[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Synthesis of Antimalarials. VII.[1,2] Synthesis of Certain 8-Aminoquinolines

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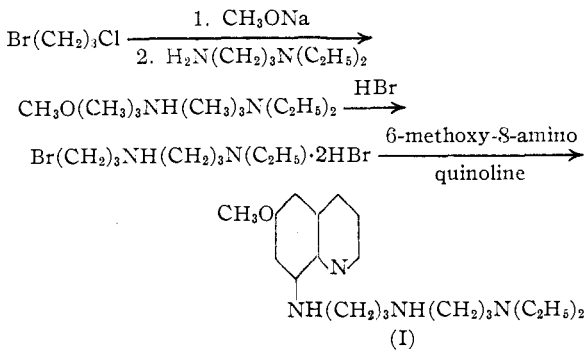
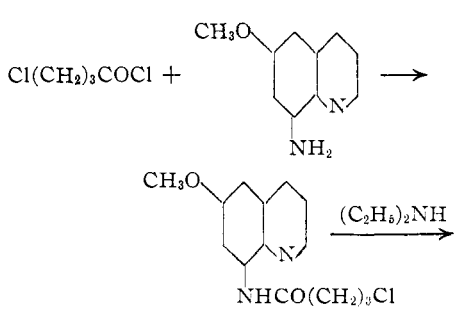
Recently interest in the 8-aminoquinoline series, of which plasmochin is the best known example, has been revived because certain members appear to be of value in treating relapsing malaria. In the present investigation two analogs of plasmochin, having variations in the side chain, and a related compound having a new nucleus have been synthesized.

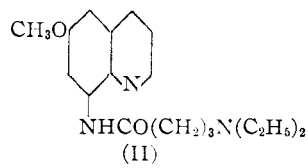
Since Glen and Robinson[5] have reported that the plasmochin analog (I) having a triamine side chain is much less toxic than plasmochin itself, a relatively large amount of this compound has been prepared for further study. We have prepared this compound by the following series of reactions, which are different from those used by Robinson. The product was isolated as its trihydrochloride.



(I)

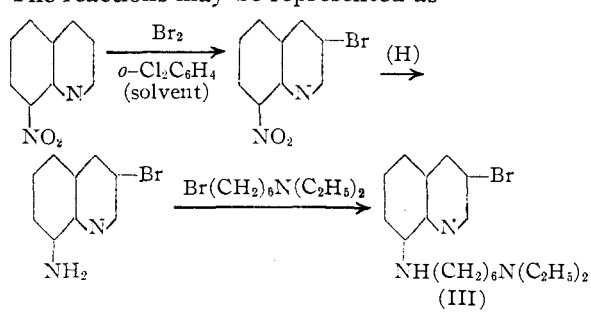
Another plasmochin analog having an amide group in the side chain (II) has been synthesized by the following series of reactions; the product was isolated as its dihydrochloride.





(II)

Apparently relatively little has been known previously concerning the effect of a substituent in the 3-position in the 8-aminoquinoline series. 3-Bromo-8-aminoquinoline has been prepared by brominating 8-nitroquinoline in *o*-dichlorobenzene,[6,7] followed by reduction with iron and acetic acid[8] and coupling with 1-bromo-6-diethylaminohexane hydrobromide in the presence of sodium acetate as buffer to form 3-bromo-8-(6′-diethylaminohexylamino)-quinoline (III). The product was isolated as its monohydroiodide. The reactions may be represented as



(III)

Evidence that 3-bromo-8-nitroquinoline was obtained on bromination of 8-nitroquinoline are the facts that its melting point and also that of its reduction product agree with those reported in the literature[9] for these compounds prepared by the nitration and reduction of 3-bromoquinoline. Moreover, our 3-bromo-8-aminoquinoline has been deaminated to form 3-bromoquinoline.

Experimental

3-(3′-Diethylaminopropylamino)-1-methoxypropane.—To 103 g. (0.792 mole) of 3-diethylaminopropylamine in a 500-ml. three-necked flask heated on a steam-bath was added with stirring 43 g. (0.396 mole) of 3-methoxypropyl

(1) Paper VI of this series, Adams, Bradsher, Breslow, Amore and Hauser, THIS JOURNAL, **68**, 1317 (1946).

(2) 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 Duke University.

(3) Present address: Hercules Experiment Station, Wilmington, Delaware.

(4) Present address: Carbide and Carbon Chemicals Corp., Charleston, West Virginia.

(5) Glen and Robinson, *J. Chem. Soc.*, 557 (1943).

(6) Although the method was satisfactory for small scale work (see experimental), a difficultly removed impurity was produced when the reaction was carried out on a 10–30-g. scale.

(7) Attempts to effect this bromination in chloroacetic acid, similar to the procedure of Kermack and Wright (*J. Chem. Soc.*, 1424 (1935)) for brominating 6-nitro-8-methylquinoline, gave a very impure product.

(8) The method of Affronte, Goldman and Sherman, Cooper Union, for the reduction of 6-chloro-8-nitroquinoline (private communication) has been adapted to the present case.

(9) Claus and Howitz, *J. prakt. Chem.*, [2] **48**, 157 (1893). In this paper, Claus and Howitz assumed they had the 4-bromo derivative but they later (*ibid.*, **50**, 239 (1894)) pointed out that they actually had the 3-bromo derivative. Later work appears to support this view; see Jansen and Wibaut, *Rec. trav. chim.*, **56**, 701 (1937).

chloride.[10] The heating and stirring were continued for four hours and, after standing overnight, the reaction mixture was stirred with 50 ml. of water and excess potassium hydroxide, and finally with ether. The mixture was centrifuged, and the ether phase (combined with an ether extract of the aqueous-solid phase) was dried over potassium carbonate. The solvent was distilled, and the residue was fractionated yielding two fractions, boiling at 60–70° at 15–18 mm. and at 102–110° at 3.5 mm. The second fraction was redistilled at 95–98° at 2.2 mm., yielding 43.5 g., 54%, of 3-(3′-diethylaminopropylamino)-1-methoxypropane. Neutral equivalent. Calcd. for $C_{11}H_{26}ON_2$: 101. Found: 99.7. 3-Diethylaminopropylamine (41 g.), b. p. 169–172°, was recovered from the first fraction.

3-(3′-Diethylaminopropylamino)-1-bromopropane Dihydrobromide.[11]—In a 500-ml., round-bottomed flask was carefully mixed 34.7 g. (0.171 mole) of 3-(3′-diethylaminopropylamino)-1-methoxypropane with 320 g. (1.88 moles) of 48% hydrobromic acid solution. After refluxing for five hours, the excess hydrobromic acid solution was distilled *in vacuo* from the solution using an aspirator (20 mm.) and an oil-bath at 125°. When most of the acid had been removed, the residue became very viscous and, soon afterward, crystalline. This residue was then heated *in vacuo* in an oil-bath at 135° for seven hours, the compound being protected with a drying tube of calcium chloride. The crude product, 68 g., was recrystallized from a mixture of absolute ethanol and isopropyl ether, yielding 62 g., 87%, of white solid, m. p. 144–145°, cor.

Anal.[12] Calcd. for $C_{10}H_{23}N_2Br \cdot 2HBr$: Br^-, 38.68. Found: Br^-, 38.99.

6-Methoxy-8-[3-(3′-diethylaminopropylamino)-propyl]-aminoquinoline (I, SN 11,226.[13]—3-(3′-Diethylaminopropylamino)-1-bromopropane dihydrobromide (90 g., 0.22 mole), 6-methoxy-8-aminoquinoline (36.5 g., 0.21 mole) and 135 ml. of absolute ethanol were heated and stirred in an oil-bath at 110–115° for forty-eight hours essentially as described by Rohrmann and Shonle[14] for couplings with disubstituted aminoalkyl chlorides. The reaction mixture was cooled, 500 ml. of water was added followed by sufficient 50% sodium hydroxide to liberate the free base. The mixture was extracted with ether, the ether phase dried over anhydrous sodium sulfate followed by Drierite, and the solvent distilled. The residue was distilled at 0.1 mm., yielding a fraction (10.3 g.) collected up to 200°, consisting presumably of recovered 6-methoxy-8-aminoquinoline and the coupled compound, an orange oil, b. p. 200–220°; yield 50.7 g., 70%.

The coupled product was dissolved in 150 ml. of methanol and excess methanolic hydrogen chloride was added. The trihydrochloride, precipitated by the addition of isopropyl ether, was recrystallized twice from a mixture of methanol and isopropyl ether. The salt was air-dried and then dried *in vacuo* for one hour, 50 g. of orange crystals, m. p. 217–219°, being obtained.

Anal.[15] Calcd. for $C_{26}H_{32}ON_4 \cdot 3HCl \cdot {}^1/_2H_2O$ (sample air-dried): C, 51.89; H, 7.84. Found: C, 51.74; H, 7.84. Calcd. for $C_{26}H_{32}ON_4 \cdot 3HCl$ (sample dried to constant weight): C, 52.93; H, 7.77; Cl, 23.43. Found: C, 52.97; H, 8.09; Cl, 23.11.

6-Methoxy-8-(γ-chlorobutyramido)-quinoline.—γ-Chlorobutyryl chloride was prepared by the method of Wohlgemuth[16] from 50 g. (0.41 mole) of γ-chlorobutyric acid and 56 g. (0.47 mole) of thionyl chloride. The mixture was stirred and heated on a steam-bath for an hour, the excess thionyl chloride removed *in vacuo* and the residue distilled, yielding 47 g., 81% of the acid chloride, b. p. 66–67° at 15 mm.

To 21.8 g. (0.125 mole) of 6-methoxy-8-aminoquinoline dissolved in 90 ml. of anhydrous benzene was added with stirring 8.8 g. (0.062 mole) of γ-chlorobutyryl chloride. The mixture was heated on a steam-bath for an hour, then filtered and the yellow precipitate washed with anhydrous benzene. The benzene filtrate, after extracting twice with 10% acetic acid solution and once with 10% sodium carbonate solution, was dried over Drierite, and the solvent evaporated. There was obtained an oil which crystallized on cooling; yield 15.6 g., 90%, of a lemon-yellow solid, m. p. 65–68°.

Anal.[15] Calcd. for $C_{14}H_{15}O_2N_2Cl$: C, 60.32; H, 5.42. Found: C, 60.31; H, 5.62.

6-Methoxy-8-(γ-diethylaminobutyramido)-quinoline (II, SN 12,022).—A mixture of 14 g. (0.05 mole) of the preceding compound and 11 g. (0.15 mole) of diethylamine was refluxed and stirred on a steam-bath for eighteen hours. The mixture was filtered, the precipitate washed with ether, and the ether and excess diethylamine distilled from the filtrate. The oily residue remaining was dissolved in anhydrous ether and the solution saturated with anhydrous hydrogen chloride. The gummy precipitate was filtered and recrystallized from a mixture of absolute ethanol and isopropyl ether, yielding 13.9 g. of the amide as a yellow dihydrochloride. On standing in air it formed a trihydrate, m. p. 91–93°. When dried to constant weight *in vacuo*, it formed a hemihydrate, m. p. 177–179°.

Anal.[15] Calcd. for $C_{18}H_{25}O_2N_3 \cdot 2HCl \cdot {}^1/_2H_2O$: C, 54.40; H, 7.10; Cl, 17.85. Found: C, 54.53; H, 7.11; Cl, 18.21.

3-Bromo-8-nitroquinoline.—In a 200-ml. round-bottomed flask equipped with a reflux condenser (with ground glass connections) was placed 100 ml. of *o*-dichlorobenzene, 5 g. of 8-nitroquinoline and 2.5 ml. of bromine. The mixture was refluxed in an oil-bath for one hour. During this time a considerable amount of hydrogen bromide was evolved. The mixture was extracted with five 20-ml. portions of concentrated hydrochloric acid and the combined acid extracts neutralized with ammonia. The yellow solid was collected on a Buchner funnel, washed with water, dried and recrystallized from isopropyl ether. The yield was about 4 g. (55%), melting at 117–120°. After two recrystallizations the m. p. was 123° (Claus and Howitz[9] reported 124°).

When the reaction was carried out on five times the above scale using stirring, there was obtained after two recrystallizations from isopropyl ether only a 29% yield of product melting at 117–118°.

3-Bromo-8-aminoquinoline.—In a 1-liter three-necked flask fitted with a reflux condenser and mercury-sealed stirrer were placed 22 g. of 3-bromo-8-nitroquinoline (m. p. 117–120°) and 400 ml. of 50% acetic acid. The stirred mixture was heated on the steam-bath and 32 g. of iron powder was added in small portions during one and one-half to two hours. Stirring and heating were continued for four to six hours longer. The mixture was made alkaline with 40% sodium hydroxide and steam distilled until eight to ten liters of distillate were collected. The distillate was filtered and the yellow solid dried in air; yield, 14–15 g. (77%), m. p. 106–107° (Claus and Howitz[9] reported 107–108°). Deamination of a sample of the amine was effected by treating the diazonium salt with hypophosphorous acid to form 3-bromoquinoline; picrate, m. p. 190° (uncor.), in agreement with m. p. reported in literature.[17]

3-Bromo-8-(6′-diethylaminohexylamino)-quinoline (III, SN 13,792).—A mixture of 18.5 g. (0.083 mole) of 3-bromo-8-aminoquinoline, 31.7 g. (0.1 mole) of 1-bromo-6-diethylaminohexane hydrobromide, 80 ml. of absolute ethanol, and 8.2 g. (0.1 mole) of anhydrous sodium acetate[18] was

(10) Haworth and Perkin, *J. Chem. Soc.*, **65**, 596 (1894).

(11) The directions of Dr. N. L. Drake, University of Maryland, for the preparation of 1-diethylamino-8-bromohexane hydrobromide were adapted to the present case.

(12) Analysis by B. A. Taylor of this Laboratory.

(13) The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of these compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

(14) Rohrmann and Shonle, THIS JOURNAL, **66**, 1640 (1944).

(15) Analysis by Arlington Laboratories, Fairfax, Virginia.

(16) Wohlgemuth, *Ann. chim.*, [9] **2**, 307 (1914). This worker gave no details.

(17) Claus and Tornier, *Ber.*, **20**, 2872 (1887).

(18) The coupling failed in the absence of sodium acetate; 3-bromo-8-aminoquinoline was recovered.

heated for two days in an oil-bath at 110–115°. The mixture was poured into 250 ml. of water, made strongly basic with sodium hydroxide solution, and extracted with ether. After drying the ether solution over potassium carbonate, the ether was removed, and the residue was distilled *in vacuo*. Some quinoline nucleus (5.3 g. after recrystallization) was recovered. The coupled product (14.9 g., 48%) was obtained as a viscous yellow oil, b. p. 180–195° at 0.006 mm.

The free base (0.04 mole) was converted to the monohydroiodide by dissolving in 50 ml. of absolute ethanol and adding 21.8 g. of 47% hydriodic acid solution in 50 ml. of absolute ethanol. This solution was heated to 60° and cooled overnight. The crystallized hydroiodide salt was filtered off, a second crop being obtained by adding ether to the filtrate. After two recrystallizations from absolute ethanol, the yield of lemon-yellow monohydroiodide, m. p. 147–148° (cor.), was 13.6 g.

Anal.[15] Calcd. for $C_{19}H_{28}N_3Br \cdot HI$: C, 45.07; H, 5.77; I^-, 25.06. Found: C, 45.15; H, 5.82; I^-, 24.97.

Some higher melting salt (tan color) was isolated from a second crop in one case. This may have been the dihydroiodide; after recrystallization from water, the product melted at 147–148° (cor.).

Summary

1. Two plasmochin analogs having variations in the side-chain have been prepared.

2. 3 - Bromo - 8 - (6′ - diethylaminohexylamino)-quinoline has been synthesized.

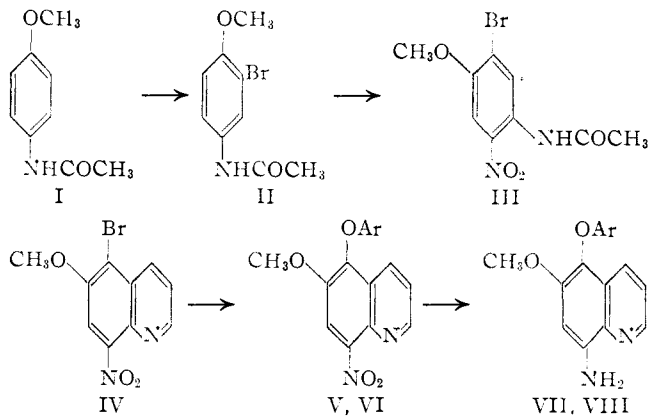
DURHAM, NORTH CAROLINA RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA, AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Some Derivatives of 8-Aminoquinoline[1]

BY WALTER M. LAUER,[2] CHRISTIAN RONDESTVEDT,[2,4] RICHARD T. ARNOLD,[2] NATHAN L. DRAKE,[3] JOHN VAN HOOK[3] AND JOHN TINKER[2]

In the twenty-two years which have elapsed since the discovery of plasmochin, numerous derivatives of 8-aminoquinoline have been prepared in an effort to modify the toxic properties of the parent compound without sacrificing its anti-malarial properties. The workers at the I. G. Farbenindustrie have been especially active in this field. Attention was focused on 8-aminoalkylamino derivatives of 5,6-dimethoxyquinoline by Schönhöfer and his co-workers. In several patents issued in 1930 and later,[5,6] they reported the preparation and properties of a number of these derivatives. Subsequent work in this country has established their activity as antimalarials. In view of this, it was desirable to prepare compounds in which the nucleus was further modified by replacing the methoxyl group in the 5-position by aryloxyl. Accordingly, 5-phenoxy-6-methoxy-8-aminoquinoline (VII) and 5-(*p*-anisyloxy)-6-methoxy-8-aminoquinoline (VIII) were synthesized according to the following plan.



V, VII, Ar = C_6H_5; VI, VIII, Ar = *p*-$CH_3OC_6H_4$

The reactions leading to IV were carried out according to previously published procedures, modified as indicated in the experimental section to permit rapid operation on a larger scale. The replacement of the bromine atom in IV by aryloxyl was not successful if a large excess of phenol was used as solvent. However, when commercial butyl cellosolve (b. p. 171°) was substituted as the solvent, the reaction gave satisfactory yields of easily purified material. The use of ethylene glycol as solvent, in an effort to achieve more rapid reaction at the higher reflux temperature, gave a tarry product; operation at lower temperatures required an unduly long time, and the product was contaminated with unchanged IV.

Reduction of V (or VI) to VII (or VIII) could not be accomplished with hydrogen and Adams catalyst or palladium–charcoal catalyst. The only product obtained was the hydroxylamine, and this could not be reduced further without its isolation and unnecessary losses. Reduction was effected with iron filings and water containing a small amount of acetic acid.

The amines VII and VIII were converted to diamines by alkylation with γ-diethylaminopropyl chloride in a sealed tube at 175° in the presence of benzene as solvent.

(1) This work was carried out under contracts, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Universities of Minnesota and Maryland.

(2) School of Chemistry, University of Minnesota.

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(5) German Patent 531,083, in *Frdl.*, **18**, 2717 (1931).

(6) German Patent 536,447, *ibid.*, p. 2718.