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THE SEARCH FOR SUPERIOR ANTIMALARIALS. I. EXPERIMENTS IN THE VERATROLE GROUP[1]

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Veratrole was selected for this particular investigation because of its ready availability and the ease with which it can be converted into a 5,8-diamino-6,7-dimethoxyquinoline (IV), which carries one of its methoxyls, and both of its amino groups, in chemotherapeutically favorable positions. What will be the effect of the additional methoxyl at 7 is problematical. It is true that not infrequently the introduction into a molecule of a second group of the same kind, instead of increasing the physiological effect, destroys it. On the other hand, the veratrole structure, carrying adjacent methoxyl groups, is present in such physiologically active alkaloids as papaverine, laudanosine, narcotine, narceine, hydrastine, berberine, corydaline, brucine, and a host of others.

The most valuable three antimalarials at present, it is quite generally agreed are, in the order of their usefulness, quinine (and its associated alkaloids), Atabrine, and Plasmochin. These three have in common certain structural features, as will be obvious by an examination of their graphic formulas. It is not an illogical deduction, therefore, that their antimalarial properties are in some way dependent upon the existence in their molecules of such common features. Thus, all of these three drugs are derivatives of quinoline (acridine being a benzoquinoline). All of them carry a methoxyl group in position 6, and a basic group at 4 or 8, on the quinoline nucleus. The function of the chlorine in Atabrine is obscure.

We are focusing our attention upon Plasmochin types, rather than upon quinine or Atabrine substitutes because, in spite of certain valid and familiar objections to Plasmochin, it still remains about the only available antimalarial which is strongly gametocidal in cases of *P. falciparum* infections. The problem is therefore to synthesize a compound which will retain, or even improve upon, the valuable antimalarial properties of Plasmochin, and be free from its objectionable characteristics.

In this preliminary article, a number of simple veratrole derivatives are described which were used as initial materials either in the present communication or in others which will appear shortly.

Some interesting condensations were carried out with the 5,8-diamino-6,7-dimethoxyquinoline (IV) and the anhydrides of succinic, maleic, and phthalic acids, following in general the procedure of Bergmann and Schapiro (1) in their acylation experiments with sulfanilamide and heterocyclic amines. Under the

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conditions of our experiments, the three anhydrides reacted smoothly with both amine groups, giving excellent yields of compounds (V), (VII), and (VIII).

The imides (VI and IX) corresponding to two of these acids (V and VIII) were obtained readily by heating together the diamine (IV) and the acid anhydride, either dry or in boiling dioxane (b.p., 101.5°) solution; but maleic anhydride refused to yield an imide by either process. This agrees with the experience of Bergmann and Schapiro in analogous cases.

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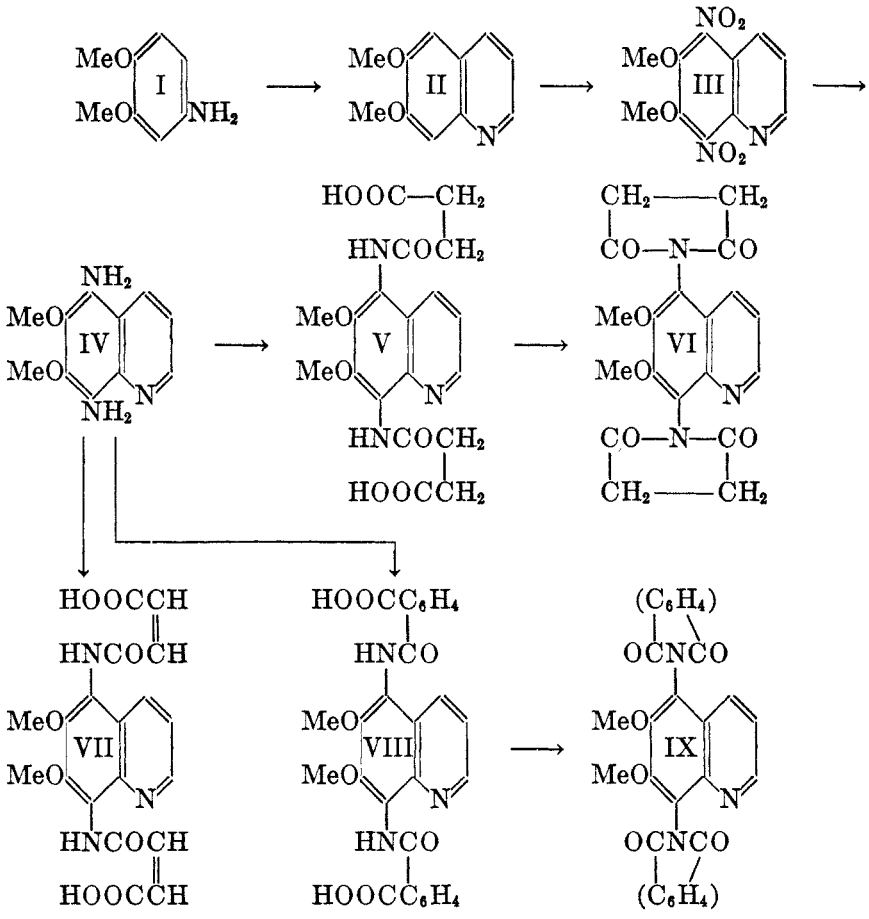

One reason for some experimentation in this direction was that Oesterlin (2) has recently reported that the antimalarial action of Plasmochin is increased by succinic and fumaric acids, which play an important part in cell respiration, and this is probably referable to the action of the drug upon the gametocytes.

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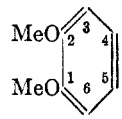
EXPERIMENTAL

All temperatures recorded, unless otherwise stated, have been corrected for thermometer stem exposure.

All veratrole derivatives are numbered consistently throughout according to the following formula:



4-Nitroveratrole (m.p. 96°) and *4,5-dinitroveratrole* (m.p. 127–128°) are easily obtained by the direct nitration of veratrole, the dilute acid giving the mono-, and the concentrated acid the di-nitro derivative, as already described in various articles in the literature. The yield in both cases is practically that calculated.

3,4,5-Trinitroveratrole has been prepared by the action of fuming nitric acid, or of a mixture of concentrated nitric and sulfuric acids, upon 4-nitroveratrole or veratric acid (3, 4).

By direct nitration of veratrole with a mixture of equal parts of concentrated nitric acid and concentrated sulfuric acid, we have obtained a 75% yield of the trinitro derivative, in pale yellow crystals, m.p. 143° (lit., 144–145°). In carrying out this nitration, the veratrole must be added very slowly and carefully to the mixed acids, or the reaction is likely to become violent. After all of the veratrole has been added, the nitration is completed by heating for an hour at 100°. When cold, the mixture is poured into ice-water, the precipitate collected, washed with water, and crystallized from alcohol.

This trinitro derivative was prepared also from 6-nitroveratraldehyde as follows:

To 50 cc. of a mixture of equal parts of concentrated nitric acid and concentrated sulfuric acid was added slowly 5 g. of the nitro aldehyde, while the reaction vessel was immersed in cold water and the mixture mechanically stirred. After about 30 minutes, the mixture was poured into 500 cc. of ice-water, the precipitate removed and purified as before. White prisms were obtained, m.p. 143°; yield 75%.

Anal. Calc'd for $C_9H_7N_3O_8$: C, 35.2; H, 2.6.
Found: C, 35.4; H, 2.7.

In this nitration presumably the aldehyde group is first oxidized to COOH and the latter then is displaced by the nitro group, as in the oxidation of veratric acid to trinitroveratrole noted above.

4-Aminoveratrole (I). The reduction of 4-nitroveratrole to the corresponding aminoveratrole has been achieved by the action of hydrogen in the presence of the Adams platinum oxide catalyst (5), as well as by other methods. It has now been found that this reduction can be accomplished more satisfactorily and more economically by the use of palladium black. A solution of 30 g. of 4-nitroveratrole in 180 cc. of alcohol, containing 0.3 g. of palladium, was hydrogenated at about three atm. pressure; yield, 24.5 g. (calc'd, 25 g.); m.p. 86° (lit., 86°). Exposed to light and air, this amine gradually turned reddish.

4-Amino-5-nitroveratrole. When a solution of 15 g. of 4,5-dinitroveratrole in 150 cc. of alcohol was hydrogenated at 3 atm. pressure in the presence of excess of palladium catalyst, and the current of hydrogen was continued for some time after the absorption of the gas had ceased, an orange-red precipitate separated, which was removed and purified by recrystallization from alcohol, when it melted at 171° (lit., 171°); yield 70–75%.

To discover whether or not this method of reduction could be used for the conversion of

other aromatic dinitro derivatives into the corresponding amino nitro compounds, it was tried on *o*- and *m*-dinitrobenzenes, and on 2,4-dinitroaniline, but in every case both nitro groups were reduced. It is worth noting, therefore, that in the veratrole series this method of reduction pursues a somewhat different course from that which it follows in the benzene series.

4,5-Diaminoveratrole was prepared most conveniently by reduction of the dinitro compound with tin and hydrochloric acid, as described by Moureu (6); m.p. 131° (lit., 131°); yield, good.

3,4,5-Triaminoveratrole. To a mixture of 9 g. of the trinitro compound and 27 g. of tin was added 100 cc. of concentrated hydrochloric acid, and the mixture was heated for an hour at 100° with frequent stirring. The resultant clear, dark red solution was made alkaline to litmus by sodium hydroxide solution, with external cooling, and extracted with chloroform. Concentration of the chloroform extract deposited the triamine in nearly colorless needles which darkened rapidly when exposed to light and air; m.p., 150–152°; yield, 70%.

Picrate. Purified by repeated crystallization from alcohol, it formed yellow needles, m.p. 86°.

Anal. Calc'd for $C_{14}H_{16}N_6O_9$: C, 40.8; H, 3.9.
Found: C, 40.7; H, 3.9.

6,7-Dimethoxyquinoline (II). Goldschmiedt (7) prepared this compound by the application of the Skraup reaction to 6-aminoveratric acid, the COOH group being eliminated simultaneously. The yield, however, was only "sehr mässige," and his product admittedly was not pure. It is interesting that in this case the tendency to form the 6,7- rather than the 5,6-dimethoxyquinoline, is so strong that the cyclization, instead of occurring at the free *ortho* position 5, displaces the COOH at 1.

We have found that this quinoline derivative is more conveniently prepared by the application of the same reaction to 4-aminoveratrole. After removal of excess nitrobenzene by steam distillation, the solution was made alkaline and distilled again with steam, to eliminate any unchanged aminoveratrole. No unaltered nitrobenzene or aminoveratrole was recovered in these distillations. Since the dimethoxyquinoline itself is not volatile with steam, it was isolated by extraction with ether. The base remaining after evaporation of the dried ether extract was dissolved in dilute hydrochloric acid. The clear solution was warmed and a mixture of zinc chloride and 2 *N* hydrochloric acid added. As the solution cooled, the double zinc chloride salt of the quinoline crystallized out. These crystals were removed, washed, decomposed by concentrated sodium hydroxide solution, and the quinoline again extracted with ether. The ether extract was dried again with sodium sulfate, and the solvent evaporated. The dimethoxyquinoline remained as a brownish yellow oil. By using a continuous extractor for the ether extraction, and omitting the zinc chloride purification, an 83% yield of the dimethoxyquinoline was secured, of sufficient purity for the succeeding reactions. When the crude product was subjected to distillation, in an atmosphere of nitrogen, it came over as a pale yellow oil at 164°/2.3 mm., n_D^{25}, 1.6150.

Anal. Calc'd for $C_{11}H_{11}NO_2$: C, 69.8; H, 5.8.
Found: C, 69.5; H, 5.9.

Hydrochloride. Evaporation of a dilute hydrochloric acid solution of the base, left this salt in pale yellow crystals, which were recrystallized from alcohol, and then appeared in white needles, m.p. (uncorr.) 222°.

Anal. Calc'd for $C_{11}H_{12}ClN_2O$: C, 58.5; H, 5.3.
Found: C, 58.6; H, 5.6.

N-Methyl methosulfate, $C_{11}H_{11}NO_2Me \cdot OSO_3Me$. To a solution of 2 g. of the base in benzene, 1.5 g. of methyl sulfate was added, and the mixture was refluxed for 30 mins. A dark oil collected below the benzene. Most of the benzene was decanted and the residual mixture was heated at 100° to drive off the remainder. The oil remaining was dissolved in warm acetone and precipitated in crystalline form by the addition of ether. Repetition of this

acetone and ether treatment gave pale yellowish crystals, which melted with decomposition at 232°.

Anal. Calc'd for $C_{13}H_{17}NO_6S \cdot H_2O$: C, 46.8; H, 5.7.
Found: C, 46.7; H, 5.2.

The same product was obtained by heating together equimolecular amounts of the base and methyl sulfate for 10 mins. at 100°. On cooling, the quaternary salt crystallized out and was purified from acetone and ether as above. In both cases, the yield was practically that calculated.

Picrate. M.p. 257° (lit., 257°); yellow needle crystals (from alcohol).

Methiodide. A mixture of equal moles of the dimethoxyquinoline and methyl iodide was heated at 100°. As the tube cooled, the methiodide separated as a yellow powder; m.p. (with decomposition) 242°; yield, 90%.

Anal. Calc'd for $C_{12}H_{14}INO_2$: C, 43.5; H, 4.3.
Found: C, 43.4; H, 4.6.

Similar quaternary salts have been made with ethyl iodide; ethyl, *n*-propyl, and *n*-butyl bromides, but not analyzed. These salts may prove interesting for the preparation of new photosensitizing cyanine dyes; and physiologically may possess some curare action.

5,8-Dinitro-6,7-dimethoxyquinoline (III). To a solution of 5 g. of the dimethoxyquinoline in 20 cc. of concentrated sulfuric acid at 0°, 20 cc. of oleum was added slowly. The mixture was transferred to a 3-necked flask, stirred mechanically, and 25 cc. of yellow fuming nitric acid added gradually, maintaining the temperature at or below 10°. After an hour's stirring, the mixture was poured upon ice and left until the yellow precipitate had settled completely, when it was removed, washed with water, and crystallized from alcohol, giving white crystals, m.p. 155°; yield, 90%.

Anal. Calc'd for $C_{11}H_9N_3O_6$: C, 47.3; H, 3.2.
Found: C, 47.5; H, 3.5.

The position of the nitro groups assumed in this compound is based upon the following considerations:

(a) The fact that the benzene nucleus in quinolines is much more sensitive to nitration than the pyridine cycle.

(b) Direct nitration of quinolines by mixtures of nitric acid and sulfuric acid results preferably in 5- or 8-nitro derivatives, and not in nitration of the pyridine cycle (8, 9, 10).

(c) Since the position of the two methoxyl groups is fixed at 6 and 7, positions 5 and 8 are the only ones left free for nitration on the benzene nucleus.

5,8-Diamino-6,7-dimethoxyquinoline (IV). This was prepared by reduction of the corresponding dinitro derivative (VII) with tin and hydrochloric acid, stannous chloride and hydrochloric acid, or by hydrogen in the presence of palladium as catalyst. Of these three methods, the second proved most satisfactory, and was carried out as follows:

A mixture of the dinitro compound with a slight excess of stannous chloride was covered with concentrated hydrochloric acid and vigorously stirred. Reaction took place cold, with formation of yellow crystals presumably consisting of the double tin salt of the diamine hydrochloride. This salt was removed, dissolved in an equal volume of water, the solution made alkaline by the careful addition of concentrated caustic alkali solution, extracted with ether, the ether extract dried with sodium sulfate, and the solvent removed. The residual reddish oil (yield 85%) was purified by distillation under diminished pressure, in an atmosphere of nitrogen, and an orange oil obtained, b.p. 170°/0.2 mm., which was analyzed.

Anal. Calc'd for $C_{11}H_{13}N_3O_2$: C, 60.3; H, 5.9.
Found: C, 60.3; H, 6.2.

Picrate. As soon as the picric acid solution was added to the solution of the diamine, the mixture turned dark and a dark picrate separated, from which a lighter colored product could not be obtained by repeated crystallization from alcohol in the presence of a decolorizing carbon. The crystals so obtained were large needles, m.p. 185–186°.

Dihydrochloride. Dry hydrogen chloride was passed into an anhydrous ether solution of the diamine for 10 minutes. The red precipitate was crystallized repeatedly from alcohol and then formed pinkish crystals, m.p. 186–187°; yield, approximately that calculated.

Anal. Calc'd for $C_{11}H_{15}Cl_2N_3O_2$: C, 45.2; H, 5.2.

Found: C, 45.5; H, 5.3.

Condensation of 5,8-diamino-6,7-dimethoxyquinoline with anhydrides of dibasic acids. The method of preparation was the following: To a solution of 1.5 g. of the diamine (I) in 25 cc. of acetone, there was added 2 equivalents of the anhydride and the mixture was refluxed for three minutes. As the dark red solution cooled, a copious orange brown precipitate separated, which was washed with acetone and purified by repeated crystallization from alcohol. Yields were about 90%.

The condensation products with maleic and phthalic anhydrides both carried water of crystallization, which was not lost when those compounds were heated to 100° over calcium chloride under diminished pressure. On the other hand, the succinic anhydride product crystallized without any solvent of crystallization.

Analyses, etc., of these condensation products are given below:

COMPOUND	FORMULA	APPEARANCE	CALC'D		FOUND		M.P. DECOMP.
			C	H	C	H	
V	$C_{19}H_{21}N_3O_8$	White crystals	54.5	5.0	54.4	5.2	159–160°
VII	$C_{19}H_{17}N_3O_8 \cdot H_2O$	Pale brown crystals	52.7	4.4	53.1	4.7	219–220°
VIII	$C_{27}H_{21}N_3O_8 \cdot 0.5H_2O$	Nearly white crystals	61.9	4.1	61.9	4.2	173–175°

5,8-Disuccinimido-6,7-dimethoxyquinoline (VI). A mixture of 0.7 g. of the diamine (I) with 3.5 g. of succinic anhydride was heated for 2 hrs. at 120°. Excess of succinic anhydride collected as a sublimate in the upper part of the test tube. When the pale brown melt had partly cooled, it was treated with hot water, to remove unchanged succinic anhydride, and then crystallized twice from alcohol. White crystals were obtained, m.p. above 310° (subl.) (Maquenne block); yield, 80%. For analysis, a sample was dried for 5½ hrs. at 100°, over calcium chloride, in an Abderhalden pistol.

Anal. Calc'd for $C_{19}H_{17}N_3O_6$: C, 59.6; H, 4.4.

Found: C, 59.9; H, 4.5.

5,8-Diphthalimido-6,7-dimethoxyquinoline (IX). To a solution of 0.7 g. of the diamine (I) in 10 cc. of dioxane, 1.6 g. of phthalic anhydride was added, and the mixture was refluxed for 2 hrs. A solid separated during the refluxing. When the mixture had cooled, this precipitate was collected and was found to consist of bright yellow prisms, in a yield of 85%. Purified by recrystallization from alcohol and drying over calcium chloride under diminished pressure at 100°, these crystals melted with decomposition at 236–238° (Maquenne block).

Anal. Calc'd for $C_{27}H_{17}N_3O_6 \cdot 2H_2O$: C, 62.9; H, 4.1.

Found: C, 63.1; H, 4.3.

The fact that this product was insoluble in sodium carbonate solution, but dissolved in dilute sodium hydroxide, argues in favor of the imide structure (IX), rather than the dibasic acid (VIII). Further, it melted about 63° higher than that acid, which was prepared in acetone solution. The bright yellow color of (IX) compared with the nearly colorless crystals of (VIII), also indicates an imide rather than a dibasic acid structure. On boiling (VIII) in alcohol for 10 minutes, (IX) is formed, which can be shown easily by the color and the melting point. This transition from an open chain acid to the imide in boiling alcohol was also observed by Shapiro and Bergmann (11).

SUMMARY

(1) A number of nitro- and amino-veratroles have been prepared, either by new methods or as new compounds.

(2) 6,7-Dimethoxyquinoline has been synthesized from 4-aminoveratrole, and converted into its 5,8-dinitro and diamino derivatives.

(3) 5,8-Diamino-6,7-dimethoxyquinoline condenses easily with the anhydrides of succinic, maleic, and phthalic acids to the corresponding amidic acids.

(4) The amidic acids from succinic and phthalic acids readily form the corresponding imides, whereas the maleamidic acid does not.

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