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Antimalarials. 7-Chloro-4-hydroxy- and 4,7-Dichloro-1-methylcarbostyrils[1]

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2,4,7-Trichloroquinoline (VII) was made previously as an intermediate in the synthesis of some novel dialkylaminoalkylaminoquinolines which were desired for testing as possible antimalarial drugs.[3] This paper deals with the synthesis of certain incidental N-methylation products which were obtained during this work, and with a second synthetic approach to 2,4,7-trichloroquinoline through these compounds.

The synthesis of 4,7-dichloro-1-methylcarbostyril (III) was accomplished in three steps from 4-chloroanthranilic acid,[3a] as follows: (a) methylation by means of dimethyl sulfate to N-methyl-4-chloroanthranilic acid (I) according to the method of Willstätter and Kahn,[4] (b) acylation and cyclization to 7-chloro-4-hydroxy-1-methylcarbostyril (II) by means of acetic anhydride, according to the method of Meister Lucius and Brüning for making 4-hydroxy-1-methylcarbostyril itself,[5] and (c) hydrochlorination in the usual way with phosphorus oxychloride.

bostyril (II) by means of diazomethane, gave the same product, 7-chloro-4-methoxy-1-methylcarbostyryl (IV).

The relationship between the two 1-methylcarbostyrils, II and III, and 2,4,7-trichloroquinoline and its derivatives, is of particular interest in connection with the N-methylation of carbostyrils by means of diazomethane.[3b] 7-Chloro-4-hydroxycarbostyril (V) reacted with methyl iodide and alkali to give the N-methyl derivative (II); and 4,7-dichlorocarbostyril (VI) reacted similarly to give III. In the methylation of 4,7-dichlorocarbostyril with diazomethane, N-methylation to III was the chief result but a small amount of the oxygen-alkyl derivative, 4,7-dichloro-2-methoxyquinoline, was also formed and isolated.[3b] The above synthesis of the N-methylation products of the two carbostyrils (V and VI) from 4-chloro-N-methylanthranilic acid serves as confirmation of the structures and of the mode of the methylations.

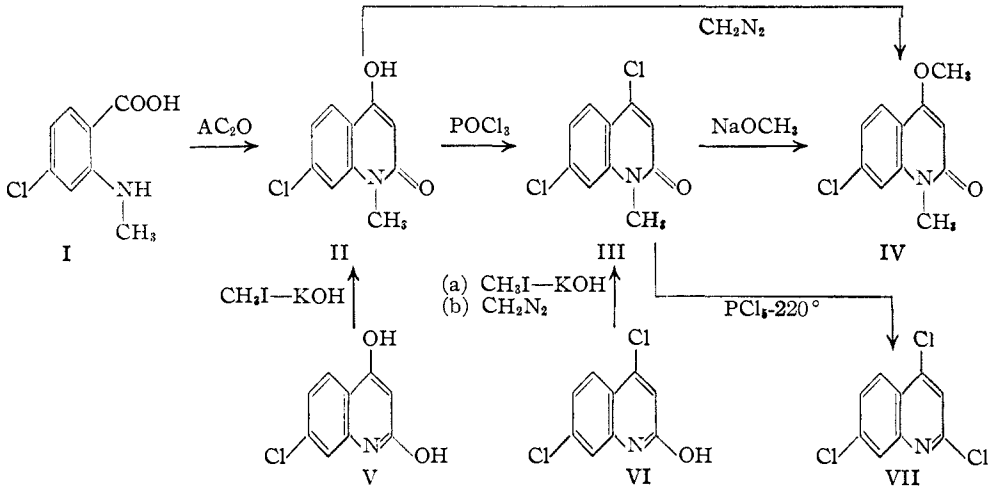

Fig. 1.

Methanolysis of 4,7-dichloro-1-methylcarbostyril (III) by means of sodium methoxide, and methylation of 7-chloro-4-hydroxy-1-methylcar-

The conversion of 4,7-dichloro-1-methylcarbostyril (III) into 2,4,7-trichloroquinoline (VII) by means of phosphorus pentachloride, following the analogous and facile conversion of 1-methylcarbostyril into 2-chloroquinoline,[6] failed to go appreciably at 170°; however, the reaction proceeded satisfactorily in a sealed tube at 220°.

Preceding this synthesis, a model synthesis of 2,4-dichloroquinoline (X) by the same scheme had been run. 4-Hydroxy-1-methylcarbostyril (VIII), which had been prepared[5] from N-methylanthranilic acid, was converted by means of phosphorus pentachloride and oxychloride into a mixture

(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.

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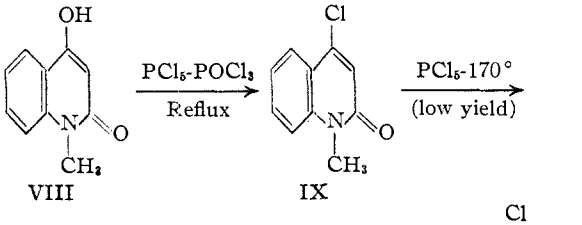
(3) (a) Lutz, Ashburn, Freek, Jordan, Leake, Martin, Rowlett and Wilson, THIS JOURNAL, **68**, 1285 (1946); (b) Rowlett and Lutz, *ibid.*, **68**, 1288 (1946); (c) Lutz, Ashburn and Rowlett, *ibid.*, **68**, 1322 (1946).

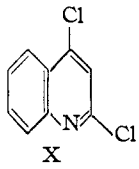
(4) Willstätter and Kahn, *Ber.*, **37**, 405 (1904).

(5) Meister Lucius and Brüning, *Chem. Zentr.*, **86**, II, 1034 (1915); (Hochst, German Patent 287,803).

(6) (a) Fischer, *Ber.*, **31**, 609 (1898); (b) Perkin and Robinson, *J. Chem. Soc.*, **103**, 1977 (1913).

consisting chiefly of 4-chloro-1-methylcarbostyril (IX) and a very small amount of the desired 2,4-dichloroquinoline (X); at 170° 4-chloro-1-methylcarbostyril was converted only partially into 2,4-dichloroquinoline. Doubtless this reaction would go satisfactorily at higher temperatures as in the case of III.

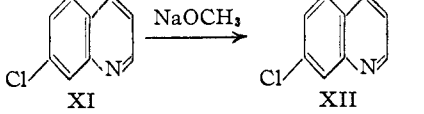




X

The above experiments show that the 4-chlorines of both N-methylcarbostyrils III and IX exert a noticeable stabilizing influence and interfere markedly with the hydrochlorinative demethylation reaction.

An unsuccessful attempt was made to relate 4,7-dichloroquinoline (XI) and also 7-chloro-4-methoxyquinoline (XII), which is easily made from XI by methanolysis, to the compounds described in this paper thus to achieve a third synthesis of 2,4,7-trichloroquinoline.



XI XII

The methiodides of these two compounds were easily made; however, the subsequent alkali ferrocyanide oxidation by the method of Decker,[7a] which worked well in the synthesis of 2-chloro-5-nitroquinoline,[7b] failed here in a number of trials to give the expected N-methylcarbostyrils, and gave instead compounds the nature of which has not yet been determined.

Experimental[8]

N-Methylanthranilic acid was prepared by the method of Willstätter and Kahn[4]; yield 73%; m. p. 172–177° (W. and K.[4] 179°).

4-Hydroxy-1-methylcarbostyril (VIII), which is reported briefly in the patent literature,[5] was prepared by treating one part of N-methylanthranilic acid with three parts of acetic anhydride under conditions varying from a temperature of 60° to refluxing, and for a period of ten minutes to twelve hours. Larger amounts of acetic anhydride also were tried. The following method gave the best results.

A solution of 45 g. of N-methylanthranilic acid, 150 ml. of acetic anhydride, and 150 ml. of acetic acid, was refluxed for four hours and poured onto ice. After basification, the resulting solution was acidified to litmus and cooled. The solid precipitate was filtered and washed with acetone; yield 18.5 g. (35%); m. p. 252–262° (M. L. and B.[5] 250°).

Conversion into 4-Chloro-1-methylcarbostyril (IX) by the Action of Phosphorus Pentachloride.—A mixture of 7 g. of 4-hydroxy-1-methylcarbostyril (VIII) and 25 ml. of phosphorus oxychloride was warmed until solution occurred; 17 g. of phosphorus pentachloride was added and the mixture was refluxed for one hour. Hydrolysis gave 3 g. of precipitate; ether extraction of this gave a very small amount of 2,4-dichloroquinoline (X) of m. p. 61–64°, which was identified by mixture melting point with an authentic sample made by the directions of Buchmann and Hamilton.[9] The aqueous filtrate from the hydrolysis of the reaction mixture upon neutralization with sodium carbonate gave 4.5 g. of halogen-free material which melted at 112–116° and was not soluble in sodium hydroxide. Several recrystallizations from ethanol gave a product of m. p. 117–119° which corresponds to the melting point reported in the literature[10] (117°).

Anal. Calcd. for $C_{10}H_8ClNO$: C, 62.03; H, 4.16. Found: C, 62.67; H, 4.15.

This product was itself treated with phosphorus oxychloride–pentachloride mixture for two and one-half hours (refluxing), and was recovered largely unchanged. However, upon fusion of 1 g. with 4 g. of phosphorus pentachloride (5 min. at 170°), 0.3 g. of crude 2,4-dichloroquinoline (X) was isolated (m. p. 53–56°) which was recrystallized from ether and then from ethanol (0.1 g.; m. p. 63–65°) and identified by mixture melting point; 0.8 g. of starting material was recovered. Fusion of 3.5 g. of VIII with 20 g. of phosphorus pentachloride at 170° for fifteen minutes gave 2.2 g. of IX.

4-Chloro-N-methylanthranilic acid (I) was obtained by a procedure similar to that for N-methylanthranilic acid itself.[4] A solution of 24.3 g. (0.2 mole) of 4-chloroanthranilic acid and 8.0 g. (0.2 mole) of sodium hydroxide in 100 ml. of water was cooled to 5°, and 25.2 g. (0.2 mole) of dimethyl sulfate was added dropwise with stirring over a period of thirty minutes; a white solid precipitated. Stirring was continued for two hours after which the mixture was allowed to stand for an additional fifteen hours before filtration. The residue was washed with water and recrystallized from 95% ethanol; yield 12.5 g. (47.5%); m. p. 174–186°. Several recrystallizations from 95% ethanol gave white crystals; m. p. 185–187°.

Anal. Calcd. for $C_8H_8ClNO_2$: C, 51.76; H, 4.35; N, 7.55. Found: C, 51.48; H, 4.34; N, 7.60.

7-Chloro-4-hydroxy-1-methylcarbostyril (II) (a) From 4-Chloro-N-methylanthranilic Acid (I).—A solution of 6.2 g. (0.033 mole) of 4-chloro-N-methylanthranilic acid (I) and 20 g. (0.2 mole) of acetic anhydride was heated at 90° for four hours. The resulting orange mixture was poured, with stirring, onto 100 g. of crushed ice; the mixture was allowed to stand for twelve hours, made basic with sodium hydroxide solution and filtered to remove a small amount of red sludge. The orange filtrate was barely acidified with hydrochloric acid and filtered, and the resulting orange solid was washed thoroughly with water and dried; yield 3.0 g. (43.5%); m. p. 284–286°. It was recrystallized several times from glacial acetic acid (once with Darco treatment); m. p. (*in vacuo*) 291–305°.

Anal. Calcd. for $C_{10}H_8ClNO_2$: N, 6.68. Found: N, 6.89.

(b) **From 7-Chloro-4-hydroxycarbostyril (V).**[3a]—A mixture of 4 g. (0.02 mole) of 7-chloro-4-hydroxycarbostyril (V),[3a] 2.3 g. (0.04 mole) of potassium hydroxide and 50 ml. of methanol was warmed until solution was complete; 6 ml. (0.075 mole) of methyl iodide was added and the solution was refluxed gently for three hours; light tan solid precipitated after one hour. The mixture was cooled, filtered and the residue was washed thoroughly with

(7) (a) Decker, *J. prakt. Chem.*, **45**, 175 (1892); (b) Deinet and Lutz, THIS JOURNAL, **68**, 1325 (1946).

(8) All melting points are corrected. The microanalyses reported herein were carried out by Miss Joyce Blume and Mr. C. S. Floyd.

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

(10) Friedlander and Müller, *Ber.*, **20**, 2010 (1887).

water; yield 2.6 g. (62%); m. p. 285–290°. A mixture melting point with the sample from (a) showed no depression.

4,7-Dichloro-1-methylcarbostyril (III).[3b]—A solution of 1.1 g. of 7-chloro-4-hydroxy-1-methylcarbostyril (II) in 10 ml. of phosphorus oxychloride was refluxed for two hours, and poured, with stirring, over crushed ice. The resulting mixture was allowed to stand overnight and was filtered from a small amount of sludge; the filtrate was made alkaline by the addition, with stirring, of solid sodium bicarbonate. The resulting precipitate was filtered, washed thoroughly with water and recrystallized (with Darco treatment) from absolute ethanol. This product was sublimed under reduced pressure (80° (2 mm.)) and two volatile fractions were obtained, which melted, respectively, at 159–159.5° and 161–161.5°; total yield 0.14 g. (11.6%). Two recrystallizations from 95% ethanol gave colorless crystals, m. p. 161–162°, which showed no mixture melting point depression with a sample prepared from 4,7-dichlorocarbostyril[3b] (III).

Anal. Calcd. for $C_{10}H_7Cl_2NO$: N, 6.14. Found: N, 6.11.

Hydrochlorinative-demethylation to 2,4,7-Trichloroquinoline (VII).—A sample of 4,7-dichloro-1-methylcarbostyril (III) was recovered unchanged after mixing with twice its weight each of phosphorus pentachloride and *p*-dichlorobenzene and heating at 170° for one and one-half hours.

A small sample of the dichloro-N-methylcarbostyril, mixed with approximately twice its weight of phosphorus pentachloride and twice its weight of *p*-dichlorobenzene, was placed in a sealed tube and heated at 220–225° for six hours. The material was then hydrolyzed in water, made alkaline with sodium hydroxide, filtered, washed with water and dried; m. p. 88–91°. Recrystallization from dilute alcohol gave a sample of m. p. 99–100°. A mixture melting point with an authentic sample of VII showed no depression.

7-Chloro-4-methoxy-1-methylcarbostyril (IV). (a) By Methanolysis of 4,7-Dichloro-1-methylcarbostyril (III).—A solution of 0.3 g. of sodium in 10 ml. of methanol was added to a mixture of 0.94 g. of 4,7-dichloro-1-methylcarbostyril (III) and 10 ml. of methanol and the resulting mixture was refluxed for two hours, cooled and filtered. The white solid was washed repeatedly with water and dried; yield 0.57 g. (58.1%); m. p. 167–170°. The product was recrystallized three times from 60% ethanol; white needles; m. p. 165.5–166.5°.

Anal. Calcd. for $C_{11}H_{10}ClNO_2$: C, 59.06; H, 4.51; N, 6.26. Found: C, 59.30; H, 4.73; N, 6.12.

(b) By Diazomethylation of 7-Chloro-4-hydroxy-1-methylcarbostyril (II).—A small sample of II was added to an ether solution containing an excess of diazomethane and the resulting mixture was allowed to stand at room temperature for thirty hours; an amber-colored solution resulted. The ether was evaporated under a stream of dry air and the remaining brown residue was recrystallized twice (once with Darco treatment) from 95% ethanol; white crystals; m. p. 165–177°.

Anal. Calcd. for $C_{11}H_{10}ClNO_2$: N, 6.26. Found: N, 6.43.

A mixture melting point of this product with the sample prepared in (a) showed no depression.

4,7-Dichloroquinoline methiodide was made in 74% yield by the direct action of excess methyl iodide in dry benzene under refluxing for twenty-four hours; m. p. 200–207° (dec.); recrystallized from methanol; m. p. 216–218°.

Anal. Calcd. for $C_{10}H_8Cl_2IN$: I, 37.30. Found: 37.42.

An **oxidation**[7] was run by adding over a half hour a hot solution of 4 g. of the methiodide in 500 ml. of water to a solution of 100 g. of potassium ferricyanide in 250 ml. of 10% sodium hydroxide at 65°, with continued heating at this temperature for another half hour. After cooling the crystalline product was filtered, washed with water and dried; yield 2 g. This material was dissolved in hot ethanol, filtered from a small amount of red insoluble residue, and crystallized by addition of water; white needles; m. p. 140–141°. Another recrystallization followed by sublimation in vacuo (80° (1 mm.)) gave a product of m. p. 145–146°. A qualitative test for iodine was positive.

Repetition of this oxidation on a small scale in 2% sodium hydroxide at room temperature gave the same results.

Anal. Found: C, 44.70; H, 2.68; N, 6.78; halogen, 28.60.

7-Chloro-4-methoxyquinoline (XII).—A solution of 5 g. of 4,7-dichloroquinoline (XI) and 2.7 g. of sodium methoxide in 55 ml. of dry methanol was refluxed for 45 min. Upon filtering and diluting with water to 400 ml., white crystals were obtained; 4.5 g. (92%); m. p. 129–135°. Three recrystallizations from methanol gave a sample melting at 137–138°.

Anal. Calcd. for $C_{10}H_8ClNO$: C, 62.03; H, 4.16. Found: C, 61.72; H, 4.41.

The **methiodide** was made in 86% yield by refluxing a benzene solution of XII and methyl iodide for eight hours; m. p. 225–230°. Recrystallization from methanol gave a sample melting at 233–234°.

Anal. Calcd. for $C_{11}H_{11}ClINO$: I, 37.8. Found: I, 37.7.

Oxidation of 2.5 g. of the methiodide by adding the solution in 60 ml. of hot water slowly to a stirred solution of 10 g. of potassium ferricyanide in 25 ml. of 10% sodium hydroxide at 65°, with continued heating for a half hour, gave on cooling a crystalline solid which was filtered, washed with water and dried; 1.5 g.; m. p. 233–235°. Recrystallization from hot ethanol gave a sample melting at 238–239°. A test for iodine was negative.

Repetition of this oxidation on a smaller scale in 2% sodium hydroxide at room temperature gave similar results.

Anal. Found: C, 61.67, 61.83; H, 4.10, 4.26; N, 7.08, 7.06; Cl, 21.63.

Summary

4,7-Dichloro-1-methylcarbostyril (the N-methylation product of 4,7-dichlorocarbostyril) was synthesized through the 7-chloro-4-hydroxycarbostyril from 4-chloro-N-methylanthranilic acid. Attempts to make this compound from 4,7-dichloroquinoline were unsuccessful. It was converted into 2,4,7-trichloroquinoline by phosphorus pentachloride at 220°.

4-Hydroxy-1-methylcarbostyril has been converted into 7-chloro-1-methylcarbostyril and 2,4-dichloroquinoline by the action of phosphorus pentachloride.

7-Chloro-4-methoxy-1-methylcarbostyril is described.

CHARLOTTESVILLE, VA. RECEIVED JUNE 28, 1946