[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

THE SEARCH FOR SUPERIOR ANTIMALARIALS. II. THE SYNTHESIS OF 6,7-DIMETHOXYQUINOLINE DERIVATIVES AND OF SOME INCIDENTAL COMPOUNDS

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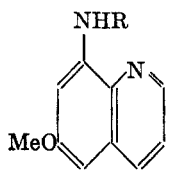
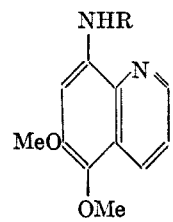
A recent German patent (1), covering the preparation of N-substituted 5,6-dialkoxy-8-aminoquinolines, in one of its opening paragraphs, contains the following: "On further study of this class of compounds, it has been found that the hitherto undescribed 5,6-dialkoxy-8-aminoquinolines, with a basic substituent on the amino group, are prominently distinguished from the already known nuclear substitution products of N-substituted aminoquinolines, by their especially favorable ratio between therapeutic and toxic action."

In a later publication (2), Schönhöfer expressed the opinion that the high plasmodicidal activity of Plasmochin (I) was due in part to the 6-methoxyl group, and claimed that an additional methoxyl at 5 enhanced still further the specific gametocidal action of the compound. Plasmochin subjected to the Roehl test with canaries, showed a therapeutic index of 1:30, whereas the index for 5-methoxy-Plasmochin (II) was 1:125. Surprisingly, when a third methoxyl group was present at 7 (III), the compound was entirely inactive. Hence he blamed this inactivity upon the methoxyl at 7, and cited as further proof of the dystherapeutic effect of a 7-methoxyl the inactivity of compounds IV and V.



I



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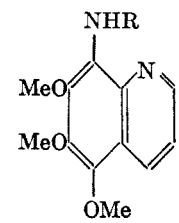

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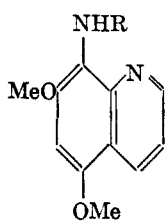
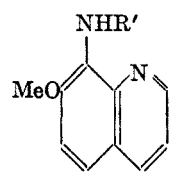


IV



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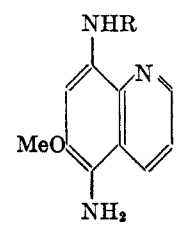

Va

R = —CHMe$(CH_2)_3NEt_2$

R′ = —$CH_2CMe_2CH_2NMe_2$

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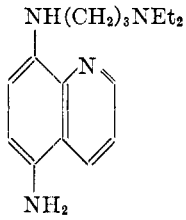
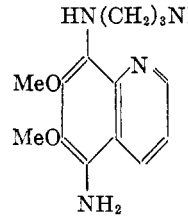
This article by Schönhöfer did not come to our attention until it appeared in the September 10, 1943 issue of *Chemical Abstracts* (p. 5064), by which time practically all of the work described in the following pages had been completed.

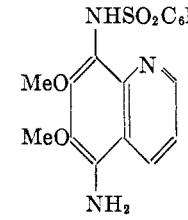
It is of interest, therefore, that two of our products which have been tested for antimalarial properties, *viz.* VII and VIII, on white Pekin ducks (*P. lophurae*) also proved to be inactive.



VI



VII



VIII

6,7-Dihydroxyquinoline and its ethers have been studied but little (3, 4, 5, 6, 7, 8, 9). The purpose of this and of the antecedent communication (10) has been to explore further the possibilities of discovering useful antimalarials in this group, and the compounds described were built up with this in mind. In comparison with Plasmochin, the likelihood that an additional methoxyl group at 7 would prove dystherapeutic seemed at the time to be offset by the favorable effect of a similar addition at 5, as recorded in the excerpt from the German patent (1) noted above. Further, since Fourneau and his co-workers (11) found such compounds as VI decidedly active against *P. relictum* in canaries, and Va is one of the products cited as an example in the aforementioned German patent (1), it seems unlikely that the inactivity of VII and VIII is due to the amino group at 5.

In the previous paper (10), the preparation of 5,8-diamino-6,7-dimethoxyquinoline and certain of its condensation products with bibasic acid anhydrides, was described. In all cases, both amino groups reacted, and the yields of the corresponding amidic acids were excellent. On the other hand, when experiments were conducted for the replacement of the amino hydrogens by acetyl, sulfanilamido, or dialkylaminoalkyl groups, involving condensations in which acid molecules were split out, but one of the two amino groups reacted, with formation of monosubstitution products only. The fact that one amino group seemed to be more basic than the other was confirmed by diazotization. Under normal diazotization cold, the uptake of sodium nitrite corresponded to only one amino group instead of two, and again only monosubstitution products were obtained. The phenomenon that diazotization occasionally occurs instead of the expected tetrazotization in diamines has been reported in the literature (12, 13, 14), and has been proved to be due to a decreased basicity of one amino group.

In the 5,8-diamino-6,7-dimethoxyquinoline (IX) there are three centers of basicity, namely the two amino groups and the heterocyclic nitrogen. *A priori*, each nitrogen atom carries an unshared pair of electrons, is basic, and can participate in the displacement reaction: $N: + RX \rightarrow \overset{+}{N} - R + X^-$.

Reaction on the quinoline nitrogen would give an N-substituted quinolone imine (A) (15, 16). Inasmuch as the monosubstitution products obtained in this work could not be diazotized, and in the case of the diamine itself (IX), only one amino group reacted, it is believed that in the acylation and alkylation leading to monosubstitution products, one of the two amino groups has reacted, and not the quinoline nitrogen. For this reason, such a structure as (A) for the monosubstitution product is considered improbable.

A choice between the structure shown in VII or VIII, involving a reaction upon the 8-amino group, and (B) representing a similar reaction on the 5-amino group, may be made by consideration of the following facts: (a) The two amino groups are each ortho to a methoxyl group, and in view of this equivalence one can assume a correlation between the tendency of an amino group to share its unshared pair of electrons with a proton, and the ease with which it takes part in the displacement reaction by sharing its pair of electrons in a C—N covalent bond and displacing a halide ion.

(b) A consideration of the electronic and resonance structures of the molecule will show that the 8-amino is more basic than the 5-amino group, and hence structures VII and VIII for the monosubstitution products are probably correct as given.

The well-known behavior of the quinoline ring on attack by electrophilic reagents can be explained from the resonance picture of quinoline, where there is an increased electron density at the nitrogen at the expense of that about carbon atoms 2, 4, 5, 7, and 9, this unbalancing of the electron density being accomplished by regular shifting of the electrons. Amino groups may become part of this resonating picture by carrying some of the electron deficiency imposed on the ring by the heterocyclic nitrogen. Since the amino group has an octet of electrons, its participation can only involve the formation of a C—N double bond accompanied by assumption of a positive charge, as shown in (H) and (J).

The result of the resonance is simply a further increase in the electron density of the heterocyclic nitrogen and a decrease in the availability of the amino groups in unshared pairs of electrons below that observed in aniline. Therefore the amino groups in the positions mentioned are extremely weak bases or, stated in a different manner, addition of the proton to the 5-amino group in (J), for example, leads to a fixed position of the positive charge (I), whereas addition of the proton to the quinoline nitrogen, leads to a monobasic resonating system in which both nitrogen atoms may bear a positive charge (L and M). Accordingly, in dilute acid, quinolines carrying an amino group in the "critical positions" form only monohydrochlorides. Theory and experimental results are in agreement with respect to the formation of a dihydrochloride by 5,8-diaminoquinoline and IX, which salts can therefore be represented by (N) and (O).

These conclusions bear upon the results of the diazotization experiments, since the salt of an aromatic amine is required for such a reaction. It is therefore probable that the amino group diazotized was the one in position 8 (N and O). Other examples of this apparently anomalous behavior appear in the litera-

ture (12, 13, 14), and are likewise explainable by the decreased basicity of one of the amino groups.

In further support of the greater basicity of the 8-amino group may be mentioned the fact that in 8-aminoquinoline chelation occurs in which one hydrogen atom of the amino group is bonded to the heterocyclic nitrogen. This causes a weakening in the covalent bond between the amino nitrogen and the hydrogen atom and the 8-amino nitrogen is therefore able to attract more readily a proton.

It is believed, therefore, that of the two amino groups present in (IX), that in position 8 is the more strongly basic, and therefore participates more readily in the displacement reactions described, and the monosubstitution products formed are hence believed to be the 8-N-substituted derivatives.

The greater reactivity of the group in the 8-position is utilized in German Pat. 536,447 (1) for the synthesis of antimalarials from 5,8-dinitro-6-methoxyquinoline.

6,7-Dimethoxyquinoline was readily prepared from 4-aminoveratrole by the Skraup reaction (10), and the corresponding quinaldine (XVIII) was obtained in good yield from the same initial compound, by the Doebner-von Miller reaction. XVIII was synthesized some time ago, by Rilliet (18), by condensing 6-aminoveratraldehyde with acetone.

Condensation of 4-aminoveratrole (XVII) with acetoacetic ester, followed by cyclization (Knorr-Conrad-Limpach reactions), gave 4-methyl-6,7-dimethoxycarbostyril (XX).

Application of the same reaction to 3-nitro-4-aminoveratrole (XXI), depending upon the conditions, produced either the corresponding acetoacetamino derivative (XXII), or the *beta*-aminocrotonic ester (XXIV), the former being cyclized by sulfuric acid to the 4-methyl-6,7-dimethoxy-8-nitrocarbostyril (XXIII), the latter to the 4,6(?)-dihydroxy-7(?)-methoxy-8-nitroquinaldine (XXV). The crotonic ester was obtained in two allotropic forms, m.p. 76–78° and 91–92°, which were interconvertible under conditions described in the experimental part.

An attempt to synthesize the 8-bromo-6,7-dimethoxyquinoline from 3-bromo-4-aminoveratrole failed because it was found impossible to degrade the 2-bromoveratramide to the corresponding amine by the Hofmann reaction. Recourse must therefore be had to different processes, such as those of Curtius (8), Lossen, and others.

As reported in the previous paper (10), direct nitration of 6,7-dimethoxyquinoline, yielded the 5,8-dinitro derivative. All attempts to obtain the mononitro compound by varying the conditions of nitration proved futile. Either the quinoline remained un-nitrated, or the dinitro derivative was the sole product isolated.

Acknowledgments. Without the generous support of Mr. Russell Hopkinson, of New York, N. Y., in maintaining at Columbia University a Hopkinson Research Fellowship, this investigation could not have been carried out. We are also deeply grateful to the following corporations, through the courtesy of the individuals mentioned, who kindly helped us by contributing various much-

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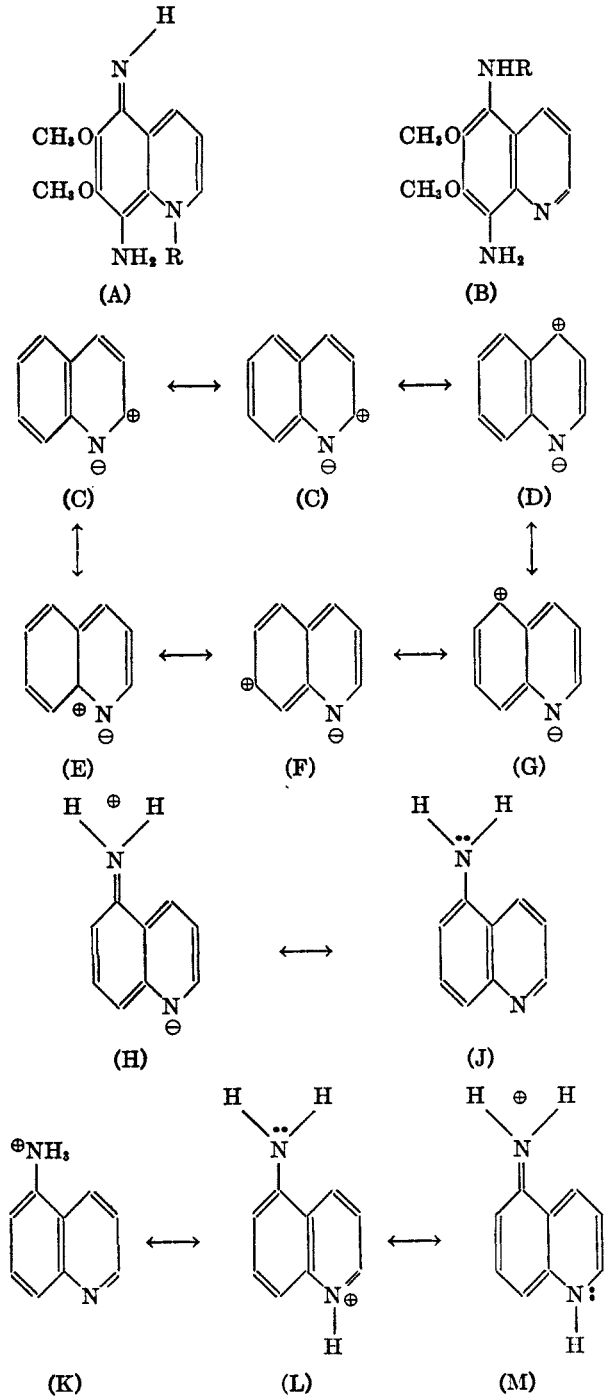

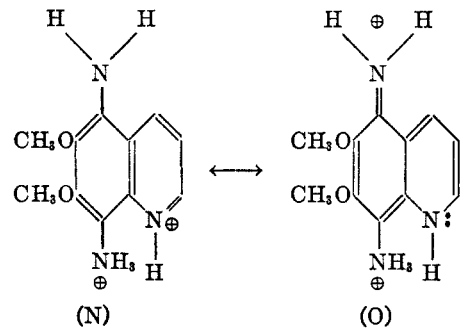

(N) (O)

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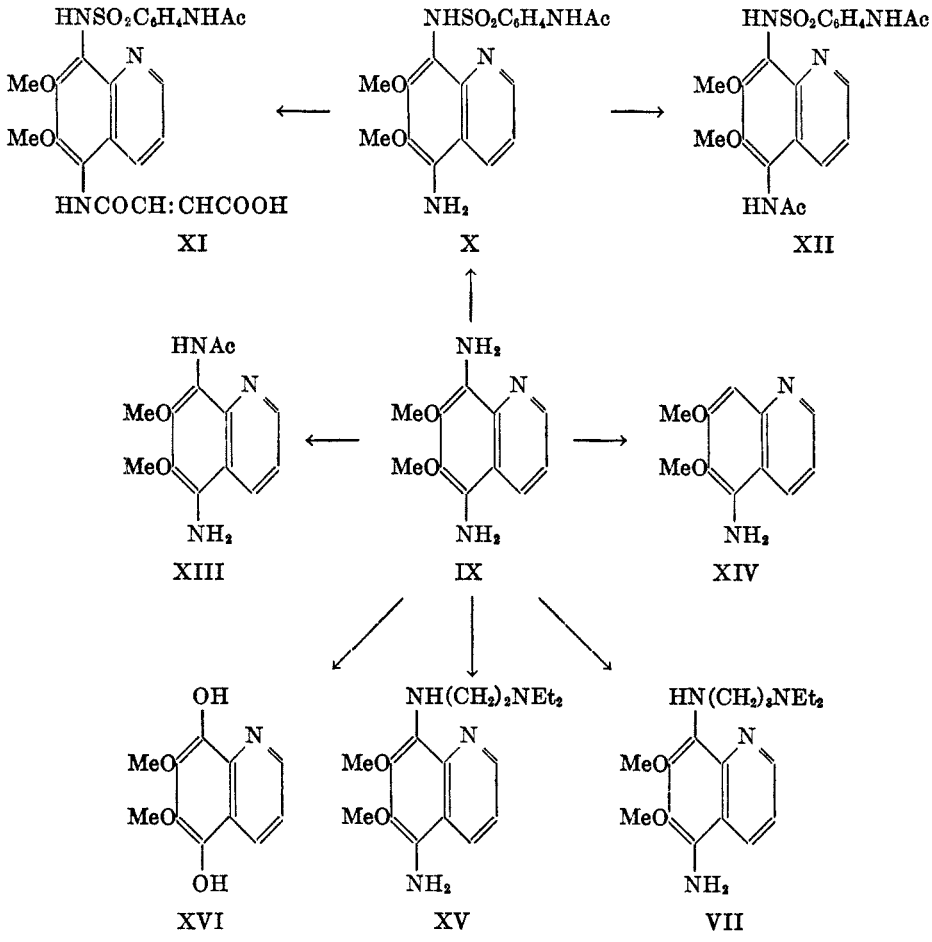

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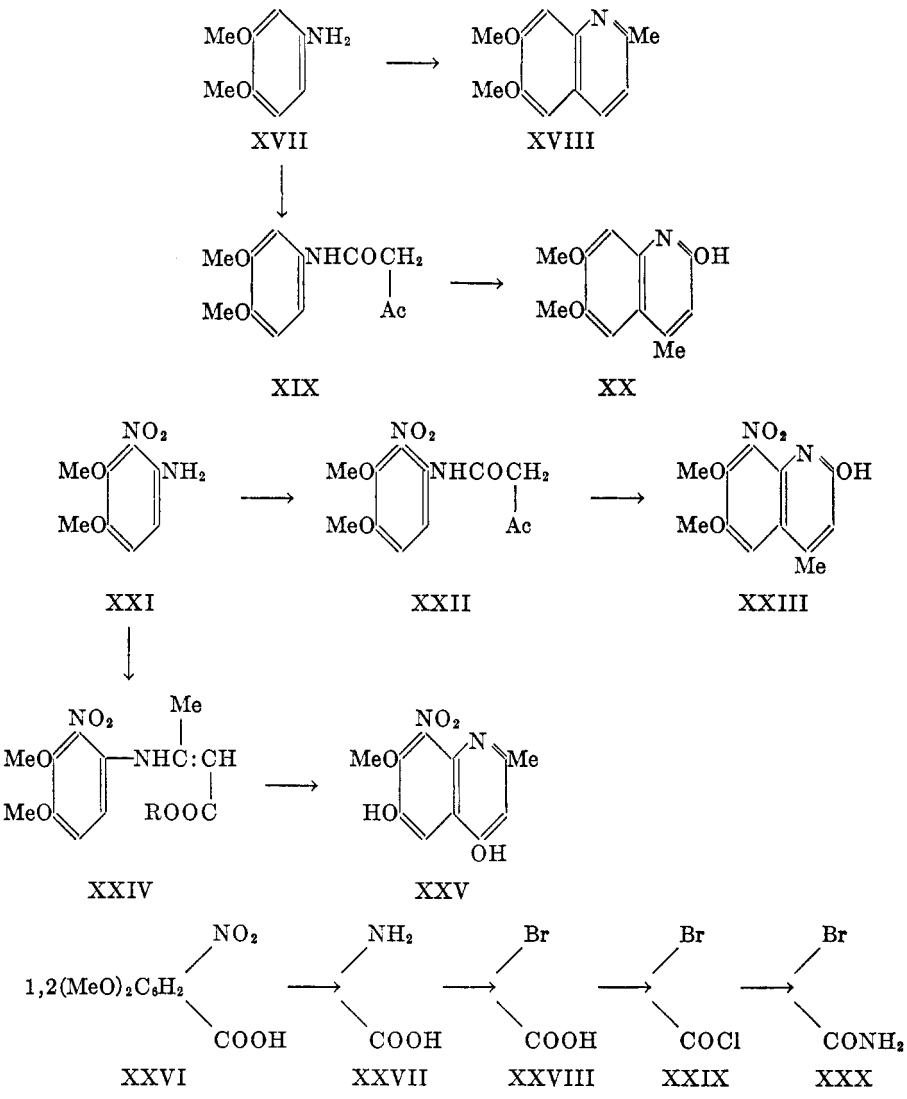

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extensive field. To Miss Frances Marx, we owe the microanalyses recorded in the experimental part of this communication.

EXPERIMENTAL

Unless otherwise stated, all temperatures recorded have been corrected for thermometer stem exposure.

DMQ. To economise space, this abbreviation is used for *dimethoxyquinoline* in naming compounds in the following pages.

5-Amino-8-acetylsulfanilamido-6,7-DMQ (X). The condensation of 5,8-diamino-6,7-DMQ with *p*-acetylsulfanilyl chloride was carried out in two different ways:

(a) According to the procedure of Juneja, Narang, and Rây (19), 1.2 g. of the diamine was dissolved in 75 cc. of dry chloroform and 2 g. of *p*-acetylsulfanilyl chloride was added. The mixture was refluxed for 30 minutes on the steam-bath. On cooling, bright red crystals separated, which were filtered out and recrystallized several times from alcohol. The melting point of the pure product was 204–205°. It was found that this red compound was not the free base but the hydrochloride of X, since it gave a positive chlorine test and was easily converted into the free amine by ammonium hydroxide.

Anal. Calc'd for $C_{19}H_{21}ClN_4O_5S$: C, 50.3; H, 4.6.
Found: C, 50.3; H, 4.8.

The formation of the hydrochloride can be explained by the fact that the hydrochloric acid split off in the course of the condensation then combined with the quinoline nitrogen.

The *free base* was obtained in pale yellow needles which, when recrystallized from alcohol, melted at 209.5°.

Anal. Calc'd for $C_{19}H_{20}N_4O_5S$: C, 54.8; H, 4.8.
Found: C, 55.1; H, 4.9.

(b) The second procedure led directly to the free base. A solution of 1.2 g. of the diamine was prepared in 20 cc. of acetone, and to this solution was added 1 g. of potassium carbonate dissolved in the minimum amount of water, followed by a solution of 3 g. of *p*-acetylsulfanilyl chloride in 40 cc. of acetone. A small amount of potassium carbonate which separated was dissolved by the addition of a few cc. of water. The mixture was refluxed for 30 minutes on the steam-bath, and the acetone was then removed by distillation. The resulting greenish solution was poured into water and a pale greenish precipitate soon separated. This was collected, washed with a small amount of water, and crystallized thrice from alcohol and water, giving pale yellow needles, m.p. 209.2°; yield, about 80%. This product was identical with that obtained by the first procedure, as determined by melting point and analysis.

Anal. Calc'd for $C_{19}H_{20}N_4O_5S$: C, 54.8; H, 4.8; N, 13.45.
Found: C, 54.95; H, 5.2; N, 13.3.

In this reaction it was observed that, in spite of the presence of potassium carbonate to absorb the by-product hydrochloric acid and an excess of *p*-acetylsulfanilyl chloride, only the monosubstitution product was formed.

Experiments were carried out, to introduce an acetylsulfanilamido side chain also into the unchanged amino group at 5, by condensing the above compound (X) with *p*-acetylsulfanilyl chloride, according to procedure (b), but only the original monosubstitution product was recovered from the reaction mixture.

5-Amino-8-sulfanilamido-6,7-DMQ (VIII). The deacetylation of X was effected as follows: 1 g. of X was dissolved in 20 cc. of hydrochloric acid (sp. gr. = 1.15) and refluxed for 10 minutes on the steam-bath. On making the cooled solution alkaline with ammonium hydroxide, there first resulted a greenish-grey sludge which became entirely crystalline when scratched. This product was removed, washed with water, and dried at 100°; yield of crude product, 90%. Recrystallized from alcohol, in the presence of charcoal, it formed pale brown crystals, m.p. 213.5–214.5° (dec.).

Anal. Calc'd for $C_{17}H_{18}N_4O_4S$: C, 54.5; H, 4.8.
Found: C, 54.8; H, 5.05.

8-Acetylsulfanilamido-6,7-dimethoxyquinolyl-5-maleamic acid (XI). The presence of a free primary amino group in X was demonstrated by condensation with maleic anhydride. To a solution of 1.5 g. of X in 25 cc. of acetone, one equivalent of maleic anhydride was added and the mixture refluxed for 3 minutes. As the solution cooled, a precipitate separated, which was removed and crystallized from alcohol, giving pink crystals, m.p. 212° (dec.).

Anal. Calc'd for $C_{23}H_{22}N_4O_8S+0.5H_2O$: C, 52.8; H, 4.4; N, 10.7.
Found: C, 53.1; H, 4.7; N, 11.0.

It is interesting to note that the di-maleamic acid described in the earlier paper (10) contained one molecule of water of crystallization.

5-Acetylamino-8-acetylsulfanilamido-6,7-DMQ (XII). The monoacetyl derivative (X) was heated with an excess of acetic anhydride on the steam-bath for 15 minutes. As the solution cooled, a copious white precipitate formed, which was repeatedly recrystallized from alcohol, and gave white needles, m.p. 248–248.5° (dec.); yield, about 90%.

Anal. Calc'd for $C_{21}H_{22}N_4O_6S$: C, 55.0; H, 4.8; N, 12.2.
Found: C, 55.1; H, 4.6; N, 11.9.

5-Amino-8-acetylamino-6,7-DMQ (XIII). The preparation of this acetyl derivative was carried out by adding an excess of acetic anhydride to the diamine and heating the reaction mixture for 30 minutes at 100°. Even while hot, a pale yellowish precipitate formed. This was removed, washed with petroleum ether (Skellysolve B), and then with a small amount of alcohol. The white product, recrystallized from alcohol, formed white needles, m.p. 270.5° (dec.).

Anal. Calc'd for $C_{13}H_{15}N_3O_3$: C, 59.8; H, 5.7.
Found: C, 59.7; H, 5.6.

As the above analysis indicates, acetylation of the diamine also led only to the monosubstitution product, in spite of the presence of an excess of acetic anhydride.

5-Amino-8-(β-diethylaminoethylamino)-6,7-DMQ (XV). The condensation of the diamine (IX) with dialkylaminoalkylamines was carried out essentially according to the procedure of Magidson and his co-workers (20, 21, 22).

A mixture of 9 g. of the diamine with 12.5 g. of β-diethylaminoethyl chloride hydrochloride in a wide test tube, protected from moisture by a calcium chloride guard tube, was heated for 8 hours at 120–130°, with occasional stirring.

After the heating was completed, the dark oily residue was dissolved in hot water, the solution saturated with potassium carbonate, and extracted repeatedly with ether. The ether extracts were dried over anhydrous potassium carbonate, the solvent driven off, and the resulting dark oil distilled at low pressure in an atmosphere of nitrogen. The pure product came over at 168°/0.03 mm., as a viscous red oil. On prolonged standing in the air, it darkened considerably.

Anal. Calc'd for $C_{17}H_{26}N_4O_2$: C, 64.1; H, 8.2.
Found: (sample 1) C, 63.8; H, 8.2. (sample 2) C, 64.1; H, 8.4.

The above analytical figures show that again only monosubstitution occurred.

5-Amino-8-(γ-diethylaminopropylamino)-6,7-DMQ (VII). A mixture of 14 g. of the diamine (IX) with 19 g. of γ-diethylaminopropyl chloride hydrochloride was heated for 8 hours at 125–130° (oil-bath temperature). The residue was worked up as described above for the preparation of (XV). The product from the ether extraction was a dark oil, which was subjected to further purification by high-vacuum distillation in an atmosphere of nitrogen. The yield of crude product was about 12 g. The pure product distilled over at 170–180°/0.03–0.04 mm., as a dark red viscous oil.

Anal. Calc'd for $C_{18}H_{28}N_4O_2$: C, 65.0; H, 8.4.
Found: C, 64.9; H, 8.3.

Analogous condensations of the diamine (IX) with 1-methyl-4-diethylaminobutyl chloride hydrochloride and 1-methyl-4-dimethylaminobutyl chloride hydrochloride were

carried out. The yields in these reactions were much smaller than in the two reactions described above, and the amounts of the resulting viscous dark red oils too small to subject them to a final purification by high vacuum distillation.

The dialkylaminoalkyl chloride hydrochlorides which were used in these condensations were prepared according to the following general procedure:

A solution of 2 moles of thionyl chloride in 1 liter of benzene was placed in a three-necked flask, equipped with thermometer, dropping-funnel, mechanical stirrer, and gas outlet tube. The solution was kept in an ice-bath and 1 mole of the corresponding dialkylaminoalkanol (commercially available) was added slowly with stirring, keeping the rate of addition such that the temperature did not rise above 25°. After all of the alcohol had been added, the temperature was raised to 60° and kept there for 3–4 hours. The solvent was then removed under reduced pressure and the residue purified by several distillations with small amounts of alcohol and benzene, leaving a crystalline product in the flask. Most of these dialkylaminoalkyl chloride hydrochlorides were hygroscopic and were best kept in a vacuum desiccator. The yields were 80–90%.

The same observation, that generally only one amino group of the diamine (IX) was attacked, was made in the diazotization of this substance. At 0° the uptake of sodium nitrite corresponded to the diazotization of a single amino group.

Furthermore, monosubstitution products of the diamino-DMQ (IX), such as the 5-amino-8-acetylamino-(XIII), and 5-amino-8-acetylsulfanilamido-(X) derivatives, possessing a free amino group in the 5 position, do not undergo diazotization under ordinary conditions.

5-Amino-6,7-DMQ (XIV). The replacement of the 8-amino group by hydrogen in the diamine (IX), was accomplished as follows: 1.8 g. of the diamine was dissolved in a mixture of 2.5 cc. of sulfuric acid and 6 cc. of water and the mixture cooled to 0°. A 20% sodium nitrite solution was added dropwise with constant stirring until the end of the reaction was indicated by starch-potassium iodide paper.

The diazonium solution was poured into a mixture of concentrated sodium hydroxide solution and ice, and a solution of sodium stannite (3 g. of stannous chloride dissolved in just sufficient excess of sodium hydroxide to dissolve all of the stannous hydroxide formed) was added with stirring. The reaction mixture was then kept on a steam-bath until no more evolution of nitrogen took place. The alkaline mixture, possessing a distinct ammoniacal odor, was extracted with ether or ethyl acetate, the extracts dried over anhydrous sodium sulfate and the solvent evaporated. The amine remained as a reddish oil, which was not analyzed but was identified by its derivatives. The procedure used in the above reaction is that of Friedländer (23).

5-Acetylamino-6,7-DMQ. The acetylation of the above amine (XIV) was carried out with acetic anhydride. The crude product, several times recrystallized from alcohol, gave white needles, m.p. 141.5°.

Anal. Calc'd for $C_{13}H_{14}N_2O_3$: C, 63.5; H, 5.7.
Found: C, 63.4; H, 5.6.

Picrate. Recrystallized from alcohol, it formed orange needles, m.p. 229–230°.

Anal. Calc'd for $C_{17}H_{15}N_5O_9$: C, 47.2; H, 3.5.
Found: C, 47.3; H, 3.6.

That tetrazotization of the diamine (IX) may occur under more drastic conditions, was shown by the preparation of the dihydroxy compound.

5,8-Dihydroxy-6,7-DMQ (XVI). Four grams of the diamine was dissolved in a mixture of 5 cc. of concentrated sulfuric acid and 15 cc. of water. The solution was heated to 80°, and a solution of 2 g. of sodium nitrite in 16 cc. of water slowly added through a dropping-funnel, whose end reached almost to the bottom of the flask, in order to prevent decomposition of the sodium nitrite by falling upon the hot surface. The addition of the nitrite took about 10–15 minutes, keeping the temperature of the solution at 80–90°. When the addition was complete, the heating was continued at the same temperature for 30 minutes, by which time no more evolution of nitrogen was observed. After cooling, the acid solution was

extracted with ether, the yellow ether extracts dried over anhydrous sodium sulfate and the solvent evaporated. The orange-red oil which remained was taken up in alcohol and, on scratching the sides of the container, changed over to an orange-yellow crystalline solid, m.p. 77–79°, which darkened on standing in the light. Since the analytical figures for carbon and hydrogen in the dihydroxy compound and in the aminohydroxy compound are about the same, a nitrogen analysis was run.

Anal. Calc'd for $C_{11}H_{11}NO_4$: N, 6.4.

Found: N, 6.8. For the aminohydroxy compound, N = 12.7.

This dihydroxyquinoline gave a characteristic chelate metallic complex with copper salts, and it has been shown by various investigators (17) that only those hydroxyquinolines which carry their OH in position 8 are able to form such internal metallic complexes and lakes between the quinoline nitrogen and the OH group.

6,7-Dimethoxyquinaldine (XVIII). This has been previously prepared by Rilliet (18) by treatment of 6-aminoveratraldehyde with acetone. A more convenient synthesis, however, was found in the application of the Doebner-von Miller reaction to 4-aminoveratrole (XVII), which latter is easily available in excellent yields (10).

To a mixture of 31 g. of 4-aminoveratrole and 60 cc. of concentrated hydrochloric acid, was added 45 cc. of paraldehyde, and the mixture was refluxed for 3.5 hours. The reaction set in only after warming and proceeded without violence. After cooling, the reaction mixture was made alkaline with concentrated sodium hydroxide solution and steam-distilled.

The residue was transferred to a continuous extractor and extracted with ether overnight. The ether extracts were dried with anhydrous sodium sulfate and the solvent evaporated. The dark oil which remained was subjected to a vacuum distillation. Rejecting the forerun, a pale yellow, viscous oil was obtained, distilling at 135°/0.45 mm. The yields were good.

Anal. Calc'd for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.4.

Found: C, 70.6; H, 6.6.

The identity of this compound (XVIII) was established by comparing the m.p. of its *picrate* (from an alcoholic solution) with that obtained by Rilliet (18). Rilliet gave the m.p. of his picrate as 217°, which is the figure found for the picrate of the above product.

4-Methyl-6,7-dimethoxycarbostyril (*6,7-dimethoxy-α-lepidone*) (XX). Ten grams of ethyl acetoacetate was heated in an open flask to 160°, and 3 g. of 4-aminoveratrole (XVII) slowly added, so that the internal temperature did not fall below 160°, which took about 25 minutes. The contents of the flask were stirred occasionally, to facilitate removal of the alcohol formed and heating was continued for 30 minutes after all of the aminoveratrole had been added. On cooling, the mixture formed a dark liquid which was concentrated under reduced pressure, to remove the excess of acetoacetic ester. The residual oil, representing the *4-acetoacetaminoveratrole* (XIX) was not crystallized, but used directly for the ring closure.

To this oil was added an equal volume of concentrated sulfuric acid, and the mixture was carefully heated to 90–95°. Fumes developed at this temperature, indicating that the reaction had set in. After this reaction had subsided (the temperature of the reaction mixture must not exceed 95°), the mixture was heated at 95° for 10 minutes, then cooled to 60° and poured into water. A grey precipitate formed, which was removed and recrystallized from alcohol and water, giving white needles, m.p. 236–237° (dec.).

Anal. Calc'd for $C_{12}H_{13}NO_3$: C, 65.7; H, 5.9.

Found: C, 65.7; H, 6.1.

The yield of this substance was about 70%, calculated to the 4-aminoveratrole.

3-Nitro-4-acetoacetaminoveratrole (XXII). Ten grams of acetoacetic ester was heated to 160° (inside temperature) and 3 g. of 3-nitro-4-aminoveratrole (24) (XXI) was slowly added, maintaining the temperature at 160°. This took about 10–15 minutes. After 30 minutes longer at 160°, with occasional shaking, to facilitate removal of the alcohol formed, the clear orange liquid was allowed to cool; yellow crystals separated on short standing.

These crystals were filtered out, washed with a small amount of cold alcohol, and recrystallized thrice from alcohol. Light yellow needles were obtained, m.p. 118.5–119.5°; yield (first crop), 2.5 g.

Anal. Calc'd for $C_{12}H_{14}N_2O_6$: C, 51.0; H, 5.0.
Found: C, 51.3; H, 5.2.

4-Methyl-6,7-dimethoxy-8-nitrocarbostyril (6,7-dimethoxy-8-nitro-α-lepidone) (XXIII). A mixture of 9.5 g. of the above XXII with 10 cc. of concentrated sulfuric acid was heated to 95°, forming a dark red solution. The heating was continued for 10 minutes at the same temperature and the mixture was then cooled and poured into water. A yellowish-brown precipitate resulted, which was filtered out and dried at 100°; yield of crude product, 2.5 g. This crude product was crystallized several times from alcohol, giving light yellow needles m.p. 210° (dec.).

Anal. Calc'd for $C_{12}H_{12}N_2O_5$: C, 54.6; H, 4.6; N, 10.6.
Found: C, 55.0; H, 4.9; N, 10.6.

This procedure for the ring closure is that of Michailov (25).

The filtrate from the ring closure product was made alkaline, whereby 3-nitro-4-aminoveratrole came down (4 g.), indicating hydrolysis of some of the XXII.

Ethyl 2-nitro-3,4-dimethoxy-β-anilinocrotonate (XXIV). The condensation of 3-nitro-4-aminoveratrole (XXI) with acetoacetic ester was carried out exactly as described above for the preparation of XXII, except that the temperature was allowed to go up to 173°. When the crude mixture was cooled, poured into water, and chilled with ice, deep yellow cubical crystals separated, which were filtered out and washed with alcohol; m.p. 76–78°.

On standing in the sunlight, these deep yellow crystals faded to a pale yellow, a transformation which took place also when the deep yellow form was recrystallized from alcohol. The pale yellow crystals melted at 91–92° and, on prolonged standing, reverted partially to the deep yellow form.

Anal. Calc'd for $C_{14}H_{18}N_2O_6$: C, 54.2; H, 5.8.
Found: C, 54.1; H, 5.8.

4,6(?)-Dihydroxy-7(?)-methoxy-8-nitroquinaldine (XXV). The ring closure of XXIV was carried out with concentrated sulfuric acid as described for the preparation of XXIII. Under the conditions of the experiment, this took place with simultaneous hydrolysis of one methoxyl group, presumably that at 6. The yield of this product was very small. It formed bright yellow needles, m.p. around 300°.

Anal. Calc'd for $C_{11}H_{10}N_2O_5$: C, 52.8; H, 4.0; N, 11.2.
Found: C, 52.7; H, 4.2; N, 10.9.

2-Aminoveratric acid (XXVII). The reduction of 2-nitroveratric acid (XXVI) to the corresponding aminoveratric acid by tin and hydrochloric acid in alcoholic solution, is not a satisfactory method, as Tiemann and Matsmoto (26) have reported. Catalytic reduction of the nitro acid with palladium black in alcoholic solution was tried, but no hydrogen uptake could be observed, even during a period of many hours.

The reduction was successfully carried out, however, with ferrous sulfate and ammonium hydroxide, following the procedure of Pschorr and Sumuleanu (27); m.p. 186°; (lit., 184°); yield, 83%.

2-Bromoveratric acid (XXVIII). The diazotization of 2-aminoveratric acid and the replacement of the amino group by bromine were accomplished as described by Zincke and Francke (28). The bromo acid was obtained in white needles, m.p. 206–208° (lit. 201–202°); yield, 62%.

2-Bromoveratroyl chloride (XXIX). This compound was prepared by dissolving 1.2 g. of 2-bromoveratric acid in 8 cc. of thionyl chloride, refluxing the solution for 30 minutes, and distilling off excess thionyl chloride under diminished pressure. The acid chloride was not isolated from the residue, which was used directly for the preparation of the amide.

2-Bromoveratramide (XXX). The crude acid chloride was added slowly to a concentrated ammonium hydroxide solution with constant stirring, keeping the reaction mixture ice-cold. The white precipitate which formed was filtered out, washed with water, and

dried at 100°; yield, 1.2 g., which is nearly that calculated. Recrystallized from alcohol, it gave colorless prisms, m.p. 197–198°. Another sample, recrystallized from benzene, showed the same melting point, indicating that no esterification had taken place in the recrystallization from alcohol.

Anal. Calc'd for $C_9H_{10}BrNO_4$: C, 41.4; H, 3.8.
Found: C, 41.1; H, 3.7.

2-Bromoveratramide was subjected to the Hofmann degradation, under various conditions of temperature, amounts of reagents, etc., but in no case could the corresponding amine be isolated from the reaction mixture. Other methods therefore, such as the Curtius and Lossen rearrangements, must be tried for the preparation of the amine.

SUMMARY

1. From 5,8-diamino-6,7-dimethoxyquinoline, derivatives have been prepared in which hydrogens of the amino groups have been replaced by —Ac, —$SO_2NHC_6H_4NHAc$, —$(CH_2)_nNR_2$, —COCH:CHCOOH. In all cases where such substitutions involved elimination of molecules of an acid, only one of the two amino groups participated in the reaction. An explanation of this, along electronic lines, is suggested. The antimalarial inactivity of the few compounds tested so far, supports Schönhöfer's (2) conclusion that a methoxyl group at 7 in such quinoline derivatives is definitely dystherapeutic.

2. Under ordinary conditions, only one of the two amino groups could be diazotized. One amino group thus has been removed, without affecting the other one. Using concentrated acids and higher temperature, both amino groups have been diazotized.

3. In the above reactions, it is believed that the 8-amino group is the more reactive one and hence is the one primarily attacked.

4. 4-Aminoveratrole has been converted into 6,7-dimethoxyquinaldine, by the Döbner-von Miller reaction; and into the 6,7-dimethoxy-α-lepidone by the Knorr-Conrad-Limpach procedure.

5. 3-Nitro-4-aminoveratrole, likewise by the Knorr-Conrad-Limpach reactions, has been converted into 6,7-dimethoxy-8-nitro-α-lepidone, or 4,6(?)-dihydroxy-7(?)-methoxy-8-nitroquinaldine, the course of the reaction depending upon the temperature used in the condensation.

6. An attempt to synthesize 3-bromo-4-aminoveratrole from 2-nitro-3,4-dimethoxybenzoic acid proved unsuccessful, because it was found impossible to degrade the 2-bromo-3,4-dimethoxy-benzamide by the Hofmann reaction.

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