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

SOME 4,8-DIAMINOQUINOLINES[1]

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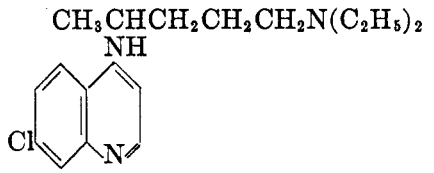
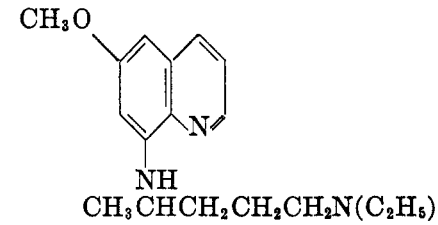
Certain 4-aminoquinolines, especially those bearing a 7-chlorine atom, such as Chloroquine (I), have value as antimalarial drugs (1). The preparation of compounds of this type, containing in addition an amino group in the eight position, was undertaken in the hope that the amino group might add some of the desirable pharmacological characteristics of Pamaquine (II). The compounds selected for preparation were the 6-methoxy and the 7-chloro derivatives of 8-amino-4-(4-diethylamino-1-methylbutyl)aminoquinoline.



I



II

The preparation of the 7-chloro compound was carried out in the following manner. Nitration of 4,7-dichloroquinoline (III) gave 4,7-dichloro-8-nitroquinoline (IV) in 90% yield. The 4,7-dichloro-8-nitroquinoline was reduced by treatment with iron and aqueous acetic acid to give 8-amino-4,7-dichloroquinoline (V) in 88% yield. When the 8-amino-4,7-dichloroquinoline was treated with an excess of 4-amino-1-diethylaminopentane and the mixture heated at 180° for ten hours, the desired 8-amino-7-chloro-4-(4-diethylamino-1-methylbutyl)aminoquinoline (VI) was formed in 67% yield.

In order to prove that the nitration and reduction had occurred as expected, a portion of the 8-amino-4,7-dichloroquinoline was converted by catalytic hydrogenation to 8-amino-7-chloroquinoline (VII). The 8-amino-7-chloroquinoline thus obtained was shown to be identical with an authentic sample (2) by the method of mixed melting points.

8-Amino-4-chloro-6-methoxyquinoline was prepared by reduction of the corresponding nitro compound (4), but it failed to couple with 4-amino-1-diethylaminopentane under the conditions tried.

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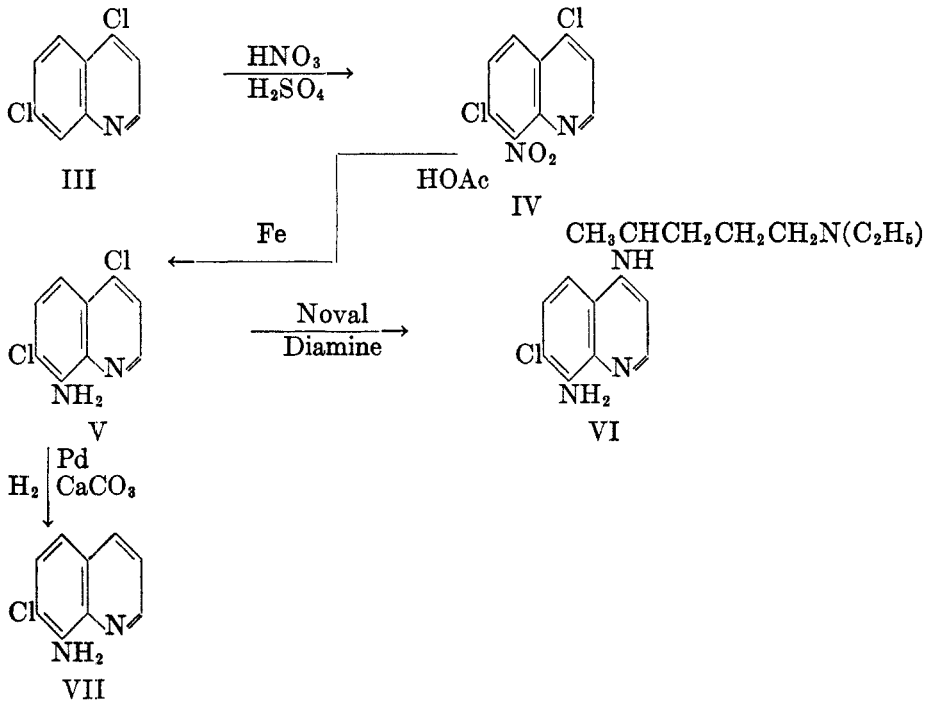

EXPERIMENTAL[5]

4,7-Dichloro-8-nitroquinoline (*IV*). Technical nitric acid (30 ml.) was added slowly to a solution of 4,7-dichloroquinoline (3) (19.8 g., 0.1 mole) in concentrated sulfuric acid (25 ml.) cooled in an ice-bath. The temperature was allowed to rise slowly until room temperature was reached and then the mixture was heated on a steam-bath for nine hours. After the mixture had cooled, it was poured over cracked ice. The yellow solid that precipitated was collected on a filter and washed with water. There was obtained 22.0 g. (90%) of crude product which melted at 148–149°. Crystallization of a sample from ethanol yielded light yellow plates that melted at 150–151°.

Anal. Calc'd for $C_9H_4Cl_2N_2O_2$: C, 44.48; H, 1.66.
Found: C, 44.88; H, 1.72.

8-Amino-4,7-dichloroquinoline (*V*). A mixture of the crude 4,7-dichloro-8-nitroquinoline (30 g., 0.12 mole) and 50% aqueous acetic acid (450 ml.) was heated on a steam-bath. Powdered iron (21 g., 0.36 mole) of 100 mesh was added in small portions at a rate which caused gentle boiling. Heating of the mixture was continued for one hour after the last portion of iron had been added. The mixture was then cooled slowly and diluted with 300 ml. of water. The addition of water completed the hydrolysis and precipitated the 8-amino-4,7-dichloroquinoline as the free base. The dirty brown solid thus obtained was placed in a Soxhlet extraction apparatus and the free base was extracted with 200 ml. of ether. Removal of the ether from the extract left 23.0 g. (88%) of light yellow needles which melted at 110–111°. The product showed the same melting point after crystallization from ethanol.

Anal. Calc'd for $C_9H_6Cl_2N_2$: C, 50.73; H, 2.84.
Found: C, 50.69; H, 3.09.

[5] All melting points are corrected. Microanalyses by Miss Theta Spoor and Miss Lillian Hruda.

Catalytic reduction of 8-amino-4,7-dichloroquinoline. Freshly-prepared palladium hydroxide on calcium carbonate (5.0 g.) was added to a solution of 8-amino-4,7-dichloroquinoline (1.0 g.) and potassium hydroxide (5.0 g.) in ethanol. The suspension was treated with hydrogen at half an atmosphere pressure until the expected quantity of hydrogen had been absorbed. After removal of the catalyst by filtration, the solvent was removed *in vacuo*. The residue was dissolved in ether and washed with water. Evaporation of the ether yielded a brown oil. This was treated with an aqueous methanol solution to give light yellow needles, m.p. 72–73.5°. A mixture of this compound with an authentic sample of 8-amino-7-chloroquinoline (2) showed the same melting point.

8-Amino-7-chloro-4-(4-diethylamino-1-methylbutyl)aminoquinoline (VI). A mixture of 8-amino-4,7-dichloroquinoline (30.0 g., 0.14 mole) and 4-amino-1-diethylaminopentane (120 g., 0.76 mole) was heated in an atmosphere of nitrogen at 180° for ten hours. The reaction mixture darkened only slightly under this treatment. The mixture was then taken up in ether (300 ml.) and washed successively with water (150 ml.), 5% sodium hydroxide (150 ml.), and water (150 ml.). After removal of the ether and the remaining 4-amino-1-diethylaminopentane *in vacuo*, the residue was distilled using a mercury-vapor diffusion pump. There was obtained 30.0 g. (64%) of a light yellow oil; b.p. 165–170° at 10^{-3} mm., n_D^{20} 1.6920.

Anal. Calc'd for $C_{18}H_{27}ClN_4$: C, 64.55; H, 8.12.
Found: C, 64.66; H, 8.23.

Treatment of a sample of the oil in ether with either anhydrous hydrogen chloride or syrupy phosphoric acid gave a white crystalline salt. However both of these salts were extremely hygroscopic, and they were not isolated. The *dipicrate* was readily prepared using alcohol as a solvent. Recrystallization from alcohol yielded bright yellow needles, m.p. 190–191°.

Anal. Calc'd for $C_{18}H_{27}ClN_4 \cdot 2C_6H_3N_3O_7$: C, 45.42; H, 4.16.
Found: C, 45.51; H, 4.25.

Treatment of 4,7-dichloro-8-nitroquinoline with 4-amino-1-diethylaminopentane. A mixture of 4,7-dichloro-8-nitroquinoline (20.0 g., 0.8 mole) and 4-amino-1-diethylaminopentane (35.0 g., 0.22 mole) was heated in an atmosphere of nitrogen. When the temperature reached 150°, a vigorous exothermic reaction occurred. Considerable decomposition resulted before the reaction subsided. The viscous mixture was treated with ether (300 ml.), and the ether extract was worked up in the usual manner. However only tarry material was obtained.

4-Chloro-6-methoxy-8-nitroquinoline.[6] 6-Methoxy-8-nitro-4-quinolinol (25.0 g., 0.11 mole) was heated with phosphorus pentachloride (25 g., 0.11 mole) and phosphorus oxychloride (60 ml.) at 130° for one hour. The phosphorus oxychloride was removed *in vacuo*, and the residue was decomposed with ice-water. The flocculent, white precipitate was removed by filtration and dried. There was obtained 22.0 g. (82%) of a white solid, m.p, 172–175°. Crystallization of the product from glacial acetic acid yielded white needles, m.p. 177–178° [lit. (4), 187–188°, but the nitrogen analysis reported differed from the theoretical by 0.86%].

Anal. Calc'd for $C_{10}H_7ClN_2O_3$: C, 50.33; H, 2.96.
Found: C, 50.13; H, 2.92.

8-Amino-4-chloro-6-methoxyquinoline. A mixture of 4-chloro-6-methoxy-8-nitroquinoline (22.0 g., 0.09 mole) and 50% aqueous acetic acid (320 ml.) was heated to boiling and 7 g. of powdered iron was added in small portions. The mixture was boiled for an hour, cooled, and diluted with two volumes of water. This caused hydrolysis with precipitation of the free base. The precipitate was collected, dried, and extracted with ether (200 ml.), using a Soxhlet extraction apparatus. The ether was removed from the extract, leaving 13.0 g. (68%) of grey needles, m.p. 90–94°. This product was recrystallized several

[6] We are indebted to John S. Meek for the preparation of this material.

times from alcohol and obtained almost white, m.p. 97–100°. The substance was analyzed as its *acetyl derivative* m.p. 206°, prepared in refluxing acetic anhydride.[7]

Anal. Calc'd for $C_{12}H_{11}ClNO_2$: C, 57.49; H, 4.42.

Found: C, 57.29; H, 4.67.

Hydrogenation of the nitro compound in ethanol over Adams' catalyst gave a reddish solid, m.p. 98–100°, which yielded the same *acetyl derivative*, m.p. and mixed m.p. 206°.

Treatment of 8-amino-6-methoxy-4-chloroquinoline with noval diamine. A solution of 8-amino-6-methoxy-4-chloroquinoline (12.0 g., 0.057 mole) in 4-amino-1-diethylaminopentane (50 g., 0.30 mole) was heated at 175° for ten hours in an atmosphere of nitrogen. The solution was then taken up in ether (200 ml.) and washed successively with water (100 ml.), 5% sodium hydroxide (100 ml.), and water (100 ml.). After removal of the ether and excess diamine *in vacuo*, the product was distilled under high vacuum. There was obtained 9.0 g. of a white solid; b.p. 125–135° (0.001 mm.), m.p. 90–94°. This was shown to be 8-amino-6-methoxy-4-chloroquinoline by the method of mixed melting points.

SUMMARY

The nitration of 4,7-dichloroquinoline has been shown to give 4,7-dichloro-8-nitroquinoline which has been converted into 8-amino-7-chloro-4-(4-diethylamino-1-methylbutyl)aminoquinoline. The preparation of the 6-methoxy analog was carried through to 8-amino-4-chloro-6-methoxyquinoline, but this substance failed to couple with 1-amino-4-diethylaminopentane under the conditions tried.

URBANA, ILL.

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[7] We are indebted to Robert E. Jones for the preparation of the acetyl derivative for analysis.