[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

SYNTHESIS OF Bz-POLYMETHOXY-8-AMINOQUINOLINES AND SOME DERIVATIVES THEREOF[1]

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In order to explain the unique property exhibited by several derivatives of 8-aminoquinoline of effecting radical cures of vivax malaria, the theory has been advanced that an intermediate metabolite of the quinone or quinone-imine type is the actual curative agent (1–3). Much of the evidence on which this theory was originally based was put forward by Schönhöfer (1) who reported that of all the substituted aminoquinolines, only those carrying amino groups in the 4, 6, or 8 positions, for which quinonoid structures may be written, showed antimalarial activity. Schönhöfer further reported that certain derivatives of 8-aminoquinoline, in which the critical 5- and 7-positions were presumably protected from oxidative attack by substitution of methoxyl groups, were devoid of schizonticidal activity. The evidence on which Schönhöfer's theoretical considerations are based, however attractive they may be, is open to criticism on several counts. The pharmacological data were obtained with only one strain of avian malaria in one host. More serious from a chemical point of view is the fact that several of the methoxy-substituted 8-aminoquinolines on which the theory was based have not been characterized chemically or analytically by Schönhöfer. Further, a search of the literature does not reveal methods by which these substances were synthesized.

In order to complete in a satisfactory manner our knowledge of the effect of substitution of methoxyl groups on the antimalarial activity of 8-alkylaminoalkylaminoquinolines the synthesis of three polymethoxy-8-aminoquinolines carrying methoxyl groups in the benzene ring has been accomplished. These are 6,7-dimethoxy-, 5,7-dimethoxy-, and 5,6,7-trimethoxy-8-aminoquinoline. The remaining possibility, 5,6-dimethoxy-8-aminoquinoline has been reported previously (4).

Previous attempts to prepare 6,7-dimethoxy-8-nitroquinoline, from which the amino compound may readily be obtained, have raised several interesting problems. Frisch and Bogert (5) subjected 4-aminoveratrole to the Skraup reaction with glycerol, nitrobenzene, and sulfuric acid, and obtained a product assigned the structure of either I or II.

Structure I was favored on the basis of earlier evidence obtained by Goldschmiedt (6) and by the fact that the product on nitration gave a dinitro derivative, presumably the 5,8-dinitro compound. The structure of I was further sub-

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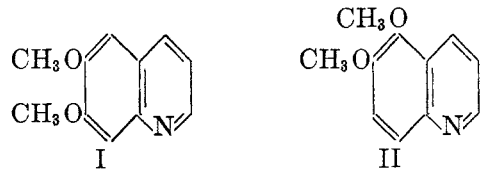
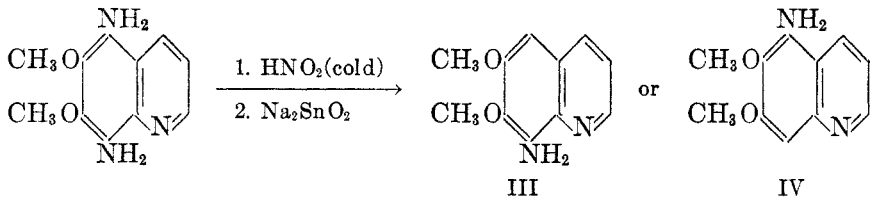


I II

stantiated by its identity with the substance prepared by alternate, apparently unequivocal methods (7, 8).

Compound II has not been described in the literature and has been prepared in the course of the present work by deamination of 5,6-dimethoxy-8-aminoquinoline. It is different from the substance of Frisch and Bogert.

In an attempt to prepare 6,7-dimethoxy-8-aminoquinoline, Frisch and Bogert (9) investigated the diazotization of 5,8-diamino-6,7-dimethoxyquinoline. Under the conventional diazotization conditions only one mole of sodium nitrite per mole of diamine was consumed. Tetrazotization was accomplished only under drastic conditions. Treatment of the monodiazonium salt of the diamine with sodium stannite resulted in elimination of one amino group with the formation of either III or IV.



III IV

Structure IV was favored by Frisch and Bogert on theoretical grounds and without experimental evidence.

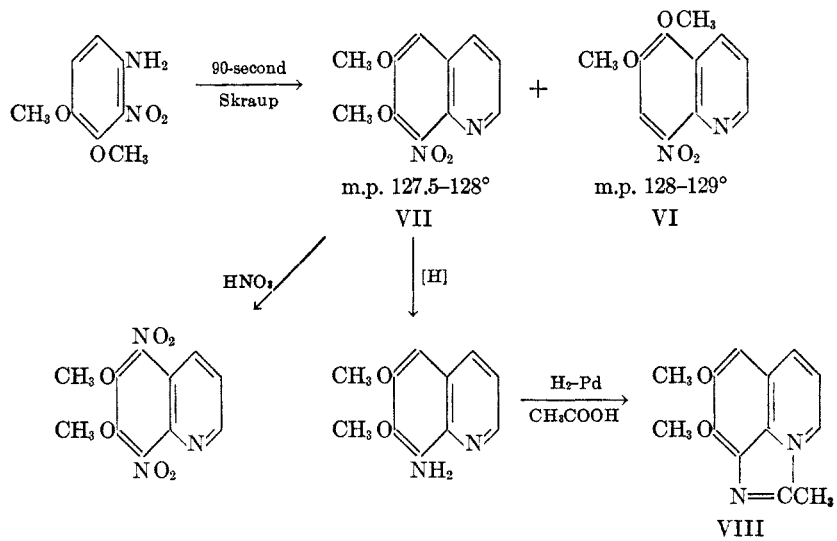
Subsequently, 5-bromo-6,7-dimethoxyquinoline (V) was prepared by application of the Skraup reaction to 4-amino-6-bromoveratrole. Although the bromine in V could be replaced by hydrogen by catalytic reduction, attempts to accomplish its ammonolysis with the formation of IV were unsuccessful (10).

Finally, in an effort to prepare the desired 6,7-dimethoxy-8-nitroquinoline, 4-amino-3-nitroveratrole was subjected to the Skraup reaction (11). However, under the experimental conditions used, no substituted quinoline was formed. Rather, rearrangement of the 4-amino-3-nitroveratrole to 4-amino-5-nitroveratrole occurred.

In the present work the so-called "90-second" Skraup reaction conditions (4, 12, 13) have been applied to 4-amino-3-nitroveratrole. By fractional crystallization of the resulting product from heptane two isomeric dimethoxynitroquinolines, m.p. 128–129° and 127.5–128°, (VI and VII), were obtained. These showed melting point depressions when mixed in various proportions. Clearly, rearrangement had occurred during the course of the reaction.

The substance of m.p. 128–129° was identified by mixture m.p.'s as 5,6-dimethoxy-8-nitroquinoline (VI) (4). Further, it was reduced to 5,6-dimethoxy-8-aminoquinoline which was identified by mixture m.p.'s with a known sample as well as by mixture m.p.'s of its picrate and phenylthiourea with known samples.

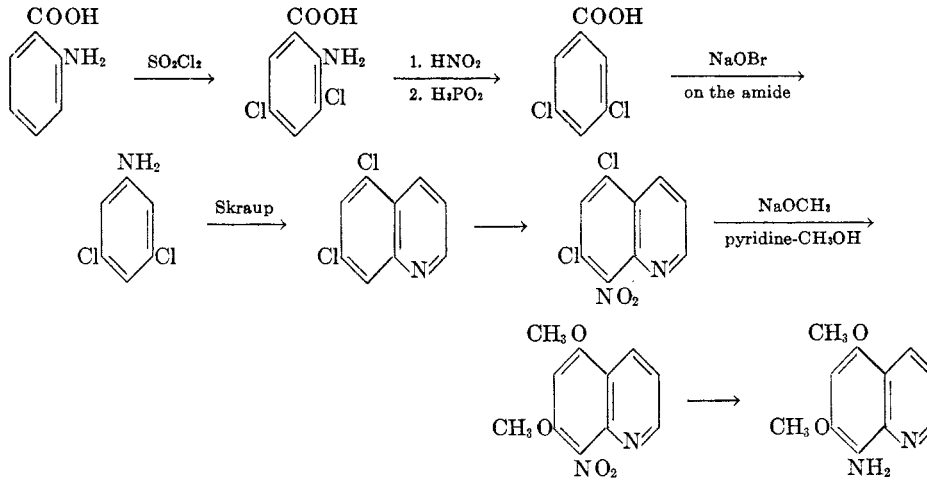
The isomer of m.p. 127.5–128° was also reduced to a dimethoxyaminoquinoline; this had m.p. 77–78°. The nitroquinoline on further nitration gave a dimethoxydinitroquinoline of the same m.p., 156–156.5°, as that reported by Frisch and Bogert (5) for 6,7-dimethoxy-5,8-dinitroquinoline. Therefore the two methoxyl groups in the original dimethoxynitroquinoline are in the 6- and 7-positions, the nitro group must occupy the 5- or 8-position, and the amino group formed on reduction must also be in the 5- or 8-position. In order to differentiate between these possibilities, the dimethoxyaminoquinoline was reduced in glacial acetic acid over palladium catalyst at 140° and yielded an imidazole (VIII). Since it has been shown that 8-amino-1,2,3,4-tetrahydroquinolines readily yield imidazoles of the type of VIII (14, 15), a reaction which is obviously impossible if the amino group is in the 5-position, it follows that the dimethoxyaminoquinoline is 6,7-dimethoxy-8-aminoquinoline. It further follows by elimination that the dimethoxyaminoquinoline of Frisch and Bogert (9) was correctly assigned the structure (IV) of 6,7-dimethoxy-5-aminoquinoline on theoretical grounds. The above reactions may be summarized by the following formulas.



Obviously, partial rearrangement of the 4-amino-3-nitroveratrole to 4-amino-5-nitroveratrole must have occurred prior to the closure of the quinoline ring. The exact amounts of VI and VII in the reaction product cannot be stated. Preliminary purification of the crude reaction product with carbon was necessary. Both VI and VII are white when pure; short exposure to air and light results in browning and in depressions of the m.p.'s of 1–3° which precluded the use of m.p. diagrams to determine the composition of the mixture. All that can be said is that VI and VII were isolated in the pure state in yields of 6.8% and 19.3% respectively.

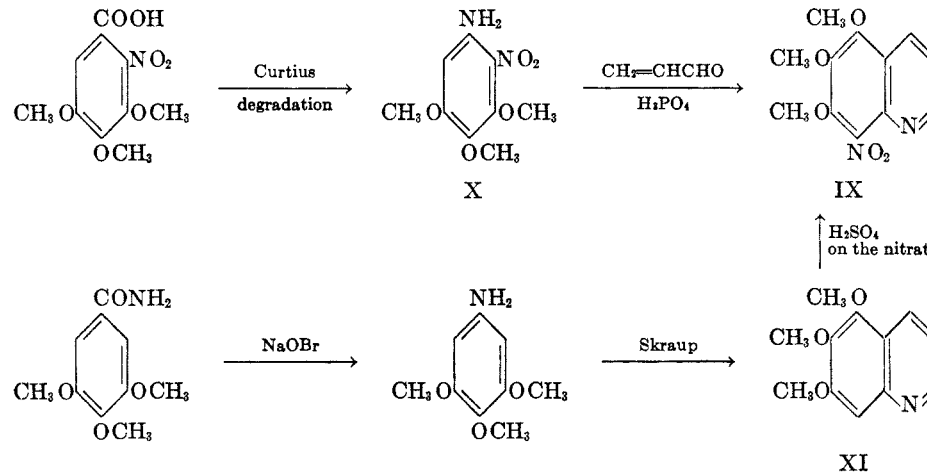
When 4-amino-3-nitroveratrole was subjected to the Skraup reaction with substitution of acrolein for glycerol (16), no rearranged product was formed and VII was isolated in 33% yield.

5,7-Dimethoxy-8-aminoquinoline (17) was prepared by the reactions summarized in the following formulas.



The difficult preparation of 3,5-dichloroaniline from *sym*-trinitrobenzene (17) was circumvented as shown by proceeding from anthranilic acid. Reaction of 5,7-dichloro-8-nitroquinoline, in which the chlorines are active, with sodium methoxide in pyridine and methanol[3] readily gave the dimethoxy compound.

The preparation of 5,6,7-trimethoxy-8-nitroquinoline (IX), accomplished at best in only poor yield, occasioned considerable difficulty. The reactions involved are shown in the following formulas.



Two routes to IX were investigated. In the first of these 2-nitro-3,4,5-trimethoxyaniline (X) was treated with acrolein and phosphoric acid at a relatively low temperature yielding IX in 9% yield. Application of the "90-

[3] The advantageous use of pyridine in these reactions was first noted by Dr. Oskar Birsten of these laboratories.

second" Skraup reaction to X gave an acid-insoluble tar. Alternately, the Skraup reaction with 3,4,5-trimethoxyaniline using a reaction time of 7–10 minutes gave a 46% yield of 5,6,7-trimethoxyquinoline (XI). Attempts to nitrate XI by conventional methods resulted either in complete decomposition or in recovery of unchanged XI. Ultimately, a low yield of IX was obtained when the nitrate of XI was dissolved in sulfuric acid at 0 to −10°.

Preliminary alkylation experiments with the three polymethoxy-8-aminoquinolines have been carried out. These, in general, resulted in poor yields of the desired alkylaminoalkylaminoquinolines. From 5,7-dimethoxy-8-aminoquinoline and 1-isopropylamino-4-bromopentane, a 23.6% yield of 5,7-dimethoxy-8-(4-isopropylamino-1-methylbutylamino)quinoline was obtained. 6,7-Dimethoxy- and 5,6,7-trimethoxy-8-aminoquinoline could not be alkylated with the same amino bromide. However, 6,7-dimethoxy-8-aminoquinoline reacted with 1-isopropylamino-5-bromopentane to yield 20% of 6,7-dimethoxy-8-(5-isopropylaminopentylamino)quinoline.

In view of the inaccessibility of the 8-aminoquinolines here described, further alkylation experiments have been discontinued pending completion of studies now in progress in these laboratories on the optimum conditions for the alkylation of 8-aminoquinolines.

EXPERIMENTAL[4, 5]

4-Amino-3-nitroveratrole. This was prepared more advantageously by Curtius degradation of 2-nitroveratric acid than by the conventional Hofmann procedure. Schlittler and Muller (18) have described a similar synthesis.

2-Nitroveratric acid (19), prepared from 2-nitroveratric aldehyde (20), was converted to the acid chloride by refluxing with thionyl chloride (2 ml. per g.) for 4 hours. Excess thionyl chloride was removed at the water pump, and finally by distillation with dry benzene. To a solution of the acid chloride from 71 g. of the acid in 200 ml. of acetone at 0° a solution of 21 g. of sodium azide (freshly precipitated from hot water and acetone) in 100 ml. of water was added from a dropping-funnel with stirring at 0–5°. After addition of the sodium azide was complete, the mixture was stirred for a half hour at 0° and poured into 800 ml. of ice-water. After collection, the pale pink azide was dried to constant weight over calcium chloride and dissolved in 500 ml. of sodium-dried benzene. The solution was heated gently at first and then at reflux until evolution of nitrogen ceased (4–6 hours). After cooling to room temperature, the reaction flask was fitted with an efficient mechanical stirrer and 250 ml. of cold 50% potassium hydroxide solution was added cautiously with vigorous stirring. A yellow solid separated immediately. Recrystallization of a small portion from ethyl acetate gave the *sym*-urea as yellow needles, m.p. 255–257° (uncorr.)

Anal. Calc'd for $C_{17}H_{18}N_4O_9$: C, 48.3; H, 4.3.

Found: C, 48.6; H, 4.1.

As benzene was slowly distilled from the reaction mixture, the urea was hydrolyzed to a red oil which, on cooling, solidified to 52 g. (85%) of deep red, crude 4-amino-3-nitroveratrole, m.p. 69–71°. One recrystallization from heptane, or from a 1:1 mixture of ethyl acetate and pentane, gave long, red needles, m.p. 74°. Reported m.p. 74° (18, 19). The m.p.

[4] Melting points are corrected for stem exposure unless otherwise noted; boiling points are uncorrected.

[5] Microanalyses by Miss Lois May of these laboratories; Clark Microanalytical Laboratory, Urbana, Ill; Oakwold Laboratories, Alexandria, Va.; or Dr. Francine Schwarzkopf, Elmhurst, N. Y.

of this material was not depressed on admixture with a sample prepared from 2-nitroveratramide and sodium hypobromite.

6,7-Dimethoxy-8-nitroquinoline and 5,6-dimethoxy-8-nitroquinoline. To an intimate mixture of 19.8 g. of 4-amino-3-nitroveratrole and 23 g. of arsenic oxide in a 1 l. flask was added 121 ml. of "dynamite" glycerol which had been heated previously to 170° for half an hour. The mixture was swirled gently and 50 ml. of sulfuric acid (sp. gr. 1.84) was cautiously poured down the side of the flask. An exothermic reaction ensued during which the mixture boiled gently, reaching a temperature of 165°. After 90 sec., the mixture was poured into 500 ml. of ice. The filtered solution was made basic with ammonia, keeping the temperature below 20° by addition of ice. The precipitated dark brown solid was filtered, washed with water, and air-dried. The combined filtrate and washings was exhaustively extracted with ether and the additional material obtained from the extract was added to the main lot. The combined crude product (10.5 g.) was dissolved in hot ethyl acetate, boiled with decolorizing carbon, and the solution was filtered and concentrated, yielding 8.9 g. of tan solid, m.p. 86–115°. Four recrystallizations from heptane yielded 4.5 g. (19.3%) of 6,7-dimethoxy-8-nitroquinoline as white needles, m.p. 127.5–128°. This depressed the m.p. of an authentic sample of 5,6-dimethoxy-8-nitroquinoline (4) when the two were mixed in several proportions. The pure compound slowly turned brown on exposure to light and air.

Anal. Calc'd for $C_{11}H_{10}N_2O_4$: C, 56.4; H, 4.3; N, 12.0.
Found: C, 56.4; H, 4.3; N, 12.0.

When the combined heptane mother liquors were concentrated to dryness, the residual tan solid melted at 114–123°. Two recrystallizations from 80% alcohol and one from heptane gave 1.6 g. (6.8%) of 5,6-dimethoxy-8-nitroquinoline as white needles, m.p. 128–129° which did not depress the m.p. of an authentic sample (4).

Reaction of 4-amino-3-nitroveratrole with acrolein. This is essentially the procedure of Yale and Bernstein (16). A mixture of 46 g. of arsenic oxide and 100 ml. of 85% phosphoric acid was warmed to 70°. Heating was discontinued and 19.8 g. of 4-amino-3-nitroveratrole was added. As 9.5 ml. of acrolein was added dropwise over a period of 15 min., the vigorously stirred mixture darkened and the temperature rose to 90–95°. The temperature was held at 100–106° for 45 min. and the mixture was poured into 300 ml. of ice-water. The filtered solution was made ammoniacal and the dried solid was extracted with ethyl acetate in a Soxhlet extractor for separation from inorganic salts. Concentration of this extract and recrystallization of the residue once from heptane gave 7.7 g. (33%) of 6,7-dimethoxy-8-nitroquinoline, m.p. 127–128°.

6,7-Dimethoxy-5,8-dinitroquinoline. To 1 ml. of sulfuric acid (sp. gr. 1.84) cooled to 0° was added 0.23 g. of 6,7-dimethoxy-8-nitroquinoline. The well stirred mixture was cooled to −20° and 1 ml. of 65% fuming sulfuric acid was added cautiously. The white solid which separated dissolved when 4 ml. of yellow fuming nitric acid (sp. gr. 1.5) was added at 0–10°. After standing for 2 hours in the refrigerator, the solution was poured into twice its volume of ice-water. Fine, white needles (0.21 g.) separated which melted at 156–156.5° after recrystallization from 80% alcohol. Reported, m.p. 155° (5).

Anal. Calc'd for $C_{11}H_9N_3O_6$: C, 47.3; H, 3.3; N, 15.1.
Found: C, 47.5; H, 3.2; N, 15.3.

6,7-Dimethoxy-8-aminoquinoline. (a). Using stannous chloride. To a solution of 20.8 g. of stannous chloride dihydrate in 60 ml. of hydrochloric acid (sp. gr. 1.19) cooled to 0° was added dropwise, with stirring, a solution of 5.2 g. of 6,7-dimethoxy-8-nitroquinoline in 20 ml. of hydrochloric acid (sp. gr. 1.19). The mixture was stirred for an hour at 0° and for an additional hour at room temperature. The resulting tin complex was dissolved in water and made strongly alkaline with 50% potassium hydroxide solution, and the yellow alkaline solution was extracted with three 50-ml. portions of ether. The residue from the ether extract, on leaching with hexane, gave 3.5 g. (78%) of glistening white rods, m.p. 77–78°.

Anal. Calc'd for $C_{11}H_{12}N_2O_2$: C, 64.7; H, 5.9.
Found: C, 64.9; H, 5.9.

The *picrate* formed orange needles, m.p. 205.5–209° (dec.), from ethanol.

Anal. Calc'd for $C_{17}H_{15}N_5O_9$: C, 47.1; H, 3.5; N, 16.2.

Found: C, 47.3; H, 3.6; N, 16.4.

6,7-Dimethoxy-8-acetaminoquinoline. To a solution of 0.5 g. of 6,7-dimethoxy-8-aminoquinoline in 5 ml. of acetic anhydride was added 2 drops of conc'd sulfuric acid. After 30 min. the solution was poured into 10 ml. of ice-water and made alkaline, yielding slim, white needles (58%), melting at 164–165° after recrystallization from 80:20 hexane-ethyl acetate.

Anal. Calc'd for $C_{13}H_{14}N_2O_3$: C, 63.4; H, 5.7; N, 11.4.

Found: C, 63.5; H, 5.4; N, 11.1.

(*b*). *Catalytic reduction.* When a solution of 1.2 g. of 6,7-dimethoxy-8-nitroquinoline in 20 ml. of ethyl acetate was hydrogenated over 50 mg. of palladium black at room temperature at atmospheric pressure, reduction was complete in 4 hours. The yield of amino compound was 88%.

Attempted synthesis of 6,7-dimethoxy-8-amino-1,2,3,4-tetrahydroquinoline. Several procedures reported in the literature for the reduction of 8-aminoquinolines to the tetrahydro compounds were applied to 6,7-dimethoxy-8-aminoquinoline. Reduction with sodium in methanol or ethanol (14, 15) and catalytic reduction over Raney nickel at 130° and 500 lb. (21) gave only starting material in 75% or greater yield. With sodium and butanol, 25% of starting material was recovered, but no other product could be isolated.

2-Methyl-8,9-dimethoxy-5,6-dihydro-4-imidazo[i,j]quinoline (VIII). A solution of 0.80 g. of 6,7-dimethoxy-8-aminoquinoline in 25 ml. of glacial acetic acid was shaken in a steel bomb with 50 mg. of palladium black at 500 lb. hydrogen pressure and 140–160° for 5 hours. The filtrate from the catalyst was diluted, made basic with ammonia, and extracted with ether. The red residue from the dried ether extract, on recrystallization from heptane, gave rosettes (60.5%) of hygroscopic, white needles, m.p. 105–105.5°.

Anal. Calc'd for $C_{13}H_{16}N_2O_2$: C, 67.2; H, 6.9; N, 12.1.

Found: C, 67.9; H, 7.1; N, 12.3.

The *picrate* formed long, golden needles, m.p. 193–195°, from absolute alcohol.

Anal. Calc'd for $C_{19}H_{19}N_5O_9$: C, 49.5; H, 4.1; N, 15.2.

Found: C, 49.4, 49.4; H, 4.2, 4.1; N, 15.3.

5,6-Dimethoxy-8-aminoquinoline. This was prepared either chemically or catalytically as described above. With stannous chloride, the yield of material, m.p. 149–150°, was 92%. Reported m.p., 148–149° (4). The catalytic reduction was complete in 50–60 min. and characterized by the appearance of a yellow crystalline solid when a little more than half the calculated amount of hydrogen had been absorbed. This substance, presumably the hydroxylamine, redissolved on further reduction, and the aminoquinoline was isolated in 90% yield.

The *picrate*, previously reported (22) as melting at 186–187° (dec.), melted with decomposition at 187–188° (dec.).

8-(5,6-Dimethoxyquinolyl)phenylthiourea was prepared by warming the aminoquinoline (either the material obtained as above or an authentic sample) with excess phenyl isothiocyanate. It formed yellow-green prisms, m.p. 157–158°, from absolute alcohol and pentane.

Anal. Calc'd for $C_{18}H_{17}N_3O_2S$: C, 63.7; H, 5.0.

Found: C, 63.7; H, 5.1.

5,6-Dimethoxyquinoline. To a solution of 2.0 g. of 5,6-dimethoxy-8-aminoquinoline in 15 ml. of hydrochloric acid (sp. gr. 1.19) and 10 ml. of water cooled to −10° was added a solution of 0.7 g. of sodium nitrite in 5 ml. of water. After stirring for an hour, 75 ml. of 50% aqueous hypophosphorous acid, pre-cooled to 0°, was added dropwise while the temperature was maintained at −10°. Evolution of nitrogen began about half way through the addition. The mixture was stored at 0° for 24 hours, then warmed to room temperature, made ammoniacal, and extracted with ether. After drying over potassium hydroxide, concentration of the ether extract yielded a red-brown oil which was converted to the *picrate* without further purification. Recrystallization from ethanol gave yellow needles, m.p. 165–168°.

Anal. Calc'd for $C_{17}H_{14}N_4O_9$: C, 48.8; H, 3.4; N, 13.4.
Found: C, 48.5; H, 3.2; N, 13.2.

2-Nitro-3,4,5-trimethoxyaniline. Gallic acid trimethyl ether (23) was converted to the methyl ester, m.p. 82–83°, in 90% yield in absolute methanol with hydrogen chloride. Nitration of the ester in acetic anhydride with yellow, fuming nitric acid at 0° gave the 2-nitro ester (24) which was saponified to 2-nitrogallic acid trimethyl ether, m.p. 165–167°, by refluxing with methanolic potassium hydroxide. The over-all yield from trimethylgallic acid was 35%.

(*a*). *By Hofmann rearrangement.* 2-Nitrotrimethylgallamide was prepared from the acid chloride (from the acid and thionyl chloride) and concentrated ammonia. The amide, after recrystallization from dilute alcohol, melted at 182–184°. Reported m.p. 187° (24). Rearrangement of the amide (2.56 g.) to the nitroaniline with sodium hypobromite according to a procedure for the corresponding reaction of 2-nitroveratramide (19) gave 0.6 g. (26%) of lustrous, orange needles, m.p. 82–83°, after recrystallization from hexane.

Anal. Calc'd for $C_9H_{12}N_2O_5$: C, 47.4; H, 5.3; N, 12.3.
Found: C, 47.5; H, 5.3; N, 12.2.

(*b*). *By Curtius rearrangement.* The crude acid chloride was converted to the azide and thence to the isocyanate by the same procedure employed for the preparation of 3-nitro-4-aminoveratrole. The yield was 48.5%.

2-Nitro-3,4,5-trimethoxyacetanilide was prepared from the amine in acetic anhydride with addition of 2 drops of sulfuric acid at room temperature. The feathery, yellow needles melted at 112–113° after crystallization from hexane.

Anal. Calc'd for $C_{11}H_{14}N_2O_6$: C, 48.9; H, 5.2.
Found: C, 49.1; H, 5.4.

4-Nitro-(2'-nitro-3',4',5'-trimethoxy)benzanilide, prepared from the amine and *p*-nitrobenzoyl chloride, formed bright yellow needles, m.p. 210°, after recrystallization from ethyl acetate.

Anal. Calc'd for $C_{16}H_{15}N_3O_8$: C, 50.9; H, 4.0; N, 11.1.
Found: C, 51.1; H, 4.1; N, 11.5.

3,4,5-Trimethoxyaniline. Trimethylgallamide, prepared in quantitative yield by treatment of the acid chloride (thionyl chloride) with concentrated aqueous ammonia, melted at 175–177° after recrystallization from 80% ethanol. Reported m.p. 176–177° (25). This was subjected to the Hofmann degradation by the procedure for the preparation of 4-aminoveratrole from the corresponding amide (26) except that sodium hypobromite was substituted for sodium hypochlorite. The average yield of amine in a number of runs was 50%. In every run, rearrangement was accompanied by hydrolysis of the amide to the acid which was recovered by acidification of the aqueous alkaline filtrate after removal of the amine. Yields of the recovered acid which could be recycled to the amine represented 20–30% of the starting amide. 3,4,5-Trimethoxyaniline was isolated as white needles, m.p. 111–114°, which turned pink on exposure to air. Crystallization from ethyl acetate and pentane raised the m.p. to 113–114°. The *acetyl* derivative formed fine white needles, m.p. 124–125°, after recrystallization from ethyl acetate. Reported m.p. 124° (25).

Skraup reaction with 2-nitro-3,4,5-trimethoxyaniline. The "90-second" Skraup reaction as described above for the preparation of 6,7-dimethoxy-8-nitroquinoline resulted in the formation of intractable tars.

When 2-nitro-3,4,5-trimethoxyaniline was subjected to reaction with acrolein in a manner analogous to that described above for 4-amino-3-nitroveratrole, the strongly acid reaction mixture was relatively free of tars. After a quantity of inorganic material was removed by filtration, the filtrate was made alkaline in the cold with 10% potassium hydroxide solution and continuously extracted with ether. After drying the ether extract over sodium sulfate and concentration to dryness, the residual reddish, oily residue solidified on triturating with 3% hydrochloric acid. The dried, crude material was repeatedly crystallized from hexane yielding stout white rods melting at 94–95°. The yield was 9%.

Anal. Calc'd for $C_{12}H_{12}N_2O_5$: C, 54.5; H, 4.6; N, 10.6.
Found: C, 54.3; H, 4.6; N, 10.9.

5,6,7-Trimethoxyquinoline. To 9.2 g. of 3,4,5-trimethoxyaniline and 11.3 g. of sodium *m*-nitrobenzene sulfonate was added 36.5 ml. of "dynamite" glycerol (preheated to 170° for a half-hour). After cautious addition of 15 ml. of sulfuric acid (sp. gr. 1.84) the molten mixture was swirled vigorously and then heated over a free flame until ebullition ensued. The reaction was continued with intermittent heating for 7 min. and then poured into ice-water. The filtered, strongly acid solution was made ammoniacal in the cold and the crude product was continuously extracted with ether. The ether extract, after drying over potassium carbonate and concentration left an oil which was distilled under nitrogen at reduced pressure. The first fraction, b.p. 130–140° (1 mm.) (1.3 g.), was recovered 3,4,5-trimethoxyaniline. The main fraction, b.p. 145–147° (1.3 mm.) (4.6 g.), was a yellow viscous oil. A portion of this material was redistilled under nitrogen and boiled at 147° (1.3 mm). No satisfactory analytical data could be obtained from this material which darkened on standing even in a sealed ampoule. The picrate, nitrate, and sulfate of 5,6,7-trimethoxyquinoline were stable. These were prepared by addition of an alcoholic solution of the acid to an alcoholic solution of the freshly distilled main fraction. Addition of ether then precipitated the desired salt.

The *picrate* formed yellow needles, m.p. 206–207.5°, from absolute methanol.

Anal. Calc'd for $C_{18}H_{16}N_4O_{10}$: C, 48.2; H, 3.6; N, 12.5.

Found: C, 47.9; H, 3.5; N, 12.6.

The *sulfate* formed hygroscopic, white needles, m.p. 180–182°, from absolute ethanol and pentane.

Anal. Calc'd for $C_{12}H_{15}NO_7S$: N, 4.4; S, 10.1.

Found: N, 4.6; S, 10.3.

The *nitrate*, m.p. 173–174°, formed shiny white plates from ethyl acetate.

Anal. Calc'd for $C_{12}H_{14}N_2O_8$: C, 51.1; H, 5.0; N, 9.9.

Found: C, 51.5; H, 5.0; N, 9.9.

In subsequent experiments it was found that 5,6,7-trimethoxyquinolinium nitrate could be prepared in 42% yield (based on the 3,4,5-trimethoxyaniline taken). The crude Skraup reaction product was dissolved in ethanol and the crude nitrate was precipitated. It was then purified by recrystallization from ethyl acetate with decolorizing carbon.

Several experiments were carried out in which the time of the Skraup reaction was varied. With time intervals of 1.5 to 3 min. starting material was recovered almost exclusively. When the reaction proceeded for 15 min., a tarry, ether-insoluble by-product resulted, and the yield of trimethoxyquinoline was lowered. Reaction times of 5–7 min. gave optimum yields of the desired quinoline. Substitution of arsenic oxide for sodium *m*-nitrobenzenesulfonate as the oxidant did not affect the yield; however this substitution required the removal of a quantity of inorganic material from the aqueous acidic reaction mixture.

5,6,7-Trimethoxy-8-nitroquinoline. To 6 ml. of 90% sulfuric acid cooled to −10°, 2.8 g. of solid 5,6,7-trimethoxyquinolinium nitrate was added with vigorous stirring while the temperature was maintained at −10°. Within 10 min. the nitrate had dissolved; the solution was immediately poured into 10 volumes of ice-water, and then was cautiously neutralized with ammonia. At the neutral point 1.1 g. (42%) of 8-nitro-5,6,7-trimethoxyquinoline, m.p. 92–94° after crystallization from hexane, separated. When the aqueous neutral mother liquor from the above was made alkaline (*p*H 8–10) a deep green solid precipitated. This was soluble in both acid and water, but decomposed on attempted recrystallization from a variety of solvents. Attempted nitration of 5,6,7-trimethoxyquinoline in mixtures of fuming nitric and fuming sulfuric acid resulted in decomposition with gas evolution. With acetic anhydride or 80% sulfuric acid and concentrated nitric acid, the trimethoxyquinoline was not attacked.

5,6,7-Trimethoxy-8-aminoquinoline. A solution of 0.8 g. of 5,6,7-trimethoxy-8-nitroquinoline in 10 ml. of ethyl acetate was reduced over palladium black at room temperature and atmospheric pressure in 4 hours. The crude oily amine was recrystallized from pentane giving 0.5 g. (71.5%) of canary-yellow needles, m.p. 53.5–54°. The amine is unstable to light and air.

Anal. Calc'd for $C_{12}H_{14}N_2O_3$: C, 61.5; H, 6.0; N, 12.0.
Found: C, 61.3; H, 6.2; N, 12.2.

The *picrate* formed reddish-orange needles from absolute methanol which softened slightly at 180° and melted at 194–195° (dec.).

Anal. Calc'd for $C_{18}H_{17}N_5O_{10}$: C, 46.6; H, 3.7; N, 15.1.
Found: C, 46.6; H, 3.8; N, 14.8.

3,5-Dichlorobenzoic acid. A suspension of 206 g. of 3,5-dichloroanthranilic acid (27) in one liter of glacial acetic acid and 325 ml. of hydrochloric acid (sp. gr. 1.19) was refluxed until solution was complete. On cooling the hydrochloride of the acid crystallized. The flask was equipped with a Hershberg stirrer and the mixture was cooled to 0 to −5°. A solution of 72.5 g. of sodium nitrite in 200 ml. of water was added slowly at this temperature with stirring. The mixture was stirred for an hour at −5° after addition of the sodium nitrite during which period solution was complete. The temperature was lowered to −15° and 520 ml. of 50% aqueous hypophosphorous acid (previously cooled to 0°) was added dropwise with stirring. When addition was complete, nitrogen evolution occurred, slowly at first, and then vigorously and exothermally. A heavy white precipitate separated and the mixture was stirred overnight in the refrigerator at 0°. The precipitate was recrystallized from water, yielding 159 g. (83%) of 3,5-dichlorobenzoic acid, m.p. 186–188°. Reported m.p. 188° (28).

3,5-Dichloroaniline. The Hofmann degradation of the amide of the above acid was carried out with sodium hypobromite as previously described (26). The crude product was recrystallized from hexane and formed white needles, m.p. 52–53°. Reported m.p. 50.5° (29). The average yield was 65%.

Application of the Curtius degradation as described above to 3,5-dichlorobenzoic acid met with little success. On hydrolysis of the benzene solution of the isocyanate with base, quantities of solid were formed. This was presumably the substituted urea which resisted hydrolysis in alcoholic or aqueous acid or base in marked contrast to the ready hydrolysis of the ureas carrying a nitro group in the *ortho* position previously described.

When the Curtius reaction was modified by dissolving the crude dry azide in absolute methanol, the methyl urethan was formed. This was not isolated but was hydrolyzed in 50% aqueous potassium hydroxide. 3,5-Dichloroaniline, volatile with steam, was obtained in 40–45% yield.

5,7-Dichloroquinoline. This is a modification of the procedure described by Ammelburg (17). In a one-liter flask equipped with stirrer, dropping-funnel, and reflux condenser was placed on a mixture of 20 g. of 3,5-dichloroaniline, 7 g. of nitrobenzene, and 32 g. of glycerol (previously heated at 145° for 1.5 hours). To the well-stirred mixture, 28 g. of sulfuric acid (sp. gr. 1.84) was slowly added. When the initial exothermic reaction subsided, the mixture was warmed at gentle reflux for 3 hours and then poured into 500 ml. of ice-water. Excess nitrobenzene was removed by steam-distillation. However, when most of the nitrobenzene had distilled, 5,7-dichloroquinoline began to distil, even from the strongly acid solution. The distillation was discontinued as soon as solid appeared in the condenser. The residual solution was made alkaline and steam-distillation was continued yielding 12 g. (51%) of 5,7-dichloroquinoline, m.p. 116–117° after recrystallization from absolute ethanol. Reported m.p. 116–117° (17).

5,7-Dichloro-8-nitroquinoline. The above quinoline was nitrated with yellow, fuming nitric acid (sp. gr. 1.52) in concentrated sulfuric acid at 0–5° as described by Ammelburg (17). The yield of material, m.p. 166–167° after recrystallization from alcohol, was 67.5%.

5,7-Dimethoxy-8-nitroquinoline.[3] To a solution of 6 g. of sodium in 300 ml. of anhydrous methanol were added 24.3 g. of 5,7-dichloro-8-nitroquinoline and 70 ml. of dry pyridine. The mixture was refluxed with stirring for 4 hours during which period sodium chloride precipitated. On pouring the mixture into 2 l. of water a yellow-green flocculent solid precipitated. After recrystallization from alcohol, the pure product (79% yield) melted at 184–185°.

Anal. Calc'd for $C_{11}H_{10}N_2O_4$: C, 56.4; H, 4.3; N, 12.0.
Found: C, 56.3; H, 4.5; N, 11.9.

5,7-Dimethoxy-8-aminoquinoline. The above nitroquinoline was reduced with stannous chloride and hydrochloric acid as described above for 6,7-dimethoxy-8-aminoquinoline. Crystallization of the crude product from heptane gave yellow-green needles, m.p. 92–93.5°. The yield was 84.5%. Schönhöfer reports m.p. 92°, but no mention is made of the mode of synthesis, nor is an analysis reported.

Catalytic reduction in ethyl acetate over palladium gave the amine in 75% yield. It is extremely susceptible to air-oxidation, darkening to a deep, reddish-brown color.

Anal. Calc'd for $C_{11}H_{12}N_2O_2$: C, 64.7; H, 5.9; N, 13.7.
Found: C, 64.9; H, 6.1; N, 13.5.

The *picrate* formed red-brown needles, m.p. 219–220°, from alcohol.

Anal. Calc'd for $C_{17}H_{15}N_5O_9$: C, 47.1; H, 3.5; N, 16.2.
Found: C, 47.2; H, 3.5; N, 16.3.

5,7-Dimethoxy-8-acetaminoquinoline was prepared as in the preceding cases in 62% yield. The compound crystallized from ethyl acetate as hygroscopic, white needles, m.p. 180–182°.

Anal. Calc'd for $C_{13}H_{14}N_2O_3$: C, 63.4; H, 5.7.
Found: C, 63.4; H, 5.9.

Alkylation experiments. 5,7-Dimethoxy-8-(4-isopropylamino-1-methylbutylamino)quinoline. To a mixture of 8.43 g. of citric acid monohydrate, 14.3 g. of disodium hydrogen phosphate dodecahydrate, and 20 ml. of water were added 11.5 g. of 1-isopropylamino-4-bromopentane hydrobromide (30) and 7.7 g. of 5,7-dimethoxy-8-aminoquinoline. The mixture was heated under reflux with stirring at 70° for 15 hours, and then at 102° for an additional 5 hours. The cooled reaction mixture was made strongly basic with 50% potassium hydroxide and extracted with ether. After drying over potassium carbonate, the ether extract was concentrated to a viscous oil which was distilled under nitrogen at reduced pressure. The forerun, b.p. 50–90° (21 mm.), was 1-isopropyl-2-methylpyrrolidine. The main fraction was collected at 105–185° (0.45 mm.) and was refractionated yielding 2.2 g. (29%) of recovered 5,7-dimethoxy-8-aminoquinoline, b.p. 136–140° (0.6 mm.), m.p. 92–93°, and 2.9 g. (23%) of 5,7-dimethoxy-8-(4-isopropylamino-1-methylbutylamino)quinoline as a yellow oil, b.p. 182–182.5° (0.6 mm.).

Anal. Calc'd for $C_{19}H_{29}N_3O_2$: C, 68.8; H, 8.8.
Found: C, 68.6; H, 8.8.

The *hydrochloride* of the oily base was prepared by adding an anhydrous ether solution of hydrogen chloride to an absolute alcoholic solution of the base. An extremely hygroscopic solid separated. The supernatant liquid was decanted and the crude hydrochloride was recrystallized several times from methanol-ethyl acetate to yield yellow needles which decomposed at 124–125°. Some decomposition occurred during drying of the analytical sample. Analyses indicated that the salt was the *trihydrochloride.*

Anal. Calc'd for $C_{19}H_{29}N_3O_2 \cdot 3HCl$: N, 9.5; Cl, 24.1.
Found: N, 9.3; Cl, 23.5.

Attempts to prepare other salts gave uncrystallizable oils.

6,7-Dimethoxy-8-(5-isopropylaminopentylamino)quinoline. A mixture of 6.6 g. of 6,7-dimethoxy-8-aminoquinoline, 3 g. of fused sodium acetate, 9.5 g. of 1-isopropylamino-5-bromopentane hydrobromide (see below), and 12 ml. of water was heated with stirring at 80° for 20 hours and then at 100° for 4 hours. The crude product was isolated as in the preceding experiment, and was distilled at a diffusion pump. The first fraction boiled at 42–50° (4 μ), solidified on cooling, and was discarded. The second fraction, b.p. 123–130° (4 μ), was unreacted, starting aminoquinoline. The final fraction (2.1 g., 19.8%), b.p. 174–176° (4 μ), was a yellow viscous oil. The free base was not analyzed, but its ethereal solution was treated with a 10% solution of oxalic acid dihydrate in absolute ethanol. The oxalate which precipitated was repeatedly recrystallized from ethyl acetate, yielding pale yellow micro crystals, m.p. 102–105° (dec.). After drying *in vacuo* at 56°, the analytical data corresponded with those for a *monooxalate.*

Anal. Calc'd for $C_{21}H_{31}N_3O_6$: C, 59.8; H, 7.4; N, 9.8.
Found: C, 59.9; H, 7.7; N, 10.1.

A small part of the crude oxalate was insoluble in ethyl acetate. After recrystallization from 1:5 ethanol-ether a buff solid, m.p. 148–150° (dec.) was obtained. Analytical data agreed roughly with those calculated for the half oxalate. Attempted preparation of the phosphate gave an oil.

6,7-Dimethoxy-8-aminoquinoline could not be alkylated under similar conditions with 1-isopropylamino-5-chloropentane, nor with 1-isopropylamino-4-bromopentane under the conditions previously described for the alkylation of 5,7-dimethoxy-8-aminoquinoline.

Attempted alkylation of 5,6,7-trimethoxy-8-aminoquinoline. This aminoquinoline resisted alkylation when it was refluxed with 1-phthalimido-4-bromopentane for 2 days in alcohol, or in a solution buffered at *p*H 8 (30). It also failed to alkylate with 1-isopropylamino-5-chloropentane.

1-Isopropylamino-5-bromopentane hydrobromide.[6] The hydrobromide of 5-isopropylaminopentanol-1 was prepared by passing dry hydrogen bromide into a heptane solution of the amino alcohol. A solution of 225 g. of the hydrobromide in 100 ml. of 48% hydrobromic acid was saturated with hydrogen bromide with stirring and warmed at 100° for 3 hours. Excess reagent was removed at the water pump and the semi-crystalline residue was dissolved in 500 ml. of hot absolute alcohol, boiled with decolorizing carbon, and filtered. To the cooled solution was added 500 ml. of anhydrous ether; the precipitated bromide-hydrobromide (88%) melted at 108–115°. One recrystallization from ethyl acetate-pentane (1:1) raised the m.p. to 117–119.5°. Drake[6] reports m.p. 117.5–119.1°.

SUMMARY

1. The structures of the two isomeric dimethoxynitroquinolines formed in the Skraup reaction with 4-amino-3-nitroveratrole have been demonstrated.

2. 6,7-Dimethoxy-, 5,7-dimethoxy-, and 5,6,7-trimethoxy-8-aminoquinoline have been prepared and characterized.

3. Preliminary alkylation experiments with these polymethoxy-8-aminoquinolines and alkylaminoalkyl halides have been described.

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[6] This compound has not been described in the literature. Details for its preparation were kindly supplied by Dr. Nathan L. Drake, to whom we express our appreciation.

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