water, shaken with Darco, filtered and dried over sodium sulfate. An excess of ethereal hydrogen chloride was added and a resinous precipitate formed and was crystallized from 12 ml. of a 2:1 mixture of ether and ethanol; yield 0.94 g. (56%); white powder. An additional recrystallization yielded white plates which decomposed at 135–140°.

Anal. Calcd. for $C_{15}H_{17}ClN_2 \cdot 2HCl$: N, 8.40. Found: N, 8.14.

***dl*-7-Chloro-2-(4-diethylamino-1-methylbutylamino)-quinoline** (SN11,427).—A mixture of 10 g. (0.05 mole) of 2,7-dichloroquinoline (IV) and 50 ml. of purified[11] noval diamine was heated for seventeen hours at 131–134°. After cooling, the resulting mixture was dissolved as completely as possible in 100 ml. of petroleum ether (b. p. 30–65°) and the solution washed successively with 300 ml. of 1.5% sodium bicarbonate and three 60-ml. portions of water. The solvent was evaporated under reduced pressure and the residual oil was fractionally evaporated onto a cold finger condenser at low pressure ($1–2 \times 10^{-3}$ mm.; oven temperature 130–140°). The yield was 12.5 g. (77%) of a light yellow-green, viscous oil; $n^{20}D$ 1.5907. Attempts to form a crystalline salt were unsuccessful. The oil was stable in acid and alkali, was soluble in ethanol or dilute hydrochloric acid and was insoluble in water. When exposed to moist air there was an increase in weight to an equilibrium point corresponding to the absorption of very close to one equivalent of water; this was accompanied by a marked increase in the viscosity ($n^{20}D$ 1.5855).

Anal. Calcd. for $C_{18}H_{26}ClN_3$: C, 67.58; H, 8.19; N, 13.14. Found: C, 67.58; H, 8.07; N, 13.05.

(11) Procedure recommended by N. L. Drake; private communication.

Summary

The synthesis of 2,7-dichloroquinoline has been accomplished through 4,7-dichlorocarbostyril by selective partial hydrogenolysis, followed by hydrochlorination.

This product was condensed with noval diamine to give the 2-positional isomer of SN 7618, namely, 7-chloro-2-(4-diethylamino-1-methylbutylamino)-quinoline.

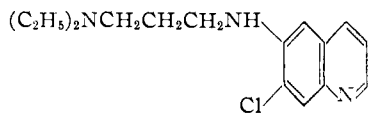
CHARLOTTESVILLE, VIRGINIA RECEIVED APRIL 5, 1946

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

Antimalarials. Some Notes on the Attempted Synthesis of 7-Chloro-6-dialkylaminoalkylaminoquinolines[1]

BY ROBERT E. LUTZ, PHILIP S. BAILEY,[2] TELLIS A. MARTIN AND JASON M. SALSBURY[3]

The objective of this investigation was twofold, one (unsuccessful) to prepare a typical 7-chloro-6-dialkylaminoalkylaminoquinoline (I) through 6-



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amino-7-chloroquinoline, and the other to make quantities of 6- and 8-nitro-5-chloroquinolines, which were obtainable through the same synthetic approach, to be used elsewhere in a similar synthesis of dialkylaminoalkylaminoquinolines.

The method of Fourneau[4] was used to make the chloronitroquinolines with some modifications which seemed helpful in achieving the best results. The principal steps were nitration of *m*-chloroacetanilide with separation of the ortho and para nitro compounds, followed by individual Skraup reactions, with separation of the isomeric 5- and 7-chloro-6-nitroquinolines.

The 6-amino-7-chloroquinoline was made and characterized. However, condensations with noval bromide and especially with 1-[N,N-diethylamino]-propyl chloride following the method of Rohrmann and Shonle,[5] with considerable variations in the molar ratios, temperature and time, and in two cases using the aminoquinoline hydrochloride, failed to give a tractable product. Doubtless the chlorine adjacent to the amino group was responsible for this difficulty.

(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) Present location: University of Texas, Austin, Texas.

(3) Present location: American Cyanamid Co., Stamford, Connecticut.

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

Experimental[6]

Nitration of *m*-Chloroacetanilide and Separation of the Isomers.—The chief deviation from Fourneau's directions[4] was the use of a much lower nitration temperature.

m-Chloroacetanilide (550 g.) was added over one hour with stirring to 2 liters of fuming nitric acid (sp. g. 1.49); the temperature was −50° initially and rose to −35 to −30°. The mixture was poured into 6 gallons of crushed ice and water. The product was filtered, washed, slurried with 5 gallons of water (slightly alkaline with ammonium hydroxide), again filtered, washed and dried; yield 600 g.; m. p. 96–130°. It was digested with 12 liters of boiling benzene and filtered (hot); this gave 261 g. of the crude 4-nitroanilide which melted at 134–141°; on cooling the filtrate, 109 g. more of this anilide was obtained; m. p. 142–145°. Recrystallization of the 261-g. batch from 1.8 liters of ethyl acetate by addition of petroleum ether gave 212 g. which melted at 143–146° (Fourneau 144°). The total yield of pure material was 321 g. (46%). The benzene filtrate on concentration and dilution with petroleum ether gave 216 g. (31%) of the 6-nitroanilide; m. p. 110–114° (Fourneau 118°).

Hydrolysis of these products was effected by means of refluxing concd. hydrochloric acid instead of the dilute acid used by Fourneau; the 3-chloro-6-nitroaniline melted at 124–125° (Fourneau 125°) and the 3-chloro-4-nitroaniline at 155–157° (Fourneau 157°).

The Preparation of 5-Chloro-8-nitroquinoline.—In the Skraup method on a large scale, following Fourneau's conditions (which was for a small scale), we were unable

(5) Rohrmann and Shonle, THIS JOURNAL, **66**, 1640, 1643 (1944).

(6) Melting points reported herein are corrected.

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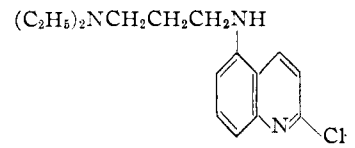
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

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-dialkylaminoalkylaminoquinolines as possible antimalarials the preparation of 2-chloro-5-(γ-diethylaminopropylamino)-quinoline (I) was undertaken. The most



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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).