boxylic acid, melting at 220° with gas evolution and formation of a solid melting at 268–270°.

Anal. Calcd. for $C_{16}H_{10}N_2O_5$: C, 61.9; H, 3.2. Found: C, 62.2; H, 3.6.

The acid was decarboxylated by heating it in a beaker in a Wood's metal bath at 280° until gas evolution ceased. The material melted at 265–270° and was used without further purification. The yield was 97%.

2-(4'-Nitrophenyl)-4-chloroquinoline.—The above compound was treated with phosphorus oxychloride as in the other cases, yielding 55% of material melting at 149–150° after crystallization from alcohol.

Anal. Calcd. for $C_{15}H_9ClN_2O_2$: C, 63.2; H, 3.1. Found: C, 62.8; H, 2.9.

Summary

1. A detailed study of the synthesis of 2-aryl-4-hydroxyquinolines from iminochlorides and diethylmalonate has been made.

2. The synthesis of various substituted 2-phenyl-4-chloroquinolines has been described.

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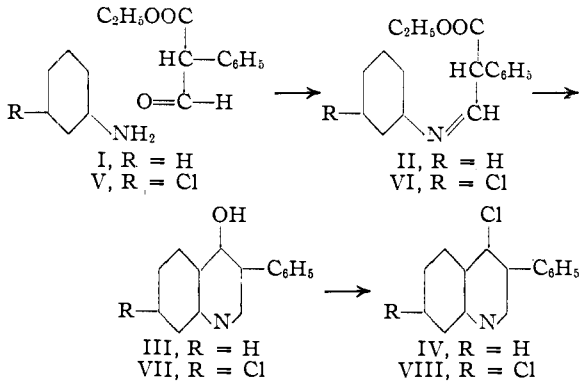
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

3-Phenyl-4-chloro- and 3-Phenyl-4,7-dichloroquinoline[1]

BY ROBERT C. ELDERFIELD AND JOHN B. WRIGHT

Derivatives of 4-aminoquinoline containing a methyl group in the 3-position are characterized by relatively high antimalarial activity and, in some cases at least, by favorable toxicity.[2] Since the effect of other substituents in the 3-position in this series is unknown, it was of interest to determine the effect of a phenyl group. In the present paper the synthesis of 3-phenyl-4-chloroquinoline (IV) and 3-phenyl-4,7-dichloroquinoline (VIII) is described. Conversion of these substances into derivatives of the corresponding 4-aminoquinolines is described elsewhere.[3]

3-Phenyl-4-hydroxyquinoline (III) was prepared by condensation of aniline with ethyl α,α-formylphenylacetate and cyclization of the intermediate anil (II) in a mixture of diphenyl and



diphenyl ether. Wislicenus[4] describes the synthesis of the same compound from methyl α,α-formylphenylacetate and cyclization by heating the anil alone. III has also been prepared by Börner.[5] III was converted to IV with phosphorus oxychloride.

3-Phenyl-4,7-dichloroquinoline was prepared in the same manner from *m*-chloroaniline. Ring closure leading to VII was accompanied to a certain extent with formation of presumably the 5-chloro isomer. However, it was possible to isolate either pure VII or VIII from the mixture of isomers by crystallization. The structure assigned to VII, and hence to VIII, was proved by oxidation of VII to 4-chloro-N-benzoylanthranilic acid.[6]

Experimental[7,8]

3-Phenyl-4-hydroxyquinoline, III.—A mixture of 230.4 g. of ethyl α,α-formylphenylacetate and 111.7 g. of aniline was allowed to stand overnight at room temperature, then taken up in ether and dried with anhydrous magnesium sulfate. After removal of the ether, the light yellow oily anil was added dropwise to 900 ml. of diphenyl–diphenyl ether (26:74) (Dowtherm A) at 200° during ten minutes with agitation by a stream of nitrogen. The mixture was then heated at 230–240° for five hours. The precipitate which separated from the cooled solution overnight was washed thoroughly with petroleum ether (1 l.) and then with ether (500 ml.), yielding 132 g. (50%) of III which melted at 259–260°. Wislicenus[4] reports a melting point of 255–257°.

3-Phenyl-4-chloroquinoline, IV.—To 260 ml. of phosphorus oxychloride at 100° was added 126.5 g. of III, and the mixture was refluxed for two hours, during which solution of III was complete. An additional 125 ml. of phosphorus oxychloride was added, and refluxing was continued for another one and a half hours. A white solid separated. The mixture was poured into a liter of ice water and made alkaline with 10% sodium hydroxide solution with addition of more ice to control the temperature. The yield of crude IV which separated was 130 g. (95%). Two recrystallizations from methanol (carbon) gave 86 g. of colorless needles melting at 74–75°.

Anal. Calcd. for $C_{15}H_{10}ClN$: C, 75.2; H, 4.2. Found: C, 75.4; H, 4.4.

3-Phenyl-4-hydroxy-7-chloroquinoline, VII.—This was prepared as was III except that *m*-chloroaniline was used. The yield of crude product was 36.5%. Recrystallization from alcohol (700 ml. per g.) gave pure VII as needles melting at 360.5–361.5°.[9]

Anal. Calcd. for $C_{15}H_{10}ClNO$: C, 70.4; H, 3.9. Found: C, 70.3; H, 4.0.

(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 Columbia University.

(2) "Antimalarial Drugs, 1941–1945," published by the Survey of Antimalarial Drugs, in press.

(3) Drake and co-workers, THIS JOURNAL, **68**, 1208 (1946)

(4) Wislicenus, *Ann.*, **413**, 248 (1917).

(5) Börner, Dissertation, Wurzburg, 1899, pp. 38, 43.

(6) Kretschy, *Monatsh.*, **4**, 156 (1883).

(7) All melting points are corrected.

(8) Microanalyses by Misses Frances Marx and Lois May of these laboratories.

(9) Maquenne block.

3-Phenyl-4,7-dichloroquinoline, VIII.—This was prepared by the same method as was IV. From 175 g. of crude VII, 190.5 g. of crude VIII was obtained. One recrystallization from alcohol (3 l.) gave 150 g. of a mixture of the assumed 5-chloro isomer and the desired 7-chloro isomer melting at 103–110°. Pure VIII was obtained as colorless needles melting at 121–122° by three additional recrystallizations from methanol–ethanol (1:2). Pure VIII was also obtained directly starting from pure VII. However, because of the great insolubility of VII it is more convenient to purify the final product at the stage of VIII.

Anal. Calcd. for $C_{15}H_9Cl_2N$: C, 65.7; H, 3.3. Found: C, 66.0; H, 3.5.

Oxidation of 3-Phenyl-4-hydroxy-7-chloroquinoline.[6]—Six grams of VII was refluxed five hours with a solution of 25 g. of potassium permanganate and 2.5 g. of potassium hydroxide in 1500 ml. of water. After acidification of the filtrate from the manganese dioxide, the excess permanganate was destroyed with sulfurous acid. The precipitate (3 g.) melted at 222–223° after one recrystallization from acetic acid. Hann[10] gives 223.5° as the melting point for 4-chloro-N-benzoylanthranilic acid. The identity of the latter acid was confirmed by hydrolysis of the benzoyl group on heating the benzoyl acid with hydrochloric acid (sp. gr. 1.19) in a sealed tube at 130–150° for two hours. From the reaction mixture benzoic acid and 4-chloroanthranilic acid melting at 234–235° (dec.) after recrystallization from dilute alcohol, were obtained. 4-Chloroanthranilic acid is reported as melting at 235–236° and 6-chloroanthranilic acid (which would arise from 3-phenyl-4,5-dichloroquinoline) at 146–147°.[11]

Summary

3-Phenyl-4-chloroquinoline and 3-phenyl-4,7-dichloroquinoline have been prepared. The structure of the latter has been demonstrated.

(10) Hann, THIS JOURNAL, **45**, 1024 (1923).

(11) Cohn, *Monatsh.*, **22**, 485 (1901).

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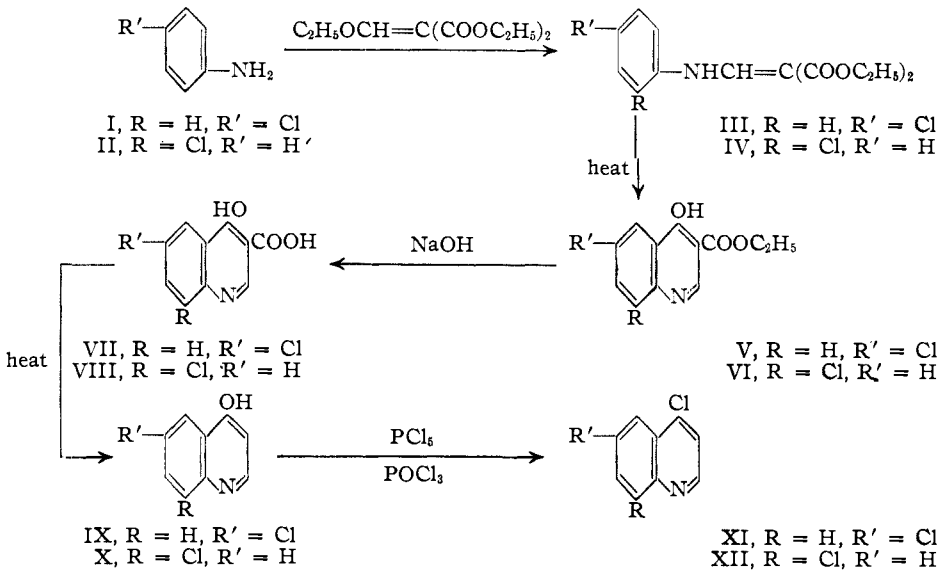
The Synthesis of 4,6- and 4,8-Dichloroquinoline[1]

BY D. STANLEY TARBELL

4,6- and 4,8-dichloroquinoline have been prepared from *p*-chloroaniline and *o*-chloroaniline respectively by the Price–Roberts synthesis.[2] The reactions involved are



The ring closure of the anilino compound IV to the 3-carbethoxy-4-hydroxy-8-chloroquinoline VI proceeded much more slowly than in the case of the *p*-chloro compound III, or the corresponding *m*-chloro derivative of Price and Roberts. The products VI, VIII and X were more difficult to purify than V, and some by-product seemed to be formed; this situation was unchanged by rigorous purification of the starting *o*-chloroaniline through its crystalline acetyl derivative. The whole series of reactions with the *p*-chloro isomer was far more satisfactory. Bachmann and Cooper[3] have previously prepared 4,6-dichloroquinoline (XI) by the Meisenheimer[4] procedure from the N-oxide, and have hydrolyzed it to the hydroxy compound IX.

Experimental[5]

Ethyl α-Carbethoxy-β-(2-chloroanilino)-acrylate (IV).—*o*-Chloroaniline (148 g.) was heated at 120–130° for one

(1) The work described in this report was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Rochester.

(2) Price and Roberts, THIS JOURNAL, **68**, 1204 (1946).

(3) Bachmann and Cooper, *J. Org. Chem.*, **9**, 302 (1944).

(4) Meisenheimer, *Ber.*, **59**, 1848 (1926).

(5) All melting points corrected; analyses by Lois E. May, Columbia University, and by the Micro-Tech Laboratories.