[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Some 4-Amino-7-chloroquinoline Derivatives[1]

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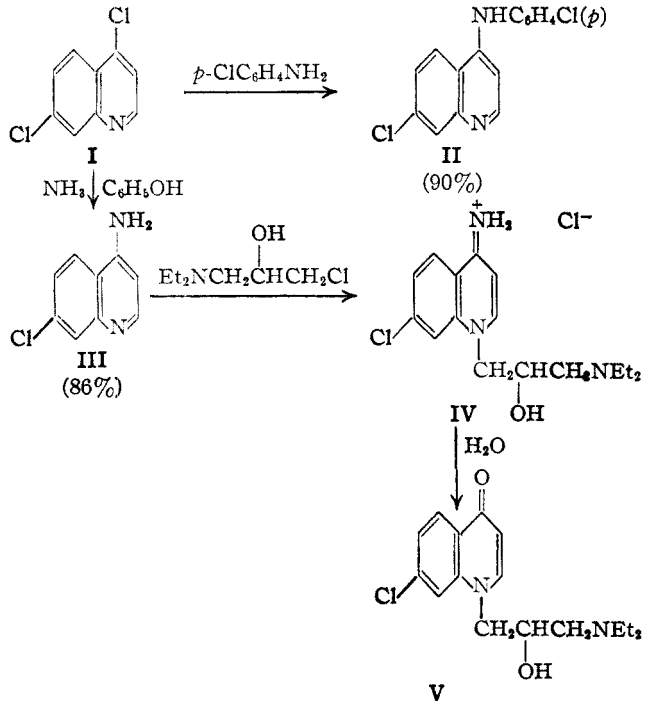
In connection with the preparation of compounds of possible pharmacological interest, 4-amino-7-chloroquinoline and a few related compounds were prepared and characterized for the first time. The reactions, starting from 4,7-dichloroquinoline (I),[5] are outlined below.



The hydrochloride and picrate of the amines II (SN-11,364-4)[5a] and III were isolated and characterized. Amine III was found to form a stable monohydrate.

Compound IV (SN-11,666-5)[5a] an isomer of the drug with the side-chain attached to the 4-nitrogen (SN-8137),[5a] was submitted for assay against avian malaria but possessed no antimalarial activity.

Experimental[6]

4-(*p*-Chloroanilino)-7-chloroquinoline Hydrochloride (SN-11,364-4).—A suspension of 9.6 g. (0.075 mole) of *p*-chloroaniline (m. p. 69–70°) and 14.85 g. (0.075 mole) of 4,7-dichloroquinoline (m. p. 84–85°)[5] in 500 cc. of water and 4 cc. (0.048 mole) of concentrated hydrochloric acid was heated with occasional shaking. The reactants were insoluble in the cold mixture, began to dissolve on warming, and melted into a heavy oil when hot. By the time the solution began to reflux, the oil began to solidify, and crystals of the product appeared through the solution. Refluxing was continued for two hours, the mixture was chilled, and the product was filtered with suction. The crude, dry product weighed 22 g. (90%); after one recrystallization from ethanol and ether the yield was 17.2 g., or 71%. The product consisted of fine, lemon yellow crystals; it darkened at about 310° and melted with decomposition at 330–358° (uncor.) on a block. After four recrystallizations, the pure material melted at 335–360° (uncor.) with decomposition.

Anal. Calcd. for $C_{15}H_{10}Cl_2N_2 \cdot HCl$: C, 55.32; H, 3.41; N, 8.61. Found: C, 55.20; H, 3.62; N, 8.39.

4-(*p*-Chloroanilino)-7-chloroquinoline.—A 1.5-g. sample of 4-(*p*-chloroanilino)-7-chloroquinoline hydrochloride was stirred with 50 cc. of 10% sodium hydroxide solution and allowed to stand overnight. The product, which was creamy white, was filtered, washed and dried; three recrystallizations from ethanol gave white needles melting at 253 254°. The free base may also be recrystallized with better recovery from aqueous ethanol.

Anal. Calcd. for $C_{15}H_{10}Cl_2N_2$: C, 62.30; H, 3.49; N, 9.69. Found: C, 62.18; H, 3.80; N, 10.00.

4-Amino-7-chloroquinoline.—A modification of the procedure of Andersag, Breitner and Jung[7] was utilized for the amination of 4,7-dichloroquinoline. A solution of 62 g. (0.312 mole) of 4,7-dichloroquinoline in 300 g. of phenol was heated in an oil-bath to 170° and gaseous ammonia was bubbled through it at a moderate rate. The temperature of the oil-bath was raised to 200° and the ammonia passed through the refluxing solution for two and one-half hours. A voluminous precipitate which formed during the first half hour redissolved within two hours.

After cooling to room temperature, a solution of 75 cc. of glacial acetic acid in 150 cc. of water was added to dissolve the solidified mixture. Addition of 500 cc. of ether to the resulting solution caused the precipitation of the aminoquinoline hydrochloride which was removed by filtration and washed with 500 cc. of ether. A second precipitate was obtained by adding this ether wash to the mother liquor. After a similar third treatment with ether and filtration, only 2 to 4 g. of impure 4-amino-7-chloroquinoline remained in the mother liquor. This was demonstrated by extraction of the ether layer with water. The combined aqueous extracts were washed with ether and the solution was made basic with sodium hydroxide to yield 4-amino-7-chloroquinoline.

The hydrochloride was soluble in hot water and in ethanol, insoluble in ether. A small portion, recrystallized once from ethanol and ether, melted with decomposition at 292–297° (uncor.). The main portion was dissolved in 400 to 500 cc. of hot water and treated with an excess of sodium hydroxide. The product was filtered from the cold alkaline solution and washed with water. The 4-amino-7-chloroquinoline hydrate, after one recrystallization from water, weighed 52 g. (86%). This material melted at 105–110°, resolidified below 120° and finally re-

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

(5a) 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.

(6) All melting points reported are corrected unless otherwise indicated.

(7) U. S. Patent 2,233,970; see Elderfield, Gensler, Birstein, Kreysa, Maynard and Galbreath, THIS JOURNAL, **68**, 1250 (1946).

melted at 146–147.5°. After the water of hydration was removed by drying a sample several days in a vacuum desiccator over phosphorus pentoxide, the 4-amino-7-chloroquinoline melted at 147–148° without preliminary softening.

The **picrate** was prepared in 95% ethanol and, after one recrystallization, darkened at 293° and finally melted with decomposition at 306–308°.

4-Amino-7-chloroquinoline **hydrochloride** was prepared by dissolving the free base in 4 *N* hydrochloric acid or by addition of concentrated hydrochloric acid to an ethanol solution of the base. After recrystallization from water or from ethanol and ether, the salt decomposed at 294–296° (uncor.). The analysis corresponded to that of a monohydrate.

Anal. Calcd. for $C_9H_8Cl_2N_2 \cdot H_2O$: C, 46.37; H, 4.33. Found: C, 46.87; H, 4.29.

Attempted Alkylation of 4-Amino-7-chloroquinoline.—A mixture of 8.5 g. (0.0475 mole) of 4-amino-7-chloroquinoline and 6.5 g. (0.05 mole) of diethylaminoepihydrin[8] was stirred and warmed at 55° for five hours. After the dark red reaction mixture had stood overnight, 3 *N* hydrochloric acid was added. The light yellow precipitate was recrystallized from water to produce a good yield of 4-amino-7-chloroquinoline hydrochloride as shown by a mixed melting point. The free base similarly failed to repress the melting point of an authentic sample of starting material.

1-(3-Diethylamino-2-hydroxypropyl)-7-chloro-4-quinolinimine Diphosphate (SN-11,666-5) and Dipicrate.—3-Diethylamino-2-hydroxypropyl chloride was prepared by stirring a mixture of 3.7 g. (0.04 mole) of epichlorohydrin and 2.92 g. (0.04 mole) of diethylamine for six hours. This mixture was added to a solution of 5 g. (0.028 mole) of 4-amino-7-chloroquinoline in 30 cc. of absolute ethanol. The solution was stirred for forty-eight hours at 110–120°. After five hours, a canary yellow solid began to form on the walls of the flask. About 100 cc. of ether was added to the cold reaction mixture and the solid was broken up and collected on a filter. This material melted at 260–267° and gave a slight test for halide ion with silver nitrate solution. It dissolved slowly in water but was completely soluble in very dilute cold hydrochloric acid.

The yellow reaction product was taken up in warm water and a slight excess of sodium hydroxide was added. A white solid precipitated immediately which melted at 140–180°. After recrystallization from dilute methanol, 2.7 g. (63%) of the free base melting at 157–160° was obtained. To 1.0 g. of this material was added dilute phosphoric acid (1 cc. of 89% phosphoric acid per 8 cc. of water) until the solution was acid to congo red paper. The mixture was warmed to effect complete solution and an equal volume of isopropyl alcohol was added. The solid which appeared after cooling was collected on a filter, dissolved in 5 cc. of water and treated with Darco. To the clear filtrate was added 5 cc. of isopropyl alcohol. The solution was cooled and the solid product which was removed by filtration was dried in a vacuum desiccator over phosphorus pentoxide. The product melting at 178–181° weighed 0.82 g. (51%). After two additional recrystallizations, the **diphosphate** melted at 180–181.5°.

Anal. Calcd. for $C_{16}H_{23}ClN_3O_9P_2$: C, 38.14; H, 5.60; Cl, 7.04; N, 8.34. Found: C, 38.24; H, 6.08; Cl, 6.94; N, 8.32.

The salt was somewhat hygroscopic and after standing in a sample tube for two weeks, analyzed for the **diphosphate dihydrate.**

Anal. Calcd. for $C_{16}H_{23}ClN_3O_9P_2 \cdot 2H_2O$: C, 35.60; H, 5.98. Found: C, 36.00; H, 5.94.

The **dipicrate** of the product, which was prepared in ethanol, was oily at first but finally was converted by numerous recrystallizations to a solid, m. p. 220–222°.

Anal. Calcd. for $C_{28}H_{27}ClN_9O_{15}$: C, 43.90; H, 3.68; N, 16.45. Found: C, 43.93; H, 3.58; N, 15.98.

The isomeric dipicrate prepared from 4-(3-diethylamino-2-hydroxypropyl)-7-chloroquinoline (SN-8137) also melted at 220–221°.[9] The mixed melting point of these two picrates was 200–207°. The production of ring-nitrogen alkylated derivatives is the normal reaction of 2- and 4-aminopyridines and quinolines with alkyl halides.

1-(3-Diethylamino-2-hydroxypropyl)-7-chloro-4-quinolone.—The solid precipitated from a solution of the above crude alkylated 4-amino-7-chloroquinoline by addition of sodium hydroxide was recrystallized repeatedly from aqueous methanol. The product, m. p. 173–174°, had the composition of 1-(3-diethylamino-2-hydroxypropyl)-7-chloro-4-quinolone.

Anal. Calcd. for $C_{16}H_{21}ClN_2O_2$: C, 62.21; H, 6.85; N, 9.07. Found: C, 62.20; H, 6.79; N, 8.95.

Summary

4-Amino-7-chloroquinoline and 4-(*p*-chloroanilino)-7-chloroquinoline have been prepared from 4,7-dichloroquinoline. Alkylation of 4-amino-7-chloroquinoline with 3-diethylamino-2-hydroxypropyl chloride gave 1-(3-diethylamino-2-hydroxypropyl)-7-chloro-4-quinolinimine, from which the corresponding quinolone was obtained by hydrolysis.

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(8) Drozdov and Cherntzov, *J. Gen. Chem. U. S. S. R.*, **4**, 969 (1934); *C. A.*, **29**, 2148 (1935).

(9) Private communication from Dr. Albert Pohland.