The N,N''-[sulfonylbis(*p*-phenyleneazo-1,4-naphthylene)]bis(N',N'-dialkylalkylenediamines) (XIII, XIVa, and XIVb) were also tested in mice against a Puerto Rican strain of *S. mansoni*.[16] Drugs were given in a powdered diet for 14 days and drug amounts are expressed as free base. Compounds XIII, XIVa, and XIVb were highly active and effected a 53–100% reduction of live schistosomes in mice at doses ranging from 86 to 364 mg/kg/day.

Against representative bacteria *in vitro*, including *Staphylococcus aureus* (UC-76), *Pseudomonas aeruginosa* (28), *Mycobacterium tuberculosis* ($H_{37}Rv$), *Escherichia coli* (Vogel), *Diplococcus pneumoniae*, *Streptococcus pyogenes* (C203), *Proteus mirabilis* (MGH-1), and *Salmonella typhimurium* (V-31),[8] compound XIII caused complete inhibition of *M. tuberculosis* $H_{37}Rv$ at a concentration of 20 μg/ml and XIVa caused complete inhibition of the following organisms: *S. aureus* (UC-76), 20 μg/ml; *M. tuberculosis* ($H_{37}Rv$), 20 μg/ml; *D. pneumoniae*, 1.25 μg/ml; and *S. pyogenes* (C203), 0.63 μg/ml. 1,1'-{Sulfonylbis[*p*-phenyleneazo(5,6,7,8-tetrahydro-1,4-naphthylene)iminotrimethylene]}dipiperidine (XIII) was inactive against *M. tuberculosis* $H_{37}Rv$ in mice when administered at 0.04 (45 mg/kg/day) and 0.25% (142 mg/kg/day) in the diet for 7 days.[8]

Experimental Section[17,18]

1,1'-{Sulfonylbis[*p*-phenyleneazo(5,6,7,8-tetrahydro-1,4-naphthylene)iminotrimethylene]}dipiperidine (XIII).—A solution of 12.4 g (0.05 mole) of 4,4'-sulfonyldianiline (DDS)[12] in 800 ml of H_2O and 17 ml of concentrated HCl was cooled to 0° and the amine was tetrazotized by the slow, portionwise addition of 6.9 g (0.1 mole) of $NaNO_2$ in 100 ml of cold H_2O. The mixture was stirred at 0° for 15 min and then added at 0–5° to a solution of 27.2 g (0.1 mole) of 1-{3-[(5,6,7,8-tetrahydro-1-naphthyl)amino]-propyl}piperidine[8] in a mixture of 200 ml of H_2O and 7.2 ml of concentrated HCl. The mixture was stirred for 2 hr at 0–5° and made alkaline with 5% NaOH. The crude product was collected by filtration, washed (H_2O), and dried. Crystallization from DMF afforded 28.0 g (69%) of red crystals, mp 180–186°. *Anal.* ($C_{48}H_{62}N_8O_2S \cdot 0.25H_2O$) C, H, N.

The base (5.0 g, 0.006 mole) was dissolved in DMF and treated with an excess of an *i*-PrOH–HCl mixture. Upon cooling, the dark purple HCl salt precipitated. The salt was collected by filtration and dried *in vacuo* at 60° for 3 days. The product was thus obtained as the tetrahydrochloride hexahydrate, 5.4 g (85%), mp 180° dec. *Anal.* ($C_{48}H_{62}N_8O_2S \cdot 4HCl \cdot 6H_2O$) C, H, Cl^-, N.

N,N''-[Sulfonylbis(*p*-phenyleneazo-1,4-naphthylene)]bis(N',N'-diethyl-1,3-propanediamine) Tetrahydrochloride (XIVa).—4,4'-Sulfonyldianiline (DDS)[12] (6.2 g, 0.025 mole) was tetrazotized and coupled with 12.8 g (0.05 mole) of N,N-diethyl-N'-1-naphthyl-1,3-propanediamine[15] according to the procedure for XIII. The HCl salt of the product (XIVa) was obtained as deep green crystals from DMF–*i*-PrOH–HCl, mp 290°, yield 13.6 g (52%). *Anal.* ($C_{46}H_{54}N_8O_2S \cdot 4HCl \cdot 6H_2O$) C, H, Cl^-, N.

1,1'-[Sulfonylbis(*p*-phenyleneazo-1,4-naphthyleneiminotrimethylene)]dipiperidine (XIVb).—4,4'-Sulfonyldianiline (DDS)[12] (6.2 g, 0.025 mole) was tetrazotized and coupled with 13.4 g (0.05 mole) of 1-[3-(1-naphthylamino)propyl]piperidine[15] according to the procedure for XIII. The product (XIVb) was obtained as dark red-brown crystals from DMA–MeCN, mp 160–163°, yield 6.8 g (33%). *Anal.* ($C_{48}H_{54}N_8O_2S \cdot 0.5H_2O$) C, H, N.

Acknowledgments.—The authors express their appreciation to Dr. Paul E. Thompson, Dr. M. W. Fisher, and coworkers of these laboratories for the antiparasitic and antibacterial evaluation of these compounds. We also thank Dr. J. M. Vandenbelt and coworkers for the spectral studies and Mr. Charles E. Childs and associates for the microanalyses.

(16) For a description of test methods, see P. E. Thompson, J. E. Meisenhelder, and H. Najarian, *Am. J. Trop. Med. Hyg.*, **11**, 31 (1962).

(17) Melting points (corrected) were taken on a Thomas–Hoover capillary melting point apparatus.

(18) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Water determinations were by the Karl Fischer method.

2-(Alkyl- and Arylamino)-5-nitrothiazole Derivatives with Antiamebic, Antitrichomonal, and Antimalarial Properties[1]

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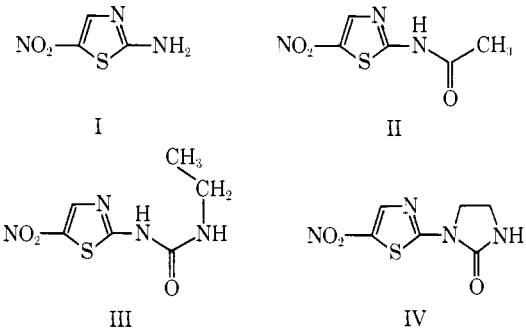
Numerous 2-amino-5-nitrothiazole derivatives exhibit antiamebic,[2,3] antihistomonal,[4] antitrichomonal,[3,5] and antischistosomal[3] properties. Among them, 2-amino-5-nitrothiazole (enheptin) (I), 2-acetamido-5-nitrothiazole (aminitrozole) (II), and 1-ethyl-3-(5-nitro-2-thiazolyl)urea (nithiazide) (III) have been employed



I II III IV

in the control of histomoniasis (blackhead) in turkeys and other domestic fowls caused by *Histomonas meleagridis*. Aminitrozole has also been used for the oral treatment of human trichomoniasis due to *Trichomonas vaginalis*, and 1-(5-nitro-2-thiazolyl)-2-imidazolidinone (niridazole) (IV) is effective against amebiasis and schistosomiasis in man.

Most of the synthetic work on 2-amino-5-nitrothiazole derivatives as potential antiprotozoal and antischistosomal agents[2–5] has dealt with amide and urea analogs of aminitrozole, nithiazide, and niridazole, and relatively few simple 2-(alkyl- and arylamino)-5-nitro-

(1) This is paper IX of a series on synthetic amebicides; for paper VIII, see E. F. Elslager, F. W. Short, and F. H. Tendick, *J. Heterocyclic Chem.*, **5**, 599 (1968). This is paper XVI of a series relating to antimalarial substances; for paper XV, see E. F. Elslager and A. A. Phillips, *J. Med. Chem.*, **12**, 519 (1969).

(2) For a recent review, see E. F. Elslager in "Medicinal Chemistry," A. Burger, Ed., 3rd ed, Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1969.

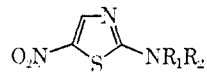
(3) For recent reviews, see (a) E. F. Elslager in "Annual Reports in Medicinal Chemistry, 1965," C. K. Cain, Ed., Academic Press, New York, N. Y., 1966, p 136; (b) E. F. Elslager in "Annual Reports in Medicinal Chemistry, 1966," C. K. Cain, Ed., Academic Press, New York, N. Y., 1967, p 131.

(4) For a recent review, see L. P. Joyner, S. F. M. Davies, and S. B. Kendall in "Experimental Chemotherapy," Vol. I, R. J. Schnitzer and F. Hawking Ed., Academic Press, New York, N. Y., 1963, pp 333–346.

(5) For a recent review, see R. J. Schnitzer, ref 4, pp 289–321.

TABLE I

2-(ALKYL- AND ARYLAMINO)-5-NITROTHIAZOLES



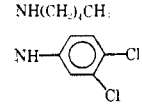
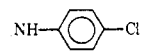
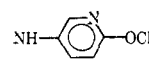
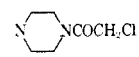
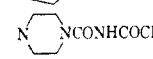
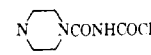
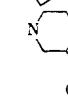
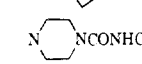
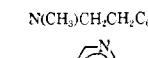
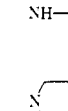
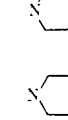
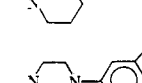
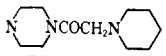
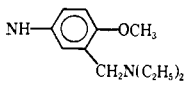
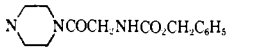
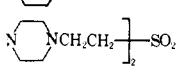
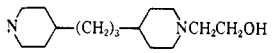
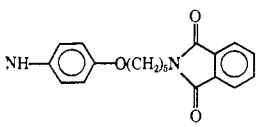
No.	NR_1R_2	Mp, °C[a]	Yield purifd, %	Method	Purifcn solvent	Formula	Analyses[b]	*In vitro* trichomonacidal act., μg/ml	*In vitro* amebicidal act., μg/ml
1		151.5–154	56	C	EtOH	$C_6H_7N_3O_2S$	C, H, N	25	40
2		86–88	66	C	*i*-PrOH	$C_6H_7N_3O_3S$	C, H, N	>25	40
3		174–176	45	C	*i*-PrOH	$C_7H_7N_3O_2S$	C, H, N	25	>80
4	$N(CH_3)CH_2CH_2CN$	99–101	80	C	*i*-PrOH	$C_7H_8N_4O_2S$	H, N; C[c]	>25	>40
5		162–165	56	C	EtOH	$C_7H_6N_3O_2S$	C, H, N	25	
6		145–147	82	C	*i*-PrOH	$C_7H_7N_3O_3S$	C, H, N	25	>40
7	$NH(CH_2)_4OCH_3$	118–121	12	*h*	MeCN	$C_7H_{11}N_3O_3S$	C, H, N		
8		135–137	44	C	*i*-PrOH	$C_6H_{11}N_3O_3S$	H, N; C[c]	6.25	40
9	$NH(CH_2)_4CH_3$	111–114	45	B	Heptane	$C_8H_{13}N_3O_2S$	C, H, N	>25	
10		190 dec	55	A	*i*-PrOH	$C_9H_5Cl_2N_3O_2S$	C, H, N	1.56	10
11		230 dec	72	A	EtOH–H_2O	$C_9H_6ClN_3O_2S$	C, H, N	1.56	20
12		244 dec	82	A	DMF–H_2O	$C_9H_8N_4O_3S$	H, N; C[c]	25	>80
13		174–175	34	*k*	EtOH	$C_9H_{11}ClN_4O_3S$	C, H, N	6.25	10
14		92–93	45	C	*i*-PrOH	$C_9H_{13}N_3O_2S$	H, N, S; C[d]	>25	>40
15		227–228 dec	73	D	EtOH	$C_{10}H_{12}ClN_5O_4S$	C, H, N	6.25	10
16		155–157	72	C	*i*-PrOH	$C_{10}H_{13}N_3O_4S$	C, H, N	25	20
17		166–168 dec	12	*k*	*i*-PrOH	$C_{11}H_9N_3O_4S$	C, H, N	>25	
18		154–155 dec	57	D	EtOH	$C_{11}H_{14}BrN_5O_4S$	C, H, N	25	>40
19		141–143	79	C	*i*-PrOH	$C_{11}H_{15}N_3O_2S$	C, H, N	25	>40
20		86–88	62	C	MeCN	$C_{11}H_{13}N_3O_4S$	H, N; C[e]	6.25	40
21		190–191	59	D	EtOH	$C_{11}H_{15}N_5O_4S$	C, H, N	6.25	40
22		145.5–147.5	51	C[f]	MeCN	$C_{12}H_{11}N_3O_4S$	C, H, N	>25	
23	$N(CH_3)CH_2CH_2C_6H_4Cl$-*o*	114–116	76	C	*i*-PrOH	$C_{12}H_{12}ClN_3O_2S$	C, H, N	>25	>40
24		132–134	54	A	*i*-PrOH	$C_{12}H_{14}N_4O_3S$	C, H, N	6.25	10
25		103–105	71	C	MeCN	$C_{12}H_{17}N_3O_4S$	C, H, N		
26		135–137	79	C	*i*-PrOH	$C_{13}H_{20}N_4O_3S$	H, N; C[f]	6.25	>40
27		180–181	77	A	Me_2CO–H_2O	$C_{14}H_{15}ClN_4O_2S$	C, H, N, Cl	25	>80

TABLE I (*Continued*)

No.	NR_1R_2	Mp, °C[l]	Yield purifd, %	Method	Purifcn solvent	Formula	Analyses[m]	*In vitro* trichomonicidal act., μg/ml	*In vitro* amebicidal act., μg/ml
28		135	48	*k*	EtOH	$C_{14}H_{21}N_5O_3S$	C, H, N	>25	40
29		128–130	37	C	*i*-PrOH	$C_{15}H_{17}N_3O_3S$	C, H, N, S	>25	80
30		195 dec	71	A	EtOH–H_2O	$C_{15}H_{20}N_4O_3S$	C, H, N	6.25	>80
31		156	85	*k*	EtOH	$C_{17}H_{19}N_5O_5S$	C, H, N	6.25	>40
32		188–190	75	*k*	DMF	$C_{18}H_{26}N_8O_6S_3$	C, H, N	>25	>40
33		88–91	30	C	*i*-PrOH	$C_{18}H_{30}N_4O_3S \cdot H_2O$	C, H, N, H_2O	6.25	>40
34		217–218 dec	97	A	DMF–H_2O	$C_{22}H_{20}N_4O_5S$	H, N; C[g]	>25	>40

[a] C: calcd, 39.61; found, 40.61. [b] C: calcd, 41.91; found, 42.37. [c] C: calcd, 42.85; found, 43.28. [d] C: calcd, 47.56; found, 48.04. [e] C: calcd, 46.30; found, 46.77. [f] C: calcd, 49.98; found, 50.44. [g] C: calcd, 58.40; found, 58.97. [h] The reactants were stirred without solvent at room temperature overnight, washed (H_2O), extracted with cyclohexane, concentrated, and recrystallized. [i] CH_2Cl_2 was used in place of Et_2O. [j] The reactants were heated in THF under reflux for 12 hr. [k] Described in Experimental Section. [l] Melting points (corrected) were taken in open capillary tubes in a Thomas–Hoover capillary melting point apparatus. [m] Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

thiazoles have been synthesized for biological evaluation.[6–12] Therefore, we have prepared a series of representative 2-(alkyl- and arylamino)-5-nitrothiazole derivatives (**1–34**, Table 1) to enable a determination of relative structure–antiprotozoal–antischistosomal activity relationships. These compounds were prepared from 2-bromo-5-nitrothiazole and the corresponding amine utilizing the general procedures summarized below.

The compounds described in the present communication were tested against *Entamoeba histolytica in vitro*,[13] *Trichomonas vaginalis in vitro* and in mice,[13] *Plasmodium berghei* in mice,[14] and *Schistosoma mansoni* in mice[15] by Dr. Paul E. Thompson and coworkers of these laboratories utilizing the biological test methods described previously.[13–15] Compounds **8**, **10**, **13**, **15**, and **24** (Table I) killed *E. histolytica in vitro* at concentrations of 10 μg/ml, but were somewhat less potent than emetine or paromomycin.[2,13] Twelve of the aminonitrothiazoles (**8**, **10**, **11**, **13**, **15**, **20**, **21**, **24**, **26**, **30**, **31**, and **33**, Table I) were trichomonicidal against *T. vaginalis in vitro* at concentrations of 1.56–6.25 μg/ml. This group also included the most potent substances against *E. histolytica*. Compounds **1**, **15**, **18**, **21**, **28**, and **33** cured intraperitoneal *T. vaginalis* infections in mice when administered by gavage in 100-mg/kg doses twice daily for 3 days, but none was more than one-fourth as potent as metronidazole.[3,5]

4-{3-[1-(5-Nitro-2-thiazolyl)-4-piperidyl]propyl}-1-piperidineethanol (**33**) and 1-(3-chloro-*p*-tolyl)-4-(5-nitro-2-thiazolyl)piperazine (**27**), when administered in respective daily drug-diet doses of 240 and 312 mg/kg for 6 days to mice infected with *P. berghei*,[14] produced a 77 and 36% reduction in parasitemia among each treated group but were not potent enough to warrant a precise determination of the SD_{90} dose. 2-{3-[(Diethylamino)methyl]-*p*-anisidino}-5-nitrothiazole (**30**) showed modest activity against a Puerto Rican strain of *S. mansoni* in mice[15] and killed 33% of the worms when administered at 0.25% in the diet for 14 days. All of the other aminonitrothiazole derivatives lacked appreciable antischistosome properties.

(6) American Cyanamid, U. S. Patent 2,547,677 (1949).
(7) Ortho Pharmaceutical Corp., U. S. Patent 2,915,526 (1959).
(8) H. N. Prince, *Nature*, 186, 816 (1960).
(9) Wallace and Tiernan, U. S. Patent 3,021,333 (1962).
(10) Eisai Co. Ltd., Japanese Patents 14,586/63 and 25,388/63 (1963).
(11) Ciba Ltd., Netherlands Patent Application 6,610,369 (1967).
(12) Farbenfabriken Bayer, Netherlands Patent Application 68/00,740 (1968).
(13) For a description of test methods, see P. E. Thompson, A. Bayles, S. F. Herbst, B. Olszewski, and J. E. Meisenhelder, *Antibiot. Chemotherapy*, 9, 618 (1959).
(14) For a description of the test method, see P. E. Thompson, A. Bayles, and B. Olszewski, *Exp. Parasitol.*, in press.
(15) For a description of test methods, see P. E. Thompson, J. E. Meisenhelder, and H. Najarian, *Am. J. Trop. Med. Hyg.*, 11, 31 (1962).

Experimental Section

Method A. 1-(3-Chloro-*p*-tolyl)-4-(5-nitro-2-thiazolyl)piperazine (27).—A solution of 2.09 g (0.01 mole) of 2-bromo-5-nitrothiazole (Eastman) and 2.1 g (0.01 mole) of 1-(4-methyl-3-chlorophenyl)piperazine in 50 ml of EtOH containing 2.52 g (0.03 mole) of $NaHCO_3$ was heated under reflux for 1 hr. The reaction mixture was chilled in ice and the precipitate was collected, washed with H_2O, air dried, and recrystallized from Me_2CO–H_2O to give 2.6 g (77%) of the product, mp 180–181°.

Method B. 5-Nitro-2-(pentylamino)thiazole (9).—To a C_6H_6 solution of 3.0 g (0.0143 mole) of 2-bromo-5-nitrothiazole was added a C_6H_6 solution of 2.5 g (0.0286 mole) of $AmNH_2$. The reaction mixture was heated under reflux for 1 hr. The solid present was removed by filtration, and the filtrate was evaporated to dryness. The residue was washed with H_2O and extracted with Et_2O. The extracts were dried and evaporated to dryness, and the residue was recrystallized from heptane to give 1.37 g (45%), mp 111–114°.

Method C.—The procedure used was the same as for method B except that ether was the solvent, and the reaction mixture was stirred for 1 hr at room temperature.

Method D. 4-(5-Nitro-2-thiazolyl)-N-propionyl-1-piperazine-

carboxamide (21).—Propionyl isocyanate (2.2 g, 0.024 mole) in 5 ml of THF was added dropwise to a suspension of 4.3 g (0.02 mole) of 1-(5-nitro-2-thiazolyl)piperazine[9] in 50 ml of THF, and the mixture was stirred at room temperature for 45 min. The solid was collected and recrystallized from EtOH to give the product.

1-(Chloroacetyl)-4-(5-nitro-2-thiazolyl)piperazine (13).—Chloroacetyl chloride (1.13 g, 0.01 mole) in 5 ml of THF was added dropwise to a mixture of 1-(5-nitro-2-thiazolyl)piperazine[9] (2.14 g, 0.01 mole) and Et_3N (1.38 ml, 0.01 mole) in 45 ml of THF at 0°. The mixture was stirred for 3 hr at room temperature, and the solid was collected, washed with H_2O, and recrystallized from EtOH.

{o-[(5-Nitro-2-thiazolyl)amino]phenyl}acetic Acid (17).—To a solution of 6.3 g (0.03 mole) of 2-bromo-5-nitrothiazole in 250 ml of MeOH was added 3.0 g (0.03 mole) of Et_3N and 80 ml (1 equiv) of a H_2O solution of sodium *o*-aminophenylacetate. The reaction was exothermic. The mixture was allowed to stir for 4 hr, poured into about 3 l. of iced H_2O, and acidified with concentrated HCl. The pale green solid which formed was removed by filtration and dried. This material (3.6 g) had a broad melting point and could not be purified. The filtrate upon standing deposited a yellow solid. This material was dried (1.7 g) and recrystallized from *i*-PrOH to give 1.0 g (12%) of the product, mp 166–168° dec.

Sodium o-Aminophenylacetate.—To 1 l. of H_2O vigorously stirred was added 38 g (0.306 mole) of $Na_2CO_3 \cdot H_2O$. *o*-Nitrophenylacetic acid (100 g, 0.56 mole), was added portionwise (4 drops of 2-octanol was added to suppress foam). The solution was hydrogenated over 1 g of 20% Pd–C at 24° for 16 hr. The mixture was filtered through Supercel, the yellow solution was diluted to 1475 ml, and aliquots were used as needed.

1-(5-Nitro-2-thiazolyl)-4-(piperidinoacetyl)piperazine (28).—Piperidine (1.63 g, 0.0192 mole) was added dropwise to 2.9 g (0.01 mole) of 1-(chloroacetyl)-4-(5-nitro-2-thiazolyl)piperazine in 45 ml of THF at 0°, and the mixture was stirred for 1 hr at room temperature. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was recrystallized from EtOH.

Benzyl ({[4-(5-Nitro-2-thiazolyl)-1-piperazinyl]carbonyl}methyl)carbamate (31).—A solution of 2.1 g (0.01 mole) of dicyclohexylcarbodiimide in 5 ml of THF was added to a solution of 2.14 g (0.01 mole) of 1-(5-nitro-2-thiazolyl)piperazine[9] and 2.1 g (0.01 mole) of benzyloxycarbonylglycine in 30 ml of THF, and the mixture was stirred for 1 hr at room temperature. The solid was collected, washed with Et_2O, and recrystallized from EtOH.

1,1′-(Sulfonyldiethylene)bis[4-(5-nitro-2-thiazolyl)piperazine] (32).—A solution of 1.22 g (0.0103 mole) of divinyl sulfone in 12 ml of EtOH was added dropwise to a suspension of 4.4 g (0.0206 mole) of 1-(5-nitro-2-thiazolyl)piperazine in 25 ml of EtOH, and the mixture was stirred for 4 hr at room temperature. The mixture was allowed to remain at room temperature overnight and then heated under reflux for 1 hr. The product was removed by filtration and recrystallized from DMF.

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Antimalarials. Some Quinuclidine Derivatives of 7-Chloro-4-aminoquinoline and 6-Methoxy-8-aminoquinoline

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Quinuclidine is an important moiety of cinchona alkaloids. The recent availability of quinuclidinone (Aldrich) and the facile preparation of 2-methylene-3-quinuclidinone, reported earlier from our laboratories,[1] put at our disposal the suitable starting materials. These were used to incorporate this important feature of quinine as a side-chain amine in the ring systems of two well-known antimalarial drugs, chloroquine and primaquine.

Pharmacology.—The compounds were tested for their antimalarial activity against *Plasmodium berghei* in mice. The screening was carried out by Dr. L. Rane of the University of Miami, Miami, Fla., by the screening procedure described previously.[2] Two compounds, **1** and **2**, were found to be curative. Compound **1** cured two mice at 160 mg kg and all five in the test at 640 mg kg. Compound **2** showed slight activity at 160 and 320 mg kg and cured all five mice at 640 mg kg. All other compounds were inactive and toxic.

Experimental Section

All melting points were determined in open capillary tubes in a Thomas–Hoover Unimelt and are uncorrected. Reference should be made to Table I for relevant information.

7-Chloro-4-(3-ketoquinuclidinyl-2-methyleneamino)quinoline (1).—A mixture of 7-chloro-4-aminoquinoline[3] (2.0 g, 0.011 mol) and 2-methylene-3-quinuclidinone[1] (3.0 g, 0.022 mol) was heated at 80° with stirring for 1 hr. The reaction was cooled and diluted with 200 ml of MeOH when a white solid (1.0 g) precipitated.

7-Chloro-4-(3-hydroxyquinuclidinyl-2-methyleneamino)quinoline (2).—The quinuclidinone derivative 1 (2.0 g, 0.006 mol) was dissolved in 60 ml of MeOH at 0° and to this was added $NaBH_4$ (5.0 g) in small portions. The mixture was allowed to stand at room temperature for a few hours, and then worked up as usual to give 1.3 g of the product.

7-Chloro-4-(3-quinuclidinylamino)quinoline (3).—A mixture of 4,7-dichloroquinoline (25.0 g, 0.125 mol), 3-aminoquinuclidine dihydrochloride (25.0 g, 0.125 mol), NaOMe (12.0 g, 0.233 mol), and 100 ml of phenol was heated at 140° for 3 hr. Excess phenol was removed *in vacuo* and the residue was cooled, triturated with 30% NaOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4) and filtered and the product was converted to the hydrochloride with dry HCl; yield 5.58 g. It was crystallized several times from a large volume of EtOH until it melted at 330–335° dec. The HCl salt was extremely difficult to purify. The content of H_2O appeared to depend on the degree of drying. This sample was dried at 100° (0.03 mm) for 20 hr.

7-Chloro-4-[1-methyl-4-N-methyl-(3-hydroxyquinuclidinyl-2-methylene)aminobutylamino]quinoline (4).—A solution of 7-chloro-4-(1-methyl-4-methylaminobutylamino)quinoline[4] (12.5 g, 0.045 mol) and 2-methylene-3-quinuclidinone in 300 ml of MeOH was stirred at room temperature for 14 hr. The reaction was cooled in an ice bath, treated with $NaBH_4$ (15.0 g) in small portions over a period of 1 hr, and allowed to stand at room temperature for 2 hr. MeOH was evaporated off *in vacuo*, and the residue was treated with 300 ml of H_2O and extracted with C_6H_6. The C_6H_6 extract was dried (K_2CO_3) and evaporated to give a glass which was passed through a basic alumina column (30 g of alumina to 1.0 g of material) in C_6H_6 solution. After eluting with 3 l. of C_6H_6 to wash off impurities, the product (12.5 g) was eluted with MeOH–C_6H_6 (1:19). It was still a glasslike material and melted over a wide range.

7-Chloro-4-[1-methyl-4-N-ethyl-(3-hydroxyquinuclidinyl-2-methylene)aminobutylamino]quinoline (5) was prepared from the corresponding N-ethyl compound[4] and purified in the same way as **4**.

7-Chloro-4-[N′-(3-quinuclidinyl)hydrazino]quinoline (6).—A solution of 7-chloro-4-hydrazinoquinoline[5] (3.86 g, 0.02 mol), 3-quinuclidinone (2.5 g, 0.02 mol), and 0.1 g of *p*-toluenesulfonic acid hydrate in 100 ml of MeOH was refluxed for 12 hr. The

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