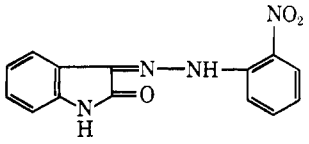
of hydrazines, hydrazides, amines, and related compounds.

Although screening data on all of the compounds have not yet become available, the representative results listed in Tables I and II indicate that the intramuscular activity of I against Walker carcinosarcoma 256 does not extend to the related derivatives. I was subsequently found to be inactive against L1210 lymphoid leukemia.



I

Experimental Section

Condensation Reactions.—Equimolar quantities of isatin and the hydrazine (in several cases the HCl salt was used) or related compounds were dissolved in warm EtOH and heated on the steam bath for 20–40 min. After standing for approximately 24 hr at room temperature the products described in Tables I and II were collected by filtration. The compounds exhibited ir peaks (KBr) at 3.12 ± 0.11, 5.80 ± 0.11, and 6.14 ± 0.04 (and at 2.95 ± 0.05 in compounds containing =NNH–).

Quinoline Antimalarials. Folded Chloroquine

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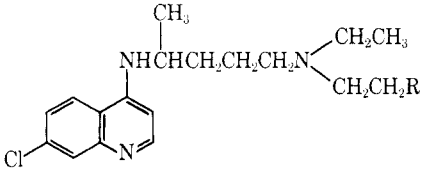
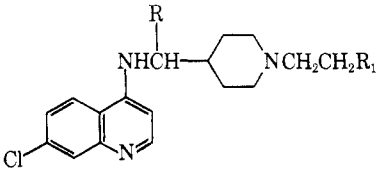
Chloroquine[1a] (**1a**) and hydroxychloroquine[1b] (**1b**)



1a, R = H
b, R = OH

have been widely used in the treatment of malaria and collagen diseases.[2] In an effort to increase the magnitude or duration of activity and/or reduce the toxicity of this class of compounds, we have examined the effect of "folding" the side chain to give compounds of structure **2**.[3] The syntheses of these compounds were



2a, R = CH_3; R_1 = H
b, R = H; R_1 = H
c, R = H; R_1 = OH

accomplished by the interaction, at elevated temperatures, of 4,7-dichloroquinoline and the appropriate side-chain diamine[4] (see Experimental Section).

Biological Activity.—None of the new compounds showed any advantage over **1a** or **1b**. When tested in Swiss mice against blood-induced infections with two species of rodent malaria, *i.e.*, *Plasmodium berghei* and *Plasmodium vinckei*, **2a** and **2b** were found to have antimalarial activity comparable to chloroquine, having oral minimum curative doses[5] of about 10 and 5 mg/kg/day, respectively, for 5 days compared with about 5 mg/kg/day for 5 days for chloroquine. Against NK65 strain of *P. berghei*, **2c** cleared all animals of parasitemia during a 4-week postinfection period at a dose of 12.5 mg/kg/day for 5 days but was ineffective at a similarly administered dose of 6.25 mg/kg/day.

In the carrageenan edema test[6] at a dose of 100 mg/kg *po*, **2a–c** reduced the average edema weight by 42, 37, and 36%, respectively. Hydroxychloroquine (**1b**) reduced edema by 29% at the same dose.

The acute oral toxicities are given in Table I.

TABLE I
ACUTE ORAL TOXICITY IN MICE

Compd	Oral LD_{50}, mg/kg[a] 24 hr	7 day
1a	580 ± 114	580 ± 114
1b	2340 ± 384	1240 ± 170
2a	1240 ± 294	1090 ± 220
2b	1050 ± 200	770 ± 144
2c	2040[b]	1040[b]

[a] As free base. [b] ALD_{50}.

Experimental Section[7]

4-(1-Aminoethyl)-1-ethylpiperidine.—4-Acetyl-1-ethylpyridinium iodide oxime[8] (149 g) was hydrogenated in 350 ml of absolute EtOH over 1.5 g of PtO_2 at an initial pressure of 57.5 kg/cm² and an initial temperature of 23° followed by a 4-hr heating period at 80–90°. The uptake was 85% of theory. The catalyst was filtered off and most of the solvent was removed through a short column. The pot residue was digested with 1 equiv of dry $NaOCH_3$. Et_2O was added and the precipitated salts were removed by filtration. Concentration of the filtrate and fractionation of the residue gave 29.9 g (37.6%) of product, bp 91–94° (7 mm), $n^{25}D$ 1.4654–1.4662. *Anal.* Calcd for $C_9H_{20}N_2$: N, 17.93. Found: N, 17.46.

4-Aminomethyl-1-ethylpiperidine.—The N-acetyl derivative of 4-cyanopiperidine prepared from 45 g of amine,[9] and 150 ml of Ac_2O was added as a slurry over a period of 4 hr to a stirred suspension of 24 g of $LiAlH_4$ in 600 ml of THF. The mixture was refluxed for 16 hr, decomposed by the dropwise addition of 74.4 g of ethylene glycol in 400 ml of THF, and filtered through Filter-cel. Distillation of the filtrate gave 23.9 g (41% from 4-cyanopiperidine) of product, bp 87.5–90.1° (6–7 mm).

4-Aminoethyl-1-(2-hydroxyethyl)piperidine.—A mixture containing 55 g of 4-cyanopiperidine,[9] 26.4 g of ethylene oxide, and 0.2 g of *p*-toluenesulfonic acid was stirred at 60° for 13 hr. Fractionation of the reaction mixture gave a 13% recovery of starting amine, bp 56–64° (1 mm), and 47.1 g (61%) of 4-cyano-1-(2-hydroxyethyl)piperidine, bp 122–123° (1 mm), $n^{25}D$ 1.4890.

(1) (a) Aralen®; (b) Plaquenil®.

(2) For a discussion see I. M. Rollo "The Pharmacological Basis of Therapeutics," 3rd ed, L. S. Goodman and A. Gilman, Ed., The Macmillan Co., New York, N. Y., 1965, p 1091 ff.

(3) For related structures see H. C. Scarborough, Y. H. Wu, and R. F. Feldkamp, U. S. Patent 3,184,462 (1965), and Regents, University of Michigan, British Patent 1,113,804 (1968).

(4) H. Andersag, S. Breitner, and H. Jung, U. S. Patent 2,233,970 (1941); *Chem. Abstr.*, **35**, 3771 (1941).

(5) Dose required to produce parasite-free blood in more than 50% of the tested animals, 46 days postinoculation.

(6) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).

(7) Melting points were taken in a Mel-Temp apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

(8) J. Druey and K. Schenker, U. S. Patent 3,004,979 (Oct 17, 1961).

(9) T. S. Gardner, E. Wenis, and J. Lee, *J. Org. Chem.*, **22**, 984 (1957).

Anal. ($C_8H_{14}N_2O$) N. A glpc analysis indicated a purity of 97%. A mixture of 46.4 g of the above nitrile, 350 ml of 23% (w/w) of NH_3 in MeOH, and 5–10 g of Ra Ni under H_2 at an initial pressure of 57.2 kg/cm^2 was heated to 100° for 8 hr. Removal of the catalyst and fractionation of the filtrate gave 36 g (76%) of oil, bp 99–100° (0.3 mm), $n^{25.2}D$ 1.5046. *Anal.* ($C_8H_{18}N_2O$) C, H, N.

Preparation of Final Products. General Procedure.—A mixture of 4,7-dichloroquinoline (Winthrop Laboratories) and 2 molar equiv of amine was stirred under N_2 in an oil bath at 150–160° for 4–10 hr. The product was taken up in dilute HCl and the pH was adjusted to *ca.* 7 with concentrated NH_4OH. The mixture was extracted twice with Et_2O which was discarded. The aqueous portion was made strongly basic with 35% NaOH solution and the oily product was extracted (Et_2O). Removal of solvent and unreacted amine was accomplished by heating under reduced pressure, finally at 100° (0.1 mm). The aminoquinolines were isolated as the free bases or as salts (Table II).

TABLE II

Compd	Salt	Mp, °C	Formula	Analyses
2a	$2H_3PO_4$	272–275 dec	$C_{15}H_{24}ClN_3 \cdot 2H_3PO_4$	N, Cl
2b		125.5–126.5	$C_{17}H_{22}ClN_3$	N, Cl
2c	$2HCl \cdot H_2O$	265–268	$C_{17}H_{22}ClN_3O \cdot 2HCl \cdot H_2O$	N, Cl, H_2O

Antimalarials Related to 2-Bromo-4,5-dimethoxy-N,N′-bis(diethylaminoethyl)aniline. Piperazine Modifications[1,2]

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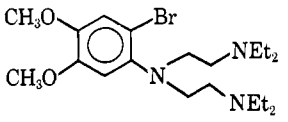
It has recently been reported that 2-bromo-4,5-dimethoxy-N,N′-bis(diethylaminoethyl)aniline (I) is effective against the exo-erythocytic stages of *Plasmodium cathemerium* in canaries.[3] From an evaluation of



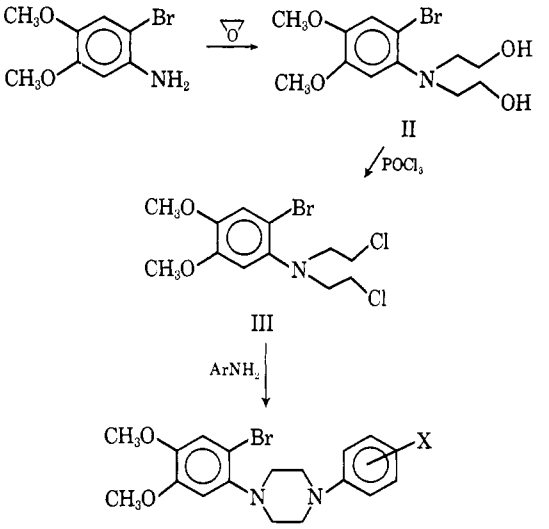
I

I against *Plasmodium cynamolgi* in rhesus monkey Schmidt[4] concluded that I shows considerable promise as a radical curative agent. This revived interest in the aminopyrocatechol[5] class of antimalarials prompted us to investigate structural modifications of the basic side chain.

Schoenhofer's[6] work demonstrated that the basic side chain must conform to the rigid structural features depicted by I. We decided to synthesize and evaluate piperazines and spiropiperazinium salts, related to I, as radical departures from the already studied aminopyrocatechols.

Chemistry.—Synthesis of the modifications described in this paper were realized by the reactions in Scheme I. The key intermediate to this scheme, 2-bromo-4,5-

SCHEME I



dimethoxyaniline,[7] can be prepared by the bromination of 3,4-dimethoxyacetanilide. Since this procedure did not appear to be capable of yielding substantial quantities of the desired material as the free base, several alternate routes were examined.[8] The best technique found for the preparation of 2-bromo-4,5-dimethoxyaniline was the reduction of the corresponding nitro compound by the reducing system N_2H_4–Raney Ni, after the procedure of Leggetter and Brown.[9] Yields of 85% of the desired arylamine, as the free base, were consistently obtained, even on large-scale reductions.

Hydroxethylation of 2-bromo-4,5-dimethoxyaniline with ethylene oxide by the procedure of Freifelder and Stone[10] gave only the monoalkylated product. Extending the reaction to 3 days at 90° gave 90% of II. Careful control of reaction conditions and stoichiometry was necessary to suppress the formation of polyethylene oxides, the presence of which made purification of II difficult. $SOCl_2$[11a] or preferrably $POCl_3$[11b] was used to convert II to the nitrogen mustard III. This compound (III) was obtained in 89% yield as a nondistillable viscous oil. To circumvent the laborious purification procedure of III we attempted to synthesize a variation of III that was a solid at room temperature. Synthesis of III wherein chlorine was replaced by bromine, mesylate, tosylate, or brosylate did not yield a solid precursor to IV.

Reaction of the appropriately substituted anilines with III, according to the procedure of Davis and Ross[12] gave modest yields of the N-phenylpiperazines listed in Table I. The *m*- and *p*-nitroanilines failed to react with III. Treatment of bis(chloroethyl)-*m*-nitroaniline

(1) This work was supported by the U. S. Army Medicinal Research and Development Command under Contract No. DA-49-193-MD-2900. This is Contribution No. 413 from the Army Research Program on Malaria.

(2) Presented in part at the symposium on The Resistant Malaria Problem before The Medicinal Chemistry Section, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

(3) L. J. Bruce-Chwatt, *Trans. Roy. Soc. Trop. Med. Hyg.*, **59**, 105 (1965).

(4) L. H. Schmidt, *et al.*, *Bull. World Health Organ.*, **34**, 783 (1966).

(5) W. Schulemann and W. Kropp, U. S. Patent 1,757,394 (1930).

(6) F. Schoenhofer, *FIAT, Rev. Ger. Sci.*, PB-85033:33 (1939–1946).

(7) J. L. Simonsen and M. G. Rau, *J. Chem. Soc.*, 782 (1918).

(8) Direct bromination of 4-aminoveratrole gave intensely colored materials which were difficult to purify. Catalytic hydrogenation of 4-bromo-5-nitroveratrole were intolerably slow or under more drastic conditions complicated by extensive loss of bromine accompanying reduction of the nitro group.

(9) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **38**, 2363 (1960).

(10) M. Freifelder and G. R. Stone, *J. Org. Chem.*, **26**, 1477 (1961).

(11)(a) W. E. Hanby and H. N. Rydon, *J. Chem. Soc.*, 513 (1947); (b) W. C. Ross, *ibid.*, 183 (1949).

(12) W. Davis and W. C. Ross, *ibid.*, 2831 (1949).