synthesis of Certain Simple 4-Aminoquinoline Derivatives[1]

BY ROBERT C. ELDERFIELD, WALTER J. GENSLER, OSKAR BIRSTEIN, FRANK J. KREYSA, JOHN T. MAYNARD AND JEAN GALBREATH

Quinoline derivatives containing a primary amine group in the 4-position have, as a general rule, been prepared in the past from the corresponding quinoline-4-carboxylic acids by either the Hofmann or Curtius degradations. The ready availability of derivatives of 4-chloroquinoline[2] suggests that the amino derivatives might be prepared more conveniently by replacement of the 4-chlorine atom. Whereas 4-chloroquinoline and its derivatives react readily with primary aliphatic amines,[3] the chlorine atom has now been found to be remarkably inert toward reaction with ammonia. Thus when 4,7-dichloroquinoline was heated with anhydrous ammonia at 170° for three hours, it was recovered quantitatively; at 230–240° for five hours, extensive decomposition occurred. When it was fused with potassium phthalimide at 170° or when it was heated with sodamide in dioxane at 100° for twelve hours, recovery of unreacted material was also quantitative. However, reaction of 4,7-dichloroquinoline with ammonia in the presence of phenol by a modification of the procedure of Andersag, Breitner and Jung[4] furnished 4-amino-7-chloroquinoline readily. In a similar fashion, 4-amino-6-methoxyquinoline was prepared.

When 4,7-dichloroquinoline was subjected to the action of dimethylamine in phenol under conditions which led to ammoniation, no reaction occurred and the material was recovered quantitatively. Use of a higher temperature and pressure for the reaction with dimethylamine resulted in replacement of both chlorine atoms with the formation of 4,7-bis-dimethylaminoquinoline.

4-Amino-7-chloroquinoline has also been prepared by the general method of Backeberg[5] by reduction of 7-chloroquinoline-4-phenylhydrazine, and 4-amino-6-methoxyquinoline has been prepared by an improvement of the Hofmann degradation of quininic acid amide as given by Hirsch.[6]

Reaction of 4,7-dichloroquinoline with ethanolamine to yield 4-(β-hydroxyethyl)-7-chloroquinoline and conversion of the latter to 4-(β-chloroethyl)-7-chloroquinoline and 4-(β-bromoethyl)-7-chloroquinoline have been described briefly in the patent literature.[4] In connection with other work we have had occasion to prepare these substances and the opportunity is now taken to record their preparation and properties.

Experimental[7,8]

4-Amino-7-chloroquinoline: (a) From 7-Chloroquinoline-4-phenylhydrazine.—The hydrazine was prepared in 43% yield exactly according to Backeberg[5] from 4,7-dichloroquinoline. It was reduced directly, after one recrystallization from water, with zinc dust and hydrochloric acid according to Backeberg,[5] yielding 42% of 4-amino-7-chloroquinoline melting at 150–152.5° after recrystallization from benzene (carbon).

Anal. Calcd. for $C_9H_7ClN_2$: C, 60.5; H, 3.9. Found: C, 60.9; H, 4.0.

(b) By Ammoniation of 4,7-Dichloroquinoline.—A mixture of 66 g. of 4,7-dichloroquinoline and 300 g. of phenol was heated in an oil-bath to 170° in a three-necked flask equipped with a stirrer, reflux condenser, thermometer and gas inlet tube. Dry ammonia was then passed through the mixture at 170–175° for six hours. At the start a solid separated which went into solution as the reaction proceeded. The cooled solution was poured into 10% sodium hydroxide solution, yielding crude 4-amino-7-chloroquinoline as a tan solid. Solid carbon dioxide was added to the solution of the crude material in moist ether (1 liter) until no further precipitation of the amine carbonate occurred. The carbonate was filtered and dissolved in hot 10% hydrochloric acid from which the hydrochloride separated on cooling. This was decomposed with 10% sodium hydroxide yielding 52% of 4-amino-7-chloroquinoline melting at 150–151°.

4-Amino-6-methoxyquinoline (a).—This was prepared by exactly the same procedure as was used for the synthesis of 4-amino-7-chloroquinoline. The substance melted at 119–120° after recrystallization from benzene and showed no depression in melting point when mixed with a sample prepared by degradation of quininic acid.

(b) **From Quininic Acid Amide.**—The procedure of Hirsch[6] has been improved by the use of dioxane as solvent. To a well-stirred mixture of 25 g. of quininic acid amide (m. p. 197°), 104 ml. of pure dioxane, 5 g. of sodium hydroxide and 50 ml. of water at 25–30° was added dropwise a solution of 20.5 g. of bromine in 25.6 g. of sodium hydroxide and 120 ml. of water. Stirring was continued for fifteen minutes, when solution was substantially complete. The mixture was then heated at 85° for an hour. The two-phase mixture was concentrated to about one-fourth its volume, cooled in ice and the precipitate filtered off. The crude tan product was crystallized from water, yielding 68% of 4-amino-6-methoxyquinoline melt-

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

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

(3) Steck, Hallock and Holland, *ibid.*, **68**, 129, 132 (1946); Surrey and Hammer, *ibid.*, **68**, 113 (1946), where a good review of previous work is found.

(4) Andersag, Breitner and Jung, U. S. Patent 2,233,970, *C. A.*, **35**, 3771 (1941).

(5) Backeberg, *J. Chem. Soc.*, 1083 (1938).

(6) Hirsch, *Monatsh.*, **17**, 327 (1896).

(7) All melting points are corrected.

(8) Microanalyses by Mr. William Saschek and Miss Lois May.

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.

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

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

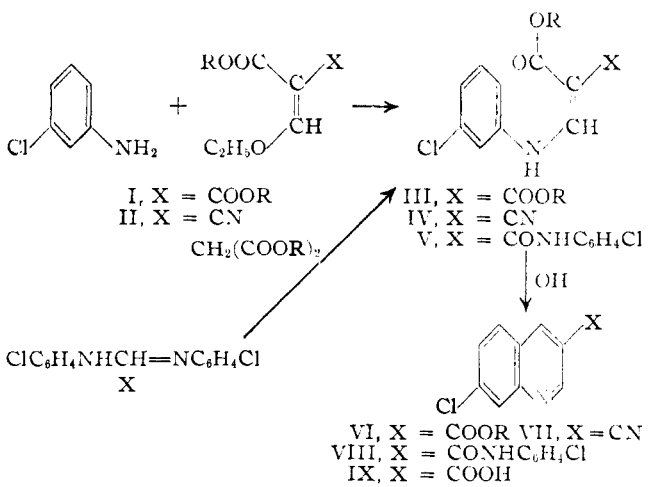
Synthesis of 4-Hydroxyquinolines. II. Preparation Through 3-Cyano and 3-Carbanilido Derivatives[1]

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.

(2) Present address, University of Notre Dame, Notre Dame, Indiana.

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