to approach the reported yield (80%). However, using arsenic oxide instead of arsenic acid and by extracting the product from inert material by means of ether, and upon further purification, a 50% yield was obtained of m. p. 134–135° (Fourneau 136°).

5- and 7-chloro-6-nitroquinolines were made according to Fourneau[4] but with a few changes in procedure. A mixture of 200 g. of 3-chloro-4-nitroaniline, 136 g. of arsenic oxide, 280 ml. of glycerol and 174 ml. of concd. sulfuric acid was refluxed for six hours (bath temperature 130–140°) and poured into 7 liters of ice water. The precipitate (largely 5-chloro-6-nitroquinoline) and that obtained on neutralizing the filtrate (largely the 7-chloro isomer) were each digested twice with a total of 10 liters of boiling carbon tetrachloride and the resinous residues were discarded. The combined filtrates on cooling gave 65 g. of nearly pure 7-chloro compound (m. p. 140–150°). The filtrate was evaporated under reduced pressure and the residue was dissolved in 2 liters of hot 1.4 *N* sulfuric acid; cooling gave 37 g. of nearly pure 5-chloro compound (m. p. 148–151°). Neutralization of the filtrate gave a mixture which was re-processed.

Recrystallization of the 7-chloro compound from carbon tetrachloride (cooling only to 35°), and solution in hot 6 *N* hydrochloric acid, filtering and precipitating by ammonium hydroxide gave a pure product of m. p. 153–155° (Fourneau 155–156°). The 5-chloro compound was recrystallized several times from 1.4 *N* sulfuric acid (cooling only to 40°; below this the mixture separates); it was then dissolved in hot 6 *N* hydrochloric acid, filtered and precipitated by ammonium hydroxide; m. p. 153–154° (Fourneau 153°).

6-Amino-7-chloroquinoline.—Fourneau[4] reduced the 7-chloro-6-nitro compound to the amine (without isolating it) and diazotized, for his structural proof.

The nitro compound (29 g.) was added slowly with stirring to 150 g. of stannous chloride dihydrate in 200 ml. of 6 *N* hydrochloric acid with heating for one hour. The product was filtered, suspended in 20% sodium hydroxide, filtered, washed, dissolved in 300 ml. of 8 *N* hydrochloric acid (with darco treatment), and precipitated by ammonium hydroxide; yield 24 g. Recrystallization from dilute ethanol gave 14 g. (57%) of m. p. 134–136°. Repeated crystallizations gave slender needles of m. p. 141–143°. It is soluble in organic solvents and dilute acids.

Anal. Calcd. for $C_9H_7ClN_2$: N, 15.69. Found: N, 15.99.

Catalytic reduction[7] of 10.4 g. of the nitro compound with Raney nickel in 200 ml. of acetone gave 6 g. (67.5%) of nearly pure product of m. p. 136–138°. However, similar reduction in absolute ethanol as the solvent gave only a 28% yield.

The **hydrochloride** was precipitated from dry ether by ethereal hydrogen chloride and was recrystallized from ethanol; m. p. 239–246° dec.

Anal. Calcd. for $C_9H_7ClN_2 \cdot HCl$; Cl^-, 16.48. Found: Cl^-, 16.51.

Summary

6-Amino-7-chloroquinoline is described. It failed to undergo condensation with diethylaminopropyl chloride.

Some notes on Fourneau's synthesis of chloronitroquinolines from *m*-chloroaniline are recorded.

(7) *Cf.* Similar reductions by Capps and Hamilton, THIS JOURNAL, **60**, 2104 (1938).

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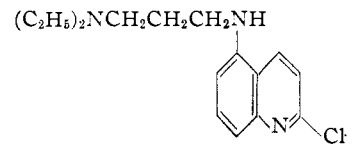
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Antimalarials. 2-Chloro-5-(3-diethylaminopropylamino)-quinoline. Useful Preparations of 2-Chloro-5- and 8-Nitroquinolines[1]

BY ADOLF J. DEINET AND ROBERT E. LUTZ

In connection with the study of γ-dialkylamino-alkylaminoquinolines as possible antimalarials the preparation of 2-chloro-5-(γ-diethylaminopropylamino)-quinoline (I) was undertaken. The most



I

direct approach appeared to consist in the nitration of 2-chloroquinoline, previously reported to give the 5- and 8-nitro isomers in unspecified yields.[2] Unfortunately, the nitration as described[2] was found to give the desired 2-chloro-5-nitroquinoline in a yield of less than 5% along with the isomeric 2-chloro-8-nitroquinoline in a yield of about 20%. A study of the reaction resulted in its development as a useful synthesis of the 8-nitro compound (52% yield of the pure substance) but the highest yield of the 5-nitro isomer attained was less than 10%.

The difficult availability of 5-nitrocarbostyril precluded application of the preparation of 2-chloro-5-nitroquinoline[3] from this substance and phosphorus pentachloride. However, 5-nitro-1-methylcarbostyril appeared to be potentially available in quantity through oxidation of the methiodide of the easily accessible 5-nitroquinoline,[4] this oxidation having been reported[5] many years ago, but apparently without subsequent development into a preparative method. This nitromethylcarbostyril would be expected to react with phosphorus pentachloride to give the desired 5-nitro-2-chloroquinoline, in analogy to the conversion of 1-methylcarbostyril to 2-chloroquinoline.[2] The processes indicated were found to provide a very satisfactory preparation of 2-chloro-5-nitroquinoline; the methiodide of 5-nitroquinoline was obtained in 85% yield and the oxidation to 5-nitro-1-methylcarbostyril proceeded in 94% yield. 5-Nitro-2-chloroquinoline was obtained from the carbostyril in 57% yield

(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 the University of Virginia.

(2) Fischer and Guthmann, *J. prakt. Chem.*, [2] **93**, 382 (1916).

(3) Claus and Setzer, *ibid.*, [2] **53**, 395 (1896).

(4) Dufton, *J. Chem. Soc.*, **61**, 783 (1892).

(5) Decker, *J. prakt. Chem.*, **45**, 175 (1892).

and its hydrogenation to 5-amino-2-chloroquinoline was substantially quantitative. The compound I was obtained by alkylation of the amine with γ-diethylaminopropyl chloride;[6] it was found inactive against avian malaria.

Experimental

The nitration of **2-chloroquinoline** was carried out as nearly as possible under the conditions described by Fischer and Guthmann,[2] namely, addition of 30 g. to a mixture of 150 ml. of concd. sulfuric acid and 150 ml. of nitric acid (sp. gr. 1.5) at 30°, heating at 100° for fifteen minutes, pouring into water and separating by superheated (250°) steam distillation for eighteen to twenty-four hours. The yield of the volatile 5-nitro compound was 2.7%. Crystallization from ethanol of the non-volatile products gave the 8-nitro isomer in 21% yield. From this ethanol crystallization an insoluble yellow residue (10 g.) was obtained and after elaborate purification and separation from much intractable material was identified as 5-nitrocarbostyril, a byproduct evidently formed by hydrolysis under the prolonged heating. The crude carbostyril from another run (10 g.) on treatment with phosphorus oxychloride and pentachloride gave 1.2 g. of the 2-chloro-5-nitroquinoline which brought the total yield to 5.9%.

When nitration was again carried out under the original conditions[2] but with separation of the isomers by distillation with ordinary steam, the yields were raised, that of 8-nitro isomer to 42% and the 5-nitro to 5.4%. Under these conditions the yield of by-product 5-nitrocarbostyril became negligible.

Identical yields were obtained when 2-chloroquinoline was added to the nitrating mixture at a maintained temperature of 100°; the mixture was held for fifteen minutes at this temperature, poured into water and the two isomers separated by steam (100°) distillation.

The best procedure developed for the preparation of the **2-chloro-8-nitroquinoline** is as follows: Thirty grams of 2-chloroquinoline (Eastman Kodak Co.) was cooled in an ice-bath and 20 cc. of fuming nitric acid (sp. gr. 1.5) was added. This resulted in the formation of the nitrate which remained liquid if not cooled below 5°. This was slowly added dropwise to a mixture of 150 cc. of concd. sulfuric acid and 130 cc. of fuming nitric acid, keeping the temperature below 20°. When the addition was complete the nitrating mixture was allowed to warm slowly to room temperature and to stand for eighteen hours, and was then poured into 4 l. of ice water. The resulting solid was filtered, washed with water till acid-free and steam distilled for eighteen hours. The 5-nitro isomer which crystallized from the distillate was recrystallized from alcohol; yield 3.5 g. (9.4%); m. p. 128–129°. The residue from the steam distillation was digested with boiling alcohol for several minutes and the hot mixture was filtered to remove the 5-nitrocarbostyril which was negligible in amount. The 2-chloro-8-nitroquinoline crystallized on cooling; yield 19.5 g. (52%); m. p. 145°.

1-Methyl-5-nitrocarbostyril.[5]—A mixture of 100 g. of 5-nitroquinoline (prepared according to the method of Dufton[4]), 100 cc. of dry benzene and 50 cc. of dry methyl iodide was refluxed gently for six hours. The bright red crystalline methiodide was filtered, washed with benzene and allowed to dry. The filtrate was concentrated and again refluxed with methyl iodide (30 cc.) to obtain more product. This process was repeated until any further yield became negligible. It was found that longer refluxing of the original mixture did not improve the initial yield nor render further treatment with methyl iodide unnecessary. The total yield was 154 g. (85%); m. p. *ca.* 250° (dec.).

A mixture of 200 g. of potassium ferricyanide and 500 cc. of 10% sodium hydroxide was heated to 60–65° and stirred vigorously while a solution of 50 g. of the methiodide in 500 cc. of warm water was run in dropwise. A yellow crystalline precipitate of the carbostyril formed. After stirring for a half hour at this temperature the reaction mixture was cooled, and the product filtered, washed with a small amount of cold water and dried; yield 30 g. (94%); m. p. 162°.

2-Chloro-5-nitroquinoline.—A mixture of 360 g. of *p*-dichlorobenzene, 183 g. of the 1-methyl-5-nitrocarbostyril and 183 g. of phosphorus pentachloride was heated at 160–170° for two hours, allowed to cool to 70–80° (a lower temperature results in solidification) and poured over 2 liters of crushed ice. After stirring for a half hour the reaction mixture was made slightly alkaline with sodium hydroxide and the solid was filtered off, washed with water and dried. Recrystallization from 2 liters of high boiling petroleum ether removed the dichlorobenzene and gave 104.5 g. (57%) of pale greenish-yellow needles; m. p. 127°. Alcohol[3] was inferior for recrystallization because it did not hold the dichlorobenzene as well.

2-Chloro-5-(γ-diethylaminopropyl)-aminoquinoline (SN 12405).—A mixture of 10 g. of 5-amino-2-chloroquinoline and 25 g. of γ-diethylaminopropyl chloride was heated at 130° for twenty hours. The reaction mixture now consisted of two distinct layers the upper one of excess γ-diethylaminopropyl chloride, and the lower (semi-solid) of the hydrochloride of the desired product. The upper layer was poured off and the residual semi-solid material was dissolved in absolute ethanol and precipitated with dry ether (an excess had to be avoided because the material then became resinous). It was recystallized twice. The bright orange product was immediately placed in a vacuum desiccator.

Since the hydrochloride was found to be too hygroscopic to handle conveniently it was converted into the diphosphate as follows:[7] The free base was dissolved in cold absolute ethanol and stirred vigorously. Phosphoric acid (85%) was slowly dropped in until no more precipitate formed. The resulting salt was filtered off, washed first with cold ethanol and finally with ether, and then dried in a vacuum desiccator. It was a bright orange crystalline solid which was only slightly hygroscopic and very soluble in water; yield, 6.7 g. (27%); m. p. 175–180°.

Anal. Calcd. for $C_{16}H_{22}ClN_3 \cdot 2H_3PO_4$: Cl, 7.27. Found: Cl, 7.44.

Summary

The synthesis of 2-chloro-5-(3-diethylaminopropylamino)-quinoline diphosphate is described, involving an improved preparation of 2-chloro-5-nitroquinoline. An improved procedure for the preparation of 2-chloro-8-nitroquinoline is reported.

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(6) Supplied by R. C. Fuson's group at the University of Illinois.

(7) According to suggestions by N. L. Drake.