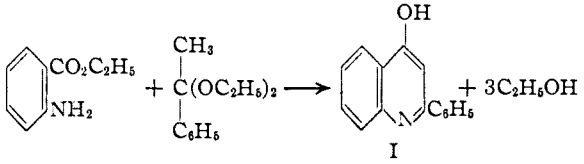
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A New Synthesis of 2-Aryl-4-hydroxyquinolines[1]

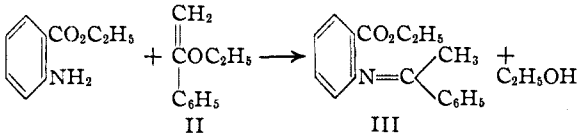
BY REYNOLD C. FUSON AND DONALD M. BURNESS

It has been discovered that 2-aryl-4-hydroxyquinolines can be made conveniently and in satisfactory yields by heating an anthranilic acid or its ester with the acetal of an alkyl aryl ketone. For example, when ethyl anthranilate was heated in phenyl ether with slightly more than an equimolecular amount of the diethyl acetal of acetophenone, 4-hydroxy-2-phenylquinoline (I) was formed in a yield of 84%.



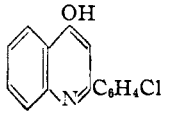
I

Formation of the anil (III) by elimination of ethanol appears to be the first step in the reaction. It seems probable too that the acetal, under the influence of heat, loses a molecule of ethanol to yield α-ethoxystyrene (II) and that this compound rather than the acetal combines with the amino ester to give the anil.



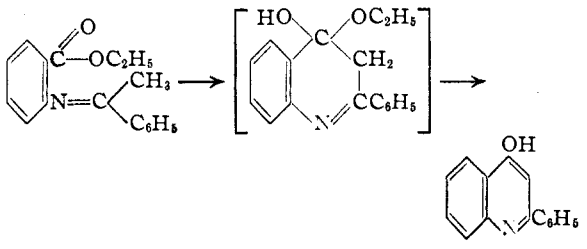
II III

Support for this mechanism was obtained by condensing ethyl anthranilate with *p*-chloro-α-ethoxystyrene; a 74% yield of 2-(*p*-chlorophenyl)-4-hydroxyquinoline (IV) was obtained.



IV

The final step in the synthesis, the ring closure, appears to be a condensation of the Claisen type.



A few experiments were carried out to determine the scope of the new method. When anthranilic acid was used in place of its ester the yield of product fell to 50%, probably because of decarboxylation of the acid at the high temperature required for the ring closure. With the diethyl acetal of propiophenone anthranilic acid reacted to give 4-hydroxy-3-methyl-2-phenylquinoline in 70% yield. However, when anthranilic acid was replaced by its ethyl ester, the reaction was so sluggish that only 52% of the hydroxyquinoline was obtained after heating for thirty-seven hours.

That the method is useful for the unequivocal synthesis of the *five* and *seven* substituted 2-aryl-4-hydroxyquinolines was demonstrated by the preparation of 7-chloro-4-hydroxy-2-phenylquinoline. The yields based on 4-chloroanthranilic acid and its ethyl ester corresponded closely to those obtained with the parent compounds. The remarkable purity of the crude reaction product was shown by its nearly quantitative conversion to 2-phenyl-4,7-dichloroquinoline by the action of boiling phosphorus oxychloride.

The reaction failed completely with methyl 3,5-dibromoanthranilate and with 3-aminopicolinic acid. It is probable that in the first case failure was due to the decreased basicity of the amino group, while in the latter instance decarboxylation may have occurred before ring closure could be effected.

The new method is a useful modification of a reaction reported by Niementowski,[2] who discovered that when anthranilic acid and acetophenone were heated at 120–130° for two days a 3 to 5% yield of 4-hydroxy-2-phenylquinoline was obtained. When Niementowski's reaction was carried out with ethyl anthranilate, rather than the free acid, the yield was somewhat better (10%), but use of the ketal appears essential for the quantitative formation of the intermediate anil. Thus Hoch[3] succeeded in preparing the anil of acetophenone in 90% yield from aniline and the diethyl acetal of acetophenone, whereas other methods give less satisfactory yields.[4]

Several other methods are available for the synthesis of 2-aryl-4-hydroxyquinolines. Of these, the methods of Just,[5,6] Camps,[7,8] and Dziewonski[9] have been the most widely used; nevertheless, difficulties in the preparation of the intermediates or low yields in the ring closures limit the value of these earlier methods.

(1) The work described in this paper was done under a contract recommended by the National Defense Research Committee between the Office of Scientific Research and Development and the University of Illinois.

(2) Niementowski, *Ber.*, **27**, 1396 (1894).
(3) Hoch, *Compt. rend.*, **199**, 1428 (1934).
(4) Reddelien, *Ann.*, **388**, 185 (1912); *Ber.*, **46**, 2712 (1913).
(5) Just, *Ber.*, **19**, 1462, 1541 (1886).
(6) Shah and Heeramaneck, *J. Chem. Soc.*, 428 (1936).
(7) Camps, *Arch. Pharm.*, **239**, 597 (1901).
(8) Wohnlich, *ibid.*, **251**, 526 (1913).
(9) For a leading reference see Dziewonski, Marusinska and Moszew, *Bull. intern. acad. polonaise*, **1938A**, 331; *Chem. Zentr.*, **110**, I, 1174 (1939).

Experimental[10]

Acetophenone Diethyl Acetal.—The directions of Adkins and Pfeiffer[11] were followed except that the amount of hydrogen chloride was trebled. From 400 g. of acetophenone was obtained 488 g. (75.3%) of the acetal; b. p. 101.5° (15 mm.); $n^{20}D$ 1.4773.

Synthesis of 4-Hydroxy-2-phenylquinoline

A. From Acetophenone Diethyl Acetal and Ethyl Anthranilate.—The apparatus consisted of a 250-ml., three-necked flask, equipped with a thermometer, a gas inlet tube, and a partial reflux condenser filled with xylene and leading to a trap bathed in ice water. The trap, in turn, was connected to an aspirator adjusted to give a very slight reduction in pressure, to aid in the removal of the alcohol. Heating was accomplished with a hemispherical Glas-Col mantle.

A mixture of 10.3 g. of ethyl anthranilate, 12.6 g. of acetophenone diethyl acetal and 100 ml. of phenyl ether was placed in the reaction flask and through it was bubbled a stream of oxygen-free nitrogen. The temperature of the reaction mixture was maintained at 120° for thirty minutes, at 200° for thirty minutes and finally at the boiling point for ten hours. Formation of the anil with accompanying evolution of ethanol occurred below 120°. The flow of nitrogen was discontinued when the reflux temperature was reached. The reaction mixture was cooled and the 4-hydroxy-2-phenylquinoline was collected on a filter and washed successively with ligroin and ether. It formed cream-colored platelets melting at 250–250.5°; yield 84% of the theory. Two recrystallizations of the product from ethyl acetate gave white platelets melting at 250.3–250.7°. Recrystallization of a sample from ethanol yielded yellow prisms melting at 259–260°. A mixture of white and the yellow forms melted at 259–260°. The melting point of 4-hydroxy-2-phenylquinoline was given by Just[5] as 253°.

Anal. Calcd. for $C_{15}H_{11}ON$: N, 6.33. Found: N, 6.25.

Failure to remove traces of oxygen from the nitrogen was found to reduce the yield, presumably because of oxidation of the anil. When the condensation was run in the presence of 0.5 g. of hydroquinone, the yield was not improved. The 4-hydroxy-2-phenylquinoline dissolved in phenyl ether only to the extent of 0.1 g. per 100 g. of solvent; hence, it is certain that only a negligible amount of product remained in the mother liquor.

B. From Anthranilic Acid and Acetophenone Diethyl Acetal.—When anthranilic acid (8.3 g.) was condensed with the acetal (12.2 g.) by the foregoing procedure, refluxing being continued for seventeen hours, a 50.7% yield of 4-hydroxy-2-phenylquinoline was obtained; m. p. 250.2–250.8°.

C. From Ethyl Anthranilate and Acetophenone.—A solution of 10 g. of ethyl anthranilate in 100 ml. of phenyl ether was heated to 150°. A solution of 7.5 g. of acetophenone in 15 ml. of phenyl ether was added dropwise during the course of one hour, the reaction chamber being kept at a slightly reduced pressure. The reaction mixture then was heated, over the course of seventy minutes, to 250° and overnight under reflux at atmospheric pressure. The product, recovered as indicated previously, consisted of 1.3 g. (9.7%) of khaki-colored 4-hydroxy-2-phenylquinoline; m. p. 248.5–250.5°.

Ethyl 4-Chloroanthranilate.—4-Chloroanthranilic acid was prepared by a method which was essentially that described in the literature.[12] From 986 g. of 2,4-dichlorobenzoic acid was obtained 626 g. (71%) of 4-chloroanthranilic acid. Recrystallization from aqueous methanol produced nearly white needles melting at 234–235°.

The acid was converted to the ester by treatment with ethanol in the presence of sulfuric acid. It crystallized from low-boiling petroleum ether in white, asbestos-like needles; m. p. 35.5–36.0; $n^{20}D$ (of molten material) 1.5760; yield 64.5%. The melting point, which is 5° lower than the value reported by Heller and Hessell,[13] could not be raised by further recrystallization.

Anal. Calcd. for $C_9H_{10}O_2NCl$: C, 54.15; H, 5.05. Found: C, 54.41; H, 5.14.

7-Chloro-4-hydroxy-2-phenylquinoline

A. From Ethyl 4-Chloroanthranilate and Acetophenone Diethyl Acetal.—The method was similar to that for the chlorine-free analog. The 7-chloro-4-hydroxy-2-phenylquinoline formed white crystals melting at 361–362°; yield 74%.

Anal. Calcd. for $C_{15}H_{10}ONCl$: C, 70.46; H, 3.91. Found: C, 70.53; H, 3.79.

B. From 4-Chloroanthranilic Acid and Acetophenone Diethyl Acetal.—The method was similar to that used with anthranilic acid. A mixture of 103 g. of 4-chloroanthranilic acid, 136 g. of the acetal, and 1300 ml. of phenyl ether was heated (under nitrogen) at 100° for three hours and then heated under reflux for eight hours. It was cooled and the 7-chloro-4-hydroxy-2-phenylquinoline was collected on a filter and washed successively with ligroin and ether. The product formed pale yellow crystals; m. p. 362.5–363°; yield 48%.

4,7-Dichloro-2-phenylquinoline.—A mixture of 109.5 g. of 7-chloro-4-hydroxy-2-phenylquinoline and 240 ml. of phosphorus oxychloride was heated under reflux for two hours, cooled, and poured into a mixture of ice, benzene and ether. Neutralization was followed by thorough stirring. After separation of the two layers the water layer was extracted with benzene and the benzene solution added to the organic layer. After removal of the solvent, the product was recrystallized from ethanol, Darco being used to remove the color. The yield of pure white product, m. p. 99–100.5°, was 94.5%. The melting point reported by Frohardt, Kremer and Bembry[14] was 101–101.5°.

4-Hydroxy-3-methyl-2-phenylquinoline

A. From Ethyl Anthranilate and Propiophenone Diethyl Acetal.—Ethyl anthranilate (10 g.) was condensed with propiophenone diethyl acetal (13.1 g.), prepared by the method of Beals and Gilfillan,[15] by a procedure similar to that used with the acetal of acetophenone. The reaction mixture was maintained at 140° for thirty minutes, at 200° for twenty minutes and at the reflux temperature for eighteen hours. The product, separated by filtration, formed fine white needles melting at 283–285°; yield 4.5 g. The filtrate was returned to the reaction vessel and heated for a further period of nineteen hours. An additional 3 g. of product was obtained. The total yield was 52.6%.

Anal. Calcd. for $C_{16}H_{13}ON$: C, 81.68; H, 5.57. Found: C, 81.84; H, 5.55.

B. From Anthranilic Acid and Propiophenone Diethyl Acetal.—A mixture of 8.3 g. of the acid, 13.1 g. of the acetal and 100 ml. of phenyl ether was subjected to the usual treatment. In contrast to the results obtained with ethyl anthranilate, heating under reflux for only eight hours gave a 69.5% yield of the 4-hydroxy-3-methyl-2-phenylquinoline.

***p*-Chloro-α-ethoxystyrene.**[16]—This compound was prepared from *p*-chloroacetophenone and ethyl orthoformate by a procedure similar to that of Adkins and Pfeiffer[11] for acetals. The yield of product boiling at 132–134° (28 mm.) was 76%. It was distilled repeatedly until the refractive index remained constant, $n^{20}D$ 1.5402, d^{20}_4 1.099.

Anal. Calcd. for $C_{10}H_{11}OCl$: C, 65.12; H, 5.94; Cl, 19.45. Found: C, 64.88; H, 5.84; Cl, 19.20.

(10) All melting points are corrected.

(11) Adkins and Pfeiffer, THIS JOURNAL, **53**, 1048 (1931).

(12) German Patent 244,207 (*Frdl.*, **10**, 171 (1910–1912); (*C. A.*, **6**, 2293 (1912)).

(13) Heller and Hessel, *J. prakt. Chem.*, (2) **120**, 64 (1928).

(14) Private communication from R. P. Frohardt, C. B. Kremer and T. H. Bembry, Columbia University.

(15) Beals and Gilfillan, *J. Am. Pharm. Assoc.*, **25**, 426 (1936).

(16) This preparation was carried out by Mr. Elmer R. Trumbull.

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.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

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

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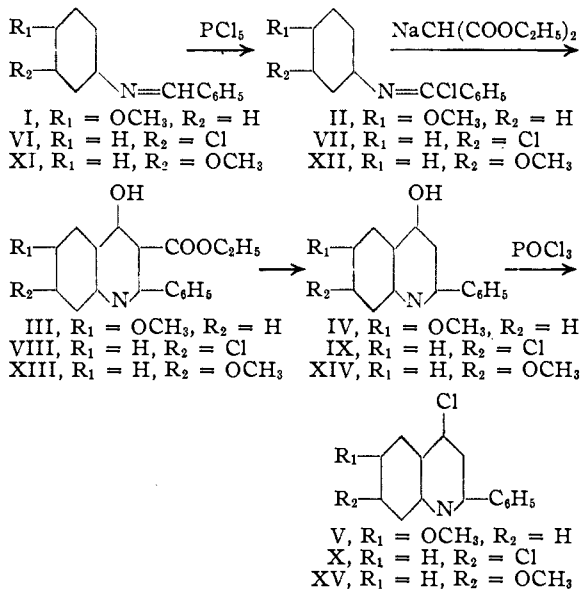
The observation that quinine suffers attack *in vitro* in the presence of liver slices to yield the 2-hydroxy derivative[2,3] suggested that if this position in the quinoline ring be blocked in other active groups of antimalarials, enhanced activity might be expected. The synthesis of a series of quinoline-4-amino-carbinols 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).