5-Methyl-8-nitroquinoline was prepared by a modification of the procedures of Manske, Marion and Leger.

5-Methoxy-8-nitroquinoline was prepared by methoxylation of 5-bromo-8-nitroquinoline.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Synthesis of Simple 2-Phenyl-8-aminoquinoline Derivatives[1]

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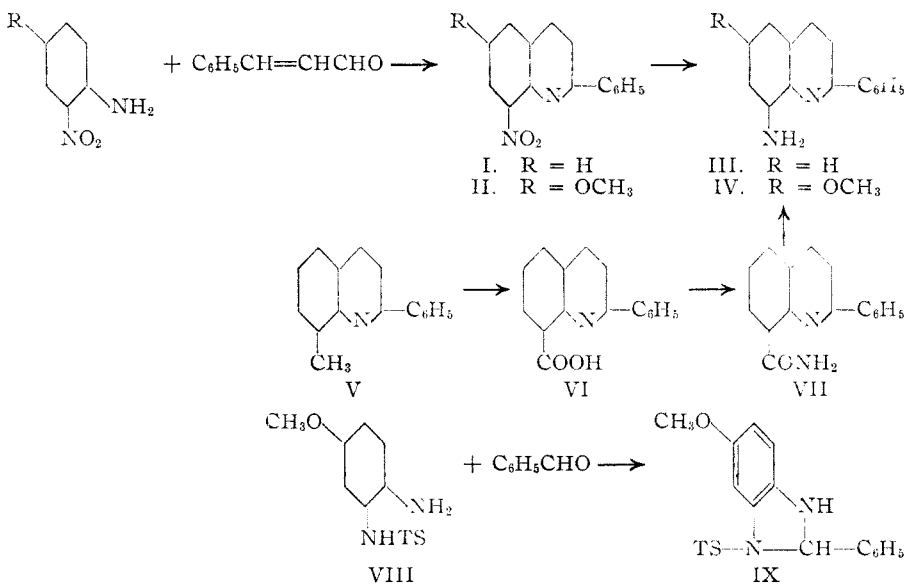
In a preceding paper[2] the synthesis and reasons therefor of certain 2-phenyl-4-chloroquinolines to be used as intermediates in the preparation of antimalarial drugs of the 4-aminoquinoline series has been described. For exactly similar reasons it was desired to ascertain the effect of the introduction of a phenyl group in the 2-position in the 8-aminoquinoline series. In the present paper we wish to present the results of a study of the synthesis of 2-phenyl-8-aminoquinoline and certain of its derivatives. The conversion of these substances to drugs of the Pamaquine (Plasmochin) series is described in a succeeding paper.[3]

The synthesis of 2-phenylquinoline by the general Doebner–Miller method has been studied by Murmann.[4] Apparently the method has not been applied to the synthesis of other derivatives of 2-phenylquinoline. We have now extended the method to the synthesis of 2-phenyl-8-nitroquinoline (I) and 2-phenyl-6-methoxy-8-nitro-quinoline (II), although the yields leave something to be desired Since the possibility of the formation of a 4-phenylquinoline derivative by the above method is not completely eliminated, the structure assigned to I was definitely proved by synthesis of 2-phenyl-8-aminoquinoline (III) from 2-phenyl-8-methylquinoline (V-III).[5] Samples of III obtained by either method were identical.



An attempted alternative synthesis of II involved application of the familiar Pfitzinger method to the reaction of 2-(*p*-toluenesulfonamido)-4-methoxyaniline (VIII) with benzaldehyde and pyruvic acid. When VIII was warmed with benzaldehyde, the expected anil was not obtained, although the analytical figures agreed with those for the anil. Since the product of the reaction was insoluble in dilute alkali and since it did not react with pyruvic acid in the desired sense, it is assigned the structure of the isomeric 2-phenyl-3-(*p*-toluenesulfonyl)-5-methoxy-1,2-dihydrobenzimidazole (IX). When IX was allowed to stand in ether solution with pyruvic acid at room temperature, a product furnishing analytical figures agreeing with those demanded by VIII was obtained. However, this substance was not identical with VIII. Its nature was not investigated further.

Finally, use was made of the method of Gilman and Spatz[6] involving the use of phenyllithium for the preparation of IV. The reaction failed when applied to 6-methoxy-8-aminoquinoline itself, but was successful when applied to 6-methoxy-8-acetaminoquinoline. Introduction of a phenyl group into other 8-aminoquinoline derivatives by this method was investigated. The results are shown in Table I. From this it appears neces-

(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) Elderfield, *et al.*, THIS JOURNAL, **68**, 1272 (1946).

(3) Elderfield, *et al.*, *ibid.*, **68**, 1516 (1946).

(4) Murmann, *Monatsh.*, **25**, 621 (1904).

(5) Doebner and Gieseke, *Ann.*, **242**, 298 (1887).

(6) Gilman and Spatz, THIS JOURNAL, **66**, 621 (1944).

sary to block any free amino groups by acetylation. However, in the case of 6-methoxy-8-(N-acetyl-3′-diethylaminopropylamino)-quinoline, the acetyl group was removed during the reaction. Where 5,6-dimethoxy-8-acetaminoquinoline was treated with phenyllithium, a dihydro derivative of the expected product was apparently formed.

Experimental[7,8]

2-Phenyl-8-nitroquinoline, I.—In a 5-liter three-necked flask equipped with an efficient stirrer, a reflux condenser, and a dropping funnel with a long stem which reached below the surface of the reaction mixture, was placed 2 liters of hydrochloric acid (sp. gr. 1.19), 138 g. of *o*-nitroaniline, 115 g. of arsenic pentoxide, and 80 g. of fused zinc chloride. The contents of the flask were heated on the steam-bath until gentle refluxing began, at which time 396 g. of cinnamic aldehyde was added slowly through the dropping funnel over a period of four hours. At the end of this time, the contents of the flask were allowed to cool, and the reaction mixture was extracted with 2 liters of chloroform or tetrachloroethane for the removal of tarry impurities. To the dark red hydrochloric acid solution a solution of 670 g. of potassium hydroxide in 670 ml. of water was added with cooling. On standing overnight in the refrigerator, an amorphous red precipitate formed, which was collected, thoroughly washed with water, and dried. After recrystallization from alcohol, 33–43 g. (13–17%) of heavy red needles melting at 88–89° was obtained. A sample purified for analysis formed fine pale yellow needles melting at 90–91°.

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 72.0; H, 4.0. Found: C, 72.0; H, 4.0.

2-Phenyl-6-methoxy-8-nitroquinoline, II.—This was prepared substantially as was I by adding 400 g. of cinnamic aldehyde with stirring over six hours to a boiling solution of 250 g. of 3-nitro-*p*-anisidine, 225 g. of arsenic pentoxide, and 225 g. of fused zinc chloride in 3 liters of hydrochloric acid (sp. gr. 1.19). Boiling was continued for an hour after addition of the cinnamic aldehyde. Considerably more tar was formed than in the case of I. To the hot reaction mixture 600 ml. of tetrachloroethane was added and the clear aqueous layer was decanted. The tetrachloroethane layer was extracted three times with hydrochloric acid (sp. gr. 1.19) by stirring and decantation. The combined acid solutions were cooled and diluted with three volumes of water on which the weakly basic nitroquinoline separated. After recrystallization from alcohol, 35 g. (8.5%) of material melting at 141–142° was obtained.

Anal. Calcd. for $C_{16}H_{12}O_3N_2$: C, 68.6; H, 4.3. Found: C, 68.2; H, 4.3.

The use of cinnamaldehyde diacetate or of nitrobenzene or nitrobenzenesulfonic acid[9] gave no better results.

2-Phenyl-8-aminoquinoline, III.—I was reduced with stannous chloride in hydrochloric acid solution at room temperature substantially as described previously.[10] After recrystallization of the material extracted by ether from the alkaline reaction mixture, from 50% alcohol, it melted at 111–111.5°. The yield was 80–90%.

Anal. Calcd. for $C_{15}H_{12}N_2$: C, 81.8; H, 5.5. Found: C, 81.4; H, 5.7.

If the reduction is carried out at temperatures higher than 20–25°, nuclear chlorination takes place. Thus in one experiment in which the mixture was heated with stirring on the steam-bath for one hour, a crude reaction product was obtained which was acetylated with acetic anhydride without further purification. After several crystallizations from 95% alcohol, the acetyl derivatives formed fine white needles melting at 227–228°. The analytical figures indicated that this product consisted largely of a chloro derivative rather than 2-phenyl-8-acetaminoquinoline.

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.8; H, 5.3. Calcd. for $C_{17}H_{13}ClN_2O$: C, 68.6; H, 4.4. Found: C, 69.1; H, 4.6.

2-Phenyl-6-methoxy-8-aminoquinoline, IV.—II was reduced in 43% yield with sodium hydrosulfite, in 67% yield catalytically over Raney nickel and in 92% yield with stannous chloride as above. After recrystallization from alcohol, the amino compound melted at 117.5–118°.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.8; H, 5.6. Found: C, 76.5; H, 5.8.

2-Phenylquinoline-8-carboxylic Acid, VI.—This was prepared by an adaptation of the procedure of Axe.[11] In a 2-liter three-necked flask equipped with a stirrer and a dropping funnel was placed 83 g. of 2-phenyl-8-methylquinoline and 500 ml. of 6 *N* sulfuric acid. To this boiling solution was added a solution of 196 g. of potassium dichromate in 259 g. of sulfuric acid (sp. gr. 1.84) and 361 g. of water through the dropping funnel over a period of ninety minutes. The mixture was heated with stirring for five hours and then for an additional sixteen hours without stirring. After cooling, the solution was carefully neutralized with ammonia until incipient precipitation of chromium hydroxide took place. It was then extracted with six 200-ml. portions of tetrachloroethane. The tetrachloroethane extracts were washed with 600 ml. of 5% sodium hydroxide solution and again with 300 ml. of 5% sodium hydroxide solution. An emulsion may form at this point; however, it can be broken by addition of a little alcohol. The sodium hydroxide extracts were carefully acidified with hydrochloric acid in the cold to *p*H 2.3. 2-Phenylquinoline-8-carboxylic acid precipitated. After recrystallization twice from acetone–water (2:1), the substance formed white needles and melted at 158–159°. The yield was 20 g. From the tetrachloroethane solution about 8 g. of unreacted 2-phenyl-8-methylquinoline was recovered by extraction with concentrated hydrochloric acid.

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.1; H, 4.5. Found: C, 77.0; H, 4.4.

2-Phenyl-8-aminoquinoline by Hofmann Degradation of 2-Phenylquinoline-8-carboxylic Acid.—To a solution of 8 g. of sodium hydroxide in 42 ml. of water was added 7 g. of bromine. To this was added a paste of 8 g. of 2-phenylquinoline-8-carboxylic acid amide (m. p. 210–212°) [*Anal.* Calcd. for $C_{16}H_{11}N_2O$: C, 77.5; H, 4.8. Found: C, 77.2; H, 4.9] prepared by treating the acid chloride with ammonia, with stirring and cooling in an ice-bath. To the resulting suspension, 0.5 g. of potassium hydroxide was added and the mixture was heated gently on the steam-bath during which time a dark material separated. This was extracted with ether and the combined ether extracts were decolorized with charcoal. After removal of the ether at reduced pressure, the residue was recrystallized from alcohol, giving 2-phenyl-8-aminoquinoline melting at 110–111° in low yield. The mixed melting point with material prepared by the Doebner–Miller method was not depressed.

Anal. Calcd. for $C_{15}H_{12}N_2$: C, 81.8; H, 5.5. Found: C, 81.4; H, 5.7.

2-(*p*-Toluenesulfonamido)-4-methoxyacetanilide.—A mixture of 6 g. of 2-amino-4-methoxyacetanilide (m. p. 146–148°)[12] prepared by catalytic reduction of 2-nitro-4-methoxyacetanilide over Raney nickel, 6.3 g. of *p*-toluenesulfonyl chloride, 9.5 g. of sodium acetate trihydrate and 150 ml. of 50% alcohol was refluxed for two hours and then poured into ice water. The solid was recrystallized from dilute alcohol, yielding 6.2 g. (55%) of material melting at 133–134°.

Anal. Calcd. for $C_{16}H_{18}N_2O_4S$: C, 57.5; H, 5.4. Found: C, 57.8; H, 5.4.

2-(*p*-Toluenesulfonamido)-4-methoxyaniline VIII.—The above compound (18 g.) was refluxed with excess

(7) All melting points are corrected.

(8) Microanalyses by the Misses Lois May and Frances Marx.

(9) Utermohlen, *J. Org. Chem.*, **8**, 544 (1943).

(10) Elderfield, *et al.*, THIS JOURNAL, **68**, 1584 (1946).

(11) Axe, *ibid.*, **61**, 1017 (1939).

(12) monov, *J. Gen. Chem.* (U. S. S. R.), **10**, 1588 (1940).

TABLE I

	Quinoline	Product	Identification of product
1	6-Methoxy-8-aminoquinoline	6-Methoxy-8-aminoquinoline	HCl salt m. p. and mixed m. p. 226–228°
2	5,6-Dimethoxy-8-acetaminoquinoline[a]	Probably a dihydro-2-phenyl derivative	M. p. 155–156°[b] (needles from alcohol)
3	Pamaquine (Plasmochin)	Probably Pamaquine with decomposition products	Did not form a solid derivative
4	6-Methoxy-8-(N-acetyl-3′-diethylaminopropylamino)-quinoline (Acetyl Plasmocide)[c]	Plasmocide	Di-HI salt. m. p. and mixed m. p. 206–207°[d]
5	6-Methoxy-8-(3′-diethylaminopropylamino)-quinoline (Plasmocide)	Plasmocide	Di-HI salt m. p. and mixed m. p. 206–207°[d]

[a] Elderfield, *et al.*, THIS JOURNAL, **68**, 1584 (1946). [b] *Anal.* Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.3; H, 6.2. Found: C, 70.6; H, 6.5. [c] Characterized as the dihydroiodide, m. p. 145–146° from alcohol. *Anal.* Calcd. for $C_{19}H_{29}I_2N_3O_2$: C, 38.9; H, 4.9. Found: C, 39.1; H, 5.0. [d] *Anal.* Calcd. for $C_{17}H_{27}I_2N_3O$: C, 37.6; H, 5.0. Found: C, 37.8; H, 5.2.

15% sodium hydroxide solution for five hours. The solution was diluted and just neutralized with acetic acid. The precipitate was recrystallized from dilute alcohol, yielding unstable brownish needles which melted at 135–136°. When this was mixed with the preceding compound, the melting point was depressed to 110–115°. No analysis was obtained, but the observed instability and amphoteric nature of the substance served as evidence for its structure.

Reaction of VIII with Benzaldehyde.—When equimolecular quantities of VIII and benzaldehyde were warmed in absolute alcohol for five minutes and the solution then cooled, an 80% yield of yellow prisms separated. After recrystallization from alcohol, the substance melted at 119–120°. It was insoluble in and unchanged by dilute alkali and did not condense with pyruvic acid. It is therefore assigned the structure IX.

Anal. Calcd. for $C_{21}H_{20}N_2O_3S$: C, 66.4; H, 5.3. Found: C, 66.6; H, 5.3.

When IX was allowed to stand with an equimolar amount of pyruvic acid in a large volume of ether at room temperature for two days, a tan solid separated. After recrystallization from alcohol, it melted at 141–143°. Although the analytical data agreed with those for VIII, the non-identity of the two substances was shown by melting point and mixed melting point.

Anal. Calcd. for $C_{24}H_{20}N_2O_5S$: C, 64.3; H, 4.5. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.6; H, 5.5. Found: C, 57.7; H, 5.5.

2-Phenyl-6-methoxy-8-acetaminoquinoline and 2-Phenyl-6-methoxy-8-aminoquinoline.[6]—To phenyllithium prepared from 0.84 g. of lithium and 9.42 g. of bromobenzene in 100 ml. of dry ether under an atmosphere of nitrogen was added a suspension of 6.5 g. of 6-methoxy-8-acetaminoquinoline[13] in 50 ml. of dry ether. The reaction was warmed to a gentle boiling for five minutes, after which the bath was removed and refluxing was maintained by the heat of the reaction. After one hour, all of the 6-methoxy-8-acetaminoquinoline was in solution and the solution was poured into water. The solid material which separated was recrystallized from alcohol, yielding 2-phenyl-6-methoxy-8-acetaminoquinoline (47%) as fine white needles which melted at 174–175°.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.9; H, 5.5. Found: C, 74.2; H, 5.3.

A suspension of 2 g. of the above compound in 100 ml. of 10% sodium hydroxide was refluxed for three hours. After an hour the oily material went into solution and on cooling an oil separated which soon solidified to a yellow solid. This was collected, taken up in ether to remove inorganic material, and after filtering and drying the ether was evaporated. The residue was crystallized from alcohol, yielding 2-phenyl-6-methoxy-8-aminoquinoline as light yellow needles melting at 116–116.5°. The yield was almost quantitative.

Anal. Calcd. for $C_{16}H_4N_2O$: C, 76.8; H, 5.6. Found: C, 77.0; H, 5.9.

The results of the application of this method to other 8-aminoquinoline derivatives are summarized in Table I.

Summary

The synthesis of 2-phenyl derivatives of 8-aminoquinoline has been investigated by several methods.

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(13) Robinson and Tomlinson, *J. Chem. Soc.*, 1524 (1934).