[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY,
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# BIGUANIDE AND THIOUREA DERIVATIVES OF QUINOLINE[1]

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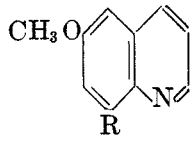
The outstanding value, as antimalarials, of Chloroquin[2] and Plasmochin[3] on the one hand and the exceedingly interesting properties, in experimental and clinical malaria, of Paludrine[4] on the other, prompted us to attempt the synthesis of drugs carrying a biguanidyl group in place of the side chain in Chloroquin and Plasmochin. In view of the low toxicity of Paludrine and of its analogs in the phenanthrene series (1, 2), one could reasonably expect a similar property in the planned compounds.

Many attempts, under varied conditions, to induce 4-amino-7-chloroquinoline to react with cyanoguanidine or isopropylcyanoguanidine failed. Moreover, we did not succeed in converting this aminoquinoline to the corresponding isothiocyanate, a potential intermediate to biguanide derivatives (1, 2). These failures may be attributed to the distinct character of the 4-amino group in the quinoline nucleus (3, 4, 5, 6).

In contrast to our experience with 4-amino-7-chloroquinoline, no difficulties were encountered in bringing about the addition of the cyanoguanidines to 8-amino-6-methoxyquinoline to give satisfactory yields of 1-(6-methoxy-8-quinolyl)biguanide (I) and 1-isopropyl-5-(6-methoxy-8-quinolyl)biguanide (II)[5]. Furthermore, 8-amino-6-methoxyquinoline and isopropylisothiocyanate produced readily, 1-isopropyl-3-(6-methoxy-8-quinolyl)thiourea (III) which was converted, with methyl iodide, to 1-isopropyl-3-(6-methoxy-8-quinolyl)-2-methyl-2-thiopseudourea (IV).




I R = $NHC(:NH)NHC(:NH)NH_2$
II R = $NHC(:NH)NHC(:NH)NH\text{-}i\text{-}C_3H_7$
III R = $NHC(:S)NH\text{-}i\text{-}C_3H_7$
IV R = $N:C(SCH_3)NH\text{-}i\text{-}C_3H_7$

None of the compounds tested showed any effectiveness against blood-inoculated *gallinaceum* malaria (7).

*Acknowledgment.* We wish to express our thanks to Dr. Reynold C. Fuson for supplying us with 4-amino-7-chloroquinoline. The microanalyses were carried out by C. A. Kinser and Betty Mount of this Institute.

[1] Attempts to find New Antimalarials XXV.

[2] 7-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline.

[3] 6-Methoxy-8-(4-diethylamino-1-methylbutylamino)quinoline.

[4] 1-(p-Chlorophenyl)-5-isopropylbiguanide.

[5] While this paper was in press, we were informed by private communication that Curd, Hendry, Kenney, Murray, and Rose, of Imp. Chem. Ind., Ltd., have prepared, among others, compound II. Their work will be published in the Journal of the Chemical Society.

## EXPERIMENTAL[6]

*Experiments with 4-amino-7-chloroquinoline (V).* A mixture of the hydrochloride of V and cyanoguanidine or 1-cyano-3-isopropylguanidine (1) in boiling alcohol gave V-HCl. When the alcoholic mixture was heated in a sealed tube at temperatures of 150–190° only 40% of the V-HCl was recovered, and intractable oily hydrochlorides were obtained. Fusion of the reactants gave essentially the same results. A mixture of the components in boiling, aqueous copper sulfate yielded only starting material.

When V was treated with carbon disulfide and aqueous (8) or alcoholic ammonia or alcoholic sodium hydroxide, it was recovered quantitatively. In the course of these reactions, the nitrate and acid sulfide salts were obtained. Efforts to prepare the diquinolylthiourea by refluxing V and carbon disulfide together in pyridine, alcohol, or dilute aqueous alcoholic potassium hydroxide were essentially without success.

4-Amino-7-chloroquinoline nitrate crystallized from alcohol-water in needles, m.p. 274° (dec.).

*Anal.* Calc'd for $C_9H_8ClN_3O_3$: C, 44.7; H, 3.3.
Found: C, 44.9; H, 3.5.

4-Amino-7-chloroquinoline acid sulfide crystallized from chloroform in small, yellow prisms, m.p. 150° (dec.).

*Anal.* Calc'd for $C_9H_9ClN_2S$: C, 50.8; H, 4.3.
Found: C, 50.8; H, 3.9.

*1-(6-Methoxy-8-quinolyl)biguanide hydrochloride (NIH 2303)*[7] *(I).* A mixture of 5 g. of 8-amino-6-methoxyquinoline hydrochloride, 2 g. of cyanoguanidine, and 25 ml. of 95% ethanol was refluxed for four hours to give 3.0 g. (43%) of I, m.p. 238–240°. It crystallized from 80% ethanol in needles, m.p. 243–245.5° (dec.).

*Anal.* Calc'd for $C_{12}H_{15}ClN_6O$: C, 48.9; H, 5.1.
Found: C, 49.3; H, 5.1.

The base, prepared from the hydrochloride with dilute, aqueous ammonia, crystallized from ethanol in oblong plates of m.p. 165.5–166.5° (gas evolution). The analysis indicated 0.5 mole of solvate water, but loss-in-weight determinations for the percentage of water gave no consistent results.

*Anal.* Calc'd for $C_{12}H_{14}N_6O + 0.5H_2O$: C, 53.9; H, 5.7.
Found: C, 54.3; H, 5.7.

*1-Isopropyl-5-(6-methoxy-8-quinolyl)biguanide hydrochloride (NIH 2302) (II).* A mixture of 3.5 g. of 8-amino-6-methoxyquinoline hydrochloride, the 1-cyano-3-isopropylguanidine from the desulfurization of 3 g. of 1-isopropyl-2-methyl-2-thiopseudourea (1), and 20 ml. of 95% ethanol gave, after refluxing for six hours, 2.5 g. (50%) of II hydrochloride, m.p. 230–233°; needles from 95% ethanol, m.p. 234–236°.

*Anal.* Calc'd for $C_{15}H_{21}ClN_6O$: C, 53.5; H, 6.3.
Found: C, 53.7; H, 6.4.

*1-Isopropyl-3-(6-methoxy-8-quinolyl)thiourea (NIH 2309) (III).* A mixture of 7.5 g. of 8-amino-6-methoxyquinoline, 4.4 g. of isopropylisothiocyanate (1, 9), and 30 ml. of ethanol was refluxed for two hours, diluted somewhat with water, and cooled in ice to give 7.1 g. (60%) of III, m.p. 135–137°. It crystallized from methanol in rods of m.p. 136–137.5°.

*Anal.* Calc'd for $C_{14}H_{17}N_3OS$: C, 61.1; H, 6.2.
Found: C, 61.0; H, 6.3.

*1-Isopropyl-3-(6-methoxy-8-quinolyl)-2-methyl-2-thiopseudourea (NIH 2812) (IV).* Six grams of III and 50 ml. of absolute ethanol were treated slowly with 1.5 ml. of methyl iodide. After refluxing gently for ten minutes, conc'd ammonia and water were added to give, after

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[6] All melting points given are uncorrected.

[7] Compounds tested are designated by an NIH number; results on these were obtained too late to be classified in the Survey monograph.

long standing and finally ice-cooling, 3.5 g. (55%) of IV, m.p. 71–77°. After two recrystallizations from aqueous methanol, it melted at 82–83.5°; prisms.

*Anal.* Calc'd for $C_{15}H_{19}N_3OS$: C, 62.1; H, 6.6.
Found: C, 62.2; H, 6.6.

SUMMARY

Some biguanide and thiourea derivatives of 8-amino-6-methoxyquinoline were prepared for antimalarial tests.

Attempts to prepare biguanide derivatives from 4-amino-7-chloroquinoline failed.

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