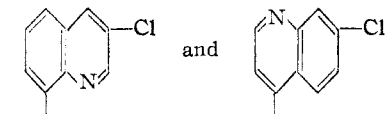
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Synthesis of Some 8-Aminoquinolines[1]

BY ROBERT H. BAKER, CHARLES J. ALBISETTI, JR., R. M. DODSON, GERALD R. LAPPIN AND BYRON RIEGEL

In order to advance our knowledge of the effect of nuclear substituents on the antimalarial activity of 8-aminoquinolines it has been necessary to develop methods of synthesis of a number of compounds. This paper describes the preparation of 8-alkylaminoquinolines with methoxyl and alkylthio groups at position 4 and with chlorine at position 3. The 4-substituted compounds are related to plasmochin and the 3-chloro compound, SN 13,641,[2] bears a striking steric resemblance to SN 7,618. In addition to these nuclear variations one side chain variant, 2-methyl-6-methoxy-8-(5-isopropylaminopentylamino)-quinoline, has been prepared from a previously known nucleus.



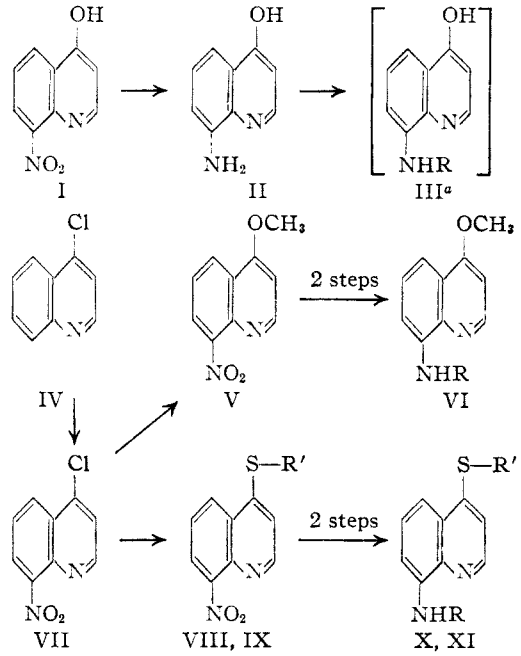
SN 13,641 SN 7,618

Generally, easily attached side chains have been selected for the new nuclei since the primary interest was in the activity of the nucleus itself.

The preparation of 8-nitro-4-quinolinol (I) is described elsewhere.[3] Catalytic reduction converted it into the amine which we were unable to couple with diethylaminopropyl chloride to produce III in a state of analytical purity. Attempts to methylate the quinolinol, I, to produce V were unsuccessful but it was possible to prepare the ether in quantitative yield by reaction of sodium methoxide with 4-chloro-8-nitroquinoline (VII). The latter compound may be prepared from *o*-nitroaniline,[4] but it has been found to be more expedient to prepare it from 4-chloroquinoline[4] by high temperature nitration. Catalytic reduction of the methoxy-nitro compound followed by alkylation produced the final drug, VI.

Metathesis of the chloro compound VII with alkyl pseudothiouronium salts produced the 4-alkythio-8-nitro compounds, VIII and IX which were reduced to the corresponding amines by means of stannous chloride.

The synthesis of 3-chloro-8-aminoquinoline, a necessary intermediate for SN 13,641, presented



[a] This compound was not isolated in a state of purity sufficiently high for characterization.

considerable difficulty.[5] The material prepared by Dikshoorn[6] by the reduction of 8-nitroquinoline in the presence of excess amounts of stannous chloride and hydrochloric acid and reported to be 3-chloro-8-aminoquinoline has been found to be the 5-chloro isomer.[7] This has been confirmed in this laboratory by making a direct comparison with the reduction product obtained from 5-chloro-8-nitroquinoline which was prepared in an unequivocal manner according to Fourneau.[8] Mixed melting points of the acetyl derivatives of the two amines showed no depression. It should be noted that the compound reported by Dikshoorn to be 5-chloro-8-aminoquinoline has in like manner been shown to be the 7-chloro isomer.

Chlorine is most easily introduced at the 3 position in quinoline by use of sulfur dichloride according to the directions of Edinger and Lubberger[9]; however, the principal nitration product

(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 Northwestern University.

(2) The notation SN refers to survey numbers of compounds whose antimalarial activities will appear in a publication by F. Y. Wiselogle, "A Review of Antimalarial Drugs, 1941–1945."

(3) R. H. Baker, G. R. Lappin, C. J. Albisetti, Jr., and B. Riegel, THIS JOURNAL, **68**, 1267 (1946).

(4) B. Riegel, G. R. Lappin, B. H. Adelson, R. I. Jackson, C. J. Albisetti, Jr., R. M. Dodson and R. H. Baker, *ibid.*, **68**, 1264 (1946).

(5) The exploratory work on this preparation was carried out by Dr. Leonard G. Ginger and Mr. John G. Burr.

(6) R. P. Dikshoorn, *Rec. trav. chim.*, **48**, 147 (1929).

(7) Private communication from Prof. C. C. Price.

(8) E. Fourneau, J. Tréfouël, Mme. J. Tréfouël and A. Wancolle, *Bull. soc. chim.*, [4] **47**, 738 (1930).

(9) A. Edinger and H. Lubberger, *J. prakt. Chem.*, **162**, 340 (1896).

of 3-chloroquinoline is the 5-nitro compound. This was not definitely proven by Edinger and Lubberger[9] and it was hoped that their nitration product might be the 8-isomer. Accordingly 3-chloroquinoline was nitrated to produce in good yield the isomer melting at 125–126°. When this was reduced by stannous chloride and hydrochloric acid a chloroamine, m.p. 121° was produced, and this when subjected to hydrogenation over palladium-on-charcoal in alkaline solution produced 5-aminoquinoline, m.p. 105–107°.

Although the nitration of 3-chloroquinoline fails to produce the desired 8-nitro compound, it has been possible to modify the Edinger process and so to chlorinate 8-nitroquinoline in the 3 position. The identity of the product, 3-chloro-8-nitroquinoline, has been established by reduction to the amine followed by deamination. A picrate of the product, 3-chloroquinoline, was identical with that obtained from an authentic sample.

Another approach to the problem of obtaining 3-halo-8-nitroquinoline that was investigated started with 8-nitro-4-quinolinol. It was hoped that this might be halogenated at position 3 to produce a quinolinol which could be converted into a 3,4-dihaloquinoline which might suffer selective hydrogenolysis at the active position 4 and thus yield the desired product. Difficulty was encountered in monochlorinating 8-nitro-4-quinolinol but it could be monobrominated in good yield. Difficulty was again encountered in attempting to replace the hydroxyl group by halogen and this approach was abandoned.

The 6-methoxy-8-nitroquinaldine needed for the preparation of a side chain variant has been prepared previously by reaction of 4-methoxy-2-nitroaniline with paraldehyde and hydrochloric acid.[10] Attempts to duplicate the yield reported to be about 50% by Mathur and Robinson were unsuccessful and it was found to be better to use a modified Skraup reaction with crotonaldehyde and arsenic acid.[11] An improvement in the method of reducing the methoxynitroquinaldine was found. Mathur and Robinson[10] added stannous chloride in hydrochloric acid to the nitro compound in glacial acetic acid solution, but considered this to be inferior to two other methods the best of which (catalytic reduction) produced only 40% of the amine. It has been possible to obtain the amine in 73% yield by adding the nitro compound to stannous chloride in alcoholic hydrochloric acid.

No difficulty was encountered in attaching the side chains except to nuclei containing the 4-hydroxyl group. The best procedure for the attachment of the 5-isopropylaminopentyl side chain was one in which the reaction mixture was buffered with a molecular excess of the aminoquinaldine, a good part of which was recovered.

(10) F. C. Mathur and R. Robinson, *J. Chem. Soc.*, 1520 (1934).

(11) This method is similar to that suggested by W. P. Untermohlen, Jr., *J. Org. Chem.*, **8**, 544 (1943).

Experimental[12]

8-Amino-4-quinolinol.—8-Nitro-4-quinolinol[3] was hydrogenated in ethanol using palladium-on-charcoal catalyst at 25°. Some high melting polymeric material precipitated during the hydrogenation and the ethanol solution was filtered free of catalyst and precipitate. The free amine was very unstable and was not isolated in a pure form, the crude residue after removal of the ethanol *in vacuo* being used. A portion of the ethanol solution was saturated with dry hydrogen chloride and diluted with ether to incipient turbidity. Cooling to 0° gave 8-amino-4-quinolinol hydrochloride.

Anal. Calcd. for $C_9H_9ClN_2O$: N, 14.28. Found: N, 14.16.

4-Chloro-8-nitroquinoline.—To a mixture of 40 g. of concd. sulfuric acid and 40 g. of fuming nitric acid at 0° was added 10 g. (0.06 mole) of 4-chloroquinoline.[4] The mixture was allowed to stand thirty minutes at 0° and was then heated for five hours on the steam-bath. The cooled mixture was poured over crushed ice and the resulting solution made alkaline with ammonia. The precipitate was collected, washed with water, dried, dissolved in 125 ml. of hot ethanol, and the solution was filtered free of undissolved material. The material which crystallized on cooling was collected and dried to give 5.1 g. (40%) of 4-chloro-8-nitroquinoline, m. p. 126–127°. Mixed with an authentic sample[4] of 4-chloro-8-nitroquinoline the melting point was 126–127°.

4-Methoxy-8-nitroquinoline was prepared by refluxing 4-chloro-8-nitroquinoline for one hour with an excess of sodium methoxide in dry methanol. The product was precipitated from the methanol solution by dilution with water and was recrystallized from ethanol, m. p. 185–186°.

Anal. Calcd. for $C_{10}H_8N_2O_3$: N, 13.72. Found: N, 13.69.

4-Methoxy-8-aminoquinoline was obtained by catalytic hydrogenation of the nitro compound at one atmosphere pressure in ethanol solution using palladium-on-charcoal catalyst at 25° to give an 80% yield. After crystallization from ethanol the compound melted at 107–107.5°.

Anal. Calcd. for $C_{10}H_{10}N_2O$: N, 16.09. Found: N, 15.83.

8-Amino-4-benzylthioquinoline.—A solution of 20.5 ml. (0.178 mole) of benzyl chloride, 13.5 g. (0.178 mole) of thiourea, and three drops of concd. ammonium hydroxide in 100 ml. of ethanol was heated under reflux for three hours. To this solution was then added 37.2 g. (0.178 mole) of 4-chloro-8-nitroquinoline and 300 ml. of ethanol and the resulting mixture was heated until complete solution was effected. A solution of 25 g. (0.45 mole) of potassium hydroxide in 150 ml. of ethanol was then added slowly. The resulting suspension was heated for thirty minutes on the steam-bath, allowed to stand at room temperature for twelve hours, and then cooled to 0°. The precipitate was collected, slurried with water, again collected by filtration and dried at 60° to give 48.8 g. (93%) of **4-benzylthio-8-nitroquinoline**, m. p. 168–169° after crystallization from benzene.

Anal. Calcd. for $C_{16}H_{12}N_2O_2S$: N, 9.46. Found: N, 8.98.

This nitro compound was reduced in 73% yield with stannous chloride and hydrochloric acid in ethanol to 8-amino-4-benzylthioquinoline, m. p. 131–132° after crystallization from water–ethanol mixture.

Anal. Calcd. for $C_{16}H_{14}N_2S$: N, 10.52. Found: N, 10.72.

8-Amino-4-methylthioquinoline.—4-Methylthio-8-nitroquinoline was prepared by the method described for 4-benzylthio-8-nitroquinoline using dimethyl sulfate instead of benzyl chloride. The yield was 64% of the theoretical, m. p. 152–153.5° after crystallization from benzene–heptane mixture and again from ethanol.

(12) We are indebted to Margaret Ledyard, Winifred Brandt and Rita Pivan for the microanalyses.

Anal. Calcd. for $C_{10}H_8N_2O_2S$: N, 12.73. Found: N, 12.91.

This was reduced by the above method to give an 85% yield of 8-amino-4-methylthioquinoline, m. p. 130–133°. Recrystallization from dilute alcohol raised its m. p. to 133.5–135°.

Anal. Calcd. for $C_{10}H_{10}N_2S$: N, 14.72. Found: N, 14.76.

Attempted Preparation of 8-Amino-6-methoxy-4-quinolinol.—The hydrogenation of 6-methoxy-8-nitro-4-quinolinol with palladium-on-charcoal catalyst in ethanol solution gives a high melting, ethanol insoluble material amounting to 10–20% of the weight of starting material. Removal of the catalyst and precipitate by filtration gave a dark red filtrate which darkened rapidly on standing and deposited a black tarry substance. Removal of the ethanol *in vacuo* or in an atmosphere of nitrogen gave a black tarry residue.

Attempted Preparation of 8-(3-Diethylaminopropylamino)-4-quinolinol (SN 12,008).—The coupling reaction of the crude 8-amino-4-quinolinol and 3-diethylaminopropyl chloride appeared to take place except that the reaction mixture was darker than usual. High vacuum distillation of the reaction mixture gave a viscous oil which analyzed for 70.3% C and 9.60% H. This oil was tested for its antimalarial activity although later tests showed that it contained 30% inhomogeneity. Repeated attempts to obtain the oil in a state of analytical purity were unsuccessful because of its ease of oxidation and polymerization.

8-(3-Diethylaminopropylamino)-4-methoxyquinoline (SN 12,009).—A solution of 24.3 g. (0.14 mole) of 8-amino-4-methoxyquinoline and 30 g. (0.20 mole) of 3-diethylaminopropyl chloride in 100 ml. of ethanol was refluxed for seventy hours. The solution was poured into 300 ml. of water and treated with decolorizing charcoal and the clarified solution was made strongly alkaline with sodium hydroxide. The product was extracted with four 75-ml. portions of ether, the ether extract dried over anhydrous potassium carbonate, and the ether removed *in vacuo*. The residue was distilled, giving a fraction of 26.2 g. (64%), b. p. 145–150° at 0.01 mm., which crystallized on cooling to a yellow solid. A portion of this solid was redistilled giving a pale yellow crystalline solid, m. p. 41–42°.

Anal. Calcd. for $C_{17}H_{25}N_3O$: N, 14.21. Found: N, 13.82.

4-Benzylthio-8-(3-diethylaminopropylamino)-quinoline (SN 13,718).—A mixture of 32.6 g. (0.12 mole) of 8-amino-4-benzylthioquinoline and 20.1 g. (0.13 mole) of 3-diethylaminopropyl chloride was coupled by the method described for 8-amino-4-methoxyquinoline. The product was extracted from the diluted reaction mixture with benzene after making strongly alkaline. The benzene solution was dried over anhydrous sodium sulfate, evaporated to 50 ml. volume, and to it was added 220 ml. of heptane. On cooling to 0° a crystalline precipitate formed and was collected and dried to give 24.0 g. (52%) of product, m. p. 60–62° after crystallization from heptane.

Anal. Calcd. for $C_{23}H_{29}N_3S$: N, 11.07. Found: N, 11.24.

8-(2-Diethylaminoethylamino)-4-methylthioquinoline (SN 13,794).—This was prepared from 8-amino-4-methylthioquinoline and 2-diethylaminoethyl chloride by the method described for 4-benzylthio-8-(3-diethylaminopropylamino)-quinoline. From 25.3 g. (0.13 mole) of 8-amino-4-methylthioquinoline was obtained 16.2 g. (42%) of a yellow crystalline solid, m. p. 57–58° after crystallization from Skellysolve B (petroleum ether, b. p. 60–70°).

Anal. Calcd. for $C_{16}H_{23}N_3S$: N, 14.52. Found: N, 14.43.

3-Chloro-8-nitroquinoline.—A mixture of 200 g. of sulfur dichloride and 60 g. (0.345 mole) of 8-nitroquinoline[13] was heated gently under reflux until the inside temperature of the solution reached 140°. The mixture was kept at this temperature for six hours. After cooling, 500 ml. of dry ethyl ether was added and the solid product obtained was removed by filtration and washed with 500 ml. of ether. This solid was suspended in 500 ml. of water and the mixture was made strongly alkaline with sodium hydroxide, cooled and filtered. The precipitate was dissolved in 1.5 liters of boiling 95% ethanol and the solution was clarified with 15 g. of decolorizing carbon (Norit A). After evaporation to 500 ml. of volume and cooling, there was obtained 38 g. of a yellow crystalline material, m. p. 115–134°. Two crystallizations from 95% ethanol gave 31 g. (43%) of material, m. p. 137–139°. Repurified from ethanol, a small amount of the material was found to melt at 139–140°.

Anal. Calcd. $C_9H_5ClN_2O_2$: Cl, 16.99; N, 13.43. Found: Cl, 16.76; N, 13.54.

Mixed melting points with authentic samples of 4-, 5-, 6- and 7-chloro-8-nitroquinolines were depressed.

In some experiments where the reaction mixture did not solidify, the solution was evaporated to dryness with an air stream and the solids obtained were digested with a 10% sodium hydroxide solution at steam-bath temperatures for two hours. The mixture was then treated as described above.

8-Amino-3-chloroquinoline.—3-Chloro-8-nitroquinoline was reduced to the amino compound with iron and acetic acid in the manner described by Dikshoorn[6] for the preparation of 8-aminoquinoline. The product was isolated from the reaction mixture by steam distillation and was purified by crystallization from 95% ethanol. From 31.2 g. (0.15 mole) of the nitro compound, there was obtained 20.5 g. (76.5%) of 8-amino-3-chloroquinoline, m. p. 99–104°. Crystallized twice from ethanol, the material formed long yellow needles, m. p. 105°.

Anal. Calcd. for $C_9H_7ClN_2$: N, 15.69. Found: N, 15.86.

Proof of Structure of 8-Amino-3-chloroquinoline.—To a mixture of 6 ml. of concentrated sulfuric acid, 12 ml. of ethanol and 1.2 g. of 8-amino-3-chloroquinoline cooled to 5°, was added a solution of 0.75 g. of sodium nitrite in 2 ml. of water. The mixture was stirred and kept at 5° for one-half hour. To it was then added 0.5 g. of copper powder and the suspension was heated on a steam-bath for one hour. The mixture was made strongly alkaline and steam distilled. From the distillate there was obtained 0.50 g. of a yellow oil. Its picrate derivative was found to melt at 187–189,[14] and a mixed melting with the picrate derivative obtained from an authentic sample of 3-chloroquinoline[4] showed no depression.

3-Chloro-8-(2-diethylaminoethylamino)-quinoline (SN 13,641).—A mixture of 60 ml. of absolute ethanol, 17.8 g. (0.10 mole) of 8-amino-3-chloroquinoline and 16.2 g. (0.12 mole) of 2-diethylaminoethyl chloride was refluxed for forty-eight hours. The cooled mixture was added to 400 ml. of water and there separated 1.8 g. of 8-amino-3-chloroquinoline, m. p. 93–97°, which was recovered by filtration. The filtrate was clarified with 3 g. of decolorizing carbon (Norit A) and was made strongly alkaline with sodium hydroxide. The mixture was extracted with four 250-ml. portions of ethyl ether, the ether solution was dried with magnesium sulfate and the ether was removed by distillation. The product was distilled from a small Claisen flask and there was obtained 13.5 g. of a yellow oil, b. p. 159–161° at 0.2 mm. of pressure. The yield was 54% after correcting for 10% recovery of the nucleus.

Anal. Calcd. for $C_{15}H_{20}ClN_3$: N, 15.15. Found: N, 15.25.

5-Chloro-8-aminoquinoline.—A. The yield of the 85° melting isomer reported by Dikshoorn[6] was increased by adding conc. hydrochloric acid to the hot stannous chloride hydrochloric acid reduction mixture from time to time. Only by this modification was it possible to reduce (and chlorinate) large quantities of 8-nitroquinoline. From 25 g. (0.15 mole) of the nitroquinoline there was obtained

(13) L. F. Fieser and E. B. Hershberg, THIS JOURNAL, **62**, 1640 (1940).

(14) The reported m. p. is 182°, J. Meisenheimer, *Ber.*, **59**, 1848 (1926).

14.8 g. (57.8%) of mixed chloroaminoquinolines which upon steam distillation gave 5.2 g. (20.4%) of yellow needles, m. p. 86.5–87.5°.

B. 8-Nitro-5-chloroquinoline[8] (143 mg.) was reduced with iron and acetic acid. The yellow needles obtained after crystallization from hexane melted at 86.5–87.5° and no depression in the m. p. was observed on mixing with the compound obtained by Dikshoorn's method.

3-Chloro-5-aminoquinoline.—Nitration of 3-chloroquinoline according to Edinger and Lubberger[9] produced a yellow chloronitro compound, m. p. 125–126°. To a hot solution of 10 g. of this in 200 ml. of concentrated hydrochloric acid was added rapidly a solution of 100 g. of stannous chloride in 100 ml. of concentrated hydrochloric acid. The solid which separated was combined with that obtained by making the reaction mixture basic and the whole was crystallized from a liter of hot water to produce 7 g. (82%) of light green needles, m. p. 119–122°. Recrystallized from 50% alcohol it melted at 122–124°.

Anal. Calcd. for $C_9H_7ClN_2$: N, 15.68. Found: N, 15.57.

The structure of the above amine and consequently of the nitration product of 3-chloroquinoline was proved by catalytic removal of the halogen. An alcoholic solution of 0.005 mole of the amine was half saturated with potassium hydroxide and was hydrogenated at 1 atmosphere pressure and 30° over palladium-on-charcoal in the presence of calcium carbonate. The theoretical amount of hydrogen was absorbed in fifteen minutes and upon working up the reaction mixture **5-aminoquinoline**, m. p. 105–107°, was obtained in 60% yield.

3-Bromo-8-nitro-4-quinolinol.—A 10-g. portion of 8-nitro-4-quinolinol[3] was dissolved in 150 ml. of hot glacial acetic acid. The theoretical amount of bromine (8.4 g.) was added slowly with stirring, and the mixture was allowed to stand at room temperature overnight. Upon cooling in an ice bath the hydrobromide was precipitated. This was collected, washed with water and dissolved in 10% sodium hydroxide solution. The alkaline solution, after removal of a small amount of insoluble material, was treated with solid carbon dioxide to precipitate 10 g. (71%) of product, m. p. 276–279°. Crystallization from acetic acid raised the melting point to 279–281°.

Anal. Calcd. for $C_9H_5BrN_2O_3$: N, 10.41. Found: N, 10.65.

6-Methoxy-8-nitroquinaldine.—To a solution of 84.1 g. (0.5 mole) of 4-methoxy-2-nitroaniline in 76 ml. of concentrated sulfuric acid and 25 ml. of water there was added 69 g. (0.3 mole) of arsenic pentoxide. The mixture was heated and to it there was added, with stirring, 42 g. (0.6 mole) of redistilled crotonaldehyde. The mixture was heated on the steam-bath with stirring for five hours; then it was poured into one liter of 12% aqueous sodium hydroxide and the resulting suspension collected by filtration. The cake was thoroughly dried, then powdered, mixed with an equal weight of kieselguhr and continuously extracted with ether. Evaporation of the ether followed by crystallization from ethanol gave 39.3 g. (36%) of product, m. p. 182–186°. The reported melting point is 186–187°.[10]

6-Methoxy-8-aminoquinaldine.—The nitroquinaldine (30 g., 0.138 mole) was slowly added to a solution of 103 g. (0.456 mole) of stannous chloride in 120 ml. of concentrated hydrochloric acid and 240 ml. of ethanol. The solution was cooled in ice during the addition, and it was then heated on a steam-bath for two hours. The solution was poured into 600 ml. of 20% aqueous sodium hydroxide; the resulting suspension was diluted with water to a volume of 2 l. and filtered. The precipitate was dissolved in 400 ml. of methanol; then, after decolorizing with 2 g. of Nuchar C and diluting with water, there was obtained 18.9 g. (73.5%) of crystals, m. p. 101–103° (reported,[10] 102°).

6-Methoxy-8-(5-isopropylaminopentylamino)-quinaldine.[15]—A mixture of 18.8 g. (0.1 mole) of 6-methoxy-8-aminoquinaldine, 10 g. (0.05 mole) of 5-isopropylaminopentyl chloride hydrochloride,[16] and 12.5 ml. of water was stirred and heated for six hours at 90°, internal temperature, and then for eight hours at 100°. The reaction mixture was then poured into 100 ml. of warm (50°) water and the flask was rinsed with an additional 50 ml. of water. To the resulting suspension there was added 8.5 ml. of concentrated hydrochloric acid. The acidic solution on cooling to 15° deposited 6.3 g. of 6-methoxy-8-aminoquinaldine hydrochloride. This was removed by filtration and was washed with 100 ml. of ice water. The filtrate and washings were made basic to congo red with sodium acetate then 15 g. more of sodium acetate was added. Extraction with ether to remove more unreacted nucleus caused the precipitation of the hydrochloride of the final product. This was removed by filtration, and it was added to the original aqueous solution after the ether extraction was completed. The aqueous solution was made basic to phenolphthalein with concd. sodium hydroxide solution, and the resulting suspension was extracted with ether. The ether solution, after drying with potassium carbonate and evaporation, gave 10.2 g. (64.5%) of the free base, b. p. 210–220° (bath temperature) at 1 mm. in a short-path apparatus.

Anal. Calcd. for $C_{19}H_{29}N_3O$: N, 13.32. Found: N, 13.25.

6-Methoxy-8-(5-isopropylaminopentylamino)-quinaldine Dihydroiodide.—**A.** To a solution of 10.2 g. of the base in 40 ml. of absolute ethanol there was added 29 g. of 55–58% hydroiodic acid in 40 ml. of ethanol. The resulting solution was warmed to 60°; and, after it had cooled to room temperature, ether was added until turbidity was observed. Further cooling to 0° with scratching of the vessel produced 18.6 g. (94%) of a monoalcoholate, m. p. 162–167°. Crystallization of this compound from absolute alcohol raised the m. p. to 167.5–169.5°.

Anal. Calcd. for $C_{19}H_{29}N_3O \cdot 2HI \cdot C_2H_5OH$: I, 41.11; N, 6.80. Found: I, 41.45; N, 6.76.

B. The dihydroiodide monoalcoholate could also be made without preliminary isolation and distillation of the free base. The mixture from the reaction of 26 g. of the methoxyaminoquinaldine and 14 g. of 5-isopropylaminopentyl chloride was worked up as previously described. The aqueous buffer solution remaining after ether extraction was made basic to phenolphthalein and steam distilled until only water came over. The aqueous residue was saturated with potassium carbonate and thoroughly extracted with ether. The ether solution was dried over potassium carbonate, then most of the ether was evaporated. The oil was then dissolved in 200 ml. of absolute ethanol and decolorized with 3 g. of Nuchar C. To the clarified alcoholic solution was added 32.5 g. of 55% hydroiodic acid, then ether until cloudiness and crystallization was induced as previously described. The yield of dihydroiodide monoalcoholate was 24 g. (55%), m. p. 162–165°. Some unreacted 6-methoxy-8-aminoquinaldine (7.8 g.) was recovered.

Summary

1. The methods for the syntheses of the following 8-aminoquinolines are described: SN 12,009 8-(3-diethylaminopropylamino)-4-methoxyquinoline, SN 13,718 4-benzylthio-8-(3-diethylaminopropylamino)-quinoline, SN 13,794 8-(2-diethylaminoethylamino)-4-methylthioquinoline, SN 13,641 3-chloro-8-(2-diethylaminoethylamino)-quinoline, SN (none) 6-methoxy-8-(5-isopropylaminopentylamino)-quinaldine.

2. They were all prepared by the condensation of the appropriately substituted 8-aminoquinoline with the alkyl or dialkylaminoalkyl chloride.

(15) General directions for attachment of this side chain were kindly furnished by Prof. N. L. Drake.

(16) This was generously supplied by Prof. R. C. Elderfield.

3. The preparation and properties reported in the literature for 3-chloro-8-aminoquinoline are corrected.

4. The methods used for the preparation of each quinoline nucleus are indicated.

EVANSTON, ILLINOIS RECEIVED APRIL 15, 1946

[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

Synthetic Antimalarials. Some Derivatives of 8-Aminoquinoline[1]

BY NATHAN L. DRAKE, HARRY D. ANSPON, J. DANIEL DRAPER, STUART T. HAYWOOD, JOHN VAN HOOK, SIDNEY MELAMED, RICHARD M. PECK, JOHN STERLING, JR., EDWARD W. WALTON, AND ALFRED WHITON

Plasmochin (pamaquine), 8-(4-diethylamino-1-methylbutylamino)-6-methoxyquinoline, and its derivatives have been the subject of an immense amount of research because of the reported curative action of Plasmochin on vivax malaria[2] when the drug is administered with quinine at approximately the maximum tolerated dosage level. The high toxicity of Plasmochin which is reputedly greater for non-Caucasian races, has prompted an intensive search for a better drug which will possess the curative action of plasmochin and be less toxic.

The present paper describes the preparation and properties of a number of plasmochin derivatives which were prepared with the above end in view.[3] The pharmacology of these drugs will be found elsewhere.[2]

N-Alkyl derivatives of 8-aminoquinoline are prepared by treating 8-aminoquinoline with a suitable alkylating agent, usually an alkyl halide. The desired compounds have a methoxyl group in the 6-position, and it has proved impossible in our laboratories and elsewhere[4] to use the Bucherer reaction to introduce a desired side chain in place of the hydroxyl group of a 6-methoxy-8-quinolinol, although the reaction is successful when applied to 8-quinolinol. Reductive alkylation has also proved impossible thus far. Alkylation, therefore, remains the only useful method of preparing the desired compounds.

In our work, alkylation was carried out by one of three general procedures as shown in Table I.

Method I consisted essentially in heating together two moles of the appropriate 8-aminoquinoline, one mole of the proper 1-halo-x-alkyl (or dialkyl) aminoalkane hydrohalide, and a small amount of water at successively higher temperatures until the mixture was eventually heated under reflux for several hours (about 100–105° inside t.). The resulting melt was poured into excess hydrochloric acid and the precipitated hydrochloride of the nucleus was removed by filtration and washed with cold water. The resulting filtrate was brought to about *p*H 5 by the addition of sodium acetate, and extracted with ether to remove the remainder of the nucleus. The extracted solution was made strongly basic by the addition of concentrated sodium hydroxide solution and again extracted with ether. The ether was then removed from the combined extracts by distillation, and the residue was distilled in high vacuum.[5] Method II was essentially that described by Rohrman and Shonle,[6] and method III was a variation of this procedure according to which Cellosolve (ethyleneglycol monoethyl ether) and water were used in place of alcohol, and some sodium acetate was added as buffer.

By far the majority of the drugs were submitted as salts; in a few cases where crystalline salts could not be obtained the compounds were submitted as a salt in an aqueous-alcoholic solution.

Table I lists the compounds prepared with the exception of SN-13,276 and some closely related compounds.[3] Those bases for which no carbon and hydrogen analyses are given were analyzed as salts, and the analytical data appear in the experimental part. The free bases are heavy, high-boiling oils which are very susceptible to air oxidation and are difficult to keep in a state of analytical purity; for this reason it was customary to purify salts for analysis.

Procedures are given for the preparation of intermediates only when the methods used are new or represent a substantial improvement over methods to be found in the literature.

Of these intermediates, only 5,6-dimethoxy-8-aminoquinoline deserves special mention here. This compound was prepared by a four-step process from veratrole. Nitration of veratrole in acetic acid produced 4,5-dinitroveratrole in one step. This substance in methanol was subjected to ammonolysis in a standard hydrogenation bomb. The resulting aminonitroveratrole was obtained from the ammonolysis by crystallization and after drying was used in a Skraup synthesis. The secret of the success of this Skraup reaction is

(1) This work was carried out under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Maryland.

(2) A Survey of Antimalarial Drugs 1941–1945, F. Y. Wiselogle, Editor, Survey Office Monograph, in press. The term curative is used to designate that the drug prevents the relapses which occur in the absence of an additional infection and which are characteristic of vivax malaria.

(3) See also Drake *et al.*, THIS JOURNAL, **68**, 1529 (1946).

(4) Dr. R. C. Elderfield, Columbia University, private communication.

(5) For an alternate procedure which makes possible a cleaner separation of nucleus see ref. 3.

(6) Rohrman and Shonle, THIS JOURNAL, **66**, 1640 (1940).