[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF COLUMBIA UNIVERSITY AND THE UNIVERSITY OF MICHIGAN]

Synthesis of Primaquine and Certain of its Analogs[1]

BY ROBERT C. ELDERFIELD,[2] HOLLY E. MERTEL, RICHARD T. MITCH, IRIS M. WEMPEN AND ELEANOR WERBLE

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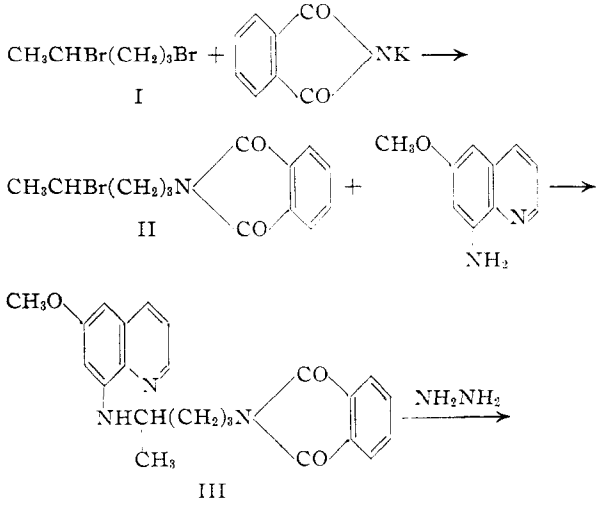
A new and commercially practical synthesis of 6-methoxy-8-(4-amino-1-methylbutylamino)-quinoline (primaquine) is described. Synthesis of several analogs of primaquine is presented. Improved preparations of 4-amino-5-nitroveratrole and 5,6-dimethoxy-8-nitro- and 8-aminoquinoline are given.

Primaquine (SN-13,272)[3] is 6-methoxy-8-(4-amino-1-methylbutylamino)-quinoline (IV). It was described first by Elderfield and co-workers.[4] In recent years the drug has assumed increasing importance as a permanent curative agent for relapsing vivax malaria[5-8] and it is now the drug of choice for this purpose. The method of synthesis originally reported left considerable to be desired when the operation was transferred to large scale operation. Accordingly it became mandatory that a more practical route to the drug be found. We wish to report at this time such a practical synthesis of primaquine and also the synthesis of several analogs of the drug.

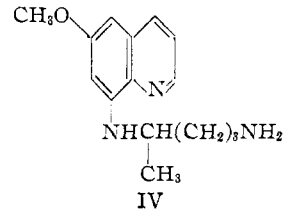
The new preparation of primaquine which has been successfully transferred to manufacturing operations is represented by the sequence



I

II

III



IV

Advantage is taken of the greater reactivity of the primary bromine as compared to the secondary bromine in 1,4-dibromopentane (I) (readily available from 2-methyltetrahydrofuran). When I is refluxed with potassium phthalimide in acetone solution 1-phthalimido-4-bromopentane (II) was formed in good yield. The use of acetone as a solvent for this reaction is vital. When it was carried out in boiling ethanol extensive dehydrobromination occurred and only polymeric materials were formed. Condensation of II with 6-methoxy-8-aminoquinoline paralleled similar condensations reported elsewhere[9] with one major change. Inasmuch as the phthalimido group in II effectively blocks cyclization to a pyrrolidine such as readily occurs with 1-amino-4-bromopentane, particularly in alkaline media,[10] it is possible to carry out the condensation at *p*H's in the range of 8 with a marked improvement in the yield of III. Removal of the phthalimido group of III was done by the hydrazine method of Ing and Manske.[11] In practice it has been found to be entirely practical to carry the entire series of reactions through without purification of either the phthalimido bromide II, the phthalimido intermediate III or the free drug base of primaquine IV. The drug is best isolated as the diphosphate.

By similar condensation of II with 6-methoxy-8-aminolepidine, 6-methoxy-8-(4-amino-1-methylbutylamino)-lepidine (CN-1101)[12] was prepared and isolated as the diphosphate.

Although it has been observed that 6-methoxy-8-aminoquinoline drugs carrying a terminal tertiary amino group on the side chain and with two or three carbon atoms between the nitrogens of the side chain uniformly display undesirable toxic reactions,[13] such is not the case with similar drugs carrying a terminal primary amino group in the side chain.[14] It therefore seemed desirable to prepare

(1) The work here reported was done in part under National Institutes of Health Grant RG-195 to Columbia University and in part under contracts DA-49-007-MD-64 and DA-49-007-MD-334 between the Medical Research and Development Board, Department of the Army and Columbia University and the University of Michigan, respectively.

(2) Department of Chemistry, University of Michigan, Ann Arbor, Mich., to whom inquiries regarding this paper should be addressed.

(3) This number identifies the drug in F. Y. Wiselogle, "Survey of Antimalarial Drugs," Edwards Brothers, Ann Arbor, Mich., 1946.

(4) R. C. Elderfield, *et al.*, THIS JOURNAL, **68**, 1524 (1946).

(5) A. S. Alving, J. Arnold and D. H. Robinson, *J. Am. Med. Assoc.* **149**, 1558 (1952).

(6) P. L. Garrison, D. D. Hankey, W. G. Coker, W. N. Donovan, B. Jastremski, G. R. Coatney, A. S. Alving and R. Jones, Jr., *ibid.*, **149**, 1562 (1952).

(7) C. B. Clayman, J. Arnold, R. S. Hockwald, E. H. Yount, Jr., J. H. Edgcomb and A. S. Alving, *ibid.*, **149**, 1563 (1952).

(8) R. S. Hockwald, J. Arnold, C. B. Clayman and A. S. Alving, *ibid.*, **149**, 1568 (1952).

(9) *E.g.*, R. C. Elderfield, *et al.*, THIS JOURNAL, **68**, 1568 (1946).

(10) R. C. Elderfield and L. E. Rubin, *ibid.*, **75**, 2963 (1953).

(11) H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2348 (1926).

(12) The numbers prefixed by CN identify a drug in the files of Columbia University or the University of Michigan.

(13) I. G. Schmidt and L. H. Schmidt, *J. Comp. Neurol.*, **91**, 337 (1949); *J. Neuropathol. Exptl. Neurol.*, **7**, 369 (1948).

(14) Private communication from Dr. A. S. Alving of the University of Chicago.

the two lower homologs of primaquine for clinical evaluation. These are 6-methoxy-8-(3-amino-1-methylpropylamino)-quinoline (V) (CN-1103) and 6-methoxy-8-(2-amino-1-methylethylamino)-quinoline (VI) (CN-1110).

Preparation of V paralleled that of primaquine except that 1,3-dibromobutane was substituted for 1,4-dibromopentane in the preparation of the phthalimido bromide analogous to II.

However when the preparation of 1-phthalimido-2-bromopropane was attempted from potassium phthalimide and 1,2-dibromopropane the reaction took an anomalous course. No phthalimido bromide could be isolated and apparently extensive dehydrobromination occurred. However, the desired phthalimido bromide was obtained readily by addition of hydrogen bromide to alkyl phthalimide.[15] Condensation of this with 6-methoxy-8-aminoquinoline and with 6-methoxy-8-aminolepidine did not proceed satisfactorily by the usual method. However direct fusion of the reactants resulted in satisfactory yields of condensation products.

5,6-Dimethoxy-8-(4-isopropylamino-1-methylbutylamino)-quinoline (SN-9972) has been found to exert a favorable synergistic action on vivax malaria when administered in conjunction with other 8-aminoquinoline drugs.[14] As in the case of primaquine it thus became desirable to develop a more convenient synthesis for SN-9972 than the one described earlier.[4] To this end we have prepared 5,6-dimethoxy-8-(4-amino-1-methylbutylamino)-quinoline (CN-1104) in a manner completely analogous to that used for primaquine. From CN-1104, SN-9972 is readily accessible by reductive alkylation with acetone.[16]

Finally, the published methods[17,18] for the preparation of 5,6-dimethoxy-8-nitroquinoline, required as an intermediate in the synthesis of CN-1104, leave considerable to be desired. Accordingly attention was given to improvements in this synthesis.

Drake and co-workers[18] converted 4,5-dinitroveratrole to 4-amino-5-nitroveratrole by high temperature ammonolysis under pressure under very carefully controlled conditions. It now has been found that the ammonolysis can be carried out at substantially atmospheric pressure in the presence of an acidic catalyst such as ammonium acetate or phenol.

Preparation of 5,6-dimethoxy-8-nitroquinoline by the Skraup reaction substituting acrolein for glycerol and phosphoric acid for sulfuric acid as suggested by Yale and Bernstein[19] was investigated. Although some advantage was gained in that the rigid time control previously required[17] was eliminated, no yield advantage was obtained and technical difficulties involved in working up the product militated against this method.

What appears to be the most convenient preparation of 5,6-dimethoxy-8-nitroquinoline proceeds in two steps from commercially available 6-methoxy-8-nitroquinoline. It is based in part on a method originally described by Tatsuoka, Ueyanagi and Kinoshita[20] and in part on previous experience in these laboratories.[21] Bromination of 6-methoxy-8-nitroquinoline in the presence of iron, calcium carbonate and water readily yields 5-bromo-6-methoxy-8-nitroquinoline from which 5,6-dimethoxy-8-nitroquinoline results on refluxing with sodium methoxide in the presence of pyridine.

Finally a reliable procedure for the reduction of 5,6-dimethoxy-8-nitroquinoline to 5,6-dimethoxy-8-aminoquinoline has been developed.

The results of experiments on the evaluation of these drugs will be reported elsewhere.

Experimental[22,23]

4-Bromo-1-phthalimidopentane (I).—A mixture of 460 g. (2 moles) of 1,4-dibromopentane, 278 g. (1.5 moles) of potassium phthalimide and 1.5 l. of acetone was stirred and refluxed for 24 hr. After filtering off the precipitated potassium bromide, the solvent and excess dibromopentane were distilled off and the phthalimido bromide was distilled at reduced pressure giving 67% of pale yellow oil, b.p. 165–167° (0.25 mm.).

Anal. Calcd. for $C_{13}H_{14}BrNO_2$: C, 52.7; H, 4.8. Found: C, 53.2; H, 4.8.

6-Methoxy-8-(4-phthalimido-1-methylbutylamino)-quinoline (II).—A solution of 348 g. (2 moles) of 6-methoxy-8-aminoquinoline and 296 g. (1 mole) of 4-bromo-1-phthalimidopentane in one liter of ethanol was refluxed with stirring for 72 hr. After cooling, ether was added to the mixture and the precipitated hydrobromide of 6-methoxy-8-aminoquinoline was filtered off and washed with ether. The filtrate was washed with potassium carbonate solution, then with water and dried over anhydrous potassium carbonate. After removal of the ether, alcohol was added to the dark brown residue and the solution was boiled with decolorizing carbon. The product (40–50% yield) slowly crystallized from the cooled filtered solution. After recrystallization from ethanol the substance melted at 89–90.5°.

Anal. Calcd. for $C_{23}H_{23}N_3O_3$: C, 70.9; H, 5.9. Found: C, 71.0; H, 5.8.

Alternately, a mixture of 17.4 g. (0.1 mole) of 6-methoxy-8-aminoquinoline, 29.6 g. (0.1 mole) of 4-bromo-1-phthalimidopentane, 30 ml. of ethanol and 100 ml. of phosphate buffer (*p*H 8) was stirred and heated at 75–80° for 79 hr. giving 49% of crude product.

It is not necessary to use distilled 4-bromo-1-phthalimidopentane. The material as obtained after removal of the solvent and excess dibromide is perfectly satisfactory. However, in this instance, the crude oily product was converted to a mixture of the hydrobromides of 6-methoxy-8-aminoquinoline and 6-methoxy-8-(4-phthalimido-1-methylbutylamino)-quinoline with aqueous hydrobromic acid. Extraction of the mixed hydrobromides with hot benzene left the hydrobromide of 6-methoxy-8-aminoquinoline as an insoluble fraction and the desired compound was obtained readily from the benzene extracts.

6-Methoxy-8-(4-amino-1-methylbutylamino)-quinoline. (Primaquine, SN-13,272).—The above phthalimido compound was hydrolyzed according to Ing and Manske[11] by refluxing its alcoholic solution with the calculated amount of hydrazine hydrate for 2 hr. The free drug base was extracted into ether and the drug was obtained as the diphosphate by adding an alcoholic solution of the calculated amount of 85% phosphoric acid to the dilute ether solution of the base with swirling. The salt came down as an orange oil which crystallized on addition of alcohol. After recrystallization from 90% alcohol it melted at 197–198°. The yield was 80%.

(15) T. B. Johnson and D. B. Jones, *Am. Chem. J.*, **45**, 343 (1911).
(16) A. C. Cope, *et al.*, THIS JOURNAL, **71**, 554 (1949).
(17) R. C. Elderfield, *et al.*, *ibid.*, **68**, 1584 (1946).
(18) N. L. Drake, *et al.*, *ibid.*, **68**, 1536 (1946).
(19) H. L. Yale and J. Bernstein, *ibid.*, **70**, 254 (1948).
(20) S. Tatsuoka, J. Ueyanagi and T. Kinoshita, *J. Pharm. Soc. Japan*, **69**, 33 (1949).
(21) R. C. Elderfield and G. L. Krueger, *J. Org. Chem.*, **17**, 358 (1952).
(22) All melting points are corrected and boiling points are uncorrected.
(23) Microanalyses by Schwarzkopf Microanalytical Laboratory Woodside 77, N. Y.

Anal. Calcd. for $C_{15}H_{21}N_3O \cdot 2H_3PO_4$: C, 39.6; H, 6.0. Found: C, 39.9; H, 6.3.

The half oxalate was obtained by addition of an alcoholic solution of the calculated amount of oxalic acid to the ether solution of the drug base. After recrystallization from 80% ethanol it melted at 182.5–185°.

Anal. Calcd. for $C_{15}H_{21}N_3O \cdot C_2H_2O_4$: C, 63.1; H, 7.3. Found: C, 63.1; H, 7.5.

6-Methoxy-8-(4-phthalimido-1-methylbutylamino)-lepidine.—This was prepared by condensation of 6-methoxy-8-aminolepidine with 1-phthalimido-4-bromopentane by the phosphate buffer method described above. The substance melted at 110.5–112° after recrystallization from ethanol.

Anal. Calcd. for $C_{24}H_{25}N_3O_3$: C, 71.4; H, 6.2. Found: C, 71.8; H, 6.2.

6-Methoxy-8-(4-amino-1-methylbutylamino)-lepidine (CN-1101) was obtained as the diphosphate (54% over-all yield for the two steps), m.p. 203–205° from 60% ethanol.

Anal. Calcd. for $C_{16}H_{23}N_3O \cdot 2H_3PO_4$: C, 40.9; H, 6.2; P, 13.4. Found: C, 41.3; H, 6.2; P, 13.6.

1-Phthalimido-3-bromobutane.—When a mixture of 223 g. (1.2 moles) of potassium phthalimide, 371 g. (1.72 moles) of 1,3-dibromobutane and 1100 ml. of acetone was refluxed until neutral (24 hr.) and worked up as in the case of 1-phthalimido-4-bromopentane, 1-phthalimido-3-bromobutane, m.p. 61.5–62.5°, after recrystallization from absolute alcohol was obtained in 93% yield.

Anal. Calcd. for $C_{12}H_{12}BrNO_2$: C, 51.1; H, 4.3. Found: C, 51.4; H, 4.5.

6-Methoxy-8-(3-amino-1-methylpropylamino)-quinoline (CN-1103).—Condensation of the above phthalimido bromide with 6-methoxy-8-aminoquinoline was done in a solution buffered at *p*H 8 as described above. The intermediate phthalimido compound (50% yield) melted at 108° after recrystallization from absolute alcohol.

Anal. Calcd. for $C_{22}H_{21}N_3O_3$: C, 70.4; H, 5.6. Found: C, 70.1; H, 5.8.

The diphosphate of the drug (80% yield) melted at 183.5–184.5° after slow recrystallization from 80% ethanol. Ether was added to the mother liquor from the recrystallization to complete the process.

Anal. Calcd. for $C_{14}H_{19}N_3O \cdot 2H_3PO_4$: C, 38.1; H, 5.7; P, 14.0. Found: C, 38.0; H, 5.9; P, 14.0.

N-Allylphthalimide.—The procedure was based on that of Vanags.[24] To a mixture of 222 g. (1.5 moles) of phthalic anhydride and 1300 ml. of glacial acetic acid cooled in an ice-bath 57.1 g. (1 mole) of allylamine was added in small portions. The mixture then was refluxed for one hour and the hot solution was poured into 1700 ml. of water. After bringing the solution to a boil and cooling, allyl phthalimide, m.p. 65–69°, crystallized. The yield was 90% and the material was sufficiently pure for further use.

6-Methoxy-8-(2-phthalimido-1-methylethylamino)-quinoline.—An intimate mixture of 134 g. (0.5 mole) of N-(2-bromopropyl)-phthalimide[15] and 104.4 g. (0.6 mole) of 6-methoxy-8-aminoquinoline was heated in a nitrogen atmosphere at 115–125° (internal temperature) for 72 hr. During the first few hours rigid temperature control must be maintained. The flask then was equipped with a reflux condenser and 200 ml. of benzene was added without cooling. After breaking up the solid, the mixture was refluxed for 30 min. and the benzene was decanted. The residual solid was extracted with two additional 200-ml. portions of benzene. After boiling with decolorizing carbon, the benzene was removed under reduced pressure at room temperature. After one recrystallization from absolute ethanol the product melted at 107–109°. The yield was 45–58 g. (25–32%). The material insoluble in benzene was 6-methoxy-8-aminoquinoline hydrobromide the recovery of which was 45%.

The phthalimido compound was purified by conversion to its phosphate and subsequent regeneration. It shows bimorphism. When recrystallized from absolute ethanol it melted at 108–109.5°. However, when recrystallized from petroleum ether (90–100°) it melted at 135° without melting at the lower temperature.

(24) G. Vanags, *Acta Univ., Latviensis Kim. Fakultat.*, [4] **8**, 405 (1939).

Anal. Calcd. for $C_{21}H_{19}N_3O_3$: N, 11.6. Found: N, 11.3.

6-Methoxy-8-(2-amino-1-methylethylamino)-quinoline (CN-1110) Diphosphate.—This was prepared as in the preceding case and melted at 184–185° after recrystallization from 80% ethanol. The yield from the phthalimido compound was 94%.

Anal. Calcd. for $C_{13}H_{17}N_3O \cdot 2H_3PO_4$: C, 36.5; H, 5.4; N, 9.8; P, 14.5. Found: C, 36.3; H, 5.6; N, 9.3; P, 14.8.

6-Methoxy-8-(2-phthalimido-1-methylethylamino)-lepidine.—Condensation of the reactants was done by the direct fusion method at 115–125° for 48 hr. The product was purified by recrystallization from ethyl acetate without conversion to the phosphate. It melted at 168–169°. The yield was 15–27%.

Anal. Calcd. for $C_{22}H_{21}N_3O_3$: C, 70.4; H, 5.6; N, 11.2. Found: C, 70.5; H, 5.3; N, 11.2.

6-Methoxy-8-(2-amino-1-methylethylamino)-lepidine. (CN-1118) Diphosphate.—Hydrolysis of the above phthalimido compound caused some difficulty because of its extreme insolubility in ethanol. A mixture of 104 g. of the phthalimido compound, 21 g. of 100% hydrazine hydrate, 250 ml. of benzene and 750 ml. of absolute ethanol was refluxed for 31 hr. About 500 ml. of solvent was distilled off during 3.5 hr. and the remainder was removed under reduced pressure. After washing the ether solution of the residue with potassium hydroxide solution, the diphosphate, m.p. 177.5–178.5° (93% yield), was precipitated as usual and recrystallized from 85% ethanol.

Anal. Calcd. for $C_{14}H_{19}N_3O \cdot 2H_3PO_4$: C, 38.1; H, 5.7; N, 9.5; P, 14.0. Found: C, 38.1; H, 5.7; N, 9.1; P, 13.9.

5,6-Dimethoxy-8-(4-amino-1-methylbutylamino)-quinoline (CN-1104) Diphosphate.—5,6-Dimethoxy-8-aminoquinoline (20.4 g.) and 4-bromo-1-phthalimidopentane (29.6 g.) were condensed by the buffer method as above. The reaction time was 72 hr. The crude phthalimido compound was hydrolyzed directly. The ether solution of the drug base, after washing with 4 *M* potassium hydroxide solution for removal of phthalhydrazide, was washed once with water and three times with a phosphate buffer (*p*H 5.8). The combined buffer washes were made basic and extracted with ether. The diphosphate, m.p. 140–142° after recrystallization from ethanol containing 1% of phosphoric acid, was obtained in 33% yield. However, some 30–50% of the starting 5,6-dimethoxy-8-aminoquinoline was recovered from the ether solution after the buffer washes.

Anal. Calcd. for $C_{16}H_{23}N_3O_2 \cdot 2H_3PO_4$: C, 39.6; H, 6.1; P, 12.8. Found: C, 40.1; H, 6.2; P, 12.6.

4-Amino-5-nitroveratrole.—A number of experiments were run to determine the optimum conditions for conversion of 4,5-dinitroveratrole to 4-amino-5-nitroveratrole under mild acid catalysis. Fusion of 4,5-dinitroveratrole in phenol at various temperatures during which anhydrous ammonia was passed into the melt gave an optimum yield of about 35% when the reaction temperature was 125°, the reaction time was 24 hr., and the ammonia was under a positive pressure of 12.7 mm. What is considered the best procedure is as follows.

A mixture of 2 kg. of ammonium acetate and 684 g. of crude 4,5-dinitroveratrole was heated with stirring at 130–135° for 24 hr. during which an atmosphere of dry ammonia was maintained over the melt at 12.7 mm. pressure. The hot reaction mixture was poured into 10 l. of ice and water with stirring. The crude product was air-dried and extracted with 5 l. of 8 *M* hydrochloric acid. The acid extract was filtered from neutral material through a sintered glass funnel, poured over an equal volume of ice and neutralized with 30% sodium hydroxide solution. Recrystallization of the precipitated crude product from ethanol gave 208 g. (35%) of 4-amino-5-nitroveratrole, m.p. 167–169°, and an additional amount was obtained from the mother liquors. The neutral material, insoluble in hydrochloric acid, was mostly unreacted 4,5-dinitroveratrole which was suitable for recycling.

5,6-Dimethoxy-8-nitroquinoline. A. By a Modified Skraup Reaction.—Four runs were made using the modified Skraup reaction conditions described by Yale and Bern-

stein[19] or variations thereof. The results are summarized in Table I.

TABLE I

PREPARATION OF 5,6-DIMETHOXY-8-NITROQUINOLINE

	Run number 1	2	3	4[a]
4-Amino-5-nitroveratrole, mole	0.18	0.42	0.70	0.18
Acrolein, mole	.30	.63	0.80	.23
H_3AsO_4, moles	.36	.80	1.4	.36
85% H_3PO_4, ml.	175	400	750	200
Temperature, °C.	100 ± 2	95–100	96–98	100 ± 2
Time of addn. of acrolein, min.	40	45	45	30
Time of heating, min.	30	15	30	30
Yield, %[b]	40	37.7	36	40

[a] Acrolein acetal was substituted for acrolein. [b] After recrystallization from ethyl acetate.

B. From 6-Methoxy-8-nitroquinoline.—To a mixture of 408 g. of 6-methoxy-8-nitroquinoline, 152 g. of calcium carbonate, 8 g. of iron filings, 2 l. of chloroform and 400 ml. of water was added 400 ml. of bromine. The mixture was heated under reflux with stirring for 6 hr. and then allowed to stand at room temperature for 15 hr. The solid which separated was collected and pressed dry. Additional amounts of crude material, the total yield of which was 580 g., were obtained from the mother liquors. After recrystallization from benzene, 351 g. (62%) of 5-bromo-6-methoxy-8-nitroquinoline, m.p. 204–205°, was obtained. Concentration of the benzene mother liquor gave 135 g. of a mixture of product and unreacted starting material, m.p. 148–195°, which could not be separated easily into its components but which gave more bromo compound on recycling.

To 3000 ml. of anhydrous methanol in a 3-necked flask was added 46 g. of sodium. When the sodium had dissolved, the flask was fitted with a stirrer and reflux condenser and 700 ml. of pyridine and 568 g. of 5-bromo-6-methoxy-8-nitroquinoline were added. After refluxing with stirring for 96 hr., the mixture was poured into 30 l. of water. The crude product (460 g.), m.p. 116–120°, was recrystallized from methanol with decolorizing carbon giving 290 g. (62%) of 5,6-dimethoxy-8-nitroquinoline, m.p. 128–129°. An additional 86 g. of material, m.p. 116–121°, was obtained from the mother liquor.

5,6-Dimethoxy-8-aminoquinoline.—The previously described reduction of 5,6-dimethoxy-8-nitroquinoline has given erratic results.[17] Further study of the reaction has resulted in the following consistent and reliable procedure.

A mixture of 640 g. of stannous chloride dihydrate (analytical reagent grade) and 700 ml. of hydrochloric acid (sp. gr. 1.19) in a 5-l. 3-necked flask equipped with an efficient Hershberg stirrer, pentane thermometer and dropping funnel was chilled to 0° in an ice–salt-bath. In a separate flask, with cooling, a solution of 165.5 g. of 5,6-dimethoxy-8-nitroquinoline in 700 ml. of hydrochloric acid (sp. gr. 1.19) was prepared and chilled to 10°. After addition of 20 g. of granulated tin to the reducing solution stirring was started and the solution of the nitroquinoline was added dropwise with strong cooling at such a rate that the temperature never exceeded 10°. After the addition was complete the mixture was stirred for one hour at 10° and for 3 hr. at room temperature. The canary-yellow suspension was diluted with 2.5 l. of warm water which resulted in partial solution of the solid and a sharp color change of the remainder to scarlet. An excess (about 3 l.) of 8 *M* sodium hydroxide solution was added dropwise to the red suspension with stirring during which the temperature was kept below 20° to prevent occlusion of the stannic chloride complex. If excess alkali sufficient to redissolve the precipitated tin salts is not added, filtration of the amine is very slow with consequent large losses by air oxidation. The greenish-yellow amine was collected and washed thoroughly with water. The crude yield was 94%. Recrystallization from heptane with carbon gave 78% of yellow needles, m.p. 147.5–148°.

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Further Syntheses of Primaquine Analogs[1]

BY ROBERT C. ELDERFIELD,[2] ELIZABETH F. CLAFLIN, HOLLY E. MERTEL, ORVILLE L. MCCURDY, RICHARD T. MITCH, CHARLES D. VER NOOY, BRUCE H. WARK AND IRIS M. WEMPEN

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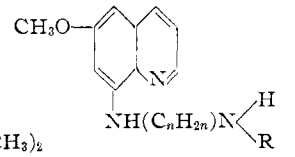
Synthesis of five analogs of primaquine in which the carbon skeleton of the side chain is branched in positions other than at the 1-carbon atom is presented. Preparation of the requisite phthalimido bromides is described.

Derivatives of 6-methoxy-8-(ω-dialkyl- or monoalkylaminoalkylamino)-quinoline previously have been described as effective agents against the exoerythrocytic forms of *Plasmodium vivax*.[3] However, derivatives of 6-methoxy-8-aminoquinoline typified by the general formula I are not as common.



I, R = H
II, R = $CH(CH_3)_2$

For the most part, such compounds have been characterized by a straight carbon chain in the fragment C_nH_{2n}.[4] Notable exceptions to this generalization are found in the drug, primaquine, and its analogs[5] in which the C_nH_{2n} fragment of I is branched at the 1-carbon atom. As far as we are aware, there are no instances of the synthesis of drugs of the type of I on record in which the branching of the C_nH_{2n} fragment occurs other than at the 1-carbon atom. Elderfield, Pitt and Wempen[6] reported the synthesis of a number of ω-isopropylaminoalkylamino bromides suitable for condensation with 6-methoxy-8-aminoquinoline with formation of compounds of the type of II. In this series of amino bromides the total number of carbon atoms in the fragment C_nH_{2n} was limited to 5 or 6

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(2) Department of Chemistry, University of Michigan, Ann Arbor, Mich., to whom inquiries regarding this paper should be addressed.

(3) F. Y. Wiselogle, "Survey of Antimalarial Drugs," Edwards Bros., Ann Arbor, Mich., 1946.

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