The analytical sample was recrystallized from xylene. It had a melting point of 214–215°.

Anal. Calcd. for $C_{12}H_5ON_2$: C, 73.46; H, 4.11. Found: C, 73.73; H, 4.20.

(e) **4-Chloro-1,10-phenanthroline.**—To a mixture (at 90°) of 11 g. of phosphorus pentachloride and 20 ml. of phosphorus oxychloride was added 10 g. of the hydroxy compound. The temperature of the mixture was then raised to 130° and maintained there for two hours.

The crude chloro compound, after it was dried in an oven at 80° for five hours, melted at 180–230° and weighed 10 g. (95%). The chloro compound apparently exists as a hydrate as the solid melts at 80° and then solidifies. This vesicant product was not purified. However the monopicrate was prepared and analyzed; after recrystallization from nitromethane the picrate melted at 203–206°.

Anal. Calcd. for $C_{18}H_{10}N_5O_7Cl$: C, 48.72; H, 2.27. Found: C, 48.89; H, 2.27.

(f) **4-(3-Diethylaminopropylamino)-1,10-phenanthroline** (III).—A mixture of 23 g. of crude chloro compound and 65 g. of 3-diethylaminopropylamine was heated at 165° for two and one-half hours. To the red colored solution was added 100-ml. of concentrated potassium hydroxide and the mixture was then cooled in ice. The amine layer separated and was extracted with 250-ml. of chloroform. The chloroform solution was thoroughly washed with cold water, dried over potassium carbonate, filtered, and the solvent was removed by distillation. After the excess 3-diethylaminopropylamine was removed *in vacuo*, the solid residue was washed with petroleum ether (b. p. 50–60°). The crude product which melted at 130–150° weighed 30 g. To this was added 2500-ml. of methylcyclohexane and the mixture was boiled for a few minutes and then filtered. The red oil which did not dissolve was discarded. The methylcyclohexane solution was cooled in an ice-bath and the product which was collected by filtration was recrystallized from 2500 ml. of methylcyclohexane.

The yield of white crystalline product melting at 166–168° was 10 g. (32%).

Anal. Calcd. for $C_{19}H_{24}N_4$: C, 73.99; H, 7.84. Found: C, 73.86; H, 8.06.

The dipicrate after recrystallization from acetone melted at 172–174°.

Anal. Calcd. for $C_{31}H_{30}N_{10}O_{14}$: C, 48.57; H, 3.94. Found: C, 48.68; H, 4.11.

Summary

A series of reactions is described for the preparation of dialkylaminoalkylamino-1,10-phenanthrolines. The steps include condensation of the appropriate phenylenediamine or aminoquinoline with ethoxymethylenemalonic ester, ring closure in diphenyl ether, hydrolysis, decarboxylation, treatment with a mixture of phosphorus oxychloride and phosphorus pentachloride, and the condensation of the chloro compounds with dialkylaminoalkylamines.

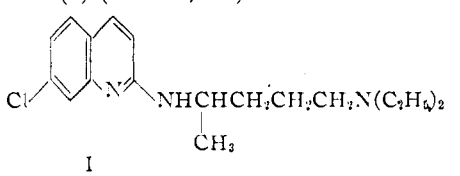
URBANA, ILL. RECEIVED APRIL 5, 1946

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

Antimalarials. *dl*-7-Chloro-2-(4-diethylamino-1-methylbutylamino)-quinoline[1]

BY ROBERT E. LUTZ, GILBERT ASHBURN AND RUSSELL J. ROWLETT, JR.[2]

Because of the antimalarial activity shown by 7-chloro-4-(-diethylamino-1-methylbutylamino)-quinoline (SN[1] 7618), it seemed important to synthesize for comparison the isomer in which the diamine chain is located in the 2- instead of the 4-position (I) (SN[1] 11,427).



I

In this synthesis 2,7-dichloroquinoline (IV) was needed as the intermediate for condensation with noval diamine. Because of the availability in this Laboratory of a quantity of 2,4,7-trichloroquinoline which could be hydrolyzed easily to 4,7-dichlorocarbostyril (II),[3] the quickest and most straightforward path to 2,7-dichloroquinoline which presented itself was the partial and selective catalytic hydrogenolysis of the latter (II) to 7-chlorocarbostyril (III) and subsequent replacement of the hydroxyl by chlorine. The obvious alternative syntheses were (a) the Skraup reaction on *m*-chloroaniline,[4] separation of the 7-chloroquinoline from the mixture of isomers, introduction of the 2-chlorine by the method of Decker[5] through the N-methyl compound, oxidation and replacement by chlorine chlorination, and (b) a similar synthesis from the now available 4,7-dichloroquinoline, involving partial catalytic reduction to eliminate the 4-chlorine,[6] a path which was excluded at the time because all of the available starting material was needed for the preparation of SN-7618 for the Armed Forces.

The dichloroquinoline reported long ago by Fischer[4c] as the 2,7-compound (m. p. 98–99°) was made from the supposed 7-chloroquinoline.[4a,b] Fourneau[4d] showed later, however, that the structures of the 5 and 7-chloroquinolines made by the Skraup reaction on *m*-chloroaniline were re-

(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.

The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

(2) Present location: Jackson Laboratory, E. I. du Pont de Nemours and Co., Wilmington, Del.

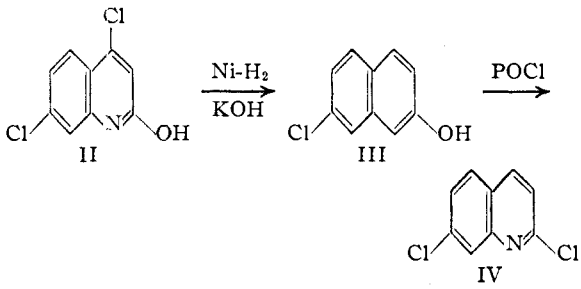
(3) (a) Lutz and co-workers, THIS JOURNAL, **68**, 1285 (1946); (b) Rowlett and Lutz, *ibid.*, **68**, 1288 (1946).

(4) (a) La Coste, *Ber.*, **18**, 2940 (1885); (b) Claus and Junghanns, *J. prakt. Chem.*, [2] **48**, 253 (1893); (c) Fischer, *Ber.*, **35**, 3683 (1902); (d) Fourneau, Tréfouel, Tréfouel and Wancolle, *Bull. soc. chim.*, [4] **47**, 749 (1930).

(5) Decker, *J. prakt. Chem.*, [2] **45**, 171 (1892).

(6) Surrey and Hammer, THIS JOURNAL, **68**, 116 (1946), reported after the completion of this work.

versed. Consequently the dichloroquinoline of Fischer must have been the 2,5-isomer, a conclusion which is confirmed by its obvious difference from our authentic 2,7-dichloroquinoline, which melts at 120°.



The crucial step in the synthetic path chosen was the selective catalytic hydrogenolysis of the 4-chlorine of 4,7-dichlorocarbostyril (II). Previously in the proof of structure of II[3b] by catalytic reduction to carbostyril in the presence of Raney nickel and an excess of alkali, a noticeable decrease in the rate of absorption of hydrogen was observed after one mole had been absorbed. This indicated that probably the rate of catalytic hydrogenolysis of the 4-chlorine was considerably greater than that of the 7-chlorine, and was in keeping with the known reactivity of the 4-chlorine toward amines[6] and in hydrolysis[3b] and methanolysis.[3b] After extensive study the optimum practical conditions for the successful stepwise catalytic hydrogenolysis (II to III) were found to be room temperature, atmospheric pressure and an alcoholic solution containing 1.25 equivalents of potassium hydroxide; the 7-chlorocarbostyril (III) was obtained in 93% yield. The fact that this product is different from the known 4-chlorocarbostyril[7] furnishes additional evidence for the location of the chlorine at the 7-position.

The 7-chlorocarbostyril was converted to 2,7-dichloroquinoline (IV) in the usual manner by means of phosphorus oxychloride.

The 2,7-dichloroquinoline (IV) was condensed with noval diamine and gave 7-chloro-2-(4-diethylamino-1-methylbutylamino)-quinoline (I) (SN 11,427) in good yield. This compound proved to be inactive against avian malarial infection.

Acknowledgment.—The authors wish to thank Dr. P. S. Bailey for help in the hydrogenolysis of 4,7-dichlorocarbostyril and Miss Joyce Blume, Curtis S. Floyd and Robert T. Hite for the microanalyses reported in this paper.

Experimental[8]

7-Chlorocarbostyril (III).—A warm solution of 17.5 g. (0.313 mole) of potassium hydroxide in 250 ml. of 95% ethanol was added to a suspension of 53.5 g. (0.25 mole) of recrystallized 4,7-dichlorocarbostyril (II)[3b] in 750 ml. of 95% ethanol, and the resulting mixture was warmed until solution was complete. The solution was reduced with Raney nickel catalyst and hydrogen at atmospheric pressure. Over a forty-five-hour period 1.25 equivalents of hydrogen was absorbed; the white, flaky 7-chlorocarbostyril (III) precipitated. A 20% solution of aqueous sodium hydroxide was added until all of the white solid dissolved. The catalyst was removed by filtration and the filtrate was acidified and cooled overnight. The resulting mixture was filtered and the white residue was washed repeatedly with water; yield 41.8 g. (93%), m. p. 287–292°. The crude product was used directly in the next step. Repeated recrystallization from absolute ethanol gave a pure sample, plates, m. p. 296–297°.

Anal. Calcd. for C_9H_6ClNO: C, 60.19; H, 3.37; N, 7.80. Found: C, 60.04, H, 3.22; N, 7.72.

Numerous experiments showed that the maximum yield (93%) of 7-chlorocarbostyril (III) was obtained when 1.25 equivalents of potassium hydroxide was employed (1.0 equivalents gave a 44.5% yield, 1.10 gave 59% and 1.35 gave 70.5%). The presence of two or more moles of alkali brought about the hydrogenolysis of both the 4- and 7-chlorines and carbostyril itself resulted.[3b] One mole of alkali was necessary to obtain complete solution of the difficultly soluble 4,7-dichlorocarbostyril (II). However, as the hydrogenolysis proceeded the alkali was neutralized and a mixture of the starting material (II) and the product (III) precipitated. The obvious effect of the excess alkali (0.25 equivalent) used in the above procedure was to hold the starting material (II) in solution in the form of the salt until the hydrogenolysis was completed.

One hydrogenolysis was carried out at two atmospheres pressure and the length of time necessary for the absorption of one mole of hydrogen was reduced approximately 50%. However, the limited size of the medium pressure equipment available reduced the size of the run possible to one-fifth.

The use of palladium–barium sulfate catalyst[9] in the reduction was investigated. More than one mole of hydrogen was absorbed and a mixture of carbostyril itself and 7-chlorocarbostyril was obtained. The method of Rabe[10] for the removal of the 2-chlorine in 2-chloro-6-methoxylepidine with aluminum and acetic acid was also tried without success.

2,7-Dichloroquinoline (IV).—A mixture of 20 g. (0.11 mole) of crude 7-chlorocarbostyril (III) and 100 ml. of phosphorus oxychloride was refluxed for two and one-half hours. The resulting mixture was cooled and added slowly (thirty minutes) with rapid stirring to 1 liter of a mixture of ice and water, adding more ice (1500 g.) from time to time to prevent a temperature rise. (Pouring the phosphorus oxychloride mixture directly onto ice shavings resulted in local overheating and hydrolysis of some of the dichloro product (IV) back to 7-chlorocarbostyril.) The dichloroquinoline was collected on a filter and recrystallized (with a Darco treatment) from ligroin (b. p. 65–110°); concentration of the solution yielded 18.8 g. (85%); white needles; m. p. 120°.

Anal. Calcd. for $C_9H_5Cl_2N$: C, 54.58; H, 2.54. Found: C, 54.35; H, 2.52.

2,7-Dichloroquinoline could also be purified by vacuum sublimation (100° (2 mm.)).

In order to ascertain feasible reaction conditions for the condensation of 2,7-dichloroquinoline (IV) with a water-soluble primary amine the condensation of IV with cyclohexylamine was studied, and the conditions which proved successful were then applied to the condensation with noval diamine.

7-Chloro-2-cyclohexylaminoquinoline Dihydrochloride.—One gram (0.005 mole) of 2,7-dichloroquinoline (IV) and 2 g. (0.02 mole) of cyclohexylamine were heated together for five hours at 123–127°. The resulting gelatinous mass was dissolved in 15 ml. of petroleum ether (b. p. 30–65°). This solution was extracted successively with 10 ml. of 4% sodium bicarbonate and four 10-ml. portions of

(7) Buchmann and Hamilton, THIS JOURNAL, **64**, 1357 (1942).

(8) All melting points are corrected.

(9) Prepared according to the method of Houben, "Die Methoden der organischen Chemie," 3rd ed., Vol. II, p. 500. Verlag Georg Thieme, Leipzig, 1925; also Schmidt, *Ber.*, **52**, 409 (1919).

(10) Rabe, *et al.*, *ibid.*, **64B**, 2492 (1931).

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** (SN[11]11,427).—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.

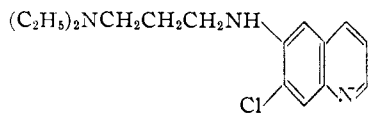
CHARLOTTESVILLE, VIRGINIA RECEIVED APRIL 5, 1946

[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-



I

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.