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

5- and 7-Chloro-8-aminoquinoline[1]

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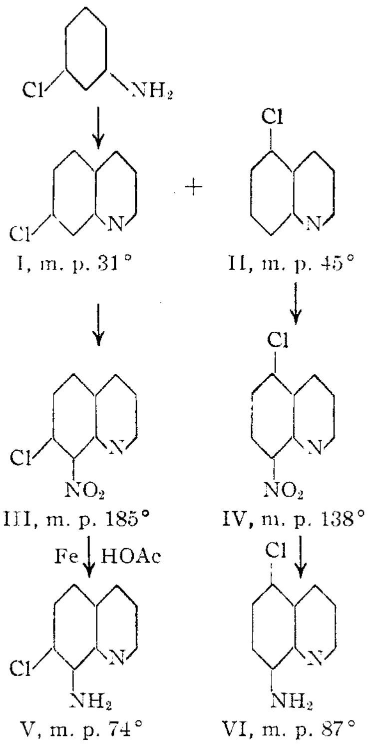
In the antimalarial drugs of the 4-dialkylaminoalkylaminoquinoline series, it has been reported that the presence of a group, especially a chlorine atom, in the 7-position gives drugs superior to those having a methoxyl group in the 6-position.[3] This observation has suggested the preparation of the corresponding analog of pamaquine (Plasmochin) with a 7-chlorine rather than a 6-methoxyl substituent.

Unfortunately 7-chloro-8-aminoquinoline failed to couple with a dialkylaminoalkyl halide under all conditions employed. Since 6-methoxy-8-aminoquinoline itself has a considerable proportion of the antimalarial activity of pamaquine, 7-chloro-8-aminoquinoline (SN-11,419),[4] and 5-chloro-8-aminoquinoline (SN-11,629) were submitted to test against avian malaria and found to be devoid of activity.

Incidental to this work, some discrepancies in the literature concerning the identity and properties of 5- and 7-chloro-8-aminoquinoline and several related compounds have been clarified. 7-Chloroquinoline (I), m. p. 31°, was first prepared by La Coste and Bodewig[5] in 1884 by the Skraup reaction on *m*-chloroaniline. Nitration converted it to 7-chloro-8-nitroquinoline (III), m. p. 185–186°, but the position of the chlorine atom was not established.

Claus and Junghanns[6] have reduced this nitro compound to the aminoquinoline (V), m. p. 69°. These investigators also isolated a second chloroquinoline (I), m. p. 45°, from the Skraup reaction. The chlorine atom in this product was also assigned to the 7-position[7] but it has been definitely shown to be in the 5-position.[8,9] Nitration[6] yielded the 8-nitro derivative (IV), m. p. 138°. The latter was reduced by stannous chloride in hydrochloric acid[6] to an amine, m. p. 114°, which it now appears must have been 5,7-dichloro-8-aminoquinoline, since reduction with iron and acetic acid has produced 5-chloro-8-aminoquinoline (VI), m. p. 87°.



In 1929 Dikshoorn[10] demonstrated that three products were obtained from the reduction of 8-nitroquinoline with stannous chloride and hydrochloric acid. 8-Aminoquinoline, m. p. 63°, was the principal product, but small quantities of two chloroaminoquinolines, A, m. p. 70–72°, and B, m. p. 85°, were also isolated. In attempting to identify the chloroaminoquinolines, Dikshoorn assigned structures based upon the work of Claus,[6,7] which has now been shown to be incorrect. Thus, the material melting at 85° (B) was assigned the structure of 8-amino-3-chloroquinoline and that melting at 70–72° (A) that of 5-chloro-8-aminoquinoline. It now appears however that A must have been 7-chloro-8-aminoquinoline (V) and B must have been 5-chloro-8-aminoquinoline (VI). This latter compound was obtained in the present investigation together with 5,7-dichloro-8-aminoquinoline (VII), m. p. 119–120°,[11] from the reduction of IV with stannous chloride and hydrochloric acid. When the reduction was carried out with powdered iron and acetic acid, only 5-chloro-8-aminoquinoline was obtained.

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(1) The work reported in this paper was done 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) Andersag, Breitner and Jung; German Patent 683,692, Oct. 26, 1939; *C. A.*, **36**, 4973 (1942).

(4) The Survey Number, designated SN-, refers to the number assigned a drug by the Survey of Antimalarial Drugs. The activities of these compounds will be tabulated in a forthcoming monograph.

(5) La Coste and Bodewig, *Ber.*, **17**, 926 (1884); La Coste, *ibid.*, **18**, 2940 (1885).

(6) Claus and Junghanns, *J. prakt. Chem.*, (2) **48**, 254 (1893).

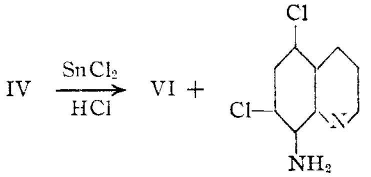
(7) Claus and Massau, *ibid.*, (2) **48**, 170 (1893).

(8) Kochanska and Bobranski, *Ber.*, **69B**, 1807 (1936).

(9) Howitz, Fraenkel and Schroeder, *Ann.*, **396**, 53 (1913).

(10) Dikshoorn, *Rec. trav. chim.*, **48**, 147 (1929).

(11) This product has been prepared by Claus and Ammelburg, *J. prakt. Chem.*, (2) **51**, 419 (1895), by nitration and reduction of 5,7-dichloroquinoline. They report the melting point as 125°.



VII, m. p. 120°

Experimental[12]

5- and 7-Chloroquinolines.—The preparation of this mixture was carried out essentially according to Fourneau, Tréfouel, Tréfouel and Wancolle.[13] From 175 g. of *m*-chloroaniline, 90 g. of *m*-chloronitrobenzene, 380 ml. of glycerol and 35 g. of ferrous sulfate, 180 g. (79%) of product boiling from 139 to 144° (22 mm.) was obtained.

The mixture of 5- and 7-chloroquinolines was redistilled under vacuum in a 125-ml. modified Claisen flask. The first fraction (principally 5-chloroquinoline) was yellow, b. p. 133–135° (22 mm.); the second fraction was small and was light yellow in color; the third fraction (principally 7-chloroquinoline) was colorless, b. p. 139–141° (23 mm.).

Preparation of 7-Chloro-8-nitroquinoline.—A 31.5-g. (0.19 mole) sample of chloroquinoline from the colorless fraction above was nitrated according to the directions of Fourneau[13] to yield 20 g. of 7-chloro-8-nitroquinoline, m. p. 182–184°, and 10 g. of 5-chloro-8-nitroquinoline, m. p. 135–136°.

Preparation of 7-Chloro-8-aminoquinoline.—A solution of 19 g. (0.091 mole) of 7-chloro-8-nitroquinoline in 200 ml. of 50% glacial acetic acid was heated on a steam-bath and 16 g. of powdered iron (100-mesh) was added in small portions over a period of one and one-half hours with stirring. The heating was continued for twenty minutes after the last portion of iron was added. The mixture was cooled, made alkaline and the 7-chloro-8-aminoquinoline was distilled with steam. The product was a white solid, m. p. 67–69°. The yield of the crude 7-chloro-8-aminoquinoline was 14 g. (86%). Further recrystallizations from an ethanol–water mixture gave a product melting at 72–73.5°.

Anal. Calcd. for $C_9H_7N_2Cl$: C, 60.50; H, 3.92; N, 15.68. Found: C, 60.49; H, 4.02; N, 15.73.

Approximately 0.5 g. of 7-chloro-8-aminoquinoline was acetylated by boiling in 5 ml. of acetic anhydride for five minutes. The *acetyl* derivative crystallized from hot water as white needle-like crystals, m. p. 184–186°.

Anal. Calcd. for $C_{11}H_9ON_2Cl$: C, 59.86; H, 4.08; N, 12.70. Found: C, 59.85; H, 4.22; N, 12.38.

Preparation of 5-Chloro-8-aminoquinoline.—A solution of 10 g. (0.048 mole) of 5-chloro-8-nitroquinoline in 100 ml. of 50% glacial acetic acid was heated on a steam-bath and 8 g. of powdered iron (100-mesh) was added in small portions over a period of forty-five minutes. The heating was continued for fifteen minutes after the final portion of iron was added. The mixture was diluted with water, made alkaline and the 5-chloro-8-aminoquinoline was distilled with steam. The yield was 6.8 g. (79.4%) of long, light yellow, hair-like crystals, m. p. 86.5–87.5°.

Anal. Calcd. for $C_9H_7N_2Cl$: C, 60.50; H, 3.92; N, 15.68. Found: C, 60.23; H, 4.04; N, 15.25.

Approximately 0.5 g. of 5-chloro-8-aminoquinoline was acetylated by boiling in 5 ml. of acetic anhydride for five minutes. The *acetyl* derivative crystallized from an ethanol–water mixture as short needle-like crystals, m. p. 140.5–141.5°.[9]

Anal. Calcd. for $C_{11}H_9ON_2Cl$: C, 59.86; H, 4.08; N, 12.70. Found: C, 59.70; H, 4.04; N, 12.14.

Reduction of 5-Chloro-8-nitroquinoline with Stannous Chloride and Hydrochloric Acid.—A solution of 30 g. of stannous chloride dissolved in 150 ml. of 18% hydrochloric acid was added to 3 g. (0.0144 mole) of 5-chloro-8-nitroquinoline and 30 ml. of concentrated hydrochloric acid. The mixture was heated for eighteen hours on a steam-bath. It was cooled, made alkaline and subjected to steam distillation. The reduction product was washed with very dilute hydrochloric acid and the insoluble residue was repeatedly recrystallized from a water–ethanol mixture. This compound, 0.3 g., m. p. 119–120°, was evidently 5,7-dichloro-8-aminoquinoline, reported by Claus and Ammelburg[11] to melt at 125°.

Anal. Calcd. for $C_9H_6N_2Cl_2$: C, 50.70; H, 2.81; N, 13.15. Found: C, 50.27; H, 2.85; N, 12.55.

The acid filtrate, which was red in color, was made alkaline and after repeated recrystallizations from an ethanol–water mixture, 1.5 g. of a yellow solid melting at 85–86° was obtained. The properties are those of 5-chloro-8-aminoquinoline.

Preparation of the Picrate of 7-Chloroquinoline.—A portion of the crude mixture of chloroquinolines from the Skraup reaction was treated with an alcoholic solution of picric acid. There was an immediate yellow precipitate of the mixed picrates, m. p. 193–196°. The picrate of 7-chloroquinoline was isolated by fractional recrystallization from an ethanol–acetone mixture, from acetone, and finally from a dioxane–ethanol mixture. The picrate of 7-chloroquinoline melted at 220–222°.

Anal. Calcd. for $C_9H_6NCl \cdot C_6H_3O_7N_3$: C, 45.86; H, 2.29. Found: C, 45.98; H, 2.39.

Preparation of 7-Chloroquinoline.—The picrate of the 7-chloro-quinoline was placed in a separatory funnel and a small portion of concentrated hydrochloric acid was added. The mixture was extracted three times with 15-ml. portions of benzene. The acid solution was made alkaline and was extracted three times with 15-ml. portions of ether. The ether solution was dried over anhydrous magnesium sulfate and then was treated with Darco. The ether was removed by evaporation and the 7-chloroquinoline was crystallized from low boiling petroleum ether. The melting point was 31–32°.

The 7-chloroquinoline was treated with 10 ml. of concentrated sulfuric acid and 15 ml. of fuming nitric acid and heated on a steam-bath for twelve hours. Ice was added and the mixture was made alkaline. The solid material was collected by filtration and, after recrystallization, the melting point was 185–187°.

Summary

7-Chloro-8-aminoquinoline, m. p. 72–73.5°, has been obtained by the reduction of 7-chloro-8-nitroquinoline with powdered iron and acetic acid.

5-Chloro-8-aminoquinoline, m. p. 86.5–87.5°, has been obtained by the reduction of 5-chloro-8-nitroquinoline with powdered iron and acetic acid. This material is apparently identical with material described by Dikshoorn as 3-chloro-8-aminoquinoline.

5,7-Dichloro-8-aminoquinoline, m. p. 119–120°, has been isolated in small yield by the reduction of 5-chloro-8-nitroquinoline with stannous chloride and hydrochloric acid.

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[12] Analyses by Miss Theta Spoor and Miss Lillian Hruda.

[13] Fourneau, Tréfouel, Tréfouel and Wancolle, *Bull. soc. chim.*, [4] **47**, 738 (1930).