2-(*p*-Chlorophenyl)-4-hydroxyquinoline.—A solution consisting of 10 g. of ethyl anthranilate, 100 ml. of phenyl ether and 11.5 g. of *p*-chloro-α-ethoxystyrene was subjected to the usual treatment. The white, crystalline 2-(*p*-chlorophenyl)-4-hydroxyquinoline melted at 340–342°; yield 74.2%.

Anal. Calcd. for $C_{15}H_{10}ONCl$: C, 70.46; H, 3.91. Found: C, 70.36; H, 3.84.

Summary

The synthesis of 2-aryl-4-hydroxyquinolines has been accomplished by a new method which involves the reaction, under the influence of heat, of an anthranilic acid or ester with the acetal of an acylophenone.

The method has proved to be convenient for the unequivocal synthesis of 7-chloro-4-hydroxy-2-phenylquinoline. Other compounds which have been prepared by the new method are 4-hydroxy-2-phenylquinoline, 4-hydroxy-3-methyl-2-phenylquinoline and 2-(*p*-chlorophenyl)-4-hydroxyquinoline.

URBANA, ILLINOIS RECEIVED APRIL 5, 1946

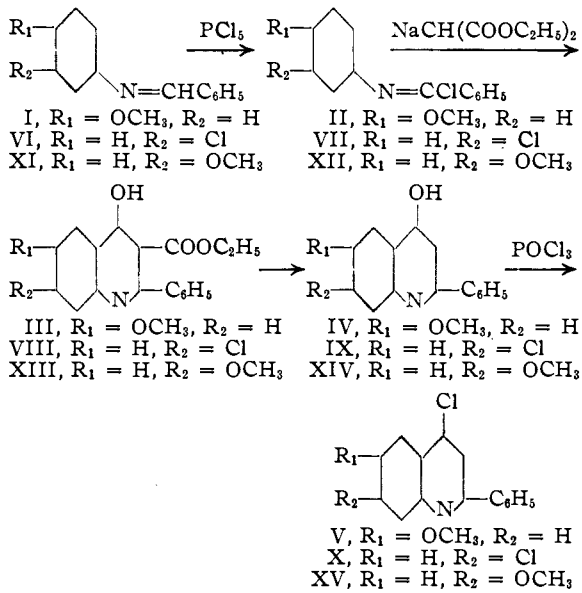
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Synthesis of 2-Phenyl-4-chloroquinolines[1]

BY ROBERT C. ELDERFIELD, WALTER J. GENSLER, THOMAS H. BEMBRY, CHESTER B. KREMER, JAMES D. HEAD, FREDERICK BRODY AND ROGER FROHARDT

The observation that quinine suffers attack *in vitro* in the presence of liver slices to yield the 2-hydroxy derivative[2,3] suggested that if this position in the quinoline ring be blocked in other active groups of antimalarials, enhanced activity might be expected. The synthesis of a series of quinoline-4-amino-carbinols wherein this position is blocked will be described in subsequent papers.[4,5,6,7] In the present communication we wish to describe the synthesis of 2-phenyl-4-chloro-6-methoxyquinoline, 2-phenyl-4,7-dichloroquinoline, and 2-phenyl-4-chloro-7-methoxyquinoline. The conversion of these intermediates to derivatives of 4-aminoquinoline will be described elsewhere.[8] The first of the two quinoline derivatives was chosen because of its obvious relationship to quinine and its 2-phenyl derivative, and the second because of its equally obvious relationship to the highly active 7-chloro-4-substituted quinolines.[9]

Syntheses of all three compounds were patterned closely after methods outlined by previous workers[10,11,12] in whole or in part for similar compounds. The synthesis of 2-phenyl-4-chloro-6-methoxyquinoline is represented by I–V. Conversion of II to III has been carried out without isolating the intermediate primary condensation product of II and diethyl malonate as was done by previous workers.[11,12] The conversion of IV to V proceeded smoothly.



I, R_1 = OCH_3, R_2 = H; II, R_1 = OCH_3, R_2 = H
VI, R_1 = H, R_2 = Cl; VII, R_1 = H, R_2 = Cl
XI, R_1 = H, R_2 = OCH_3; XII, R_1 = H, R_2 = OCH_3

III, R_1 = OCH_3, R_2 = H; IV, R_1 = OCH_3, R_2 = H
VIII, R_1 = H, R_2 = Cl; IX, R_1 = H, R_2 = Cl
XIII, R_1 = H, R_2 = OCH_3; XIV, R_1 = H, R_2 = OCH_3

V, R_1 = OCH_3, R_2 = H
X, R_1 = H, R_2 = Cl
XV, R_1 = H, R_2 = OCH_3

For the synthesis of X a similar series of reactions was utilized starting from benzo-*m*-chloroanilide (VI-X). However, in this case it was necessary to demonstrate that ring closure had proceeded with the formation of VIII rather than with the formation of the isomeric 5-chloro derivative. For this purpose X was prepared from 2-phenyl-4-carboxy-7-chloroquinoline, the structure of which has been proven by Borsche.[13] The acid was converted to 2-phenyl-4-amino-7-chloroquinoline by the Curtius method and the amino group of the latter substance was replaced by chlorine through the diazonium reaction. Samples of X prepared by either route were identical.

2-Phenyl-4-chloro-7-methoxyquinoline (XV)

(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) Mead and Koepfli, *J. Biol. Chem.*, **154**, 104 (1944).

(3) Koepfli and co-workers, THIS JOURNAL, **68**, in press (1946).

(4) Koepfli and co-workers, *ibid.*, **68**, in press (1946).

(5) Buchman and co-workers, *ibid.*, **68**, in press (1946).

(6) Jacobs and co-workers, *ibid.*, **68**, in press (1946).

(7) Lutz and co-workers, *ibid.*, **68**, in press (1946).

(8) Drake and co-workers, *ibid.*, **68**, 1208 (1946).

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

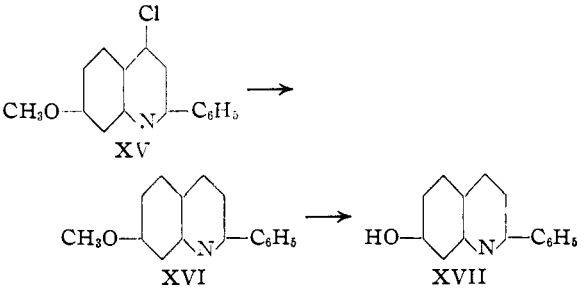
(10) Wallach, *Ann.*, **184**, 79 (1876).

(11) Seka and Fuchs, *Monatsh.*, **57**, 52 (1931).

(12) Shah and Heeramaneck, *J. Chem. Soc.*, 428 (1936).

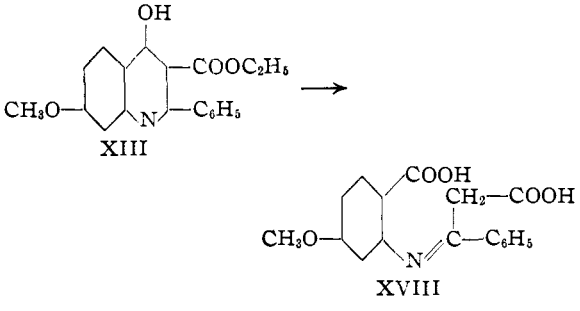
(13) Borsche, *Ber.*, **41**, 3884 (1908).

was also prepared similarly from benzo-*m*-anisidide (XI). Again in this case it was necessary to demonstrate that ring closure had taken place with the formation of the 7-methoxy derivative. For this purpose the chlorine in XV was removed catalytically, and the resulting 2-phenyl-7-methoxyquinoline (XVI) was converted to the hydroxy compound (XVII).

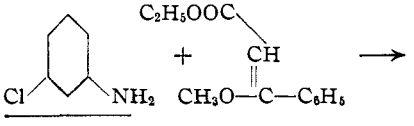


Preparations of XVI and XVII by the present method were identical with corresponding preparations by the method of Borsche and Wagner-Roemmich,[14] the investigators who established the structure of these substances. In this connection the melting point of XVI as obtained by us differed considerably from that reported by Borsche and Wagner-Roemmich.[14] We have repeated the synthesis of these workers and failed to confirm their reported melting point for XVI. It is interesting to note that 2-phenyl-4-hydroxy-7-methoxyquinoline (XIV) is completely resistant to the action of both neutral and alkaline potassium permanganate when boiled for from eight to thirty-six hours, and to the action of hot chromic acid solution in the presence of sulfuric acid.

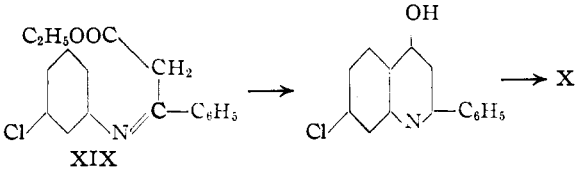
When 2-phenyl-3-carbethoxy-4-hydroxy-7-methoxyquinoline (XIII) is boiled with strong potassium hydroxide solution, ring cleavage apparently occurs and a substance giving analytical figures corresponding to XVIII results.



An alternate synthesis of X involved the reactions

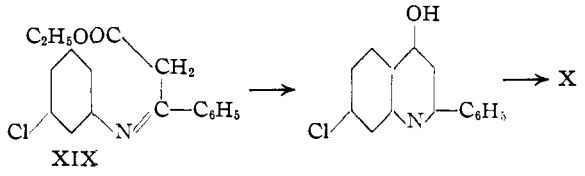


(14) Borsche and Wagner-Roemmich, *Ann.*, **544**, 287 (1940).

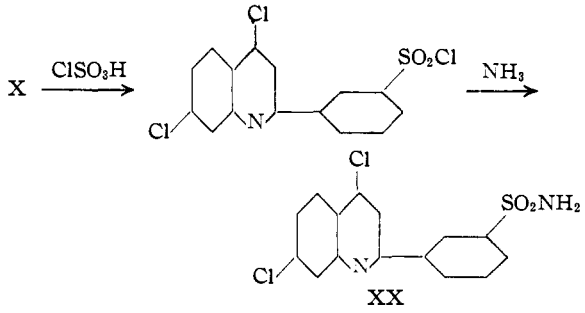


However, ring closure led to a difficultly separable mixture of the 5- and 7-chloro isomers in good yield from which only a small amount of X could be obtained. When ethyl β-ethoxycinnamate or ethyl β-chlorocinnamate was used in the above reaction, none of the desired product resulted.

Application of the familiar Conrad–Limpach synthesis to the reaction of *m*-chloroaniline with ethyl benzoylacetate under conditions which would be expected to lead primarily to the formation of the anil XIX by analogy to the corresponding reaction with ethyl acetoacetate resulted in the formation of but a small amount of X after ring closure and chlorination.



It was also desired to introduce a sulfonamido group in the 2-phenyl substituent in certain of the above compounds. For this purpose the most convenient method involved the chlorosulfonation of X followed by reaction of the sulfonyl chloride with ammonia to yield 2-(3′-sulfonamidophenyl)-4,7-dichloroquinoline (XX). That the chlorosulfonation takes place as indicated was shown by the isolation of *m*-sulfonamidobenzoic acid by oxidation of XX.



When the introduction of a sulfonamido group in V was attempted by the same method, a mixture of isomers, as judged by melting point range, was obtained. We were unable to obtain a sharp melting compound by crystallization.

Finally, the synthesis of 2-(4′-nitrophenyl)-4-chloroquinoline has been accomplished by the same general method used for V. However, attempted reduction of the nitro group to amino preparatory to the introduction of other substituents by the diazo reaction led to ill-defined products.

Experimental[15,16]

Benzo-*p*-anisidide Imino Chloride, II.—The preparation of this has been described in a very general sense by Wallach[10] and by Seka and Fuchs.[11] An intimate equimolar mixture of benzo-*p*-anisidide and phosphorus pentachloride was warmed gently under reflux on the steam-bath until a vigorous reaction set in. After the initial reaction had subsided, the mixture was heated for an additional four hours. The clear, greenish-yellow solution was decanted from a small amount of insoluble material directly into a distilling flask. After removal of the phosphorus oxychloride, the product was distilled at 2 mm. During the distillation, it is vital that the bath temperature be well below 225°, since at this temperature vigorous decomposition occurs. The yield of iminochloride boiling at 180–181° (2 mm.), which solidifies on cooling and melts at 63–64°, was 82%. Seka and Fuchs give the same melting point. This and the other iminochlorides must be rigidly protected from moisture.

2-Phenyl-3-carbethoxy-4-hydroxy-6-methoxyquinoline, III.—This was prepared essentially according to Shah and Heeramaneck,[12] except that the two steps were carried out without isolating the intermediate. Equimolar amounts of sodio diethylmalonate and II were condensed by refluxing in dry toluene for four hours. After removal of the toluene *in vacuo*, the residue was diluted with water and extracted with ether. Removal of the ether left a sticky brown residue which contained malonic ester. This was removed *in vacuo* and the ester simultaneously cyclized by heating the crude material at 150–170° for four hours until the whole mass had completely solidified. The light cream-colored solid was recrystallized from alcohol, forming fluffy needles melting at 248–249°. Seka and Fuchs[11] report 245°. The yield was 38%.

Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.6; H, 5.3. Found: C, 70.7; H, 5.5.

2-Phenyl-4-hydroxy-6-methoxyquinoline, IV.—Seka and Fuchs[11] describe the synthesis of this in very poor yield accompanied by much decomposition. The following represents a substantial improvement. In a 500-ml. round-bottom flask in a metal-bath, 79 g. of 2-phenyl-4-hydroxy-6-methoxyquinoline-3-carboxylic acid, prepared according to Seka and Fuchs[11] by hydrolysis of the ester, was heated under water pump vacuum at an initial bath temperature of 235°. The bath temperature was slowly raised at such a rate that the solid never melted until the temperature reached 300°, which required about four hours. By thus controlling the heating, the crude product required no further purification. It melted at 299–300°. A small sample crystallized from dilute acetic acid melted at 289–290°, which compares with the reported melting point of 287°.[11] The yield was quantitative.

2-Phenyl-4-chloro-6-methoxyquinoline, V.—To a suspension of 43 g. of IV in 50 ml. of phosphorus oxychloride was added 35.4 g. of phosphorus pentachloride. The mixture was boiled vigorously under reflux for an hour during which solution was complete. After cooling to 60°, the mixture was poured into ice. The sticky mass which gradually solidified when made slightly alkaline with 10% sodium hydroxide solution was collected and exhaustively extracted with ether, leaving about 10 g. of insoluble material. The crude ether soluble material was recrystallized from acetone with carbon and formed colorless needles melting at 109–110°. John,[17] who prepared the material by diazotization of the corresponding 4-amino derivative, reports it melting at 109°. The yield was 21 g. (46%).

Benzo-*m*-chloroanilide, VI.—*m*-Chloroaniline was benzoylated in sodium hydroxide solution in 30% alcohol with benzoyl chloride. The crude air-dried material (yield 93%) melted at 117–119° and was used without further purification.

Benzo-*m*-chlorophenylimidochloride, VII.—This was prepared as was the above anisidide. The yield of material boiling at 178–181° (2 mm.) (bath temperature 230–240°) was 85%.

2-Phenyl-3-carbethoxy-4-hydroxy-7-chloroquinoline, VIII.—This was prepared as was the above 6-methoxy compound, the cyclization being carried out at 180–190° for twelve hours. The crude product was triturated with benzene and the benzene insoluble material melted at 223–225°. After one recrystallization from alcohol, it melted at 237–240°. Shah and Heeramaneck[12] report 234–237°.

2-Phenyl-4-hydroxy-7-chloroquinoline-3-carboxylic Acid,—The above ester was hydrolyzed by boiling for four hours with 20% sodium hydroxide solution. Disappearance of the organic layer is no criterion of complete hydrolysis, since the ester is somewhat soluble in alkali. Neutralization to *p*H 2 precipitated the acid which, when crude, melted at 345°. Neutral equiv.: calcd., 299; found, 295.

2-Phenyl-4-hydroxy-7-chloroquinoline, IX.—The above acid was decarboxylated by heating 10–15 g. portions in a Wood's metal-bath at 360°. The yield of product melting at 355° was 95%. It was used without further purification.

2-Phenyl-4,7-dichloroquinoline, X.—This was prepared as was the corresponding 6-methoxy derivative, except that phosphorus oxychloride was used alone, being added in two equal portions during the refluxing, one at the start and one after forty-five minutes. If all the excess oxychloride is removed prior to addition of sodium hydroxide solution to the crude product, a hard, difficultly purified tar results. After crystallization from alcohol (carbon) the product melted at 101–101.5°. The yield was 40% with additional amounts recoverable from mother liquors.

Anal. Calcd. for $C_{15}H_9Cl_2N$: C, 65.7; H, 3.3. Found: C, 66.1; H, 3.4.

Benzo-*m*-anisidideiminochloride, XI.—This was prepared as in the preceding cases. The substance boiled at 155–156° (1 mm.) (bath temp. 210–215°) and remained a liquid in the refrigerator. The yield was 82%.

2-Phenyl-3-carbethoxy-4-hydroxy-7-methoxyquinoline, XIII.—This was prepared exactly as in the preceding cases. The yield of white needles melting at 232–233° after recrystallization from 10 volumes of alcohol was 35%.

Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.5; H, 5.3. Found: C, 70.2; H, 5.4.

2-Phenyl-4-hydroxy-7-methoxyquinoline-3-carboxylic Acid.—The above ester was hydrolyzed as before. After crystallization from glacial acetic acid, the acid on rapid heating melted at 238–240° with decomposition and immediate resolidification. On slow heating, no melting point was observed for the acid, but rather the melting point of the decomposition product, 282–283°.

Anal. Calcd. for $C_{17}H_{13}NO_4$: C, 69.2; H, 4.4. Found: C, 68.9; H, 4.5.

2-Phenyl-4-hydroxy-7-methoxyquinoline, XIV.—The above acid was decarboxylated as in the preceding case at 360°. The yield of white needles melting, after recrystallization first from dilute acetic acid (carbon) and then from alcohol, at 282–283° was 90%.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.5; H, 5.2. Found: C, 76.4; H, 5.4.

2-Phenyl-4-chloro-7-methoxyquinoline, XV.—This was prepared as in the preceding case, using phosphorus oxychloride alone. The yield of white needles melting at 101–101.5° after crystallization from acetone was 43%.

Anal. Calcd. for $C_{16}H_{12}ClNO$: C, 71.2; H, 4.4. Found: C, 70.9; H, 4.2.

2-Phenyl-7-methoxyquinoline.—A solution of 1 g. of 2-phenyl-4-chloro-7-methoxyquinoline in 100 ml. of alcohol was shaken with 0.5 g. of palladium on calcium carbonate under 25 lb. hydrogen pressure for one and one-half hours during which the calculated amount of hydrogen was absorbed. The product was crystallized from dilute alcohol and melted at 51–52°.

The same substance was prepared according to Borsche and Wagner-Roemmich[14] from *m*-anisidine, pyruvic acid

(15) All melting points are corrected.

(16) Microanalyses by Misses Lois May and Lathrope Baker.

(17) John, *J. prakt. Chem.*, N. F., **130**, 328 (1931).

and benzaldehyde by the Doebner synthesis to yield 2-phenyl-7-methoxyquinoline-4-carboxylic acid which melted at 237–238° in agreement with Borsche and Wagner-Roemmich.[14] However, decarboxylation of the acid by heating with copper powder above its melting point as described by them furnished 2-phenyl-7-methoxyquinoline melting at 51–52° and not at 127–128° as reported by the German workers. Mixed melting points of samples of the 51–52° material prepared by both methods showed no depression.

2-Phenyl-7-hydroxyquinoline.—The above substance (0.7 g.) was refluxed for six hours in a mixture of 25 ml. of glacial acetic acid and 25 ml. of 48% hydrobromic acid. The diluted reaction mixture was made alkaline with 10% sodium hydroxide solution, extracted with ether, and neutralized with hydrochloric acid. The product formed fluffy needles from dilute acetone and melted at 228–229°. Borsche and Wagner-Roemmich[14] report it melting at 228–229°.

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.4; H, 5.0. Found: C, 81.1; H, 5.0.

Action of Potassium Hydroxide on 2-Phenyl-3-carbethoxy-4-hydroxy-7-methoxyquinoline.—A suspension of 64.6 g. of the ester in 400 ml. of 20% potassium hydroxide solution was refluxed for six hours. During the last hour the condenser was removed and about half the solvent was boiled off. The solution, on cooling, deposited an oil which was the normal hydrolytic and decarboxylation product, XIV. The supernatant liquid, which contained the by-product, was decanted, diluted with 1.5 liters of water and acidified with hydrochloric acid. The precipitate was recrystallized from acetone–alcohol, forming white needles which melted at 264–265° with gas evolution at 270°. The yield was 30 g. The analytical figures corresponded with those for the anil of benzoylacetic acid with 2-amino-4-methoxybenzoic acid, XVIII.

Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.2; H, 4.8. Found: C, 65.3; H, 5.3.

2-(3′-Sulfonamidophenyl)-4,7-dichloroquinoline, XX.—To 20 g. of 2-phenyl-4,7-dichloroquinoline was added 60 g. of chlorosulfonic acid. After the initial vigorous reaction had subsided, the mixture was heated at 160–170° for an hour, cooled and poured onto 800 g. of cracked ice. The lumps were thoroughly broken up, filtered and washed well with water. The crude sulfonyl chloride was stirred for an hour at 0° with 200 ml. of ammonium hydroxide (sp. gr. 0.9) and finally on the steam-bath for an additional hour. The insoluble amide was recrystallized either from water or dilute alcohol and melted at 227–228°. The yield was 70–80%.

Anal. Calcd. for $C_{15}H_{10}Cl_2N_2O_2S$: C, 51.0; H, 2.9. Found: C, 51.0; H, 3.1.

Oxidation of XX to *m*-Sulfonamidobenzoic Acid.—To a mixture of 0.4 g. of XX and 100 ml. of *N* sodium hydroxide solution which had been boiled for four hours was added 3 g. of potassium permanganate. After boiling for an additional six hours, excess permanganate was destroyed with alcohol. The filtrate from the manganese dioxide was neutralized to *p*H 4 with hydrochloric acid and evaporated to dryness. The residue was extracted with two 50-ml. portions of boiling alcohol and the combined extracts were evaporated to dryness. After washing the residue well with 6 *N* hydrochloric acid, it was recrystallized from water and identified as *m*-sulfonamidobenzoic acid (m. p. 244.5–245°) by mixed m. p. with a sample prepared according to Limpricht and Uslar.[18]

2-Phenyl-7-chloroquinoline-4-carboxylic Acid Hydrazide.—A mixture of 29 g. of ethyl 2-phenyl-7-chlorocinchoninate[19] and 75 ml. of 85% hydrazine hydrate was refluxed for thirty-six hours. On addition of 500 ml. of alcohol, the hydrazide separated and was then recrystallized from alcohol. It melted at 245–245.5°.

Anal. Calcd. for $C_{16}H_{12}ClN_3O$: C, 64.8; H, 4.1. Found: C, 64.6; H, 4.0.

2-Phenyl-7-chloroquinoline-4-isocyanate.—To a mixture of 20 g. of the above hydrazide and 320 ml. of 0.5 *N* hydrochloric acid cooled to −3° was added over an hour 320 ml. of 0.5 *N* sodium nitrite solution with cooling at such a rate that the temperature did not rise above 0°. After an additional thirty minutes, the insoluble material was filtered off and recrystallized from petroleum ether. It melted at 106.5°. The yield was 10 g. (45%). From the analysis it is obvious that rearrangement of the azide occurred during the procedure.

Anal. Calcd. for $C_{16}H_9ClN_4O$: C, 62.2; H, 2.9. For $C_{16}H_9ClN_2O$: C, 68.5; H, 3.2. Found: C, 68.6; H, 2.9.

2-Phenyl-4-amino-7-chloroquinoline Ethyl Urethan.—On refluxing 3 g. of the above isocyanate in 60 ml. of absolute alcohol for two hours and concentrating to 10 ml., the urethan, melting at 148.5°, crystallized in 60% yield.

Anal. Calcd. for $C_{18}H_{15}ClN_2O_2$: C, 66.2; H, 4.6. Found: C, 66.2; H, 4.8.

2-Phenyl-4,7-dichloroquinoline.—A mixture of 12 g. of the above urethan and 200 ml. of hydrochloric acid (sp. gr. 1.19) was refluxed for eight hours. The filtrate from unreacted urethan, on being made basic with ammonia, deposited 4.2 g. of 2-phenyl-4-amino-7-chloroquinoline, melting at 175–180°, which was used without further purification.

To a stirred solution of the above amine in 50 ml. of hydrochloric acid (sp. gr. 1.19) cooled to −25°, was added dropwise during an hour a solution of 1.15 g. of sodium nitrite in 10 ml. of water at such a rate that the temperature did not exceed −20°. The mixture was then allowed to come to room temperature, 100 ml. of water was added, and the filtered solution was made alkaline with ammonia. The precipitate was extracted with 10 ml. of hot alcohol. From the extracts 10% of 2-phenyl-4,7-dichloroquinoline identical in melting point and mixed melting point with that prepared by the method given above was obtained.

2-Phenyl-4,7-dichloroquinoline from Ethyl β-Methoxycinnamate.—A mixture of 12 g. of ethyl β-methoxycinnamate[20] (b. p. 115–120° at 0.8 mm.) and 7.5 g. of *m*-chloroaniline was warmed on the steam-bath for five hours and then added dropwise to 150 ml. of diphenyl–diphenyl ether (26:74) (Dowtherm A) previously heated to 175°, after which the temperature was raised to 250° and held for three hours. On cooling, 12 g. of solid separated. This was washed with petroleum ether and treated directly with phosphorus oxychloride. The product was apparently a mixture of the 4,5- and 4,7-dichloro isomers, from which after repeated crystallization from alcohol a small yield of pure 2-phenyl-4,7-dichloroquinoline melting at 101° was obtained.

2-Phenyl-4,7-dichloroquinoline from Ethyl Benzoylacetate.—When equal molar amounts of *m*-chloroaniline and ethyl benzoylacetate were refluxed in Dowtherm A for ten hours, and the resulting product treated with phosphorus oxychloride, the yield of pure 2-phenyl-4,7-dichloroquinoline was only 3–5%. Other procedures failed to raise the yield.

2-(4′-Nitrophenyl)-1(3-carbethoxy-4-hydroxyquinoline.—Reaction of equimolar amounts of *p*-nitrobenzanilide[21] (m. p. 208–210°) with sodio diethyl malonate in toluene as in the above cases gave an oily product. This was cyclized by refluxing in 200 ml. of Dowtherm A for three hours. The yield of product, which separated on cooling and melted at 248–251° after crystallization from alcohol, was 55%.

Anal. Calcd. for $C_{19}H_{14}N_2O_5$: C, 63.9; H, 4.1. Found: C, 64.0; H, 4.1.

2-(4′-Nitrophenyl)-3-carboxy-4-hydroxyquinoline.—Hydrolysis of the above ester with 10% sodium hydroxide solution gave 2-(4′-nitrophenyl)-4-hydroxyquinoline-3-car-

(18) Limpricht and Uslar, *Ann.*, **106**, 27 (1858).

(19) Tarbell, Bunnett, Carlin and Wystrach, THIS JOURNAL, **67**, 1583 (1945).

(20) Arndt and Loewe, *Ber.*, **71**, 1631 (1938).

(21) Barsilowski, *Jahresber. Fortschr. Chem.*, 1044 (1891).

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.

NEW YORK 27, N. Y. RECEIVED APRIL 5, 1946

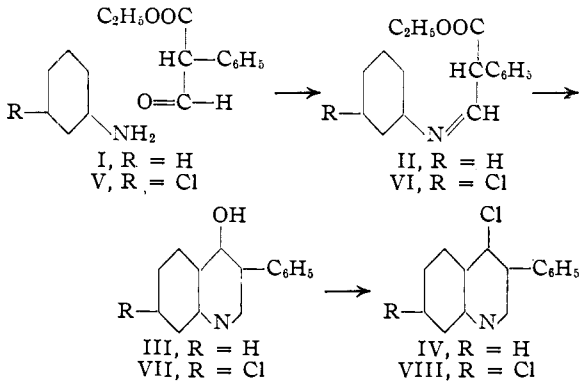
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

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.